

# **Volume II**

**Appendices I – IV**



# Appendix I

## THE CASE OF BRESAGEN

### Parcel 1: Radionucleotides

Professor Robert Symons from the Biochemistry Department at the University of Adelaide developed a technique for the efficient production of  $^{32}\text{P}$ -labelled radionucleotides that was published in a leading scientific journal<sup>1</sup> in 1977. These were radioactive compounds used to label DNA and RNA, and were widely used at the time in gene technology research. At the time, production of these radionucleotides was influenced by two factors: first, being radioactive and with a short half-life of 14 days, international shipping was difficult and costly. Second, manufacture was dominated by Amersham, a UK-based company, using inefficient technology, which kept prices high.

This meant that increasingly, when Professor Symons had radionucleotides that were surplus to the needs of his own Department and its Centre for Gene Technology (also established in 1982), he increasingly began providing them for free to other laboratories in Australia. By the early 1980s, Bob Symons's head of department, Professor Bill Elliott, suggested that rather than giving the radionucleotides away, he should set up a business. However, Bob Symons did not patent the technique; as Allan Robins, a postdoctoral researcher at the time, commented, 'this is back in the days when we were naïve academics. Nobody patented ideas, or we didn't anyway, Bob didn't' (interview, 2007).

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<sup>1</sup> Nucleic Acids Research

According to the Bresa Product Catalogue (1984):

BRESA [Ltd] was officially set up in [31] May, 1982 to develop and prepare for sale a range of high quality materials for use in gene technology. It is wholly owned by the University of Adelaide and operates from the Department of Biochemistry, which is a major customer of BRESA products.

Bresa (Biotechnology Research Enterprises South Australia) was incorporated to function as the trading arm of the Bresa Unit Trust, and at that time was located within the Department of Biochemistry at the University of Adelaide. Robins stressed that the initial intentions motivating Bresa's establishment lay in securing research funds not private gain:

The plan was to build a little reagent business ... those guys were very philanthropic in those days so there were four founders of the company and none of the founders took any stock or took any money out of it. The whole idea was to bring money in to support research in the Department of Biochemistry. My understanding is that Bob [Symons], Julian [Wells], John Wallace and Bill Elliott were all down as founders of the company. Bob and Julian were really driving it. (interview, 2007)

However, whilst the company Bresa Pty Ltd was freshly incorporated, the idea of making these radionucleotides was not! In fact, Symons had apparently been making them for years, as a former head of department, Professor George Rogers explained:

It was in the '70s, I think, yes. Because he [Symons] was in the [United] States in '71<sup>2</sup> and came back and then molecular biology took off and then there was an embargo on doing cloning because of the possible hazards and there was a Asilomar conference in California in 1974<sup>3</sup> and when they were all cleared we were able to go on with it and Bob started to supply these things [radioactive nucleotides] to the department. The then head of the department was Bill Elliott and Bill said to Bob – I was around when the conversation was going on, of course – 'You're giving the stuff to people in Australia as well as the department, you ought to set it up as a business and commercialise it properly and make some money' rather than being a

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<sup>2</sup> D.A. Jackson, R.H Symons, and P. Berg in *Proceedings of the National Academy of Sciences* (1972).

<sup>3</sup> The Asilomar conference was actually held in 1975 in California. It is seen as a landmark in the history of genetic engineering, an event that served as an influential model for policy making at that time. Its role as a model for future policy making on DNA technologies has been broadly questioned, particularly since commercial and military interests have been seen as major influences on the field's development.

benefactor, as it were. So that's really the start of it ... (interview, 2007)

Bob Symons was collaborating with Paul Berg at the time. It was Paul Berg who is credited with organising the Asilomar Conference in 1975 in California and in 1980, Berg won the Nobel Prize 'for his fundamental studies of the biochemistry of nucleic acids, with particular regard to recombinant-DNA'. On his impressive CV, only five significant papers are listed and on one of these Symons is a co-author:

A Biochemical Method for Inserting New Genetic Information into SV40 DNA: Circular SV40 DNA Molecules Containing Lambda Phage Genes and the Galactose Operon of *E. coli*. David A. Jackson, Robert H. Symons, and Paul Berg. Proc. Nat. Sci. USA, 69, 2904 (1972). (Berg, The Nobel Institute, website accessed 2008)

Moreover, an article on the significance of this paper was written by W.K.

Joklik:

Like the year 1940, the year 1970 occupies a unique position in the history of virology. In 1940, the conceptualization of the one-step growth cycle by Emory Ellis and Max Delbrück; the discovery of hemagglutination, which provided a rapid and simple means of quantitating virus particles; and the invention of the electron microscope and the ultracentrifuge, which provided the means for studying viruses by physical techniques, converged to initiate the era of molecular virology, molecular biology, molecular cell biology, and molecular genetics. In 1970, the discovery of restriction endonucleases by Ham Smith and K. W. Willcox (*J. Mol. Biol.* 51:379–391, 1970) provided the means for localizing any gene and of joining any DNA sequence to any other; the discovery of the reverse transcriptase by David Baltimore and by Howard Temin and Satoshi Mizutani extended this technology to RNA by permitting the transcription of RNA into DNA. These two discoveries initiated the age of genetic engineering.

Very soon scientists realized that these discoveries would enable them to insert new or modified genetic information into the genomes of living creatures. In order to achieve this, appropriate vectors were required. The vectors of choice for introducing DNA into cells are viruses; and since the new genetic information was to be introduced into cellular genomes, the virus had to be one whose genome was inserted into the cellular genome. The first choices here were retroviruses and papovaviruses. In this paper Jackson, Symons, and Berg chose simian virus 40 (SV40) and devised techniques for inserting foreign genetic information into its genome via use of appropriate restriction endonucleases. This paper is one of the cornerstones on which all

subsequent 'vectorology' is based, which is the reason why it was selected. Paul Berg was awarded the Nobel Prize in 1980.

In his autobiography, Berg talks about this important phase of his research career. The colleagues he refers to are Jackson and Symons:

Soon after I returned to Stanford, I conceived of using SV40 as a means for introducing new genes into mammalian cells much in the way that bacteriophage transduce cellular DNA among infected cells. My colleagues and I succeeded in developing a general way to join two DNAs together in vitro; in this case, a set of three genes responsible for metabolizing galactose in the bacterium *E. coli* was inserted into the SV40 DNA genome. That work led to the emergence of the recombinant DNA technology thereby providing a major tool for analyzing mammalian gene structure and function and formed the basis for me receiving the 1980 Nobel Prize in Chemistry. (Berg, The Nobel Foundation, website accessed 2008)

Rogers explained how the Centre for Gene Technology came about, '[it was] primarily because there was a real trend in the department for molecular biology and for gene technology and the government started to put these on paper. The whole idea of having a centre or CRC (Cooperative Research Centre) set these up to really give impetus to research in Australia' (interview with Rogers, 2007). He also talked about the advantages and disadvantages this scheme delivered: 'The point about that was that it produced a packet of money that was not what one usually got from normal grants. So, it gave a tremendous [boost] to research. Unfortunately, despite the fact that there were eight of us in the department, it was decided because there were limitations put on by the rules of the application we could have had five or six, I think, but we decided that we should just have four. That did give a little bit of ill feeling ...' (interview with Rogers, 2007).

In terms then of the arrangement of the Centre within the department, Rogers said:

... there was Bill Elliott who was head of the department, there was Bob

Symons, Julian Wells and myself and we all had projects which had [involvement with transgenics] - I mean, I was doing animal transgenesis then, which is putting genes into sheep and doing things. Bob was doing all that other thing and Bill had some work to do with diseases and then there was Julian who was into a lot of cloning work and fundamental work on genes regulating expression, but to do with cell differentiation so it was very basic stuff, so they fell together pretty well. That's sort of how it came about and we applied - we had an extension for nine years, which was quite a lot. We were able to appoint post-docs and PhD students and the groups grew within magnificently. We had equipment we couldn't otherwise afford. It was just a remarkable boost.

Julian Wells was the director and he took charge of that. Then about that time he started with Bob Seamark. The whole idea was to put growth hormone into pigs ... they were doing transgenesis here in the medical school.... (interview, 2007)

### **Bresa's Early Years**

To help establish the fledgling company, financial capital was provided by the University of Adelaide as an interest free loan of A\$35,000, to be repaid as a first call against profits, and the Government of South Australia also put up a 99-year interest-free loan of A\$95,700. The university loan was repaid within five years. Being wholly owned by the University and operating within the Department of Biochemistry, the original intention was that 90% of the profits would be reinvested for research within the Biochemistry Department and the University would keep just 10% to spend on other projects.

Whilst there were no domestic competitors to speak of, selling radioactive nucleotides was not without its challenges. Hence, initially, given the difficulties associated with transportation of the product, research institutions within Australian and New Zealand became the primary target market. Geographical closeness, responsiveness to the needs of the Australian research community, a technique that was more efficient than its competitors, quality control and even an element of 'buy

Australian' were some of Bresa's competitive advantages. The Bresa Product Catalogue (1984) also detailed these factors:

The successful establishment of BRESA has depended on a unique and close association with the Department of Biochemistry and the Adelaide University Centre for Gene Technology within that Department. There are two very important consequences to this close association:

- (1) BRESA products are subjected to rigorous quality control under actual laboratory conditions before release.
- (2) The large number of graduate research workers (about 70) in the Department of Biochemistry provides an in-depth intellectual source of continual advice to BRESA, BRESA customers and for the development of future products and services.

Production of the radionucleotides did not involve new technology, but it did require special skills and training in the technique, as well as special facilities and production techniques. Bresa was able to undercut its biggest competitor, Amersham, and its products sold well within the Australian and New Zealand scientific communities, and over time improvements were made to the product and its packaging. The product line offered expanded to include enzymes, bacteriophage vectors, DNA primers reagent kits and two customer services, custom synthesis of oligodeoxynucleotides of defined sequence and amino acid sequencing of proteins – all of which offered higher profit margins. Tech support and quality control were some of Bresa's additional competitive advantages.

When production started, there was only one full-time staff member dedicated to production, and a second member joined shortly after orders increased. Professor Symons was a keen and enthusiastic product champion and also had support from the company secretary, Ms Jan Morgan. With sales increasing steadily, by 1984 Dr Steven Wilton was appointed principal scientific manager and Bresa decided it needed to increase its manufacturing. Production processes were streamlined and new staff

members were employed, including the appointment of Mr Peter Guilhaus as a production biochemist. Guilhaus explained that he had completed a second degree in 1984 in medical laboratory science, and was contemplating doing a PhD studying under Prof. Symons. His personal situation was such though that he felt that he should look for a paying job and the opportunity to work in the new start-up Bresa was presented to him. It seemed like a good fit with his previous skills so he accepted the offer. Guilhaus described what the company was like upon his joining:

The company in 1985 was three years old. There were still only about five people in the company and we occupied the north western lab of the Biochem building – the Darling building. So at that stage, Bresa was primarily and solely an import replacement company, in the sense that it manufactured reagents and kits for researchers to use for their research purposes. Primarily, the main product was a range of <sup>32</sup>P-labelled nucleotides, which were radioactively labelled compounds used to label DNA and RNA and then they made a number of different kits that those nucleotides were used in to facilitate the labelling of people's DNA or RNA. So, the company was based around regular synthesis of these radionucleotides. The issue with that particular product is it has a very short half-life, two weeks, and so you made them pretty much fortnightly. Because of my chemistry background, I got involved in actually being a production biochemist and so I learnt how to synthesise these particular products, and at the same time, I started to learn the aspects of hands on production, kit production and so on and so forth. It was pretty good grounding in the sense that, again, with only five people, you tend to do pretty much everything from customer service through to making the product and selling and shipping the product. That really was what the company was like in the early days. It was supervised by Bob Symons ... Jan Morgan was in the head office and she was pretty much company secretary in a sense. Then there was the principal scientist manager who was Steve Wilton, there was Rhett Swanson and Dave Eckerman. There was Lisa Schulz who was the RA, and Roger Smyth, who used to work here but is no longer here. He was also involved in radioisotope production and he was an organic chemist. So that was basically it. (interview with Guilhaus, 2007)

Guilhaus also went on to talk about how the business grew organically in those early years:

It was a company that was set up mainly through the efforts of Bob Symons – and Julian Wells, obviously – to identify that the researchers out there needed these compounds for their research, and it was really starting to expand dramatically. The ability to identify and label DNA molecules or RNM

molecules was very much needed in those days and isotopes in particular, was the most sensitive and least inhibitory mechanism of doing it. But at the time of the company starting, it was monopolised by overseas companies ... So they basically dictated in terms of pricing. So there was specifically a demand for – well, certainly in the early days, Bob just saw an opportunity to make their own. He had surplus and gave it to other labs. [Then someone said] why don't we sell it? So the company [was] set up ... That was the early catalogue. It was all just sheets of paper typed up with product information and we would go to the major scientific conferences and put up a little trade booth, a stand on a trestle table. It was very basic, and with half a dozen different products. It just started from there. We had cut-out cards and put them on Velcro so you could stick up different products. It was really quite ... [simple]. [We would] fax the prices through. People would order through the phone or through fax. The fax was a very important feature. [We were also selling] a little bit into New Zealand, not a lot. Again, there were problems with regard to shipping radioactive compounds and it was inherently the issue about restricting the international aspect, restricting Bresa from being an international company. (interview, 2007)

Guilhaus simply characterised the company as 'at that stage [in the first couple of years], Bresa was primarily and solely an import replacement company, in the sense that it manufactured reagents and kits for researchers to use for their research purposes'. Set up for this purpose, the company did not have international ambitions; as Peter Guilhaus commented: 'I don't think there was ever a vision in those days to be an international company'.

Despite the importance of radioactive labelling of gene probes, scientists much preferred to work with non-radioactive reagents. Consequently, Bob Symons had been working on such a product, called Photobiotin™, for which a patent was filed in 1984. It had advantages that included a long shelf-life, no need for special protective clothing or apparatus, easy transportation and the ability to be detected by non-radioactive colour development, also making it ideal to teach biology students. Photobiotin™ was sold in kits to detect pathogenic bacteria and plant viruses.

Patents for Photobiotin™ were applied for in seven countries and the product was launched into international markets from 1985 onwards via licensing agreements:

Vector Laboratories on the west coast of America and Bethesda Research Laboratories on the east coast. Even at that early time, Bresa acknowledged the regulatory impact of the FDA and conceded that it would be preferable to enter the US market with a licensed partner who was knowledgeable of the regulations and was willing to expend the resources necessary to meet FDA requirements (Karunaratna, 1987). Further agreements were signed in 1987 with Pharmacia and Toyobo Ltd (a subsidiary of the Mitsubishi Corporation) to distribute Photobiotin in Europe and Japan respectively. On all four agreements, royalties of up 15% would be payable following the issuance of a patent. Guilhaus said he thought it had been Prof Symons himself that had negotiated these deals. Moreover, these activities were facilitated by the Commonwealth Export Market Development Grant Scheme which Bresa took advantage of, providing partial reimbursement for the various expenses incurred in the process of marketing Photobiotin™.

By the end of this period, Bresa was a small entity that was still housed in the Department of Biochemistry and still ‘very much part of the department’ (interview with Bill Elliott 2007). This sheltered existence is evident by reviewing the early financial data (see Figure 1). It seems that Bresa was being supported by the Department of Biochemistry in terms of not being asked to pay rent. And, whilst the numbers show a substantial growth in sales, in the subsequent years, i.e. 1985 and 1986 when Bresa had occupancy fees to pay, their net profit declined accordingly. Interestingly, the first rent was paid in the same year that Adelaide University’s commercial arm, Luminis, was formed – 1985. Clearly, these administrative burdens impacted the bottom line significantly, with the young company incurring a substantial loss in 1986. Contributing to this loss though was the spending on funds on R&D – potentially signifying their commitment to the market place.

## **Figure 1. Bresa Historical Results – Profit and Loss Statements**

**\$A – Thousands**

<b>Income</b>	<b>1984</b>	<b>1985</b>	<b>1986</b>
Sales of Products	156,983	241,071	389,817
Less Cost of Manufacture	<u>121,039</u>	<u>172,460</u>	<u>307,857</u>
Gross Profit	35,854	68,611	81,960
Add Licence Fees Received	nil	nil	nil
Total Gross Profit	35,854	68,111	81,960
Less Operating Costs			
Administration	23,525	39,165	56,832
Marketing Expenses	616	260	16,381
Occupancy Costs	-	26,111	50,273
Research and Development	-	-	7,719
Total Operating Costs	24,141	65,536	131,205
Net Profit Before Tax	11,731	3,075	-49,245
LESS Tax Payable	nil	nil	-
Net Profit After Tax	<u>11,731</u>	<u>3,075</u>	<u>-49,245</u>

**Source: Karunaratna (1987, Appendix K)**

Reprotec (a company formed by the Department of Obstetrics and Gynaecology) and the University Centre for Gene Technology were two of Bresa's collaborators that time. The union of these different departments resulted in the expansion of Bresa's business into the diagnostic and education market areas with self-contained kits that were aimed at teaching students. Such a long and established history of first-class teaching across the Department of Biochemistry, the Institute of Medical and Veterinary Science [IMVS] and the CSIRO was undoubtedly a contributing factor to these products' success. The entire bundle of products developed and sold by Bresa in these early years would later be referred to as Parcel 1 of their IP and this would become important several years later [1987] when the company would attempt to list on the Australian Stock Exchange for the first time.

Many years before Bresa's formation though, staff at the O&G department were developing not only their research programs, but also their in-house commercial skills. An important staff member from that period was Dr Robert (Bob) Seamark, who began

his association with the University of Adelaide in 1965 in the Department of Animal Physiology at the Waite Agricultural Research Institute. Seamark talked extensively about his role at the time and the research activities going on within the department:

I came back to Adelaide in 1964 after completing a PhD in Cambridge (UK) and a Post Doctoral Fellowship in Germany to take a position as a Research Officer in the State Government Dept Agriculture (SAGDA). In 1995, I was appointed as Lecturer in Animal Physiology in a new Dept of that name established at the Waite Institute whilst retaining strong links with the SAGDA that lasted throughout my career. Being the first University Department in animal sciences, we quickly established links to the then buoyant livestock industry. That was to prove to be a mutual lasting benefit. I guess from my perspective it was the start of my recognising the prospect of getting good support for research from other than conventional government research funding bodies. The secret was to identify a common interest with a livestock producer or researcher) and offer this as a topic of research. Working together and exchanging, knowledge, goods and services gave us access to huge animal (sheep, goats, cattle and pigs) resources and management skills, that dramatically extended the landscape of possibilities for our research activities that was to eventually lead to our playing a leading role in the development of advanced livestock production technologies such as embryo transfer, embryo cloning and transgenesis.

In 1969, I was persuaded to move across to the Department of Obstetrics and Gynaecology as a Senior Lecturer in Endocrinology. This allowed me to extend my specific research interests in the endocrinology of reproduction to problems of human fertility and fertility control. The Pill was being trialed clinically and it was an exciting time to be engaged in what was to prove was the dawn of a reproductive technology revolution. (interview, 2007)

With the move to the new department in 1969, Seamark found it a fertile field- both scientifically and entrepreneurially as he explained:

... when I joined the Dept (O&G) there were 5 clinicians and myself. The professor, Lloyd Cox was exceptional. When he came to Adelaide as founding head of the University Dept (O&G) in the early 50's, he had chosen to give up one of his clinical staff positions to employ a scientist! No medical dept had previously done such a thing as far as I knew. Scientists were then considered to be add-ons, not full time team members in a clinical department. The situation was to change dramatically over the next decade or two as evidenced by the fact that when I left the Department in 1995 to head a CRC, there were more than 140 staff in the department, two thirds of them scientists.

In 1969, the science underpinning the clinical practice of O&G was poorly understood. I remember Lloyd Cox saying to me 'Gynaecology was the lowest ranked discipline in the medical field-a place where failed surgeons went to practice'. There was certainly a lot of work to do. Prof Cox had a special interest in women who were failing to conceive through ovarian failure, so an early challenge was to develop ways of assessing ovarian function through the measurement of reproductive hormones in initially urine and later with the development of immunoassays blood. As these assays came on-line we quickly understood that we had a capacity to provide a service for the State's Obstetricians and Gynaecologists and through charging a modest fee, a capacity to generate monies for other ongoing research. We set up a fund (the Endocrine Research Fund, ERF) in 1971 or 72 and it quickly grew to the extent that by 1975 we were able to support a visiting postdoctoral fellowship and several studentships.

Its impossible to overestimate the importance of the input of knowledge and skills the young overseas post docs we were able to attract over the years brought to the Department-many are now world leaders in their field and their Departments still remain important nodes in the Dept's scientific network. This benefit aside, the thing I particularly valued was the academic freedom stemming from having an independent source of monies - the freedom it gave to explore an interesting lead, to aim high, take risks, fail, learn from mistakes and generally develop and maintain a resilience that is so often lacking in research teams. Our growing success was envied by my academic colleagues, but not many wanted to emulate us. They wanted the money but seemed unwilling to accept the responsibilities that went with offering a viable clinical service-the willingness to do the extra yards to turn out assays on time, week in, week out, the discipline necessary to ensure quality control etc. There was quite a difference in our worldviews. (interview with Seamark 2007)

Seamark had a good eye for detail, and immediately aimed to achieve efficiency and effectiveness, as well as present the setup as a 'professional outfit':

When I went to the department, there were two technicians there and they were doing assays. I looked at what they were doing and found that they were fairly inefficient, so I took one of them off the assays and put him or her into development work and I made the other one carry the burden of the assays. As we got the momentum up and made money, then I built up the analytical laboratory and we kept that separate from my development laboratory. We altered the look of it so that it looked more like a proper laboratory in delivering service. I wanted clean desks at the end of the day, nothing left on the desk, everything tidied up, all records completed, proper accountability and I employed people who were capable of providing such service, so it always looked [professional] - I could take people in there and they were impressed by it. It wasn't the usual university shemozzle laboratory that people used to imagine at the time. They wore white coats and they all had practised proper

hygiene and cleanliness. They looked the part. They looked like the proper hospital laboratory. We gained the support of the hospital for the laboratory, so they provided staff for the laboratory because we were providing a service for the inpatients. So we came to an agreement, and in the end we shared half the costs of the laboratory with the hospital because we had provided service that they evaluated each year and ascertained that we were providing a proper service and they were making enough money to enable them to continue to support our laboratory. This all happened in 1969 to 1975, I guess was the setting up phase for that – The Endocrine Research Fund. (interview, 2007)

Not content with that effort, Seamark also played a key role in setting up another clinical service that was to lead to research outcomes that enabled the later collaboration with the Department of Biochemistry:

The Gamete and Embryology Laboratory was initiated in 1970. It began as an Andrology Laboratory, one of the worlds first. Andrology is the male counterpart to gynaecology and is concerned with infertility in the male. We started our laboratory in response to a specific clinical case-a young, recently married, male who was to lose his testis to testicular cancer. We knew of this through his wife who was one of our patients. I remember asking a clinical colleague, Colin Matthews, ‘Why don’t we freeze some of his semen before the operation and unfreeze it for later use?’. I was informed that this had not yet been done in humans although it was already a procedure in common use in the livestock industry. Challenged by our clinical colleagues to do so, a student and I spent time that summer establishing a human sperm freezing technology and sperm bank and with Colin Matthews and the clinical team, produced the next year, what proved to be one of the world’s first babies by Artificial Insemination (AI) using frozen semen. This success made the clinicians want more. (interview, 2007)

Seamark continued to push the scientific capabilities of the department to new boundaries. Often inspired by the successes of his colleagues interstate or internationally, he sought to ensure that the University of Adelaide was reaching the levels of his contemporaries:

I knew Bob Edwards and Steptoe<sup>4</sup> and those people who were doing IVF and

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<sup>4</sup> 4 Dr Patrick Steptoe, a gynaecologist at Oldham General Hospital, and Dr Robert Edwards, a physiologist at Cambridge University, had been actively working on finding an alternative solution for conception since 1966. Though Drs Steptoe and Edwards had successfully found a way to fertilize an egg outside a woman’s body, they were still troubled by problems after replacing the fertilized egg back into the woman’s uterus. By 1977, all of the pregnancies resulting from their procedure (about 80) had lasted

the like, and we were challenged to set up similar programs in Adelaide. We were already skilled embryo transfer (ET) technology in goats, sheep and other livestock we had developed in collaboration with local livestock producers and it wasn't difficult for us to establish a viable human IVF program following Steptoe and Edward's initial success in product Baby Brown. (interview, 2007)

Whilst Seamark was making an impression in his department and honing his skills, Wells also had been progressing his science in the Department of Biochemistry since he joined in 1967. Seamark explained that he and Julian Wells had become great friends when they were students together at the Waite Institute:

Julian Wells used to walk through the Botanic Gardens and I was going up to the Queen's Hospital so I used to delay my journey up there so I could get there approximately the same time as he walked across the gardens.... This would have been about the early '80s. He had just come back from a period in Europe where he had been to Scotland and trained up in this new technology, molecular biology. So, he was back in Adelaide talking to the various people there, including a certain Bob Symons who said he couldn't see any application of it. It was one of those great mistakes. (interview, 2007)

Seamark and Symons were also good friends – and prior to Seamark's scientific collaboration with the department, Seamark and Symons had shared conversations concerning their commercial interests as Seamark explained:

In the early 80's, I used to cycle through the Botanic Gardens on my way to the Queen Elizabeth Hospital and timed my trips so I could meet with Julian and walk with him across the park to discuss our work, successes and frustrations and all the other things close friends share. He had recently come back from a spell in Scotland and was full of enthusiasm for the prospects offered by the then new field of Recombinant DNA technology. (interview, 2007)

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only a few, short weeks. They achieved success when Louse Brown was born to Leslie Brown on July 25 1978.

Seamark and Symons were also good friends-and prior to Seamark's scientific collaboration with the department, Seamark and Symons had shared conversations concerning their commercial interests as Seamark explained:

We established a common link - he was struggling to set up a company and I was interested in prospects of his company acting as an outlet for some of our products (antibodies) that we had developed. The two of us were probably the first people in the university with an interest in selling, so we had that common ground. (interview, 2007)

When Wells asked him if it had been his idea of selling the radionucleotides to Symons, Seamark responded:

No, his [Seamark's] department was already doing this. He [Wells] and I discussed the potential fit of our products (hormone antibodies) with his. As I remember it, we also spent a lot of time discussing issues we were facing, what was holding us back, how damnable the university was to deal with. I was lucky, I noted, to have avoided many of the problems he [Wells] was facing through our policy of avoiding University involvement whenever possible. Julian had chosen to work through more formal structures and was bogged down in University politics. Occasionally he had a big win but it seemed all his wins led to more university involvement. I much preferred to work outside the system whenever possible. (interview, 2007)

From a scientific stance, by late 1982 – early 1983, Seamark and Wells<sup>5</sup> (now deceased) started to work on a collaborative project to develop transgenic technology of direct interest to the livestock industry. Over the next three years (between 1982 and 1985) Wells and his colleagues in the Department of Biochemistry developed gene constructs, comprising sequences of DNA, to control the expression of pig growth hormones. Under Seamark's supervision, these constructs were inserted into pig cells in the laboratory to create a growth hormone gene triggered by certain concentrations of metals in the pig's body, for example, zinc or copper administered through dietary supplementation. As to the why this innovative approach to interdepartmental

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<sup>5</sup> Dr Julian Wells passed away in 1993 after a short a battle with cancer.

collaboration was allowed to flourish Seamark said:

I think the reason it happened in the two departments, Biochemistry and Obstetrics and Gynaecology, was that we were a group of friends who knew and liked each other and shared an Ag Science background. Agricultural Science offers training in a profession and many Ag Scientists are often driven, focused on making a difference to the world-outcome orientated. Many academics just don't have this drive - following their own interests is sufficient justification for them. Julian Wells and I were Ag students together at the Waite Institute and John Wallace did Ag Science at Sydney and Bob Symons at Melbourne. The other common link was Professor Bob Morton; we had all been influenced by him in some way or another. (interview, 2007)

Rogers also commented about the nature of the scientific partnership between Wells and Seamark:

Julian and Bob linked up because Bob had the ability to put the genes into eggs and all that sort of thing and Julian had the molecules, and so the two came together. It was a real positive integration of their skills. [A very deliberate strategy] to produce [results] - and then the whole idea was to put growth hormone into pigs and to get them to mature quickly and produce more meat than fat. That was the whole idea, [it] was to really twist the nutrition. When they got it going there was a lot of work and a lot of enthusiasm about the animal transgenesis in those days, [in] particular with the domesticated animals like cattle and pigs ... we were isolating genes that were involved in the growth of wool and we were putting them into sheep. We were putting it into mice as well and that's when we had quite a lot of fun but the problem was that the public acceptance of such engineering was not acceptable. (interview, 2007)

The strong link between the agricultural scientists, and their pragmatic approach to their research, had clearly been galvanised much earlier – in both Wells and Seamark's case before they had even started their post-doctorates. Both students had actually been undergraduates together. Numerous past and present staff in both these departments credited their then Head, Bob Morton (and later Bill Elliott), as being the catalysts for their creative, self-confident approaches to their respective research. Morton had been fondly regarded by all accounts, and his death, resulting from a shocking and sudden laboratory accident, rocked the department very deeply. Professor

George Rogers, who was head of department following Morton's death and before Bill Elliott's appointment, explained why Morton's influence was so pivotal:

If we go back in time, the person who gathered us all together was a fellow called Bob Morton [now deceased] who was a Professor in Agriculture Biochemistry at the Waite Institute and came in like a breath of fresh air to the university and attracted a lot of us during the course of the time to his camp. He had a major impact on the Waite Institute and the way he rejuvenated it in collaboration with the new director ... So we were lucky enough to be at the Waite Institute, Julian Wells and I at least during the time when there was a big transformation. (interview, 2007)

You have to have mentors or people that inspire you to believe that you can do things, and Morton was certainly a 'can do' person. He helped set up both Julian Wells and I to believe we could do [anything] or he saw in us something we couldn't at the time and he set us up with two scholarships; The Barr Smith Travelling Scholarship in Agriculture that allowed me to go to Cambridge, and a CSIRO scholarship for Julian. It worked out extremely well for both of us. Julian finished his PhD in Adelaide and subsequently went to Cambridge for a year, so there was a commonality in our training and experiences that helped us be entrepreneurial later on. (interview with Seamark, 2007)

## **Parcel 2: Engineered Hormones and Transgenic Pigs**

With the University of Adelaide's Department of Biochemistry and the Centre providing IP for gene technology, an understanding existed whereby both units would allow Bresa the first right of refusal over innovations for commercialisations. The combined groups contained about 100 scientific staff consisting of postgraduate students, research scientists, postdoctoral fellows and technical support staff who provided a continuous supply of new and innovative products for Bresa to develop. Additional products would also result from joint research activities with the department of O&G, IMVS and the CSIRO. This porous boundary was evidence of the virtual style of Bresa at that time. In that sense, making the company less dependent on these organisations was perhaps not the highest priority – rather growth of the firm's product line was more of a priority.

One of the first outcomes of the research collaboration between Wells and Seamark was their suite of hormones, including pGH and FSH. Their IP was more closely intertwined than it appeared in subsequent patent documents and Bresatec business plans, as Seamark explained:

Porcine Growth Hormone (PGH) was the first of our joint products, together with Follicle Stimulating Hormone (FSH) identified as the second. It's important to remember that there is a product and the application of the product and the focus of my lab was on the latter. There were issues with the administration of PGH that needed addressing with transgenesis emerging as one solution and there were technical problems with the production of a biologically active FSH using the then available DNA technology. FSH was a glyco-protein, that is, it was made up of sugars as well as the usual amino acids, and this meant it couldn't be simply produced in genetically modified bacteria like PGH. (interview, 2007)

As to whether there were issues in managing the patent suite across the departments, Seamark said, 'We never thought of ourselves as other than a team - I'm not sure that the people who were doing the deals fully appreciated this' (interview, 2007).

Seamark gave an account of exactly what were his main intellectual influences at that time and how he and Wells came to collaborate:

One day, I saw on the front cover *Nature*, a picture of a big mouse, this was the famous Palmiter and Brinster paper featuring a transgenic mouse producing extra growth hormone that increased its size dramatically. I thought, shit, this is exactly what the livestock industry needs. I thought we could handle embryology and gene injection skills and all the other animal management skills. So I immediately contacted Julian to see if he could help with the genetic engineering side. I suggested pigs as the target animal because I knew of some work in the 1970s by a guy called Macklin, who had shown that pigs responded extremely well to growth hormone with increases in growth rate, carcass composition and significantly their food conversion efficiency, which really meant their 'profitability'.

So, we put the next six students that came into our laboratories ... to do our transgenic program. I built up that program and was helped a fellow called Pat Quinn who was my embryologist at the time. One particular student that worked on the project was Anna Michalska, who was a PhD student – we got an outstanding result.

With these motivations underpinning activities, in 1985 the University of Adelaide formed another company called Reprotect:

As our interests diversified, we needed to set up more formal commercial structures within the University and Reprotect was formed as a vehicle to manage relationships with Bresa and other companies. Bruce Hundertmark, a member of the Universities Finance Committee, was important in making Julian Wells and I aware of this need and introducing us to the Business plan and all the other essential knowledge required in the business world. Unfortunately, we found the name Reprotect had already been grabbed by a car electrics company so we changed the name to RP Technologies. (interview with Seamark, 2007)

Reprotect was the vehicle used to enter a joint venture partnership with Metro Meats Ltd to develop the PGH and transgenic technology. Metro Meats was a wholly owned subsidiary of the Adelaide Steamship Company Ltd, was to build a piggery for the capital value of A\$2.1 million as well as provide the capital for the manufacturing facilities to produce porcine growth hormone (pGH). In return for the capital, Metro Farms was to have exclusive rights on a worldwide basis to manufacture and sell all products arising from this technology and a joint venture to be called Metrotec Pty Ltd was to be established about 60 km north of Adelaide. The pigs bred in the piggery were to be guaranteed disease-free stock and maintained in a strict disease-free environment. A joint venture agreement was drawn up and was submitted to the Board of Adelaide Steamship Company for consideration.

In addition to the joint venture, Reprotect was to manufacture and market a wide range of diagnostic products used by vets and farmers. These included services such as embryo transfer, breeding programs to improve herd quality and kits used for educations in universities and senior schools. Directed by the principal scientists in the venture, a business plan was drawn up showing sales projections globally of \$A20 million with two years followed by enormous growth. This caused a strong amount of

conviction and excitement for the scientists controlling Parcel 2 and they were mostly interested in pursuing this pathway. From the very outset, Bresa had anticipated capturing up to 50% of the Australian research and education market for these products, however, they also wanted to expand to the secondary schools as well as markets in Japan and Southeast Asia via licensing and distribution agreements (Karunaratna, 1987).

Seamark talked about how the connection with Metro Farms arose:

We needed access to pigs for the PGH and Transgenesis project and we contacted what was then the biggest pig producer in South Australia, Metro Farms Pty Ltd, a division of Metro Meats Ltd., a wholly owned subsidiary of Adelaide Steamship Company Ltd. The only problem with the arrangement was the distances we needed to travel to treat and collect pigs from the piggery, take them to the slaughter house where we collected the embryos, take the embryos to our laboratories at The Queen Elizabeth Hospital where they were injected with transgenes, and then transport them back to the piggery where they were transferred surgically into the uterus of sows to establish a pregnancy - a daily journey of over 200kms! But we never thought anything of it. We just did it. (interview, 2007)

In fact, Seamark's connection to the abattoir extended back at least a decade earlier, as he explained:

We were used to go to the abattoirs regularly. That started in the sixties in fact. I was interested in fetal sheep, so in order to get material for our experiments, I had people go to the abattoirs every day, I had people out there every day, to collect a whole bunch of fetal sheep and fetal calves and then bring them back to the laboratory. We just thought it was a gold mine, the abattoir. It was fantastic. (interview, 2007)

Not only did this mean a strong link with industry, but personal scientific networks were also forged:

We were the first to develop foetal cannulation, so you could put tubes into the baby and study the blood gas and things like that in utero. John Ballard and I – that's how I first got to know John – we did some work together on gluconeogenesis in the fetal lab during the birth processes, so we studied fetal lambs just before they were born, during the birth process and then afterwards. It was pretty interesting stuff. That was in the seventies. So that

was how I locked into John Ballard and his teams. (interview with Seamark, 2007)

Whilst their work may have been novel, their ideas were grounded in sound business objectives to accompany their research, as Seamark pointed out:

Julian [Wells] and I had success with those transgenic pigs ... We had big dreams and I had ideas, because I came in from a self-perspective about what they [Bresa] should be selling. One of the things that I think I was instrumental in promoting at the time was the need to develop a catalogue of products and we acted as an agent for overseas and then when we discovered the demand for assays, we basically transferred it. (interview, 2007)

Seamark was driven to recommend such practices as a result of the actions of other important industry players, such as one of the leading pathology firms at that time, Gribbles & Partners:

... in my laboratory, ... Gribble & Partners and others were looking at us and wanting to build up there stable of assays. They saw what we were making out of our assays and they wanted to put them in their catalogue, so they used us. They acted as our agent for a long while until they got on top of their assays and then they tried to gazump us. Luckily, we had a good relationship with the IMVS [Institute of Medical and Veterinary Science], so we had a lab, so we were able to maintain some of our income flow but what they taught us was how to charge, because when we started off charging for assays, I think I was charging A\$4.50 an assay and when the private people came in, they charged A\$14.00 an assay, so we charged A\$14.00 an assay, which meant there was a loss I would have had to withstand which was compensating for the fact that I was charging twice the amount or nearly three times as much for the assays, so we still continued to make money. (interview, 2007)

This growing business savvy though, was at times according to Seamark, difficult to impress upon the university. As Seamark described:

In the background, we were developing human IVF [in vitro fertilisation] and all those other things that eventually led to development of Repromed [another successful University of Adelaide spin-out company]. And there was growing opportunity to form other spinout companies but the University wasn't interested. Not true - they were interested to the extent that they would try and stop us if they knew anything about it, so I often didn't tell them of my extracurricular activities. This created a few difficulties but my conscience was clear as I always made certain that any commercial work we

did was more than compensated for by increased goods and services to the Department. Access to animal resources was very important in this regard, and that anything we did was publishable. We published all the stuff we did commercially- totalling some hundreds of papers. We were associated over the years with the setting up of 16 companies including several listed companies such as ARPAC (listed on the Wellington Stock Exchange) and Regulin Ltd (a spin-off of Genelink, the first Biotech Company listed on the Australian Stock Exchange. We were very active. (interview, 2007)

Whilst the transgenics intellectual property and Wells's gene technology were seemingly a very different line of research inquiry from the original radionucleotides, Elliott (interview, 2007) explained that in fact 'the two [the Centre and Bresa] were just inter-related tremendously ... I remember when we applied for the Centre of Excellence ... in the application, we mentioned the possibility of setting up [a company ... and I] think that helped us get it'. Indeed Elliott was the head of the department at that time, but he had strong ideas about how best to manage the arrangements between the units:

Well, I was the head of the department and in a sense, ... I was in charge, but on the other hand [because] I was the head of the department and the Centre of Gene Technology was going to be very important to the department ... [i]t didn't seem right to actually both be, you know, in charge of the department and running the Centre. But also Julian Wells, who was terribly important, I think ... he gave the biggest stimulus for the introduction of gene technology. He was the one. ... [T]he first thing we had to have was an isolation lab, because in those days P-32 was regarded as a very dangerous thing. Used to scare the hell out of me because as far as I could see, when I consulted the Vice Chancellor on who was responsible, he said, Well, I'm afraid you are. But that was just a temporary position ... [Wells had a job and come back from] Scotland. He'd learned about cloning. ... [S]o I think we'd have to say that Bob Symons's chemistry and Julian Wells' enthusiasm for gene technology were the two major [factors] .... (interview with Elliott, 2007)

### **Parcel 3: Insulin-like Growth Factors**

Initially linked to Bresa was a third parcel of intellectual property; Insulin-like Growth Factors (IGF). The inventors of this technology were Dr John Wallace from the Biochemistry Department and Dr John Ballard from the CSIRO's Department of

Human Nutrition and in 1986, a patent covering their discovery was applied for and later granted. Moreover, two additional scientists would later be included on the patent: Geoff Francis and Chris Bagely.

Work continued in this area for the next several years and another patent covering IGF-I and IGF-II was applied for in 1988. It was at this time that this research came to the attention of the US biotech company Genentech, and it was decided that this technology should be passed on to another University of Adelaide spin-off company called GroPep. Whilst GroPep was officially registered in 1988 for the sake of making the deal with Genentech 'simple' from a legal point of view, one of GroPep's *most* significant products called Long-IGF came about through the work of Julian Wells and his colleague Rob King, as well as Geoff Francis from the CSIRO. One of the postdoctoral students involved with this research, Dr Allan Robins, who had been Julian Wells's PhD student and had just returned from Cambridge University in 1981, described how this discovery came about:

... Long IGF-1 which is probably their only decent product that was made in Julian Wells' lab where I was the postdoc. And, you know, [Long IGF-I] really didn't have anything to do with GroPep, well with Ballard, and basically it was Julian Wells' idea. We couldn't make this molecular for love or money and at the same time we had a project going on pig growth hormone and we did make a bucket load of that and so Julian said 'Let's just fuse them together and put the IGF-1 on the back of pig growth hormone and we did that and made a bucket load of it and then Julian said 'Let's start trimming back the pig growth hormone gene and see how little of it we can have on the end of IGF-1' and it came down to, I think, 13 amino acids. The long bit is actually the first 13 amino acids of pig growth hormone. Rob King did the work and Rob and I were working on - well, I wasn't working on IGF-1, I was working on histones at the time and we did a parallel approach and the histone examples are actually in that patent, not that they helped. Well, they helped show that, I guess, the technique was generally applicable but anyway .... (interview, 2007)

## **Luminis and Bresatec**

As Professor Seamark commented, there was quite a lot of commercial activity revving up in the mid eighties. The official commercial arm of the University of Adelaide, Luminis, began operating in 1985, the same year that Reprotect was formed. According to Seamark, Luminis was modelled on an Israeli university company and set up largely by Bruce Hundertmark. The first CEO was Dr David Parbury, who had had a distinguished career, including a period with the World Bank. Mr Peter Hart, who became the CEO of Luminis, which later changed its name to Adelaide Research and Innovation (ARI) in 1990, described the impetus for Luminis' inception:

One of the reasons Luminis was formed, in the mid '80s, was really to apply, if you like, a little bit more of a commercial status to these sorts of things. One of the things Luminis took over, on behalf of or for or from the university, was Bresa, with a remit. Luminis, at that stage, basically acquired ownership of Bresa. There was a little bit of a loan of money. But, in the end, shares were all held by Luminis. So, Luminis was the shareholder, on behalf of the university, if you like. David Parbury was there then. I think David Parbury was then the Chairman of Bresa. (interview, 2007)

Moreover, Georgia Sherry, who became legal council for Luminis at this time, explained how the University viewed the situation:

When Luminis was finally set up by the university, what happened was that this was an obvious activity, a commercial activity, that was sitting in a department without any sort of risk management, without any sort of legal structure, and without any sort of direction, so, it was probably the first spin out if you like, that we did, and certainly the first biotech spin out in South Australia. (interview, 2005)

The next stage in the eventual formation of BresaGen came when Bresa changed its name to Bresatec Limited in 1986 and became a public company. Bresa Pty Ltd was absorbed into the new company. Bresa's Parcel 1 technology was differentiated on the basis of price and country of origin advantage only (with the exception – to some extent

– of Photobiotin™) and there was little evidence that revenues would continue to grow much further beyond 1988. Although Parcel 1 was automatically rolled into the new firm, it was evident that Bresa needed new and diverse technology, i.e. the products in Parcel 2.<sup>6</sup> In short, this meant integrating Parcel 1 and Parcel 2 technologies so that Bresatec could emerge. This decision was far from automatic, indeed the discussions were protracted and any agreement sought was largely conditional as Wells and Seamark needed reassurance of the commercial competence of the new firm, Bresatec. However, a series of long and difficult conversations between the principals of R.P. Technologies<sup>7</sup>, Bresa and Luminis resulted in agreement finally being reached enabling all of Parcels 1, 2 and 3<sup>8</sup> (at a later stage) to be transferred to the new company Bresatec.

Hart stressed the significance of Seamark's decision to provide his IP to Bresatec: it gave the company 'a bit more breadth, rather than just flogging these nucleotides' (interview, 2007). But on the other hand, the new entity would now face the challenge of managing a diverse portfolio that would include three disparate strands of research. Hart (interview, 2007) said of this:

Bresa, in its time, had funding from all ... sorts of various places. One of the things which drove BresaGen, almost for its whole life, was the continued necessity to keep getting funding, because it was never profitable, never really sold much at all. So there was this continued drive to find funds. Not unreasonably. Research companies are like that.

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<sup>6</sup> Parcel 2 consisted of porcine growth hormone (pGH) owned by Wells and Follicle Stimulating Hormone (FSH) owned by Seamark in an equity joint venture, 66:34 respectively as well as transgenic technology owned by the joint venture arising from Metro-farms.

<sup>7</sup> When Bresa was changed to Bresatec, all the rights initially aligned with R.P. Technologies were subsequently acquired.

<sup>8</sup> Parcel 3 related to insulin-like growth factors was initially offered to Bresatec, as they had first right of refusal over the technology. They eventually decided against keeping ownership of this IP and was sold to GroPep's umbrella and would go on to be the crux of deal between GroPep and Genentech in 1988. Importantly though, full ownership was not established by Luminis, only the 50% that was Dr Wallace's share of the invention. The other 50% remained the property of the CSIRO. (Karunaratna, 1987)

The deal was facilitated by two considerations: (1) the commercial synergy achieved under a company concerned with the manufacture of products based on biotechnology was greater, with Bresatec now manufacturing and selling the pGH to the joint venture partner under a distribution license agreement. Whereas previously this would have involved a duplication of some manufacturing facilities between the two companies and Metro Farms would have had to diversify their efforts and manufacture the product, now they would administer the product and take care of distribution; and (2) there was now a possibility of entering overseas markets since Metro Farms were also negotiating further joint ventures in Singapore and Taiwan.

Hence, the patent rights, licensing agreements, intellectual property and know-how to be acquired from Luminis was valued at A\$4.5 million and was satisfied with a cash payment of A\$500,000 and issue of 8 million fully paid ordinary 50 cent shares in Bresatec. Thoughts then turned to listing Bresatec as a public company, with the idea that the funds raised would be able to pay the cash component of the acquisition of rights to the technologies from Bresa and R.P. Technologies, as well as construct new expanded facilities including offices, manufacturing and production plant and warehouses. Bresatec was still housed at 233 North Terrace (within the University of Adelaide buildings) and their scientists were sharing laboratories on the main university campus (Karunaratna, 1987).

As per the agreement of the three parties, Bresatec would make an appointment of a Chief Executive with commercial skills. Wells and Seamark held the view that the new company needed strong managerial leadership including sound 'marketing' to fully capitalise on a growth strategy. Consequently, Dr John Smeaton was appointed as a Director and the Managing Director/Chief Executive Officer from late 1987. Professor Elliott spoke about the importance of appointing someone specifically into this role, 'I

don't think Bob got too much involved in that [negotiating international contracts]. Bob was first, last and in the middle a scientist really' (interview with Elliott, 2007).

Smeaton already had an impressive commercial track record to his credit, having worked in research, marketing and senior management positions with numerous leading American biotech firms such as Xerox and PerkinElmer Corporations and since 1978 he focused on the development of new businesses as President, Stat Engineering; Managing Director, Bioclone Australia Pty Ltd; General Manager, Australian Genetic Engineering Ltd; and President, Agen U.S.A. Inc.

Smeaton was not 'new' to the Bresatec scientists. On the contrary – he was a contemporary. Smeaton had been a student of the University of Adelaide and he recalled how he became involved:

Well, actually, I was living in California at the time and so I was working for a company called AGEN, and then they decided to close up the California office. I sort of passed go and collected a few dollars. It was good because I thought I would stay in California and finish building an airplane actually. Then I came back [to Australia] to sort of tidy things up with the folks at AGEN, and that was in Sydney, and took a trip to Adelaide to sort of see the parents. Dropped into the bio-chem department to say hi to the people there because I was a graduate from there from way back and I'd maintained sort of a strong contact with Bob Symons over the years. Bob says to me, 'what are you doing?' I sort of said, 'well, actually, I've just cashed in, I'm going to spend the next six months building my plane, then I might start looking for something new to do.' He said, 'no you're not, you're going to start here, help us build this BRESA thing up.' ... Bob and I had known each other since he was a sort of new lecturer at the Waite [Institute] and I was a fourth year ag student or ... honours student. I called my wife in California. I said, 'well, I guess they sort of got the handcuffs on me, I'm not coming back so you better sell the house, and when you've done that, we'll set up in Adelaide.' (interview, 2007)

Smeaton (interview, 2007) summarised his connection to the firm as being based on his personal network, '[So it was really a personal contact.] I knew all those guys'. Although modest about his memory skills, Professor Rogers also recalled those early days and the networks that operated then:

Yes, he [John Smeaton] came from ANU with Bill Elliott, I think. He was a student when Bill Elliott came to the chair in the mid sixties. God it's a long time ago. Smeaton completed a PhD ... [A]nd then there was a lab manager we had whose name I forget who went to Beckman in California, [he] left us and he became an inventor. Actually, Bill Elliott brought him over from Canberra because he was a lab manager and he installed this guy and he was the lab manager in the Darling Building. He went to California and developed amino acid analysis which got a bit of a plateau of technological development and he was very interested in getting an improved system for analysing the amino acid content of proteins. He was also connected with NASA because they wanted to analyse rocks and see if there was any living material ... so he would analyse it and fit onto a mobile thing but anyway then he invited John Smeaton - they obviously knew one another. (interview, 2007)

As to what kind of company John Smeaton found upon his arrival back into Adelaide, he described it as being small, with only about seven people:

It sort of had big ambitions to eventually raise money for the department through the bio-chem department because they foresaw the end of the Commonwealth funding and that sort of thing. So they've set up this company which will hopefully in the end pay your dividends or capital payout or whatever and hope[fully] support the department. So that was the motivation and there was a big rule about it being no personal gain. (interview with Smeaton, 2007)

Others that joined the company around that time also commented:

It was like another part of the department, I would have thought. Because I mean in the same area, there was Mark Snoswell, myself and Rodney Nichols. I mean this is before Stan [Bastiras] came back. Even after Stan came back, we still had Bruce May who was doing organic chemistry and all that type of thing. John Smeaton had only been employed the month before I had turned up, so I suppose he was the first managing director type thing after Bob [Symons] because he'd been the Chair for a while. Yes, so I think at that point it must have been the time when they were trying to get some sort of corporate organisation going. It took a while to actually find an identity. (interview with Senn, 2007)

Moreover, in Senn's opinion, there was little real talk of the company being 'internationally orientated', as she explained:

Well, when I was there, they had Metrotec so it was still pGH for the pig market and all that type of thing. The only real international thing they were

looking at then was even contract manufacturing or looking at how we would make enough of this material if it was successful, because I remember even back - I don't know whether it was 1990 was the first time or the second time, I went to Boston to use their facility at MIT. I mean, that was about the first international association I had. That was because they had a thousand litre fermenter, which we didn't have the capacity for. But there was never at that time, any intention to go into a market, over there or anything like that. Those thoughts came later. It was a slow progression. It wasn't sort of like, an international market in three years. (interview, 2007)

Up until that point, the University of Adelaide would receive any profits made, and moreover, no individual could personally benefit. This ruling would eventually change, as Smeaton explained, 'Well, then the 90/10 rule, that was a big stoush with the university with administration who wants to put their hand in the till and the biochemist fellows basically said, well yeah, if we earn anything, we're going to keep 90 percent of it. They eventually got that rule through, so it was really, you know, you're going to do that guys or we're not going to do this.' In a business plan for the company, Karunaratna also described the impact of this and other subsequent decisions:

Bresatec now has exclusive rights to manufacture and market all the technologies in parcel 1 and 2 and joint rights to parcel 3. According to its present policies, the University can only assign the rights that it owns and since the University claims only partial ownership of the intellectual properties arising from the various departments, ownership of the property is shared between the University and the inventor on an equal basis. Bresatec therefore had to negotiate an assignment of the rights to the intellectual properties on an individual basis with each inventor. In addition, Bresatec has also negotiated a first right of refusal with the departments of Biochemistry and Obstetrics and Gynaecology for all technologies arising from those Departments for a period of five years. In return, the proceeds of commercial activity are shared between the inventor and the department on an equal basis (50:50). It is not clear at this stage whether such returns are to be used solely for further research or whether the inventor is at liberty to do as he wishes. (Karunaratna, 1987)

And whilst this new rule provided a benefit to the departments financially, as well as an incentive to the respective scientists who could continue to further develop their research projects, the scientists, in fairness to the University of Adelaide, benefited in

various ways 'in kind' as well. For example, when Professor Elliott thought back to those early times of Bresa and Bresatec he recalled that he had never asked the firm to contribute in terms of rent for lab space, 'You've got to realise, I was a terrible amateur too in this business of going into business. If I remember rightly, we never even thought about it' (interview, 2007). Smeaton also confirmed this account, 'Well, it [Bresatec] really wasn't standing on its own two feet when I got there, if you'd taken into account all those sorts of costs. There are lots of costs that were being incurred that weren't being counted, like that sort of thing [paying rent]' (interview, 2007).

In the financial year 1986/1987 Bresatec earned sales in excess of A\$600,000 and this was achieved without a sales team! Of this, 65% of the sales were from NSW and Victoria. It was planned that sales people would be employed to service these regions, as well as a longer-term view of the market that included international customers. Their other marketing activities included workshops, a product catalogue and a customer newsletter (Karunaratna, 1987).

For Photobiotin, there was a patent pending in seven countries in 1987. Bresatec had agreed that four licenses would be issued and at that time, two were already issued to American companies: Vector Laboratories Ltd and Bethesda Research Laboratories Ltd (BRL). Both these companies had their own sales and distribution networks and were granted licences to manufacture and sell Photobiotin worldwide on a non-exclusive basis. Royalties up to 15 % were payable back to Bresatec once the patent was issued (Karunaratna, 1987). Smeaton described the general approach to internationalisation at that time, 'We brought that [in, i.e. the distributor agreements for Photobiotin]. I mean, Bob was interested in an international sort of approach in the long run when it was the realisation that that's where you had to go. But I think I brought quite a bit of that perspective to it' (interview, 2007).

Although there was a random, but fortuitous event that took every one by surprise as Smeaton remembered, ‘we were about to go broke [and] one day and some Finns walked into the office and wanted to licence some patents and gave us, I think it was A\$80,000, and that sort of kept us in the black’ (interview, 2007). As to the precise nature of how the deal was transacted, Smeaton retold the story, ‘They basically came in, and said they’d like to take an option on the licence. I said, how much would that cost? We thought of some outlandish number and they came back with about A\$80,000 and we’d sort of said, thank you very much, and picked up the cheque’ (interview, 2007).

**Table 1: Bresatec Staff 1987**

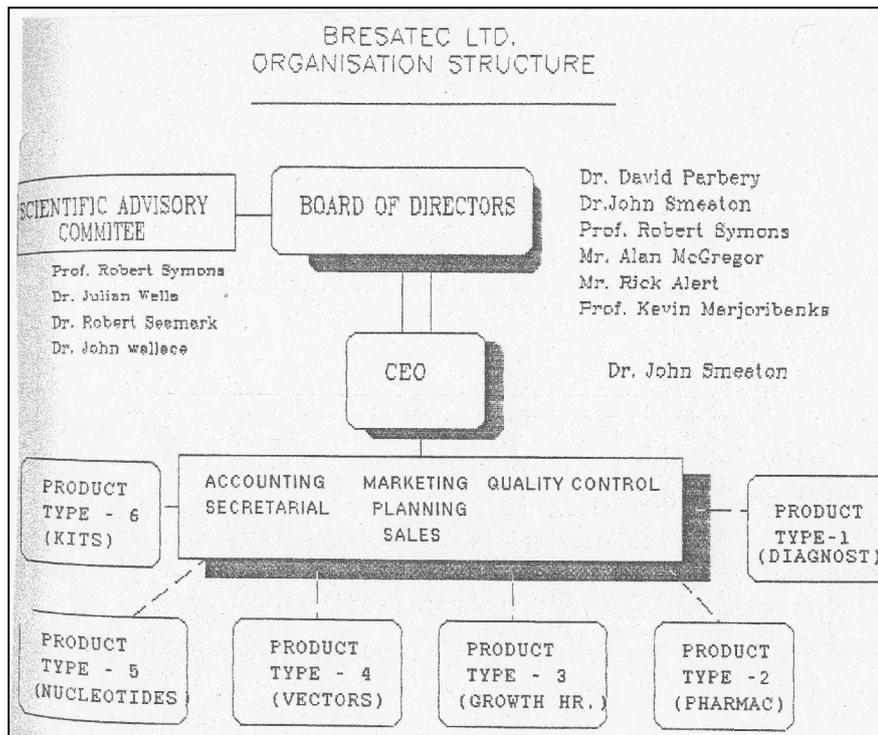
<b>Title</b>	<b>Existing</b>	<b>Function</b>
R&D biochemist	2	Initiated research programs for new products, develop prototypes for new products, carry out technical support functions and technical promotional activities, find more efficient production methods.
Production biochemist	1	Carry out manufacturing processes.
Senior technician	4	Assist in R&D projects with biochemists, support regular production runs and provide training for technical staff.
Production technician	5	Participate in all regular production related activities.
Administration	1	Order processing, accounts and bookkeeping activities, reception/secretarial functions.
<b>Totals</b>	<b>13</b>	

**Source: Karunaratna 1987, p. 25**

By the end of 1987, Bresatec had 13 full time staff and a secretary (see Table 1), with six members on the Board of Directors. The company’s organisational structure is provided in Figure 2. The portfolio was very diverse, with products in six different categories: (1) radionucleotides, (2) enzymes for molecular biology, (3) cloning vectors, (4) oligodeoxynucleotides, (5) kits, (6) nucleic acids, (7) chemical reagents for proteins and (8) Photobiotin. Further compounding this, on 29 February 1988, Bresatec purchased the intellectual property concerning the transgenic technology from Luminis

in consideration of the issue to Luminis of four million A\$1 shares (Karunaratna, 1987).

**Figure 2: Bresatec's Structure**



**Source: Karunaratna, 1987 p.54**

The diversity of its product portfolio undoubtedly contributed an element of risk, however, in Bresatec's case, the firm felt they had the following attributes working in their favour:

- (1) Extensive research facilities and personnel with the University of Adelaide without incurring the direct the costs of their employment which usually create great financial burdens on the new venture
- (2) The appointment of a CEO with strong management and marketing staff to balance and strengthen the exiting corporate structure which was technically strong
- (3) A positive cash flow with growth in sales of greater than 20% each year, to support the operations. This growth would underpin the company's planned expansion
- (4) Bresatec was well recognised in the Australia and New Zealand markets and was becoming known internationally through its promotion of Photobiotin. Overall, Bresatec felt their risk was considerably less than with similar firms who began without the resource base and who lacked the sales record of Bresatec. (Karunaratna, 1987)

Referring to the first point specifically, Professor Rogers (interview, 2007) emphasised

that even at this stage '[there was] a lot of interaction' between the Department and company. Seamark concurred and also explained the importance of the PhD students, particularly as the company expanded:

[Julian Wells had an extensive contact network ... some of his students had gone on to do great things. His Department had trained a great number of students in Molecular Biology and he had contacts everywhere, for example we were able to get hold of gene control sequences such as the human metallothionein promoter as soon as it was isolated because the person doing the isolation was one of Julian's past students. I had my networks too which meant we had good knowledge of what was happening around the world. (interview, 2007)

Strategic hiring of staff, that benefited both the company and the department, had been important to Symons, as Rogers recalled, 'One of the central things was to make sure the pieces of DNA that string the basis of DNA along to make so-called oligonucleotides and that was a very important procedure ... and oligonucleotides became very important in the research and so he [Bob Symons] set up Derek Skingle and this ... outfit produced oligonucleotides as a part of the business but also supplied the department so the integration's there' (interview, 2007).

Despite this, management felt, though, that there was still an element of vulnerability attached to the company. As Karunaratna (1987) wrote:

It is of concern, however, that diversification did not take place as part of a planned strategy – it happened more as a series of happy coincidences. As Bresatec has made a commitment to expand, diversify and grow, there are a range of issues which will confront the company as it progresses from a small business to a much larger operation.

While on the one hand its organic development and small size enabled a great deal of flexibility, the company was now at a risky nexus, as Smeaton explained, '[Bresatec] was sort of getting dangerously short of money and we were about to [try to float the company] – and then Luminis was involved ... he [David Parbury] had a

perspective that these things took a long time and ... you needed to have an equity case. That was pretty radical in Adelaide in those days' (interview, 2007).

### **Financing: Stock Markets, Schemes and Supporters**

Smeaton acknowledged that one of his main responsibilities upon assuming the role of CEO was to obtain funds to finance ongoing research. A Bresatec business plan dated March 1987 stated that management anticipated Bresatec Ltd would float on the Australian Stock Exchange by the end of 1987. Bresatec wanted to raise A\$10,000,000 by way of Initial Public Offering with 50-cent shares. The funds raised would be spent on:

- (1) Financing the construction and fit-out of a new productions facility incorporating a highly sophisticated fermentations facility, for the production of valuable proteins using recombinant DNA modified organisms
- (2) Attract new scientific, sales and marketing staff
- (3) Promote new products currently under development
- (4) Finance a number of proposed joint ventures, the first being Metrotec Pty Ltd (Karunaratna, 1987).

However, the consequences of the ASX crash in October that year put pay to that idea. Earlier, in 1986, Luminis had commissioned a business plan with the intention of raising funds for its expansion through the Management and Investment Company (MIC) Scheme which had, up to the end of 1986, been a useful source of venture capital. However, when the business plan was completed, the Luminis board members decided against this route for two reasons: (1) the money needed was too large for an MIC to accommodate, (2) diluting that much equity to an MIC was undesirable (Karunaratna, 1987).

By early 1987, most MICs appeared to be having severe cash problems, limiting their ability to initiate new investment as well as sustain current projects.

Retrospectively, this decision may have been provident as there was a sequence of events that occurred in 1987 that impacted on MICs. The Management and Investment Company Act required that 70% of the company's funds must be invested at one point in time, leaving managers of MICs concerned that 30% of fund holding would not be enough for contingencies. On top of this restriction, MICs could only raise up to A\$40 million and it was felt that 'too many' licences had already been issued and taxation requirements were about to come back to bite the MICs (Karunaratna, 1987).

Contributing to the overall financial challenge facing Bresatec during that period was the previous 'poor performance' of other biotech firms which had listed at a time when the ASX was booming. In the first half of 1987, the market capitalisation of 21 Australian biotech companies had fallen by A\$100 million, a reduction of more than 20% (De Silva, 1987, cited in Karunaratna, 1987). Therefore, after the stock market crash, and despite considerable planning leading up to an anticipated IPO in 1987, Bresa Pty Ltd merely changed its name to Bresatec Ltd and remained an unlisted public company relying on private investors until its eventual listing in September 1999.

Smeaton then went about the business of talking to the relevant parties about investing in Bresatec, as the following quotes explained:

During 1987, Dr Smeaton had discussions with Metro Farms Pty Ltd and its associated company Metro Meat (Holdings) Pty Ltd ('Metro Meat'), part of the Adsteam Group of companies, about the possibility of Bresatec and Metro Meat entering into a joint venture to develop and exploit the transgenic technology and protein production technology in pig production.

In about June 1988, Dr Smeaton commenced discussions with Hambro-Grantham and Cambooya, about a possible investment in Bresatec.

From 1988, Dr Smeaton also commenced discussions with various overseas companies with a view to an alliance, including from 1990 with Mr Robert Mooney of Cyanamid. (Administrative Appeals Tribunal, 2002, pp.18-19)

Fortunately for Bresatec, each of these deals did materialise in the next couple

of years, although not all of the deals played out according to the terms of the agreements, as will be explained later.

## **Pigs Might Fly**

Wells and Seamark were very busy pursuing technological advances in the laboratory from 1982 until about 1985, developing gene constructs that were made up of sequences of DNA. Their aim was to control the expression of pig growth hormones. This research was done with help from Metro Meats. Seamark carefully supervised the research that included inserting the constructs into pig cells in the lab to create a growth hormone gene triggered by certain concentrations of metals in the pig's body, for example, zinc or copper administered through dietary supplementation.

Around this time, 1986, Bresatec entered into its first international research collaboration with the Swedish firm, Alfa Laval. The point of this was to have access to research facilities. Seamark explained:

They [Alfa Laval] were interested in biofermentation technology and Julian had a very bright person in his lab named Mark Snoswell who was a whiz at this. We were seeking to buy a large-scale fermentor and [they] gave us access to several of their large production units in the States and Europe. I know Mark impressed them with his skills at maximizing yields from their plants. (interview, 2007)

The University of Adelaide team achieved success in the form of a world first in 1986 when six transgenic pigs were produced after microinjection of the porcine growth hormone fusion gene into the nucleus of fertilised eggs, one of whom evidenced enhanced food conversion, reaching market weight sooner than conventional pigs without any adverse effect on the pig's health. Following on from this achievement, in April 1987 a patent application was lodged in Australia, followed by international lodgements and approvals to protect the transgenic technology that had been developed,

and in 1988 Drs Seamark and Wells and others published an article on this work in the *Journal of Cell Science*. Earlier patents existed in this area, though, with Seamark and Wells receiving an earliest priority date going back to 1984 for their research on ‘Methods of creating new breeds of mammals’.

The accomplishments of Wells and Seamark maintained the strong conviction of the researchers to stay the course with this research and push for a formal agreement with Metro Meats via a joint venture. By this stage, the details of the deal were well established and had been included in the business plan for Bresatec. Their aim was:

... [T]o attain a dominant position in the Australian research market and a significant share of the world engineered protein market with project total sales of A\$20,600,000 by 1991. Significant sales of the first engineered protein product – porcine somatotropin are assured through the establishment of a joint venture – Metrotec Pty. Ltd. – with Metro Meat Ltd., a subsidiary of the Adelaide Steamship Company Limited. Under the agreement Bresatec gains 25% equity in a new 600 sow commercial piggery. This piggery will aid the commercial development of two Bresatec animal improvement technologies while producing pigs for market. The products are improved and patentable strains of transgenic pigs and porcine somatotropin. The transgenic pigs will be sold to the industry as breeding stock; initially to Metro Farms that already controls 12% of Australian pigs. The joint venture combines Bresatec technology with an established market. Though the venture alone Bresatec will achieve sales in excess of A\$6 million (in 1987 dollars) by 1991 for porcine growth hormone. Plans include expansion into South East Asia and animal production improvement products for other animal species. The planned expansion of the company is projected to yield an after-tax profit of A\$2.5 million in the 1989/1990 financial year with an increase to A\$3.6 million by 1990/1991. (Karunaratna, 1987)

Armed with this expectation, Smeaton set about formalising the deal:

Adsteam, they were really sort of keen on the pig thing. When I got there, that was sort of running along.... but it wasn't within Bresa's thing, and that'd been set up by Julian [Wells], Barry Lloyd and Bob Seamark. So the university and Metro Meat ... they handed over the transgenic pig technology [to Bresatec]. Then there was David Parbury who sort of initiated a meeting to try to get it all into one vehicle around there with lots of little pieces around the place. Eventually it came into BresaGen, but it was one thing that we could never get straight. (interview with Smeaton, 2007)

A deal was signed between Metro Farms Pty Ltd and its associated company Metro Meat (Holdings) Pty Ltd and Bresatec Ltd on 23 March 1988. From 1988 through to 1990, Metro Meat paid approximately A\$2 million into the joint venture for the purpose of R&D that was mostly undertaken at Metro Meat's piggeries in South Australia.

## **Moving Out!**

At the end of 1989, Bresatec took its first steps towards independence with a move to new premises in the recently set up 'Scientific Precinct' at Thebarton, on the outskirts of Adelaide's CBD. Guilhaus remembered that, 'We moved into [the building that] was vacated by Entrovax, that was another company that tried to get themselves going' (interview, 2007). As to what prompted the move, Guilhaus speculated it was a physical space issue, 'I'm not 100 per cent sure, but I would say it was just space limitation. There was an opportunity for commercialisation of this area for the University' (interview, 2007). However, the company *did maintain* lab space within the University of Adelaide and later used this as a strength in their Prospectus document:

Until 1989, BresaGen Laboratories were situated within the Department of Biochemistry at the University of Adelaide. From 1992, BresaGen, through an agreement with Luminis, has maintained laboratories in both the departments of biochemistry and obstetrics and gynaecology at the University of Adelaide. BresaGen staff take part in some academic activities within these departments and students from the departments work within the company's laboratories. This agreement has been beneficial to the company allowing it, under the terms of the agreement, access to new ideas, results and intellectual property. The company has a general collaborative and research agreement with the University and Luminis. (BresaGen Prospectus, 1999)

Nonetheless, this move to Thebarton solidified one of the company's purposes: developing a range of biological products to distribute to labs and research organisation

both domestically and internationally. This segment of the business was known as ‘*Bresachem*’ (Mack Consulting Group, 1991). Guilhaus’s role changed accordingly. Moreover, he stated that this seemed to be the impetus for a shift in thinking as to how the company should be structured:

When the company moved down here, my role kind of evolved into becoming the general manager of the research products division. It was given the internal name of Bresachem. We were Bresachem, then there was the recombinant project group and then there was the transgenic group, so there were the three different divisions. We were the trading arm actually making money by producing products, and the other two were really just involved in development ....

I wasn’t involved with any of the other products, however in the early days, with the view of it being commercial merit – EquiGen<sup>9</sup> I suppose is the one that comes to mind – I initiated going to certain conferences in the States and made initial connections with a few people, partly because I was looking for new products but also because I had an interest in seeing whether we could get this going. Around about that time, certain managers within the group were starting to fit into roles which were more specific and they said, well you better stay on this side and that’s going to be a new product. You could see they were starting to move towards splitting the company. That was the founding for the concept of floating the company on the IP side [i.e. R&D]. (interview, 2007)

While the move to Thebarton provided some physical distance between Bresatec and its parent organisations - the university departments, it is not clear that the company was still very removed. Allan Robins recalled the tight network that was involved with Bresatec:

When John Smeaton joined the company they set up, well not immediately but after about 18 months, they set up the Scientific Advisory Board [SAB] which was incestuous. Julian [Wells] was on the SAB, John Wallace was on the SAB, I was invited to be on the SAB, Ballard was on the SAB. John Smeaton was obviously on it and there were a couple of others but it was pretty incestuous anyway. So it turned out that I felt that some of the things that were going on were sort of, well bullshit, if you like. They weren’t particularly sound. They had this particular individual working for them and I

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<sup>9</sup> EquiGen is a horse hormone the company later successfully developed and marketed.

think he was a bit of a fringe player even though he did talk a good story. I said at a number of these SAB meetings basically I think it's bullshit and it turned out that John Smeaton agreed with me.

He [Smeaton] rang me up one day, I guess, at the end of 1991 and offered me a job. I was happy in academia, you know, reasonably easy life sitting around philosophising about science all day, doing the odd experiment, going over to the staff club having a couple of glasses of red or whatever so I thought I don't really want to go and work for a company. It doesn't sound very attractive to me but then John said, 'Well, look, I'll double your salary'. I said 'Well, when do I start?' I was already intimately involved in the company because it existed in the biochemistry department from '81 when I came as a postdoc from Cambridge and then after John Smeaton had joined, I joined the SAB. (interview, 2007)

Robins also remembered his first days in his new job: naturally they involved working on paperwork and projects to help bring funds into the company:

... [W]hen I first joined it [Bresatec], basically most things had been put on hold because the company didn't have very much money in the bank. There had been a federal grant applied for, for a million bucks, and my job on day one or day two was to talk to the guy coming in. He wanted to see a budget for this grant. To pass the scientific sniff test they wanted to see a budget. Oh good ... because there was nothing. Anyway, we doctored up a budget and we managed to get ourselves through that process so we ended up getting that million-dollar grant. (interview, 2007)

While Guilhaus was in charge of the reagents business, Robins was one of the managers on the R&D side. He was involved in protein development and he recapped how his role evolved:

At that time I was hired as laboratory operations manager and what I really had was a group of people that was really the old Bresa, so the research reagents business. They had taken over Faulding's old plant down at Thebarton and they had some fermentation equipment and things like that and we had two PhD students at the time and Stan [Bastiras] was one of them and Carol Senn was another one. That was the only thing that was going on that could have been considered to be outside of this reagents business. The first thing I tried to get going was develop a few more reagents, a few more kits and things like that. We grew that business quite handily because I think it went from a A\$150,000 a year business to when we ended up selling it, I think it was like a A\$3 million a year business. So that's what it was like and the idea at the time was to try to graft it into a position to try to take advantage of some things that were going on in terms of Stan [Bastiras] and

Carol's [Senn] PhDs and to see if we could get an angle there. (interview with Robins, 2007)

Stan Bastiras explained how he found himself in the position of working for Bresatec as well as doing his PhD on protein expression and purification of IGF:

I had actually taken a year's leave without pay from the University of Adelaide ... to work and live in France. And I came back in '88 ... [and] was re-employed by the University of Adelaide, but I was working on a project that was for the benefit of Bresa, or Bresatec ... in the Department of BioChem. And I did that for a year, so I was actually ... doing work for BresaGen, or Bresatec as they were called back then, I was still employed by the University of Adelaide. So I had sort of inadvertently become part of Bresatec ... and at the end of that year I realised that for me to get any further in my career, I had to do a PhD. As I discovered when I started my PhD, because at the beginning of – say by about March '89, I had successfully received a scholarship to do a PhD. So I actually switched from the University of Adelaide so I could do that PhD. And that was continuing the work that I had started for Bresatec. So by March 31<sup>st</sup>, I think it was the official start date of '89, I was now doing a PhD and I was doing the work totally for BresaGen, or Bresatec as they were called then. (interview, 2007)

Bastiras described the company at that time:

They were trying to find their feet. They didn't want to make too many decisions as to what area they should focus on, so they de-focused and looked at both gene control and its application, but mainly for the veterinary industry. And, I guess, initially looking at making lean pigs, eventually became – perhaps using the pigs as suppliers of human organs in the xenotransplantation area, and then eventually looking at stem cells. (interview, 2007)

Bastiras offered his thoughts on the company's approach to internal commercialisation of this technology:

I think we always were international. The pig growth hormone project, for example, whilst in the very beginning, it only would ever be profitable if it was international. It needed countries like India and China, where pork is the major [meat] – so I think it was recognised – and I guess it was John Smeaton, having lived and worked overseas say for the previous almost 20 years, it definitely was international from the very beginning. (interview, 2007)

As well, Bresatec was establishing itself as a world leader in transgenic pig technology (TGP), and they were particularly focused with establishing licenses with several US pig breeding companies.

Carol Senn recalled how she found herself studying and working for Bresatec – and like many others, her connection into the company was of a personal nature via Julian Wells:

April '87 was when I joined. I'm about to hit my 20th anniversary. I was Adelaide born, but I had been working in Sydney, got retrenched by the government and somebody there knew Julian Wells, and they said, 'Go and visit Julian'. So they offered me a job virtually as soon as I returned. I suppose he [Julian Wells] lined up an interview with Bob Symons for me. Initially I was – I don't know what the terminology was, a scientist or something. Basically working in the area of fermentation and then later on around the '89 timeframe ... [Bresatec] was supporting me and I started a PhD in fermentation. So I was still working. I worked for the company the whole time, but they supported me while I was still studying. (interview, 2007)

Bastiras characterised this period of the company as the beginning of turning it into a research and development organisation:

So the 12<sup>th</sup> employee of BresaGen, or Bresatec as it was in those days, was a guy Dr Allan Robins ... And when he joined, he and I came up with the idea of looking at porcine growth hormone as an option. So with Allan Robins joining the company, it was probably the first step towards becoming an R&D company. That slowly built up with time. (interview, 2007)

Stan Bastiras explained that there were two research streams within the company: porcine growth hormone and transgenic technology:

But the reason it became that way [two separate R&D divisions to the company], was largely because of the porcine growth hormone project, which started way back in 1986. And I'll explain why. The aim of the porcine growth hormone project was to make lean pigs. It sounds pretty silly, but that's what it was, to make lean pigs. And there was a two-pronged approach to achieving that goal. One was to make recombinant porcine growth hormone and inject it into pigs, and the growth hormone once injected into pigs, would make the pigs get to market faster with less food, and will make leaner meat. And that potentially was proven to be so.

The other approach was to make transgenic pigs. Okay, so in other words, incorporate extra genes, copies of the growth hormone gene into pigs, so that pigs could make their own growth hormone genetically. And it would then not mean daily injections of growth hormone. So to do that, to do those two things, we needed to set up an arm of expertise in protein and expression purification, and the other was to set up expertise in reproductive biology etc. So that's why with the formation of Bresatec in '87, involved the obstetrics and gynaecology department and Bob Seamark.

So there were a bunch of guys who were expert in gene manipulation, insertion of genes into mammalian cells, expression of proteins from mammalian cells. Well, let's say they weren't expert at it, [to make a commercially viable product] that's what they were aiming for. Had they been expert at it, the goal would have been achieved. But it was never quite achieved, and so by 1991, I think it was about '91, the pig growth hormone project was closed down.

I think at that stage there would have been, I think, about 25 employees. And by that stage the protein division, it was called the protein pharmaceuticals division, even by those early days, had moved to Thebarton. The move happened in early 1990, late '89, November '89. (interview, 2007)

GroPep too was housed at the Thebarton science precinct. John Smeaton shared his thoughts on the separation of the IP into the two separate companies, i.e. Bresatec and GroPep, in 1988, in order to service the arrangement between the University of Adelaide, the CSIRO and Genentech from the USA for IGF-1:

Well, in many ways, there shouldn't have been two companies, but GroPep started as a joint venture between BRESA and CSIRO. Ballard was quite a sort of a hard-driving guy in terms of getting that going, and one thing that he did, which not many people would do, is that he left CSIRO and sort of took his retirement package and put into GroPep. So you've got to sort of respect him for that. (interview, 2007)

Bastiras gave a personal account of the history of this:

I mean when I came here [back to the University of Adelaide in 1988] some of the guys that were instrumental in the beginnings of growth factors, people like Geoff Francis, a guy called Chris Bagely, he was doing his PhD ... they used to spend most of their time in the lab that I was in, that I was in charge of. But before I went to France, I was in charge of the protein chemistry unit, which was a serviced unit that the department had set up, to make sure that students within the department and external people, could use the facilities there without – in a proper manner - without damaging them. Because it was

quite expensive treatment – HPLCs – so I interacted quite heavily with, in particular Geoff Francis and Chris Bagely. (interview with Bastiras, 2007)

GroPep, I think, was changed [to that name] in probably late '88, '89, around about that time, the first time it was termed [by that name] ... And it was 50% owned by Bresatec in the early days, I think. Well – a lot of people forget that the original patent was for LONG™, the molecule that makes up 95% of gross sales [for GroPep], which is derived from protein expression work done by the biochemistry department .... The leading people on that patent, Julian Wells, Mark Snoswell, who was my boss, and a guy called Rob King, who was a molecular biologist who did all the cloning. And I think Ballard and Geoff Francis' names are on that patent, because they had – obviously they had been working on the idea ... but that came about because we originally, we were trying to express ... growth hormone. So I was involved in that work in 1988, and we were expressing – so just before I started my PhD. We did the first experiments ... and I was involved in the recombinant purification, the porcine growth hormone. And then we tried to make IGF-1 in a similar manner for GroPep, but we couldn't express this. And then [Julian said] well let's make a fusion protein, so we stuck it on the back of the porcine growth hormone as a fusion protein, and then made all these other variants with shorter proportion to the porcine growth hormone. So that's basically what that patent covered. My name is not on the patent, but I was involved in the purification of a lot of those variants. And so I'm quite aware of the early days of GroPep. (interview, 2007)

## **Crackling Cracks**

The project Metro Meats moved forward well throughout 1988 and 1989 and dozens of pigs were sold. However, this achievement would ultimately come back to bite them – not once, but twice! The first time was about two years later, as Smeaton explained:

There was an organisation called GMAC – The Genetic Manipulation Advisory Committee. That had been set up by the federal government to sort of monitor all this genetic stuff. The chairman of that was Nancy Millis, who was actually a friend of Bob's [Symons]. She'd been a professor. She was getting on a bit in those days, probably in her 70s. She was a good lady, but she couldn't quite get a hold of the fact that she wasn't involved and didn't own the pigs when Metro Meat and the university sold some pigs into the market. I think that was in about 1988. They sold 56 transgenic pigs. I mean, they weren't actually very – they weren't active or anything, but they had the gene in them. Then I think it was about 1990 there was a huge headline on front page of the Melbourne Age, 'Mutant meat sold in SA.' Actually, it was about two years down the track. (interview, 2007)

This attack was felt by the Bresatec people to be most unfair: they had gone to the appropriate bodies at the time seeking approval for the sale of their product, but running against them was the fact that no ‘official legislation’ had been enacted. They were charting unknown waters, both in Australia and overseas, as to their knowledge, there was no evidence of the meat being sold in the US. Again, Smeaton recaps the scenario they faced:

they’d sold those pigs after seeking advice from the state minister for health – sent them to, I think it was the NH&MRC, and they’d got the okay, and since they had the okay, they just sold them because these pigs were just getting bigger and bigger and actually wanted to get rid of them. So it was kind of amusing that – and there wasn’t a food authority in those days. (interview, 2007)

On 12 March 1991 Bresatec purchased Metro Meat’s share in the joint venture when the Adsteam Group was experiencing financial difficulties (Administrative Appeals Tribunal, 2002, p. 18). Seamark gave his opinion as to how and why the joint venture fell apart:

And that’s another story altogether, how that enterprise failed to get up and running. Because that would have been the biggest [piggery in the world] ... No, it’s a fascinating story. There were many threads to it. To cut to the quick, Johnny Spalvins, who was head of Adsteam, which was Metro Meats at the time, he was involved with a series of labour disputes, or his company was, in the piggery, and profitability was iffy, I suspect in some of the piggeries, and they required much bigger investment. He was the asset stripper rather than the builder in some ways. So he was there at the meetings, and said, ‘What the fuck are we in pigs for’. So Metro Meats essentially got out of pigs. We got the shares back and a million bucks. I never saw any of that. Nobody ever saw any of that. I don’t know where that went. (interview, 2007)

As a direct result, Bresatec found it had to downsize staff, reducing the company to about 9-10 people (interview with Robins, 2007). Full of confidence in his product, Seamark actually televised himself eating some of the barbequed pigs in the middle of Adelaide’s busiest shopping mall. Of the experience he said, ‘transgenic pig meat is

absolutely safe' (Administrative Appeals Tribunal, 2002, p. 16). At the same time:

... he described his eating of this being televised and of barbecuing the meat in the Rundle Mall in Adelaide. He said there was general acclaim because the meat is lean and because the skin is slightly thickened and produces very nice crackling! (Administrative Appeals Tribunal, 2002, p. 16)

Regardless of this setback, Bresatec kept pushing forward with their development plans, thanks to the investment from American Cyanamid that would come in April 1991. Additionally, Smeaton's diligence in finding potential investors to fund this collaboration of scientists and departments was about to pay off, 'the difficulty then was to fund it, and that's when we got involved with the venture capital folks. After a long negotiation, we ended up with no money. Then along came syndicates' (interview with Smeaton, 2007).

### **Not So Easy to Come-by Money**

Expansion and revenue funding remained key for the company in the years following the failed IPO in 1987. On 29 June 1989, Bresatec reached an agreement with Hambro-Grantham Ltd and Cambooya Pty Ltd, a company associated with John P Fairfax Pty Ltd, whereby each company purchased approximately 20% of Bresatec shares for a consideration of A\$1 million (Administrative Appeals Tribunal, 2002). This meant that Bresatec Ltd was formally an unlisted public company jointly owned by:

**Table 2: Brea's Ownership 1991**

<b>Partner</b>	<b>Shares</b>	<b>Percentage</b>
Luminis	3,000,150	61
Hambro-Grantham	950,000	19
Cambooya	950,000	19
Employee options	440,000	1

**Source: Mack Consulting Group, 1991, p. 5**

John Smeaton explained how these connections came into being:

Well, that was when we were looking to raise some money and the Australian government had brought in MIC management investment companies. They were sort of a government-regulated venture capital system. If ever there's an oxymoron, that would be it. So these guys were playing around a bit of funny money really, it was a government tax advantage. But there wasn't really enough of it to do very much. We were at the stage where we wanted to try and expand and, you know, needed some cash to do that and pigs, I think, were the big thing at that stage.

So we'd sort of done the rounds and at that stage, Alan McGregor was chairman. He knew the folks from Cambooya. That's how they got involved. Then this guy called Gregson from First MIC – First MIC was one of those management investment companies. After quite a lot of negotiation, they agreed to put some money in ... that was to get the pigs moving along [and to see] what we could do with the whole company. So it was after that stage it was really a VC-based type company. (interview, 2007)

Peter Hart explained the significance of this external funding as he saw it:

[This] external funding was ... a diminution of Luminis' [control and ownership], therefore the university's, 100 per cent ownership. So we dropped from 100 per cent to whatever the number was, because there was a couple of transits of it. In '89, that was actually consummated. If I said June '89, it would be closer, around there. And so – and that applied, if you like, a bit more commercial pressure .... (interview, 2007)

### **Hitting the International Radar – A US Licence**

In line with their goals as stated in the business plans of 1987, Bresatec went about exploring revenue-generating opportunities. Two of the companies they started discussions with in 1988 were Monsanto and American Cyanamid Company. Smeaton explained the genesis of an especially important linkage between one of the scientists in Adelaide, Barry Lloyd, and a colleague of his in the US:

[American Cyanamid] were interested in sort of transgenic pigs, pig growth hormone, that sort of thing with our Ag division. They'd had a pig program sort of trying to make pig growth hormone, etcetera and with through Barry Lloyd's contacts we went and talked to them in about '89 and as a result of that, we had a long sort of drawn out negotiation with them, with Bob Mooney; and we sort of became quite friendly with them then. He's [Mooney] now retired, but they, in the end, decided I think partly as a hedge, you know, well, if something happens to you, we'd better be part of it. [They]

put A\$2 million into the company, Bob was on the board for a while and that was quite good. So we had a big American company as an investor at that stage. (interview with Smeaton, 2007)

Robins recalled the connection in a similar way, providing further insight:

The guy, Bob Mooney, he was sort of a scout for American Cyanamid and he would go around the country – Australia was part of his territory – looking for new projects. There had been a little bit of both [us approaching them and them approaching us] because John [Smeaton] and Julian [Wells] and Ballard, I guess, had talked to Genentech and talked to various companies. Remember, at this stage we owned half of GroPep so we were talking about IGF-1 and growth hormones more or less at the same time. I mean, IGF-1 is basically downstream of growth hormone, sort of endocrinology I guess. (interview, 2007)

Bob Seamark also had involvement in the process, confirming, ‘Yes, Julian and I went across to talk to them. We were basically responsible for bringing them in. They came to us. They were interested in the growth hormone and we had a significant [profile] – through our pig transgenesis publication, and they were interested in understanding that better’ (interview, 2007).

Another employee commented:

Our connection was a strategic decision with American Cyanamid, which was then overtaken by AHP.<sup>10</sup> AHP bought out American Cyanamid. American Cyanamid had an interest in our technology where we were looking at making growth hormones as well as doing transgenic pig growth hormone. So American Cyanamid was interested in ... back in 1993/1994. (interview with Verma, 2005)

Moreover, the earlier discussion that the Bresatec people had with Monsanto would prove to be very helpful later on; Clifton Baile would join their SAB, and he would prove invaluable in terms of contacts and experience when the time came for BresaGen Inc. to be established in Georgia, Atlanta:

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<sup>10</sup> American Cyanamid was purchased by American Home Products and it ceased to exist on 31 December 1994

Well, we'd been to Cyanamid and Monsanto on a sort of a trek looking at companies that were interested in pigs back in '89. Julian and Barry Lloyd and I did that, we met Cliff Baile in Monsanto. He seemed like a fairly reasonably upfront interesting sort of guy. So we sort of opened the conversation with him. We said, well look, if you guys have got a patent on growth hormone which we think we might be infringing and we want to talk about a licence. So Cliff said, well, that's a refreshing approach, most people come in here and tell us our patents aren't worth, you know .... So we sort of hit it off from that and then we had some discussions with Monsanto which, in the end, didn't come to really anything.

Then Cliff was working for a couple of ladies at Monsanto who were known as the dairy queens because they were involved in dairy products; they had the bovine growth hormone - all that stuff. Then the upshot of that was then Monsanto had to sort of a contraction and Clifton – he was the head of research there, so he got offered a package to leave, so he did. We heard that Cliff was leaving ... so I called him up and said, hey, Cliff, what are you up to? Would you be interested in joining our Scientific Advisory Board being a consultant? Because I thought he was a pretty sharp guy. So he said yes, so that's how that started. Then he moved to Georgia to the University there. He was then keen – so when we were looking at coming to the States and he actually was the one that gave us a bit of paper that drew our attention to Cytogenesis. So he suggested looking into Georgia, so that's why we went up there. (interview with Smeaton, 2007)

In April 1991, American Cyanamid Company did sign a deal and took out an option of 20% equity in Bresatec. Additionally they were helping Bresatec with their negotiations in the US. The opportunities included Bresatec licensing their transgenic boars to one or more pig breeding companies. These boars would provide large benefits for pig producers with their offspring having 'increased food conversion ration, fat to lean meat ratios and reduced growing time' (Mack Consulting Group, 1991, p. 2).

As part of the deal with American Cyanamid, Bresatec received a licence fee of A\$4,000,000 in the form of staggered payments on achievement of particular milestones. They would also earn a royalty fee for each transgenic boar sold once the project reached the production phase (Mack Consulting Group, 1991). However, there was a slight discrepancy between various documents as to the exact nature of the deal. For example, the Administrative Appeals Tribunal document dated 4 September 2002

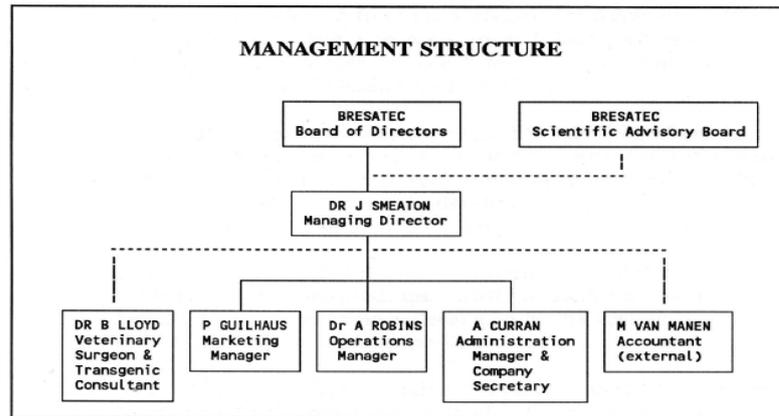
stated:

On 1 April 1991, Bresatec concluded an agreement with American Cyanamid Company ('Cyanamid') whereby Bresatec, in consideration of a payment of A\$250,000, granted Cyanamid two options exercisable within 12 months: first, an option to purchase a licence for Bresatec owned technology and, second, an option to purchase shares in Bresatec. If the options were exercised, the consideration of A\$250,000 was also convertible into shares. In March 1992, Cyanamid exercised the second option with the result that it invested A\$2.25M in Bresatec shares, and obtained an extension to the first option to purchase a licence in respect of Bresatec technology until 28 February 1998. (p. 4)

Several months after the deal was signed, Bresatec delivered a success – they had produced a number of healthy transgenic pigs 'by the insertion of the porcine growth hormone GH gene, and had achieved 'some level of control of expression in the transgenes in mice'. In the pig, control was sought of the transgene's expression of a protein (a growth hormone), naturally occurring in the pig, to promote the more efficient growth of the pig and the production of a better quality animal' (Administrative Appeals Tribunal, 2002, p. 19).

This research pressed on, particularly as all the parties had not anticipated any issues in terms of regulatory approval because there was no conceivable risk to human health and especially since they had made some initial sales of the pigs in 1988. The organisational structure of Bresatec in 1991 is shown in the figure.

**Figure 3: Bresatec's Organisational Structure in 1991**



Source: Mack Consulting Group Business Plan, 1991, p. 7

### **MBL: Big Dreams, Big Bucks and an Angry Taxman**

The research continued on following the injection of funds thanks to Cyanamid's investment; however, there were still obstacles to overcome. But by 1992, 'the team had clear evidence of the inheritance of the 'transgene' in the next generation of pigs following natural mating, and that the transgene could be switched on and off by modifying the animal's diet. While success to date had largely been in the laboratory, the transition to commercialisation had begun' (Administrative Appeals Tribunal, 2002, p. 15).

This research was also making use of stem cell technology (ESC) to help improve the growth rates and types of livestock. Stem cell technology was viewed as being more efficient and reliable, thus having greater potential for meeting growth objectives in animal production. A third string to Seamark and Well's bow was application of transgenic technology to xenotransplantation<sup>11</sup> within the Australian context (Administrative Appeals Tribunal, 2002).

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<sup>11</sup> Xenotransplantation involves the transplantation of the cells, tissues or organs from one species of animal to another.

It was clear to Bresatec and Luminis that they needed to raise additional funds (even considering the investments of Hambro-Grantham, Cambooya and American Cyanamid), if they were going to be able to carry on with their development of transgenics and stem cell therapy. They estimated they would need about another A\$9 million to have their technology ready for commercialisation. Luminis did not see themselves in the role of being a financier to Bresatec – so any additional funding through the University of Adelaide was not considered an option (Administrative Appeals Tribunal, 2002).

The Chairman of Bresatec's funding committee at that time was Dr Gregson. Gregson first approached Macquarie Bank Limited (MBL) in about July 1991 about the possibility of an R&D Syndicate with a bank. Interested in this, MBL sent back an indicative proposal to Bresatec the same month. This sparked Gregson and Smeaton's interest and the two attended meetings in Sydney with various institutions including Macquarie Bank, Bankers Trust, Bain and the Commonwealth Bank to discuss syndication possibilities. In one of their meetings with MBL, they were introduced to Nick Lattimore, whom they asked to send them a second proposal (Administrative Appeals Tribunal, 2002).

By September, Smeaton had left Australia to attend meetings overseas with pig producers and in early October he went to England to meet with a biotech company in Cambridge to discuss the possibility of a collaborative agreement which, ultimately, did not eventuate. Meanwhile, in mid-October Smeaton received a fax from Lattimore concerning MBL's successful conclusion of an R&D syndicate with another company called Paxus. Smeaton took this information back to the Bresatec Board (Administrative Appeals Tribunal, 2002).

In late November 1991, Smeaton received a telephone call from Daniel Phillips

who was employed by the Corporate Finance and Leasing Services Division at MBL and the two organised to meet in Adelaide to discuss funding of a syndicate. From Phillips's point of view, he saw an opportunity for MBL in the relatively underdeveloped technology sector in Australia and he planned to set about building a presence for MBL in that sector (Administrative Appeals Tribunal, 2002). The researchers who were involved at that time, i.e. Seamark, understood that the negotiations were with a view to Bresatec and MBL entering into an R&D syndicate to raise funds for a three year combined transgenesis and Embryonic Stem Cell (ESC) research program (Administrative Appeals Tribunal, 2002).

Syndication was in its infancy within the Australian industry; it was considered the financial option de jour, particularly in the absence of a formalised venture capital system. Additionally, high-profile Australian individuals were taking up strategic positions within the regulatory framework of the syndicates, e.g. John Bertram, who had been the captain of the successful Australia II yachting campaign that had captured the prized America's Cup trophy from the Americans for the first time in history back in 1983<sup>12</sup> (Smeaton, 2007). In fact, Phillips said of the syndicates, 'the Federal Government wished to encourage syndicated R and D as a means of attracting private capital for innovative projects' (Administrative Appeals Tribunal, 2002, p. 25).

In his own words though, Smeaton explained how Bresatec came to be involved with MBL:

Well, how did Macquarie get involved? They ... approached us. See, Macquarie was looking for things to syndicate. I mean, as you, know they're a fairly sort of entrepreneurial type group. So Macquarie had figured out that these syndicate things were a pretty sharp deal financially. Yeah, there was some tax rules, so I think a bunch of smart lawyers in Sydney went through

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<sup>12</sup> Australia II had been funded and campaigned by Alan Bond – a prominent Western Australian entrepreneur who was later prosecuted for tax evasion and embezzlement. In 1983 though, Bond had achieved an almost 'hero' status with the Australian public via the success of Australia II.

the – whatever the section was in the Tax Act – and worked out this syndicate structure which became supported by the Labor government. So it was kind of a government-approved tax evasion scheme. Seems kind of weird, but that's really what it boiled down to. Macquarie worked out a way to package it that there were no losers other than the government. So they came to us and made us an approach and said did we have any technology that was involved in patents and high-risk, etcetera, etcetera, which of course we did. After a big drawn-out negotiation, we ended up putting together a syndicate. That was one of the sort of early ones and I think we ended up with 9 million bucks out of that which was a lot more than we had to progress technology, but the restrictions on the syndicates were the things had to be very high risk. So they couldn't finance anything that sort of made money. (interview, 2007)

Early the following year, the next steps in the process of getting the syndicate off the ground were taken when in March 1992, MBL engaged a valuer, Dr Maurice Venning, to undertake an independent evaluation of the project and a valuation of the core technology. From Smeaton's point of view, the syndicate had a longer-term significance: should the technology succeed, this would form part of the process of Bresatec moving towards its aim of listing on the Australian Stock Exchange and becoming 'a major local and international biotechnology company' (Administrative Appeals Tribunal, 2002, pp. 20-23).

Bresatec initially was not going to include Luminis in the syndicate from a legal perspective, however in early part of 1992 there were some changes to the taxation rulings, including the exemption status, and at the Board meeting in February 1992 it was decided that Luminis would be included in the Syndicate proper to gain the benefit of its tax-exempt status. Luminis would, in any event, have had some involvement because it owned some of the relevant intellectual property, in particular in relation to the embryonic stem cell (ESC) technology, which it had always been intended would be part of the core technology included in the Syndicate transaction.

Venning met with Smeaton and Robins in Adelaide in March 1992. The meeting led the group to have a certain sense of optimism; Smeaton thought it would be likely

that Venning's valuation would come within the same 'ballpark' as his, which meant that the project would most likely go ahead. Venning had a background in microbiology, having earned a PhD in that field, as well as a degree in economics, and Smeaton felt confident that Venning had a very good understanding of the technology involved, which would further give merit to the valuation that Venning would return to MBL.

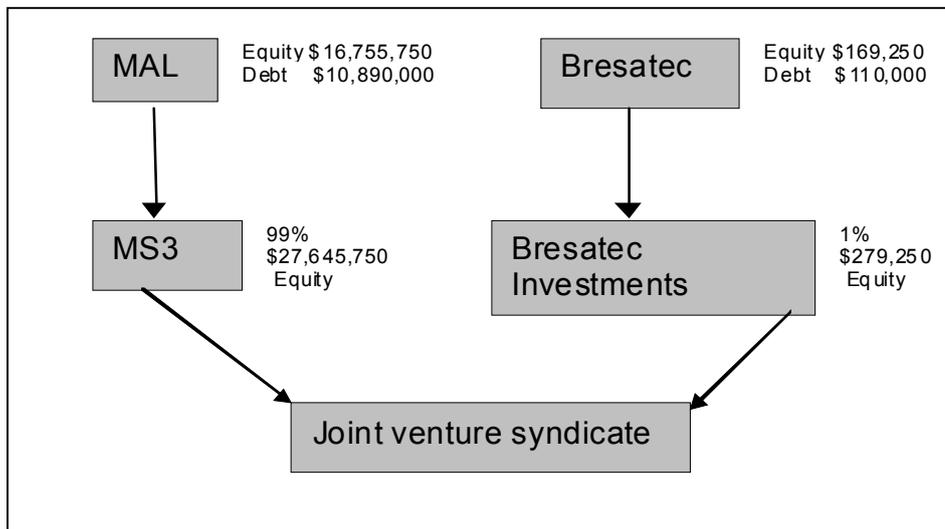
Because of his confidence in Venning's skills, Smeaton asked Venning to take a look at and comment on a draft letter Smeaton was preparing to the Industry Research and Development Board (IRDB) as part of the Syndication approval process. One of Venning's suggestions to Smeaton was to include a paragraph noting that the Syndicate was 'an attractive opportunity for prospective research and development investors to invest in a totally indigenous technology with commercial potential'. On 16 June 1992, the IRDB determined that the proposed project satisfied the definition of 'research and development'. A couple of weeks later, Venning sent his final report to Phillips and Smeaton stating that he considered a value of A\$15.35 million for the core technology used by the syndicate to be a reasonable one. This meant that the agreement would now be drawn up and enacted. This occurred on the 30 June 1992 and 1 July 1992. The following arrangements were made for the Transgenic Syndicate:

- (a) Bresatec granted Luminis a 15-year non-exclusive licence in respect of the Bresatec owned transgenic pig technology in consideration of a payment of A\$269,000 and a royalty. On 16 September 1992, an amended agreement was concluded whereby the licence granted was exclusive.
- (b) MS3 and Bresatec Investments Pty Ltd entered into a joint venture syndicate (the Syndicate) in the ratio respectively of 99:1. MS3's equity in the Syndicate amounted to A\$27,645,750 and Bresatec Investments' amounted to A\$279,250. MBL was appointed to manage the Syndicate, incurring management fees of A\$425,000 (including set up costs of A\$150,000) to MBL.
- (c) MS3's equitable investment in the Syndicate of A\$27,645,750 comprised equity capital of A\$16,755,750 and debt funding of A\$10,890,000 borrowed from Macquarie Acceptances Ltd (MAL), another subsidiary

company of MBL.

- (d) Bresatec Investments' equitable investment in the Syndicate of A\$279,250 comprised equity capital of A\$169,250 and debt funding of A\$110,000 from its parent company Bresatec.

**Figure 4: Structure of the BresaGen and MBL Syndicate**



- (e) Luminis granted the Syndicate a 15-year exclusive licence/sub-licence in respect of Luminis' embryo stem cell (ESC) technology and Bresatec's transgenic pig technology (the core technology) in consideration of A\$15,350,000 (the core technology licence fee). (This was attributable in the relative proportions A\$15,196,500 to MS3 and A\$153,500 to Bresatec Investments.)
- (f) The Syndicate appointed Luminis to carry out a program of R&D in consideration of A\$12,150,000 comprising a \$9,000,000 R&D budget plus an R&D profit margin of A\$3,150,000. The agreements provided for an R&D period of three years followed by a commercialisation period of five years. Luminis, being wholly owned by the University of Adelaide, had a tax-exempt status. Luminis deposited A\$27,225,000 with Macquarie Finance Ltd (Macquarie Finance), from which it drew down A\$8,910,000 in four instalments to pay for the conduct of the R&D which it had sub-contracted to Bresatec.
- (g) The Syndicate granted a marketing option to Bresatec Marketing Pty Ltd (Bresatec Marketing) which, if exercised, entitled Bresatec Marketing to market products resulting from the commercialisation of the Syndicate's core technology in consideration of the payment of a licence fee of 15% of gross commercialisation income derived prior to completion of the R&D programme and, thereafter, 20% of the gross income actually received or receivable during the marketing period.
- (h) Bresatec granted to MAL a put option exercisable at the conclusion of the commercialisation period in 2000 whereby Bresatec would be required to purchase from MAL the issued share capital in MS3 for a price equal to the put option price, as at the put option settlement date. The agreement was later amended, in October 1992, to the effect that 'the Put Option Price is

A\$45,350,817.06', payable on the review date. (Administrative Appeals Tribunal, 2002, pp. 6-7)

The reason Phillips included a put option in MBL's R&D investments was so that the investments were not at risk and MBL could exit the transaction. If the research was commercially successful so that MBL received royalty payments, MBL could choose not to exercise the put option and remain in the Syndicate.

In selecting appropriate projects around that time, Phillips looked at the reputation of the researchers and any business people already involved in the project: for example, American Cyanamid. He relied on the IRDB's review of the technology as well as Venning for an evaluation. His rule of thumb was that the R&D funding should be 60% – 70% of the value of the core technology. Around 1991-92, Phillips involved MBL in six proposed R&D syndicate arrangements.

However, by June 1995 the program ceased; the funds were all spent, several hundred prototype stage transgenic pigs were produced and attempts had been made to commercialise the core technology, with discussions being held with pig producers in Australia, the US and Europe. From Bresatec's point of view, they had achieved technological success but it seemed they were doomed to commercial failure. The problem was that discussions with the NH&MRC were unsuccessful in reaching regulatory approval for the sale of transgenic pigs for human consumption. This was complicated by the fact that there were no relevant standards or guidelines in force in Australia at that time.

One of their partners at the time was Bunge Meat Industries, which was responsible for supplying the pigs for the field trials. Bunge was concerned with the legal implications and did not want to continue in light of the lack of legislation. Therefore, in about February 1996, the Bresatec Board decided against selling the pigs

because of concerns about legal liability. According to a parliamentary report:

BresaGen [Bresa] produced a line of commercially viable pigs with enhanced growth hormone production with the advantage that the pigs grew faster for a given amount of food, putting on more muscle and less fat. Because there was no regulatory agency prepared to approve the use of these animals for human consumption and declare the technology safe, Bunge has slaughtered all the pigs and the germplasm is in existence as semen (and perhaps ova) stored in liquid nitrogen. It is highly likely that this technology will go overseas. It is not the inability of the Australian company that produced the pigs to commercialise them but the lack of a regulatory pathway that has caused the problem. (CSIRO, Submission no. 56, Attachment 2, p. 17. cited in House of Representatives Standing Committee on Primary Industries and Regional Services, June 2000, Canberra)

Sadly, about 300 transgenic pigs were slaughtered and buried (Administrative Appeals Tribunal, 2002). Smeaton felt that the major stumbling block to the success of the Syndicate was the failure of the Federal, State and Territory Governments to introduce regulations governing the sale of genetically manipulated organisms (GMOs) and, in particular, transgenic pigs (Administrative Appeals Tribunal, 2002). He also later said, 'the whole thing became much more difficult in terms of you couldn't sort of prove a negative and prove that these weren't going to cause any problems. But it all got much too hard' (interview with Smeaton, 2007).

At a later tribunal hearing, Robins submitted the following evidence:

... [F]ield trials to breed transgenic animals and test their progeny were completed in 1995 or 1996 but, at that time, it became obvious that there would be regulatory requirements that they had not anticipated. Dr Robins said he had been involved in earlier discussions with South Australian regulators who had then been very positive about regulatory approval. In 1992, they could not have predicted that genetically modified food was likely to be a huge consumer issue. Dr Robins said the project team had thought they would have a marketing advantage because their product was leaner and a better quality product as a result of a genetic modification that was entirely safe. However, in 1995/1996, the pig producers, Bunge Meat Industry, with whom they were working, were unwilling to conduct further field trials because they were concerned about a consumer backlash. As a result, the project has since been on hold. (Administrative Appeals Tribunal, 2002, p. 17)

Robins also gave a recent personal account of how he saw the situation at the time including the factors leading up to the cessation of the program in 1995, i.e. the sale and eating of the first pigs in 1988:

Yeah, I mean, I think what happened, the first transgenics that were made were actually sold into the food chain and there was apparent reason that they shouldn't have been and some of them were eaten by us and they were fine. But then ... there was a government inquiry and people started to get very nervous about was this natural, was this safe and so we started having discussions, I guess, with the NFA. I think they were called NFA at the time, National Food Association or something. Anyway, it became obvious that they wanted to regulate this and they wanted us to prove - and the pig growth hormone gene was controlled by a promoter called the metallothionein promoter, which is induced with heavy metal. So if you put zinc into the drinking water or whatever this turns on the growth hormone gene and then you get increased production of protein, decreased production of fat et cetera. They wanted us to do environmental studies and what would happen if one of these pigs escaped and it ended up in Broken Hill where some of the groundwater has higher levels of zinc and it mated with a wild pig. I mean, so much bullshit. This project really got bogged down because of - this just shows if you've got people that don't want something to go ahead they can put a halt to it. I think one of the reasons Bunge stopped is because they realised this was not going to be easy to get these animals into the food chain. (interview, 2007)

Furthermore, of the decision made by Bunge Meats to withdraw support, Smeaton said, 'they were just corporate. But I think we were trying to pass off the pig thing to the pig industry when someone lost interest in pigs at that stage. We weren't going to be a pig company. Well, I sort of looked at it and thought, well, looks like there's the potential here to make a human pharmaceutical company. But it became apparent as to why that was so in the end; partly was a matter of where you could get funding' (interview with Smeaton, 2007). Regrettably for Bresatech, in 1999 the Food Acts were modified to allow the sale of GMOs but by then sale of transgenic pigs was outside BresaGen's core business, although in 2001 BresaGen signed an agreement with an international pig company to sponsor BresaGen's continuing research into transgenesis with a view to commercialising transgenic pigs.

John Smeaton, though, paid credit to the scientists – after all, their technology had been successful. He said:

Seamark had the transgenic sort of interest and this would probably have all gone into the human sphere, probably 10 years ahead of Wisconsin, if Australia hadn't had a law which stopped you sort of doing things with human embryos. We could probably have isolated human embryonic stem cells way back then. That was all sort of thought about, but that was illegal, so it didn't happen. But certainly those guys had the ideas and they were working with mouse embryonic stem cells and we were trying to make pig ones, which proved more difficult than one would've expected. No, [Seamark didn't lack imagination.] He was way out there on all that stuff. But there were some legal restrictions, which is probably unfortunate. (interview, 2007)

On a positive note though, the technology developed during the life of the Syndicate did in fact underpin Bresatec's work on protein drugs and embryonic stem cell (ESC) based products, which enabled BresaGen to proceed with its stock market floatation in September 1999 and to establish its reputation as a leading biotechnology company.

However, some 10 years later a cloud hung over things. The Australian Taxation Office took MBL to court in 2002 – claiming tax evasion. This was in spite of the fact that R&D had ceased in about 1995/96 due to the regulatory environment that prevailed at the time. In 2002, the case was heard by the Administrative Appeals Tribunal in August and the findings were handed down a month later. Smeaton, Robins, Seamark and Hart were all called to give testimony.

Some of their testimony included:

Dr Seamark believed that funds of \$9 million would enable the research team to overcome current problems with the transgenic technology and found a commercially valuable breeding stock. It would also advance the research team's understanding of ESC technology and allow them to apply this in advancing the production characteristics of the pig, and to facilitate better understanding of the use of this technology in such applications as xenotransplantation and cloning.

Dr Seamark agreed that it was likely that the commercial product of this

research might be controversial. There were groups who, for religious or other strongly held reasons, said that interfering with nature was wrong, and the federal and State regulators were not prepared to give unequivocal approval. Although Dr Seamark was confident that such issues could be addressed in time, he acknowledged that he is not aware of any transgenic pig meat or other animal flesh being sold in Australia today. Nevertheless, he said transgenic pig meat is absolutely safe. He described his eating of this being televised and of barbecuing the meat in the Rundle Mall in Adelaide. He said there was general acclaim because the meat is lean and because the skin is slightly thickened and produces very nice crackling! (Administrative Appeals Tribunal, 2002, pp. 15-16)

Of the nature and state of the research at that time, Robins said:

... [A]s at 1991/1992, the University of Adelaide team had the most advanced transgenic pig research project in the world, something which was confirmed by American Cyanamid's investment in Bresatec in 1991. Nevertheless, the team were still experiencing technical and commercial problems with the transgenic technology. In particular, the technology had yet to be tested in a large-scale commercial environment. While Dr Robins agreed that, in 1992, millions of dollars were still required in research funding, he said that, nevertheless, he thought that field trials could be completed within three years. (Administrative Appeals Tribunal, 2002, p. 17)

On top of the challenges presented to them externally, there were some shifts occurring throughout the development phase. For example, Seamark had started to pull back from the syndicate work in about 1992. He explained why:

By then, I was pretty disenchanted with what became BresaGen and Bresatec. I didn't get on particularly well with the chair of the board ... Alan McGregor. He was somebody who I just couldn't talk to and didn't particularly like. And I had financial independence through the departments other commercial activities. If there's one reason for generating your own independent source of money, it's so you can tell everybody else to go to hell when you get pissed off, so I just pulled out. I just got on with the other projects.

I left the BresaGen thing in 1992, really because I thought they were going the wrong way, particularly in relation to what they were doing with our pig project. We had set up an opportunity for them, a big opportunity to develop the Tailem Bend site. They had the land and everything. We had the permission, we had potential investors, we had the expertise, we had the plans, it was a state of the art piggery. We had done hundreds of thousands of hours, if you like, of understanding what needed to be done to make this happen, but it was more an attitude of the Bresatec/BresaGen board towards

how they saw their future. They saw themselves as a small chemical manufacturer and not an animal production unit, not an animal enterprise. I think it was probably because they didn't know. I was the only person who was embedded in the animal world, and Barry Lloyd was a stranger to them. He was extremely able and he and I had our dreams. We should have really gone off and done it independently and been given permission to do it ourselves. They didn't want that. It never got a proper hearing at the board, it was never properly advocated for. (interview, 2007)

Seamark's disappointment was undoubtedly amplified because of two key points: (1) he and his colleague, Julian Wells had put countless hours into thinking though the venture, both in terms of technology and as well in terms of commercial interests, and (2) the way in which the decision was transmuted to 'others' within the University. He gave an impassioned account of this:

[Pigs] are very smart animals and learn quickly that they don't like being injected with pGH or other growth promotants so we saw transgenesis as the only viable way forward. The focus of our interest at the time was establishing a relationship with a top pig breeding company so we could access their top breeding stock. We saw no purpose in creating transgenic stock with other than the best animals available. The UK based Pig Improvement Company (PIC) interested us most and Barry Lloyd and I had a good understanding with them of the future we might have together. Our plan was to build a new state of the art pig breeding unit to produce genetic stock by conventional breeding means that would form the basis of a future transgenic herd. The research would be funded from the sale of conventional high value breeding stock. PIC was convinced the enterprise would be a viable one and, after a few abortive attempts to find a location for the piggery, detailed plans were formulated for a piggery at Tailem Bend sited on land owned by Metro Meat Ltd. It was all ready to go when the University started playing political games and wanting to site the piggery on the Roseworthy Campus. From our perspective the proposal was just not commercially viable or even sustainable as a research project.

I resigned because I was very disappointed with the outcome of the Metrotec and the way the original concept and the one that we had formulated. It was fairly well thought through and it was being gazumped by negotiations with Roseworthy. It was one of the great lost opportunities. A telling example of why Universities rarely succeed in the commercial field. The entrepreneurial energy was just dissipated into the world of small things that is University politics. The grand idea was lost. Universities are spread thin, in ambition, money and energy. (interview, 2007)

Seamark was philosophical though:

University companies are always coloured by University politics. They don't make commercial decisions. They make decisions, which are political decisions. ...[C]ommercialism is commercial. You basically run with the opportunities and you make the hard decisions when you have to. The fact that Bresatec decided against us going that way, I accepted as a commercial decision and moved on. By then, we were into cloning technology and embryo ... technology.' (interview, 2007)

### **From Pigs to Goats**

Seamark's entrepreneurial flair remained with him after he moved away from the Bresatec syndicate – as his following comments demonstrated:

[We went in this direction] partly because we had the appropriate expertise and we knew we could do it. We were internationally competitive and we had only ever measured ourselves against the best and there were a lot of questions that were emerging at the time that could only be addressed by cloning.

When cloning came along, I thought this is fantastic. What I will do, is set up an enterprise creating clone animals for experimentalists. As soon as you start thinking about these things, you realise a thousand other opportunities, all the questions that can be addressed and answered by clones, all the biochemical molecular biology questions which are best serviced by clones. We went on very quickly to discover even bigger questions such as epigenesis. We had made some interesting observations during our early IVF and embryo transfer in sheep. Taking a normal embryo out of an animal for three days and keeping it in culture medium led to a spread of birth weights and some extremely large lambs, the biggest we ever got was five times the normal weight at birth! In discussions of that phenomena, I linked in with the people who were then pioneering the epigenesis field, that is a study of the environmental determinants of gene expression. So that became a key interest of our laboratory and by the time, I left in 1995 we were more interested in that than anything else. (interview, 2007)

In 1995, Bob Seamark resigned from the University of Adelaide, taking on a senior role in Canberra with the CRC for Vertebrate Biocontrol. As for asked how he would describe himself, Seamark proudly replied, 'I'm a biotechnologist. That's what I do. I provide a consultancy in the biotechnology area. I am interested in deliverables. If

it can be delivered, I'm interesting in delivering it' (interview, 2007).

Seamark gladly recalled with excitement and fondness what this particular time was like within the research institutions of greater Adelaide:

We were states, little city states at the time, which meant that in the clinical field, for example, if you were like Lloyd Cox, a professor of obstetrics and gynaecology in the medical school in Adelaide, you were responsible for the whole of the obstetrics and gynaecology service for the state, its structure and shaping and everything else. This is apart from university duties. You had your hospital; you ran the department in the hospital. You did all those things, and as a member of the university department, we were participants in that. We were small teams, so we had to share all that. So even though I wasn't a clinician, I was fully engaged with so many things. I was also lucky in maintaining such a good relationship with the State Department of Ag as an outsider. I had been one of them - I was one of their cadets and I was still one of them. (interview, 2007)

And like Elliott and Rogers, Seamark confirmed the mateship that characterised the scientific departments within the University of Adelaide:

We were just a bunch of people that got on well together and had huge respect for each other. I think that was the clue to it. It was robust. We weren't frightened of saying what we felt at the time. There was no bullshit, as far as I was concerned. If we didn't want to do it, we didn't do it. If we were enthusiastic it, we would do it or we would accept responsibility. We would pick up the tabs and responsibility for whatever we decided to do, collectively or individually. (interview, 2007)

On a personal note, Seamark talked about his connection with Wells, 'I remember that Julian and I always worked together on a general understanding that we would share anything we got, but of course when we involved the university and particularly Luminis and things with our activities, we had to be much more specific. It was a pain in the arse, really' (interview, 2007).

This mutual respect and trust between the scientists led to a synergy that was best described as tangible and yet hard to quantify. In Seamark's own words, he said 'Julian and I concocted lots of applications for various things, and we became quite

good at it in the end'. But typically, the tide of politics would wash over their projects and plans, 'They were all applauded, but we got swept up in university politics in relation to them. We had the go ahead at one stage for a Centre of Gene Technology. This was a great application and I still have a copy of it. It more or less foreshadowed everything that has happened over the last ten years including embryonic stem cells and their use in xenotransplantation' (interview, 2007).

However, things changed quickly and the University of Adelaide withdrew its support:

Yes, it was between essentially Julian and I together, putting up an application, but the university decided not to support us at the last moment, because they wanted to support an application, but the university, for political reasons, decided not to support us at the last moment and instead supported an application by the new Director of the Waite Institute. So we went off interstate and joined with a team in Victoria that allowed us to continue some aspects of our work that led to several commercial ventures that were to employ some of my ex grad-students in due course. (interview, 2007)

Seamark told a story of his links to the goat field that demonstrated beautifully the powerful union of serendipity, individual decision-making, complexity and the unintended consequences of their actions:

Our interest in goats started in the early 70's with a comment made by a sailing mate, Dr Alan Cotton. He said something like 'my daughter wants a horse and I'm going to have to get some land but I don't want it to be a Micky Mouse farm, I want it do be a real farm doing real things, you 're an Aggie what can we do?'

Purely by chance I was thinking of goats at the time because I'd recently learned [from Dr John Smith] that the Australian feral goat herd had as much cashmere in it as many of the cashmere flocks of China and suggested that someone should take advantage of this. I knew feral goats were being killed in large numbers at a local abattoir and I thought we it would be possible to scan these for potential cashmere genestock. Alan [Cotton] immediately expressed interest in this possibility and arranged to join me in a livestock conference in Sydney the following week, which featured speakers who knew something about goat husbandry. One of the speakers was a Dr Neil Moore, who was advocating embryo technology as the only way forward for serious animal breeders. Interestingly his talk was based on data he had generated in

an impressive series of sheep experiments with a PhD student Alan Trounson [the now famous human reproduction expert Professor Trounson]. Cotton asked me if I could do ET and my response was ‘If Neil can do then I can too!’ So I was challenged to come back and develop a goat ET program. On the basis of what we learnt at that conference, we decided that while we might use feral goats for experimentation, it was less risky to develop the farm as a mohair goat breeding enterprise.

In typical Cotton fashion, within a few weeks we had a farm and a nucleus of a mohair goat herd. It took about two years to get a viable technology package together but we did it and Colchis [Cotton’s farm] became a key site where my staff and students honed their ET and other assisted reproductive technology skills. It was a great learning experience as we only had a shoestring budget during those early years. The enterprise grew to become Southern Angora Breeders Pty Ltd, then ARPAC, one of the biggest goat breeding enterprises in the world. We did all the negotiations at the Chile end all the quarantines stuff. ARPAC had ambitions. It flew for a long while. There was no limit to the extent of our ambitions at the time. The company had its own private jet to go to Chile and things like that. ARPAC listed on the Wellington Stock Exchange in the early 80’s but fell victim to the 1987 market crash. (interview with Seamark, 2007)

## **Medvet and E21R**

Even with the enormous activity happening in the transgenics area, Bresatec did not stop its R&D activities there. Concurrent with its efforts to develop the pig transgenic technology, Bresatec became aware of some research that was being developed by Medvet Science Pty Ltd.<sup>13</sup> The compound was aimed at treating breast cancer and was considered to be a novel therapeutic. In 1993, the product (codenamed E21R) was in-licensed by Bresatec. The nature of the deal was that Bresatec would develop E21R and take it to Phase 1 clinical trials under exclusive license. To help with this, the Australian government funded a three-year R&D Start grant worth A\$2.6 million, with their expenditure to be matched by Bresatec’s dollar for dollar. To protect themselves Medvet and Bresatec took out two joint patents covering the technology, one covering

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<sup>13</sup> Medvet Science Pty Ltd is the commercial trading arm of the Hanson Centre for Cancer Research of the Institute of Medical and Veterinary Science in Adelaide.

its mode of action and the other covering its production.

Although there was much excitement about E21R, what no one knew, or could have even possibly predicted at this early stage, was that E21R almost single handedly brought not only one company, i.e. what would by then be known as BresaGen, but two companies to their knees just a few years later.

## **Backing the Right Horse**

The following year, 1994, another agreement was entered into between Bresatec, Rutgers University, Texas AMU and Louisiana State University. The group was researching and developing a new hormone Bresatec had identified in 1993, equine somatotropin (eST), commonly referred to as equine growth hormone. It was thought that eST could be used as a remedy for improving nitrogen balance in aged horses. In fact, what the Bresatec scientists had identified was a synthetic copy of the naturally-occurring equine growth hormone molecule produced using recombinant DNA technology. The hormone would later take on the commercial name of EquiGen.

Robins was the key scientist behind this discovery, as he explained:

The other idea I came up with was why don't we look at things that might have some value add? Not pig growth hormone, why don't we look at equine growth hormone? Why don't we look at canine growth hormone which happens to have the same sequence as equine so it's the same molecule. Why don't we look at camel growth hormone because camel racing is big in the Middle East and you get a lot of rich sheikhs looking for the edge and so why don't we look at these things?

So that's what we started to do pretty early on there, was to steer away from domestic or livestock animal production and looking at products that were more value add either in human health care or in veterinary health care but where the molecule was more than just going to make a pig grow a bit more quickly.

[EquiGen] That was my idea. I cloned it and I was the first one to express it and it was driven by me. The players there were myself and Stan Bastiras, Carol Senn and Meera [Verma] took over running that operation in about '95

or '96 .... (interview, 2007)

The research collaboration with the US partners would investigate the safety and efficacy of the equine growth hormone to be used as an anabolic for aged horses.

Robins outlined the reasons behind the collaboration:

... [W]e did some clinical trials at Rutgers University, at Texas AMU and then we did some pharmacokinetic work at Louisiana State University. These were trials that we sponsored but when you go to see the FDA the standard for registering a veterinary drug in this country is more or less the same as the standard for registering a human drug. Our facility didn't come up to scratch in terms of FDA GMP and they didn't really like our clinical data. (interview, 2007)

As Robins stated, at the time, the production facility Bresatec had in Australia did not meet Good Manufacturing Process (GMP) standards required by the US Food and Drug Administration (FDA). Hence, it was important to have these US based alliances. This research collaboration lasted approximately three years, from 1994 until 1997. The product was never registered in the US as Bresatec did not have distributors there. Instead, the product was imported to the US on a case-by-case basis, as Robins informed:

... BresaGen did it itself ... Sue Gayle was her name but she was very vivacious and outgoing and she used to go around and basically market EquiGen. After Sue left, Edwina Lamkin [joined] ... she was a vet with an interest in horses and that's how that product was sold.

[With regards to the US] we could sell into the space. You could sell to individual vets or whatever. You could market it via the Internet or whatever but you couldn't go into trade journals here or go to conferences or whatever ... and you allowed vets to import drugs from other countries on a case-by-case basis. (interview, 2007)

In terms of how exactly these associations came about, Dr Robins explained:

I was at an animal and dairy science meeting, I think, in Minneapolis or somewhere like that and I met the Rutgers folks at that meeting. They may have done some work with Monsanto or somebody putting bovine - because

Monsanto has made and commercialised bovine somatotropin and I think they were doing some horse trials with bovine somatotropin so I went and introduced myself to them. [So just typical networking] Yes, it was an opportunity that came up at a conference. The guy at Texas AMU actually, Gary Potter, I was put onto him by another horse person and the LSU folks, again we met them at a conference. They've done a lot of work with horses and were very good at pharmacokinetics studies. (interview, 2007)

It is important to contextualise the history of EquiGen's development pathway. Just as the porcine growth hormones and the pig transgenic technology had been inextricably intertwined due to Seamark and Wells's joint research, much of the later technology that was developed or imported into the company was also a legacy of the close-knit nature of the scientific community and the departments, and even perhaps to an extent the geography and size of Adelaide. Smeaton gave an illustration of this with regard to the connections involved in EquiGen's development team and in particular one of its founding scientists, Robins:

Well, see he [Robins] was always keen [on proteins, and] when he came into the company [he] made a condition that he wanted to pursue the whole growth hormone area because they made some human growth hormone in the Biochem department. [Some of that initial technology was part of BRESA and it virtually got cleaved off to GroPep...]. Allan was one of those guys who invented that [and Julian Wells had been heavily involved in that, too.] See, Julian and Ballard were fairly sort of close, I guess, and John Wallace in the Biochem department was involved in that. [So Allan was involved in EquiGen and the hormones, the growth hormones.] Yeah, all those sort of growth hormone things and general protein-type stuff. (interview, 2007)

E21R also provides an insight to some extent as to the importance of the networks and even the close geographic nature of these departments. The Hanson Centre for Cancer Research<sup>14</sup> was located literally across the road from the old Darling

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<sup>14</sup> The Hanson Centre for Cancer Research is a child of the IMVS. But it's an independent research institute, but the IMVS has funded it and championed its capital grants that allow buildings to be built – which were Government grants. IMVS is a separate entity from the [Royal] Adelaide [Hospital], but it is a Government organisation. [Understanding the background to this] is quite important because the IMVS comes into many of these things. (interview with Juttner, 2007)

Building where the Department of Biochemistry had first been housed. Even with the move to the new building on the main campus of the University of Adelaide, the distance between the Royal Adelaide Hospital, the Hanson Centre, IMVS, Luminis and the Department of Biochem was only a matter of a couple hundred metres and was, and still is, well dotted with lovely cafes down beautiful tree-lined streets. This situation was highly conducive to regular contact and meetings, as too was a well-appointed staff club sitting in the middle of the diameter of the circle. Moreover, Thebarton, where Bresatec had moved to was still only a few kilometres way.

### **From Bresatec to BresaGen**

With the transgenic technology winding up in 1995, the commercial focus of the company shifted toward development of products using growth factors and growth hormones for treatment of human disease and productivity improvement in animal production. It was believed that efficient production of the technology could then be redirected toward the human health area generating more attractive margins. This meant adopting a proactive approach toward securing intellectual property protection and led to the appointment of a full-time senior professional to manage this area. This person would be Dr Meera Verma, who had also sprung from the University of Adelaide. At the same time, the company spun off the research reagent part of the business. The business would be known as Bresatech Pty Ltd and the remaining part of the company would be known as BresaGen Limited. This was formalised on December 21, 1995.

Meera Verma described the situation:

The life science company that we spun off, that company took the name Bresatec, because they were selling products and were known by that name. We had, I guess, a bit of an emotional attachment to the BRESA part of it, so we kept that and it became BresaGen. (Verma, 2001)

Peter Guilhaus was the manager for Bresatec. Guilhaus explained that the impetus for this split had started the previous year in 1994:

That was initiated back in 1994 ... One of the things which that led to was the company divesting the training up of the Bresachem division ... So the die was cast back then so that I wasn't involved in anything to do with the other products [meaning the protein division], to the point where initially you had business meetings and management meetings where everyone got together ... Eventually it became more of 'no, you're not involved with this anymore'. So from that point on, we became a separate company and entity, but sharing the same sort of system. (interview, 2007)

Although there was an emotional and mental separation, the physical division did not take place until after the year 2000, 'Here in this building [the old Faulding's site in Thebarton], we shared with BresaGen then, from 1996 through to 2000 and something' (interview with Guilhaus, 2007).

John Smeaton, who had been involved in this strategic decision, described how and why it came about:

Well, at that stage, we were talking to Gerard Law who established VC companies. We were talking to Rothschild in London and Jeremy Kernot-Cook ... I met Jeremy and I'm not quite sure how we got first involved with them. But someone gave me an introduction to Jeremy, I went over to London and Jeremy said – he's a very engaging sort of guy, too, sort of the English rouge and with a sort of twinkling in his eye, so he was fun. So we sort of hit it off and we had a negotiation [that] probably went over about two years. I mean all these things take a long time. We kept his sort of interest in the company and he was running a fund, and in the end he decided to invest. But one of his concerns was whether the company was spread in too many areas, and the reagent business was never something that was going to turn into a huge business. So he encouraged us to think about selling it off and get focused. So that's what we did. Then they invested and I think it was reasonable. (interview, 2007)

This was not the end of the changes for Bresatec Pty Ltd as Guilhaus went on to explain. Three years later, their name changed again to Geneworks Pty Ltd, although they kept their same company registration details, i.e. ABN:

In 1999, we changed to GeneWorks, and it had become an issue to do that for

a number of reasons. One was that again, the confusion of Bresatec, which was the original company name, which we retained but people still associated it with the other divisions. It was important to keep it initially for the isotope businesses which we had, which people identified with Bresatec or Bresa, but by the end of the 1990s, I assessed that the isotope business was in rapid decline, costs were going up and people were still arguing that they needed cheaper prices, and so we were getting squeezed, and non-radioactive systems were becoming better and better. So I felt that because of all the confusion and the fact that we wanted to identify ourselves with what we were involved with, which was selling products for gene research, that we changed our name and did a search and found a name which we thought would be good and which more reflected what we were about. So we changed in 1999. (interview with Guilhaus, 2007)

From Guilhaus's point of view, this was a significant milestone for the company, along with several others he mentioned:

I think that the partnerships with regard to bringing on board John Smeaton, getting the deal to develop Bresatec as an amalgamation of the groups between the university, O&G and Bresa were definitely significant milestones. I think the move out of the university to here was another milestone and of course the other one was the divesting of the trading arm, which was at the end of 1995/96. (interview, 2007)

Throughout the 1980s, competition for these products that Bresatec had been selling had increased. Consequently, Bresatec needed to adjust its strategy to remain viable. As such, Guilhaus described how they began distributing other people's products as part of the product-offering bundle:

Bresa started as an import replacement business trading to sell these products, but one of the limitations of a business of that type ... was competing with these big multinational companies that have a catalogue three inches thick, or should I say 5cm thick or whatever, and not being able to compete, even though you might have a cheap product that everyone likes, because there are only five other products from this company, that company will discount it and you can get locked out. That was the limitation that we felt that was impacting on our growth.

It [our product line] wasn't wide enough. In the late '80s, we initiated a program of product acquisition, becoming a distributor of other research products .... So if you look at our website today or if you looked at catalogues from back in the '80s ... you could see that there was again, if you look at that, that's just purely what we made and then as you go further up the

evolution scale, you will see that things became a little bit more professional and then in terms of presentation, bound, professionally printed and pictures and what not with a product portfolio which expanded dramatically to include agencies that we were representing, complimentary agencies. (interview, 2007)

As before, distribution internationally was challenging and the company was predominately aiming for just the Australian and New Zealand markets as, ‘if you are an importer, it is kind of hard to export those imported products to others ... There’s no rationale there, unless you happen to be geographically located close enough and there is no other support for that product. We have sold things to Indonesia, for instance ...’ (interview with Guilhaus, 2007). The core business remained though:

Notwithstanding the direction taking on agencies, we still had a core business of manufacturing, which gave us a competitive advantage to some degree in servicing new neighbour markets like New Zealand, like Indonesia and South East Asia to a much lesser extent. Export business was probably less than 5 per cent. It always has been. [It is still the case today]. You can argue that’s not healthy, but then when you’re looking at it, the market is growing in a healthy way and is still meeting the demands of local customers. Again, you need to be able to have a competitive advantage for intellectual property on a product that can reach those markets. In the research area, there is nothing in Australia that has been able to do that really, because it gets gobbled up by some other company. The advantages in servicing the Australian market is that it is geographically isolated, we have the ability to make things quickly and to service that market quicker than anyone who makes it overseas can do and bring it in. Our core business is custom DNA synthesis, which is still growing and we service our market here, and in New Zealand with those products, so that still goes quite well.

Yes, well as I said, if you think about the business that Bresatec Ltd was involved in, as it grew from being Bresa before it became Pty Ltd., the trading arm needed to grow and it was limited by the fact that it only had a handful of products that it could make, and of those products the competitive advantage of overseas companies was there for them to be able to swamp the market with their alternatives at a competitive price, so you needed to add things that would complement your range to make your range of products more attractive to the customer base, and that is what we initiated in the latter quarter of the 1980s and into the 1990s. It was a very good strategy, because the revenue strengths took off from that point. We started in the hundreds, 100,000 to 200,000 and quickly went into the million dollar range of revenues ... [It] was probably around the 1990 to 1992, that we started to bring in about a million to a million and a half ... Profit margins were reasonable. Again, it was a

blend between manufacturing and distribution. Distribution lines, you try and run a distribution business to have a GP [gross profit] of around 30 per cent, and hopefully a return at the end of about 10 to 15 [net profit percentage] (interview with Guilhaus, 2007)

In addition to manufacturing and distributing ‘research consumables,’ Guilhaus spoke of the strategic decision to move into the ‘hardware’ side of the business and aim to have a vertical solution per se for their customers:

The other thing that is evident is that the company was initially a reagent business. Of course it was called Bresachem because it had radioisotope compounds, it had kits ... It had buffers and standards and markers that all based around consumables that were bought and used in experiments. Nothing in the portfolio in the earlier days was hardware. One of the aspects of becoming a distributor was the ability to look at the tools, the hardware tools that are used by researchers to do things. So if you are doing PCR [polymerase chain reaction], you need a thermocycler, you become a distributor of a thermocycler and suddenly rather than selling a hundred kits at a hundred dollars each to make 10,000 dollars, you have got to sell the machine to make a certain amount of money. We wanted to be a hardware store for scientists. You can come and shop and get all the tools that you wanted to do your project. We tried to be as much as we could.

And with regard to the IT developments in the late nineties, the internet and websites made things extremely [easy]. It was advantageous, in terms of being able to present yourself and your products. So part of the thing which we have is now the ability for people to order online with custom DNA synthesis, which is what we manufacture. That’s ideal because in the early days, a customer would want a short segment of DNA, so they would fax through the sequence on a piece of paper. We would get it and the production person would look at it and transcribe it onto another sheet or into a computer and then go over to the machine and download it in. You had a system whereby there was so many points where human error could occur, and reading what someone had scribbled on a piece of paper ... So the ability for someone to go online, onto our website, download their own sequence onto our website, press go, it goes immediately into the machine, we have no dispute. We can say, well that’s the sequence ... But it also speeds things up. And it reduces our costs, obviously. That’s a great advantage. We are doing the same now with other products, enabling people to get a shopping cart and they can put whatever they want in there and it goes through and gets processed. (interview, 2007)

Whilst their product lines were becoming more sophisticated, so too were their marketing efforts, including the use of the Internet to service their clients. Of these

initiatives, Guilhaus said:

With regard to the buy-out of the company in 1995/96, there was a period of just continuing on improving our marketing presence by better glossy brochures and catalogues. I expanded the team and we took on product managers and marketing managers, marketing people and consulted from time to time. Then we associated ourselves with a company called Fusion ... Paul Quirk was our IT manager here in the early days. Paul was our contact to help to get the information that they required so we could get our website up. So they were responsible for the design of our website to make it as innovative and user friendly as possible and they have subsequently been involved in two generations since then in designing what we have now, which is a site which has got application focus in terms of what type of work you are doing, specials, news items and then you can click under that and then go straight into the area which allows you to order online. It has registered users. It's got great capabilities of doing post analysis of who's hitting your site, what sort of things they are after and so on. So you can get an idea of marketing trends.

We have just recently become an ISO accredited company. The process is pretty painstaking, but it's very useful as a trading business, especially when you are looking at a lot of government institutions that are providing and requiring tenders for supply. (interview, 2007)

These developments certainly helped maintain Geneworks' position in the market – but the real benefit was their dual role of being both a manufacturer and a distributor that was *local* i.e. Australian:

We have a unique position as a supplier of research products, because you have either got subsidiaries set up in Australia from overseas companies, the Amersham's (they are now called GE) ... [Y]ou have got Bio-Rad; they are all companies that have their own offices here and their own managers and they are globally recognised. Then you have the distributors that handle the companies that aren't big enough to have their own direct presence and those distributors sell a portfolio of products, and in most cases try to be fairly focused in certain areas, but others can be more general.

We have the distinction of being a manufacturer and a distributor, because we do make things, so we have a little bit more credibility as a company from the point of view that some of the things that we represent, we actually use. We know what they're like and how they work and we can talk to customers about their research. That provides us with a bit of a distinction. [It's like to be a legacy too from the earlier customers]. There is an association that what we are trying to do, because we are manufacturing and trying to keep honest by providing an alternative which gives quality indicators like better turnaround times, cheaper prices, better quality. Some people appreciate that

and recognise that .... [B]ut it is still, for all intents and purpose, a global market where people will buy whatever is the cheapest. They are all on government research funding, or most primarily. They have to watch the dollar and they will go with whatever is convenient. But there are still determinants of ‘if it’s half the price and it takes a month to get here, and we need the results next week, we will find something that will get here quicker’ and so on. (interview with Guilhaus, 2007)

To this day (August, 2008) GeneWorks is still headquartered in Adelaide, with sales offices in all Australian capital cities as well as Auckland NZ. They service and supply the Australian and New Zealand markets with a range of equipment, reagents, consumables and associated services and consider their core business to be the synthesis and supply of custom oligonucleotides - manufactured in Adelaide.

### **BresaGen is Born**

With the sale of Bresatec Ltd completed at the end of 1995, early 1996, BresaGen was able to focus on the development of therapeutic products that had IP protection. EquiGen remained a high priority at this time, and it was moving successfully though the development phase. As part of the process, BresaGen needed to get approval for the sterile production of goods from both the National Registration Authority (NRA) and the Therapeutic Goods Administration (TGA) each in Australia, for veterinary and human products respectively. It was thought that these licences would not only be necessary for EquiGen, but would also be used at later stages as BresaGen developed new products to go into their pipeline. As such, the experiences with EquiGen would be highly beneficial with respect to the company’s learning capacity.

Bastiras described this period as being a highly significant milestone, even though it took them several years to achieve their GMP status:

[It] was probably about 1997 or so and a guy from the UK joined us, a guy called Steve Hart. And Steve came from a manufacturing background in the

UK. He used to work for a device company. And Steve basically turned our R&D focus into more of a GMP focus. So Steve taught us things about GMP, doing things the right way. And so Steve was an absolutely valuable asset for the company, in our work with the TGA. Steve was instrumental in getting us from being basically an R&D company but that is good R&D, but he got us to turn that R&D with a GMP focus. So we became [good] – and the amazing thing is, we went from being a totally R&D company to a document driven GMP company by about – I think it was ... that was the time we floated, about 1999. The building that we were in [the old Fauldings building] was an absolute dump. You couldn't believe that in that facility we were making drugs, protein based drugs that were to be injected into people.<sup>15</sup> (interview, 2007)

Moreover, the development of expertise in animal embryo manipulation, initially supported by MBL R&D Syndicate, would soon go on to be of the utmost importance to the company when they would acquire IP for the University of Adelaide in 1999 as part of their strategic plan for listing on the stock exchange. Ultimately they would be positioned as an early leader in the ESC field, which was beginning to really gain a foothold in terms of being recognised as a useful medical tool to treat a raft of the then (and still) incurable diseases such as Parkinson's disease, spinal cord injury, stroke, diabetes and heart failure, where failure of cellular function will be treated by provision of cultured healthy cells (Edgar Online, BresaGen Ltd Form 20 F/A, 2 September 2003).

However, R&D activities were a strain on the company's finances. In July 1997, BresaGen was able to raise an additional A\$4 million in funds for E21R's development. The key investors were as follows:

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<sup>15</sup> The injectable proteins were never classified as sterile, and still to this day we're not classified as sterile. But they're classified as low bioburden, and that means that you've got very few bugs in it, probably no bugs, but you can't say – sterile means zero bugs, whereas low bioburden means probably zero bugs, but you haven't proven it. So all the products leave our facility as low bioburden, and then as they get built in another facility, someone else's facility, a special filling chemist facility, where they have proper procedures for classifying the final product as sterile. Those sorts of facilities, you've got to have for example, a sterile micro lab, and you've got to swab things often. (interview with Bastiras, 2006)

**Table 4: BresaGen's Ownership in 1997**

<b>Investor</b>	<b>Amount in A\$ millions</b>
Biotechnology Investments Ltd (BIL)	\$2.5
Luminis Pty Ltd	\$0.5
Hambro-Grantham Capital Ltd	\$0.5
Cambooya	\$0.5

**Source: Karunaratna, 1997**

At the time, a press statement quoted Dr Geoff Brooke, the director of Rothschild Bioscience Unit in Australia, as saying, 'Biotechnology Investments Limited (BIL), a UK-listed investment company advised by the Rothschild Bioscience Unit (RBU) announced today that it has invested A\$2.5 million in BresaGen Limited, an Adelaide-based biopharmaceutical company. The Rothschild Bioscience Unit led the A\$4 million investment round' (*Australasian Biotechnology*, 1997). In the same statement, Brooke also stated, 'We believe that BresaGen has significant growth prospects and represents an excellent opportunity for investment in an Australian technology-based company' (*Australasian Biotechnology*, 1997).

Additionally, the same piece described BresaGen's current research interests and aims, including the fact that E21R was slated to start its Phase I/II trials in 1997, but moreover, there was a second human health drug on the horizon, a human Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) antagonist for the treatment of certain types of leukaemia (including the often fatal juvenile onset leukaemia). Like E21R, this drug was being developed in collaboration with the Hanson Centre for Medical Research (*Australasian Biotechnology*, 1997).

### **Early successes with EquiGen**

Field trials for EquiGen began in 1996, based on research between Australian and American scientists that had started in 1994. The trials took place in both Australia and

the US, with a view to BresaGen retaining manufacturing rights in Australia and registration was planned for Australia, US, Southeast Asia, the Middle East, South America, Africa and Canada. The results of the trials showed that nitrogen balance, food digestibility and nutrient utilisation were all improved and plasma urea nitrogen was decreased by eST treatment indicating an anti-catabolic effect on nitrogen metabolism (Australasian Biotechnology, 1999). Musculation was clearly enhanced as was overall body condition and animal well-being. These results were the basis of the regulatory submission. Furthermore, based on the published effects of somatotropins in a number of other species, it was predicted that EquiGen might have a range of potential therapeutic applications. Some of these were under investigation, including accelerated and improved soft tissue healing, assisted recovery from musculoskeletal injuries, improved body condition in debilitated horses and improved mare fertility (Australasian Biotechnology, 1999).

Within two years, 1997 BresaGen had successfully met the trial requirements and achieved marketing approval for EquiGen Injection. Remarkably, this took less than four years. In their favour, though, was BresaGen's reputation in and closeness to the equine market. Their decision to employ product specialists to market this product who were veterinarians with special interests in horses seemed to have paid off. Whilst EquiGen was gearing up for launch in 1997, BresaGen was further developing its animal health pipeline; this included a canine growth hormone that had applications for obesity and wound healing (Australasian Biotechnology, 1997).

BresaGen started receiving orders via the Internet from South East Asia and the USA. Clearly, the US was a very significant market in terms of sales potential and BresaGen began the process of conducting a study to examine the viability of registering the drug for use in the USA, either on its own or in conjunction with another

organisation. The Middle East was another important market, especially Dubai, which has a world famous horse racing industry and the livestock are worth millions of dollars in terms of race earnings as well as their siring of progeny. Greater Europe did though prove problematic, as it is considered acceptable in many European countries to consume horsemeat, thus posing regulatory complications.

In 1998, two agents were appointed, one in Malaysia and the other in Dubai. The agents were given marketing and distribution agreements, as Dr Carol Senn explained, ‘We had a guy in Malaysia ... he was a distributor, but he would buy and on-sell as an agreed arrangement to various places in South East Asia, and then there was also a company in Dubai that would sell to the Middle East, so they were primarily it, just across that region’ (interview, 2007).

The ongoing strategy was to broaden the label claims and develop a slow release delivery system, and although there was no specific intellectual property protection on the EquiGen(R) Injection, there was proprietary manufacturing technology involved which was important to help protect the products. Perhaps even more important than the product though, was the experience gained in bringing this type of product to market.

During this period, the team was also researching the use of ESC technology as a means of improving the growth characteristics of livestock. The ESC technology developed was considered to be more efficient and reliable and was thought to have greater potential in achieving the objective of an improved growth rate for livestock animals.

### **E21R – A Disaster Waiting to Happen**

In 1997, BresaGen was offered a A\$2.9 million AusIndustry R&D Start grant to assist further development of its drug known as E21R. The grant was to commence in 1998

and run for a period of three years (Australasian Biotechnology, 1997). As part of the grant conditions, BresaGen would match the funding offered by the government dollar for dollar. BresaGen was to manufacture the hormone locally during the trial stage and if approved, BresaGen would upgrade its manufacturing capacity on site to handle worldwide production. The Phase I trials showed E21R to be highly effective against certain acute myeloid leukaemias (AMLs) as well as certain types of solid tumours, including breast cancer. At this stage, 1998, the drug had completed one round of safety testing.

As mentioned earlier, in 1993 E21R had been in-licensed from Medvet, which was the commercial arm of the Institute of Medical and Veterinary Science (IMVS), the overseeing organisation for the Hanson Centre for Cancer Research where the original research scientists had emanated from: Professor Angel Lopez and Professor Mathew Vadas. In simple terms, the deal involved BresaGen producing the hormone, securing regulatory approvals and marketing it, with the IMVS receiving a royalty.

### **Human Growth Hormone (hGH)**

Leading into the floating of BresaGen, the Prospectus detailed another technology that BresaGen had been working on, an advanced process to make human growth hormone.

In a profile of the company in the *Bioshares Magazine* (2000) it read:

BresaGen have developed non-patent infringing methods to manufacture hGH. This is an extremely lucrative product, which BresaGen could be manufacturing and selling in Australia in 18 months. Bioshares estimates the value of this at A\$0.60 per share. The global market is worth about \$1.8 billion (hGH sells for US\$30,000 a gram). hGH may be worth A\$5.30 per share if BresaGen is able to enter the world market in 24 months time. The company claims they can undercut the market substantially and is confident they have significant pricing power at their disposal. (Bioshares, June 2000, p. 14)

The strategy for this project was to register the product as an Active Pharmaceutical Ingredient (API) with the FDA and an Active Substance (AS)

with the EMEA. Both agencies recommended a procedure called Drug Master File (DMF) to 'register' the active. The DMF was necessary if BresaGen wanted to sell the API to other companies for use in their final product. On achieving registration as an API or AS it would open up the possibility of sale of clinical grade hGH to drug delivery companies. (Edgar Online, 27 August 2003, p.32)

In fact, Allan Robins gave a very detailed explanation of exactly how this research came to be and, like most of the technology within the company, it had be derived from previous research and re-jigged, re-hashed, re-invented to get the maximum potential out of it:

When I come into the company [1991] I said this pig growth hormone idea - transgenic animals maybe - but the idea that you're going to put up a 50,000 litre fermenter, have millions of dollars worth of stainless steel and you're going to have to sell this stuff at A\$10 or A\$20 a gram doesn't make any sense. We should be looking at human health and so we had been playing around in Julian's lab with a human growth hormone gene.

We looked at the intellectual property position on human growth hormone and it turns out it's been around for a long time. People had previously been isolating it from cadavers and injecting it into children of short stature, pituitary dwarfs and girls with Turner Syndrome and there were three or four players making it and selling it. That was the birth of our idea to have a generic biopharmaceutical and I guess that would have been probably '92, '93 we started making human growth hormone.

We started collecting physicochemical data on that human growth hormone. We had meetings with the TGA to see if we could convince them, even though it was a biological it's not post translationally modified, it's a relatively simple four-alpha helix bundle protein, the structure is very well known, to see if we could convince them that using physicochemical data alone you could show equivalency which is what they do in the drug world. I think we got quite a way down that track. (interview, 2007)

Moreover, this action would lead to the eventual position being offered and taken up on the Board, as Robins stated:

It was actually where we met Geoff Vaughan who ended up on our board. He was the head of the TGA at the time but I think some of the big pharma companies got wind of the fact that we were doing this and so put a harder press on the TGA or PBS or whoever to make sure that this didn't happen. (interview, 2007)

Bastiras also spoke of the research that he and Robins were involved with around that time and characterised the work they were undertaking in the early nineties as being influential:

The next influential period was around that time we decided [to do] some R&D work in looking at expressing proteins. And eventually we came up with the idea of way back in 1992-93, came up with the idea of perhaps making biosimilars or biogenerics. So that's trying to make copies of biologicals, and our first role was going to be pursuing the growth hormone. So way back in 1992, we came up with a conceptual idea of producing a copy of one of the growth hormone molecules that were available on worldwide market. So we built on the protein expertise that we had when working on the porcine growth hormone project. And I guess that team slowly built up to several employees, and I think in about 1995, Meera Verma, who had been in charge of Bresa's marketing ... had been appointed as the general manager of the protein pharmaceutical division. So Meera joined the group, and she basically gave the R&D group some sort of leadership in terms of managing the group. (interview, 2007)

## **Xenotransplantation**

In 1999, another agreement was signed by BresaGen, Baxter Healthcare (Illinois, USA), and Nextran Inc. (Princeton, NJ, USA, a fully-owned subsidiary of Baxter) and St. Vincent's Hospital, Melbourne, and BresaGen Xenograft Marketing (BXM).<sup>16</sup> This agreement was a continuation of the Xenograft Syndicate that commenced in 1994.

BresaGen granted a licence to St Vincent's Hospital (Melbourne) to enable St Vincent's Hospital (in combination with other intellectual property) to grant a core technology licence to the Xenograft Syndicate. The Xenograft Syndicate engaged St Vincent's Hospital to act as researcher and St Vincent's Hospital engaged BresaGen as a sub-contractor to undertake a component of the research. The intellectual property developed by the Syndicate could be commercialised by BresaGen Xenograft

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<sup>16</sup> BresaGen Xenograft Marketing, which was a joint venture between BresaGen and St. Vincent's Hospital)

Marketing Pty Limited (a company 50% owned by BresaGen and 50% owned by St Vincent's Hospital) subject to payment of agreed royalties. These were 2% for Xenograft and 10% for all other research results.

The connection with Baxter involved BresaGen Xenograft Marketing Pty Limited entering into a licence agreement with Baxter Healthcare in relation to Xenograft applications of the technology in return for an agreed royalty of 5% of revenues of Baxter and sub-licensees. BresaGen Xenograft Marketing Pty Ltd was entitled to commercialise the research results of the Xenograft Syndicate in relation to other applications.

The agreement (the extension of the Syndicate) provided research funding that would support continued xenotransplantation research at BresaGen specifically in the area of pig cloning technology and was a continuation of a xenotransplantation<sup>17</sup> research program that been funded between 1994 and 1999 by a Research and Development Syndicate. The research leader of this R&D Syndicate was St. Vincent's Hospital with BresaGen the subcontractor. Baxter/Nextran would continue to retain exclusive Intellectual Property commercialisation rights for xenotransplant applications of the research, and the Syndicate Investors, through the commercialisation and marketing entity BXM, would retain rights in all other areas (Australasian Biotechnology, 1999).

As part of the 1999 deal, BresaGen Xenograft Marketing Pty Ltd negotiated with the Xenograft Syndicate to amend the Syndicate documents so that royalties in relation to research results other than Xenografts would be calculated only on royalty receipts by BresaGen Xenograft Marketing Pty Limited and excluding sub licensees.

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<sup>17</sup> Xenotransplantation (*xeno-* from the Greek meaning 'foreign') is the transplantation of living cells, tissues or organs from one species to another such as from pigs to humans (see Medical grafting). Such cells, tissues or organs are called xenografts or xenotransplants

Royalties on Xenograft applications remained calculated based on receipts by BresaGen Xenograft Marketing Pty Limited and sub-licensees (including Baxter Healthcare). BresaGen was not exposed to the same type of taxation related risks in relation to the Xenograft Syndicate as it was in the Transgenic Syndicate. The research funding for the Xenograft Syndicate ceased on 30 June 1999 at the end of the agreed research period. (BresaGen Prospectus, 1999)

BresaGen's role was to produce genetically modified pigs whose organs, e.g. hearts and kidneys, were suitable for transplant into humans (xenotransplantation). The program was conducted in collaboration with St. Vincent's Hospital, Melbourne, and was funded through an R&D<sup>18</sup> syndicate. As part of this program, cloning technology was being developed which would also enable genetic manipulation of pigs by eliminating, or 'knocking out' genes in the pig genome. It was also thought that the development of cloning technology in pigs could also have agricultural applications. It would allow pig producers to obtain large numbers of identical individual pigs derived from current best stock. Availability of cloned animals would substantially speed up the process of transmitting their current best genetics from breeding herds into production

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<sup>18</sup> Research and development syndicates were a structured funding mechanism whereby a researcher gained funding from an investor to complete a R&D project and the investor and receive tax benefits, the R&D project had to involve innovation and technical risk which had to be real and substantial. These syndicates are no longer available. During the 1990s, Macquarie Bank Ltd organised two &D syndicates where BresaGen was involved as a subcontractor. Some A\$18 million of work was contracted by 30 June 1999, when the second contract finished.

The work has involve developing the technology for genetic manipulation and cloning of pigs, with the objective of one of the syndicates contributing to an international effort to produce pig organs suited to transplantation into humans (xenotransplantation). While most of the project milestones were achieved, other problems not anticipated at the start of the program have added to the difficulty in genetically manipulating pigs for successful organ transplant into humans. Rights to the xenotransplantation application have been licensed to an international pharmaceutical company in return for a royalty on product sales. Other applications of the syndicate funded technology have commercial potential in the area of animal production and attempts are being made to secure further agreements to extend and commercialise this work. BresaGen, through subsidiaries (and associated companies) that have secured commercialisation rights to this technology, stands to benefit from any further commercialisation activity. Many of the skills developed in these projects are relevant to cell therapy and some of the employees involved in the syndicated research may be transferred to the cell therapy project.

herds.

Smeaton (2007) explained how BresaGen came to be involved with this research:

Well, that was through Tony D'Apice in Melbourne and we were faced with an interesting choice between McKenzie and D'Apice who were both claiming much the same thing. We chose to go with D'Apice. He was with St Vincent's. He was a transplant surgeon. He was interested in the whole pig thing, of what we were doing with pigs at that stage, because of xenotransplantation. It was all very relevant to xenotransplantation and was a bit sort of buzz thing in those days. Tony had a contract as a researcher from Baxter. So he was the connection to Baxter and it got – and he sort of put a whole thing together there. (interview, 2007)

Furthermore, Robins added some insight into the workings of the deal between Baxter and St Vincent's:

Tony D'Apice already had a deal with Baxter. When I say deal, they were funding research in the laboratory. I think it was the Mayo [they eventually sold their rights to]. So there were two companies involved, there was us and there was Nextran. They ended up doing a deal with Nextran and not with us. [So that one just sort of got closed down eventually]. We had syndicate money to support that so it was ongoing with D'Apice's group and I think some of that work is probably still ongoing. (interview, 2007)

Invariably, Seamark's roots extended into this work, as he explained when asked he had been involved with the xenotransplantation work. Naturally, he had a very long association with some of the founding scientists:

Yes, we were [involved]. In fact, we were associated with David White and the Cambridge Group. We had David White, who was the fellow who developed cyclosporin. I have forgotten how I got to know him, but somewhere along the line, he came out [to Australia] to see whether we would be willing to provide a service in this regard, and he was very interested in us doing that.

Eventually, he decided against it and gave it to an old mate of mine from Cambridge. In fact, the person who first introduced me to pigs, a fellow called Chris Bolsch, so there were government incentives set up to help persuade him. He probably used us in part as a leverage, but I got stuff from the Australian ... work there, and then he would have gone off and used that, and that's fair enough. But we kept a strong interest in what went on, and

eventually tied up with some medicine people to develop an alternate understanding of major attributes that were involved. But in order to do that, we had to develop cloning technology, because it required gene knockout, and so one of the drivers for us to develop clone technology was to service that project, but there were many others too. (interview, 2007)

Bastiras provided some more clarity as to why the xenotransplantation work kicked off:

... [R]ather than sort of relinquishing all of that technology [with pig transgenics] and know how that they'd developed in the gene manipulation area, they sort of used the same people to get into an area called [xenotransplantation] ... what was the next thing. So the same people, the same team, went on to work on xenotransplantation. And then that same team, the same people, went on to do stem cell research. So the reason the company was two pronged, was that the key arms of research were being done by the same group of people. (interview, 2007)

Ultimately though, this deal would fall away due to a very set of unpleasant circumstances that were not obvious to BresaGen at that time. Smeaton explained:

some of the pig data was falsified a little bit there. Yeah, some of the key transgenic data though, that was our first encounter with data fraud. There was a guy who had worked in Seamark's department then came to work for the company, and he falsified data in terms of pig embryonic stem cells. This happened at just the time we did the deal with Baxter and we didn't know, and as soon as we did know – Allan was the one that found this out – we instantly dismissed this guy. There was a confidentiality agreement – so I can't tell you [any further details]. As soon as we knew, we advised Baxter and that really sort of hung over that relationship from that day forward. That was very costly because they didn't really believe that we didn't know. These things can have very [bad long term impact.] (interview, 2007)

## **Consolidating into 2 Key Divisions: Cell Therapy and Proteins**

Leading up to the major event of 1999 for the company, namely the Initial Public Offering (IPO) on the Australian Stock Exchange in September, BresaGen had grown its their staff numbers to an impressive 46 employees and 19 with post-doctoral experience. This experience spanned such fields as biochemistry, molecular biology,

embryology, cell biology, chemical engineering and bioprocessing. (Australian Biotechnology, 1999)

Moreover, BresaGen had a stellar Scientific Advisory Board comprising experts with pre-eminent international reputations:

BresaGen has a Scientific Advisory Board (SAB) *Bioshares* believes is the envy of every other biotech in Australia. The SAB includes Australia's most recent Nobel Prize winner for Medicine, Professor Peter Doherty. The SAB is comparatively large, comprising eight members. The SAB reflects associations with the University of Adelaide, St Jude's Research Hospital, the University of Georgia, the National Institute of Medical Research (London), the Walter and Eliza Hall Institute (WEHI), St Vincent's Institute of Medical Research and the University of Arizona. This is one of the most outstanding advisory boards in Australia. At the most basic level a SAB gives a 'public relations' edge to a company's technology development program. The presence of North America based members on BresaGen's SAB means the company is promoted in research and investment circles in the USA. (*Bioshares Magazine*, 2000, p. 13)

Table 5 below shows adjusted historical financial details for BresaGen in 1996, 1997 and 1998. The Prospectus also noted there was still a potential liability with respect to the put option that was set up allowing MBL to disengage itself from the Transgenic Syndicate. Luminis agreed to provide funds to BresaGen to help satisfy this requirement. The put option price could vary in certain circumstances but as at the anticipated date for the unwinding of the Syndicate, it was expected to be approximately A\$45 million.

**Table 5: BresaGen's Financial Performance 1996-1998**

<b>Years ended 30 June</b>	<b>1996</b>	<b>1997</b>	<b>1998</b>
	<b>Audited</b>	<b>Audited</b>	<b>Audited</b>
	<b>\$'000</b>	<b>\$'000</b>	<b>\$'000</b>
Operating Revenue (1)	3,493	3,225	3,227
Research & Development expenses	4,589	4,604	5,304
Operating Profit/(Loss) before depreciation & amortisation	(856)	(1,515)	(2,185)
Depreciation & amortisation	(527)	(301)	(307)
Operating Profit/(Loss) before tax	(1,383)	(1,816)	(2,492)
Income tax expense			
Operating Profit/(Loss) after tax (2)	(1,383)	(1,816)	(2,492)

**Source: BresaGen Prospectus, 1999, p. 44**

- Notes: 1. Operating revenue for the 1996 financial year has been adjusted to exclude sales revenue from the Company's Research Products division sold in December 1995 of A\$1.7 million, and gross proceeds from the sale of the division of A\$1.4 million. Operating revenue for the 1996, 1997 and 1998 financial years relates predominantly to syndicated research sub-contract income (1996: A\$2.8 million, 1997: A\$2.6 million, 1998: A\$2.4 million). Syndicated research sub-contract income of A\$1.3 million (unaudited) has been earned during the 9-month period ending 31 March 1999. The R&D syndicate contract finished on 30 June 1999.
2. Operating profit/(loss) for the 1996 financial year has been adjusted to exclude an abnormal income item of A\$1.2 million relating to the profit on sale of the Company's Research Products division.

Shareholding patterns had not changed considerably in the past several years, as is evident from the table produced for the Prospectus:

**Table 6: BresaGen's shareholding in 1999**

<b>Shareholder</b>	<b>%</b>
Luminis Pty Ltd	44%
American Cyanamid Company (a division of can Home Products)	15%
Hambro-Grantham Investments Ltd	14%
Cambooya Pty Ltd (a company associated with the Vincent Fairfax family)	14%
Biotechnology Investments Ltd	13%
<b>Total</b>	<b>100%</b>

**Source: BresaGen Prospectus, 1999, p.9**

In the Prospectus, BresaGen presented itself as having consolidated their

business along two key divisions: (1) cell therapy or transgenics,<sup>19</sup> using healthy cells to replace diseased non-functional cells, and (2) therapeutic proteins, using a proprietary bacterial expression system that cost effectively expressed and purified a range of recombinant proteins, including growth hormones and cytokines, on a commercial scale. Bastiras gave an honest account of how these two divisions emerged:

... [I]t's a long story ... BresaGen, I think, in its early days lacked a bit of direction in that the company was always quite diverse. I guess it stems from they had quite a spread of technologies, so much so, that by the time we listed – we really were two companies. One company was doing stem cell research, and the other company was doing protein recombinant ... purification ... manufacture, so two quite disparate arms, if you like. (interview, 2007)

In terms of understanding what was meant by 'Cell Therapy', the Prospectus explained it as:

Cell Therapy<sup>20</sup> is the use of healthy cells to replace diseased non-functional cells. This is a technology widely considered to be one of the major directions in the future development of medical practice. It is currently in use in clinical practice, but restricted predominantly to bone marrow transplantation and skin replacement. However, there are a large number of potential applications if the hurdles of adequate supply of cell materials, and the rejection of transplanted cells, could be overcome.

Recently recognised as a practical medical tool, Cell Therapy has the potential to revolutionise the treatment of intractable diseases such as Parkinson's disease where failure of cellular function will be treated by provision of cultured healthy cells. Emerging technology, to which BresaGen's intellectual property rights pertain, if successful, will mean that it will be possible for the patient to be offered cells which retain the patient's own genetics and avoid the rejection problems which limit the usefulness of current cellular transplantation therapies.

BresaGen would initially target the Parkinson disease market. However, many potential applications exist, including neurodegenerative diseases, e.g.

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<sup>19</sup> In a profile printed in *Australasian Biotechnology* 1999, the Cell Therapy was termed 'The Transgenics Division' with its focus being on research in the field of mammalian transgenic and cloning technologies. This division's efforts have resulted in a proof of concept demonstration of genetically enhancing growth rates and carcass quality in pigs through the introduction of additional copies of the pig growth hormone gene. The division operates at the leading edge of the application of molecular biology and cell and reproductive biology.

<sup>20</sup> Embryonic stem cells can be directed to follow a particular development route.

Alzheimer's disease, Multiple Sclerosis, and muscle wasting disorders, such as the muscular dystrophies. Additionally, gene therapy techniques could be used in conjunction with the Cell Therapy approach, to provide curative procedures for many common genetic diseases, including Gaucher's Disease and several bone marrow diseases, the haemophilias and possibly insulin-dependent Type-1 diabetes. The market potential for such cell therapies is large, with estimates made for a world market of US\$20 billion per annum for all cell and tissue therapies by 2007. (BresaGen Prospectus, 1999, p. 19)

A particular 'ace card up their sleeve' was the nature of the patents the company filed:

The first application describes identification of primitive ectoderm-like cells, their culture and back conversion to embryonic stem cells, and the second describes conditions for the reprogramming. The uniqueness of the technology is the identification of an intermediate cell phase that embryonic cells must pass through during or prior to differentiation. It is this cell stage to which the patent applications apply.

Other organisations may have patents on the use and modification of embryonic cells for therapy. These other companies, it is claimed, will need to access the Cell Therapy patents, if granted, in order to exploit their own technology. (BresaGen Prospectus, 1999, p. 32)

BresaGen had genuine confidence in the 'blue sky' value of this technology, as the Prospectus stated:

This is potentially the most valuable technology being developed by BresaGen. We concede that our valuation is conservative but it reflects the fact that proof of principle for cell reprogramming and hence therapeutic utility has still to be demonstrated. Concomitant with its high potential returns, are a significant R&D spend and high risk. The cost of initial investigations, to demonstrate that the technology is viable, however, is minor relative to the overall cost of developing a novel treatment modality. It should also be appreciated that this is a platform technology with considerably broader applications than the two currently proposed. The Company's strategy is to obtain proof-of-concept that cells can be programmed to become neuronal, blood precursor, or other cell types and to license the IP to a large pharmaceutical company. It is reasonable to expect that licences will be issued for various therapeutic applications. (BresaGen Prospectus, 1999, pp. 32-33)

Equally, the Prospectus detailed the company's plans for its other division,

which produced their range of therapeutic proteins:

The Company has developed the capacity to make a range of recombinant proteins including growth hormones and cytokines. A number of these proteins have the potential to be therapeutic drugs for human or veterinary use. Medically, protein drugs have been used to supplement a shortfall of the naturally occurring product in the body. They can also be used to target specific cell is in a variety of disease conditions.

Worldwide, the first recombinant protein drugs to be marketed were insulin registered in 1982 and human Growth Hormone registered in 1985. Since then a range of protein drugs including G-CSF and Erythropoietin have been developed and marketed by various biotechnology and pharmaceutical companies, contributing to a world market estimated to be in excess of \$10 billion.

BresaGen's first protein drug is EquiGen™ Injection, which is being marketed directly by the Company as a veterinary therapeutic. The Company plans to expand its marketing and distribution capacity as the product is registered for sale in additional territories. The drug will continue to be marketed directly by the Company in selected territories and distribution partnerships will be negotiated with appropriate animal healthcare companies to access markets in other major territories such as the USA and Europe.

The lead potential human drug (E21R) is in Phase I clinical trials as a potential treatment for certain cancers. The intellectual property and commercialisation rights for this and a related product are licensed exclusively to BresaGen by Medvet Science Pty Ltd (the commercial arm of the Institute of Medical and Veterinary Science).

A standard manufacturing process developed around a proprietary expression system and in-licensing of some steps of the processing technology is in place. BresaGen's manufacturing plant is licensed by the NRA to produce veterinary therapeutic products under GMP (Good Manufacturing Practice) and by the TGA to produce human therapeutic proteins under GMP The manufacturing plant is also ISO9002 accredited. The world market for protein drugs at that time (1999) was estimated to be in excess of \$US10 billion. (BresaGen Prospectus, 1999, p. 20)

The Prospectus also detailed two other fairly advanced products in the company's portfolio:

E13R (cytokine antagonist) is a potential asthma treatment. A patent application has been made to cover this molecule. The Company has identified a potential animal model for asthma and, if promising results are obtained, will progress the molecule through animal pre-clinical trials. Then if safe and effective the product may progress to human clinical trials. The long-

term strategy is to partner the molecule with a Pharmaceutical company after Phase I1 trials. The potential world market for asthma for treatment using E13R is estimated to be \$1 billion.

Canine somatotropin, a synthetic form of dog growth hormone, is being safety tested. The strategy is to register the product for healing of fractures. A number of studies have already shown that the molecule is likely to be efficacious for this use. Going forward, the Company will seek to register the product in Australia and other territories while new trials are conducted with a view to broadening the indications to include treatment of obesity in dogs. The world market for all potential uses is estimated to be \$500 million. (BresaGen Prospectus, 1999, p. 22)

For the key products discussed, E21R, EquiGen, canine somatotropin and cell therapy, an independent expert valuation performed by Acuity Technology Management was tabled for the potential shareholders give the minimum and maximum estimation of value. The range of values estimated by Acuity is shown in Table 7:

**Table 7: Estimated Value of E21R**

	Lower Value	Upper Value
E21R	\$9.6m	\$11.6m
EquiGen™ Injection	\$7.0m	\$8.5m
CST	\$8.6m	\$2.5m
Cell Therapy	\$1.5m	\$2.5m
	\$26.7m	\$33.3m

**Source: BresaGen Prospectus, 1999, p. 13**

In terms of the state of development for each of their products, the following figure summarises their position, as wells as each product’s estimated worth with respect to potential sales revenue.

**Table 8: BresaGen's Drug Development**

	<b>Application</b>	<b>Potential World Market</b>	<b>BreasGen's Product/Project</b>	<b>BresaGen's Position</b>
Cell Therapy	Parkinson's disease	\$1.6 billion	Neural cell implants	Discovery R&D
Therapeutic Proteins	Breast cancer	\$2 billion	E21R	Phase I clinical trial
	Myeloid Leukaemia	\$300 million	E21R	Phase I clinical trial
	Asthma	\$1 billion	E13R	Discovery complete
	Human growth hormone	\$1 billion	hGH	Pre-clinical feasibility
	Horse growth hormone	\$200 million	EquiGen <sup>TM</sup> Injection	Australian Registration
	Dog growth hormone	\$500 million	cST	Safety trials
	<b>Total</b>	<b>\$6.6 billion</b>		

**Source: BresaGen Prospectus, 1999, p.7**

Regarding the company's longer term plans for cell therapy and proteins, the Prospectus stated:

Having secured a key patent application in this area, BresaGen intends to add value to the project by defining and achieving key research milestones including demonstration of a positive effect in an animal model of disease\*, eg, Parkinson's Disease. If achieved this may add considerable value triggering alliances with major pharmaceutical companies to partner the clinical trials, registration and marketing phases of this product category.

Additional sources of funding, i.e. via grants such as R&D START, will also be sought to fund some of the pre-clinical and clinical studies. *\*Achievement of this milestone within three years will result in a milestone payment to Luminis of 500,000 shares and A\$500,000 in cash or shares at BresaGen's discretion.*

BresaGen has developed a robust manufacturing process for the production of high margin protein drugs. Licenses to manufacture both human and veterinary drugs under GMP are in place with the TGA and NRA respectively. The Company is in a position to manufacture a number of human and veterinary therapeutics and progress them through clinical trials.

BresaGen intends to drive some of these opportunities through registration and marketing in selected territories while other novel human therapeutics, if effective, will be partnered with major pharmaceutical companies during Phase II clinical trials. (BresaGen Prospectus, 1999, p. 24)

Moreover, alongside its two major research streams, BresaGen also had its record of GMP manufacturing. Its plant was designed for the mass culture of genetically modified bacteria (specifically recombinant E. coli) and the recovery and purification of proteins expressed by the bacteria:

In parallel with its core scientific strengths, BresaGen continues to build a manufacturing base for the production of recombinant proteins. This base is strengthened by a growing expertise in regulatory compliance with Good Manufacturing Practice. From its earliest days, the company recognised the benefits of establishing external links to complement its core capabilities and streamline the development process and successful partnerships have been set up with industry, as well as with groups in Universities and Research Institutes, in Australia and abroad. (BresaGen Prospectus, 1999, p. 24)

The plant also had approval from the National Registration Authority (NRA) for veterinary products Australian Genetic Manipulation Advisory Committee (GMAC) guidelines for large-scale work with recombinant organisms. It was intended that BresaGen products would be manufactured in Australia, except those produced under licence. The GMAC guidelines were the only genetic manipulation guidelines or regulations that are necessary for sale of product overseas (BresaGen Prospectus, 1999, p.34).

In the first half of 1999, the key executives were preparing the Prospectus documents and gauging interest from the investment community. However, even with a ‘decent’ portfolio under the dual umbrellas of cell therapy and protein, some people in the company thought that might be a ‘tough sell’ considering the company was aiming to raise A\$12 million. Consequently, it was decided that some ‘sexy’ IP should be included into the portfolio. Bastiras explained the logic underpinning this decision:

we always were a protein focused company, and then it became proteins and molecular biology with animal husbandry, with Bob Seamark in that, and transgenics, xeno, stem cells. And the stem cell decision came about purely because in the middle of 1999, we were looking to float the company. And the senior management team went off to speak with various brokers,

underwriters etc, to try and fund the group that had E21R, a promising drug that was completed to phase one trial, and was about to start a phase two trial for the treatment of leukaemia. It had a registered equine growth hormone on the market, EquiGen. And it also had a team looking at producing the world's first biogeneric, so yeah, a lot more than a lot of other companies at the time. For example, Metabolic in Melbourne floated and raised A\$12 million on the strength of just one molecule, this anti-obesity drug that they're still pursuing. But we couldn't raise money for those three projects, so to feed that – I was involved in those. But all I can say, is why shouldn't we raise money for those two projects, probably because the team that went off to try and sell the idea ... to have a product. And the product was those three goals, but they just couldn't sell it to people who had the money to buy it. They were told, look, this isn't sexy enough, go away and come back with something else. And that's when they bumped into, well Allan Robins had been a mate of Peter Rathjen's, and they dreamed up this – we can get into stem cells. So they went away and just rewrote the prospectus, and said we're going to do those three things plus stem cells. (interview, 2007)

One of the executive directors of BresaGen from 2000 until 2004, Dr Chris Juttner, confirmed Bastiras's impression of the situation leading up to that decision and the impact the inclusion of the stem cell therapy IP had on the University:

... the IPO was very much based on Rathjen's work. That was the highly prospective major upside stuff. I remember being very surprised that the company had made a commitment to give Rathjen A\$6 million or something.

It was very difficult [for Luminis to consent to this as it was highly unusual that a scientist and employee of the Uni be paid such a large figure for their research]. But Rathjen had had a long relationship. He was chairman of the Scientific Advisory Committee [of BresaGen] and had been for some time, so there was a close relationship between Rathjen and Smeaton and Robins. And it was an opportunity, it was a major opportunity. (interview with Juttner, 2007)

Consequently, a deal was negotiated between the company, the University of Adelaide and Professor Peter Rathjen<sup>21</sup> to acquire Rathjen's technology concerning

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<sup>21</sup> He is a leader in the applications of stem cell technology. He has performed ground-breaking work and generated important intellectual property in an area of research directly relevant to cell-based therapies. Professor Rathjen was the 1985 recipient of a Rhodes Scholarship and completed his doctoral and post-doctoral studies at Oxford University in 1990. He is presently Head of the Department of Biochemistry at the University of Adelaide. Professor Rathjen is currently Chairman of BresaGen's Scientific Advisory

stem cells. The deal took into consideration the legality of the patents and was structured as follows:

Through an agreement with Luminis, Professor Peter Rathjen will direct the science on the cell therapy programme. The research results from this work have been the subject of a patent application. Under the terms of the agreement between BresaGen and Luminis, BresaGen will own existing and future intellectual property generated by the research program to be conducted by Luminis which BresaGen has agreed to fund up to A\$6.2 million over 3 years.

Luminis will ensure that Professor Rathjen devotes at least 60% of his time and attention during his normal working hours to the Research Program. Professor Rathjen will direct the science of the Research Program (unless BresaGen otherwise agrees) and will be responsible for selection, direction and allocation of tasks to technical staff. Luminis has concluded a 3-year service contract with Professor Rathjen to secure 60% of his time and attention during his normal working hours. (BresaGen Prospectus, 1999, p.58)

Whilst the press release seemed like a simple document, the negotiations that had gone into the Rathjen – Luminis deal were anything but straightforward as Hart, at that stage the head of Luminis, explained:

Of course, come the IPO time ... flogging the [story] – if you like – the story around the brokers, you know, there was this continued divergence between those who were saying stick to your knitting and those who are saying its not sexy enough. Let's go with the stem cell, sort of thing. Well, that was where I [had to get involved] – because, if you like, my major involvement came because it was Luminis who was controlling Peter Rathjen or who owned – I mean, after the university, Peter Rathjen's IP. [I was wearing my Luminis hat] very much so. I was the director of, then, BresaGen. As far as I was concerned, I was acting for Luminis and therefore the university. Over some very long nights, there were some very serious conversations. I always wanted to put Rathjen's IP out to the market, just the market. I'm not saying BresaGen didn't have the rights to bid for it, if you like, but I was convinced that if Peter Rathjen's IP was as good as Peter Rathjen said it was, that ... there were runaways to commercialise it. My view is it should have been sold off. If it was as good as Peter Rathjen said it was, it should have been sold off to an American company ... either licensed out or sold. (interview with Hart, 2007)

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Board and serves on a subcommittee of the South Australian Council on reproduction which is addressing the issues arising from applications of cloning technology.

Rathjen though, according to Hart, had clearly decided he wanted his IP to be involved with his colleagues at BresaGen. As Hart explained, ‘... the nub of it all was ... in the end, BresaGen convinced Peter Rathjen into going with them, to the extent that Peter Rathjen was [holding me to ransom] – essentially he said to me ‘Well, okay you might own the IP on behalf of the department and me and all the rest of it, sort of thing.’ But he said ‘I go with BresaGen [or I am] going to make it public’ (interview with Hart, 2007).

For Hart the saga did not stop there:

So the IPO got up. That’s fine. There was an agreement with the university to fund Peter Rathjen’s work, I think. Peter Rathjen had, if you like, an agreement with Luminis, with respect to his ownership or his being the beneficiary of, if you like, a certain amount of the shares. That caused enormous angst inside the university, particularly with Mary [O’Kane]. I don’t know why, but she just was just dead-set against BresaGen, for starters, for some unknown reason and certainly dead-set against the fact that Peter Rathjen was going to end up with being the beneficial owner of two million shares.

[The old 90/10 rule of profit sharing] got changed to the third, a third, a third rule about the time, in 1990 when I took over at Luminis. So, of the six million shares that we got, as a result of tipping Rathjen’s IP into the flow, Peter Rathjen and his wife were the beneficial owners of two million shares. This caused – you’ve got to believe – unbelievable angst inside the university and the university community. (interview, 2007)

Besides being relevant to the market needs at the time, i.e. a strong interest in stem cells especially in the United States, there was an intrinsic connection to the IP that had been developed through Bresa and Bresatec’s earlier work with porcine growth hormones and pig transgenesis. As Smeaton explained, ‘I think that’s where we sort of got into stem cells; we pulled that apart from the pig stuff. So we pulled that technology in from the university and that gave us a bit of extra oomph for the float’ (interview, 2007).

At the time of the writing of the Prospectus, the Transgenic Syndicate was still

being audited, which was seen as a ‘material risk’. On the positive side, the Prospectus also highlighted the linkage between the research conducted in the 1990s and how it could be utilised in the current research environment:

The development of expertise in animal embryo manipulation, supported by Research and Development Syndicate contracts, now combined with the proposed acquisition (subject to the successful completion of this Offer), of intellectual property developed at the University of Adelaide presents a possibility for the Company to become an early leader in Cell Therapy. (BresaGen Prospectus, 1999, p.19)

The IPO finally took place on September 21, 1999 and A\$12.0 million was raised in an initial public offering in Australia by offering and selling 12,000,000 ordinary shares at an issue price of A\$1.00 per share. Immediately after that offering the company had 30,000,000 ordinary shares outstanding, which were listed on the ASX. The market capitalisation was estimated to be as high as \$90 million. Verma felt that this was really the beginning of BresaGen, ‘Really when we went to IPO in ’99 is when you can talk about founding of the company’ (interview, 2005).

## **Media Stars**

In October 1999, Drs Vadas, Lopez and Professor Rathjan, gave an interview to Leigh Dayton of the ABC’s scientific news show, called Quantum, detailing how their E21R discovery came about. The interview was prefaced by Dayton’s explanation of the basic concept of E21R’s mechanism of action: ‘You see, E21R is the first of a whole new class of cancer drugs. Unlike conventional medications that blast both cancerous and healthy cells, E21R is highly selective. It targets a single protein, one which regulates the growth of normal blood cells and some cancer cells. And that makes medical researchers very happy indeed’ (Dayton, 1999). The interview then proceeded:

**Quantum:** The story of E21R began in an Adelaide café. Matthew Vadas and

Angel Lopez were having a chat. The topic was a protein, a growth hormone called ‘granulocyte-macrophage colony-stimulating factor’, GM-CSF for short. Moreover, healthy humans need GM-CSF to regulate the production of blood cells which help fight infection. So Mathew and Angel decided to take the protein apart, hoping to gain important scientific and medical insights. Moreover, healthy humans need GM-CSF to regulate the production of blood cells which help fight infection. They already knew that GM-CSF was made up of a long chain of building blocks, much like these paper clips. But how did it work?

**Mathew Vadas:** So what we decided to do is just to cut pieces of the end of it off, or actually replace some of these building blocks with another building block. And one of these replacements turned out to be especially informative.

**Quantum:** That’s science speak for ‘really important’. Now, what Mathew and Angel had found was that replacing building block 21 - an amino acid called glutamic acid - with another one, arginine, seemed to block the action of GM-CSF. This was an amazing discovery. It suggested that this re-jigged protein, which they called E21R, might stop some cancers dead.

To find out, they whipped up a batch of pure E21R in Angel’s lab, part of the Institute of Medical and Veterinary Science. It took an entire nail-biting year. At last, all was in readiness. The first experiment of an incredible week began, as a team member carefully added E21R to cultured cancer cells.

The result was astounding - their designer growth factor stopped cancer cells dead. This seemed too good to be true. But more experiments confirmed the finding. Moreover, other tests revealed that E21R also prevented ordinary GM-CSF from stimulating cancer growth. An astounding feat!

Did they bring out the champagne at that point? Next day, that’s just what they did! And once more, E21R halted the growth of cancer cells. It worked like this: the replacement building block in E21R locked onto the cancer cell, preventing the *real* building block from attaching and becoming active.

**Mathew Vadas:** Well at the end what we had learnt is that we really had a decoy molecule. This decoy molecule was able to bind on a normal receptor and prevent the real molecule from binding. And thereby preventing a lot of the biological actions that were important to the growth factor that we we’re trying to block. And this has medical and scientific importance.

**Quantum:** That evening, a very excited Angel went to his regular Thursday night soccer practice. After training he went out for a beer with Peter Rathjen of the University of Adelaide.

**Peter Rathjen:** It was pretty obvious from what Angel told me up-front that he had something that was very exciting, and at the time I don’t think he knew that I was the Chairman of the Scientific Advisory Board of a company called BresaGen, a biotech company which had been set up within the

Department of Biochemistry where I worked, and I asked if he'd mind if I took it to them to see what they thought of it. They were very interested also and really preceded extremely fast from there.

**Angel Lopez:** That's right.

**Quantum:** So guess what happened on Friday.

**Matthew Vadas:** We had a lots and lots to drink. (laughter). Lots and lots of celebrations.

**Quantum:** With BresaGen on side, the team quickly moved to test E21R, first with mice, then baboons. And last July Des Norris became one of the first six people-each with advanced cancer - to trial the drug. Today, his tumour has stabilised, maybe thanks to E21R. If so, that's very unusual so early in the life of an experimental drug.

The timing of this interview was ideal, with BresaGen having floated only one month earlier, in September 1999.

## **Alza Deal**

Also in October 1999, an interim agreement was signed to develop a sustained release formula for EquiGen with a US company called Alza Corporation. Under the agreement, the parties would develop a product incorporating EquiGen in Alza's injectable sustained release delivery system and BresaGen would test the product in a clinical trial in horses. If preliminary work was successful, it was expected to take between 18 months and two years to develop a new generation slow release EquiGen product (BresaGen Press Release, 13 October 1999).

Allan Robins clarified what had been driving this research collaboration:

... [W]ith the equine growth hormone we were looking at ways of maybe [changing the delivery system] - one of the problems is you have to give at a daily injection so we were looking at ways that we might be able to get around that and so we ended up working with Alza which had all sorts of interesting technology.

One of the guys who worked at Alza was a guy called Steve Prestrelski. J&J

[Johnson & Johnson] acquired Alza, that group got broken up, Steve left. He went to work for a company called PowderJect. PowderJect spun part of their technology out into AlgoRx and so that's how we got involved with - we already knew Steve because he'd been working on a project we worked on at Alza to try to develop some sort of sustained delivery for equine growth hormone. (interview, 2007)

Overall, though, the deal did not amount to anything significant, as Smeaton explained:

In the end that didn't really come to much. We made a few visits there and got to know a guy called Jim Brown who subsequently went [on to another company] – he took that stuff out. Was it Xeriject or something like that? It was a little implant. But he started another company with a couple of people which assumed that Alza decided not to go through with that technology. (interview, 2007)

Seamark added his thoughts on the issue of using injectable products:

American scientists are interested in two things. They are interested in the growth hormone and at the time, there was discussion on injectables ... - injecting growth hormone is not simple. It requires repeat injections unless you put it in with something that delays the release of the hormone. And one of the things we were arguing is that you couldn't have - if you put in too high an amount, then you would be in trouble, you would cause the pig [or other animal] ill health, so we wanted one injection lasting for a long while. So that was the technology needed for the development. They had things being developed for the cow industry at the time, that were being used in the dairy industry, but cows are available every day, so it's easy enough for a farmer to just inject the pigs. They learn very quickly that if you come in with a needle, they are not interested in you. (interview, 2007)

## **BresaGen Inc.**

With the company successfully floated, the need to move ahead with the stem cell research was pressing. As a result, in November 2000, BresaGen acquired CytoGenesis Inc., a company focused on cell therapy products to treat Parkinson's disease. The key CytoGenesis founders included Dr Steve Stice, a pioneer in therapeutic cloning technologies, Dr Mike Moseley of Stanford University, and imaging specialist Dr John

Kucharczyk. The main attractions for BresaGen to acquire the firm were the skills of the research and management team, and its work in developing proprietary cell delivery and imaging systems in the treatment of Parkinson's disease. This acquisition meant that BresaGen acquired technologies being developed to accurately deliver cells into the human brain and to monitor the well being of transplanted cells. The CytoGenesis Inc. acquisition also meant that BresaGen had access to medical device and brain imaging technology for the cell-based treatment of neurodegenerative disease.

The technology could provide a safe and accurate means of delivering cells to the brain of Parkinson's disease patients and with the company's own cell biology R&D into controlled and directed cell development, the catheter and imaging technologies provided BresaGen with an integrated set of technologies with which to target the treatment of Parkinson's. With less than 150 neurosurgeons in the USA capable of surgically treating Parkinson's disease, the value of a vertically integrated solution was that it would standardise the treatment processes. BresaGen began working to develop a kit that contains all a doctor will need - the defined dose of cells, the catheter, and imaging software. (BresaGen Press Release, 29 August 2000)

The acquisition of CytoGenesis and its merging into BresaGen was in line with the stated goals of the Prospectus, but moreover, it served as a catalyst for BresaGen to set up operations in the United States. Out of this BresaGen Inc. was registered and found a new home at the University of Georgia in Atlanta. Juttner explained why he felt the Board of BresaGen supported this decision:

... [A]t the time I joined [BresaGen], they were in the process of purchasing the company CytoGenesis, and I supported that venture, because it seemed a smart idea. And that was incorporated into a view that some of the company, for the cell therapy work, should move to the US. Which was argued and the board supported it on the basis that it was likely to be easier to raise continuing funds in the US for something like this. That indeed happened early in 2001. (interview, 2007)

The year 2000 was capped off in late December by signing a deed activating a Commonwealth Government A\$4,928,550 R&D Start Grant that had been awarded during the year. The funds received were to support the cell therapy program for a period of 3 years commencing 1 June 2000 and the grant provided up to 50% of the costs incurred by the company on the research.

The Atlanta labs were opened almost a year after buying CytoGenesis, in October 2001. Smeaton spoke about how they came to find themselves setting up a company within the halls of the University of Georgia:

Well, I was always keen on the US, but by that stage, probably Allan Robins and I would've been the main drivers of that. [As to why the University of Georgia] it's called a bribe. Yeah, I mean, they gave us a huge deal. We looked at California, which was the logical place to go, but you know, for communications, time zone issues and where most of the industry was, that if we'd gone to California and the prices were completely out of sight. I'd sold a house in California when I went to Australia but couldn't afford to buy back anything. And for any of the sort of scientists that we wanted to hire, they'd have had to live an hour away from work or more and live in a tiny little place in pretty substandard conditions because of the just extraordinarily high costs in California. So we looked there and we looked at – we had a consultant in Denver, and Denver was redeveloping the area which had been the old Staple Command Port and that sort of looked mildly interesting, but they weren't offering any sort of super deals. But Georgia [was] and one of our consultants was there, Cliff Baile. He had said, hey, you guys really ought to be looking at Georgia. So we did and the State of Georgia offered us a deal which we couldn't turn down. It was basically a million bucks worth of equipment and stuff. We needed the support and they came through on that, and that's actually worked out really very well. It's still happening. (interview, 2007)

Robins added, ' ... [W]e had zero capex budget coming here, whereas California was just interested in how much tax you're going to pay. Plus there's innovation grants here so we can work with the universities in Georgia and we can get sponsored research supported dollar for dollar by the state. There was a lot of economic reasons to come to Georgia. It is, I have to say, a very nice place to live so I think it was the right decision.' (interview, 2007)

There were other benefits to arise from being situated in Atlanta – namely the close proximity to Washington DC to attend any hearings required by the FDA, ‘Yeah, that’s right, it’s [the FDA] about an hour up the road, so it was a fairly easy commute. We were going to Washington on September the 11<sup>th</sup>, too. We were going to testify for a Senate committee on stem cells. So we were at Greenville Airport in South Carolina waiting for a plane to Washington when the guys hit the Trade Center’ (interview with Smeaton, 2007).

Allan Robins also detailed some of the challenges the company faced when they arrived in the US:

... [T]he company was incorporated as a Delaware company before we got here. When we got here BresaGen Inc. existed as a legal entity. We rented lab space off the university and that was one of those rude awakenings. I was the first person here so it’s sort of like you walk into a bare room and you don’t have a desk and the phone isn’t connected and you go down to Office Depot and you buy a desk and you buy a chair and you bring it back. Of course, everything comes in 20 bits and you put it together and ring up BellSouth and have the phone put on and quite a bit of time not doing anything. We hired a few people, I brought a few people over from Australia and we built the team from there. (interview, 2007)

The management of the company was still very much integrated with the Australian team:

There was involvement from Adelaide ... I mean, actually we were on the phone most nights of the week to Adelaide. John Smeaton and myself are over here so he was the CEO of the company. I was still the Chief Scientific Officer of the company. We had Meera [Verma] and Chris Juttner and Linton Burns and Jackie Zanetti so we had other senior managers back in Adelaide. We would talk on the phone constantly and John and I both did five to six trips to Adelaide a year for board meetings or whatever. We had some board meetings over here as well. Basically it was still run as one company. BresaGen Inc. in some ways was virtual - it was the stem cell operation. Actually I was employed by BresaGen Inc. but John was still a BresaGen Limited employee and so we ran the company as one. (interview with Robins, 2007)

## **E21R – Safe and Maybe Sound?**

The year 2000 was one of activity and major milestones for BresaGen. At the same time as BresaGen Inc was making great inroads in terms of its cell therapy division, there was also much excitement and progress with the protein work. The initial safety and efficacy trials in humans for E21R that began in 1999 were announced as being successfully completed in June 2000. This had involved 19 patients receiving a daily injection of E21R for 10 days, and then monitoring the patients for a further 18 days. Consequently, Phase II was planned to begin in September 2000 (Press Release, June 28 2000).

Following on from the clinical successes, BresaGen signed a deal with a large UK pharmaceutical company, British Biotech Plc on 20 December 2000 for a global marketing and licensing agreement for E21R (BresaGen Annual Report, 2001). The deal stated British Biotech would carry out the clinical studies necessary to obtain regulatory approval for the treatment of acute myeloid leukaemia (AML) in Europe and North America, commencing with a Phase II clinical study, which was expected to start in the third quarter of 2001 in the UK, followed by Phase III studies also in the UK. BresaGen would be responsible for the manufacture of materials for clinical trials and commercial supply (BresaGen Annual Report, 2001).

For their part, British Biotech was granted an exclusive worldwide licence to commercialise E21R for all indications and would reimburse BresaGen for the cost of clinical trial supplies. In exchange, British Biotech would make an equity investment of US\$1 million through the issue of 1.1 million new shares at a price of A\$1.67 per share and British Biotech would make payments totalling US\$7 million that included an up-front payment and milestone payments conditional on the successful development and

approval of E21R for AML (BresaGen Annual Report, 2001). If the collaboration was successful in developing E21R for other indications, further milestone payments of up to US\$6 million for each indication would be payable to BresaGen. BresaGen would also receive royalties on sales of E21R.

As to how the initial contacts were made with British Biotech, Smeaton said, ‘the British Biotech deal that came in, I think, through one of Chris Juttner’s contacts’ (interview, 2007). However, Robins held the view that it was through another contact, ‘Michael [Elliott – Professor Bill Elliott’s son] basically knew some of the folks involved at British Biotech and so that’s how that introduction came about. We didn’t actually know Michael beforehand even though we’d known Bill Elliott forever’ (interview with Robins, 2007). Others though were not overly impressed by the use of personal networks:

I think some of the personal linkages were a bit too personal. It always came back to personal linkages. For example, the E21R link was a personal link. I think when British Biotech were looking at acquiring some IP, one of their global IP scouts was a guy called Michael Elliott, who was Professor Bill Elliott’s son ... You could say that the deal happened so that Michael Elliott could visit his family once every six months. So there’s things like that that happen all the time, and yeah, some of the connections that we’ve had, I think some of the connections weren’t necessarily good connections for the company, and they steered the company in the wrong direction. (interview with Bastiras, 2007)

## **The Pigs Return**

In September 2000, Macquarie Acceptances Ltd (MAL) exercised its put option<sup>22</sup> and BresaGen purchased all MAL’s shares in MS3 and the debt of A\$28,449,330 (the debt

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<sup>22</sup> A put option (sometimes simply called a ‘put’) is a financial contract between two parties, the buyer and the writer (seller) of the option. The put allows the buyer the *right but not the obligation* to sell a commodity or financial instrument (the underlying instrument) to the writer (seller) of the option at a certain time for a certain price (the strike price). The writer (seller) has the obligation to purchase the underlying asset at that strike price, if the buyer exercises the option.

comprised of A\$10,890,000 plus capitalised interest of A\$17,559,330 in respect of the period 1992 to 2000) for A\$45,380,817. This was covered by the deposit in Luminis's name, accruing since 1992, with Macquarie Finance. Unfortunately, this would not be the last page in the Transgenics Syndicate story. Having filed their tax return for the 1999/2000 financial years, BresaGen managers were notified they were being audited. Of particular interest was their treatment concerning the year 1992, as the Syndicate had just reached its completion. The hearing date was set down for 5 August 2002 and it was to be held in Sydney. In accordance with good corporate governance, BresaGen had to set aside A\$750,000 to be held in escrow should the judgement require an unfavourable tax adjustment. Unknown to the company at this stage, this would prove disastrous when the deal with British Biotech would turn sour some two years later.

In May 2001, BresaGen and the team at Melbourne's St Vincent's Hospital announced the birth of Australia's first cloned pig. The female piglet, known simply as Pig, was the first of two cloned from a batch of pigskin cells frozen more than two years ago. Pig was the fourth successfully pig cloning in the world and was the result of techniques that BresaGen was aiming to have patented. These proprietary methods were the first step in developing technology for xenotransplantation. The University of Adelaide presented the research in a media dated 9 May 2001, with a headline reading 'BresaGen Announces Australia's First Cloned Pig':

It is anticipated that the new cloning technology will have a major impact in guarding against the outbreak of animal disease and in the area of xenotransplantation - the use of animal organs for transplantation into humans. The most obvious commercial use for cloning technology is the improved breeding of livestock. Cloning allows breeders to take a small number of animals with superior genetics and rapidly produce more.

BresaGen Program Leader Dr Mark Nottle described it as 'a very good result considering that this was the first transfer using our new method.' 'In addition to gains in productivity, cloning could be very useful in guarding against an outbreak of diseases such as Foot and Mouth,' Dr Nottle said. 'Once an

animal is identified as having natural resistance to a particular disease, a breeding company would use cloning to produce large numbers of animals. These animals would be supplied to farmers as breeding stock for new herds.'

BresaGen President & CEO, Dr John Smeaton, said the technology used to clone the pig was unique. 'It is significantly different from the technology used to make Dolly the sheep,' he explained. 'Basically what works in sheep doesn't work in pigs, so we had to start from scratch. Consequently we have something new for the pig and have filed a patent application. This is an excellent result for BresaGen and is indicative of the technical strength the company has in the field of reproductive biology and embryo research.'

A further application, and one of particular interest to the medical community, is xenotransplantation. Every year thousands of people around the world die while waiting for organ transplantation. Pigs are a potential source of these organs but the pigs need to be genetically modified so that their organs are not rejected by the human immune system. Professor Tony d'Apice of St Vincent's Hospital Melbourne said: 'This cloning technology will provide a method whereby the function of one of the genes thought to be important in the rejection of these organs can be eliminated or 'knocked out'. The gene, called the 'Gal gene', is present in pigs but absent in humans. It will be possible to produce pigs without this gene and provide donor organs more compatible for human transplantation.' (The University of Adelaide, 9 May 2001)

BresaGen filed a patent in Australia and the US that differed from others in its timing and the manner in which the cell and the transferring DNA were brought to the same stage and the success was important for the xenotransplantation industry that anticipated to see the transplant of pig organs to humans. In a press release dated 21 May 2001, BresaGen President and CEO Dr John Smeaton said:

With the Stanford agreement and BresaGen's recent acquisition of US-based CytoGenesis Inc., we now have two product development programs running in the US, and an emerging profile within the American investment community. The timing of our recent cell therapy acquisition and entry into the US capital markets is appropriate. There is a growing interest in cell therapy technologies on the part of US investors. These investors recognize the potential of cell therapy to become a major medical technology within this decade. BresaGen is well placed with its proprietary cell therapy program to be a leader in this field.

Following their announcement in May 2001 of the birth of Pig, BresaGen

secured additional external funding for this division (reproduction).<sup>23</sup> They were awarded A\$285,000 per annum grant for five years from the Juvenile Diabetes Foundation of Australia to research a new treatment for juvenile diabetes that utilised its cloning expertise. A Prese Release dated 21 July 2001 said:

The National Health and Medical Research Council of Australia and the Juvenile Diabetes Research Foundation will fund A\$874,000 per annum over five years to the program, which also includes the National Pancreas Transplant Unit at Westmead Hospital, Sydney, the Immunology Research Centre at St Vincent's Hospital, Melbourne, and the Autoimmunity and Transplantation Department at the Walter & Eliza Hall Institute, Melbourne. BresaGen will receive about A\$250,000 per year. BresaGen's involvement will be to develop cloning technologies that allow the deleting and inserting of genes to overcome rejection of pig tissue transplants.

Moreover, their Amended Annual report stated:

In addition we also secured a grant from an international pig breeding company to develop efficient cloning technology. This should allow pig producers to obtain large numbers of identical individual pigs derived from the best genetic stock and substantially speed up the process of transmitting genetics from breeding herds into production herds.

In 2001, BresaGen signed an agreement with an international pig company to continue its research into transgenesis with a view to commercialising transgenic pigs. (Amendment to Annual Report of a Foreign Private Issuer, Form 20-F, June 2002, p.33)

Unfortunately, the identity of the international company was not specified and other documents failed to make any reference to them. Smeaton and Robins were not readily able to recall who they might have been, but some suggestions were:

We were certainly talking to the PICs [Pig Improvement Company] of the world about pig cloning and we did manage to reduce that to practice but I don't know that there was any deal done. If there was a deal done it may have been - because that technology actually got spun out of whatever the syndicate was called. It got spun out of that and ended up back at St Vincent's so they may have done a deal (interview with Robins, 2007).

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<sup>23</sup> In the Amended Annual Report submitted 30 June 2002, it was stated there were three key areas in the business; Cell Therapy, Therapeutic Proteins and Reproductive Biotechnology.

Yeah, it may have been [the PIC], it may have been something we were trying to do with Metamorphics. But I mean nothing came of anything of that. (interview with Smeaton, 2007)

### **Cell Therapy: 3 Ways to Success**

By the middle of the year 2001, BresaGen had filed a total of 13 patent families, evidence of the wide scope of the research effort at this time. In the US, the company was actively pursuing possibilities following the acquisition of CytoGenesis and the decision to set up laboratories in Atlanta. At this time, the cell therapy division was viewed as having three major programmes:

- (1) Cell differentiation (of cells down the neural pathway, and testing the ability of these cells to rescue animal models of Parkinson's disease),
- (2) Human stem cells (identification of the appropriate cell type for a cellular product for disease targets such as Parkinson's disease), and
- (3) Catheters and imaging (to maximise cell viability and minimise trauma to surrounding brain tissue during implantation).

BresaGen Inc now had access to sophisticated IP relating to a cell delivery system as part of a cure for Parkinson's disease. Therefore, in May 2001 for BresaGen Inc signed a research agreement with Stanford University. Under the terms of the agreement, Drs Michael Moseley and Dan Spielman, Stanford faculty members in radiology, would carry out BresaGen-sponsored research to develop an image-guided cell delivery device with the capacity for monitoring cell metabolism following the transplantation of cells into the brain of patients with Parkinson's disease. Not surprisingly, one the key scientists involved in this research was also one of the founders of CytoGenesis, i.e. Mike Moseley.

On 23 July 2001, BresaGen Ltd announced it had successfully derived four human embryonic stem cell lines and by using proprietary cell differentiation

technology developed in mice, it was although it was not possible to transfer the human embryonic stem cell lines. The next step in the research process was to be able to isolate and characterise the human equivalent of EPL (Embryonic Primitive-ectoderm-Like) stem cell, which was thought to be a superior stem cell in that it could be controlled to yield relatively pure populations of therapeutic cell types in large quantities. (BresaGen Press Release, 23 July 2001)

Robins pointed out the importance of their earlier decision to set up BresaGen Inc in relation to their current stem cell research:

One of the reasons for coming here [to the US] was that we wanted to work with human embryonic stem cells and at the time you couldn't isolate them in Australia ... it was illegal to isolate human ES cells in Australia and so we wanted to isolate our own cell lines so we came to the US. You will find all the stem cell companies actually [in the US] - (there's ESI now in Singapore that are now here and there's stem cell scientists that do have some operations in Melbourne but they're based in Edinburgh.) Three stem cell companies that are centred in Australia are now overseas. (interview, 2007)

Moreover, Robins highlighted the issue of lack of funding once more, 'One of the reasons I've discussed is lack of stomach for funding something that was a long way down the track before you could commercialise it' (interview, 2007).

There was a question though over the value of the work, as there was much uncertainty about how President George W. Bush would view embryonic human stem cell research. On 9 August 2001, Bush announced that he was restricting government (NIH) funding to the 60 existing embryonic stem cell lines. At that time, ten organisations had been identified as having cell lines that qualified for funding and BresaGen was the only listed company. BresaGen's existing four human stem cell lines would ultimately receive NIH funding and in May 2002, the company was issued a grant worth A\$1.3 million plus indirect costs for expansion, testing, quality assurance and distribution of these cell lines.

Robins explained that it could have been four lines, but one line of cells was accidentally destroyed:

In the first six months of operation, we isolated three ES cell lines and so that really helped put us on the map, I think. Then Bush made his decision that any line isolated before August 9 2001 would be the line that would be available for federal funding and anything after that would not be, you couldn't use that line with federal government funding. Four were isolated so what happened was we were working in an IVF clinic to isolate these ES cell lines and the IVF clinic coincidentally in – I think it was May or June of 2001 – was moving premises and we had to freeze down what we had because they were moving and they were shutting down for a month while they did this. So the four cell lines - I hesitate to call it a cell line. It was just really an expanded inner cell map and we had two or three vials of this and to thaw it out we could not recover it. So there were four isolated but only three recovered. (interview, 2007)

Juttner summarised how he viewed the situation and benefits that the move to the US brought to the company in terms of both IP and skills as well as having access to prominent scientists dotting the chairs of the boardroom:

... [T]he company established itself in Athens, Georgia, because of relationships that existed with particularly a guy called Steven Stice, who's a first rate scientist whose name you probably first came across, and who was based there, but also other people who were on the Scientific Advisory Board. Clifton Baile who is a powerful person and an intelligent person, and a good adviser, who was based in Athens as well, and he was able to help the company to get a good deal, to establish in a nascent biotech type in the University of Georgia at Athens. All of those [the other economic benefits] were reasonable arguments. It [Georgia] was a small and relatively quiet place, but it worked alright. And I mean the proof was that Baile and Steve Stice were able to bring on board some very talented scientists, so that in the early part of 2000 the company was able actually to isolate some human embryonic stem cell license. And that was critically important because it was in August 2001 that Bush and the FDA – but largely Bush – came out with an embargo against further isolation. And that driven by religious conservatism nevertheless helped the company, because it was one of the few companies with viable human lines. And a lot of those 60-odd lines turned out not to be real. So that led to the company being in a good position to get funding from the NAH and things probably would not have happened in Australia, so that it was an important move then. It meant that you move from a company that had largely Australian directors, to a company that suddenly had two US directors, Rudy Mazzocchi and John Kucharczyk. Mazzocchi was a businessman, a successful entrepreneur John – he's another friend of mine. He was an expert in neuroradiology, and the target was Parkinson's disease

and implanting cells in there. That also led to linkage with a person called Curt Freed, who's an eminent neuroscientist based at the University of Colorado. And all of those things were real assets for the company, so the board changed enormously. (interview, 2007)

This view was also supported by a leading Australian industry journal in an article it published on BresaGen in June 2000, 'The presence of North America based members on BresaGen's SAB means the company is promoted in research and investment circles in the USA' (Bioshares, June 2000, p. 13). BresaGen's prominence in the market was not disputed – certainly in terms of profile and importance, their lines were significant, 'Basically if you look at the research papers there's the Wisconsin lines, the WiCell lines, there's the ESI lines and there's our lines. Apart from that, there's hardly any publication on the other lines' (interview with Robins, 2007).

### **Catheters, Cells and Collaborations**

With stem cell therapy showing signs that it could be effective in the treatment of traumatic spinal cord injury and stroke, as well as for neuro-degenerative disorders such as Huntington's disease, Alzheimer's and Parkinson's, BresaGen were aiming to ramp up the development of their catheter and imaging programs. Consequently, BresaGen Inc entered into a manufacturing and marketing agreement with Image-Guided Neurologics (IGN). The agreement was advancing the technology stated in programs one and three listed above. BresaGen had previously announced their collaboration with researchers at Stanford University for an imaging device.

IGN issued a media release stating:

Image-Guided Neurologics (IGN), based in Melbourne, FLA., a medical device company developing access, navigation and delivery products for less invasive neurosurgical techniques, and BresaGen Inc., an Australian biotechnology company with U.S. operations in Athens, GA., have signed an agreement to produce and distribute a specialized catheter which is intended

to be used for delivery of stem cells into the brain. This procedure has the potential to treat neurological diseases, including Parkinson's disease. In the United States, an estimated two million patients suffer from Parkinson's disease.

Under the terms of the agreement, IGN will develop the proprietary catheter for BresaGen, which has an exclusive license to commercialize the device. BresaGen will test the cell delivery catheter in pre-clinical sponsored research studies at Stanford University, the University of Toronto, the University of Minnesota and the University of Virginia. IGN has rights to negotiate exclusive distribution of the cell delivery catheter once FDA approval has been obtained.

'This agreement with BresaGen is an excellent opportunity to expand our product line in key medical applications,' said Rudy Mazzocchi, IGN President and CEO. 'We expect that the cell delivery catheter will eventually be used with IGN's Navigus Trajectory Guide to maximize the benefits to Parkinson's patients who undergo cell therapy. When used together these products can reduce operating time, cut health care costs and eliminate the patient trauma associated with stereotactic head-frame placement.'

BresaGen President and CEO, Dr. John Smeaton, added, 'We are pleased to have reached this agreement with IGN, which has an outstanding reputation for producing high-quality medical devices. The license agreement with IGN significantly extends BresaGen's cell delivery development program.'

BresaGen's Chief Scientific Officer, Dr. Allan Robins, explained: 'The cell delivery catheter that IGN is developing will cause minimal damage to brain tissue. The catheter tip is visible under magnetic resonance imaging (MRI), allowing cells to be delivered to target locations with greater accuracy than possible with currently used catheters. This catheter has a unique design and specialized biomaterials which minimize shear force stress on cell membranes as the cells are injected through the catheter and may result in a higher fraction of viable stem cells delivered into the brain.' (Press Release: Image-Guided Neurologics, Inc. 24 September 2001)

BresaGen's cell therapy research was still being serviced by the funds remaining from the A\$4.9 million R&D Grant awarded the previous year (December 2000). The company had until December 2003 to utilise these funds (Amended Annual Report, Form: 20-F/A27 August 2003)

## **International Marketing and Distribution for EquiGen**

BresaGen announced in December 2001 that it had entered into an agreement with CSL Ltd to distribute and market its specialist horse product EquiGen in Australia and New Zealand. Since its launch in 1998, EquiGen sales had grown steadily in both the Australian market and overseas. In a company press release dated 21 December 2001, John Smeaton commented, ‘... although we have established a good market for the product it is now time to pass it on to a focused animal health group who can take sales to a new level. CSL’s Animal Health division has a highly skilled sales team and strong product portfolio complementary to the needs of a specialist product like EquiGen’ (interview, 2007).

The same press release also stated that the two companies would look to collaborate on a program to register the product in the United States: ‘The lucrative U.S. market represents a big opportunity for EquiGen with its high value racing horse industry and significant sport horse population. We expect the product to be highly successful there – we have a unique product, more than five years experience working with it and a low cost manufacturing base from which to export to the U.S.’, Dr Smeaton was quoted as saying. The company planned to expand its marketing and distribution capacity by registering the product for sale in additional territories. Marketing and distribution in all other territories remained with BresaGen at that stage. At that time the company had not ruled out negotiating distribution and marketing deals with relevant partners in the US and Europe.

## **This Little Piggy Did Not Get to Market and BresaGen Went to Court**

August 2002 rolled around quickly and BresaGen/Luminis executives, Smeaton, Robins, Seamark and Hart arrived in Sydney to give evidence to the Administrative

Appeals Tribunal. The hearing lasted 18 days. Smeaton recalled some interesting aspects:

We did the syndicate and part of it was that ... we had to sort of indemnify them [Macquarie Bank] against any bad tax activity down the track which they assured us was never going to happen. The university had their lawyers drag all through these documents again. I think that was Finlayson's in those days. These documents got examined by sort of our lawyers, the university's lawyers and Macquarie lawyers, and concluded there was really no risk.

Well, it turned out they were wrong .... [W]hen the Liberal government came in [to office] in '96, they stopped syndicates and it'd been something like, I don't know, 230 of them set up. But I think the most famous or infamous one was Bertram's one for Australia I, II, III, whatever it was, for those sailing in the America's Cup, Bank of San Diego. And that sort of drew a lot of attention to things because it turned out they'd built the boat mainly in San Diego, not in Australia, and they felt it was tax-advantaged syndicate money. Bertram at the time was the chairman of the IR&D Board, which monitors all these syndicates. So you know, a fair bit of shit hit the fan. The government looked to stop syndicates and then they looked through all this stuff and then decided they wanted a test case and they picked on us. Which turned out wasn't such a good idea then.

So they got a precedent all right, they lost. But it was really quite funny, and the transgenic pig thing was the fact that they'd sold those pigs which turned out to be very relevant because the first question the government's QC asked me was, he said, when you set out to make those and set up the syndicate, you knew that you couldn't possibly sell these pigs because of all the GMO-type scare. I was able to say, well, 'that's absolutely not true because in fact, we'd sold 56 pigs in 1988 with the approval of the government.' The look on that guy's face was absolutely unbelievable. It was worth going to court for that. He kept looking daggers at his team who suddenly made their way on the back foot. So he wasn't properly briefed and they'd missed that, and it was downhill after that. (interview, 2007)

Smeaton described the tone that the rest of the hearing took was 'light hearted' but simultaneously nerve wracking:

... We had to stick with it [the tone] because it's a bit light-hearted there, you sort of have to ... [T]here were sort of four stock answers, I think [we gave] with his [the QC's] questions which were sort of 'not in my presence' and 'yeah', 'don't know' and the final one was 'can I have a glass of water please' if you got another question! So we had a sort of a private competition going as to who could ask for the most glasses of water. By the time I got there, they had a jug on the desk! So we sort of had a bit of fun at times. (interview, 2007)

The judgement was handed down in favour of MBL and Bresatec, finding that there was no evidence that the purpose of the scheme was to merely avoid paying tax on MBL's behalf. Instead, the court found evidence to the contrary – including the substantial payment MBL made towards investing in the licence, as well as the protracted and involved negotiations between the parties during 1992, justifying the fact that the deal was not done at arm's length, rather it was motivated and genuine, with the aims being to fully commercialise the research and to make a return on the investment. Furthermore, American Cyanamid played an important role in the handing down of this decision, as there was much evidence to support an 'authentic' and realisable investment; hence Cyanamid's 1991 deal with Bresatec.

Smeaton pointed out that whilst the judgement was in their favour the entire exercise was nevertheless costly:

You know, the Macquarie guys, it was a bit daunting, you're sitting there and they've got all these lawyers sitting behind their computers and they've got all the information and you're sitting out there trying to remember what the right answer is. So at the end of the day, we won. We got half of it [the money], but it was sort of a costly exercise. We took a lot of management time and stuff and we were somewhat distracted with all that. (interview, 2007)

## **Patents and Problems**

Driving the interest in cell therapy technologies in the late 1990s and first several years of the next decade was the success already had with such procedures as bone marrow transplantation and skin replacement. The new research was moving toward tissue and organ replacements through laboratory generated biological materials rather than donated organs, and from recent reports of the isolation of human embryonic stem cells, a potential source of any desired cell or tissue type.

BresaGen's area of expertise in the development of embryonic stem cell

technologies for the treatment of neurodegenerative disease came from three competing fields of research that can be broadly classified as foetal stem cell, adult stem cell and xeno (porcine) foetal cell approaches. One unique problem facing the players in the area was that of ‘freedom to operate’. Within the foetal cell area some companies, e.g. Stem Cells Inc. and NeuralStem, were aiming to isolate and proliferate foetal stem cells while other groups, e.g. ReNeuron, were using cancer related genes to genetically modify fetal stem cells to allow indefinite proliferation.

The recent discovery of adult neural stem cells within the adult brain meant there was some hope that such cells could become the starting material for producing cells for treatment of neurodegenerative disease. Companies competing in this field included Titan Pharmaceuticals and mostly small start-ups. In the embryonic stem cell field, where BresaGen was active, Geron Inc. and Australian based ESI Pty Ltd were considered to be the most competitive. Geron had certain rights to US patents for human ES cells and their uses but when BresaGen began its own research into cell therapy, no patents had been issued in the area of human ES cells so BresaGen thought the IP they acquired from the University of Adelaide (i.e. Rathjen’s technology that was included in their Prospectus) would allow them to develop treatments for Parkinson’s disease globally without infringing any patents. Subsequently certain patents licensed by Geron from Wisconsin Alumni Research Foundation (WARF) were published. These patents covered the composition and method for deriving human embryonic stem cell lines (Amendment to Annual Report of a Foreign Private Issuer, Form 20-F, June 2002, p. 34). These patents became collectively known as the Thompson patents and the claims granted in these patents were very broad – so much so that they could cover certain aspects of BresaGen’s technology. The Thompson patents effectively prohibited any company from deriving ES cells and using ES cells for commercial purposes

without obtaining a licence from WARF and, for certain applications including central nervous system applications, a sub license from Geron (Amendment to Annual Report of a Foreign Private Issuer, Form 20-F, June 2002, p. 34).

### **Cooking in the MedVet Kitchen**

The year 2002 started well for BresaGen with the European Commission designating E21R as having orphan drug status<sup>24</sup> for the treatment of juvenile myelomonocytic leukaemia (JMML), a rare and deadly disease affecting very young children. The announcement was made in March 2002. The orphan designation was based on the rare and serious nature of the disease, the lack of satisfactory therapy and the product's potential to have significant therapeutic benefit. At that time, there was no consistently effective treatment, with a five-year survival rate in just 5% of cases (Reuters Health, 5 April 2002).

However, the good news concerning E21R's performance was short lived. The previous year, BresaGen announced that British Biotech had received approval to begin Phase II trials for AML and E21R (BresaGen Press Release, 27 July 2001). But in July 2002, BresaGen announced it would suspend the Phase II trials in acute myeloid leukaemia with E21R because an independent pre-clinical study failed to support the previous high incidence of apoptosis (cell killing) in AML. However the data did not call into question the rationale for the development of E21R in the treatment of myelomonocytic leukaemias, chronic myelomonocytic leukaemia (CMML), and juvenile myelomonocytic leukaemia (JMML) (British Biotech Press Release, 5 July 2002). As a result, BresaGen continued to recruit patients to a pilot Phase II study in

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<sup>24</sup> Orphan drug status is designed to stimulate research and development of products to treat rare diseases. It brings benefits that include a period of marketing exclusivity.

CMML. This study had commenced in March 2001 and was being conducted in four sites in Australia (BresaGen Press Release, 8 March 2001).

In addition to the suspension of the AML trials, several weeks later, the company also made the regrettable announcement that BresaGen Ltd and British Biotech would terminate their collaborative agreement. British Biotech wrote off £0.3 million in respect of the unamortised amount of milestone payments made to BresaGen (British Biotech Press Release, 23 July 2002). Although BresaGen had licensed the worldwide commercialisation rights to British Biotech for all clinical indications, these rights would now revert to BresaGen. This had implications on a broader scale as a subsequent restructure was announced: nine staff were made redundant, there was a hiring freeze and a 10% cut in remuneration for senior management and directors.

BresaGen took the decision though to continue to evaluate E21R in Phase I/II trials for rheumatoid arthritis. They anticipated these studies would be finished by mid-2003 and if they were successful, they would have to find a partner to move the drug through its next phase of development, i.e. Phase III trials. However, in their Annual Report for a Foreign Private Issuer they said:

There are drugs currently registered, or being developed, that also treat these diseases. We ceased our clinical trials into RA due to difficulties with patient accrual due to competitor's treatments. We are currently in discussion with several pharmaceutical companies on licensing E21R. Amendment to Annual Report of a Foreign Private Issuer, Form 20-F, June 2002, p. 35)

This decision to license E21R to another organisation represented a way to try to move forward through a very challenging time for the company, although at that early stage, it is unclear whether the BresaGen executives were in full possession of all the details surrounding E21R and its failure in its trials.

What was about to become known to BresaGen was that they (along with

British Biotech and the volunteers and patients that had been administered E21R in the trials) had been the victims of data fraud. For scientists and companies involved with human health pharmaceutical R&D, this was considered to be heinous behaviour. Chris Juttner gave an informed account of the period when the fraud was uncovered:

... [D]oubt was cast upon some of the issues to do with E21R. And E21R's commercial application depended very much on its ability to kill cells. And the first thing that happened was that some people related to the licensees in the UK, tried to repeat some of the data that had been published by Lopez's group [originating from a postdoctoral researcher] and they couldn't.

Secondly, as a haematologist, I have never understood the reasoning why some of the major claims should have worked. It led me to go back and re-read the papers, and that led me to ask to see non-photocopied issues of the papers. And that then led to a situation where when I saw the non-photocopied versions of the papers, it looked as if all was not right ... But it led to a situation where we obviously felt we needed to inform our licensee, and we informed British Biotech. And I was sent by the Board to fly to England and talk to them about the issues, which I did.

The deal was reverted and various agreements were arranged and various press releases were made. British Biotech withdrew the drug from development, and in the end, British Biotech sacked its key people and the company dissolved and no longer exists. Largely as a result of this. (interview, 2007)

When asked if he thought this issue concerning the veracity of the science effectively brought down two companies, Juttner (interview, 2007) simply replied, 'Yeah, you could say that'.

Juttner was in a unique position to comment on the issues with E21R because his background prior to joining BresaGen's board was highly relevant:

What prompted me to join the board at BresaGen was that I'd come back to Australia at the beginning of '99, having worked in San Francisco for four years. I was working amongst other things for an organisation called Medvet Science. Medvet Science had a licence for E21R to BresaGen, and had some rights and responsibilities to look at the ongoing development of E21R ... so that during that time, I became involved in reviewing that deal and that science. And because I'd had experience in clinical haematology and in commercial clinical research, both in Australia and in the US, BresaGen actually asked me to look at protocols that they were writing to investigate

E21R. That was through the first part of 2000, and I offered a lot of advice to them. (interview with Juttner, 2007)

Furthermore, Juttner gave an account of how he started to ‘sniff out’ the IP fraud:

Actually, one of the things that I found strange was that one of the key papers – see, I’d run the haematology unit at the Adelaide [Royal Adelaide Hospital] and the research unit there – and one of the key papers talked about there being 30 new cases of a particular kind of leukaemia that had been investigated, and it said that the cells were examined fresh. And I knew, because I knew a hell of a lot about what the incidences were of this, and it was impossible. That was one of the first things that led me to go back and start asking questions. And then it became clear, well actually the cells weren’t fresh they were frozen. There’s an article in a highly prestigious journal, where you’re saying the cells are fresh but in fact they weren’t fresh. And it was only me who could have known, so it was pretty tough for some of these elements to have been picked up by the company’s due diligence process, primarily led by Allan Robins and Meera Verma. You needed that inside information that only I had. (interview, 2007)

Having access to the original data led Juttner to make the connections necessary to provide an explanation for E21R failing the phase II trials. Upon acquiring this knowledge he talked about the feelings he experienced and the next steps he took:

And then you say well oh right, well that’s a mistake. That’s an honest mistake. They meant to say frozen but they said fresh. Well, I guess when you’ve got three senior people – when you write a scientific paper, people read it and read it and read it again. And I believe you have a huge responsibility for those data to be absolutely correct and honest. [You need to] go back and look at the workbooks. So it was the disappearing workbooks and all this sort of stuff, stuff didn’t exist. And most scientific organisations now have got an obsession about ensuring that workbooks are signed and that they are there, and they just disappeared. (interview, 2007)

Other senior executives shared their personal thoughts on the sad and sorry episode:

That was a great opportunity which in the end sort of basically sank the company. Yeah, well we spent I think something like 9 million bucks on that molecule and what it turned out was it meant that basic science was fundamentally dishonest ... We’d sort of asked questions about [E21R] for

quite a long time, and I'd asked the scientific crew in the company, you know, 'is this stuff for real or what?' ... I don't think that they knew that their visiting student or scholar, or whatever he was, had cooked the data. (interview with Smeaton, 2007)

Robins spoke of the episode very candidly and shared his feelings of betrayal over the falsified data that E21R had been built upon early in its life:

Well, basically it's falsified to tell you the truth ... It's interesting you're asking me about this because I actually had friends over for dinner the other night and ... [one of them] said to me, 'I want to know about betrayal. What is the biggest betrayal that's ever happened to you in your life?' I thought about that quite a bit and it turned out that this for me was the biggest betrayal because basically this nearly sunk the company. Well, it certainly put the company into receivership and while I think the postdoc that did this acted as a lone agent, there were plenty of warning signs in the Hanson Centre.

At some stage they realised this is what was going on, we didn't know that, and they allowed us to spend millions of dollars and they allowed us to inject something into human beings that they knew the data was false. That is bloody frightening. I'm not supposed to tell you that but I didn't sign any confidentiality agreement. I know this has been a source of great frustration for Meera [Verma], there was the private settlement in which IMVS paid but I don't know what that settlement was but from what I've heard it's a pittance.<sup>25</sup>

That basically brought the company to its knees when that happened. When we found that out I was over here and I went racing back to Australia the next day but basically the company was dead in the water at that stage. (interview with Robins, 2007)

Robins was quick to absolve Lopez from any involvement in the falsification of data, but the fact that the two were linked by friendship heightened the sense of betrayal.

The press releases issued by both parties were largely polite and understated, however the consequences of E21R's failure did not just stop as neatly as the press release. In anticipation of the drug progressing through development, BresaGen had

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<sup>25</sup> According to the 2005 Annual Report, it was stated that the amount could not be disclosed for privacy reasons; a statement referred the reader to see the balance sheet for the cash injection surrounding the settlement with IMVS. The amount was \$900,000.

been investigating what resources would be required and was gearing up accordingly, as Carol Senn explained:

I suppose with E21R, before that came to its demise, we at one stage had been looking at where we were going to be doing Phase III trials, so Stan [Bastiras] and I had already been off to Europe to work out with a few CMOs, [clinical manufacturing organisation] to get some quotations, see what was available, what kind of prices we were going to be looking at if we had to transfer our technology ... I [was involved in] making sure that their freeze drying cycles were going to work and the validation of the cycles and timing and logistics and all that type of thing, sampling programs [were going to be appropriate so we could produce the product]. What we would have been setting up – [according] to my recollection was ... the bulk API. We never did sterile manufacture at that point, so we would have - obviously, if we'd gone to Europe to get a larger scale of manufacture, we would have used a European to fill it, but British Biotech was the one that were doing the trials and coordinating [things] ... We were supplying the materials to British Biotech. (interview, 2007)

The total impact of these activities was that BresaGen committed to building a new production facility as a result:

Indeed, because E21R was looking like getting into Phase III, and BresaGen had the contract to provide it, it had to be a higher standard and so on. It was kind of forced into a situation of either building a new plant, or spending a huge amount of money to get a contract research organisation to make the drug. But that was the precipitant to build a new plant. Before that plant had been moved into, the whole E21R thing had turned into a total debacle, so it was very difficult. (interview with Juttner, 2007)

Smeaton summed up the episode as positively as he could, saying of the deal with British Biotech, 'the only reason we sort of feel slightly good about that is that they did a lot of due diligence and got the wool pulled over their eyes, too. So that was – so it wasn't obvious' (interview, 2007).

Juttner though, was more empathetic about how it was even possible this situation presented, explaining how he saw things:

Well, I think there was too much trust. I'd see it another way. I came into this knowing the people, the academic collaborators as well, particularly Lopez, I'd worked with him, we'd published together, because I was at the IMVS

centre. And I think that what BresaGen's problem was, that while they did due diligence, it's always difficult to do someone else's science, about which they know a hell of a lot. And both of these principals, BresaGen and Lopez, were very intelligent and persuasive people.

You can criticise BresaGen for not assessing that stuff properly, but on the other hand it was extremely difficult. And betrayal and a lack of – destruction of trust and all those sorts of things, clearly come into it. But in the end, those issues I think had a huge amount to do with bringing the company down. I mean, it still exists, having been in administration, but it then meant that the board had to look at other approaches. (interview, 2007)

Notwithstanding all the issues around the fraud, the deal itself was, in Juttner's opinion, a function of the nature of the Australian industry at that time. He accused the biotech industry of being, in part, guilty of forcing these kinds of deals to be initiated in the first instance due to lack of funding and support:

[The] deal for E21R with British Biotech, I strongly supported too, because while it wasn't an absolutely brilliant deal, it nevertheless had royalty lines associated with it. It was a relatively early stage drug, and I felt strongly [about it] – my view about Australian biotech of course then, and still is - that it's a bit ephemeral and it goes to IPO much too early. And the companies tend to be single-issue [product] companies and so on and so on. So the fact that they were able to do an international deal that had some cash associated with it, some stock associated with it and royalties associated with it, and a co-development arrangement, with a company that was capable of doing the clinical development, all had major bonuses. It seemed like the company was moving to a stage of growth and maturity, and then the wheels started falling off. (interview, 2007)

### **Intracranial Catheter Approval for the US**

At the same time the E21R fiasco was playing out in Australia and Britain, an announcement was made that the company had received approval from the FDA to market its proprietary catheter, which was intended to be used for delivery of therapeutic agents into the brain. Under the FDA clearance, the catheter could be marketed for intracranial delivery of stem cells and drugs in patients with stroke and neurodegenerative diseases and disorders. Having a proprietary catheter and method for

delivering living cells into patients with neurological diseases, such as Parkinson's, was a major step toward the commercialisation of the treatment of these diseases. The press release stated that the University of Minnesota had licensed the product exclusively to BresaGen and scientists and engineers at the University of Minnesota, Virginia Commonwealth University, and the University of Toronto performed the research on the catheter. According to Robins, 'This all came with CytoGenesis. These were all deals that were in place so we inherited those by acquiring Cyto' (interview, 2007).

This deal also represented BresaGen remaining focused on its intended business strategy: developing a comprehensive cell therapy product line that included cells derived from stem cells, catheter devices to accurately deliver the cells into target locations, and imaging technologies to evaluate pre and post-operatively the condition of the local tissue environment.

### **protEcol™ - Moving into the Services Sector**

In light of the anticipated development of E21R, the decision followed that BresaGen needed to improve its manufacturing facilities. This would also service the manufacturing of the rest of the protein division, including EquiGen and hGH. As a result, an agreement was signed in early in 2002 with the State Government of South Australia to provide finance for the construction of a new building and production facility. The term of the loan was 10 years while the security for the loan was charged over the land and building.

However, in between negotiating this finance deal and signing the paperwork and beginning the construction of the new facility, E21R had imploded. This left the Board in a very difficult position; one that they needed to address quickly and aim to steer the company through. This led to the setting up of a service division called

protEcol. It was treated as a separate business unit within the protein division and it offered process development and manufacture of recombinant peptides<sup>26</sup> and proteins – basically, ‘value-added’ contract manufacture. BresaGen was aiming to utilise their existing skills and expertise that they had developed over 15 years with cGMP production and quality documentation. These skills were viewed as a ‘life raft’ of sorts.

The senior executives of the protein division at that time, Verma and Bastiras, explained the circumstances facing the company at the time when protEcol was established:

We started that [protEcol] back in end of 2002. When we first committed to this facility actually, end of 2001 ... we were developing our own drug which was in clinical trials and we had a really nice deal with British Biotech, the English biotech where we retained manufacturing rights ... So we were positioning ourselves to then produce for market and knew we couldn't do any of that credibly unless we had a facility. We had to build for a facility and then our back-up stream was well if the drug then failed at the end of these two or three pre-clinical trials, what then? (interview with Bastiras, 2007)

We started protEcol looking at, well our team is really experienced now taking this and this and this and we should now see there is obviously a need for what we do out there, let's see if we can play to our core strengths and this came out also. Again some of the lessons I learnt in early '02 was that this was something we really need to do. So we'd just started to get our heads down, doing something like protEcol services when E21R failed and we were recommitted to building this. Halfway through '02, because we moved in here [i.e. new manufacturing facility] in early '03 and luckily we had actually got our heads around the protEcol patent because we had clients come in. We eventually got in A\$1 million from one of our lead clients at the time over a period of 18 months and realised this was a credible thing to be doing and we could actually build ourselves a business that would take us to break even on protEcol while we worked on other strategies to grow the company. I think it is actually working really well; we are getting a lot of interest for the local biotech companies. That is par for the course. There is a need of fulfilling it in the local market but we are well aware that you really need international business to one give credibility and two there is not enough happening with local market .... (interview with Verma, 2005)

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<sup>26</sup> Recombinant proteins are the basis of pharmaceuticals such as insulin and human growth hormone and unlike the traditional method of making drugs – chemical synthesis – recombinant techniques harness the ability of bacteria such as *E. coli*, to produce large amounts of protein by the introduction of a specific gene into the bacterium. The protein can then be purified to produce a therapeutic drug.

A press release dated 31 May 2002 was issued announcing a contract had been signed between BresaGen and another Australian company, EvoGenix Pty Ltd. The statement said:

BresaGen will conduct feasibility studies and process development for a class of small protein molecules which EvoGenix plans to develop as an entirely new approach to finding and treating difficult targets such as viruses and cancer. BresaGen's expertise in process development for producing protein pharmaceuticals will be applied to finding an effective way of making the targeting proteins reliably and cheaply. (EvoGenix website, 31 May 2002)

Several months later, in October 2002, protEcol Services was engaged by Metabolic Pharmaceuticals Ltd to develop a method for large-scale manufacture of a new anti-obesity drug. An article appeared in the *Sydney Morning Herald* newspaper stating:

Under the six-month feasibility trial, Adelaide's BresaGen will test a large-scale production process for Metabolic Pharmaceuticals' key obesity drug. The drug, AOD9604, is yet to complete large-scale phase II trials of its effectiveness and, under the best of expectations, could be on the market by late 2006. BresaGen will test whether the drug, now manufactured by chemical synthesis, can be made using its cheaper bacterial production methods. (Rochfort, 30 October 2002)

In the same year, Swiss company Lonza AG also contracted protEcol to work on process development of biopharmaceuticals (BresaGen Press Release, 14 November 2002).

BresaGen moved into their new purpose built facility in May 2003. The production plant was fully compliant to European Medicines Agency (EMA) and the US Federal Drugs Administration (FDA) cGMP standards and certified as PC2-Large Scale by the Office of the Gene Technology Regulator (OGTR). This enabled the company to supply low bioburden Active Pharmaceutical Ingredients (API), as well as the ability to offer customers cGMP manufacture of pre-clinical and clinical trial materials. The company's Quality system complied with the Pharmaceutical Inspection

Co-operation Scheme (PIC/S) and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Based on mutual recognition agreements, the cGMP status was also recognised by all member states of the EU, Canada and Singapore. Whilst the company had been cGMP approved by the Australian Pesticides and Veterinary Medicines Association (APVMA) since 1995 and by the Australian Therapeutic Goods Administration (TGA) since 1998, the new facility would be a major boost for their future plans.

Additionally the manufacturing plant had a 100-litre fermenter to make their therapeutic proteins, and the new facility was capable of housing one 500 litre and one 200 litre fermenters. These were to be purchased when production requirements demand additional capacity. The new plant housed all research and development laboratories as well as administration and management offices. The total cost of these facilities, including land, was estimated at between A\$11.7 million and A\$13.0 million (Amended Annual Report, Form: 20-F/A, 2 September 2003).

### **Clearing a Path for Stem Cells**

In November 2002 BresaGen announced it had in-licensed key intellectual property from Plurion Inc. This transaction involved BresaGen purchasing patent rights including exclusively licensed rights from Vanderbilt University in Tennessee in return for a 30 percent stake in BresaGen. The patents showed methods for the isolation of pluripotent stem cells and were known as the Hogan patents. Issued between 1992 and 1995, these were the earliest priority dates for these patents. In its press release announcing the acquisition of the licence, BresaGen stated:

We therefore believe that by acquiring the rights to these patents we may have a path to commercialisation without infringing current patents. As cell therapy is early stage research with products not expected to be available for

at least 10 years there is a significant risk that BresaGen will need to licence further intellectual property in this field to be able to commercialize its product. (BresaGen Press Release, 18 November 2002)

As part of the transaction, two of Plurion's directors – David Perryman, a partner at Needle & Rosenberg, which prosecuted the Hogan patents, and Mark Germain, a biotech investor – joined BresaGen's board. The acquisition was subject to shareholder approval by both companies; BresaGen's shareholders were to vote to approve the deal at their Annual General Meeting in Adelaide the following year. However, the transaction did not ultimately push through:

The Company subsequently announced on April 2, 2003 that the transaction as originally proposed would not be in the shareholder's best interests given their assessment of Plurion's IP following due diligence and having regard to the broader market uncertainty that has emerged in recent months resulting in substantial reduction in market values. The Company is continuing to re-negotiate more favourable revised terms with Plurion that properly reflects the current and future value of this IP. (Amended Annual Report, Form: 20-F/A27 August 2003, pp. 76-77)

### **Picking Up the Protein Business**

In an interesting twist, BresaGen issued a press release in March 2003 stating that E21R was going to head in a 'new direction' following the discovery of a new indication:

Adelaide-based biotechnology company, BresaGen Ltd today announced that it had identified a prospective new indication for its drug E21R. This is supported by exciting pre-clinical laboratory data showing synergy with an established anti-cancer drug, and BresaGen has initiated discussions on collaborative development with a major pharmaceutical company. (BresaGen Press Release, 21 March 2003)

The same document announced the discontinuation of the rheumatoid arthritis trials for E21R, because the new drugs coming onto the market were making patient recruitment difficult. Additionally, the trial of E21R in Chronic Myelomonocytic Leukaemia (CMML), which had been on hold since July 2002, was now also going to

be discontinued. These changes were to help to conserve BresaGen's cash reserves. (BresaGen Press Release, 21 March 2003)

BresaGen continued to have success with protEcol and in May 2003 signed an exclusive licensing agreement with a Nebraska-based company called Restoragen Inc. for a suite of seven patent applications covering production methods for recombinant proteins and peptides. It was a significant investment and reinforced BresaGen's strategy to exploit the worldwide shortage of protein manufacturing capacity. The intellectual property covered methodologies for molecular engineering, optimisation of high-yield fermentation, and robust downstream processing. One of the inventors, Professor Fred Wagner, who developed a number of the methodologies in the Restoragen patent suite, acted as a consultant to BresaGen, who was seeking new partners in the USA. (BresaGen Press Release, 23 May 2003)

In the same month, May 2003, Australian Cancer Technology (AustCancer) announced plans for forthcoming Phase 2 clinical trials of its highly promising Pentrix™ anti-cancer vaccine. BresaGen would collaborate with AustCancer by manufacturing a highly purified version of the p53 molecule, the ultimate target of AustCancer's Pentrix vaccine. A diagnostic test based on BresaGen's manufactured p53 will help determine whether the Pentrix™ vaccine (DTH) developed was successful in targeting tumour cells with p53 markers on their surface. (BresaGen Press Release, 8 May 2003)

## **Back to Court**

On 1 July 2003, a headline appeared on a press release, 'BresaGen instigates legal action over E21R data'. BresaGen had begun proceedings in the Supreme Court of South Australia against the Institute of Medical and Veterinary Science, MedVet

Science Pty Ltd. Additionally Angel Lopez, who undertook the initial research, was included in their claim. Until this time though, the parties had been trying to reach a settlement. Since this was not forthcoming, BresaGen made the decision to pursue A\$7 million in direct costs incurred in relation to the project. Moreover, they were also going to seek further amounts for additional costs that had not yet been fully quantified (BresaGen Press Release, 1 July 2003).

Peter Hart, Chris Juttner and John Smeaton all recalled that period:

I was involved in those discussions. Smeaton was ... here for some of them, but mostly Meera and I were. Oh, it was horrendous. We just sort of sat there – I won't say in a state of shock, but yeah, state of shock! Only, of course, we were then told that we had a very good case for malfeasance, or whatever it was, against the [South Australian] government, etcetera, etcetera. The government managed to successfully stall that until the company went into administration and settled that with the administrators.

Oh, there were proceedings which were going, but it was just dragging and dragging and dragging and, of course, with the proceedings dragging, they were – you know, the government was perfectly aware of what was going on, in terms of our financial position. You didn't have to be a rocket scientist to work that out. Just read the press. They just delayed and delayed and delayed. Again, if it had gone to court, who would have won? There was no doubt about it, in my mind, that BresaGen was misled, but there's also no doubt that it should have been picked up. It went back to the time it was signed. (interview with Hart, 2007)

Juttner (2007) concurred with Hart's assessment that the case was being stalled:

'Oh absolutely. I was involved in those discussions. Smeaton was ... here for some of them, but mostly Meera and I were.' Smeaton's recollection was the same:

But I think that down the track, I think they [IMVS] realised that it wasn't ridgy didge, and they didn't let on, they just let us continue and let us spend money, let us put stuff into patients. They should've, [disclosed what it was they knew, any warning bells or signs that things might not have been right.] And I think it went further than that, I think they already made efforts to cover it up, and then I think that extended up to the State government [South Australia]. I wasn't involved because I was in the States, [America] but we went and talked to Foley, the Treasurer, trying to get them to at least bring some sort of an arbitration on quickly. They basically said they were trying to run us out of cash and put us into administration, which they were successful

at. (interview, 2007)

Even though a settlement of A\$900,000 was reached out of court, no admission of liability was made on MedVet's behalf. Of this Juttner said, 'And so I always thought that was interesting, because it implies that there was an admission of [guilt] – the fact that a settlement was done, implies some admission of guilt on the part of the Government, however much they deny that and the company is not allowed to say it. But it's all water under the bridge' (interview, 2007).

### **Divisions Become Companies**

By August 2003, BresaGen embarked on a strategic undertaking: to restructure the company's divisions, i.e. protein pharmaceuticals and cell therapy. These divisions were to be spun off as separate private companies, both headquartered in the United States, and BresaGen Ltd to be the holding company with an equity stake in both companies. The Amended Annual Report document read:

The Company has engaged a US investment banker to raise finance to exploit prospective opportunities in the Protein Pharmaceutical business. Subject to the completion of this fund raising the Protein Pharmaceutical division will be spun out into a separate US-headquartered company.

The Cell Therapy Division will gradually relocate to the US. The Company is currently in discussions with several other companies with complementary interests in the ES cell field and the cell delivery and imaging fields.

The Company's main source of revenue to the fourth quarter of calendar year 2003 is likely to be from grants. The Start Grant that supports the Cell Therapy research in Adelaide expires in December 2003, or when A\$4.9 million has been claimed by the Company based on eligible expenditure. The Company, based on current estimates, does not expect to draw down the full A\$4.9 million by December 2003. The A\$1.3 million NIH grant has been approved and BresaGen, Inc is currently drawing down funds provided by this grant to cover direct costs incurred. The Company is currently of the view that revenues from these sources are reasonably assured. (Amended Annual Report, Form: 20-F/A, 26 August 2003, p. 51)

With these initiatives in place, there was a strong focus on the company's financial position, essentially justifying the strategic choices they were making. Again the Amended Annual Report documented the fiscal issues:

As at June 30, 2003 the Company had A\$5.9 million in cash. Borrowings as at June 30, 2003 totalled A\$7.3 million (both current and non-current). Borrowings relate to a loan agreement with the State Government of South Australia to provide finance for the construction of a new building and production facility. This loan is repayable over 10 years commencing on building completion and when final construction costs have been determined. The maximum amount of funding available under the agreement is A\$8.0 million. Interest is payable on the loan at commercial rates. As at June 30, 2003, A\$7.3 million has been drawn down under the terms of the agreement. The Company expects to complete draw downs under the A\$8.0 million loan facility by November 2003 and begin making quarterly repayments in early 2004. The mix of debt to equity will therefore increase as draw downs are made under the terms of this loan facility. Our % of interest-bearing debt to equity increased from 6.6% as at December 31, 2002 to 12.3% as at June 30, 2003. (Amended Annual Report, Form: 20-F/A, 26 August 2003, p. 50)

We estimate that our existing capital resources, expected sales, grants and interest income will be sufficient to fund our current level of operations through to December 2003. Revenue from our newly established ProtEcol(TM) business unit which totalled A\$90,000 for the year ended June 30, 2002, is expected to increase as we pro-actively market this service and complete our new production facility (Amended Annual Report, Form: 20-F/A, 26 August 2003, p. 52)

The reproductive technology division was transferred back to the University of Adelaide in July 2003 and Baxter granted their xenotransplantation assets to the Mayo Clinic, who continued research in the area:

Many other companies, notably PPL Therapeutics and ACT have been active in the cloning area although some of their proprietary technology does not transfer well to pigs. In the xenotransplantation field three companies PPL Therapeutics, Novartis and Nextran a subsidiary of Baxter, have had programs to develop genetically modified pigs for organ transplants. PPL has recently sold their assets in this area to University of Pittsburgh spinout company, Regenecor. Baxter have granted their xenotransplantation assets to the Mayo Clinic, which will be continuing research in this area. (Amended Annual Report, Form: 20-F/A, 2 September 2003, p. 34)

BresaGen has licensed certain rights to this technology to other parties and BresaGen is not the beneficial owner of these patents or patent applications. Under the licensing agreements BresaGen stands to gain royalties from any

revenues derived from the use of this licensed technology. (Amended Annual Report, Form: 20-F/A, 2 September 2003, p. 33)

## **Generipharm is Conceived**

September 2003 proved to be a very important time for BresaGen with four key events occurring in or around this month. The first milestone occurred when BresaGen Ltd established a wholly owned but US incorporated subsidiary, Generipharm Corporation Inc. Generipharm was to be a self-funded private company and BresaGen pursued Caymus Partners to help raise finance. BresaGen Ltd intended to transfer its Protein Pharmaceutical business into Generipharm Inc. on the successful completion of the Caymus Partners led financing.

Allan Robins explained the strategic link between severing the divisions into separate companies and the creation of Generipharm Inc:

This was an initiative that I guess John [Smeaton] and I started. I don't want to say it [was] anybody's idea, being a management decision that we basically had two businesses and if either business was going to survive we're going to have to split them up. To fund the stem cell stuff, the cell therapy stuff, we needed to be a US-driven initiative and protein pharmaceuticals probably - we were looking at setting up - well, we did set up a company over here with the idea of having a US-based company with an offshore manufacturing facility in Australia. So this is the whole Generipharm idea.

It was kind of post the E21R but it's pretty obvious that generic biopharmaceuticals were getting a bit of a run over here [in the USA] and since that time it's got a lot more serious. I think if we had have been able to execute on this plan it would have worked but anyway it didn't ... Anyway, we engaged a firm [Caymus Partners] to help us talk to potential investors. It actually went quite well but we kind of ran out of runway. Generipharm is a name I dreamed up. (interview, 2007)

John Smeaton also gave a coherent description of the situation the company found themselves in and how that led them to the idea of manufacturing generic pharmaceuticals:

... [W]e were facing sort of some financials running down and I think I

probably came up with the concept as to how to try to restructure the company into a generic pharmaceuticals and the stem cell play. Then Allan [Robins] and I collaborated a lot on that. We tried to think of names and that [Generipharma] was his, there were lots of names bandied around. We<sup>27</sup>[Robins and Smeaton], through one of our contacts in Georgia we were introduced to, Caymus, they were a sort of small merchant bank who could raise money, and we actually talked to, I think, four similar-type outfits: one in New York, one in California, those guys from Atlanta, and then we decided to go with Caymus. We put that document together with their help of whatnot, we were trying to raise money and I think it was a pretty good chance of it being successful if been a little bit of time. (interview, 2007)

Smeaton spoke highly of the senior employees and founders of Caymus Partners, citing the fact that they had an excellent set of connections in terms of potential investors, but additionally they had a strong scientific grasp of what was involved:

Then I went to talk to Rom Papadopoulos. Rom is somebody who's probably worthwhile talking to and he was the guy that was sort of on the case, as it were. He's been moved on from Caymus and has been raising money for various Biotech things. But Rom's a great sort of enthusiast, he's a medico. He went down to Adelaide and fetched all the stuff there and so we wrote up this prospectus-style of a memorandum and we were out trying to raise money when the board decided to pull the plug on us. (interview, 2007)

Caymus Partners prepared a Memorandum of Information document dated October 2003. Several interesting sections explaining the purpose of the company and its strategic intent have been included below:

Generipharma Inc. (the 'Company') is currently a wholly owned subsidiary of BresaGen Limited ('BresaGen'), an Australian company listed on the Australian Stock Exchange. The Company does not currently hold the assets and rights that make up the business described herein. BresaGen holds those assets and rights and will continue to operate the business until successful completion of the investment contemplated hereby. Prior to or at that time, BresaGen will contribute to the Company the assets and rights that make up the business described herein.

This Information Memorandum presents the Company as if the contribution

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<sup>27</sup> 'Caymus are in Atlanta and we were introduced to them by a friend of mine actually.' (Robins, 2007)

of assets and rights making up the business had been contributed to the Company from inception of the business. For this purpose, the terms 'Company' and 'Generipharm' shall be deemed to include the division of BresaGen that currently operates the business and holds its assets and rights, even though these assets and rights have not been conveyed to the Company and the Company has not operated the business. Further, all financial information relating to the business, the Company or Generipharm is presented herein on a *pro forma* basis as if the contribution by BresaGen to the Company of the rights and assets of the business had occurred at the beginning of all periods presented. (Caymus Securities, October 2003, p. iii)

The second critical event was the acquisition of the XeriJect drug delivery platform. The BresaGen press release said:

Under the agreement with US company AlgoRx Pharmaceuticals, Inc., a specialty pharmaceutical company with significant expertise in the development of pain therapeutics, AlgoRx will assign the XeriJect technology to BGen Corporation, a wholly owned subsidiary of BresaGen Ltd. AlgoRx retains rights to the technology for pain applications. Dr Steve Prestrelski, a key inventor of the technology and a world-leading expert in protein formulation and delivery, has been instrumental in the transfer of the technology to BGen and will continue to support its development. Further development work on the technology should see it reach the market with its first drug application by 2008.

The pivotal advantage of the XeriJect technology is that it enables a small amount of highly concentrated drug to be injected into the upper layer of skin using a very fine needle. The proprietary device and formulation will be tailored to ensure drug stability and rapid absorption into the blood stream. These features will result in a virtually pain free injection and allow room temperature storage of the product without the need for reconstitution prior to use.

BresaGen Chief Executive Dr John Smeaton said that the company anticipated numerous product opportunities with XeriJect technology because it potentially eliminated patient issues with needle and syringe injection while not fundamentally altering the drug administration. 'As well as the opportunities around currently marketed drugs, its simplicity will enable the XeriJect system to be incorporated in development programs for emerging biopharmaceuticals,' Dr Smeaton added.

Recently BresaGen announced plans to restructure the company which would see the Protein Pharmaceutical division spun off as a separate private company, headquartered in the United States. The aim of the new company will be to exploit BresaGen's expertise, technology and intellectual property to address the emerging and highly favoured biogeneric space. The XeriJect technology will be a key asset of the new company, allowing the company to

create 'supergenerics' in which the original drug is presented in a differentiated delivery system. (BresaGen Press Release, 12 September 2003)

The third positive milestone happened when BresaGen with received a financial boost to BresaGen Inc via a shot in the arm from a government grant. BresaGen Inc. was a co-recipient, along with the University of Georgia, Georgia Tech, Emory University, Yale University and others, of a grant from the National Center for Research Resources, a component of the US National Institutes of Health. The grant was for five years and worth a total of US\$7.6 million, with a focus on technologies to map the 'glycome' of stem cell lines. BresaGen's portion of the grant was worth US\$150,000 per year, and partially funded the salary of one BresaGen Inc. employee and the salaries of two additional University of Georgia employees working under BresaGen's direction. (BresaGen Press Release, 8 September 2003)

The fourth helpful event in September took place when the American Depository Receipts (ADR) program granted BresaGen Inc. Level II status, requiring the company to comply with US SEC reporting requirements including lodging accounts under US-GAAP and was a precursor to a potential NASDAQ listing of the company's ADRs (BresaGen Press Release, 9 September 2003).

However, the mood produced by this encouraging chain of events may have been tempered somewhat by the announcement of the increase of loss of earnings, up from the previous year:

September 15 – BresaGen, an Adelaide biotechnology company, has announced a consolidated loss for 2002-2003 of A\$13.95m, up from A\$11.86m in 2002. Revenues were down from last year, at A\$5.27m, compared to A\$6.05m. The company announced a major restructure last month, including the spin-off of its protein pharmaceutical and cell therapy divisions into separate companies. The results reflect the impact of the termination of trials for BresaGen's anti-cancer drug E21R at the start of the year, the subsequent focus on manufacturing opportunities in the emerging biogeneric market and reduced spending on R&D. (Allens Arthur Robinson

Company Website, 16 September 2003)

In October 2003 the company signed an agreement to transfer its interest in BresaGen Xenograft Marketing Pty Ltd to St Vincent's Hospital. However, despite the agreement, by 2006 the company had yet to transfer the shares (BresaGen Press Release, 14 August 2008; BresaGen Annual Report, 2007).

In November 2003, BresaGen Ltd agreed to assign a number of its licenses relating to catheters for cell delivery to the US-based devices company NexGen Technologies, Inc. The intellectual property licenses had originally come from the University of Virginia, University of Minnesota, Virginia Commonwealth University and Stanford University. In return, NexGen provided BresaGen with a non-exclusive license to use the FDA-approved neurological cell therapy catheter with its own products, such as a treatment for Parkinson's disease. BresaGen received CA\$350,000 (approximately A\$380,000) as an upfront payment for the assignment and was granted shares representing four percent of NexGen. The former BresaGen consultant and then Director, Dr John Kucharczyk, was one of the founders of NexGen (BresaGen Press Release, 25 November 2003).

### **BresaGen Inc: Spun and Merged**

Another critical event happened in late 2003: BresaGen Ltd announced the spin-off and merger of BresaGen Inc. with the San Diego based company, CyThera Inc. BresaGen Ltd funded the move and the aim was to create one of the leading human stem cell therapy research companies in the world. The new entity would pursue diabetes research and would benefit from rationalised operating costs as well as building on synergies of stem cell biology research within the two companies.

The merger included BresaGen's Cell Therapy division that operated at the University of Georgia, and combined BresaGen's work on degenerative diseases of the central nervous system with CyThera's work on stem cell treatments for diabetes. CyThera had developed its own cell line at its R&D facility in San Diego and formed relationships with key clinicians in diabetes therapy at several leading US universities, and with the originators of the 'Edmonton Protocol' at the University of Alberta, in Edmonton, Canada (BresaGen Press Release, 27 November 2003).

A leading life sciences US venture capital firm, Sanderling Ventures, committed \$US1.5 million to the newly merged entity and assisted the new company with raising an additional \$US3.5 million in funding. The expanded company had a post funding valuation of \$US16.0 million and BresaGen Ltd owned approximately 30% of the new company. In relation to the 2001 Bush announcement of human Embryonic Stem (hES) cell lines federal funding eligibility, like BresaGen, CyThera also had their own lines that qualified for government grants (BresaGen Press Release, 27 November 2003).

The deed of agreement that cemented the merger was finally signed in June 2004, however at that stage operations were being wound down in Australia, as the funding from the START grant had expired and more funds were difficult to obtain. John Smeaton also said another expected benefit of the merger included some new stem cell derivation research to be conducted in primate studies and human clinical trials in Australia (BresaGen Press Release, 27 November 2003).

As part of the statement, CyThera's Chairman and CEO Fred Middleton said, 'the combination of the two companies would provide additional access to US government grant opportunities as well as creating the research critical mass necessary to attract private funding. There are major synergies between the two merging companies which have the potential to greatly advance the human clinical promise of

stem cell therapies in the not too distant future,' Mr Middleton said (BresaGen Press Release, 27 November 2003).

This would mean that in effect BresaGen would most likely become a holding company with stakes in several other businesses, i.e. its subsidiaries. Smeaton was reported as saying of this: 'as a holding company, BresaGen could become a vehicle to do other things within the biotechnology sector. He [Smeaton] drew parallels with long-time public biotech investment companies like Circadian Technologies, which has been behind the formation of several listed companies including Metabolic Pharmaceuticals, Optiscan, Axon Instruments and Antisense Therapeutics' (*Australian Life Scientist News*, 28 November 2007).

Furthermore, in the interview with *LifeScientist* Smeaton stated:

'It's a good marriage in good hands, Smeaton told *Australian Biotechnology News* after yesterday's meeting. The combination of cash received and grants available from the US government should be enough to fund activities for two years, Smeaton said, and by then significant milestones should be achieved to attract further funding.

At Thursday's AGM, Smeaton told shareholders that the next step would be to pin out the protein pharmaceuticals business into a new entity. Two options are potentially open to the company here. Earlier in the year BresaGen engaged US merchant bankers Caymus to raise funds for a new private company to hold the protein pharmaceutical division's assets, but so far no firm offers have been received by US investors. But the company has approved a term sheet with Queensland VC group CM Capital, involving formation of a new private company to which BresaGen would contribute its protein pharmaceutical assets, including IP and personnel. Smeaton said an extraordinary general meeting would be held in late January or early February to vote on the transaction.

The company also cancelled its plans to raise \$5 million through a private placement of convertible preference shares. Investors reacted cautiously to yesterday's announcements, and at press time today the company's shares were trading slightly lower at \$0.26 on moderate volumes. (*LifeScientist News*, 28 November 2007)

Allan Robins gave his account of how and why the CyThera deal had come

about:

This was a deal put together [because] it was pretty obvious that BresaGen Limited was running into some financial difficulties. We weren't going to be able to raise more funds and so we were looking at what's the best way to fund this vehicle and CyThera was a company that had complementary technology. They had potentially nine ES cell lines, none of which turned out to be real.

As a side note, everybody knew in about May of 2001 that the [US] federal government was going to make this decision to only fund cell lines that had been derived by a certain time. We didn't know what that time would be so lots of people went around basically just plating down embryos and then freezing them away not only to grow the ES cell lines but saying we'll figure that out afterwards. Bush's policy actually led to the destruction of a lot of embryos for no good reason. Cythera had nine of them but none of them recovered. Bush announced at the time that there were 68 so everybody thought that's bullshit.

As you know, there's 20 or 21 on the federal register so CyThera had an investor, Fred Middleton from Sanderling, who's very willing to listen to a proposal to put the companies together and willing to fund that and so that's what we did. We put the two companies together and Fred put up the funding for that. That was the reason to do it. On the back of that, unbeknownst to us at the time, but they were also talking to Novocell, which is a cell encapsulation company. After we merged with CyThera only about three or four months later we merged with Novocell and so there were two mergers sort of back to back. (interview, 2007)

Smeaton could recall the connections in further detail:

Well, that was getting towards sort of the end of the end days, as far as I was concerned, and we were running out of money, though we still had a couple of million bucks in the bank and the board were getting a bit anxious. Then we were looking at how should we take this forward, and I'd been invited to speak at a meeting on the west coast, which I'd done, and that was all about human embryonic stem cells; had people like Geron and whatnot there. I met a woman there who was also a specialist, Jean Loring, and she'd been involved in the founding of CyThera. Anyway, so Jean and I got talking and found we had common interests and a common view of Geron, who were trying to sort of dominate the field and make it very difficult for everybody else. So we invited her to come over and just talk to our group and see what there was in common with us and she might be able to work with us, which actually didn't happen. But we maintained contact with her. She was sort of interested in the field and she'd said, well you know, you guys really ought to talk to Fred [Middleton] ... He was the VC behind CyThera. She eventually organised that meeting and we went up to San Diego and met up with him and that was the beginnings of putting CyThera and BresaGen together. [It

was] just trying to get a bit of critical mass in the stem cell area. It was Fred Middleton who's with one of the big VC firms. He was originally the first financial controller for Genentec. (interview, 2007)

## **Resignations and Administration**

The first month of 2004 heralded turbulent times ahead for BresaGen that would last almost 12 months. On January 19, three directors of board resigned: Peter Hart (Chairman), Chris Juttner and John Harkness. The following day, the company made a further difficult announcement – the company was to go into voluntary administration, and Bruce Carter and Martin Lewis of Ferrier Hodgson were appointed Administrators.

Several factors had contributed to this situation, including the termination of negotiations with CM Capital, which had been continuing for several months, with the objective of restructuring the company. Moreover, there was still no firm investor from the US with respect to Generipharm. One of the reasons according to Smeaton was geography – Australia is a long way away from the US: ‘when we were doing the Generipharm thing, we had comments from a couple of people because we were looking to raise a fair chunk of money, sort of 30 million or so, and the response was positive except if this was in New Jersey, we'd fund it. But because it was in Australia, it was too hard, too far away, you know’ (Smeaton, 2007). Realistically, the company was running very short on money and there was nothing on the horizon in terms of an investor either locally or abroad.

Hart had a different view as to what some of the problems were:

John Smeaton always was and, I guess, always will be a blue-sky optimist, etcetera, etcetera, and ‘all I need's another five, ten, 15, 20 million dollars’. He tried to raise if you like, private venture funding out of Atlanta. Tried to sell the company to each and anybody, including Cythera. They were involved. He was just looking to raise funds to keep going. He used to spend so much time, really, just sitting around dreaming up ideas, etcetera, etcetera ... [I]n the end, it just didn't – the company ran out of the money. It didn't

have the legs, in the first place. It didn't make the best use of the opportunities that it had, in the fields that it could have. You know, stem cell technology – perhaps it is the future. In 20 years time, we'll still be saying stem cell technology will be the future. (interview, 2007)

On 19 January 2004, the Australian Board members placed a phone call to their US-based colleagues to inform them of their position with respect to allowing BresaGen to continue to trade, considering in the opinion of the Australians, the firm was excruciatingly close to being deemed insolvent. Hart explained:

We were out of money. So we put it into voluntary administration. I mean, the fact the way it actually went was that – through a quirk of fate – we actually ran out of money on – whatever it was – the 20<sup>th</sup> January. We had a board meeting that day to put it into administration. The board split, three, three, on whether it should go into administration. I resigned that day. Yeah. Because the other three, who were all in America, didn't want to put it into administration. They wanted to give something else one last fling or do something. No. We had a vote and the vote was tied. So I had the binding – I had the casting vote. I declined to use it. I resigned. Those who want to stay, they did – so three of us resigned and the other three put it into administration the next day.

We were really in an absolute bind at the end. We were running out of money by the day. We had it down to days...almost hours. I have a very heightened awareness of my responsibilities, but also of my – what's the word I'm looking for? You know, duty to myself, i.e., I am not going to trade while insolvent. (interview, 2007)

Juttner confirmed that in his view, the company should not have aimed to keep trading, and they were actually approaching insolvency, 'Smeaton and the Americans were prepared to spend the money that was an entitlement for employees, in order to keep trying to raise money on this plan' (interview, 2007).

Smeaton gave his detailed account of how things happened as he saw them:

I think we were really on the right track and I think they [the Board] got [bad advice] – though Australian law is difficult for a start and the directors become personally liable if you trade insolvent. But we were a long way from

that, and the people here [in the US] who were involved in the board,<sup>28</sup> they just couldn't believe it. They said, well, we got a couple of million dollars in the bank, why aren't we keeping on going? [If] it doesn't all sort of work out, well then everybody walks away and that's that.

Well, the money, there was ... money in the bank, it was just the company's sort of obligations in terms of things like your long-service leave and that sort of thing ... employee contracts. They put a lot of people off [with] sort of six months severance pay. So it's a very different scene to here [in the US] where in those sorts of companies ... – entrepreneurial-type companies –... people accept the risk, but they also get the rewards, you know, through stock options and stuff. But in Australia, the cultural [practice] hadn't quite crossed that divide at that point.

Then in the end, I think we got some fairly self-serving advice from the lawyers because when this got down to the wire, there was a sort of a board meeting and the three Australian directors resigned. That left me and a couple of other guys who were over here [the US] and they were CytoGenesis people.

So we thought we'd keep going when there was a meeting called by phone for the next day with Linton Burns who was the company secretary, and Hart who had become Chairman ... The lawyers were there and they told us, I think in a quite self-serving way, that we had to basically go into administration because we didn't have two Australian directors which we were required to have. They didn't say that we any time to find them. So we thought well, we were getting this legal advice from our lawyers and we were sort of caught between a rock and a hard place, so somewhat hypocritically we decided we had to accept the administration option and the lawyers and administrators, I think they made A\$1.7 million in fees or something out of it. So that's where the A\$2 million went.

The people who really got sort of screwed out of it were the shareholders. I mean ... I think it got cut off a little soon. Subsequently when the administrators were [removed] – because they pulled out of the picture and the CBio folks sort of took over. They then [Cbio and the Board] made a few sort of self-serving remarks saying this was all a new company and people like me and the other directors had sort of screwed up and that they were going to do a new thing. What do they do? They produced a generics biopharmaceutical company. The money document [memorandum of understanding/prospective type document] that they put out in the end wasn't successful. There were paragraphs in that that were paraphrased directly or taken directly out of our generic fund. They didn't do anything new. Anything

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<sup>28</sup> Rudy Mazzocchi, from the United States was appointed the Chairman of the BresaGen Ltd board from 19 January 2004, following the resignation of Peter Hart who had held the position until that time. (BresaGen Annual Report, 2004)

new they did was they wrote down to zero the investment in the stem cell stuff, which is going well. That company's likely to be sold in the next year or so for several hundred million dollars. So you know, the shareholders have missed out completely and the Cbio people didn't attach any value to that when they sold the company to [Hospira]. They sold it for about the same price that the shares reached on the day that they came back on the market. Meanwhile, they'd let some of their mates in at 5 cents a share, which they haven't offered to existing shareholders, but they offered them 10 cents.

[The stem cell therapy business] that was sort of high risk, but it looks like there is something going to come out of that by getting it together with CyThera, but more importantly, with a real venture capitalist [Fred Middleton] and he [Middleton] wanted the presidential cell lines that we had. So that had some value and he had sort of seen how to play it and has been able to raise quite a bit money. They spent quite a lot of money since. Yeah, so anyway, we had some interesting science going.

I think the sort of basic strategy of stem cells and to go for generic pharmaceuticals was right, but we just weren't able to sort of hang in there and get the money back from Macquarie. It was the escrow over the court case and was three-quarters of a million there and then collect the money out of the IMVS settlement. Those things were pending and the administrators and the lawyers had the benefit of all that instead of the shareholders. [If we had been given time to find two directors, then] I think it may have turned out differently, but finding a couple of directors in Australia and why we had to have them, I don't know, but that's the law. How long we would've had, I'm not certain, but we were told we had no option. (interview, 2007)

Robins also echoed Smeaton's sentiments about the way the company had been abruptly halted, 'He [Smeaton] feels extremely jaundiced about it and I think he has some good reasons to feel jaundiced about it. I think the lawyers were very self-serving and we had about A\$2 million in the bank when the board decided to put us into receivership. Just criminal and I don't think we were that far away from getting Generipharm off the ground here in the US. That was Caymus's opinion. I just think that was criminal' (interview, 2007).

Like coins, stories also have two sides. Juttner and Hart told the flipside of this story:

But during all that there was this dream of getting into generic bio-products, which was going to be extremely tricky for a company that hadn't got very

far. But it led to a huge amount of effort being put into trying to develop a floatable entity, a fundable entity, US based. [Generipharm] working with these people from Atlanta, these merchant banker types, [Caymus Partners] And basically a huge amount of time and energy and money was put into developing business plans and scientific codes and so on and so on and so on. But that proved to be unfundable as well, which then takes you to the beginning of 2004, where the board disintegrated in a board meeting. (interview Juttner, 2007)

Hart retold the events of that day in January:

The other three, who were all in America, didn't want to put it into administration, they wanted to give something else one last fling or do something. No. We had a vote and the vote was tied. So I had the binding – I had the casting vote. I declined to use it. I resigned. Those who wanted to stay they did – so three of us resigned and the other three put it into administration the next day. (interview, 2007)

With regards to Peter Hart not using his casting vote, Juttner made his position on the matter clear – both now and then to Hart himself:

I've said to him I think he didn't make the right decision, because I think frankly he should have used his casting vote, because it was split between the two. I mean it was an issue really, over entitlements, so that because the company had been running for 20 years, there were a couple of million dollars worth of entitlements associated with long service leave and all that sort of thing. (interview, 2007)

Juttner also spoke of how he saw the issue being with respect to the US based board members: 'Smeaton and the Americans were prepared to spend the money that was an entitlement for employees, in order to keep trying to raise money on this plan' (interview, 2007). And when the suggestion was raised that Smeaton had thought they were 'close' to getting funding, Juttner replied:

Well, they had failed I think was the message, and it had been floated long and hard for months and months and months, and there was no one interested. That was the message, and those of us on the board in Australia, Hart, John [Harkness and me] we simply felt that, and we thought the board had agreed. So at the last board meeting it was really quite surprising when suddenly Smeaton and the two Americans wanted to continue trading.

... [T]he board was deadlocked 3/3 and Hart resigned, rather than use his casting vote, which I think was the wrong decision and I've said so to him. I think it would have been better to have managed it through transition with a viable board. And indeed what happened was as soon as the three of us resigned, it then became a situation whereby an Australian company could not continue operating with a majority of its board members being outside the country, and not being Australians. So the next day they went into receivership anyway. (interview, 2007)

Hart had very strong personal convictions about his role and responsibilities as a director of a Board, saying:

We kept getting the push from [the US] – we were continually getting the push from John Smeaton and the American crew to get another day, do this deal, do something else. It really – as I say – in perfect hindsight, we should have sacked Smeaton. (interview, 2007)

When it was put to Juttner that perhaps not enough time had been offered to replace the board members and the US team, for want of a better description, felt they had no other choice except to reluctantly capitulate, he replied:

I don't know what happened. I know that one of the people I think John tried to recruit was Meera [Verma] as a board member, and she didn't want to be part of it, in that short period of time. I don't know who else they spoke to. It was legal advice [we were given] that it was non-viable, but I would expect John [Smeaton] to say exactly that. (interview, 2007)

Bastiras also reflected back to that time and offered some thoughts as to the issues dogging the company:

Well, when the company went into receivership in January 2004 – BresaGen Inc, I think officially – I'm not sure whether it still exists or not – but we are still using the letterheads, maybe because they need the paper, I don't know. One of the things that I think always confused me, is that if you came into the BresaGen building, you would also find in small writing somewhere, a list of companies affiliated with BresaGen. One of the failings the managers seemed to have was that they couldn't tie up all those loose ends, so the company had all those empty shells of companies. They were bits and pieces, they were a way to achieve a certain goal, so they were vehicles for achieving something that may be a short-term goal, and then that vehicle was discarded. And rather than cleaning it up and closing it down, it just sort of remained. Even to this day there are a number of small holdings. For example, just before we went

into administration, a company was formed with the name Generipharm and the aim of that company was to make generic biologics. And then when the company went into administration, that name still existed, Generipharm. (interview, 2007)

Smeaton felt strongly about the bottom line, 'It is a pity that it ended how it did. But in the end, it's sort of come out okay, but it's unfortunate the shareholders have put up high-risk money and they're getting nothing out of it' (interview, 2007).

### **CBio to the Rescue**

On April 1 2004, Ferrier Hodgson, who had been managing the company in lieu of non-functioning Board, announced that an in-principle agreement for the re-structure and re-listing of the company had been reached with CBio Ltd, an unlisted public biotech company based in Queensland. The administrators, Carter and Lewis signed a Heads of Agreement with CBio who would acquire just over half of the company (51%). The objectives of the deal were to allow the protein pharmaceutical business to continue to operate from Thebarton, SA and to retain the majority of the workforce. One casualty of the administration was John Smeaton; his employment was terminated on 20 May. Smeaton commented on this:

Well, I sort of tried to work with the administrators a bit to make sure the deal with CyThera went through. But I don't think they've [BresaGen] done that. But I tried to push that as hard as I could and we had another potential deal on the table with NPS Pharmaceuticals, it was quite a good fit which had happened but it cost them in administration, so that was the end of that. So in the end, they figured out that they should stop paying me, so they called me up and told me that I was sort of instantly fired - after 17 years, and they paid me out. But I was planning to retire anyway so ... Then with some other guys, we got another small biotech company going. (interview, 2007)

The following month, in May, a creditors' meeting was held and it was agreed that BresaGen should execute a Deed of Company Agreement (DOCA) and Carter and

Lewis should administer this deed. The 2004 BresaGen Annual Report documented this indeed took place and this allowed the implementation of CBio's management role to commence:

On 24 May 2004 a DOCA was entered into between the Company, the Administrators and CBio, an Australian registered corporation. Under this DOCA CBio shall:

- (a) fund the Operating Cash Shortfall of the Company, to a maximum of A\$1.2 million, commencing 1 April 2004 and ending on the date that the DOCA is effectuated on which date CBio is to pay the Acquisition Sum, defined as being the sum which is sufficient to pay a dividend of 100 cents in the dollar to the Creditors of the Company.
- (b) in addition to funding for the Operating Cash Shortfall, pay a sum up to A\$1.7 million within two business days of the date of the General Meeting set down for 11 October 2004.

The amount of A\$2.9 million, being the sum of (a) and (b) above, has been received from CBio and is held in the Deed Administrators' solicitors' trust account. As part of the DOCA the Company has called a Shareholders' Meeting for 11 October 2004, at which meeting shareholders will consider resolutions to issue to CBio, shares representing 51% of the company and entering into a A\$3.4 million convertible note facility. (BresaGen Annual Report, 2005, pp.5-6)

During the next several months, two key events took place. On 28 June BresaGen Inc's deal with CyThera was finalised. Second, in August another merger was announced: this time between CyThera and Novocell, a mid-stage biopharmaceutical company based in Irvine California, who focused on commercialising encapsulated cell technology for the treatment of diabetes and other diseases. This subsequent merger left BresaGen Inc. with a 9.75% share of Novocell Inc. (BresaGen Annual Report, 2005)

For the remaining BresaGen Inc staff, namely Allan Robins, this meant a shift in terms of employers, as he explained:

I'm one of the senior managers of Novocell so I'm actually a Novocell employee and have a Novocell business card but the folks here that work for

me, work [for] BresaGen. BresaGen is a wholly owned subsidiary and still a Delaware corporation and a legal entity. Part of that is because we've got good brand recognition, I guess, from the ES cell lines and Bush's announcement and so they're known as the BresaGen line so there's an unwillingness right at the moment to change the name. This pissed Meera off in Adelaide because they were BresaGen Limited and we were BresaGen Inc and they wanted us to change our name but we didn't want to. We had more going on really in the marketplace than they did. We weren't asking them to change their name but we didn't want to change our name. (interview, 2007)

Nearly nine months after going into voluntary administration, BresaGen re-appeared from the darkness, emerging on 13 October 2004, and two months later they were re-instated on the Australian Stock Exchange on 14 December 2004. Additionally, from 11 October 2004 the company's directors duties and responsibilities were restored. As per the initial DOCA, the Annual General Meeting was held in October 2004 and the following resolutions were agreed upon: CBio Ltd would be issued 56,722,994 fully paid ordinary shares; the company would enter into a Convertible Note Facility with the proposed issue of a maximum of 34 convertible notes to CBio Limited in the company, with conversion of up to 68,000,000 ordinary shares; and Mr Stephen Jones, Dr Wolfgang Hanisch and Dr Meera Verma were appointed as directors. BresaGen was now operating under the control of the new investors, CBio Ltd, with the administrators having already stepped down (BresaGen Annual Report, 2005).

With regards to the 34 A\$100,000 convertible notes facility, CBio Limited, the company's 49.9% shareholder, established this facility to ensure that the company had access to adequate working capital. The shareholders also agreed that this facility be split and A\$900,000 (9 x A\$100,000 notes) of this facility be transferred, on the same terms, to Australian Technology Information Fund Limited to increase the flexibility BresaGen had in drawing down funds (BresaGen Annual Report, 2005).

In terms of business operations, the only division still operating at that time was

the protein pharmaceutical division, which was split into three segments. The three operating divisions comprised: (1) protEcol™ Services: offering contract process development and manufacture of recombinant peptides and proteins; (2) API (Active Pharmaceutical Ingredients): offering manufacture and sale of various growth hormone products and custom human and veterinary biopharmaceuticals; and (3) and Operational Administration: the administrative arm of the business where non-sales revenue was collected (BresaGen Annual Report, 2005).

### **Contracts and Congratulations**

Less than three months since coming out of voluntary administration, the protEcol services division announced that it had been in discussions with 12 Australian and overseas companies regarding process development and manufacture of their biologics. At the end of January 2005, BresaGen achieved a significant milestone having signed contracts totalling A\$547,000. Additionally, a collaboration agreement was executed with an undisclosed overseas pharmaceutical company. The project was valued at A\$1.2 million.

A press release from BioInnovationSA said of BresaGen's performance:

Adelaide-based biotechnology company BresaGen has rebounded strongly since re-listing on the stock exchange. BresaGen, which specialises in peptide and protein pharmaceutical production, has secured contracts and collaborations in excess of A\$1.8 million and is confident of finalising several other deals in the coming months. Chief Executive Officer Dr Wolf Hanisch said the firm had been talking to 12 Australian and overseas companies regarding process development and contract manufacturing and signed projects worth over A\$600,000 for completion this calendar year. A collaboration agreement has been executed with an overseas pharmaceutical company and commencement of the initial project, valued at A\$1.2 million, is subject to finalisation of the commercial terms. BresaGen is also currently in the midst of an A\$8.8 million rights issue, which closed on February 22. The company's re-listing and contract wins represent a revival of the company since it was put into voluntary administration in January 2004. BresaGen's emergence from administration in October last year followed a significant

capital injection from its major shareholder, Queensland pharmaceutical group CBio Ltd.

Dr Hanisch said the re-capitalisation and re-listing was an ‘excellent result that lays the foundations for the company’s continuing growth’. He said BresaGen’s focus was now firmly on proteins and peptides, due to the increasing worldwide market in biopharmaceuticals. In 2003, 12 peptides were registered globally – with just that small group representing a market of A\$9.2 billion. Dr Hanish said BresaGen’s approach to process development involved targeting customers needing a process for recombinant production of protein or peptide required in large quantities for commercial success, where cost of goods sold is a major issue. (BioInnovation News Jan-Feb Issue, 2005, p. 7)

The 2005 Annual Report also proudly highlighted the fact that since coming out of administration, protEcol™ Services business had been experiencing strong growth and the directors felt that this was the setting of foundation for the continued growth in this business segment in the future.

Throughout 2004/2005, BresaGen’s cGMP<sup>29</sup> production facility was operational, providing the infrastructure required to build a profitable biopharmaceutical business. The rapid growth of protEcol™ Services whilst establishing the Active Pharmaceutical Ingredient (API’s) supply business remained the objective of the Board. This meant using the production facility to meet short-term contracts for clinical trial material and manufacture and sell a subset of proteins/peptides to buyers locked into supply agreements for pharmaceutical drug product produced in BresaGen’s plant. (BresaGen Annual Report, 2005)

The directors had further reason to be pleased with protEcol’s performance as August was a prosperous month: a contract was signed between BresaGen and Pepgen Corporation in the USA for BresaGen to progress the development of Pepgen’s

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<sup>29</sup> United States Food and Drug Administration (FDA) requirement for Code of Good Manufacturing Practice (cGMP)

autoimmune, inflammatory and viral therapies. The press release said:

BresaGen will help Pepgen to produce a novel interferon alpha analog, Neoferon™. Under the current contract BresaGen will further develop the E. coli-based process and produce GLP recombinant protein. 'We are pleased that Pepgen has chosen to continue working with BresaGen, as it validates the technology and capabilities of our protEcol™ Services business unit,' commented BresaGen Managing Director, Dr Wolf Hanisch. (BresaGen Press Release, 2 August 2005)

Second, the company was awarded a contract for Opsona Therapeutics Ltd based in Dublin, Republic of Ireland, to progress process development of its pre-clinical immunomodulator, OPN-201. Over a 6-month period, BresaGen conducted feasibility studies and process development for the eventual large-scale cGMP manufacture of recombinant OPN-201 (BioInnovation SA Press Release, 1 August 2005). Third, another contract was signed with a second un-named Middle East pharmaceutical company to develop and register a biopharmaceutical product. The contract included a combination of upfront and milestone payments and progress over a 12- to 18-month period.

Moreover, the company were planning to install a 500 litre fermentation tank. This signalled its commitment to attaining long-term production contracts and would increase the potential output of the plant five-fold as well as significantly reduce the direct material costs of production. Furthermore, fill line equipment, enabling BresaGen to exploit the current opportunities to provide Australian companies with an aseptic filling facility, was ordered. This was in response to the increasing numbers of domestic firms undertaking their clinical trials in Australia. The facility was expected to be commissioned and ready for use by early 2006. Helping finance this capital purchase, the company had applied for and been awarded a grant for A\$200,000 from the South Australian Government under the Bio Innovation SA Commercial Infrastructure grant

scheme. (BresaGen Annual Report, 2005)

ProtEcol Services earned revenues of A\$1,887,000 for the financial year ending 30 June 2005, down from A\$2,075,000 in the previous corresponding period. However, it was stated that this reduction was due to the company having difficulty signing new contracts during the administration period. Contract numbers increased significantly though for process development services after BresaGen was released from administration. This division had an operating loss of A\$978,000 for the year ended 30 June 2005 compared with an operating loss of A\$718,000 in the previous corresponding period. Considering this was the only operating division during the 2004/2005 financial year, it was a respectable outcome. The API Supply business was started after June 2005 (BresaGen Annual Report, 2005).

In terms of their cell therapy portfolio through their 9.75% interest in Novocell Inc, the directors felt that the success of this venture was highly speculative, depending on the R&D outcomes. Additionally, as no one from BresaGen was sitting on the Board of Novocell, it was decided that it was appropriate to write down the value of this investment by A\$4.769m to nil at 30 June 2005 (BresaGen Annual Report, 2005). BresaGen's reproductive technology division had been transferred back to the University of Adelaide in 2003, along with any and all outstanding contracts. The only remaining link with this division was the transfer of A\$18,000 on the financial statements which were the costs associated with the transfer that have been reported in 2004. (BresaGen Annual Report, 2005)

Of the notes that were offered in the DOCA, four were issued and reported accordingly:

Subsequent to the balance date 10,000,000 shares were issued to holders of convertible notes who exercised their rights to convert to shares under the Convertible Note deeds. Four of these convertible notes were issued after the

balance date.

Details of all notes that were converted follow:

**Table 9: Bresagen's Convertible Notes**

<b>Note Holder</b>	<b>Value of Note</b>	<b>Date Issued</b>	<b>Date Converted</b>	<b>Conversion Rate/ Share</b>	<b>No. of Shares Issued</b>
M Monsour	\$100,000	20 Jun 2005	02 Aug 2005	\$0.05	2,000,000
M Monsour	\$100,000	01 Jul 2005	02 Aug 2005	\$0.05	2,000,000
Yarandi P/L	\$100,000	19 Jul 2005	19 Jul 2005	\$0.05	2,000,000
Yarandi P/L	\$100,000	19 Jul 2005	19 Jul 2005	\$0.05	2,000,000
M Monsour	\$100,000	02 Aug 2005	02 Aug 2005	\$0.05	2,000,000

**Source: BresaGen Annual Report, 2005**

The Adelaide-based venture capital company, Paragon Equity, took a 10% equity holding in the company in exchange for investing A\$852,350. This represented an issue of 13.9 million shares, in the form of 10 million shares from five convertibles notes with a face value of A\$100,000. Shareholders approved the conversion rate in the May 2005 to be higher than 5 cents, for 'sophisticated investors'. These notes were converted on the day of purchase at 5 cents per share and a further 3,915,000 shares were acquired at a price of A\$0.09 cents. Paragon Equity Ltd was granted, subject to shareholder approval, 3,915,000 unlisted options at an exercise price of 12 cents and a 5-year expiry term (BresaGen Annual Report, 2005).

### **The Contracts Keep Coming!**

Late in 2005, BresaGen announced its expansion into the contract process development business by moving into the lucrative area of mammalian cell-derived therapeutics, with its first client to be Sydney-based biotechnology company, Psiron Ltd. It was intended to be a staged approach, with the first stage involving the construction of a pilot plant, housed within BresaGen's premises at Thebarton. The facility had the capacity to grow

mammalian cells for the production and purification of therapeutics to be used in pre-clinical studies and clinical trials, and the company had already had positive discussions with the TGA regarding the concept, design and licensing of the new facility. In the second stage, it was intended for the facility to be used to develop and produce Psiron's anti-tumour product CAVATAK™ for an undisclosed period of time. At that time, CAVATAK™ was in Phase I clinical trials in humans with Stage 4 Melanoma. The contract had a project value of about A\$2.5 million over a 2-year period (BresaGen Press Release to the ASX, 8 November 2005).

The year 2006 started very well for BresaGen. Contracts with Caldeon Pty Ltd and Tissue Therapies Ltd, worth \$680,000 were announced. Several other Australian biotech companies were promoted on the BresaGen website as being supplied with process development and material for various stages of product development. These companies included CBio, Hunter Immunology, QRx, Imugene, PDCO, and The University of Sydney. Sales and contract revenues had almost tripled in the six months from July 2005 to December 2005 – A\$2.2 million compared to A\$800,000 for the same period the previous year (Australian Life Scientist News, 27 January 2006).

In February 2006, BresaGen announced a distribution agreement with an Indian company BV BioCorp Ltd. This agreement covered the registration and distribution of two biopharmaceutical products in India. Under the terms of the agreement, BV BioCorp would register and market BresaGen's G-CSF<sup>30</sup> and an undisclosed product in India, Sri Lanka, Bangladesh and Nepal; however the commercial details of the

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<sup>30</sup> BresaGen announced it had successfully developed a process for the production of recombinant methionyl human granulocyte colony stimulating factor (G-CSF). G-CSF is the active substance in filgrastim, used in the treatment of neutropenia. In May 2005, the company announced its intention to develop G-CSF as an active pharmaceutical ingredient (API) for sale to pharmaceutical companies targeting the registration and marketing of biosimilar products. A biosimilar (or biogeneric) is defined by a rigorous set of quality criteria as being similar to a biological medicine already authorized for use. (Lab Business Week, 20 August 2006)

transaction remained confidential. It was anticipated that the products would be ready to commence clinical trials for registration in early 2007. In a press release Wolf Hanisch, said:

This agreement is an important step in the development of BresaGen's API Supply strategy, developing biogeneric products for the emerging markets of India, China, the Middle East and South-East Asia. We are in active negotiation with several other companies to extend distribution of our products into other territories. (BresaGen Press Release, 3 February 2006)

In May, a press release headline read, 'BresaGen Wins US Contract for Domain Antibodies'. The contract was for BresaGen to supply Domantis Ltd with services on domain antibodies. The protEcol services business was responsible for examining the feasibility of producing domain antibodies efficiently in e coli for Domantis (BresaGen Press Release, 7 May 2006).

Despite a series of new clients, BresaGen faced a setback of sorts: Psiron Ltd informed the company in June 2006 that it had now decided to carry out a series of Phase 1 trials in a number of different cancers before progressing to Phase II trials. As such, it would no longer require product to be produced by BresaGen for the Phase II trials in the previously planned time frame. Consequently, BresaGen decided not to expand this part of the business.

### **BresaGen to Hospira: Lessons & Legacy**

On 4 August 2006, BresaGen Ltd wrote to the ASX asking for a trading halt, pending a further announcement, which was made on 11 August: an off market takeover offer for all of the issued capital in BresaGen from Hospira Holdings (S.A.) Pty Ltd, a wholly owned subsidiary of Hospira, Inc. The offer to acquire all outstanding fully paid ordinary shares in BresaGen for 14 cents per share in cash represented a 47.4%

premium of the share price. The offer also included acquisition of all outstanding BresaGen share options from BresaGen option holders. Separately, BresaGen's major shareholder CBio Limited had undertaken to sell a 19.95% shareholding interest in BresaGen to Hospira. The bid for BresaGen was recommended to the shareholders and the offer of acquisition accepted in 2006.

With respect to the strategic management of the various business portfolios held by BresaGen, there was some consolidation that took place around this time. The company still had 50% ownership of Xenograft Marketing Pty Ltd (in partnership with St Vincent's Hospital, Melbourne) responsible for marketing the applications of the Xenograft Syndicate Technology in both the research and commercialisation periods. The equity accounted value of the investment was reduced to zero because the company's share of accumulated losses exceeded the historical cost of the investment and the company believed it had no formal association with BresaGen Xenograft Marketing Pty Ltd. In terms of other investments held by BresaGen, it controlled 100% entity of Metrotec Pty Ltd, BresaGen Investments Pty Ltd, BresaGen Transgenics Pty Ltd, and Generipharm Inc.

Of the shareholders now controlling BresaGen Ltd, the three largest in order were Hospira Holdings (SA) Pty Ltd, CBio Ltd and Paragon Equity Ltd and to reflect the Hospira takeover, Mark Baker and Thomas Werner (from Hospira) were appointed directors<sup>31</sup> and Stephen Jones, Wolfgang Hanisch, Michael Monsour and Geoffrey Thomas resigned.

As to how the deal with Hospira came about, Robins took the credit saying, 'The whole BresaGen thing, I mean, again I introduced BresaGen Limited to Hospira. I

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<sup>31</sup> Baker and Werner were appointed directors on 12 October 2006

know the Chief Scientific Officer there - that led to their acquisition'. However, it seemed as though Robins was somewhat downhearted about BresaGen's takeover, 'You've got all that work over 10 or 15 years [and] basically it's all been capitalised on in the United States' (interview, 2007). He followed this comment up by adding:

I just don't think there's the appetite in Australia to fund research which is 10 years away from commercialisation. Any drug from discovery to commercialisation is a 12 to 15 year process and it costs a lot of money ... over half a billion ... but there's just not the appetite in Australia to do that. I mean, we'll never grow anything there while there's no appetite to fund it. The people that will reap the reward are the people that are willing to take the risk and they're not in Australia. (interview, 2007)

John Smeaton also reflected on BresaGen and its resting place under the mantle of Hospira. He too was critical of the infrastructure and the environment during which BresaGen grew up, i.e. the 1980s and 1990s in Australia, and the era of syndication in lieu of organised venture capital or seed funding, and spoke of the funding constraints at the time, which were biased towards the risky 'blue sky' projects:

We raised quite a bit of money from syndicates. The weakness of that system was that yes, you can raise money, but they had a bias towards things that were really too risky and they wouldn't let you put money into things that were very prospective. That would've made a huge difference, so we had to be very careful about just where we were spending the cash. We weren't necessarily spending it where it was probably scientifically most logical. [It was the] Government rules [that] if it didn't pass the high-risk sort of checkpoints, it didn't get syndicate approval. It didn't make a great deal of sense to us ... because some of the protein stuff, if we could've syndicated the human growth hormone project [things could have been very different ...]

[In the US] there are hundreds of VC companies which sell hundreds of million dollars, or billion dollar funds who are going to support these companies through to the stage where they really should be floated when they've got products coming into the market and likely to have billion dollar incomes.

[The biggest problem for Australia is that Australians like to invest in holes in the ground.] Yeah, that's right. This is very similar to mining, but they haven't quite figured that out yet. Mining, they drill a lot of dry holes. I mean, I think in many ways through all sorts of things, like floats and syndicates, all that stuff, I think we raised about 65 million, which is quite a bit of cash. But

unfortunately, couldn't focus it all in quite the right direction. (interview, 2007)

Juttner also contributed his thoughts on the Australian biotechnology spin-off company model:

Well of course the Australian model is stupid, because of the early IPO situation. That's one problem. And stuff gets IPO'd here, that would never get up in the US. And it's a bad thing for the Australian industry in my opinion. Secondly, I mean Amgen had to out-license a hell of a lot of stuff to survive, so they gave away a lot of their assets in the early stages to keep their survivorship, but they are successful now. (interview, 2007)

Verma added to Juttner's thoughts by saying

I'd say the environment, which the government has the major levers for, it is responsible [for companies going to IPO too early] because of the main ones – capital gains tax. It is very difficult for anyone to invest in risky activities in Australia in a sensible way because the risk factor is not recognised. But if you happen to hit a winner, so for every five ones you do, you do on the two that you might hit winners for, you lose all your upside and I think that makes it really difficult for people who invest true risk capital. Because you can't get back the reasonable quantum that true risk capital [needs]. It means people have to look elsewhere for funding and they do it by either selling the farm or listing. I think that's the problem. (interview, 2005)

Meera Verma was more pragmatic about the limitations the little biotech company Bresa had faced in the early days:

We basically spun out at a time when we built our own way along the way and tried to find a commercial niche that would work for what we were doing. It really was very much a trial and error approach as well. We initially started as a life science company and we had to be competitive with global life science companies like Amersham ... we were picked up by 40% of the local market product lines but that was really just baseless ... we didn't know that we would be able to do that. [That we were able to achieve that] I think it was more the fact that we came out of academia and the local brand that helped build that. But it was basically just a hard slog to build that because you didn't know people would give you any mileage for being a locally produced product or not. It was good service and it was the local brand that gave us that. I think after we did that it gave us the confidence and we said, 'why don't we just develop our own therapeutic drugs rather than producing tools for other people to do the work, we have access to the technology etc. (interview, 2005)

If the investment climate had been challenging, so too was the regulatory environment at times:

... [W]e had a conversation with the ... TGA back in '93, where we proposed basically a generic human growth hormone. We had a long discussion with them and in the end we convinced them that this was just a molecule and we could characterise it as an enough and therefore they should register it. Now, they sort of agreed with that, but then subsequently, they backtracked, and I think they got pressure from the big pharma companies. So it was a fairly sort of dirty game. A lot of lobbying goes on. (interview with Smeaton, 2007)

One positive that did come to fruition from this encounter though was the connection and subsequent appointment of a very good BresaGen director, Geoff Vaughan, 'The guy that was head of the TGA in those days was Geoff Vaughan; we subsequently got him on our board. He was one of the two really useful board members we had' (interview with Smeaton, 2007).

Smeaton was also complimentary about other key figures in BresaGen's life:

The other good director we had was [Alan] McGregor. Yeah, well, he was the guy that fingered Elliott in Elders. Sort of got Elliott pushed out. He left that board, but he was involved in James Hardie and all the asbestos stuff. But Alan is dead now, he died about two years ago. But he was a very interesting guy, legally trained, but somebody who could listen to a scientific discussion and then had an uncanny ability to sort of sum it up very succinctly with the key points, get it all right. Very clever guy and we developed I think a good relationship after a while.

When it came to the float, he said, the company shouldn't be floated, that wasn't the right thing to do. So he resigned. I think I almost persuaded him that he should give up the Faulding's thing, because he was Chairman of Faulding's at the time. [I asked him if he could] stay with us instead. I think he really thought about it seriously for a while and we actually lasted longer than Faulding's. Yeah, but I mean, Alan was basically right, the company shouldn't have been floated and there wasn't any other way to get any cash in Australia. [There were no other options] that's right, and that [was] exactly the situation. (interview, 2007)

Others were perhaps more negative in their views about BresaGen's history:

You know, I look back in hindsight with a certain degree – once I take the bitterness out of some of the decisions. One of the problems with the

company was the fact that it didn't really stay focused. Had these great ideas and people ... spent less time sort of sitting around, kicking tires, on the next you-beaut idea, rather than necessarily focusing on the business and driving the business forward ... (interview with Hart, 2007)

Bastiras, who had been with BresaGen since 1989, thought back over the events that had led the company to this position. He said:

I was always the Devil's Advocate. I was sort of questioning and saying, why the hell are we getting into stem cells? We don't know anything about stem cells ... Peter Rathjen [started talking] about it ... [saying] there's a lot of promise, so it was just one of those things where [we fell into it] – so we raised A\$12 million, and half of that money was going to go to stem cell stuff, and the other half was going to go into protein stuff. In the end it turned out to probably be more like 75/25, more money was spent on stem cells and less on the protein. What's a good and bad milestone? (interview, 2007)

Another critical ingredient that shaped BresaGen's sense of being was the university systems, processes and attitudes that prevailed at the time. Numerous people spoke of the role of Luminis, and how their decisions impacted on BresaGen's journey to adulthood, at times both positively and negatively. According to Hart, the key driver of setting up Luminis was the then Vice Chancellor of the University of Adelaide, Professor David Stranks. Moreover, Hart explained how Stranks had differed from his successors:

Stranks - he was the vice-chancellor at the time, in the early to mid '80s - and he apparently was a great believer in this commercialisation, was a great believer that Luminis or ARI was the way to go. He was a great supporter of it. He then died. I'm not sure if he actually died in office, but [he suffered] ill health and died.

Then Kevin Marjorie-Banks took over as vice-chancellor. I don't think Kevin really wanted to be the vice-chancellor. He taught English or something and had zero interest, zero interest in commercialisation. He was very pleasant, very pleasant to me, at the times I've met him and all the rest of it. He had zilch [interest] – he didn't want to know about commercialisation, money, anything else that interfered with him going off to Oxford every year. Got the picture? One of those old-style academics. Then, after that was Gavin Brown. Gavin was okay. Gavin paid lip service to commercialisation. Luminis was never the most popular organisation inside the university. Gavin Brown didn't

stay for long, before he marched off to Sydney.

Then Mary [O’Kane] came. Mary was a control freak. You know. There are no other words for Mary, than absolute control freak. I and my board were running Luminis as a wholly owned, but independent, organisation. We worked within a remit. We worked within the rules of the university, particularly with the commercialisation of IP and consultancies and all of those things, which are probably still issues there, which Mary just didn’t like. It was an amazing time. She wanted us to work for her ... my chairman and I ... well no. We worked within [the guidelines] – we had a deed, you know, which the university had signed off on – we had IP rules, which the university itself [specified] or they’re university rules. Mary, we never worked out. She eventually succeeded in getting rid of all of us. In the end, I said well ... Offer me a package and I’ll go. They did and I went. (interview, 2007)

Smeaton had strong views about Luminis, revealing a fundamental difference between his own goals and those of Hart:

Parbury was an entrepreneurial-type guy; he had sort of the right idea. He was probably too nice a guy, I think. He got basically screwed by the university. Then Hart took over. He was an ex-military Navy sort of guy. He hasn’t got much imagination. Luminis didn’t sort of really prosper then I don’t think. I mean he was more interested in sort of the bottom line. Well, that wasn’t what I was all about. Then the university sort of in the end, they threw him out. But as part of his consolation present, they gave him a permanent seat on the BresaGen board. They said that they’d vote for him for two more times for re-election. So he ended up as chairman sort of by default. (interview, 2007)

From his point of view, Hart saw Luminis’s role as one of independence, ‘my board was an independent board, chaired by Brian Burns, who was a Chairman. We were basically trying to run it as a business. The University was acting like a university. Bresatec was trying to run itself like it had no owner. Bresatec always tries to do that’ (interview, 2007)!

Smeaton commented on the general lack of good intellectual property arising out of the university at that time. In a sense Luminis could only be as prosperous as the intellectual property they were aiming to commercialise would allow:

I think it was David Beecher from the Adelaide University who was the

bursar. He said early in the piece that, you're pushing it uphill with a pointed stick, mate. There's nothing here. This university doesn't have anything, as we trolled through the whole lot, and it may be a little bit out of the way in farm breeding and he was right, there's nothing else at this place. (interview, 2007)

Hart was quick to mitigate some of the issues facing the various stakeholders:

[Luminis was] relatively [new]. Certainly new to Adelaide. There were a number of commercialisation companies going. We had Integrated Silicone Design going out of engineering and Repromed was starting up. It had a service base and it was going quite well. Bresatec, if you like – I'm not saying it wasn't going well, but it always had this hunger for money, and also had a difficulty, within the university, or had a difficulty caused to all the parties involved, by agreements which had been signed with the university and with the departments, etcetera, etcetera, as to rights to IP, which, I think – all I can say about those agreements were – again, I'm not saying I would have done any better had I been there – but they were written in haste and repetitive, long. (interview, 2007)

As for the name Luminis, Hart also had an opinion on this, 'Luminis – it was never a name I liked. I was never rushed about the name. It came from the university motto, but it was constantly misspelled. Luminis, the first thing you say, well, what does Luminis do? I think Jim Betterson was the guy who made up the name and me, at the time, it sounded good or whatever' (interview, 2007).

It is well known in strategic management that organisations that succeed do so with the unequivocal support of the most senior management. In some respects then it is a credit to all those involved that Luminis and its multiple spin-offs, including BresaGen and GroPep, survived at all considering the attitude of one of the Vice Chancellors during those early days, 'But Mary – I don't know. Mary just had a real set against it. She had a set against BresaGen. The BresaGen IPO she resisted, almost to the death' (interview, 2007).

## **Microscopes are for Lab Books Not Cells**

Besides the more traditional challenges that had been thrown up to BresaGen along the way, such as lack of financing, strategic goals and the like, BresaGen had suffered even more difficult to recognise, let alone manage: data fraud. This is something a biotech company does not expect to face, yet BresaGen suffered three episodes of intellectual property deception: once with pig transgenesis, once with stem cell IP, and once with E21R.

The ramifications on all occasions were extremely serious and enduring, and in the case of E21R, virtually responsible for the demise of the two companies involved – BresaGen Ltd and British Biotech. Smeaton said of this, ‘That basically what was dragged the company into administration then. That was only one of three instances of what probably be called intellectual fraud that we experienced in, what, 15, 16 years I was there. So there’s a lot more of that around than people appreciate’ (interview, 2007).

Smeaton described the first experience that happened in the late eighties:

some of the key transgenic data though, that was our first encounter with data fraud. There was a guy who had worked in Seamark’s department then came to work for the company, and he falsified data in terms of pig embryonic stem cells. This happened at just the time we did the deal with Baxter and we didn’t know, and as soon as we did know – Allan was the one that found this out – we instantly dismissed this guy ...

As soon as we knew, we advised Baxter and that really sort of hung over that relationship from that day forward. That was very costly because they didn’t really believe that we didn’t know. These things can have very [bad long term impact]. (interview, 2007)

Chris Juttner talked about BresaGen’s third instance of fraud and described the issues of how this earlier work went on to have an impact on the stem cell work:

I think the first wheel to go [in terms of BresaGen’s collapse into voluntary

administration] was the realisation that maybe some of the science and IP on which the embryonic stem cell development worked, was based, was not as strong and robust as we thought it was. No, it was more some of the stuff that had been licensed out of Rathjen's department. And I'm not sure that that ever became totally clear within press releases. It was very difficult also to work in that environment, so that there came to be a bit of uncertainty about whether the science was actually as robust as we thought it was. It was going to be applicable in transfer from mouse to human, and whether it meant what the company and Rathjen had previously thought was the case. So it meant that the whole embryonic stem cell direction started having to be re-thought. It also meant that the IP basis of that was less secure, so then the company started looking at doing other deals. There were major announcements about an IP deal to try and make the situation with embryonic stem cells stronger from an IP point of view, than it appeared to be at present. Because the Thompson intellectual property that Geron had licensed, looked like it was going to make it difficult for anyone to move in that field. Although if the science was advanced sufficiently rapidly, then it was clearly going to be possible to do deals with other companies who might hold blocking IP.

So the situation is that this is clearly incredibly complex science. And I guess, one of the things that I kept saying to them [BresaGen management] from my experience of having worked in the biotech industry in the US is that while you may not hold all the IP, because everything is so complex, the success is going to go to the people who work the science out. And the science is then going to lead to new IP, which is going to put them in a position to do deals in a better sort of way, than otherwise would have been the case, where you need to get hold of IP. It's very complicated, extraordinarily complicated, and you're doing it at a time of hypothesising an ability to commercialise something. You're developing business plans and development plans, at a time when you don't have all the pieces on the table and you don't understand it. So doing this in the context of needing to continue to raise funds in a global sense, in a highly competitive area, is very difficult. (interview, 2007)

Hart also characterised the questions marks surrounding the stem cell IP as a major turning point for the company:

John Smeaton fell out quite severely with a couple of the principals [in the US]. It was then things started to go, if you like, bad, about 2000, 2001. You go through all these things like the Bush announcement of stem cells, which could have – perhaps should have – worked to BresaGen's advantage, the complete falling out with Peter Rathjen and almost a question mark over his science. But I think, by then, it was quite clear that we were becoming [in danger of things going very wrong] – and the way around his science was to try and get a licence out of someone ... it was all pretty much unravelling. It had got to the stage where nobody was talking to anybody else. The chairman, John Hasker – suddenly just up and resigned, 2002 (interview, 2007)

The intellectual property fraud that happened with E21R was clearly the most significant and disturbing breach of trust and act of betrayal that many of the BresaGen people had ever seen or experienced, both personally and professionally. Hart felt that this event cannot just be attributed to bad luck, but took a very dim view of BresaGen's ability to successfully complete due diligence: 'I just look back at the science thing and look ... at the lack – not the rigour in the science, but the lack of rigour in the basic agreements. Once is unfortunate. Twice is pretty careless. Three times is a problem' (interview, 2007). He also stated in his opinion that was a wonder BresaGen did not have more serious repercussions in the form of legal action taken against them by British Biotech:

If you go back and look at BresaGen's history, in hindsight, and the deals that it did, it didn't do good deals. Every deal that it did fell over, usually due to lack of what you might say rigorous checking. E21R was an absolute case in point. The deal which was done with the American to buy the American company was another one. The deal, even with the university, because there are those who will say the Rathjen IP ... certainly doesn't stand up to rigour.

You go back and you look and you say look at every one of those deals that BresaGen has done. Why is it always that we come up, two, three, five years later – and these are questions which we've asked ourselves, as a Board, towards the end. What's the common thread in these? Inadequate due diligence and being over rigorous to get the deal done. You've got to say [that was] the common thread – I'd be the first. I'd go in the common thread has to be who's driving? For companies, carelessness in doing those types of things is a killer. E21R, how we didn't get our backsides sued off by British Biotech, I just don't know. Particularly when they were going through their own problems. I think there was some very dodgy dealings with Metrotec. Some of those things there, with Metrotec and Adsteam were just poorly put together. It was like the deal to buy the American company. Whatever. In the end, whatever you actually buy. We were told, as a board, this is what we're buying. We're getting services of this and that and da-da-da. In the end, it was so feathery. (interview, 2007)

Juttner was emphatic about the key lessons to be learned from this. Not only do senior staff members and supervisors need to take full responsibility for their students' work in terms of veracity, but the acquirers of the technology also have an obligation to

themselves and their shareholder to do everything possible to ensure the honesty, integrity and rigour of the data, ‘I think anyone who is going to commercialise any sciences is absolutely honour bound to go right back to the basic data. They need to see the workbooks; they need to see the workbooks, the lab books’ (interview, 2007).

Smeaton echoed Juttner’s advice. Moreover, he suggested involving a third party to help review the data saying, ‘Well, first thing you’d do, you want extreme diligence on anything any academic told you or claimed that had anything to do with what you wanted, and you’d want to see not only peer review, I think you’d want to see data from an independent lab. So first of all, don’t believe anything that the academic world tells you until it’s proven. So it’s a lie until proven otherwise, rather than the other way around’ (interview, 2007).

### **Two Degrees of Separation: Is that Enough?**

Like many small satellite cities, Adelaide’s business and commercial industries are greased by the oil of social connections and networks. Prime examples of this are evident all throughout BresaGen’s history – starting back at the very beginning with Seamark and Wells, Ballard and Wallace and the bevy of agriculture students that flooded the Darling Building. Other examples of the importance of networks include John Smeaton connecting GroPep to Genentech via a connection with Laird Varzaly to Joe McCracken.

Smeaton commented further, ‘Val Blanchet who I’d know from California days, she help[ed] me with networking in the various places. She set that deal [with Genentech] up for GroPep too’ (interview, 2007). Furthermore, on the concept of networking he said:

They’re [networks] pretty key. I mean I’ve probably ended up with a

reasonably good run for Australia, but nothing like some of the American people have got. With these industries here, it's probably a huge advantage if you've sort of gone to the Harvard Business School or gone to Stanford and whatnot, and you've got these people that you've known from a long time back and then those networks are very powerful. I think the BresaGen thing here has sort of broken into that network through the CyThera merger. Those people control an awful lot of money. (interview, 2007)

Notwithstanding their importance, the question though arose for BresaGen – can networks be too close? What role, if any, did the strong ties between the scientists play in the data fraud incidents? Juttner shared his thought process as he began to unravel the problems with the E21R data:

And as I got to know more about it, I started asking questions about this. So these miraculous things were talked about, but how do they actually happen? And I think more of those sorts of questions should have been asked, because this is where the sort of trust and relationship issue is tricky. Because I think the fact that Robins – the key scientist and the CEO [Smeaton] had such close relationships with the Chairman and the scientific advisory board, Peter Rathjen and through him [Rathjen] with Lopez. So Rathjen and Lopez were great friends too, played soccer together. So there was a sort of network of trust. (interview, 2007)

As to whether there was too much trust involved in BresaGen's case is hard to say, and adds nothing to the story in that it is water under the bridge. But in general terms, Juttner said of having 'too much trust':

I think you can. Yes, absolutely, and I think anyone who is going to commercialise any sciences is absolutely honour bound to go right back to the basic data. They need to see the workbooks, they need to see the workbooks, the lab books. When I worked in the US, I used to go to lab meetings and see the scientists work, because it was relevant to what I was trying to develop as clinical products. [T]he board ... and the company needs to have enough people with that level of scientific balance. I mean, Smeaton – you don't expect a Chairman to do that.

See, I think in the environment, doubt of the science and the veracity of science is not something that one commonly experiences, particularly with high profile people ....

You need to be critically, I repeat - you need to be absolutely critically certain of the veracity of the data – of the science you're licensing in. If you're going

to build a huge multi-million multi-billion dollar structure upon some basic science, you must know that it's right. [Because on that point, it's overwhelming in both GroPep and BresaGen's case, that personal networks played a fundamental role. So I see it's a bit like a helix twisting around between science and network and science and network.] (interview, 2007)

## **Taking the Bone Away from the Dog**

BresaGen and GroPep are probably best described as siblings or at the least cousins, with the same ancestral beginnings in terms of Julian Wells and John Wallace in particular. Judging by the final wash up of the companies and their commercialisation pathways, GroPep was the more successful. Peter Hart gave a personal appraisal of why and how GroPep had stayed the course in his opinion:

GroPep worked, I think, because – initially because of John Ballard's enthusiasm and management. Also, I think, a much tighter rein was kept on John. He wasn't – because he came out of CSIRO – he was hardly the free-wheeling, free-spending .... He was a strong personality. We had our ups and downs. I had my ups and downs with John [Ballard] on all sorts of reasons. It possibly could have gone off the rails, too. But I think the best move we made there was getting Richard England in – and Richard, I think, very clearly put his foot on John Ballard until, eventually, he gave him the push. Why was GroPep more successful? It was more product oriented. It also had cash. It had a very cosy deal with the CRC. Extraordinary cosy deal with the CRC. That was GroPep was. It was an offshoot of the CRC, sort of thing.

Why was it successful? I think – and you might also say that it stayed successful because, when things started to go rocky and John perhaps started to feel his age a little bit more, they moved him out and moved somebody else in. Businesses go through these issues and if somebody said to me what was the biggest mistake I made at BresaGen, was probably not getting rid of John Smeaton. At the time, there was an opportunity to do so. Not recognising it. Recognising wasn't right. But, essentially, not changing CEO. Perhaps we could have refocused. Probably refocused back here. Got out of America; call that a tragic mistake. (interview, 2007)

Bastiras said of Smeaton's managerial abilities:

John was entrepreneurial, but he wasn't a good manager. He couldn't direct the company, the energy that the people had, to achieve the goals he was trying to achieve. And I'm not sure why. Maybe he didn't know what the goals were. I can't speak for him, but towards the end, he was pretty stubborn,

towards the end. I had been with the company for almost 15 years, and I was making suggestions and they were what we should do, and where we should go, and they weren't being listened to ... the last year, the Generipharm idea, I was totally against, and they didn't listen to my advice. (interview, 2007)

Hart even thought that in the end BresaGen itself was a mistake, as he articulated below:

Really [Smeaton] needed a COO, a chief operations officer or something, almost to follow along behind him and pick up the pieces. John was good at opening doors, good at strategising the next deal or whatever, but then not good at filling in the numbers, to see how it was all going to work.

[Meera Verma] she was Chief Operating Officer while John [was in the US] and I think she did reasonably well. But, of course, all the action then was in America and all the money being spent was being spent in America, sort of thing. She had some part in it, because the phone bill between Adelaide and America was ginormous. But that's BresaGen. A tragic mistake, as far as I'm concerned. (interview, 2007)

Although Hart conceded that not every body shared his views on Smeaton, in fact quite the opposite:

When the company got to be a company and, a little bit later, when it got to form its own board – it was McGregor and Allert and co on it, etcetera, etcetera. John enjoyed a lot of support from Bob. Bob Symons, I think, basically died believing that John Smeaton had done everything possible. So John was very capable at getting those sorts of people [on side with him]. People in BioChem [Department] swore by him ... Julian Wells and George Rogers ... Until he [Bob Symons] died, he was a believer in John Smeaton. (interview, 2007)

Still others speculated that decisions that were made along the way might have had more of an effect than first realised; for example, the selling off of Bresa's reagents business (i.e. Geneworks). Juttner contemplated this:

It really does have a very long pathway, starting at '82? Yeah and it's interesting that it's survived as long as that – I guess it became too ambitious. You wonder whether the splitting off of the cash making business [Geneworks was part of the problem?] Was that a sensible thing, because I think it would have stabilised the company if they still had that company. Sure they got something for doing that, but ....

Well, when you contrast it to GroPep that was one of the elements that made GroPep quite successful] was keeping that element. [And when you look at the prices, that Novozymes paid, it was a A\$100 million versus A\$21 million. And yeah, John Ballard kept a really tight steady ship at that time, and they did keep that revenue clunking along.] Well, they had better revenue than Bresatec and GeneWorks did. (interview, 2007)

Needless to say, knowing the right thing to do is always easy with the benefit of hindsight. Whilst GroPep did not go into voluntary administration, it had its share of challenges and low points. For BresaGen, perhaps the difference was that they were more public, e.g. E21R failing the clinical trials, receivers taking control of the company for nine months, being acquired by Hospira for only A\$21 million. Bastiras summarised his thoughts of the various issues they faced, both good and bad:

There's been a lot of milestones in the history of the company, but I think the most important one was getting some good leadership. And strangely, it had to come from [an external person] – I think that the best leader that we had was Stephen Jones, the CEO of CBio. There's more intelligent things come out of Steve Jones in the first 15 minutes of meeting the guy, than I've heard coming from John Smeaton in the 15 years that I'd known him. Stephen Jones, he was a businessman, and he basically saw that the protein chemistry or the protein pharmaceuticals division of BresaGen had a product that was selling, there was money coming in, there were invoices going out. And he saw us ... And it was the right time too; we're talking 2004 now. Even the stock market people were no longer interested in Blue Sky big promises type companies. They went back to sort of bread and butter type companies. And so the climate was kind of ripe for that happen. And Stephen Jones, to give him credit, was only there for two years, but in that two years he really gave us focus ... [it was] an important milestone for me, around about that time. [There] was more a focus on volume, making sufficient amounts for doing pre-clinical work. (interview, 2007)

In terms of the difficult milestones, Bastiras revealed his feelings as he thought about that time:

CBio came to us on Friday January 16 [2004], and we had an all day meeting to discuss with Wolf Hanisch what we were going to do, and how we were going to make their molecule and all the assays we were going to set up etc. On the Monday, three of our directors resigned and on the Tuesday ... we went to administration. By that Friday, Wolf Hanisch and Stephen Jones had already submitted expressions of interest to buy the protein division, based on

that one meeting the Friday before. Wolf Hanisch came in and met the protein team, led by Meera and myself, and he was convinced enough to think gee, these guys know what they're doing, why have they just into administration. So they immediately set up a plan to buy just the protein division. They had no interest whatsoever in the stem cell stuff.

So when BresaGen came out of administration, we were just finally a protein company. So for me, getting back to the important dates and milestones, for me that day when we went to administration was absolutely crucial. And it took Meera a long time to realise that. Meera was depressed probably until the day we came out of administration. I think, even when I had set up protEcol, and was pursuing that, Meera was still being swayed by John's [Smeaton] ideas and the Generipharm idea. Whereas I was saying no, let's just concentrate on bringing in the money through process development, and that's what we can do. We're good at that. And we had a small number of clients; Metabolic was one of our first clients.

And in the intervening period since January 2004 till now, we've helped probably as many as – I'd guess probably 20 Australian groups, small companies, institutions, mainly small start up type companies, get their molecules into the clinic. And at the same time we've generated about – let's see, over the last two years, it would be close on probably \$10 million worth of revenue in those two years. And that's a business that's growing.

We're a protein company, and we have been since really, I guess, since January 20, 2004. Because by that stage, I think yeah, by that stage there was no active research in stem cells any more. There was no one employed in stem cells. The only people left behind were the senior management team, who were slowly one by one resigning, because there was nothing for them to do. Our plan was look, let's find our feet. So the model has been let's just concentrate on generating revenue and becoming self-sustaining. We've gone back to being the picks and shovel sellers during the gold rush, right. And then once we become self-sustaining [we can do other things]. This is the model that Stephen Jones liked – he said this is good, because I can see dollars coming in. And along the way the model basically evolved in that we would utilise that thing, working with a whole lot of these companies, probably two-thirds of IP are Australian. We were actually being paid to review companies' private IP management. So we were being paid to scrutinise how various companies worked. And we basically said look, at some stage we might want to partner with company X or Y, if we think their products are any good, if their management is good, if they're financially stable etc. So the idea was let's just keep doing what we're doing until the right company comes along, and then we might co-develop something, we might raise funds and own 60% of it. Do you know what I mean? So that became the model, the interim model of BresaGen.

Then eventually what happened was – I've said now, it's the second time in two years that a bigger fish has come along and swallowed us, and now the big fish is Hospira. So Hospira came along, and they were looking for

somebody to manufacture a molecule they were interested in, and they discovered us. And they liked us so much that they bought the whole company. A bit like the guy with the razorblades. So it's the second time in two years that that's happened. CBio and now Hospira. And it's the second time that's somebody bought us ... I think Hospira eventually will generate from a purchase of BresaGen, it's an absolute bargain. The potential for growth there far exceeds what Novozymes would ever obtain through growth acquisition. Novozymes<sup>32</sup> really have bought in my opinion – all they've bought is the remaining patent years for the LONG™R. Their goal is pretty clear. They want to get into selling products for the tissue culture industry. But that patent is going to expire in about 2011, I think. (interview, 2007)

## **Just a Great Bunch of People**

With BresaGen now under the ownership and control of Hospira, and the last remaining executive from BresaGen Inc (i.e. Allan Robins) now an employee of Novocell, the opportunity to ponder the journey presented some very interesting, personal and touching musings. For Bastiras, one of the most significant events was the day the company went into administration. He explained why he felt this way:

Well, I think it's unfortunate to say this, but one of the most important milestones was the day we ... actually went into administration. January 20 or thereabouts, 2004 ... and what that meant was that for the first time in 16 and a half years, the company was no longer in the control of John Smeaton. And that meant that there was perhaps a future there for the people that had built the expertise in proteins. (interview, 2007)

Carol Senn, who by now had been with the company over twenty years said:

I suppose moving out of the university. I suppose the cloning of the pig, you would have to put that down as a milestone. I suppose - internationally, I suppose the British Biotech connection initially was a big deal. It was our first real international association, collaboration that meant we were getting a lot of experience by the association, working out with what were the European GMP guidelines ... In some ways [they helped us] and having put together CMCs for the E21R, the advice that they gave us and the reason and judgments of how they went about making these decisions. It was very useful and I think it really helped expand our knowledge. And I suppose EquiGen itself was a pretty big deal. That was our first registered product, our first GMP product registered with the NRA at that time. Besides administration

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<sup>32</sup> Novozymes acquired GroPep in 2006 for A\$100 million.

and coming out of administration and Cbio and Hospira, they were the obvious ones more recently. [I suppose selling onto GeneWorks] Yes, that was a pretty [big thing]. Getting an NRA licence and then a TGA licence in our old facility was quite an achievement, because the facility itself was very dilapidated, so I think us being able to get accredited by those organisations really was a testament to the quality of the documentation at that time [that was also an achievement.] (interview, 2007)

Verma also shared her thoughts on this:

The key milestones or turning points would have to be I think when we finally got our head around to selling the life science business [i.e. BresaChem], it was within a few months around '96 when we first decided okay we were getting grown up and now we could give that. That was a very hard decision, emotionally. We would develop our own therapeutic products. Up to that point we hadn't probably taken ourselves seriously enough to think that we could do that and we hadn't looked at raising enough money to be able to do that. Although we were working on that in the background, I think that was ... was really a statement of okay we are going to drop that we are going to focus now on being therapeutic developers. There was no fall back position.

1999 was probably the other milestone when we listed. In hindsight we listed fairly early but that was ... again, that is a lesson companies still don't learn. We keep telling them and we both said it, 'don't list too early.' But everyone gambles through the same cycle: if you can't get enough money, you list.

As well as '99 and then probably going into voluntary administration – that had been a milestone and I can say that now in hindsight. Twenty months later I can acknowledge that that actually was a turning point for the company. John Smeaton would kill me if he heard me [say that] because I don't think he ever [thought] the company should have gone into administration but having been through it and lived through the whole exercise, I can see the positives of it now and I can see that it allowed us to stay and truly restructure the company.

What needed to be done to try to rescue the value in the company [BresaGen Inc] and put what we were doing in the right vehicle to be funded appropriately. So another [cell] therapy company and they basically are VC funded [through Fred Middleton and CyThera] until they get to the point where they can go to IPO in the US because they need to be grant funded for their early work. We have gone out there now building clients and customers because we were closest to doing that in terms of a market strategy. So VCs are not interested in funding per se because they can't see their background and nor should they. We need to basically prove there is a market out there. We need development capital - investment development capital. Working capital, development capital, because we have a short-term goal which we have identified but we need help to get there. (interview, 2005)

Do those associated with BresaGen consider the company a success? Various thoughts prevailed. Juttner spoke highly of key individuals rather than the company per se:

Robins and Meera Verma and Stan Bastiras are all really high quality, very intelligent, smart – and the role of that scientific team was development and exploratory stuff, and knowing the literature and interacting with people, and they helped make the company a success. Is the company a success? That's an interesting question. Certainly I think that Meera's personality and commitment and drive and enthusiasm had a hell of a lot to do with the, I would say, success of the company, following its time in administration. Without her [Meera] that wouldn't have happened and they wouldn't be where they are now. So she's a driving force for all that sort of stuff. (interview, 2007)

Others were sceptical of the projects from the beginning and perhaps had little expectation of great success, 'so many of the plans or the dreams or whatever you call it, BresaGen executives had hatched up, if you like, and it goes all through the history of the company and didn't have very much commercial rigour or their timeframes were grossly under-calculated.' (interview with Hart, 2007)

In terms of where the company saw itself post-acquisition, Verma and Bastiras summed up what seemed to be a collaborative feeling of the remaining employees:

I think we consider ourselves as an experienced player. [Although] I feel like a teenager, we never bloody grow up! No, I think we are still in a growing ... I think we've decided what we want to be when we grow up, finally! (interview with Verma, 2005)

I'd say, I guess looking at our current clients, I'd say probably 40% are international, and 60% Australian. Well, our biggest client is Hospira, because we are Hospira now. But prior to the Hospira takeover, I mean we were working with NovoNordisk, a huge company ... We've done work for companies based in Ireland ... in San Francisco across the road from Genentech. This is the thing – it is a global economy, because you'd think companies based in San Francisco Bay, why don't they go down the road and get so and so to make it. Why do they come all the way to Australia? Because we're just a lovely bunch of people, and we're good at what we do. And I think also, price-wise we're basically offering in Australian dollars, what people are paying probably double in US dollars. [So good value for money.] And good quality products. (interview with Bastiras, 2007)

## Appendix II

### THE CASE OF BIOTA HOLDINGS

When considering the beginnings of the company Biota Holdings Ltd, it is very easy to think this small biotech start-up put its roots down in 1985, when the firm was incorporated and floated. And whilst this is true for the *company*, nothing could be further from the truth for the company's key product, namely what would go on to be known as Relenza™. In order to fully appreciate the long and circuitous pathway of the intellectual property that would eventually reach its way to market through the efforts of Biota Holdings Ltd and its licensee GlaxoWellcome, one must be prepared to first follow Relenza's protracted, and at times serendipitous, scientific pathway. The scientific discovery, which eventually was patented as Relenza, would be nurtured by various custodians over some 30 or more years: Biota Scientific Management Pty Ltd, Biota Holdings Ltd, Glaxo, GlaxoWellcome and ultimately GlaxoSmithKline, as well as the Victorian College of Pharmacy (VCP, which later become part of Monash University), the CSIRO, and in the product's infancy, the John Curtin School of Medical Research at the Australian National University (ANU) in Canberra.

#### Early Discoveries

Sir Frank Macfarlane Burnet, the second of four Australian Nobel prize winners, had the privilege of being in a British laboratory in 1933 when he heard a cry: 'The ferrets are sneezing'. The ferrets, highly vulnerable to flu, were reacting to the throat swabs

they had been given. This meant that for the first time, the human influenza virus had been isolated. The following year, Burnet returned to the Walter and Eliza Hall Institute (WEHI) of Medical Research in Melbourne where he perfected ways of growing influenza in fertile chicken eggs, a technique still in use today in vaccine manufacture (Whittaker, 2005).

With the influenza virus isolated, the story of *neuraminidase's* role can be traced back to the 1940s when George Hirst, working at the Rockefeller Institute in New York, reported that when allantoic fluid from flu virus infected eggs was mixed with red blood cells in ice the cells were very heavily agglutinated. If these agglutinated cells were warmed to 37 degrees, they dispersed and could not be re-agglutinated in the cold by fresh virus. The virus that eluted, on the other hand, was just as able to agglutinate fresh red cells in the cold as it had done before. Hirst took this to mean that 'the red cells had receptors for the virus on their surface to which the virus particles attached in the cold, linking the red cells together, and that the virus had an enzyme that destroyed these receptors when the agglutinated cells were warmed to 37°C, where the enzyme was more active' (Laver, 2006 p. 578). Hence, Hirst had discovered that the influenza virus had haemagglutinin activity and an enzyme which destroyed receptors for the virus on red blood cells. The enzyme was named receptor-destroying enzyme (RDE) (Harrison, 2004; Laver 2007, 2006, 2004, 2000; Sanderson, 2001).

MacFarlane Burnet, who was now the director of the WEHI, had been working with *Vibrio cholerae*. He discovered they secreted an enzyme that did the same thing as RDE. Burnet was immensely curious about the nature of the substrate for RDE and persuaded a biochemist, Alfred Gottschalk, who was working on yeast fermentation in the Institute, to stop working on yeast and find out what reaction RDE catalysed. The year was 1946 (DEST website, 2006; Laver, 2006; Whittaker, 2005).

The same year as Gottschalk began his experiments, a young 16-year-old by the name of Graeme Laver left school to study for a science degree. He started working as a technician and bottle washer under the supervision of Gottschalk (Laver quoted from DEST website, 2006). Having pondered Hirst's experiments and interpretation of the results, Gottschalk came to believe that there was a 'split product'. His experiments backed this up and the split product was eventually isolated and characterised as sialic acid or N-acetyl neuraminic acid (Neu5Ac) and influenza virus RDE became known as sialidase or neuraminidase. This neuraminidase enzyme was responsible for the spread of flu virus within the body. In simple terms, this meant that the influenza virus carried the damaging enzymes, called neuraminidase, which in effect 'cleared a path' for the virus to spread. The virus should have trouble infecting other cells because they have a coating of sugar molecules that act a little like the hooks on Velcro and restrict the virus's ability to move freely. But the neuraminidase enzyme destroys these sugar molecules, smoothing the virus's way. So the key to treating or inhibiting influenza was to counteract the neuraminidase enzymes (Laver, quoted by Schlesinger, 2000).

Whilst the scientists of their day quickly realised that if a 'poison' could be developed that stopped this enzyme working, it might provide a cure for the flu. During the next decade or so, the universities and the drug companies took all the compounds they could and added them in test tubes and animals hoping to block the neuraminidase, without any success (Whittaker, 2005).

### **Soaps and Microscopes**

In 1958, Laver, having just gained a PhD in London, returned home via the overland route through Asia. In a post office in Bombay, he received word that he had been offered a job by the John Curtin School at the ANU (Whittaker, 2005). A vaccine for

the flu had been invented in the period that Laver had been in London, but its effectiveness versus its toxicity was questionable. It was made out of dead virus - and was highly poisonous. This was nevertheless an advance on the previous version. The flu vaccines in use in the 1950s contained virus particles inactivated with some agent, such as formaldehyde. These vaccines often produced toxic reactions when injected, sometimes described as worse than the disease itself. The toxicity was associated with the intact virus particle and people in Tommy Francis' lab in Ann Arbor found that ether-disrupted virus was much less toxic (Laver, quoted in Schlesinger, 2000)

Before too long after taking up his position at ANU, Laver and his collaborator Robert Webster developed a new vaccine. As he explained, he joined a team working on the molecular structure and antigenic properties of the influenza virus. Very little was known about these things at this time. In 1958, the accepted method for disrupting flu virus was to shake the virus particles with ether. It quickly became apparent that ether did very little in the way of disrupting the virus and 'we found that the detergents, sodium deoxycholate and sodium dodecyl sulphate did a much better job. This finding, in fact, formed the basis for many of the subsequent discoveries' (Laver, quoted in the DEST website 2006). The way Laver describes it to Whittaker (2005) was:

A few bright people, including a Kiwi student Robert Webster, just happened to start working on it with him - not working, more having a lark really, mixing mud pies. They put a little detergent into the vaccine to take out the fat and voila! It was safe. 'Now, every inactivated flu vaccine in the world is made that way', says Laver. 'Pretty important, except the flu vaccine has never been much good as far as I can see'. (Laver quoted in Whittaker, p.22)

By about 1966, Laver and Webster had gained world recognition with their new vaccine. This discovery would go on to be the first commercial influenza 'subunit' vaccine, produced by the Australian Commonwealth Serum Laboratories in Melbourne. Now 'most, if not all, inactivated flu vaccines made today are so-called 'subunit'

vaccines' (Laver quoted in Schlesinger, 2000). Additionally, their discovery would be published in *Virology* in 1963 (see also Laver 2006, 2000; DEST, 2006; Whittaker, 2005). But because the flu vaccine is always reacting to known strains, it cannot counter the periodic emergence of new varieties. 'What we did was convert a relatively bad, highly toxic vaccine into an equally bad but harmless vaccine' (Laver, quoted in Whittaker, p.22).

Laver made another breakthrough shortly thereafter, in 1964. He realised that some influenza viruses disrupted with sodium dodecyl sulphate (SDS) retained only their haemagglutinin activity, while in other strains the neuraminidase was fully active, but the haemagglutinin was destroyed. What was more, when these viruses, which had been disrupted with SDS, were subjected to electrophoresis on cellulose acetate strips at room temperature in buffers containing 1% SDS, with some strains the biologically active haemagglutinin and in other strains, the neuraminidase, migrated well away from the other viral proteins and could be eluted from the strips in pure form. Laver was again rewarded with another prestigious publication, this time in the *Journal of Molecular Biology* in 1964 (Laver, 2000).

The technique of electrophoresis in SDS led to another discovery that would be published in 1966. By mixing the infection of cells with two different Type A influenza viruses (at the time they were known as recombinants, but are now called re-assortants), hybrid viruses could be isolated that had the haemagglutinin from one parent and the neuraminidase from the other parent (Laver, 2006). According to Sanderson (2001), the research team consisted of Ed Kilbourne, Graeme Laver, and Rob Webster. She added further detail about the scientific process, explaining that the hybrid viruses could be formed by infecting cells simultaneously with two different Type A flu viruses. This was because the ribonucleic acid (RNA) pieces coding the various virus proteins re-

assorted, some of the viruses containing the haemagglutinin from one parent and the neuraminidase from the other. Hence this ‘mating’ of two parent viruses to give a hybrid virus explained how new pandemic strains of flu A could occur, and led to a very good way of producing influenza viruses with any desired combination of haemagglutinin and neuraminidase spikes (Sanderson, 2001). This work would receive scientific acclaim in the journal *Virology*, with Laver and Kilbourne as the named authors.

Following the outbreak of flu in Hong Kong in 1968, which killed about one million people, Laver and Webster were able to show that this virus had the same neuraminidase as the 1957 Asian flu pandemic, but the haemagglutinin matched flu seen in horses and ducks rather than anything previously seen in humans. This suggested that if the virus acquired part of an animal flu, it made the new virus invisible to human immune systems. The team came to the conclusion that deadly flu strains, and possibly all pandemic flus, were created when the virus mutated from animal to human species. This conclusion was met with scepticism from the scientific community at the time (Whittaker, 2005). Yet, it would be extremely important also in helping find a way of producing pure neuraminidase which would be essential later in crystal growth and drug design experiments.

### **1969 – The Mushroom Shape Appears**

Approximately two decades after George Hirst’s first experiments and conclusions that the influenza virus’s enzyme was both agglutinating and destroying receptors on red blood cells, his theory would be disproved by Laver and Robin Valentine who would go on to have their findings reported in *Virology* in 1969. The research group (Valentine and Laver) showed that the haemagglutinin (receptor-binding) and neuraminidase

(receptor-destroying) activities of the virus resided in two quite different spikes on the surface of the virus (Sanderson, 2001). Laver gives a personal account of what took place:

I took preparations of hemagglutinin and neuraminidase made in this way to the National Institute for Medical Research at Mill Hill in London in 1969 where Robin Valentine examined them in the electron microscope both in the presence of SDS and after the removal of this detergent. This showed very clearly that the hemagglutinin was a triangular rod-shaped molecule while the neuraminidase was mushroom-shaped with a head attached to long thin stalk with a small knob at the end. The head was square and box-shaped as Nick Wrigley so elegantly showed later but the description of the neuraminidase as 'mushroom-shaped' may have been unfortunate. I saw recently a German film in which the neuraminidase was depicted as a molecule with a round plate-like head and stalk. When I told the producer the neuraminidase had a box-like head he retorted, 'You said it was mushroom-shaped, and I have never seen a square mushroom!' (Laver quoted in Schlesinger, 2000)

Specifically, Laver described the findings this way: electron micrographs showed that the influenza virus particles were covered by a layer of surface projections or 'spikes'. These were of two kinds. One of the spikes, a triangular rod-shaped molecule, had haemagglutinin activity; the other spike, a mushroom-shaped molecule, with a square box-like head sitting on top of a long thin stalk, was the enzyme, neuraminidase. The end of the stalk was hydrophobic, which allowed the neuraminidase to be attached to the lipid membrane of the virus. Each influenza virus particle was covered by about 2000 haemagglutinin and 500 neuraminidase spikes (interview with Laver, 2007). Identifying this morphology - including the hydrophobic end of the stalk - would become more important than they realised at the time.

## **Birds and Pigs**

An appropriate starting point to explain this juncture in the research is likely to begin with Laver explaining about a skiing holiday in France one year with his colleague

Helio Pereira, who headed the Department of Virology at the National Institute for Medical Research in London, where Laver had spent time in 1969. They were trying to isolate flu from wild birds. Laver can explain the genesis of the wild birds and flu back to the 1960s when one afternoon he and Rob Webster were walking along a beach on the New South Wales south coast and they noticed that there was a dead mutton-bird (shearwater) washed up every 10 or 15 metres. They knew that terns in South Africa had been killed by an influenza virus in 1961, and considered the possibility that it was flu that was killing these birds in NSW as well.

Although bird flu was first isolated and identified in 1900, scientists did not realise that bird flu was caused by Type A influenza until 1955; some 22 years after Burnett witnessed the ferrets sneezing. The following year, 1956, two other avian influenza A viruses were isolated from ducks, with a surge in the number of flu viruses isolated from chickens, turkeys, ducks, quail, pheasants and pigeons. At the time though, it was thought that these avian viruses had their genesis in human strains and affected the domesticated birds due to their immediacy to people. Besides the single incident in South Africa in 1961, there were no other reports of influenza viruses being isolated from wild birds, and moreover, there was no recording of anyone who had tried to do this (Whittaker, 2005). But that was about to change; Martin Kaplan of the World Health Organization (WHO), and Helio Pereira were two people that wanted to explore this line of thinking further. Pereira naturally conveyed this to his skiing buddy that winter in France. Needing to find a suitable setting to carry out their research, they dabbled with the idea of using the coral islands of the Great Barrier Reef. As to why there? Laver explained it simply in his interview with Whittaker (2005): Why not! Can you think of a more unlikely place to look for flu? Beautiful islands in an azure sea, hot sand, a baking sun, and a warm coral lagoon. What better place to do flu research!

At the end of their ski trip, Laver and Pereira visited Kaplan in Geneva, and somehow talked him into chipping in \$500 towards their research fund to help pay for the costs of their trip. The Head of the ANU Department was less forthcoming with money, claiming:

Laver is hallucinating! He also said that in any case I wouldn't be able to catch the birds. But I knew that thousands upon thousands of mutton birds or shearwaters nested on the coral cays of the Reef in burrows in the sand, and that all you had to do to catch these wild, free-flying sea birds was to bend over and pick them up. (Laver, 2004, p. 592)

Unfortunately for Pereira he couldn't join the expedition just at the time the birds were nesting so Laver went with his research assistant, Alice Murdoch, for three weeks in December 1969 to an uninhabited coral cay called Tryon Island some 50 miles off the coast of Queensland. They collected sera from 201 shearwaters and tested these on the spot in double immuno-diffusion tests with a preparation of influenza type A ribonucleoprotein (RNP), which had been made in the lab before coming to the island. Laver (2005) explained, 'All type A influenza viruses have the same RNP antigen, and following infection, antibodies to RNP can be found in the sera of infected individuals' (p. 592).

To their amazement, they got a result, although the precipitin lines were faint and fuzzy so not suitable for publication. But they gave them much encouragement to continue with their testing. When they got back to the lab, they were confronted with the choice as to which viral antigen to test the sera against. They ruled out haemagglutination inhibition tests, which other researchers would have most likely used because sera often contain high levels of non-specific inhibitors of flu haemagglutinin, and these might have muddied the waters. Rather, they looked for the ability of the shearwater sera to inhibit influenza virus neuraminidase. This created another challenge

as Laver explained, ‘But which neuraminidase? Several antigenically distinct influenza Type A neuraminidase subtypes were already known, and we had to guess which was the right one to use’ (Laver, 2005 p. 592).

One of Webster’s past experiments would give them a clue:

In 1967, with Pereira and Bela Turmova, Webster had found that some avian influenza viruses possessed neuraminidase antigens that were immunologically similar to that of the ‘Asian’ (1957) H2N2 strain of human influenza. We mixed samples of influenza virus neuraminidase of the human 1957 N2 subtype with sera, from the shearwaters on Tryon Island and looked for inhibition of neuraminidase activity. We tested about 30 sera and in each case the test gave the familiar bright red color produced by active neuraminidase. And then suddenly we got one test that was completely colorless. Something in that bird’s serum had completely eliminated the activity of the neuraminidase. It was one of those rare ‘Eureka’ moments that make scientific research so exciting. (Laver, 2004, p. 593)

The ramifications of this were enormous. As Laver recalled, ‘this inhibition of the neuraminidase was due to specific antibody to human influenza virus neuraminidase of the N2 subtype. This led to the inescapable conclusion that this shearwater bird had been infected sometime in the past with a virus possessing N2/1957 neuraminidase’ (Laver, 2004, p. 593).

Of the 201 shearwater sera collected on Tryon Island and 119 sera collected from nearby Heron Island (by another research assistant), a total of 18 birds had antibody that inhibited N2/1957. The finding served as further impetus to ramp up expeditions to try to isolate live virus from birds. More trips were scheduled and in particular Webster and Laver took one at the end of 1970 on Phillip Island near Melbourne. They found a number of sera with antibody to ‘Asian’ (N2/1957) neuraminidase, confirming the previous findings, but no virus was isolated from any of the tracheal swabs (Laver, 2004). In 1971, another expedition was undertaken to Tryon Island to collect 200 tracheal swabs from the shearwaters nesting on the island. Laver

describes the rigours experienced by the research party comprising scientists and children alike:

During the day the shearwaters spent their time out at sea fishing, returning to their nesting burrows when the sun went down. The daily routine for us, therefore, was to swim and sun bake during the day and then, following the traditional sherry party on the beach at dusk, to spend two hours or so catching and swabbing the birds before returning to camp for dinner prepared by our excellent cooking team. The swabs were then stored in liquid nitrogen before being transported back to the lab. The material from the swabs was inoculated into 10-day-old embryonated chicken eggs, and after two days' incubation at 37 degrees C, the allantoic fluid around the embryo was harvested and tested for influenza virus. Most of the eggs were negative, but you can imagine our excitement when we eventually found one egg full of an influenza Type A virus which had come from the trachea of a completely healthy shearwater bird nesting on Tryon Island remote from human habitation. This finding suggested that the natural hosts of influenza A might be wild aquatic birds, and that many more type A viruses might exist in these pelagic bird populations. (Laver, 2004, p. 593)

Webster contributed further insight to those original findings of tracheal and sera swabs of the shearwaters. Considering human influenza is a respiratory virus, it was understandable that research team initially swabbed the bird's respiratory secretions. Webster found though, that in domestic ducks, avian influenza viruses replicated in the cells lining the gut instead of the lungs or trachea. Therefore, he suggested it might be better to swab the bird at the 'other end', i.e. do a cloacal swab. On their further expeditions, they followed this practice and found numerous influenza A viruses, some of which had not previously been seen (Laver, 2004).

Laver also went further afield in his quest for samples. As Laver described in Whittaker's (2005) article, way back in the 1970s, China was already showing evidence of being a furnace of flus. In 1972, Laver and Webster visited China as part of a medical delegation aiming to find out more about the flu. However, the visit was not as insightful as he had hoped. Instead, he received first-hand instruction in Communist ideology:

We did not find out much about flu. In one city we saw a group of pigs, wallowing in the mud. We asked the Chinese if we could take samples of the pigs' blood to see if any flu antibodies could be detected. There was a good deal of resistance to this request but after much haggling we were allowed to bleed one pig. Since a single sample does not do a great deal for the statistics, we asked if we could have some more. Came the answer: 'In China today all pigs are equal; you have your sample, be satisfied'. (Whittaker, 2005; see also Laver quoted in Schlesinger, 2000)

Research continued on the Great Barrier Reef in 1975. Adrian Gibbs, one of the research team, collected a swab from a white-capped noddy tern on North West Island that December that produced an influenza virus of the subtype H11N9. By 2004, 15 H and nine N subtypes had been discovered most by Webster in ducks in Canada. Viruses of the H1N1, H2N2 and H3N2 subtypes are known to be responsible for human flu pandemics (Laver, 2004) However, at the time, N9 had not been described and the team were interested in examining it in more detail. The challenge though was to isolate pure N9 from the virus. They drew upon their previous knowledge and re-assorted the virus into H1N9 using a technique of Webster's. It would be easier to purify the N9 from a re-assortment than from the parent virus (Laver, 2004). N9 crystals would take on a critical role approximately a decade later.

## **Crystallisation of N2**

In March 1977, in collaboration with the pharmaceutical company, Sandoz, Laver decided to organise a small meeting for his colleagues in Baden-near-Vienna. The area of interest was influenza virus Haemagglutinin. It was at this meeting that Don Wiley and John Skehel<sup>1</sup> described the first crystals of flu haemagglutinin - actually bromelain

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<sup>1</sup> John Skehel – now Sir John Skehel from the National Institute for Medical Research at Mill Hill, UK and Don Wiley, an expert crystallographer, who would go on to be Professor of structural microbiology at the Harvard Medical School with a career that spanned three decades and be one of the world's most distinguished scientists in the area of virology. Professor Wiley died in 2001.

derived hemagglutinin - of X-ray diffraction quality, but of course, at that stage they had little structural information to talk about. En-route home by plane to Canberra, Laver said to his colleague Gillian Air, who at that time was conducting research at ANU, 'We can't have Skehel and Wiley have it all to themselves, when I get back I am going to crystallize the neuraminidase' (Laver, quoted from Schlesinger, 2000).

The following year, 1978, Laver achieved his goal! He said, 'Well, I did just that, but it was sheer luck and not at all intentional. I was, in fact trying to show that the Asian (H2N2) and the Hong Kong (H3N2) neuraminidases had similar sequences because Ed Kilbourne had claimed that antigenic similarity did not necessarily mean sequence similarity' (Laver, quoted in Schlesinger 2000). The N2 neuraminidase crystallised into thousands of small square plates after he had dialysed the enzyme from a sucrose gradient against water. Laver had made his breakthrough and truly 'upped the ante' to his colleagues. He had crystallized N2 neuraminidase from the human H2N2 influenza virus. As for Gillian Air's reaction when he told her of his achievement he said, 'She exploded in scornful rage. 'You stupid man', she said. 'I've seen people like you before. All you have are salt crystals.' I smiled. If either NaCl or sucrose had crystallized from distilled water I could re-write the chemistry books' (Laver, quoted from Schlesinger, 2000).

Another step forward along the discovery pathway happened with some help of Laver's colleague Webster. Laver isolated one type of influenza virus by sucking off the allantoic fluid surrounding the embryo of infected chicken eggs and purifying this. The virus particles were incubated with an enzyme capable of digesting proteins. According to Sanderson (2001), 'This enzyme that was selected to split the 'heads' of the neuraminidase spikes off the virus particle without destroying them and to leave behind or destroy the haemagglutinin spike. The neuraminidase 'heads' obtained were

concentrated using high-speed centrifugation. The tiny pellet of neuraminidase heads examined had a crystalline appearance, and X-ray diffraction analysis of larger crystals showed that they were made of protein'. Laver (interview, 2007) gave further details, 'The head of the neuraminidase spike, which contains all the enzymic activity of the molecule, can be released from some influenza virus strains by digesting the virus particles with a protease. The released heads can then be purified and in some cases crystallised'.

The chance nature of the result was highlighted once again when Laver was awarded the Australia Prize – according to the DEST website (2006), Laver himself confirmed his crystallisation of the protein sialidase, the key breakthrough which led to the development of the anti-influenza drug Relenza, was an accident; 'I'd made-up some sialidase protein this day and I noticed a sheen coming off the solution,' said Laver. 'I took it to the microscope and that was that. I know organic chemistry; I know what crystals look like and I knew I'd stumbled on the sialidase crystal [neuraminidase crystal]' (Laver, quoted on the DEST website, 2006).

Laver not only had serendipity to thank; perhaps a little bit of good luck meant that he was credited with the discovery. Apparently, sialidase [neuraminidase] had been crystallised twice before Laver would go on to do it. The first time was in America in the early 1960s; a discovery few people seemed to notice. Then in the 1970s a British virologist claimed to have crystallised haemagglutinin but according to Laver, he almost certainly had crystallised sialidase (DEST website, 2006).

Not quite knowing what to do with his finding, Laver thought he might send the crystals to Don Wiley at Harvard in case he wanted to map the structure using X-rays. However, Laver explained that an Australian immunologist, Alan Williams, who was working in Oxford, stopped by the lab, saw the crystals and said: 'Those crystals must

not go out of Australia'. So, Williams introduced him to Carolyn Wright, a crystallographer at Sydney University. Wright collected the preliminary X-ray diffraction data on the neuraminidase crystals. In fact, in 1978 Wright and Laver had this work published in the *Journal of Molecular Biology*. In terms of the research to this point, Graeme Laver said of his discovery,

So there you are! There was never any 'choosing' to solve the NA [neuraminidase] structure. What started as a scheme to be one up on Skehel and Wiley just sort of developed all by itself. There are so many 'what ifs' ... What if I had dialysed the enzyme against saline instead of water? What if Alan Williams hadn't stopped in the lab that day? What if Ed Kilbourne hadn't provoked me into looking at the sequences of Asian and Hong Kong neuraminidases? I could go on and on. (Laver quoted from Schlesinger, 2000)

### **Elucidating the Structure**

With NA isolated and crystallised, and the preliminary X-rays done, Laver and Wright, decided to call Wright's fellow crystallographer, Peter Colman, who was in Munich at that time. Colman specialised in X-ray crystallography. He had been using crystals to work on the three-dimensional structure of human antibodies (Whittaker, 2005). Colman's contribution to the next step of Relenza's ultimate development would, like Laver, earn him an Australia Prize. He had obtained his doctorate from the University of Adelaide in 1968, and then spent three years as a postdoctoral fellow at the University of Oregon. Following this, Colman took up another post-doctoral Research Fellowship, this time at the Max-Planck Institut in Munich. The research director was Professor Robert Huber (later a Nobel Laureate), who offered Colman a most challenging problem: the first crystal structure analysis of a complete antibody molecule. Colman's success in meeting that challenge firmly placed him in the ranks of the world's outstanding young protein crystallographers (University of Sydney – Senate, 2000). In 1975, he returned to Australia as a Queen Elizabeth II Fellow at the

School of Chemistry of the University of Sydney.

In 1978, Colman was appointed to a research position at the CSIRO Division of Protein Chemistry at Parkville in Melbourne. The same year, according to the DEST website (2006), the two scientists (Laver and Colman) decided to collaborate. Similarly to Laver, there was an element of chance that Colman should join in the project, since Colman's initial motivation was one of intellectual curiosity. The scientists focused on the chameleon-like ability of the influenza virus to change its face from year to year and sidestep the human body's natural defences. Colman said, 'We needed to know the changes that characterised each new strain of influenza. The central question was, how different did it have to be before it could come back and infect you' (Colman quoted from DEST, 2006).

X-ray crystallography, a technique which magnified molecules to one hundred million times their real size, allowed Colman and his colleague, Jose Varghese, who joined the CSIRO in 1980, to see their every atom. 'Being able to see the protein in all its atomic glory meant we could identify all the places on the protein molecule where changes occurred from year to year and, and more importantly, we could identify the parts that never changed' (Colman quoted in DEST, 2006). Colman explained, 'It was one of those stories familiar to most scientists, where you start out to do one thing and ended up doing something else.' he recalls. 'I was fascinated by the immune system and how antibodies could detect and bind to viruses. We started looking at how one strain of influenza differed from another, with the aim of identifying how different the virus had to be, before it could elude the antibodies and reinfect' (Colman quoted in Collis, 2002 p. 194).

At this stage, Laver was busy in Canberra providing his colleagues crystals of sialidase and samples of the protein itself. They would travel by Esky on the plane

down to Melbourne (Laver, quoted in Whittaker, 2005). Colman and his team produced hundreds of x-ray diffraction images of it. It was a complicated and elusive structure that took years to solve. Working initially with a synchrotron in Hamburg, Germany, and then with the Photon Factory synchrotron in Tsukuba, Japan, the two researchers, Colman and Varghese, made the long-awaited breakthrough in August 1982. The intensely bright and laser-like nature of synchrotron light enabled the scientific duo to obtain extremely high-resolution images of these atomic structures, and observe the changes that occur in the neuraminidase when the virus mutates. The detail at which the scientists were able to study the process allowed them to notice that one tiny cleft-like part of the neuraminidase did not change. They realised this was where the virus could be attacked and that this little hole would be crucial to the enzyme's action of cutting the virus free from human cells. If the pocket could be retarded, so could the virus (Harrison, 2004).

Colman recalled the very day this happened; he went into his office as usual at the CSIRO's Division of Biomolecular Engineering in suburban Melbourne. It was a fine winter's day and he had an inkling that something big was about to happen. But after four years trying to crack the molecular structure of the key sialidase protein, he was used to that kind of feeling ending in disappointment. However, on this particular day he said, 'I'd had the answer in my hands for a few weeks but you have to stick with it to get the result. That day I found myself staring at these images, as always, trying to make sense of them when suddenly it all fell into place. By the end of the day, the images of sialidase Jose Varghese and I had generated over four years actually made sense. It was a very good day' (Colman, 1996). They had found a target, but in 1982, no drugs existed that had been designed to fit a molecular target (Whittaker, 2005).

These achievements would receive world acclaim through publication in *Nature*

in 1983. There were two publications: Varghese, Laver and Colman, ‘Structure of the influenza virus glucoprotein antigen neuraminidase at 2.9A resolutions’ (*Nature* 303, 35-40) and Colman, Varghese and Laver, ‘Structure of the catalytic and antigenic sites in influenza virus neuraminidase’ (*Nature* 303, 41-44). Not only did they achieve publication, they were awarded the prestigious front cover, and for the first time, it was in glorious colour proudly showing their elucidation of the structure.

Most recently, Laver commented on his colleagues’ achievements:

I think he [Colman] had a lot of trouble getting permission to work on this project. But he did and the rest is history. What I should tell you is that when Peter did the structure, it was – I mean, nowadays you can solve a structure with computer programmes. Peter did it almost all by hand, and he did it during the time that the lab was being renovated, so everything was full of dust and all this sort of disruption. It was very, very difficult. It was a marvellous, incredible achievement. (interview, 2007)

### **London Calling and Glaxo Answering for a Long Conversation**

The publication of Varghese, Colman and Laver’s first *Nature* article coincided with the 50<sup>th</sup> anniversary of the discovery of influenza viruses. Colman was invited to present his work at the end of 1983 in London, at a celebratory symposium held at the institute where influenza had been discovered. He concluded his presentation with the observation that he believed their discovery of the neuraminidase structure would lead them to develop drugs to treat influenza. This comment caught the attention of the Research Director of Glaxo Plc in the UK, who told Colman after the presentation that he would be interested in exploring this opportunity for drug discovery. This discussion between Glaxo and Colman, via the CSIRO’s commercial office, ‘lasted all of 1984’ (Colman, 2007). Colman recalled that the CSIRO side was ‘trying to encourage Glaxo that for a modest investment they really could have all the rights to this work’ (Colman, 2000).

The negotiations did not come to fruition and the key element in Glaxo's decision not to pursue an agreement was the failure in the 1970s of the dehydrated compound known as DANA (Neu5Ac2en) to act as a suitable inhibitor. Renowned scientist Peter Palese and his colleagues were able to show that DANA and some of its derivatives could inhibit influenza virus replication in vitro, but when tested on animals, the compounds did not prevent disease (Laver, 2000). Colman put it simply, 'It worked in the test tube but not in mice' (Colman quoted in Whittaker, 2005). Aware of Palese's work, Glaxo was very cautious about further research in the area, making the prospect of even a 'modest' investment appear unattractive. Later Colman commented, 'we shouldn't have been surprised when the negotiations were called off' (Colman, 2000, p. 7). Colman found there was another disincentive as well: 'It was hard to sell them [Glaxo] on the idea of collaborating with researchers in the southern hemisphere in a field of research that most people didn't believe was going anywhere' (Colman quoted in Collis, 2002, p. 195).

Part of that initial exchange had included Colman being offered a PC valued at about A\$70,000 to enable him to then take the work back to London and hand it over to Glaxo. Peter Andrews, Dean of the School of Chemistry at the VCP, recalled that he urged Colman not to accept but to think about trying to raise money himself. Colman declined Glaxo's offer of a PC, but fortunately, he and Varghese were still being supported by the CSIRO, which Colman explained was crucial at that time:

CSIRO provided the institutional support and the resources to pursue our ideas and develop some strategic science and intellectual property. I couldn't have equipped the laboratory we needed if we had been relying on NHMRC grants. Successive Chiefs at my Division kept backing us, even though there were many who said that the science wasn't right. (Colman quoted in Collis, 2002, p.195)

## Moving Forward: Another Baby Step

Of the science to this stage, Peter Simpson, who was later to become a CEO of Biota, details the main achievements as Colman later conveyed them to him:

The science was honest. They'd done really good stuff. But really, when you think about it in simple terms, real simple terms, what were you after? What you were after was the fact that the influenza virus has two proteins, hemagglutinin or neuraminidase – H or N - so you know, the current bird flu is H5N1. Okay. So it's only got two proteins. The one protein they were looking at was neuraminidase, now called sialidase. What did they find? They found that for each strain of the virus it looked different. It's like a ball of wool. One looks like a great big long ball of wool. One looks like a little ball of wool. They're completely different macroscopically. They had found that the active site for each of these different neuraminidases was exactly the same. Not just a little bit the same. It was exactly the same.

As Peter [Colman] rationalised – he said, look, it's the same for a reason. It's got to be that there's a docking mechanism to allow the virus out of the cell. If it's not exactly the same, then it isn't influenza and it couldn't get out anyway. So it must be linking with the neuraminidase we expect on the inside of the cell. So therefore, it has to be that shape. The fact that the virus goes to this incredible length to make sure that that active site is always the same shape, no matter what the strain, makes it – I thought that was a very good idea. He got the data there. He said, look, they're exactly the same. He said that gives you a target. I thought yep. Not often you get a target to shoot at in our game. But it gives you a target to shoot at. (Simpson, 2007)

The team gave some thought to making use of this active site discovered by Colman and Varghese to develop a universal influenza virus vaccine. However, that this approach would not work became evident when the team determined the structure of epitopes on the neuraminidase. The work by the team had showed that the epitope on the neuraminidase comprised 5 separate peptide segments with about 17 amino acid residues in contact with a similar number of amino acids in the antibody binding site. Single amino acid sequence changes in the peptide segments of the neuraminidase epitope rendered the neuraminidase invisible to the antibody so totally abolishing binding. This finding meant that even if antibody could be raised to that region on the

neuraminidase, which involved the conserved catalytic site, this antibody would still be susceptible to changes in the variable amino acids surrounding the conserved site and such a vaccine would not be effective against all strains of the virus. Small molecule inhibitors of the enzyme were therefore sought (Laver quoted from Schlesinger, 2000).

The team now had that all-important direction to follow; the importance of small molecules and their capacity to inhibit the neuraminidase enzyme. On this front though they weren't on their own. Laver said:

Attempts by others to identify such inhibitors by random screening failed. One drug company, for example, screened 25,000 compounds without coming up with a single inhibitor. Sialic acid, the substrate for neuraminidase, is itself a mild inhibitor of the enzyme, but the dehydrated compound, DANA (Neu5Ac2en), is a very much better inhibitor and in the 1970s, Peter Palese and his colleagues showed that DANA and some of its derivatives inhibited influenza virus replication in tissue culture but when tested in animals these compounds failed to prevent disease. (Laver, quoted from Schlesinger, 2000)

It was this work that led Dr Colman to advocate targeting the neuraminidase protein with an anti-viral drug. In itself, this 'wasn't a new idea,' Laver explained. 'People had tried to make inhibitors of neuraminidase in the 60s and 70s without success, and so by the 80s it was regarded as a dead end' (Laver quoted in Collis, 2002, p. 194). The most promising inhibitor was the work of two Austrian chemists, Meindl and Tuppy, who in 1969 had made the molecule DANA (Neu5Ac2en). They made it as a nonselective inhibitor of neuraminidase – whether they were of viral, bacterial or mammalian origin – hoping it would be an effective anti-influenza agent. However, they failed to demonstrate this in their animal studies of the 1970s. But the difference between this earlier work and that of the Australian team was that 'our structural work showed just how invariant this site was and I was convinced that this was the place to put pressure on the virus' (Laver quoted in Collis, 2002, p. 194).

As for Colman getting there first, sadly that did not have a happy ending

according to Laver:

Peter, [Colman] in fact, probably produced the first ever crystalline protein-antibody complex, even before the Paris crowd had one, but it is a sad story. Rob had made a small amount of monoclonal antibody to N2 neuraminidase called S10/1, and Peter grew crystals out of a mixture of N2 neuraminidase and S10/1 Fab. He sent me a photo of the thin crystals which were not big enough for X-rays and so we never knew if these were complex crystals or not. We never knew this because Rob Webster then went on holidays to some Canadian Lake for a couple of weeks and while he was away the freezer containing his S10/1 hybridoma cells broke down, and the cells were lost for ever and ever. Meanwhile Poljack grew crystals of lysozyme complexed with Fab and got the structure of this complex before we eventually got our neuraminidase-Fab structure.

Nonetheless, the team, Colman, Laver, Varghese, Baker, Tulloch, Air and Webster, would have their work published in *Nature* once again in 1987. To achieve this scientific result was an outstanding achievement; requiring nothing less than commitment and cooperation of each of the scientists, each bringing expertise to the table. Laver spoke of this:

Rob Webster made the monoclonal antibodies and selected escape mutants of the neuraminidase; I produced the flu neuraminidase, made Fab fragments of Rob's antibodies, mixed the two and crystallized the resulting complexes. Peter Colman and his colleagues determined the structure of the complexes by X-ray crystallography and Gillian Air did much of the amino acid sequencing. (Laver quoted in Schlesinger, 2000).

Besides scientific expertise, the group had Telstra on their side! NASA donated Laver a private earth station and free satellite time to talk to his American colleagues, and then OTC gave him free international telephone time. Throughout the process, Laver spent almost as much time on the telephone with colleagues around the world as he did with his eggs and test tubes: If you've got a problem you think about it, you talk about it', he was quoted as saying:

The discovery process is dreaming up an idea and then working out how to do it, the nuts and bolts, and this involves talking to lots of people ... This work is a source of joy and wonder to me and I'd be in the lab every day whether

they paid me or not ... Experimentation and discovery are great fun. Mixing things together and seeing what happens. Some people like to grow prize roses. I like to grow prize crystals. (Laver, quoted from the DEST website, 2006)

All of these advances made to this date were leading up to the next step of rational drug design.

### **Biota: A Gleam in the Eye...**

Whilst the science was progressing in the various laboratories around the country, in 1984, Peter Tulloch, a colleague from the CSIRO, introduced a young entrepreneur by the name of Mark Crosling to staff in the laboratory. In 1983, Crosling had set up a small company in Melbourne called Biota Pty Ltd. Crosling had established Biota with the vision of building a company involved in what he described as ‘genetic engineering’ (interview with Crosling, 2007) and Glaxo’s decision not to take on the project presented him with an opportunity. Colman described the fortuitous chain of events that unfolded at this time:

I first met Mark Crosling when he was interested in other things I was doing, not influenza. The birth of Biota as an influenza company was really in the beginning of 1985 when we first started discussions with him about trying to commercialise the influenza work.... When the flu work became available, or was in need of some external support early in 1985, Crosling said he’d be interested in trying to develop our ideas into new drugs for flu. But it was a company then, it was a privately owned company. It had rather little money .... (interview, 2007)

Colman (interview, 2007) described Crosling as an ‘entrepreneur’ and ‘a smart young guy wondering about marrying up biotechnology with business money’. Crosling, whilst young at that time, did come with an impressive background: he held a Bachelor of Science with majors in Genetics and Zoology, and had completed an MBA

from the Australian Graduate School of Management. It was during his final year of his MBA that he undertook an individual study in ‘Genetic Engineering – An International Perspective’ that concentrated on the competitive dynamics of the emerging biotechnology industry. It was shortly after he completed these studies that he started Biota Pty Ltd. But at this stage, Biota was ‘more a gleam in his eye than anything substantial’ (interview with Colman, 2007). After finishing his MBA, Crosling started combing through various ideas and was in the process of building his database to keep across the development of the research (interview with Crosling, 2007) And whilst there was very little government support in the early 1980s, other factors were coming into play at that time; namely macro-environmental policies such as the floating of the Australian dollar, the management investment commission (MIC) initiatives, the Campbell Report and the setting up of the Second Board in the states, e.g. Victoria, by the Australian Stock Exchange (interview with Crosling, 2007). These factors were all contributing to the momentum that was building to allow a little company like Biota Pty Ltd to take the next steps towards biotech company legitimacy. As for the scientists cooperating with Crosling at this early stage, an interesting question comes to mind: Why did the scientists, the keepers of the intellectual property, decide to go ahead with such a fledgling operation such as Biota Pty Ltd? Peter Colman explained it this way:

It wasn’t that easy to find people who were interested in long shot ideas. Glaxo had already turned it down for whatever reason, but obviously Biota was a very different proposition. It wasn’t a drug company, it was trying to be more entrepreneurial. It was happy to take a punt on earlier stage things. So there might have been others who could have been interested, but frankly we were happy to engage, to talk to [Crosling] and there were no other serious suitors.

After the deal was done, there were people who came to us and said that sounded interesting, but the fact is they weren’t talking to us at the time we needed to talk to people. There’s lots of wisdom after the event about these things. The fact is there was only one crowd who had firstly found its way into my lab because of other things I was doing, and then who grasped this

opportunity when Glaxo walked away from it. There was no bidding war going on. It was a selling war. (interview, 2007)

Even so, the launch of the influenza project by Biota would not have eventuated were it not for the involvement of another individual: Alan Woods. Alan Woods was introduced to Crosling in the early part of 1985. By this stage, Crosling had already embarked on talks with Colman, but was also running out of money. Woods, too, was impeccably credentialed to take up the challenge of getting this little company off the ground. Indeed the Woods' family background in science and pharmaceuticals spanned over a century. In tracing back the origins of his interest in Biota, Woods (interview, 2007) in fact went as far back as 1895, when his grandfather had founded a company based on his patent cough and flu medicine, *Woods Great Peppermint Cure*. The medicine became a household name, was successfully exported at an early stage, and was the basis for a flourishing family firm, W.E. Woods Ltd. The firm's management and direction was handed down to successive generations, with Alan Woods's father becoming managing director, succeeded by Alan Woods's brother, David. This family background provided Alan Woods with a powerful inheritance: 'I think the history of the company and family has been technical competence allied to entrepreneurial flair and I think financial savvy ...' – and, as well, an abiding interest in treating coughs, colds and influenza.

Alan Woods shared his family's passion for science and trained as a chemical engineer. Upon graduation, he spent 20 years working for chemical engineering companies in what he called 'technical-commercial' roles that also took him overseas (interview with Woods, 2007). His life took a new turn in 1970s when he and his family bought what was then a 'tiny' company, David Bull Laboratories (DBL) which specialised in the manufacture and distribution of sterile injectables for hospital uses. At

the time of its acquisition, the company had a 'low level of technical expertise' and was in trouble with the TGA for its poor level of GMP. The Woods brothers built a new plant in Melbourne and also invested a lot of their own energies in the venture, which saw a handsome return, with the business growing 50 to even 100 per cent a year. Alan Woods took on the roles of engineering production and research director and also explored international markets in the early 1980s. DBL was able to launch in the UK four new products; two anti-cancer drugs and two antibiotics. DBL was marketing numbers of their products in various parts of the world and the manufacturing facility in Melbourne was approved for the productions of the anti-cancer products. These achievements came at a cost:

This ... was taking a fair amount of toll out of the family, having to make yourself available for everything and ... money and the rest of it, so we were fairly stressed out. But anyway, the outcome was that there was a decision to sell that business and that occurred in '84, completing in '85. (interview with Woods, 2007)

In 1985, Alan Woods was therefore cashed up, with time on his hands for the first time in many years, and 'feeling intellectually deprived, apart from anything else'. He started to look around for a new challenge. He became aware of Biota through Darryl Alexander, a former senior pharmaceutical company executive and consultant and businessman, who had been approached by Crosling as a potential investor and consultant to Biota. Crosling mentioned the influenza project to Daryl Alexander who referred it to the Woods brothers who were which immediately attracted to the project: 'the thought of actually doing something that was technically advanced and perhaps a real contribution, rather than the sort of product we'd been making, I felt was a great challenge' (interview with Woods, 2007).

Following a crucial meeting between the Woods, Crosling, Colman and

Andrews, the Woods family interests agreed to work with Crosling on the financing of a plan and to provide A\$60,000 to cover pre IPO expenses associated with a public float proposed by Crosling. Woods's business experience, contacts and reputation were crucial at this stage, although he credits Crosling with the writing of the Prospectus, Woods gave him much assistance (interview with Woods, 2007). The planning phase involved assembling financial, commercial management and technical teams. Woods's assessment was that the parties were competent, although the board lacked pharmaceutical experience, with Woods bringing the most industry knowledge:

it was a little alarming perhaps that we had set out on a fairly ambitious programme, without too many people who really knew what they were doing, including me. But I knew a bit. I'd been around in that area for 20 years. We were heavily reliant on the research subcontracted to the CSIRO, VCP and the ANU. (interview with Woods, 2007).

Woods was therefore persuaded to take a seat on the board:

Well, I'd just come off 14 years of very heavy travelling and stuff with DBL [i.e. David Bull Laboratories], which had gone on a long time and taken a fair bit of toll on my family, and also ... health ... So at that time I was not terribly excited about taking on a director's role, but then when it came to the point it was a case of the shareholders and the other directors and I guess the financiers behind it all. They said look, unless you carried on as a director, we won't go ahead. So what do you do? So that's what I did. (interview with Woods, 2007)

On the technical side, the objective was to assemble a sufficient number of promising projects in order to attract investors (interview with Colman, 2007). Ultimately, as well as the influenza project, there were two others: (1) a synthetic influenza vaccine being developed by Laver and, (2) an angiogenesis project, aiming to isolate and test a factor responsible for the growth of body tissue containing the blood vessels, headed by another CSIRO employee, Brian McAuslan. At the same time, Biota would move into the next phase of the influenza project, the search for an inhibitor drug

for influenza, which would be headed up by the Dean of Chemistry at the Victorian College of Pharmacy (now part of Monash University), Professor Peter Andrews. Of their choice of research partners, Colman said the following, ‘We started working with the Pharmacy College because of the enthusiasm, energy and entrepreneurship of the then Dean of Medicinal Chemistry, Peter Andrews. On reflection, we could have worked with chemists from within CSIRO. But the physical proximity of the College was a telling factor’ (Colman quoted in Collis, 2002, p. 195).

The scientists involved in these projects were known to each other. Laver had been collaborating with Colman since the late 1970s, Colman and McAuslan were both employees of the CSIRO, and Andrews was located right next door to Colman. All four were to be admitted to Biota’s Scientific Advisory Board (SAB). However, the involvement of these ‘scientific founders’ (interview with Andrews, 2007) raised the dilemma of how they could be financially rewarded if the projects bore commercial results, given that the CSIRO would not allow its employees to profit from their discoveries so neither Colman nor McAuslan would be able to take equity in the new company. Peter Andrews, who described his orientation as ‘very commercial for an academic anyway’, played a leading role in negotiations:

When I first saw the cut of the deal that Mark Crosling had in mind, I said bullshit mate. The scientists are having a bigger slice than that – well the slice he was proposing was none. So I said, no we’re having a slice. (interview with Andrews, 2007)

The solution was to set up a trust, named the CLAM trust after the first letter in the surnames of each of the scientists, and which Colman was able to access once he left the CSIRO. Another issue was if the scientific founders were to benefit, what proportion should each be entitled to. Andrews was of the belief that ‘if you’re going into it together you have no choice, everyone should get the same’, but that on the other

hand, Colman had been the driver and was also going to serve on Biota's board. Thus, it was decided that Colman would be entitled to a marginally higher percentage than his three colleagues.

So with a collection of three good ideas, the reputations of pre-eminent scientists, two entrepreneurs in Woods and Crosling and a modest amount of financial support prior to listing, the initial company Biota Pty Ltd was ready to be reborn. Andrews (interview, 2007) felt that the structure of Biota was 'a very clever thing for 1985'. However, one problem, which was not resolved, was how to provide the new company with a cashflow. Woods (interview, 2007) recalled that at one stage there was even 'talk about owning a rose farm. That didn't get off the ground.'

The company that was to be floated would be called Biota Holdings Ltd and was the holding company of Biota Scientific Management Pty Ltd (BSM). Seventy-four percent of the issued share capital of the BSM was acquired by Biota Holdings. Moreover, 4,000,000 free options were given to the minority shareholders of BSM. This would form part of the consideration of the issue of Biota Holdings Ltd remaining 74%. However, any shares acquired by shareholders of BSM and any in Biota Holdings Ltd would be subjected to escrow constraints of three years. Crosling explained the significance of this point – the 74:26 split; the reason behind setting up the business this way was to overcome the issue diluting the net cash asset backing ratio of the company (NCTA). This was important to keep the ratio as high as possible in order to promote the prospectus and the imminent float of the company to the 'big end of town' investors, such as Charlie Farquharson of McKinley Wilson, Don Hulme and other advisors who Crosling had connections with; for example Noel Anderson of PriceWaterhouse, who ultimately gave them entrée into other people and organisations like Chris Beeny of Mallesons, who became Biota's legal firm (interview with Crosling,

2007). This organisational setup would later prove to be very problematic for a variety of reasons.

Table 1 shows the major shareholders of BSM Pty Ltd. The CLAM trust held 30% of BSM, with other significant shareholders being the CABG Trust<sup>2</sup>, Excelsior Run and the Woods family, which through their various investments held approximately A\$260,000 of equity at that time. Woods made some comments about the other key shareholders:

And at that time it was felt that it might work a bit like a mining company, rather than take direct shares into the company, you took the IP, and wrapped the IP in another company. Which came via the BSM and BSM 26 per cent owned by Biota Holdings and 24 by the rest of the players and pushers and worthy people. So, after a bit of argy bargy, that's how it ended up. Not terribly scientific. Clearly, Crosling got a big chunk ... The second one [trust] was the CABG Trust. Well that was ... Crosling, yeah. He also owned Excelsior Run .... He was a trustee. So that's quite an interesting document, that one ... and of course later it became quite a bone of contention around the place, the BSM shareholding. Quite painful at times .... (interview with Woods, 2007)

**Table 1: Biota Scientific Management Pty Ltd Shareholders**

Shareholders	Number of Shares	Number of Options to be offered
Andrew McKenzie Bugg and Christopher Marlin Beeny (as trustees of the Clam Trust)	780	1,200,000
Andrew McKenzie Bugg and Gretchen Mary Guest (as trustees of the C.A.G.B. Trust)	558	858,400
Excelsior Run Pty. Ltd.	363	556,400
Norflo Pty. Ltd.	260	400,000
Nukarni Pty. Ltd. (as trustee of the Woods Family Trust)	206	317,600
Thomas M. Borthwick and Wendy A. Borthwick	117	180,400
Biogenesis Pty. Ltd.	104	160,000
Wade Pty. Ltd.	65	100,000
David B. Woods	65	100,000
Gregory H. Smith	29	45,200
Melinda L. Collins	23	34,800
Jonathan H.M. Bligh	13	20,800
Michael G. Kerlake	13	20,800
Nola M. Wilkinson	3	4,000
Mark Stuart Crosling	1	1,600

**Source: The Prospectus: Biota Holdings Ltd, 1985 p. 14**

\*Norflo Pty Ltd was a company with Woods interests

\*\*Wade Pty Ltd was a Woods company

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<sup>2</sup> Chris Beeny was a Mallesons lawyer engaged by Crosling to manage the CABG trust. Beeny was also instrumental in developing the term sheets and documents of the details of the trusts.

As part of the preparations for the float, BSM Pty Ltd entered into *research contracts* with the CSIRO, the Victorian College of Pharmacy, and the ANU. It was Crosling, assisted by Woods interests, that negotiated these deals with the institutions: according to him, he spent the first part of 1985 travelling around talking to the universities and the CSIRO and when he approached them he simply said, ‘give me your wish list, what is it that you want’ (interview with Crosling, 2007)? In his opinion, he found both the universities, ANU and the VCP (later to become Monash University) easy and progressive to work with. On the other hand, he retold his frustration in dealing with the CSIRO; in particular, the head of it at the time, John Grace (interview with Crosling, 2007).

By virtue of these contracts, BSM was entitled to own the know-how and patent rights arising from the collaborative research work carried out with respect to the three projects. There were two formal agreements with CSIRO: one in relation to the influenza drug as well as for the development of a synthetic flu vaccine; the second for the angiogenesis project. The next agreement was with the Victorian College of Pharmacy (VCP), which was contracted to conduct research into the design and development of new drugs for the inhibition of neuraminidase and to provide the results of such research to BSM. The final agreement was with the Australian National University (ANU). The terms of the four agreements were laid out in the 1985 Prospectus (see Table 2).

**Table 2: BSM Research Contracts**

<b>Nature of agreement</b>	<b>BSM's obligations and entitlements</b>	<b>Research institution's obligations and rights</b>
Influenza drug project (partner: CSIRO, term: four years)	<i>Obligations:</i> a) fund and provide a suitably qualified employee to work on the neuraminidase inhibitor and flu vaccine programs under the direction of the CSIRO, b) pay \$80,000 p.a. or such greater amount as was agreed for the duration for the four year term, c) provide certain scientific equipment to	<i>Obligations:</i> make available certain existing know-how, on the basis that BSM would not have exclusive rights to the existing know-how but by way of safe guarding for BSM, CSIRO would not be permitted to work with any other persons with respect to substances to be developed in the research program,

	<p>the CSIRO including an X-ray detector, (estimated to cost \$250,000) and the ownership of which would pass on to the CSIRO at the end of the program.</p> <p><i>Entitlements:</i> the exploitation of any new know-how, which may result from the research program relating to potential neuraminidase inhibitors (NI), and influenza vaccines produced or similar substances which would be covered by patent at the relevant time.</p>	<p>except for those with BSM showed no interest in, for up to 12 months and b) provide 30% of Dr Peter Colman's working time as a team leader together with a full time senior research scientist as well as 30% of time for a full time technical officer as well as provide access to the facilities of the CSIRO's Division of Protein Chemistry.</p> <p><i>Entitlements:</i> Sirotech Ltd, the commercial arm of the CSIRO, would be entitled to a royalty of 0.75% of net sales of neuraminidase inhibitors and influenza vaccines produced as a result of the research program for a period of ten years from the first sale or the life of the patent – whichever is longer.</p>
<p>Angiogenesis project (partner: CSIRO, term: three years)</p>	<p><i>Obligations:</i> a) fund and provide three suitably qualified employees to work on the program of research and development of Angiogenic Factors and inhibitors specified in the agreement under the direction of the CSIRO which would be monitored by a management committee comprising of the CSIRO and BSM, b) pay the sum of \$83,000 p.a. (or such greater amount) for the duration of its term, c) provide certain equipment to the CSIRO including a high performance liquid chromatography (HPLC) apparatus which had an estimated cost of \$30,000 and at the end of the program, the ownership of the apparatus would pass ownership to the CSIRO.</p> <p><i>Entitlements:</i> BSM would be entitled to exploit any new know-how which may result from the research program relating to potential Angiogenic Factors/ inhibitors and in particular registrations of any relevant patents.</p>	<p><i>Obligations:</i> a) make available to BSM certain existing know-how. BSM would not have exclusive rights but by way of safe guarding the company, the CSIRO would not be permitted to work with any persons with respect to the products to be developed in the research program, except those which BSM has shown no interest in, for a period of 12 months, and b) commit to the research program approximately 15% of Dr Brian McAuslan's time as team leader together with approximately 20% of the time of a senior research scientist and access of the facilities of the CSIRO's Division of Molecular Biology.</p> <p><i>Entitlements:</i> Sirotech Ltd would be entitled to a royalty of 0.50% of net sales of any products or substances produced as a result of the research program for a period of ten years or the life of the patent, whichever is the longer.</p>
<p>Influenza drug project (partner: VCP, terms: 3¼ years)</p>	<p><i>Obligations:</i> contribute \$40,000 to the VCP towards the cost of laboratory renovations needed to do the research in addition to paying the VCP quarterly an amount to cover the VCP's cost of conducting the research which was estimated to be \$288,000 in the first year.</p> <p><i>Entitlements:</i> all the know-how developed by the VCP, BSM or either of them with respect to the designs, synthesis and testing of NI and the registration of any relevant patents.</p>	<p><i>Obligations:</i> The VCP were obliged to conduct the research into the design, synthesis and testing of NI and provide the results back to BSM. The specific research assistance required and any variance would be determined in consultation with the VCP, the CSIRO and the ANU through a management committee structure. In order to carry out the research, the VCP would make available their facilities and the services of Professor Peter Andrews and a team of qualified personnel.</p> <p><i>Entitlements:</i> royalty of 1% of the net international sales of anti-viral substances or drugs developed for a period of 10 years from the first sale.</p>
<p>Synthetic influenza vaccine (partner: Anutech Pty Ltd,</p>	<p><i>Obligations:</i> a) pay approximately \$60,000 p.a. in the first and second years of the agreement and approximately \$66,000 in the third year</p>	<p><i>Obligations:</i> procure the ANU to conduct research in to the construction of a synthetic influenza vaccine and provide the results of the research back to BSM</p>

commercial arm of ANU)	to Anutech to meet the costs of the research being carried out by the ANU and to provide the ANU with certain specific equipment, b) provide specific and general laboratory equipment and pay up to \$15,000 p.a. for the salaries of specified staff.	
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**Source: Biota Prospectus, 1985**

### **Colloquiums and Contracts**

With the board members in place, the scientists corralled and the prospectus ready to go, the company incorporated in the state of Victoria in October 1985 as Biota Scientific Management Pty Ltd and Biota Holdings Ltd. Biota Holdings Ltd was then floated on the Second Board of the Melbourne Stock Exchange on 22 November 1985, raising A\$3 million in its Initial Public Offering (IPO). Crosling, whilst absolutely delighted in this achievement, stressed the importance of the sheer timing of it all, saying, ‘If it had of been two years earlier, or even two years later, we couldn’t have done it. The timing was just right, with the MIC set up, the 2<sup>nd</sup> Board being available and the investment climate following the Campbell Report being right. Two years later, again it would have been impossible with the investment syndicates falling over and the like’ (interview, 2007).

When asked about the launch, Woods said,

Ignorance is bliss. Yes, I’m always a bit wary of knowing too much. Anyway, we got it off the ground ... [I]t was a time when the share market was looking pretty buoyant and they were prepared to take on the sort of thing that you wouldn't normally take on. So, we felt that if all things went bad, it was still looking all right and it wouldn’t suddenly go down to nothing. But the introduction of Capital Gains Tax at the punitive marginal tax rate in October 1985 was a serious disincentive to up companies such as Biota. (interview, 2007)

The float meant that there was now money for research. But at the same time, there were daunting challenges facing the fledgling public company. The three

scientific projects were still at the early discovery stage and the outcomes were uncertain. While A\$3 million had been raised, the firm did not own intellectual property (Laver's and Colman's discoveries were not patented), and did not have a regular cashflow. Moreover, it would later become clear that the various motivations of the key players in setting up the firm were diverse, if not incongruent. As a result, the directors had their work cut out for them. As Woods (interview, 2007) recalled, 'The intellectual deprivation didn't last long. Plenty of things to think about. Whether it was people or technical or whatever. Yes, really interesting.'

The scientific team was proposing to undertake the rational design of a drug. This is now an established practice, but at the time it was an approach that broke new ground, as Andrews explained:

there's all sorts of ways you can design drugs. One of them is by taking an existing drug and making things that are similar to it or similarly, like the substrate – the raw material of an enzyme catalysed reaction ... that's quite a common way to do it, or you can do it by making transition state analogues, which is picking the high point in the reactions from substrate to product and mimicking that. Of course, to do that, you have to calculate what it would look like, because you can never see it. The third way is receptor based drug design or crystallography or whatever – x-rayed structure based drug design ... In fact, this example [Relenza] is widely regarded as the first example<sup>3</sup> of receptor based drug design for viruses.

A friend of mine, Peter Goodford, who is now retired as a professor of Oxford, but at that time, believe it or not, was head of drug design at Wellcome in the UK. Peter had written a computer program specifically designed to do receptor based drug design ... So Peter [Colman] gave us that program – well allowed us to use that program to do drug design off the Colman crystal structure. (interview, 2007)

As the Goodford example showed, the Melbourne team drew on groundbreaking

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<sup>3</sup> Captopril was developed in 1975 by the U.S. drug company Squibb (now BristolMyersSquibb): The patent was granted in September 1977. The development of captopril was amongst the earliest successes of the revolutionary concept of structure-based drug design.

research from around the world. Coinciding with the Biota float (November 1985), Colman organised a small conference of the world's leading virology experts to take place in Melbourne. The conference was an invaluable way of providing ideas and insights as to how to move forward with the next phase of the research project.

Andrews describes the event:

One of the things we were hoping to do [as part of the floating of the company] was to re-package the flu virus and Graeme [Laver] was going to basically make a modified flu virus as a vaccine. Very similar to what Ian Frazer<sup>4</sup> has subsequently done with the HPV virus. But at the time, it proved to be beyond us. So, it was a very exciting little operation actually. We had a wonderful meeting of all of the flu experts around the globe – mainly Peter's mates – in Melbourne was the very first thing, which I still have the notes from somewhere. Where we all sat – 20 of us – around a table talking about what the issues were and how we would do it. We had patent attorneys there and everything. It was a really good plan. It was pretty much straight after we raised the money. We had this planning conference. Rob Webster came from the US. Vivienne Santa was our patent attorney – future patent attorney I guess at that point; the core of the team. I'm not sure whether any of the people in my lab for example, had actually been hired at that point, possibly not. It might have been in that process. We raised the money in November and we just went straight into it and it went fast. It was good. I mean it might have been we did it before raising the money, but I doubt it. (interview, 2007)

This meeting also provided the opportunity for a bright young chemist, Mark von Itzstein, not only to attend the meeting, but also to be interviewed for a position to head up the chemistry team at the VCP. von Itzstein had not been the first choice. Initially, a brilliant scientist from Shanghai, Wen-Yang Wu, had been asked by Andrews to co-ordinate the chemistry team at the VCP. However, Wu had committed himself to a postdoctoral fellowship at ANU: 'Peter Andrews and Peter Colman asked me to organise the whole group, but I declined ... because I had already had a commitment with the ANU ... So then I told Peter Andrews that after that commitment

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<sup>4</sup> Professor Ian Frazer was Australian of the Year in 2006 – following his scientific discovery of a vaccine for the Human Papilloma Virus (HPV)

is met, then I will come back to do this' (interview with Wu, 2007). Since Wu was not available, Andrews and Colman approached Mark von Itzstein. Professor von Itzstein recounted how he became involved in the project:

I was in Germany at the Marburg so I was working in the university in Germany and my background had been a mixture of carbohydrate background through my postgraduate degree mixing it then with synthetic organic chemistry in Germany which then presented a wonderful opportunity of bringing all that intellect and experience, more importantly, to that particular task. When I actually contacted Peter Andrews on that occasion to go down to VCP to talk about coming in as the, I guess, the group leader that's when I first met Peter Colman. Graeme wasn't on the scene with respect to that. I had met Graeme [Laver] subsequently, in fact, the first opportunity really was at that colloquium, if I can term it like that, that was organised at VCP which was a very nice event I must say, very enjoyable in listening to people's views and thoughts about the virus and what it can do and what it can't do and what it depends upon, of course, and all those things.

So both Peters [Colman and Andrews] in fact, sat down and interviewed me actually at that time because my mindset really wasn't to go to Melbourne. I'd already been offered two other jobs in the country. I really was engaged and enthralled by the opportunity with respect to the project and that eventually led me to say 'I think I can do this in terms of getting an outcome.' That's rather a big statement to make when you're still under 30, I think it was, and given that nobody else had done it before but nonetheless, I don't know whether I should have conveyed that to you but I said 'This sounds really straightforward in terms of the logical approach one could make in looking at enzyme mechanism' and things like that. (interview, 2007)

Concerning their respective managerial roles, Colman (interview, 2007) regarded Andrews's role as 'instrumental' in assembling the team of chemists that would be necessary in developing the target drug. He explained 'that's where the bulk of the Biota money was spent, on hiring chemists'. Peter Andrews had the role of overseeing the work at the VCP, although he found it increasingly difficult to devote time to the project as he had 60-70 people in his research group. Increasingly, he delegated leadership to Mark von Itzstein:

As time went on, Mark became ... the clear leader of the project. As time went on further, it would be very difficult to say that Mark was still within my lab, because he was very independent in his approach. I drifted out, Mark drifted

up and he took over the running of the project, which was good. It would never have been finished otherwise probably. (interview with Andrews, 2007)

At the same time, while the focus of the project had shifted to the team of chemists, Professor Andrews credited his colleague Colman as being the driving scientific force: ‘Peter Colman ... was on the [Biota] board as one of our folk, representing the science I suppose, but also because he was the one who was the real driver. He was the prime driver of the whole thing – that was where the drive to do the project clearly came from’ (interview with Andrews, 2007).

Colman, knowing his own limitations, also stressed the importance of giving the individual researchers creative freedom:

We had an overriding objective which everyone knew and supported. But we were pursuing very fundamental science, even though we had an application in mind. No one had done anything like it before, so it wasn’t really sensible to set timelines and have Gant charts and the like. Nowadays, I could confidently predict that for a known structure, it should be possible to conceive and synthesise an inhibitor within six months if all went well. But at that time, we had no idea whether it would work at all. We didn’t even know why attempts failed in the 60’s and 70’s to find inhibitors that targeted neuraminidase. What we all signed on to was to give maximum effort rather than to deliver specific outcomes within a set time frame.

The key need was to keep staff enthusiastic and owning their effort. Asking them to put in the long hours and creative thought meant trusting them to get on with the job and not looking over their shoulder all the time. It was also a multi-disciplinary effort. I was fortunate to have encountered different disciplines when, having trained as a physicist, I moved into protein crystallography and research on antibodies. But I didn’t try to prescribe what the chemists, for example, should do. There were many constraints in synthesising the possible inhibitors, including whether a particular chemical had any prospect of being manufactured on a commercial scale. The chemists were best placed to weigh up those factors. (Colman quoted in Collis, 2002, p. 196)

Professor von Itzstein explained his role in Zanamivir’s development. He clearly articulated the three-pronged research plan they had in place:

Well, in terms of the plans right from day one we had developed effectively a

three-pronged approach. One was that in the literature you could imagine that for a long time people had been claiming that this inhibits flu and this doesn't inhibit flu so we had a bunch of materials out there that really we didn't know how they worked. So we thought we should get a couple of those and see if they work against the enzyme.

The second strategy was to say how does the protein work? How does it convert A to B? This protein is key in the lifecycle of the bug so if you block that and it can't convert A to B - you stop the lifecycle. That's what Relenza does. Then we took on design based on what we understood. We did a lot of experimentation, of course, to look at what the enzyme [does] ... how it does that, goes from A to B. From there, we started to design compounds.

The third prong was to say knowing that it does give a product from this substrate, if we can look at the substrate and make a product that can't be removed or cleared then we may have a hope of getting it going. So a three-prong approach at the beginning. In the end I had to dump one aspect of that which is, in fact, where Tamiflu came from at the end of the day. (interview with von Itzstein, 2007)

### **Virtual Biotech: a Shop Front of Creativity**

Initially Biota only had one full time employee - Mark Crosling. Although there was a SAB and a Board of Directors, these members were not drawing any wages. Moreover, beyond a modest office for Crosling, who was also provided with a two-seater red Celica that he wanted, Biota for all intents and purposes was a shell company. A common description of Biota at the time is that it was a 'virtual' company:

What was it like in the beginning, 1985? It was a virtual company in the sense that it didn't do anything. But it was a powerhouse in the sense that, you know ... - I hired three post-docs. Well that's an unheard of level to have on a project in a lab in Australia - especially back then. Plus research assistants and students and everything else. I forget exactly how many, but I think we had eight to ten people working on the project almost immediately. (interview with Andrews, 2007)

It was virtual! Not a bit but it *was* virtual. The science was not done in Biota and, of course, nowadays the propaganda machine has beautifully masked that ... By the way, in this scientific arena, if you look at the publications there's no Biota address so I think ...in the scientific world it's well understood but it's quite interesting in the Australian company context some people have missed that point actually. (interview with von Itzstein, 2007)

When it was put to him, Alan Woods resisted this description (interview Woods, 2007), and he was right in that Biota could show its funding was making a tangible and immediate difference to the scientific effort. As Andrews' quote makes clear, the Biota float had given the founding scientists an unprecedented boost in resources that would not have been available through the traditional avenue of government funding. Without this injection of cash, proceeding to the next stage of discovering a drug would not have been feasible. The quest for a drug required advanced expertise in chemistry: 'the thing you really needed the money for was to put an additional chemistry team in place to make things that might be drugs' (interview with Colman, 2007).

An explanation for Biota's 'virtual' nature can be found above all in its reliance on research contracts rather than employing research staff directly. Colman, Varghese, Andrews, Laver and McAuslan remained in the employ of their original institutions, as did the scientists who were pivotal in the discoveries that would be made in the late 1980s. Mark von Itzstein, who began working on the influenza project in 1986, explained the implications of this contractual arrangement:

I certainly wasn't working for Biota. [I was contracted.] That's an important point to make. It was sometimes difficult to differentiate with people that I was actually, at that time, a VCP/university employee. I deemed myself as a usual but unusual academic in the sense that I already had a major industry contract on board to run but at the same time concomitantly, I was doing other science. So that's something that people probably don't readily appreciate. (interview with von Itzstein, 2007)

Crosling, also, shared Woods's sentiment: he definitely did not see the company as being virtual and protested loudly when the question was put to him. This perhaps was sense of irony, as many Biota management latter accused Crosling of simply wanting a cash box type company.

## Managing the Managers

By mid 1987, Crosling and the others on the board were no longer seeing eye to eye.

Woods put it this way:

He [Crosling] ... did the best he could with getting the various projects off the ground, and trying to put up with all these old men around him. But it wasn't too long before – there were some attempts to get some projects off the ground involving takeovers, and I guess conservative types in the company weren't too happy with that, because we wanted to stick with what we were doing and try and see it through. And [we] didn't want to turn it into a conglomerate without any real substance. Anyway, he got pretty impatient with all that ...

I don't think he really ever had any ... particular ambition for the project to really get off the ground ... like to obviously ... if you've got a public company and you've got some people wanting to support you, you might try lots of things to get into, just to keep the company going. I think he was pretty stretched in his finances, so it was important for him to try and get some things going ... he decided that he would form another company, Rancoo, which was set up in a similar way, ... another second board company [in Tasmania]. He approached me to agree to go into it, and I wouldn't agree. And of course, that then set up considerable differences between him and the rest of the board. Eventually he – let's say he left after having been unable to get us to leave. Then he decided that he would try and take the company over, Biota, so we were going through a period starting off with a little company trying to make its way. Suddenly we didn't have a managing director, or rather I guess we didn't have a managing director but we had somebody in the place that was actively against us. So that was a bit of a worrying time, so I was going up and down all the time down to Melbourne. (interview, 2007)

In August of that year, an *Australian Financial Review* journalist reported:

Mr Mark Crosling has left the company after a disagreement with Biota's other directors over the direction of the company. The board also accused Mr Crosling of breaching an 'agreement of service' contract he had with the company, including setting up Rancoo Ltd while a full-time employee of Biota. Some of the activities of Rancoo are parallel to those of Biota. The Chairman of Biota, Mr Collin Trumble, said Biota would continue its operations and was looking for a cash flow business to add to its research activities. Mr Crosling said he was considering a number of options and did not rule out the possibility of Rancoo increasing its equity holding in Biota beyond its present stake of 19 per cent. (Frith, 1987)

Within several months (October) Rancoo had failed in its hostile takeover of Biota due to the stock market crash of the time, destroying the value of the scrip offer (Lenthall 1993). The aftermath of this ownership struggle was that Biota was without a managing director: 'we ended up with no office, nobody, nothing, except [the board of directors] ... So you'd have to say we weren't much of a company at that stage' (interview with Woods, 2007). Somewhat rudderless without a managing director, Woods called in a favour from a senior manager who had been working under him at David Bull Laboratories, Peter Simpson. Woods had a meeting with Simpson and very quietly asked him to do some *digging around*. Even though Crosling was no longer the Executive Managing Director, he was still a board member. Crosling had made it clear that his preference was for following up the angiogenesis project over the other opportunities stated in the prospectus. Woods was very concerned about the strategic direction the company was on and wanted Simpson to stay on. He said, 'we had a round table discussion about Peter's capabilities and otherwise. We decided to offer him the job. Part-time initially, as I recall.' Peter Simpson explained his motives for accepting the job of managing director at a struggling firm and how his involvement came about:

Alan Woods ... asked me to have a look at it [i.e. Biota]. Can you just have a look at Biota? He said there's a lot of things going on here that I can't tell you about. But can you just have a look at it and see what you think? Because at the time I'd retired from David Bull and I was going to get my golf score down. But that didn't happen. So, I had a bit of a look at it. I said to Alan there's something fishy going on here. He said I'll tell you about that later. But what do you think of the science? I said well my gut feeling is the influenza one's got a lot more legs to it. The reason for that is the angiogenesis field was very cluttered really. Fifty or sixty people. Good groups around the world, in that field. We could be one of only one or two in the world in the influenza area. If we had a good enough idea. So Alan gave me permission to go and see Peter Colman and I suppose I spoke to Peter for 20 minutes. One of the most impressive people I'd ever met. I just walked out and rang Alan and said flu's got it for me. He said why? I said because I like the guy. (interview, 2007)

The following is Simpson's account of the sequence of events:

Now I think, when Biota was floated, Mark thought that the A\$3 million could much better be used elsewhere. But the board forced him to actually do what the prospectus said he was going to do. So that was, I think, when Mark sort of got the idea, you know, if I want a cash box, I'm going to have to go somewhere else ... Then they [the board] eventually found out that he had set up Rancoo and the shit hit the fan because they had to sack him. That had happened just at about the time when I was giving a report to Alan. So Alan said well, why don't you come and meet the chairman Colin Trumble and have a chat. Since we've now got no CEO, we can't have a situation where we've got no CEO and we're a publicly listed company. So, we'll appoint you in the interim and we'll see how things go. Well, like I never had an employment contract. I was there for seven years, pretty close. Like I ran the business from my home in Upper Beaconsfield for the first two years (interview, 2007)

Simpson again confirmed Woods's assessment that Crosling ultimately had a divergent vision for Biota to that of Woods and the other directors:

to him it was just a means to an end. He didn't see Biota as being a company that actually did it anyway. He saw Biota as a company which was really just a shell. There were a number of second board companies that were like this. Where you took A\$3 million out of the market and invested it wisely in other biotech companies and you grew, without actually having to do anything. That's sort of the way Mark went about his business. (interview, 2007)

During the takeover battle in 1988, the Woods family was approached by Dr Thomas Quirk, who was invited to join the board following the defeat of the takeover attempt. Quirk agreed with Simpson's assessment of Crosling's motives: 'Yes, [he wanted to turn Biota] into a cash box.' Quirk recalled that at that time 'Peter Simpson ...was the only one along with Alan Woods who knew anything about the pharmaceutical industry. I certainly didn't ... I knew a little bit, sort of a dangerous amount' (interview, 2007a). Infrastructure at that stage remained extremely limited; a mobile filing cabinet was the order of the day: '... so that's when I came across Peter Simpson with the company records in the back of the car. Because he didn't have an office. And the accountants who did the annual accounts for us, he'd met at a Christmas

party around the far side of the Dandenongs' (interview, 2007a).

Woods also added to this account:

Following the departure of Crosling and folding up the office, he [Simpson] was actually up in the bush with his files in the back of a car. I think we would bring him [Simpson] down to Sydney, or down to Melbourne. It went on for a little while. This is about the time, I think, Tom came aboard and he was pretty horrified by things like that, as I recall. It was just a phase. I think it had to happen, as you're trying to make ends meet and still look [like a shop front] ... And we were never brought up on expensive tastes, other than Crosling. (interview, 2007)

When these accusations were put to him, Crosling vigorously shook his head from side to side and said, 'no, no, no – that's not true, that's not what I wanted. It was never going to be a cashbox' (interview, 2007). Rather, Crosling described his motivation as the ability to demonstrate his skills and connections at being capable to set up 'successful' companies. That indeed seemed to be Crosling's true ambition – to build up companies, rather than strip them out (Crosling, 2007). Woods (interview, 2008) said, 'I would agree with that assessment, but I was not sure about the intent of his take over partners.'

The change in managing directors did not bring an immediate end to the turmoil. When Rancoo's bid for Biota failed, Crosling sold his shares in Rancoo to Hawke Investments, which in turn sold the Biota shares it now controlled to Biotech International. In 1988, Biotech International and some of its shareholders attempted a takeover, issuing a Part A statement in July 1988 for all of the issued capital of Biota at 38 cents per share. However, by the end of August, the directors of Biota released a Part B statement recommending the rejection of the offer. Some years later, Quirk described the take over attempt, 'Biotech International ... was eager to get its hands on Biota's A\$1.5 million in cash reserves. We were like dwarves fighting in a sandpit and running in each other's sand castles' (Quirk quoted in Caruana, 1999). The Woods family

converted some of their options into shares in order to be able to out-vote Biotech International. This was facilitated by a twist of fate; Quirk felt that the attempt would have succeeded if Biotech International had not missed a deadline in returning proxies from holders who had accepted the bid (Caruana, 2007). Woods disagreed with this point of view and said ‘I believe the day was won fair and square!’ (interview, 2008).

Ultimately the Biota board succeeded, although Biotech International lost with a small margin. Alan Woods (interview, 2007) himself described this sequence of events as a defining moment in Biota’s development as a firm: ‘Well, there was an enormous effort put into trying to get all the small shareholders together to put them [i.e. Biotech International] down, and it worked. And that was a real watershed for the company, frankly. From then on we didn’t have any more takeover attempts [until 2002]’.

This episode cost the company in a couple of ways; during the Biotech International take-over attempt, the share price fell as low as 36 cents, and from a managerial point of view it was very taxing and time consuming. On a positive note, it highlighted to the company the need to get some support and protection from a larger partner. Before long, they would begin their search for a big brother.

### **De-merger or Divorce ... Colman and Laver Part Company**

For some time the scientific research ticked over nicely: Laver would make the virus protein, crystallising some of it and then send some neuraminidase protein down to Melbourne on the plane in a little Esky. In his interview with Whittaker, Laver said, ‘For four or five years we got along very well, and then this split occurred when Peter liked to keep things secret and I liked to talk about them’ (Laver quoted in Whittaker, 2005). Whittaker’s take on this was that Laver resented the fact that Colman had used protein sequences that had been published by scientists overseas. ‘They hadn’t kept

them secret, Colman was using information which other people had got and deposited on data banks for him to get on and solve the structure' (Laver quoted in Whittaker, 2005, p. 23).

Allegedly, Colman asked Laver to stop supplying crystals to other flu researchers. Such a request affronted Laver and he felt he could no longer work with Colman. Laver (interview, 2007) confirmed unequivocally that he had indeed not limited himself to supplying Colman: 'Now, I should tell you that I did not just give crystals to Gilead. I gave crystals to Eli Lilly and BioCryst, to Pfizer – I think there were 11 companies I gave crystals to. Most of them came up with nothing.' The thought of Laver running off and collaborating with who-ever asked him to did not sit well with Colman who later said:

I had agreed not to disclose, because [the] CSIRO [his employer] had signed an agreement with Biota ... and it imposed reasonable conditions of confidentiality on us; and not only did ANU sign a parallel agreement, but ANU asked Graeme to sign every page of it himself. So you might argue the level of obligation was even higher on him. So to pretend that somehow I acted improperly or did things I shouldn't have done just gets the whole thing back to front. (Colman quoted in Whittaker, 2005 p. 23)

For Colman's part Laver commented:

The thing is ... Peter Colman's reprehensible behaviour was not to release the coordinates in the database, which upset a lot of people around the world. And the crystals we got back off the Soviet space station were used to redetermine the structure, and the coordinates them became available. I think they were the ones that Gilead used. (interview, 2007)

Laver said he could not remember what he signed, but that his obligation to science was greater than any obligation to the ANU (Whittaker, 2005). Colman maintained he could not follow this reasoning: 'The question is whether Graeme represents the old way or not. Only he can help you figure it out, why he chose not to stay with us. It couldn't have been about publication as he pretends ... Everything has

been published in the fullness of time, in a timely way' (Colman quoted in Whittaker, 2005, p. 23).

Laver reiterated his thoughts regarding his scientific contributions. When asked about them he said, 'Can I be a little bit arrogant? My attitude is that these firms were working for me, I wasn't working for them. And I wanted to get someone to come up with something, which could be used by the community, so I didn't care who did it' (interview, 2007). Asked why he felt so strongly about this altruistic approach, Laver said, 'because it boosts my ego if you like' (interview, 2007). Laver made the point that his crystal discovery was not patented knowledge and that, in fact, 'The only patent I'm aware of is held by Mark von Itzstein on the actual creation of Relenza' (interview, 2007). In retrospect, Laver was aware that he should perhaps have been more commercially oriented in his thinking:

I mean ... what I should have done, of course, I realise now, is when I gave the crystals to Gilead, which they paid me a very small amount, I should have said then please can I have 1 per cent of gross sales. They would have agreed perfectly, but I just didn't think of it. (interview, 2007)

He put this down to the fact that he really saw himself as a scientist and said, 'If I was an entrepreneur, I would have made sure I got some of the billion dollars that Roche had made out of Tamiflu, [but] I didn't get a penny. But that's because I just couldn't be bothered' (interview with Laver, 2007).

There is no doubt that this rupture was difficult at the scientific level; there were contracts in place, business plans detailed and a prospectus based around those plans. Moreover, one can only imagine the personal disappointment in the breakdown of a successful, inventive partnership. The impact of this is hard to quantify and if it were possible, it would potentially be redundant. However, some things are true; Biota did go on to successfully launch an influenza inhibitor with the partner Glaxo (and later

GlaxoWellcome) but also so did Gilead and Roche. The speed of development and the *timing* of Gilead's product would certainly become a talking point later on. Numerous Biota people (i.e. Woods, Simpson, Colman, Quirk, Reece, Wadley, Andrews) in interviews conducted in 2007 expressed disappointment and, to varying degrees, lack of comprehension, at Laver's decision to disclose elements of the research and collaborate with others.

Andrews described it this way:

Laver is very interesting. Laver is phenomenal. I like him a lot, but he's an absolute tragic when it comes to running a biotech company – he shouldn't be allowed near one. I mean he's just dead dangerous. It [the situation] was completely nonsensical, because Graeme would do things. I mean it was just a simple premise, in the pharmaceutical industry or the biotech industry, unless you can own the intellectual property and patent it, it will never be developed because who's going to put a billion bucks into developing a product if there's no protection. So Laver hops onto his high horse and I said, I love him, but he hops onto his high horse and goes on about how this is the right of all mankind to know all about it ... with the blind assumption this is actually going to lead to some outcome, when in fact all he is doing is preventing the outcome. But you know, I would have explained that to Graeme, 100 times would be an exaggeration, but 10 wouldn't and it just goes straight through the keeper. I'm sure Peter Colman – it just used to drive him nuts. (interview, 2007)

Peter Simpson also shared his thoughts on the likely reason for the rift between

Colman and Laver:

My understanding was that they fell out because ... they were sharing data and Graeme was reporting Peter's data before Peter got a chance to report it. That's the sort of guy that Laver was. I remember going to Canberra and sitting down ... over a lunch of ... Thai food and saying to Graeme, 'look, you can't publish.' Graeme looked at me and said, 'look, I value my right to publish more than I value my right to breathe.' I said to him, 'Graeme, you're mad' I said, 'We can't have a situation where you can just race off and publish without any sort of recourse to us. Because we can't share data with you.' He couldn't understand it. (interview with Simpson, 2007)

Alan Woods though, credited Laver, whom he had never actually met in person, as being responsible for 'founding the neuraminidase game years before' and believed

there were 'strong legal, moral and financial incentives on all the parties' (interview with Woods, 2007). A brief discussion of both Laver's and Colman's career stages may offer further insight into various aspects of their decision-making. Clearly, Laver had an impressive publishing record to that point, not to mention an impeccable international network of eminent scientists from the world's leading research institutions with whom he regularly collaborated. Colman, too, arguably had achieved a pinnacle in terms of research in his chosen field for the day, and at such a young age. On the matter of age, was it possibly generational differences dividing the pair; or was the philosophy of the need for 'transparency' really at the heart of the friction? Laver (interview, 2007) also said, 'In fact, there was an international meeting and one of the participants asked Colman why don't you release the structure. He got very upset. That was a bit of a niggly question.' Or was it positional power and status? Colman being up and coming and making his way in an institution that not only did not want him working in the medical research field, but also especially didn't want him benefiting financially from his endeavours; maybe he felt more compelled to approach the commercial aspects with precision. Contrastingly, Laver, with multiple runs on the board by that time, and an audacious personality to back him, adopted a laissez-faire approach to the commercial aspects of his scientific contributions. Ultimately, this attitude could be traced to his belief in the proper motivation of a scientist: 'If a scientist does something that makes a lot of money, yes of course he should get a lot of it. But scientists shouldn't have the ambition of doing something to make money, because that doesn't work' (interview with Laver, 2007).

Irrespective of the differences that separated them scientifically, Laver (interview, 2007) praised Colman's scientific capability and said of the situation they found themselves in, 'Oh no, there was a lot of what you would call bad blood there,

but I've never really ... I mean Colman was a very smart guy and I've always liked him. So even though he had this apparent difference of opinion it didn't matter.'

Perhaps it is best to put some of the tension down to the nature of their respective employers and the government funding systems. For example, traditionally the university system has rewarded academic staff with higher grading in their professional appointments, moving through to a professorial role, based chiefly on their publications and their grant funding earned. Laver (interview, 2007) commented on this, 'That's traditional but I think it's not fair. I think scientists, of course, they should be rewarded, but only on what they've discovered.' The Australian Academy of Science produced a report in 1995 (10 years post Biota's start-up) that concluded: 'On the research side, it should be recognised that researchers who commit to working with industry often risk their opportunities for personal advancement/recognition/support within their research organisations' (AAS – website, 1995).

Of this mix of tension, publications, patents and the potential financial return from their commercialisation and funding for the research, Simpson encapsulated it nicely, 'If you said to any of the scientists who work for us, we'll give you A\$2 million or a chance at the Nobel Prize ... they'd all take the Nobel. To them, the money is not important. It's about the international kudos that goes with it' (interview with Simpson, 2007). Woods (interview, 2008) pinned down this concept of tension and was unequivocal saying, 'In such matters, all parties are expected to comply with their obligations, which form the basis for funding and trust between the parties.'

### **A Time for Consolidation and Protection**

One of Peter Simpson's first tasks as the newly appointed part-time CEO was to look at streamlining the company's research projects. The Prospectus had portrayed Biota as a

company with a portfolio of three projects, however it became apparent to Simpson that it would not be possible to continue with them all. The vaccine project was the first project to be terminated. Andrews was able to elaborate on the reasons for withdrawing from this project, 'One of the things we were hoping to do was to re-package the flu virus and Graeme [Laver] was going to basically make a modified flu virus as a vaccine .... But at the time, it proved to be beyond us' (interview, 2007). In terms of winding this project up, Simpson made a trip to the ANU in Canberra with respect to discussing funding issues with Laver. Of the meeting, Simpson recalled:

I went and saw Graeme early on in the piece. It would have been in 1987. Graeme was after some more funding up at ANU. The difficulty that he had was that this funding at ANU was running out. So, he was really struggling to get funding for anything. The interesting thing was that we agreed to fund him, provided the university would accept him to do the research. The university knocked it back. So, he was in this awkward position of actually having funding from us available, but the university saying we're not going to allow you – we're not basically going to give you the lab space. So in the end, it got to a point where I had to say to him, look, you're out. (interview, 2007)

Second, the angiogenesis project was also terminated. Simpson recalled that the project was proving problematic due to lack of commitment on the part of a key person involved, 'so-so' research results and lack of patent protection, given that McAuslan had published his result prior to applying for a patent:

The problem was that the guy didn't seem to have his – in Sydney – didn't seem to have his heart in it. I think he wanted to go back and – I think it was a surgeon. He wanted to go back and start cutting people up again. He could see that this wasn't really getting anywhere. We didn't have a lot of patentable cover. There was nothing much there. It was interesting. It seemed to stimulate the growth of blood vessels. But at the end of the day, was what we are going to be able to patent anything? So after '87, the crash of '87, I took the view, which I, in the end, presented to the board, that we ought to just drop it. That's when the funding ran out there, we just put it to one side and concentrate on influenza. Well whether it's got a better future or not. Business, you've got to be somewhat pragmatic and look at things and say well, really, has this got legs? (interview, 2007)

This meant that within a short period, Simpson had terminated all but the influenza project. This was a complete turnaround from the direction taken by Crosling, who had favoured the angiogenesis project and was looking to drop the influenza project. Simpson's actions at this time were also pivotal in that he understood the importance of an intellectual property strategy. Tom Quirk, who would join the Biota board shortly after this period, stated:

So, the departure of the CEO [i.e. Crosling] then led to somebody else coming in part time – (the first CEO essentially had no experience of the pharmaceutical business) [who] had sort of boldly gone where no man had gone before to set it up. The successor [i.e. Simpson] actually came with a pharmaceutical background and one of the first things that he worried about was protection of intellectual property. In 1987, he persuaded both CSIRO and the Victorian College of Pharmacy that the idea of how to make an influenza drug should actually be patented. (interview, 2007a)

Woods also commented that the protection of intellectual property had been of great concern for him from the beginning.

### **Pressure to Produce**

Biota was burning its capital fast, and was desperate for the scientists to deliver a compound. It was a race against time to 'get your technology up to a stage which has some value, is perceived to have some value, and get a deal done' (interview with Woods, 2007). Numerous grants from the Industry Research and Development Board helped prop the firm up financially. Colman explained that these grants were 'crucial':

For example, edible birds nest was the best starting material for the compounds we wanted to make, but it couldn't be imported because of quarantine restrictions. So, we had to synthesise starting material and the IR&D Board funded our chemists to develop enzymatic methods for creating what we needed. Getting those grants involved a lot of work, especially for the company. (Colman quoted in Collis, 2002 p. 195)

In an interview several years later, Richard Wadley, who joined the firm as the

Company Secretary in 1992, said of this government support, ‘During the period between 1985 to about 1990 we received nearly a million dollars in competitive grants assistance which helped to keep the early stage projects growing’ (Wadley quoted in AusIndustry Website, March 2001).

Simpson made no secret of the fact that he drove the scientific team hard, ‘I was always putting pressure on the guys at the VCP in particular to basically shit or get off the pot. You know. Give me a compound. You know, I need a compound that works. Well you’ve got to sort of – like if you leave scientists to their own devices, they’ll wander along’ (interview, 2007). There was therefore some tension between the scientists, who wanted to keep testing to find better compounds, and Simpson, who had to keep the company afloat. von Itzstein recalled of this time:

Certainly by the end of year 3 there was high expectation from the company that we would deliver something. [We were running low on money by then] and that was why there was so much pressure, which I shielded my own group from because I don’t feel they needed to actually feel that pressure. ... in terms of getting the goods, if you’re internal within a company, you’re being hammered every day of the week which can be quite stressful for certain people. It was quite an interesting time come year 3 and looking for budget for year 4 and fortunately, as I said, well you know how the story goes. But it was a very dynamic time in the sense that I thought there was ... between industry and academia, a very good sense of collegiality. It’s quite easy when you have nothing to start with, by that I mean a scientific outcome, but as soon as you get a good outcome it’s quite interesting what it breeds and that’s a different matter though. So dynamic I think in terms of interaction in the first instance, a real can-do type attitude. (interview, 2007)

In this quest for a compound, an important event occurred in 1988: Wen-Yang Wu and his research assistant (and wife) Betty Jin joined the VCP after his stint in Canberra. Wu also spoke of the lack of funds and the pressure to not only deliver, but to estimate a delivery time:

Biota had ... only one million dollars left totally when I joined them. Only one million dollars! The whole thing is, nobody knows how long it takes. I remember the first day I met Peter [Simpson] and ... I told him honestly, I

don't know [how long it would take]. He asked a couple of questions based on the scientific background, that no one can answer. That's what is called science. (interview, 2007)

In terms of finding the right compound, various versions of the scientific events leading up to the final discovery have surfaced. Some members of the team suggested that the two lead scientists, von Itzstein and Wu were approaching the problem from different points of view and at times this may have affected the direction that the research was taking. Several key people implied that a few times the science proverbially 'went off the rails'. Laver held the following view:

The guy who invented Relenza was a Chinese called Wu. The story is that Wen-Yang Wu wanted to synthesise the molecule, which was Relenza. He was told by Mark [von Itzstein], no don't do it because the computer modelling says it won't fit into the active site. But he [Wu] took no notice of Mark and went ahead and did it anyway and found [it] ... so it wasn't rational design, it was the same old thing as the suck it and see. (interview, 2007)

Wadley (interview, 2007) also spoke highly of Wu's contribution, 'Wen Yang Wu was a leading light in the team ... When things may have gone in a particular direction was when Wen Yang Wu put it back again.' Simpson too articulated his thoughts, 'Mark was the administrative chemist ... he was good. There's no doubt about it. Mark is a very, very good carbohydrate chemist. But when it actually comes to making it, Wen Yang Wu and Betty Jin are taskmasters at it. Like they are very, very good. What I would call wet chemists. They were great. Great couple actually' (interview, 2007).

However, the answer to Simpson's question he asked of Wu would surface approximately 18 months later as Wu remembered, '... we [Wu and Jin] joined this [project team] in 1988 - actually in the one and a half years in 1989, we were able to get a first key compound' (interview, 2007). Simpson elaborated on the details of the final

steps:

Wen Yang presented this notion that Palese's work was flawed. The notion he presented to me was that, whilst Palese was a brilliant biologist, he felt he was a very poor chemist; that the compound that he said he'd made, he hadn't in fact made. So, he [Wu] asked my permission to do it again. I said to him does Mark [von Itzstein] know of this? He said no. Because he said I sort of floated the idea with Mark. But Mark's attitude was that it was a waste of time. You don't repeat other people's work. ... we had to do this whilst Mark was away ... in Germany, at a carbohydrate conference. He was gone for two and a half weeks. So, I said to Wen Yang, you got two and a half weeks' sunshine to make it. (interview, 2007)

This was made possible thanks to Jose Varghese's pictures that showed the protein in fine atomic detail. The chemists saw that opposite the 4-hydroxyl on the sialic acid there was a pocket in the neuraminidase, at the bottom of which were two glutamic acid residues. They could also see all of the interactions between the natural substrate and the enzyme pocket, and there was an excellent fit between the natural ligand, everywhere except in one region. The 4-hydroxyl of Meindl and Tuppy's compound (DANA) projected into a pocket of the enzyme, which had water molecules in it and a couple of negatively charged groups. This observation led Wu and von Itzstein to propose that replacing this hydroxyl with ammonium or guanidinium functionalities might lead to improved fit. They posited that these glutamics were too far away from the substrate to play any role in catalysis but were nevertheless totally conserved among all flu strains. When the hydroxyl at the 4 position on DANA was replaced by an amino group, the resulting compound was a better inhibitor than DANA but when 4-guanidino DANA was prepared and tested it was found to be a 1000-fold better inhibitor than DANA and this inhibition was specific for influenza neuraminidase and not for neuraminidases from other sources. So by making that one minor change improved the potency of this molecule by 10,000 times; meaning that if you needed a given concentration to inhibit the enzyme with the molecule Neu5Ac2en, you needed

only one ten thousandth of the concentration of the molecule zanamivir (the guanidinium derivative of Neu5Ac2en) to get the same degree of inhibition (Colman, 2002; Laver, 2000).

Wu said, ‘I presented the first of the amino compounds to show them the selectivity, and it was about 10,000 times different. Peter Colman immediately picked it up and said, ‘that’s it’. We were close to our goal’ (interview, 2007). If the process had at times been painfully slow from a business perspective, it was worth waiting for. Simpson paints the picture of the process beautifully:

Of course, once they got into the business of actually designing – once we got over Mark’s idea about going for non-mutable carbons and Wen Yang Wu got us on a bit of sense - once it became obvious what to look at, Relenza [the name of the final compound] fell out within three weeks. It just went bang. Wen Yang rang up one day and said I’ve got it. This is it. This is the one that’ll go. He was right. (interview, 2007)

Along the way there were numerous other silent achievers working behind the scenes. Andrews mentions one in particular, ‘One of them, a young fellow called Mark Smythe ... [I]f anyone was really involved in the design of that molecule, it was him – working in Mark von Itzstein’s lab ... [T]hat was where I saw the major brains in the design side coming from. You will find him extremely modest ...’ (interview with Andrews, 2007).

Wu has remained modest about his contribution. Of it he said, ‘The chemistry is very difficult. The chemistry itself scared people away.’ This is because ‘the chemistry is not just one kind of field of chemistry. You need quite a broader field of chemistry, so luckily I knew all of these. This is why it was straightforward’ (interview, 2007). Wu (interview, 2007) recalled from this time a supportive atmosphere and a team approach: ‘I mean, we always had group meetings’. Colman was still heavily involved and watching the research progress. For those first three or four years, he was going to the

VCP every Friday afternoon to talk with the chemists about what was being done and why. This meant that research directions were being constantly re-evaluated and updated in the light of developments. A certain amount of formal research planning also had to be done for inclusion in the applications for Government grants. Reports on developments and research directions also had to be prepared for the monthly Biota board meetings.

### **Filling up the Dance Card**

Being a small startup company, Biota had none of the resources needed to carry out a drug development program. They needed a big partner to help them do that. So they decided to start looking for a big brother to help with the development. In this process, it was inevitable that personal contacts would be an important starting point. Glaxo 'knew about the project' (interview with Woods, 2007). Thanks to Colman's efforts earlier that decade. Other key people involved in Biota also had links with Glaxo. Woods and Simpson had dealt with Glaxo during their David Bull years (in Woods's case the contact went back even further, to 1954), with personal relationships facilitated by the fact that Glaxo had a subsidiary in Boronia, Melbourne:

Bernard [Taylor] was head of Glaxo at Boronia for quite a long time. I'd known him for quite a while. My brother, David, knew him better than I did, because he at that stage was a member of the APMA [Australian Pharmaceutical Manufacturers' Association], as was Bernard. And another binding thing was the fact that Bernard had taken up some shares in our company in DBL [David Bull Laboratories], and when we sold the business, he did very well out of it. He got quite a nice lump, so there was a good connection with Bernard, friendship as well as financial gain, and respect and quite a lot of things that make things happen. (interview with Woods, 2007)

Andrews was also involved with Glaxo at the time, as well as with one of its rivals:

Well back in the '80s I was consulting for both Glaxo and Wellcome – the late '80s. I talked to the boys at both camps and they – both of them basically [said], '[W]hy would we expect this to work?' Why had they not done it, you know. I think Graham Darby at Wellcome told me that he thought it was a good project, but the powers that be just said 'bullshit'. 'If we haven't thought of the target and no-one else has thought of the target, why would some dill in Australia have thought of it' – words to that effect. (interview, 2007)

As Andrews's account indicated, other companies besides Glaxo were approached too. Simpson gives a full account of which ones, and why they were approached:

I contacted American Cyanamid [now Lederle] ... I contacted Wellcome - Burroughs Wellcome, as they were, in the UK. I contacted one other company. I think it might have been Merck in New Jersey ... We had a presentation which I did. It would have been late '88. So we went to Wellcome because they were a virology company. We went to Cyanamid because they were a US company that probably really – they were one of the companies that really needed a new product. They had a pipeline that was about zero. Well, they were actually really interested. But I never got back to them because I was just dismayed at the place. It was old. They seemed to be old scientists. They weren't of a new breed. They had a lot of trouble understanding things like x-ray crystallography and stuff like that. There was a Japanese company I went to as well, Takeda. I only went to them because I'd had, through my time with David Bull, I'd had a number of dealings with Japanese companies ... [Merck] Just because they were big. Now [with] Merck, we didn't even get to first base. They just said, look, thank you. But not our interest. We're not interested in respiratory disease. Cyanamid were interested. But like I say, I wasn't interested really in them. Wellcome were very interested because virology, right down their alley. Takeda, sort of a bit of interest. But it was going to be hard work.

So we had four. Over to one side, we had Glaxo. Now Glaxo were to one side because we knew we had an in with Glaxo. We knew we had an in because Bernard Taylor had been the managing director of Glaxo Australia. Now Bernard and Alan knew each other very well because they'd battled each other, over a number of products, when David Bull started to make generic products. A number of products that were competitive with Glaxo products. So we knew Bernard really quite well. Now Bernard had finished up in Australia and gone back to the UK. Due to a whole lot of circumstances like other people dropping dead and stuff like that, he found himself elevated up the heap at Glaxo, to the point where he was a CEO of Glaxo. We hatched the plan that we would go and see the others. The other four. See what we got from them in terms of what do we do next and all that sort of stuff. But it was always our intention that we threw this at Glaxo at some point. (interview, 2007)

Colman also commented on the choice of Glaxo:

How did Biota choose Glaxo is another long story. Biota went around and made presentations to many of the big drug companies in - it would have been around 1989, or even 1988 about what we were doing and who would like to work with us. We had a number of expressions of interest, but I think in the end we chose Glaxo partly because Alan Woods did know some of the Glaxo people, and I knew some of the local people here also. I think it ended up being a choice made on our personal knowledge of individuals within that organisation. Yes, it probably would have been a fairly good fit in terms of therapeutic areas.

Well in terms of a treatment being given into the airways, certainly Glaxo have lots of asthma treatments, not lots, but had experience with that. But no one at that stage had had any recent experience bringing influenza medicines to market. It's one of the reasons it took a long time. There just hadn't been another one. Glaxo's whole experience with that, there's one reason why Roche were able to go through so quickly. (interview, 2007)

At the same time, Simpson pointed out that they were still entering uncharted waters. None had approached Glaxo with a compound before at such an early stage of development. Ultimately there was a good deal of uncertainty over what the reaction would be: 'Are they going to tell us to just piss off or are they going to say, well, we want you to do this bit of work next, then come and see us or what? We don't know. Because none of us really dealt with big pharma before' (interview, 2007).

### **The Courting Ritual Begins**

Peter Simpson commented further on some of the business aspects that he felt were important in getting that all-important 10 minutes of time to present ideas to prospective firms:

One of the things I did know, from the times that I'd been at David Bull, was that, when you present to big pharma, you really only get one shot at it. If you don't make that shot hit, basically you're stuffed. You don't get to go back and back and back. So you've got to try and sort out what's going to work. One of the things actually that I learnt from the presentation that I think that I did to Lederle was the guy said to me, 'The way you present it is very

theatrical'. He said, 'I see a lot of presentations'. He said, 'Yours is interesting because it's theatrical'. He said, 'What you should think about is making it more theatrical'. I said, 'Well, what do you mean? Come in dressed up and ...' He said no. He said, 'Most people just come in and present data like it's bland'. He said, 'Use your skills, which is obviously you're quite skilful at talking'. I'd been a university lecturer so I was reasonably good at that. What they liked about it was that I came into the room with nothing. All I wanted was a whiteboard. I ran through the entire presentation on a whiteboard. I still do it. I never use PowerPoint. They get their knowledge and just go to sleep. Whereas if you're drawing something, you can change the way you do it. You can scribble things. It looks like you're in total charge of the way you do it. I said I want a whiteboard and a pen that works. Because the number of times I'd got in there and pens didn't work.

We made arrangements to go to London and see Bernard. Now that would have been in late '88. I [together with Woods] went to London. It was a cold day. At the time, they were just behind Green Park Station. Glaxo head office was there. At that time, it was Glaxo. Bernard [Taylor] gave us ten minutes. I took the only sample of the product we had. Peter Colman didn't like that idea necessarily. He thought that it would be better if we waited until there was another – a better compound. He spent his entire life doing this. I can understand that. But I said, 'Look Pete, in the end it's a business decision. I'm going to take the compound' ... So we saw Bernard. I'd never seen a chief executive of a big company's office before. It was – you know, a cup of tea with a bloke who wore gloves. I remember that. This bloke wore a suit and poured the tea and he wore white gloves. I thought, geez Bernard, this is alright. So he gave us ten minutes. We were there nearly an hour. Explained the story to him. He said, 'How do I know this is going to work on it?' I said, 'Well apart from trusting me, why don't you try that?' Then he said, 'Well are you telling me that that powder will work?' I said, 'It's not a cure for flu. But it's getting there. It will produce something that your scientists have never seen before and that is inhibition of the influenza virus of any strain'.

So he picked up the telephone and rang a guy called Mike Elves who was their bloke in charge of new product ideas. He was going to Switzerland the next day. Bernard said to him, 'I'd like you to postpone that. I'd like you to meet this guy and go through this project with him. If there's something wrong with it, I'd like you to ring me and tell me what's wrong with it. Because it sounds like a stunning new idea to me. I know the people that are behind this. It seems just like a good idea'. So I met Michael at the Café Royale, just off Piccadilly. That was an interesting lunch too, because the chef went mad and chased the chef's assistant out the restaurant with a knife. It was like something out of Fawlty Towers. It was amazing. So again, I went through the thing with Michael. I said to him, 'Look, try it. If it works in our house, see if it'll work in yours'. Of course, they tried it. It worked. They then kicked it up to their microbiology department. So it went to microbiology because they did viral stuff as well. That was a guy called Barry Ward ... He was terrific. Because he said to us, day one, he said, 'It's my job to find out what's wrong with this'. He said, 'I'm spending the next six or 12 months finding out what's

wrong with it. When I find out what's wrong with it, I'll throw it back at you'. So he started to test it then *in vivo*. So we had *in vitro* activity. Then he started to test it *in vivo*. The process just basically went on from there. They did preclinical toxicology. (interview, 2007)

Woods, who was also at the meeting with Bernard Taylor, agreed that the critical moment was when Taylor agreed to take their first compound for testing. At this stage there was no agreement signed but Glaxo took the compound into *in vivo* trials in animals in return for the first right of refusal to fund the project. Part of the motivation to have the development done in the UK was Glaxo's expertise in this area. Simpson (interview, 2007) explained this, 'Well, once we had a compound that we knew worked. Like we knew that it produced activity *in vitro*, the issue then was well we think we've got something here. But we need it tested *in vivo* and it's better to have that *in vivo* testing done in a place that does that sort of stuff and does it repetitiously.'

These trials led to the first activity seen in rats although, as anticipated at that stage, the level of activity reported was not high enough to warrant human testing. This was the first time that a compound of this type had demonstrated potential therapeutic activity *in vivo*. Woods felt that this was a turning point in terms of Glaxo's perceptions of Biota: 'That was a moment of respect, I think'. Over the period of time from about 1988 to the early nineties, there were three major compounds developed – each one looking for a better result than the predecessor.

### **What did the Company Look Like Then?**

Quirk presented the following table at a seminar on Biota's development pathway in August 2007 at the University of Queensland. He was eager to highlight several key features of Biota's structure; first, that company had no revenue earnings in their initial

eight years; second, they had already experience numerous managerial challenges in the form of a change of CEOs and a takeover bid; third, their cash reserves had fallen by a half and a lead compound was on the verge of being identified, and fourth, they had no significant partner identified at that stage.

**Table 3: Biota’s Position from Inception to Scientific Compound Identification**

Year	Market Cap	Subscribed Capital	Cash	CEO	Development	Projects	Progress	Relenza
1983				1	Biota Pty Ltd	ID phase		
1984								
1985	\$3.0	\$3.0	\$3.0		Biota Holdings	3		
1986	\$3.0	\$3.0	\$2.5				Patents filed for NI	
1987	\$3.0	\$3.0	\$2.0	2				1st active molecule
1988	\$3.0	\$3.0	\$1.6		Takeover bid	2	Vaccine program abandoned	
1989	\$4.6	\$3.0	\$2.7				Glaxo Heads of Agreement	

**Source: Quirk, 2007b Seminar Presentation at University of Queensland**

### **A Marriage Made in Heaven? Glaxo and Biota Unite**

Around this time, Peter Simpson became a full time employee for Biota – although he was still officially the only employee besides the board members and the contract scientists. He, Woods and Ken Windle (who had succeeded Taylor as managing director of Glaxo Australia in 1986<sup>5</sup>) made frequent trips to London as negotiations continued. On the Glaxo side, there were scientists (the head researcher, chemists and virologists) as well as senior executives. Of the meetings, Woods recalled: you’d get about 10 Glaxo people at least, and there would be another half a dozen of us. We’d all sit down over a great lunch and a great dinner, and tell each other how great we were (Woods, 2007).

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<sup>5</sup> Ken Windle held numerous senior positions with Glaxo and its subsequent companies. He was General Manager, Glaxo UK 1980 - 1983; Head of Commercial Development, Glaxo Group 1983 - 1986; MD, Glaxo Australia 1986 - 1995; Regional Director, GlaxoWellcome, Asia Pacific 1995 -2000.

Simpson also talked about this next stage in solidifying the deal with Glaxo:

So the first few months of that year [1988] we spent time obviously going backwards and forwards to Glaxo. We also spent time presenting to Wellcome. We told Glaxo that we were chatting to others. I think they probably figured out who it would be. In neither case, did we tell them what the compound was. So they had no idea and they were not to try and develop it or anything like that. That was part of the agreement. And they didn't. They played the game. (interview, 2007)

Negotiations also took place with Glaxo's subsidiary in Melbourne. In terms of the actual negotiation, the Biota people were well represented. Tom Quirk gave a full account of a typical meeting:

It was a very interesting negotiation, because the entire board of Biota would frequently turn up. So you had the Chairman, who was Colin Trumble, there was a Malleasons' lawyer. There was always a Malleasons' lawyer present. I don't think particularly. I think Colin Trumble – I don't know why he agreed to be chairman. Maybe he had known Alan somewhere else. But I don't know. But the negotiations were very funny, because there would be Peter Colman, myself and then from time to time another of the directors, Bill Kerford, who came out of Brick & Pipe or Humes or something like that, and he was a financial man, with absolutely no idea of this world of pharmaceuticals whatsoever. ... [T]his was all in Melbourne. All these negotiations were with Ken Windle and Bert Fox, who was the local finance director of Glaxo. And occasionally I think Christine Hurst, who was the regulatory lady here. They would have their lawyer who was Bernard O'Shea from Deacons who's a very good, very experienced lawyer. And every now and then we'd get down to negotiation where Peter Colman would say – give you a stage whisper saying 'I think I'm going to resign from the board.' And I'd say 'Peter that's not the thing to say in the middle of negotiations', and he'd say – Ken Windle could hear what was going on. Every now and then I would actually – Ken Windle would come out the back of the shed and say do you think we could actually cut down the number of people who came in from Biota, are they really all necessary? Because all it did was it wasted a lot of time. Not that we actually were the ones who – I mean, it's only when you deal with the international company, Ken would have to – if he wanted to agree some points, he would have to send them back to London. (interview, 2007a)

Woods (interview, 2008) noted the importance of Biota's solicitor at the time, Bill Brown from Malleasons, 'he was very helpful during these discussions' as well

other experienced directors such as Bill Kerford.

Colman, the scientific representative, explained just how important his role was, ‘Heavens yes [I was involved in the negotiations] ... I mean all the board members, all the directors of Biota, I would say every one of them was heavily involved, and [I] as the only scientifically cogent one ...’ (interview, 2007). Quirk agreed that scientific input was crucial in this process:

So this is a one-person employed company trying to get attention? Well yes but the director – in that stage of development in fact two or three of the directors were actually actively involved in all of this, plus you have the scientists who in part were actually keen to selling because you dealt with the management in say Glaxo but you also had to find scientific champions inside of the pharmaceutical company. So the scientists from the Victorian College of Pharmacy and the CSIRO were actually very important in that. (interview, 2007b)

An important aspect of the deal making to highlight is that along the way, Biota enjoyed much support from key staff at Glaxo, both in the UK and in Australia. Bernard Taylor had been pivotal, but upon Taylor’s resignation from the top job of Glaxo Plc in May 1989<sup>6</sup>, Richard Sykes<sup>7</sup> who replaced him, carried on enthusiastically sponsoring the project. Woods recalled, ‘[Richard Sykes] was interested quite early. He wasn’t – the person who took over – Bernard Taylor was in Sykes’ position, and he was known to be a fan at that time, so we were quite pleased when Bernard – we weren’t pleased to see Bernard leave. But we were quite pleased to see Sykes take it over, because we felt that he would be keen on the project, which I think he was’ (interview, 2007). Locally,

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<sup>6</sup> Taylor resigned following an announcement that Ernest Mario, who headed Glaxo Inc. (USA), was named chief executive of Glaxo Holdings Plc. (UK). This was due to a reorganisation of Glaxo’s management, Dr. Mario reported directly to Glaxo’s Chairman, Sir Paul Girolami, and all other executive directors of Glaxo reported to Dr. Mario.

<sup>7</sup> Sir Richard Sykes joined Glaxo Research Limited in 1972 as Head of the Antibiotic Research Unit, before moving to The Squibb Institute for Medical Research, Princeton, New Jersey, USA. He became Director of Microbiology in 1979 and an Associate Director of the Institute, and from 1983 to 1986 was Vice President, Infectious and Metabolic Diseases. He rejoined Glaxo in the UK as Deputy Chief Executive of Glaxo Group Research Ltd and was appointed Group Research and Development Director, Glaxo plc and Chairman & Chief Executive of Glaxo Group Research Limited in 1987

the company also had a great product champion in Ken Windle. Again, Woods recalled, ‘he had been a very good supporter all along. And we had an extremely good relationship actually in the early days’ (interview, 2007).

It is important to add the antecedence to Glaxo Australia’s relationship with their parent, Glaxo Plc. This relationship was unusual for several reasons - by the early 1960s, Glaxo Laboratories (Australia) was the third most important subsidiary in terms of capital employed. Whilst the rest of that decade was more a less a period of consolidation, the 1970s again saw the Australian division hit the parent company’s radar. Indeed, it was Taylor that championed a protracted period of firm organisation and skill development. Taylor spent time from 1963 to 1972 in expatriate roles in New Zealand, returning to the UK, only to be dispatched to Australia in 1972. On his arrival, sales rose from 1% of the total market share to 10.5% by 1991. Jones highlighted the actual significance of Taylor’s time as head of the Australian subsidiary, ‘Until the early 1980s sales in Australia were greater than in the United States, and it was an indication of the importance of the subsidiary that in 1983 Taylor was recalled to Britain to serve as chairman and managing director of Glaxo Pharmaceuticals (UK)’ (Jones, 2001, p. 426).

The first agreement signed with Glaxo was a research collaboration agreement with Glaxo Plc, signed in 1989 (see Table 4). According to an official press release issued by Biota on 25 January 1989, the company would concentrate its research efforts to produce more effective compounds based around the initial success with scientists being confident that more active anti-influenza compounds were within grasp using the technologies currently only available to Biota. The press release foreshadowed that discussions would be had in the near future with Glaxo about on-going programs and the commercialisation aspects. Within six months, on 8 June 1989, another

announcement was issued: Heads of Agreement had been signed with Glaxo Australia Pty Ltd in regard to research funding. The principal points of agreement between the parties are summarised in Table 4.

**Table 4: Agreements between Biota and Glaxo**

Type of agreement	Date	Content
Research collaboration agreement with Glaxo Plc	1989	Initial testing programme designed to ascertain whether the first in a series of novel anti-influenza drugs developed by Biota was effective when given to animals.
Heads of Agreement with Glaxo Australia Pty Ltd	Jun 1989	<p>(a) Glaxo would pay all research costs, initially for 2 years, with an option for yearly extensions. The research by CSIRO and Victorian College of Pharmacy that had been funded to date by Biota Scientific Management Pty. Ltd. would continue with funding from Glaxo. Research costs were running at the rate of A\$750,000 per annum, however the research expenditure was likely to be substantially increased.</p> <p>(b) When suitable compounds were identified, Glaxo would fund their development to the stage where they may be marketed. The ongoing pharmaceutical, toxicological and human studies were estimated to take five to eight years, and may cost Glaxo up to A\$200 million.</p> <p>(c) Glaxo would pay BSM an annual fee of A\$300,000 (indexed to CPI) in return for consultation, scientific facilities and staff for an initial period of 2 years. Glaxo then had an option to extend research for a further period and if it exercised that option it would pay a fee of A\$300,000 (indexed to CPI) in the third year, A\$200,000 (indexed to CPI) in the fourth year and thereafter a fee to be agreed.</p> <p>(d) A number of payments to BSM had been agreed for different stages of the research and clinical development. These payments would total A\$6 million.</p>
Long-term agreement between Glaxo Group Ltd (UK), Glaxo (Aust.) Pty Ltd and Biota Holdings Ltd and Biota Scientific Management Ltd	Feb 1990	<p>a) Glaxo would pay all research costs for 2 years with yearly extensions.</p> <p>b) Glaxo would pay Biota an annual fee initially of A\$300,000 in return for scientific consultation. After the third year the fee would be A\$200,000 and thereafter as agreed.</p> <p>c) A number of 'milestone' payments (totaling A\$6 million) would be made to Biota as the research reaches various stages:</p> <p>(i) when a drug candidate was suitable for on-going clinical development - A\$1 million.</p> <p>(ii) approval of a human clinical trial application - A\$2 million.</p> <p>(iii) when clinical efficacy trials were complete - A\$3 million.</p> <p>d) When product sales commenced Glaxo would pay Biota A\$4 million in advance royalties.</p> <p>e) A royalty of 7% on net worldwide sales would be paid once patented products were marketed.</p> <p>f) Biota could co-market any drugs developed in Australia, New Zealand, Indonesia and parts of Africa.</p>

**Source: Biota Prospectus, 1985**

A long-term agreement was signed between Glaxo Group Ltd (UK), Glaxo (Aust) Pty Ltd and Biota Holdings Ltd and Biota Scientific Management Ltd, on 21 February 1990. The agreement represented the commencement of the commercial thrust associated with potential drugs developed by Biota scientists, to treat influenza Virus A and B. Under the terms of the agreement (Table 4), Glaxo would now pay for all direct research costs as from 8 August 1989 for at least 2 years. As anti-influenza compounds were developed and passed to the clinical evaluation stages substantial financial and scientific input would be committed by Glaxo. Of the agreement, Peter Simpson firmly said, ‘We wrote it’, and both he and Woods both recalled the painstaking work involved in drafting and rewording each line, with the help of their legal team (see also interviews with Woods, 2007, 2008).

Several months later, in May 1990 Biota Holdings Ltd and Biota Scientific Management Pty. Ltd announced that the agreement between their companies and Glaxo Australia Pty. Ltd was now conditional. In accordance with the terms of the Glaxo Agreement, Glaxo would now pay Biota approximately A\$1,105,000 and meet all agreed research and related expenses. von Itzstein (interview, 2007) recalled that ‘on an annual basis I would present a budget to Glaxo via Biota.’

Wu explained that when Glaxo Plc took over the compound’s development in 1990, with all the testing being conducted in the UK. the flu busters team at the VCP started to wind back a bit, although to that point the team had synthesised over 60 compounds:

[We were] doing other things ... some defensive work round the compounds, doing the derivatives, all the chemistry. Afterwards, we passed [the compound] onto them. They did their own work to find out whether that candidate was worthwhile. So they did a lot of work. I remember they synthesised 10,000 compounds. I think [it took them] two or three years. Later, you just buy the synthesis and then use a robot. But that’s different. That’s our skeleton and they just put the muscle. (interview, 2007)

Woods expressed much gratitude at the ultimate choice of partner; Glaxo:

It was all in our backyards [Australia]. They'd done the asthma thing and so they knew their way around the inhalation. They're technically very good people and had very good integrity known to the personal level as well as the company. So that all fitted. I was really so pleased we didn't have to go with another foreign company, American or whatever. They were [a] far less well-known person. You're not at the same cultural level, you don't think the same way. I've known the English way, the perfidious Albion. I know that aspect of them as well as their integrity and a whole heap of stuff. We did have three million in the bank when we started anyway in '85. Then of course of as soon as we'd done the deal we were getting ongoing payments to pay for our research workers, which was good; couldn't have done it without them. (interview, 2007)

### **Who Needs an Umbrella?**

Soon after the Biota compound went into preliminary investigation, Biota discovered one of the potential downsides of collaborating with a large, sophisticated partner.

Quirk gives an excellent description of the surrounding issues:

It was very interesting because the whole issue, what this was based around was what was called structure based drug design. What you did was you – what you were trying to do was essentially stuff something into a keyhole; you were trying to block the action of an enzyme. It was very much like trying to figure out what key would fit in a lock.

This had been done before by a very distinguished x-ray crystallographer from Columbia in New York city and he had made a couple of drugs. He had the same idea, tried them on rats, it didn't work. The difference was that the Glaxo people who were actually in the pharmaceutical industry said well, influenza it is in the respiratory tract; so what we will do is we will spray the Biota compound up the nose of the rats and lo and behold it worked. What the guy at Columbia had done was actually inject the compounds and they just got flushed out through the kidneys and that was it.

So in a sense if you have been asked to invest at that early stage in Biota and you had done your homework you would probably have said it won't work, we have tried before. So it is very interesting, again the sort of – maybe the isolation in Australia and new sort of bright eyed, bushy tailed people wanting to have a go. In a sense, we were protected in terms of developing this by the knowledge in the outside world that this approach didn't actually work. Of course that was then very interesting because Glaxo saw our compound working, our compound was not as active as the two compounds which have been tried from the New York based work and we had a few wobbly moments

then about whether Glaxo would continue to play with us or not. (interview, 2007a)

Colman's role in maintaining full patent protection for Biota at this time was absolutely critical and cannot be understated. It is often said that *anyone can fly a plane!* Whilst this is fundamentally true, it is in times of crisis that you want the aircraft to be commanded by the most senior, experienced captain available. This is analogous to the situation Biota found themselves in Glaxo and their patent protection. Equally, you could say that *anyone can draw up a contract regarding a scientific discovery* but it is when someone is trying to downplay or change the nature of the patent to your potential disadvantage that you want the most experienced and articulate scientist leading those discussions and negotiations. To this end, Peter Colman fitted the bill. Quirk (interview, 2007a) said, 'We were saved by one of the scientists, Peter Colman going along and explaining where it would fit and how we had actually initiated the whole program'.

It is important to remember that on many fronts, Biota was a company of firsts: (1) its compound was the first example of receptor based drug design for viruses, (2) it was the first small company to do a deal with Glaxo, (3) it was the first human health drug biotech company in Australia, (4) it was the first company to set up an arrangement for the scientific inventors to share in the profits and (5) it was the first 'virtual arrangement' not tied to a university. These achievements were not without their frustrations though; Quirk specifically mentioned:

The only trouble, I remember the difficulty with it all, and it was because it was done so early in the scene with Biotech, is that we essentially gave over all the management of the project to Glaxo. Once we'd come upon a molecule which they took into development, then we were really out of the picture, except for developing the sort of patent suite that surrounded the main molecule. (interview, 2007a)

This consequently meant that on a practical level, Biota ‘lost control’ in terms of their active involvement: ‘we had no say in clinical trials, no say in any development at all. And not even to the extent of committees or reviews’ (interview with Quirk, 2007a). The implications of this loss of control would become clearer in subsequent years.

### **First Attempts at Product Diversification**

While Peter Simpson had made the decision to stop funding McAuslan’s angiogenesis project, he sought to capitalise on the existing IP that the company had acquired from this research program. At the start of 1989, Biota and Smith & Nephew Pty Ltd announced they were entering into an agreement that would allow for Smith & Nephew to undertake the necessary development testing of potential wound healing drugs developed by the Biota scientists. Woods (interview, 2007) explained that ‘[w]e had good connections with Smith & Nephew as well from the early days; the headquarters was in Melbourne’. However, in October 1990 the companies made a mutual decision to abandon the work. Quirk commented further about the nature of the project:

By 1990 ... we had abandoned angiogenesis project and I am afraid that was a bit like Mel Brooks and The Producers, we discovered that this thing seems to be on sold by the CSIRO a couple of times over to different people then turned out that there was no valid patent ... I think the .. decisive one [i.e. reason] - was that we had gone to one of the leading wound healing companies in the world and they had a try and it didn’t actually do anything which was exceptional compared to things which they were already looking at. So that was really abandoned from a business point of view, that there wasn’t any great advocacy there. (interview, 2007a)

Andrews also confirmed this to be the likely cause of the deal between the two firms ceasing, ‘Well it turned out that McAuslan had already sold the stuff more than once, is what basically happened, so Biota was getting a second or third go’ (interview, 2007). This meant that for the moment, Biota remained a company with a single

research program.

Clearly, the integrity of the scientists is a vital ingredient in the deal making process. As Simpson had said earlier regarding his preference for the flu project, ‘The science was honest. They’d done really good stuff’ (interview, 2007). Quirk also stressed the importance of reputation of the key stakeholders and veracity of the science in terms of attracting support from venture capitalists and shareholders alike, ‘Therefore, relationships were very easily established and that is part of the battle when you are trying to sell something which is really unknown: what’s the reputation, what’s the scientific and the business reputation of the people that are involved’ (interview, 2007a)?

Another opportunity that was identified early lay within the company’s core area of influenza. In the early 1990s there were no sophisticated or suitable tests for influenza for physicians to help diagnose patients in primary care situations, i.e. at the general practitioner’s office. Executives in Biota were conscious of this and thought this represented a good opportunity for the company, which was now amassing considerable expertise in the therapeutic area. Quirk explains the rationale behind this move in some detail:

One of the things ... was whether we should have a [flu] diagnostic. Now, the background to that was in the United States there [was] quite large industry which [was] point of care diagnostics; which are little strip tests, there are things like pregnancy tests. ... I have been involved in one, where people would say well strep throat; everybody knows when they have got something like that. But, what they had forgotten about was that the treatment with antibiotics was actually very expensive. The HMOs [Health Maintenance Organisations] who had to pay the bills got to a point where they said, doctors are over-prescribing, we need to have some proper identification for people who have actually got strep throat and that turned out to be a US\$200-300 million dollar business alone in the United States.

I had been involved in a company [Quidel] which was one of the leaders in that and so we had a look in Biota at whether we should do the same and we

discovered that there was this company, Symex, which was in Tulsa, Oklahoma, [which] had actually been looking at the work of Peter Colman on the influenza virus and had thought about making a diagnostic which was based on his work - this was the structure of the enzyme.

We actually got involved with them because we had the chemists who could make – essentially what you regarded as hook, you would take a throat swab or take a sample, wash it across a pad. If you had influenza virus it would get locked on it, it would get hooked by something which is actually done in the pad. Then you would wash that through, the virus would stay there and then you put a developer on it and if you actually had the virus, the developer would lock onto the virus and so you would change colour in a little pad. That would be the little way of identifying and diagnosing influenza. (Quirk, 2007b)

Personal networks would again come into play, albeit via a circuitous route.

Quirk explains:

Through one of my venture capital links in some way, I got a message back from somebody in Western Australia saying did we know of this company in Oklahoma, so we started to talk to them. And in fact, the essential deal was I think [if] we did buy into the company, we would have a joint project with them, and we would help provide them with some molecules which could start work ... So that was the link to Symex. And that's how all of that actually started.

So, in April 1991, Biota started these discussions with US-based Symex Corporation. Initially the talks centred on collaborating to develop a diagnostic kit for influenza. According to Woods's (interview, 2007) recollection, '[Symex] ... had initiated work on a diagnostic using, I think, a precipitation process', he was able to tell exactly how the negotiations proceeded:

Joe Tippens [the CEO] ... was an investment character with US\$10 million in his pocket and a few technology ideas, and this was one of them. Then this little company formed [Symex], which is running out of money, and we thought ... [smiling]. We had meetings with them and went through quite a bit. We came to agreement finally that Symex would send somebody out to Australia to talk to Mark von Itzstein and see how our technology would fit. (interview, 2007)

About one month later, an agreement with Symex was signed. Biota was granted manufacturing and distribution rights to the diagnostic being jointly developed with an 8% royalty on world sales payable. The 1991 Annual Report of Biota Holdings said:

At the current time the only diagnostic for Influenza is a complicated and time-consuming process. Biota's aim in developing an Influenza diagnostic is to produce a product capable of providing an effective diagnosis within a short period in a physician's office. Such a diagnostic is, we believe, desirable in certain markets. The scientific work associated with the development of such a test has progressed satisfactorily.

Shareholders have been previously made aware of our research collaboration agreement with Symex Corp, based in Tulsa, Oklahoma, USA. Over the past 6-9 months Biota and Symex scientists, in collaboration, have been instrumental in improving the specificity of the first product developed by Symex. Improved specificity means that the test will indicate the presence Influenza virus and not normal oral bacteria. Biota has used its extensive scientific knowledge in rational drug design to achieve this.

It is hoped that preliminary clinical trials will be undertaken in the northern hemisphere winter and, subject to success, major clinical trials of a product should commence towards the end of 1992. Over the next 12 months it is anticipated Biota and Symex will be able to further improve the sensitivity of this test. The parties hope to develop a test kit capable of being used in the physician's office. However, much work remains to be done. (Biota Holdings Annual Report, 1991)

Yet, within two years the deal would be terminated. Woods again goes on to explain how and why:

[Tippens] came out and was disappointed because he didn't get as much information as he'd hoped. He felt that our people were being somewhat difficult, I think, and not getting any results. So the long and the short of it was anyway that he pulled the guy out of there and went back and they terminated the arrangement. So the strange thing, I still don't know how it happened really, but I have to thank Joe because they returned our money finally, yeah. We paid about just half a million; I forget the numbers. It was quite unlikely when it happened, I couldn't quite work out why .... But that whole story was, you might say, a bit of fun on a personal basis with old Joe and his people. He had these expressions. Yeah, what was it? If it walks like a duck and quacks like a duck, it's got to be a duck. That was one of his favourites. (interview, 2007)

However, other evidence suggests the change in direction was due to a change in Symex's ownership:

Biota's involvement is now set to stop as another US company is buying Symex. Under the terms of the agreement between Biocryst, the purchaser, and Biota, Biocryst will pay Biota US\$240,000 in cash – Biota originally invested US\$325,000 in Symex – BioCryst will pay the research costs of about US\$280,000 for the three months to the end of March this year. Biota will also receive US\$480,000 in stock at Biocryst's initial public offering, and an 8 per cent royalty on worldwide sales of the diagnostic except in Biota markets (Australasia and some south-east Pacific and African countries).

Biota considered buying Symex itself, but decided that the logistics of owning and managing a subsidiary on the other side of the world were too difficult for a small company to handle. Under the deal, 'we've got our money back', says Mr Simpson.

That still leaves Biota as basically a one-product company at present. 'It goes against conventional wisdom' which argues that 'small start-up companies should have a variety of products', Mr Simpson admits. 'We could take the attitude that we have developed a cure for influenza and retire'. He reckons the company's work has more significance than that, though. 'We have developed the first major example of a rationally designed drug. The industry's been expecting it for a long time but that's the first time that someone's actually gone back and developed a drug from first principles'. (Pharmaceutical Business News, *Financial Times*, 22 April 1992)

In the 1991 financial year, another project was announced, the development of a rotavirus vaccine. During this time (from the signing of the Glaxo agreement until 1994), Glaxo were steadfast in supporting the Biota contracted scientists at the VCP to explore other templates and projects in the antiviral field. In its 1991 Annual Report, Biota notified its stakeholders of the following:

Biota scientists have commenced a programme seeking to develop a therapeutic capable of inhibiting this virus. Rotavirus is the commonest cause of infantile gastroenteritis. World Health Organization figures estimate that 3-5 billion people are infected annually and 5-10 million infants die per annum. Almost all deaths occur in third world countries although the disease is highly prevalent in developed countries. This virus was first isolated in Melbourne in 1973. Biota has commenced a chemical synthesis programme at the Victorian

College of Pharmacy together with an in-vitro testing programme at Melbourne University. Initial results are promising. (Biota Holdings Annual Report, 1991, p.4)

Industry watchers speculated at this time that a takeover of Biota was distinct possibility. For example:

[W]orldwide sales of a new drug for a previously poorly treatable disease average about A\$1 billion a year, and royalties to Biota would therefore be about A\$70 million a year of which 1 per cent would be split between the Victorian College of Pharmacy and CSIRO. Such a figure might make Biota an attractive takeover target to a large company, particularly Glaxo, considering that the royalty agreement is 'unusually high', she says. Takeover before a drug is marketed 'would seem highly likely' ... To increase the odds against this possibility, Mr Simpson argues that the company must widen its portfolio of products and research areas. At present it is working on treatments for Rotavirus .... (Pharmaceutical Business News, *Financial Times*, Business Information Ltd, 22 April 1992)

The initial Glaxo-Biota agreement was extended for a further two years, until December 31, 1993. This was viewed as a good indication of the commitment of both parties to their agreement. Quirk was quoted in the press release as saying, 'The research program ... to investigate possible drugs to inhibit influenza continues to progress satisfactorily ... but it must be appreciated that drug development is a slow and exacting process and there can be no certainty of the final result' (Porter, 1991a, p.26).

### **Changes to the Board and a Step Into the Limelight**

Mark Crosling and Colin Trumble, both foundation board members, resigned from the Board of Directors in November 1990. This signalled the shift for Alan Woods to assume the Chairmanship at the next Annual General Meeting (AGM). Trumble explained that he had many other commitments but more importantly, he felt that

Woods was really the best man for the job (interview with Trumble, 2007). Reflecting back over his chairmanship, Trumble described some of the feelings he had experienced as a board member, 'It was very lonely [the early days of the company]. There was really no back up. I can remember ... this strange feeling of holding an annual meeting and there was only one permanent employee really, and that was the chief executive' (interview, 2007). In April 1991, Peter Colman resigned his position as non-executive director of the board. Of this Colman said, 'I stayed on the board only for another year or so after Glaxo came into the project. I left the board of Biota in 1991. Just because the project now had a full development partner. But I continued to go to management committee meetings at Biota's request. I'd go to the meetings with Glaxo through into the '90s' (interview, 2007).

At the next AGM, Mark Johnson, the Chairman of Macquarie Corporate Finance Ltd, was appointed to the board of Biota. Johnson also sat on the board of other high profile companies, including Australian Gas Light Company and the Mercantile and General Reinsurance Company of Australia Ltd. Quirk commented about this appointment:

Well, Mark's one of the founders of Macquarie Bank. He's just retired as deputy chairman, and a terrific banker and really interested. I mean, a man who's ... interested in how companies grow ... [H]e was a classic merchant banker. I mean, his normal clients are people like Kerry Packer. But he knew about the Woods family ... And so when I started to talk to Mark about how interesting Biota was, he said well you understand the Woods are fairly eccentric. So he knew all about it, so that was very easy because Alan knew about Mark ... (interview, 2007a)

Biota and its management were aware of rising shareholder interest at this time. The *Sydney Morning Herald* (Porter 1991a) reported that Biota's shares had increased from A\$1 to A\$2.75 in just the previous 10 days, i.e. since 14 August, in response to an

imminent announcement from Glaxo Australia: 'A visit by representatives of Glaxo's UK parent has fuelled the speculation, although it is said to be a routine trip with time spent on projects apart from Biota's' (Porter, 1991a, p. 26). Porter also speculated as to some likely reasons:

With only 9.3 million shares on issue, Biota is thinly traded and this week's rise was generated on turnover of less than A\$300,000. Most of that volume was done by McKinley Wilson, a small Melbourne broker with a close relationship with Biota chief executive Mr Peter Simpson. Prudential-Bache Securities rated Biota as the top pharmaceutical stock earlier this year in a report recommending a buy at 70c for investors who understood the risks associated with biotechnology shares. Under an agreement signed last year, Glaxo agreed to pay all research costs for developing an anti-influenza drug as well as several 'milestone payments' when the research reached various stages. Biota would get a milestone payment of about A\$1 million if, as expected, it goes into phase-one clinical trials in about six months' time.

However, in response, Simpson said, 'there was no specific reason for the jump. The brokers involved in the sales had reported few sellers in the stock' (Porter, 1991a, p. 26). Less than a month later, Porter's suggestion of the impending announcement by Glaxo had come to fruition. On 3 September 1991 in the *Sydney Morning Herald*, Porter's story said:

Anti-flu drug researcher Biota Holdings has agreed in principle with Glaxo to extend their research agreement for a further 18 months, subject to continued progress. Biota's announcement yesterday about the deal follows a month of dazzling performance by its shares, which have shot from A\$1.65 to A\$2.80 since August 6 on about three times normal turnovers. The initial agreement, signed in May 1990 for two years, has been extended until December 31, 1993. Biota director Mr Tom Quirk said the proposed extension was an indication of the commitment of both parties to this research program. 'The research program ... to investigate possible drugs to inhibit influenza continues to progress satisfactorily', he said. Mr Quirk would not comment on how close Biota was to reaching one of the 'milestones' laid down in the Glaxo agreement that would see the Melbourne-based biotechnology group getting a special payment. 'It must be appreciated that drug development is a slow and exacting process and there can be no certainty of the final result', he said. The research agreement provides for Glaxo to cover all research costs as well as an annual access fee to a Biota subsidiary, Biota Scientific Management. (Porter, 1991b, p. 26)

Biota's share price had increased by a factor of five, although this was based on small volumes. Moreover, 'In the past month about 600,000 shares have changed hands against 200,000-odd normally' (Porter, 1991b. p.26). At this stage, Biota had approximately A\$2.35 million cash in the company at the end of the 1991 financial year.

During late 1991 several of Biota's patents were published, including the details of the structure of the 'active site' of influenza neuraminidase. It was expected that these publications would be available in the last quarter of 1992. The data would cover the Biota compounds in relation to: a) chemical structure, b) activity - significantly more active than the best anti-Influenza compound currently available on the market, c) use - compound seems to have activity as a prophylactic as well as potential use for Influenza, and d) initial reports indicating low toxicity. It was expected that this would attract worldwide attention, as it would be the first time BSM's intellectual property was in the public domain. Considering this, the company and Glaxo went to great lengths to ensure the security of the IP to preserve their leadership position in the research race (Australian Stock Exchange Company Announcements, 13 November 1992).

### **The Second Employee and Lead Compound**

In 1992, a second full-time employee, Richard Wadley, joined the company as Company Secretary. Wadley recalled how he became introduced to Biota: '[They approached me] ... through their auditors; Price Waterhouse called me to see if I was interested' (interview, 2007). The profile of the industry and the size of the company were important considerations for Wadley:

What attracted me to the company in 1992? Well it was a small company, it

was an exciting area. I like small companies. [And ...] there wasn't hell of a lot of biotech around at that time. There was Biota, there was Blood Bank, there was a company I think called Rancoo who didn't know what it was. So you know it was an area [that was new and interesting] which – plus it was sort of – raised the sort of accounting issues and management issues which you know I was sort of interested in. So I didn't want to work for a big company so when Biota was put in front of me I was quite interested in it. (interview, 2007)

Wadley, who joined the company in about February 1992, was soon confronted with the announcement by Glaxo in April that it would take a lead compound into exploratory development to determine its possible use in humans. This compound, which Wu (2007) estimated was 'about a hundred to a 1000 times better' than the first one the VCP scientists had discovered, was given the code number GR121167X<sup>8</sup> and Biota received a milestone payment of A\$1.13 million. The exploratory development phase explored the efficacy of the candidate drug in other laboratory models, as well as identified potential side effects. The next development phase was expected to take up to two years before the compound, providing it met all the scientific requirements, would move into a programme of human clinical trials (Biota Press Release, 13 November 1992). Once those trials began, the development process was anticipated to another 3 to 5 years before enough data was available to submit an application to regulatory authorities to market a product. Some of the development work was to be undertaken by Glaxo Australia at their new Boronia Development Centre. Biota would continue its research to develop further classes of new and novel compounds under an extension of the research collaboration and licensing agreement. (interviews with Quirk, 2007a; Simpson, 2007).

This was another watershed moment for Biota; Wadley described the situation

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<sup>8</sup>This was the 'first' code name given to Relenza (zanamivir). It would later be known as GG167.

that confronted him at that time:

The deal with Glaxo, what was to become Relenza, it actually progressed quite well. And Glaxo-Biota had announced, probably ... probably early in 1992 ... [they] were taking the compound - it was a little more than into the research phase, okay, and that triggered a milestone. So all of a sudden these guys have gone from basically having absolutely nothing to picking up this milestone .... (interview, 2007)

In addition to the activity associated with the compound, there were other changes occurring from an administrative point of view. Wadley again gives an account:

One of the key things I suppose at that time, which might be interesting to you, is that when ... Biota was initially floated it came onto what was the Second Board. And around about early '92, the [Stock] Exchange in its wisdom – and I think it's probably not a bad decision – decided to close the Second Board. It wasn't sort of working for them or whatever. I think two companies were being successful: Biota and some other tech company, I can't remember which now, and so providing Biota had 500 members it could migrate across to the main board. So, we struggled to get 500 members up at that time. So, that was a bit of a watershed. You know, in terms of getting the company onto the main board. Pretty much at the same time an investor by the name of Sam Isaly had picked up from documents or a presentation, I think, that Glaxo had put out and made a presentation in New York and mentioned this little company and this licensing [of] this potential flu drug. Sam, ... who is an early stage fund manager in biotechs, investigated it further and did invest in Biota and I think came in around about that time when we had that rights issue. Around about, what was it, April, May maybe July – June, July-ish we had a rights issue. And we raised A\$10 million and there was other money from the placement. So it was a mixture of moneys and Sam Isaly, who was a key investor, came in. I mean, it was very unusual for this tiny little Australian biotech to attract somebody like Sam .... [W]e had a rights issue and we gave three options ... so various things were happening and quite significant amounts of money. I mean, we accumulated up to about A\$20 million fairly quickly over the next two or three years okay. Basically, because the company was getting a lot of publicity the Joe Public was very hot to invest in it. I mean he didn't understand it, he didn't appreciate how early in its life the compound was. He didn't make the distinction between people having a cold and having influenza. You know Peter Simpson, God bless him, was a great spruiker. Relenza was ... going to fix all sorts of problems, not just influenza but Alzheimer's and Christ knows what else, so ... it was the holy grail so punters were jumping in all over it. But serious investors had been attracted because Sam Isaly had come in. Yep, yep he knew it you see and so investors here were quite comfortable in taking parts in these placements.... (interview, 2007)

From Biota's point of view, their interest in Wadley revolved around the anticipated announcement of Glaxo taking the compound on to trials. Wadley said:

... there had been a bit of a push from the Board at that time to fully utilise that money and probably try and change it from being a virtually nothing company to a company that might have a chance at developing a pipeline and all that sort of stuff. So the plan was on the strength of the milestone announcement and anticipated other announcements, because clearly Relenza ... was starting to gain a bit of traction as far as Glaxo was concerned. And the Board, which was very divided on these things, decided that they were going to have a rights issue. Well, they needed somebody in the office to start to put a business plan together and do all the things that are required for a rights issue and hence that's why they were talking to their auditors and so on. (interview, 2007)

These series of events helped give Biota the boost it needed in terms of financial resources, however it is important to capture the nature of the company structure. There were just two full-time employees, Simpson and Wadley, and the scientists were under contract and being paid a salary via the VCP. Wadley described it this way:

In meantime, the company was sort of bungling along. It wasn't really doing very much because it was all going on at the VCP. Glaxo were paying that cost at the VCP. I think the VCP had quoted a cost to employ 23 people or whatever the hell it was in the team. (interview, 2007)

Quirk still described the company as *virtual* in 1992:

But I mean it was still a virtual company in 1992. So, that was a second employee [the CFO], to bring some more discipline to the [company] – and you can see how the cash was going because it is quite right. [T]he research costs were all being met by Glaxo, and you can see there [Figure 1] in terms of the cash that in fact, we were doing it very well. In 1992, because there was an identified lead compound, I think we scored A\$4 million or A\$3 million from Glaxo as one of the first up-front payments. That is where it went into exploratory development, which was where you do all of the animal testing, essentially building up a dossier before you go to the FDA and the other regulators for approval to go into humans. (interview, 2007a)

Peter Cook, who would later become the company's fifth Managing Director and CEO, commented on Biota's early years following their initial public offering,

‘Sure [it was virtual], with the market cap at A\$3 million you are not going to be very tangible, are you’ (interview, 2007)?

Wadley also agreed that the company was in essence virtual. Asked specifically about when Biota came into its own, Wadley responded:

When was it really a company? That’s an interesting question ... I think probably when Hugh joined. Not because Hugh joined but when he joined. Because at that point the decision [was made] to build a pipeline, to build a team, to move out of the serviced offices to our own place, to set up the labs. You know we saw a virtue in virtual. But there was nothing virtuous about that. I mean you had to be a proper company, you had to have people. You had to develop your own expertise. You had to guard your own intellectual property. You just couldn’t just sort of outsource it all the time. (interview, 2007)

Whilst still virtual, Wadley felt that this in hindsight was perhaps not an optimal arrangement. He gave the following reasons:

And Glaxo paid it [the cost of the research scientists] – we didn’t pay it and were reimbursed which I suppose from a management point of view is one of my regrets but we let Glaxo pay it direct, which then sort of meant in a way that Glaxo and the VCP were talking together about what the program was doing and all that sort – what our program was doing. And they ... tended to bypass us and that sort of made it a little bit difficult. (interview, 2007)

It is therefore important to remember the roles and expectations of both parties involved. At a public seminar Quirk gave, he was asked, ‘Okay, some of the pharmacists, some of the small ones, were saying we just don’t get anywhere these days without the scientists shaking test tubes, but you did’ Quirk replied: ‘Yes, and Glaxo funded it, yes’. The question then arose as to whether this was the reason for Biota’s ‘healthy’ burn rate, in the sense they weren’t consuming vast amounts of cash too quickly. Quirk replied to this:

Oh yes, but there is a difference because if you think of the margins – I mean,

Glaxo's average costs of goods from memory is about 20 per cent. So there is a margin of 80 per cent. We got a royalty of six per cent out of that gross margin. Now, I mean I look at our little company now and I think I don't want to do royalties, I want to get as far as I can in developing the drug because the value is absolutely enormous if I have got something which is going to be even a half a billion dollar type market ... Now when we did that, I mean, that is back 1990... [W]e did something which wasn't I think unusual even in the United States in how you dealt with a drug company. Except that in the United States you - in a start-up company - could get refugees from big pharmaceutical companies who knew every aspect of the business. We have learned now but certainly not then. We were innocents in what we were doing. (Quirk, 2007b)

In his (2007b) presentation, Quirk recapitulated the key features of Biota in 1992: (1) there were two staff, (2) 22 contracted scientists at the VCP, (3) A\$6.91 million in cash in the bank, (4) two projects, influenza and the diagnostic kits, (5) one drug in exploratory investigations and 6) an estimated market capitalisation of A\$48 million.

**Table 5: Snapshot of Biota up until 1992**

Year	Market Cap	Subscribed Capital	Cash	CEO	Development	Projects	Progress	Relenza
1983				1	Biota Pty Ltd	ID phase		
1984								
1985	\$3.0	\$3.0	\$3.0		Biota Holdings	3		
1986	\$3.0	\$3.0	\$2.5				Patents filed for NI	
1987	\$3.0	\$3.0	\$2.0	2				1st active molecule
1988	\$3.0	\$3.0	\$1.6		Takeover bid	2	Vaccine program abandoned	
1989	\$4.6	\$3.0	\$2.7				Glaxo Heads of Agreement Glaxo Agreement, angiogenesis abandoned	
1990	\$2.8	\$3.0	\$2.7					
1991	\$11.1	\$3.0	\$2.4			2	Diagnostic test – Symex USA	Exploratory

Source: Quirk, (2007b)

### Argy Bargy in the Board Room

Mark Crosling was soon to become important once again. This time, he was touted as being the person responsible for Biota Holdings launching the hostile A\$10 million bid for Comlabs, a small mining exploration company that, while listed, by 1992 was no more than a shell company. In November 1992, Comlabs Ltd issued a Letter to

Shareholders and Chairman's Address that outlined a series of important changes that were implemented following the General Meeting on 23 September 1992. These included:

- (1) The reduction in the number of Issued Shares in the Capital of the Company
- (2) Acquisition of Declan Investments Ltd, which holds the 9.22% interest in Biota Scientific Management Pty Ltd from Excelsior Run Pty Ltd for \$500,000 and 19,900,000 Ordinary fully paid shares in Comlabs Limited. Excelsior Run Pty Ltd is associated with the Company's new Managing Director, Mark Crosling.
- (3) The resignation of Harry Fishman and Phillip Harvey, and the appointment of Mark Crosling and Donald Hulme to the Board of Comlabs Limited.

Part of the reason for the reduction in issued capital was to be admitted to the Official List of the Main Board of the ASX. This took place on 24 September. Several weeks later, Comlabs Ltd issued McKinley Wilson Ltd 1,600,000 fully paid ordinary share at an issue price of 28 cents each in the capital of the company. This resulted in an additional A\$448,000 in cash, and less commission, to be used for working capital purposes. The result of the capital consolidations, the share placement to Excelsior Run Pty Ltd, and the share placement to McKinley Wilson Ltd was that the Comlabs now had 26,500,000 fully paid ordinary shares of 25 cents each on issue. Their other investments included cash at call of approximately A\$620,000; and a 14.28% equity interest in the Uebel Technology Joint Venture, which held 45% of the issued capital of Archimedes Associates Inc. (a US corporation and holder of the Uebel technology). That investment was cash neutral at that point in time (Australian Stock Exchange Announcements, 16 November 1992).

The crux of the issue was Crosling owning 75 per cent of Comlabs. Hence the bid for Comlabs, which Biota launched in April 1993, centered on the strategic 9.4 per

cent stake in BSM that Crosling had earlier sold to Comlabs. This connection with Crosling and Comlabs was no coincidence. *The Age* reported that:

In October 1987, Mr Crosling attempted to buy 50 per cent of Biota through a scrip bid by another listed vehicle, Rancoo. While Rancoo managed to purchase 19.91 per cent of Biota, the bid failed when the 1987 share market crash destroyed the value of the scrip offer. The 19.91 per cent stake was sold to Hawke Investments in early 1988, and Mr Crosling resigned as managing director of Biota. However, he remained a director of BSM and retained a 9.4 per cent stake in the company. Sources said Mr Crosling then attempted to sell his stake in BSM 'to fund other business ventures'. After several possible deals failed to eventuate, Mr Crosling sold the stake into a listed company, Comlabs, in return for 75 per cent of Comlabs' ordinary shares. However, the Australian Stock Exchange ordered that the 19.9 million Comlabs shares he received be held in escrow, which meant Mr Crosling could not raise cash by selling his stake in Comlabs. It is believed Biota has been negotiating for some time over how it could purchase the 9.4 per cent BSM stake from Comlabs, a stake it sees as highly strategic. Biota unveiled its \$10 million takeover bid for Comlabs on Monday, but it is believed the bid was a last-ditch effort by Biota to lock up ownership of BSM after Mr Crosling declined to sell Comlabs' BSM stake. It is believed Mr Crosling refused to meet anybody in person while he was negotiating over the potential sale. In a statement to the ASX yesterday, Mr Crosling advised shareholders not to accept the offer, and his lawyer said Mr Crosling did not intend to accept the offer. (Lenthall 22 April 1993, p. 17)

The following day, 23 April, Biota Holdings issues another statement via the ASX reading:

On 21 April 1993 Mr Mark Crosling, a director of Comlabs Limited ('Comlabs'), wrote a letter to the ASX marked for public release responding to the announcement by Biota Holdings Limited ('Biota') of a takeover offer for all the issued shares in Comlabs. There are certain matters arising from that letter which require clarification or correction. In its letter Comlabs claimed an 'entitlement' to BSM shares of 10.17%. This is incorrect.

To the best of Biota's knowledge and belief, Comlabs' various interests in BSM are as follows: 9.22% as registered shareholder; 9.22% as beneficial owner (shares recently purchased but not yet registered - 0.23%) Total shareholding = 9.45% plus shares to which Comlabs is currently entitled - 1.17%; Total current entitlement 10.62%.

Biota understands that on 5 February 1993 Comlabs entered into an agreement with another BSM shareholder, holding a 1.17% stake in BSM, giving Comlabs power to restrain the disposal of those shares. We understand that

this agreement is not an option to purchase those shares nor is it an agreement by that shareholder to sell.

However, under the Corporations Law the terms of that agreement mean that Comlabs has an 'entitlement' to that 1.17% stake for so long as that agreement remains effective. The agreement between Comlabs and the BSM shareholder concerned expires on 5 August 1993. This point was omitted in the Comlabs letter. Accordingly, on the expiry of that agreement, Comlabs' entitlement will drop from 10.62% to 9.45%. (Biota Holdings Ltd announcement with the ASX dated 23 April 1993)

A few weeks later, another journalist commented on the next landmark in the buyout process, namely Biota agreeing to release 20 million shares from escrow: 'In a letter to the Australian Stock Exchange, Biota's chief executive, Mr Peter Simpson, said the release of the shares, held by Excelsior Run, would enable that company to accept Biota's takeover of Comlabs' (Talbot, 1993, p. 21). During the next several months, Biota regularly posted updates regarding the agreement of Comlabs shareholders to accept their offer for Comlabs in exchange for the critical 9.45% stake in BSM.

With the directors of Comlabs agreeing to accept Biota's offer, Crosling and two other directors stepped down. This announcement by Comlabs' lawyers, Minter Ellison Morris Fletcher, dated 6 August 1993 said:

We are instructed to advise that at a meeting of the board of directors of Comlabs Limited convened and held this morning, the following occurred: (1) The existing directors being Mark Crosling, Eddie Kutner, Donald Hulme and John Lovering each tendered their resignation as directors of the company with effect from the close of the meeting. Mark Crosling also tendered his resignation as the company secretary and public officer; (2) Consents by Thomas Quirk, Peter Simpson and Richard Wadley to act as directors of the company together with the consent of Richard Wadley to act as company secretary and public officer were tendered and accepted by the directors with effect from the close of the meeting. Accordingly, control of the board of directors of Comlabs Limited has changed in favour of the above named persons being the representatives of Biota Holdings Limited as a consequence of the takeover offers made by Biota Holdings Limited for all the issued shares in the capital of Comlabs Limited.

In practical terms, what all this really meant was that Crosling had successfully orchestrated a situation whereby he was in a position to play a skilful game of chess with the owners of BSM. If his motives had been pure about setting up Biota as a legitimate company in the first instance, this time he conceded ‘it was just a brilliant piece of arbitrage’ Crosling (interview, 2007) As to the winners and losers of the game, from Crosling’s point of view he felt victorious, but from the other major shareholders of BSM, the Woods family and the CLAM members, it was less clear cut. On the one hand, all the shareholders found themselves in a very good financial position as a consequence, but their interest in Biota was clearly more than just monetary. Their financial gain in paying out the owners, being themselves, in BSM meant that Biota Holdings had been put under a lot of stress financially. For these investors, their ultimate aim was to take Zanamivir through to its completion. And whilst Biota Holdings had weathered the storm during this period, in the much longer run, this tidying up of the structure of the company at this point in time was really a blessing in disguise.

Another interesting turn of events regarding share ownership occurred around this time, as Wadley recalled:

[In] 1992 – 93 Glaxo approached us to see if ... we were interested in letting them do a placement with us. And ... maybe acquire 10 per cent or whatever of the company. I think this [might have been] a Ken Windle initiative. [They also] wanted a Board seat ... Peter [Simpson] and I discussed it and I don’t think it went any further. Maybe it went to the Board but we decided that we wouldn’t do it] ... [we weren’t interested because at that stage in our lives, whilst money would have been good, we didn’t want to have a dominant sort of licence partner on our Board. It might preclude us from licensing with anybody else or got in the way a bit. (interview, 2007)

## **IND Application Filed**

Separate to the Comlabs buyout matter, in August 1993 Biota received some exciting

news from Glaxo: an Investigational New Drug application (IND) for GR121167X was to be submitted to the US Food and Drug Administration (FDA) during the last quarter of 1993. Under Biota's agreement with Glaxo, the company was to receive a milestone payment of A\$2,000,000, before a consumer price index (CPI) adjustment, within 30 days of this application. This would follow the initial milestone payment received from Glaxo when GR121167X entered exploratory development during May 1992. Moreover, Biota had the pleasure of also announcing to their shareholders that on advice from Glaxo, formal human studies in infected patients were scheduled to start early in 1994. This was on the back of successful studies showing that no untoward findings regarding toxicity in animals had been reported. Of course, long-term toxicity studies were continuing and viral resistance studies were on going, involving Glaxo Australia, Glaxo Group Research and the Bimolecular Research Institute (BMR) in Victoria.

Accordingly, Biota received their milestone payment of A\$2.3 million from Glaxo Australia Pty Ltd on 2 December 1993, representing the completion of the pre-clinical development necessary for the IND application. The application meant that clinical trials with GR121167X could commence in the United States. The initial step was to determine the efficacy of the compound in human studies before embarking on an extensive range of clinical trials. Glaxo was hopeful that this would start in the new year during the northern hemisphere winter and the following year's southern hemisphere winter, including Australia (Biota Annual Report, 2004).

In the first quarter on 1994, the Biota executives again went to London to meet with Glaxo management to discuss the progress of GR121167X. The compound had now been given a new name, GG167, and both parties were pleased to report the following in a press release dated April 1994:

- (i) A considerable amount of chemistry, toxicology, pharmacology, virology and other work had been undertaken and would continue even as GG167 proceeded through clinical trials in man. This work formed a vital platform for any future drug marketing application. The following was the anticipated schedule to date and forthcoming
- (ii) An intranasal challenge programme was underway, investigating the effect of dosage regimen in both prophylaxis and treatment of experimental influenza infection in human subjects. These trials were being conducted in the USA and it was expected that results would be available during the 3rd quarter of 1994.
- (iii) The initial Phase II programme started in December 1993 (the northern hemisphere influenza season) and would continue in the southern hemisphere during the forthcoming winter. Approval had been granted by the regulatory authorities for these trials to commence in Australia. The extent, and value, of these trials was to a large degree dependent upon the number of patients participating in the trial programme. This in turn would depend upon the incidence of influenza in the community.
- (iv) A major clinical trial programme would commence in October 1994 to coincide with the northern hemisphere winter. Both the northern and southern hemispheres were to be used for future clinical trials in order to maximize the patient numbers available. As GG167 progressed through the clinical phases of development significant amounts of data would be generated. However, Biota and Glaxo had agreed that the next routine report regarding progress with GG167 would be presented by early September 1994. (Biota Holdings Ltd Press Release, April 1994)

### **The Third Employee**

Another defining moment occurred in 1993; Biota employed their third full-time employee, Dr Phillip Reece, as R&D manager. As he recalled in a recent interview, he felt Biota held a lot of scientific promise and was attracted to the company for this as well as personal reasons:

I joined Biota in September 1993 and I was attracted by a couple of things. One, the interest in returning to Australia, because I was working then in the US in Park-Davis. Secondly, I guess I was attracted specifically to Biota because of the science behind the company. I did a little research while I was over there and learnt the *Nature* article that appeared in June, 1993 and was impressed with that and as result I came to the conclusion that this was probably a good place to work. (interview, 2007)

Again, the importance of contacts and associates would play an important role, as Reece explained:

I became aware of the job through Professor Graeme Johnson<sup>9</sup> who I know well and I was talking to him about [the fact that] I was interested in coming back [to Australia] and he said ‘well are you aware of [Biota]?’ And he sent me a sheet summarising the position and I think I contacted Pete Simpson and just said that I am interested, are you? Then Peter came over to the US and interviewed me. Then I came across here [to Melbourne] and then met the rest of the board and so on. I was also courting one other company, Faulding, at the time. (interview, 2007)

Tom Quirk explained the general position of the board members at this time:

It just came to a point where we got first Richard Wadley to get the accounts and get the company into order, and Richard was very good. I don’t think Richard put a foot wrong in his entire career in Biota. He was very good. Phil Reece had come, because that had been the next thing that we really decided. After we got Richard Wadley – we decided, and this is after we’d had our day in Sydney with the facilitator – that we were going to establish our own R&D function. And we needed to start with an R&D director, and so Phil was the one who popped up.... (interview, 2007a)

Underpinning some of these strategic changes was the ongoing tension between board members as to the intended structure and function of the company. Wadley explained:

Yeah one of the things actually in terms of how the company changed is that back in ’92 there was this big debate between the Woods, who were very much interested in having just a royalty flu vaccine, royalty trust. Run the project, don’t put any money into it because Glaxo was paying it. We’ll take the royalties when the patent expires in 2013 or whenever when it was and turn the lights out and we’ll all go home. Whereas there was Tom ... and Mark Johnson on the Board – and they were much keener and pushed for building a proper company. So there was quite a bit of tension on the Board at that time. Well Alan Woods sort of gave in and sort of agreed that, you know, we should build a proper company and that’s what they did. Now my point about that is, is that with Relenza being moderately successful ... in terms of investor risk, at least by building a pipeline and getting cash and ... building a team, they sort of kept Biota. So there was this sort of tension with the Board

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<sup>9</sup>Professor of Pharmacology at the University of Sydney and a Specialist Member, Administrative Appeals Tribunal, Commonwealth of Australia (appointed 1991)

you know which brought about a change. Whereas when I left there was no debate about that. We were building the company, we were doing this, doing that. When I left [in 2002] it was sort of in the throes of what follows on from Glaxo and, you know, how we recover from that and what do we do next? (interview, 2007)

In terms of the structure of the company in late 1993, Reece agreed that Biota was essentially still virtual, saying:

Biota was small in terms of numbers of people, you know it had only a CEO, who was Peter Simpson, Richard Wadley was company secretary and financial officer and there was a part-time secretary. The rest of the work was contracted from the VCP and CSIRO. It was a virtual integrated biotechnology company. Also, in terms of projects, it only had the Glaxo influenza project and one other project which was a Rotavirus project for infections in children which is a gastrointestinal viral infection. (interview, 2007)

Reece's remit though was to look at the scientific projects. Wadley explains this point:

When I joined I mean there was very little happening other than Relenza ... There was a rotavirus agreement with the University of Melbourne if I recall. There had been another flu – influenza vaccine program going on but I think that had died a death. Rotavirus wasn't going anywhere. Dare I say, it wasn't exactly a commercial – it wasn't a sexy area, you know. So it was really the flu. Phil came on and with the brief to build a team at Monash ... He was looking for other projects to do and hence we got involved, I think, in the diabetes project. I think there might have been an anti-cancer project that came out of Peter Andrews's team, 3D Centre, University of Queensland. So, Phil was looking for other things. And Phil actually started looking at doing an influenza diagnostic as well. (interview, 2007)

Reece, in fact, closed the rotavirus project down shortly after joining: '... it was languishing and one of my first decisions was to shut that down' (interview, 2007). Reece also spoke of a project with Peter Andrews, 'One of the other decisions that I had to make soon after joining was whether to embark on another project that was in discussion with Peter Andrews who was at the 3D (Drug Design and Development)

centre at the time and [whether] Pete [Andrews] should be picked up on that project because of the structural biology – structural design project [but] with a cancer focus’ (interview, 2007). The project did not actually go ahead.

### **Another Share Placement and a Change at the Helm**

In May 1994, Biota raised A\$9 million through the placement of 1.225 million shares at A\$7.50 per share to fund the cash acquisition of the remaining 15.51% in Biota Scientific Management Pty Ltd. (Australian Stock Exchange Announcement, 11 May 1994) The acquisition was completed on the 29<sup>th</sup> July 1994 with a cash payment of A\$11.2 million, the issue of 1,208,497 50¢ fully paid ordinary shares and 665,285 11/05/1997 options exercisable at A\$9.10 each. The offer was valued at approximately A\$22.3 million. Although it had been a long painful process, it was an important step in Biota’s maturity. Furthermore, shareholders were expected to approve a subdivision of each 50-cent share into two 25-cent shares and an increase in authorised capital to 120 million ordinary 25-cent shares, following which a 1:2 bonus issue of shares was to be made. This transaction was slated to be completed by 31 October 1994 (Australian Stock Exchange Announcement, 29 August 1994).

So with a healthy looking bank account, the company was able to move to the next stage, as Wadley (interview, 2007) explained, ‘we were looking then with this money that we were raising to develop a proper biotech company. Develop new opportunities, see what we could do’. Biota established its own research laboratories within the Chemistry School at Monash University, Clayton, Victoria in December 1994, for new development programmes in carbohydrate chemistry associated with rational drug design. The initial focus of the laboratory was to undertake chemistry for the influenza diagnostic and cancer projects. This relocation involved both a physical

move to the new premises and a symbolic move, as Quirk (interview, 2007a) recalled, ‘[it involved] moving people like Wen-Yang Wu and some of those out of the College of Pharmacy and coming to actually work and directly being part ... [of the company]’. This move was significant in that it was a coming of age for the company, albeit a decade after they started up. Quirk described it this way:

You find that in all the biotech companies, you get to a point where universities, CSIRO, institutions have different agendas to yours. And I mean, I just struck it in a whole lot of other areas as well, where they’ll look at you and say oh well yeah, but you’re going to make me do what you want, and I want to do what I want. (interview, 2007a)

This came at a time when the VCP team was winding down. While the major part of the VCP’s work had come to an end in 1994 when the drug was taken into the exploratory development phase by Glaxo in the UK, the VCP research team continued synthesising similar compounds for two more years to strengthen the patent position protecting Relenza. This left the question as to what to do next in terms of scientific projects. Wu talked about some of the research they started in their new facility:

From a scientific point of view, I think we did our best. People on the Biota Board said don’t do that flu thing [long acting compounds], because that’s Glaxo’s business ... not ours. It’s their problem, Let them do it. But Phil Reece, he supported it. If one person is in that field for too long, then you don’t want to leave it [referring to himself]. You’re familiar with it. So in that field, I thought it’s not completed yet. The mission is not completed yet, because it’s only the first one [compound of its kind]. This is why we insisted do the LANI which is a hundred thousand times better than Relenza. This is why I said the Board [they didn’t understand] - I’m not criticising anybody - in the some circumstances, they made decisions. But from today’s point of view, in Biota’s mind, they thought the flu business is packaged and finished and we’ll do other things. Which is partly right. [But in] the flu business, you still have the room to develop and it’s not got to market yet so you need to do some monitoring. You can’t control Glaxo, but you will be able to always stimulate them. (interview, 2007)

Whilst he was heavily emotionally invested in influenza, Wu was not necessarily discounting the merit of other projects, saying, ‘of course, we needed other

projects. Of all the projects you choose, you can't just grab one project in. You have to look at whether you can match it or a lot, whether there's a lot of methodology available in-house, whether you would like to develop it, and also the time frame. They are very complicated things [deciding on projects]' (interview, 2007). It was around this time also that Wu changed his employer, meaning he now became a Biota employee, 'By the time of 1995 we became a Biota employee. And then we worked there for about seven years' (interview, 2007).

Part of this process of becoming a biotech company with an in-house research program involved a change of CEO. Simpson departed and Reece took over as acting CEO while a search took place for a permanent replacement. In explaining this move, Quirk made a point of saying that matching CEO capabilities with the company's new direction was a major consideration:

Peter [Simpson] had been very good in terms of dealing with Glaxo, finding things and stumbling over things. But ... he didn't have a sort of understanding about research. I mean, he had a background in pharmaceuticals and all the rest of it, but the next stage we thought we were moving into was actually starting R&D, because we didn't want to do it with university groups, because you need to control what you're doing. Well, at that stage if you think about what we actually do, there was no expertise in the country in development. I would reckon you'd probably say that's exactly the same inside the arms of the big pharmas in Australia. Because what they would have been good at doing would have been maybe whatever phase three trials were necessary for regulatory approval and then marketing, and that was it. (interview, 2007a)

Of Simpson's contribution, Quirk made the following comment, 'the thing is that everybody makes a contribution. But then it comes to a point where their experience and what they can bring to the company, doesn't actually help in what you're going to be doing next' (2007b). Quirk elaborated further:

... Peter [Simpson] was all for getting on planes and going to conferences. And I mean, by doing that he discovered things, which were very useful. He was a good scout in turning up things, and very good at chatting people up. [A

salesman] Yes - very good at all of that, and essential stuff in terms of dealing with people. It's really interesting. ... [H]e was the first person with the exception of Alan [Woods], who actually knew something about the business. Mark Crosling didn't. None of the other directors did. I didn't. I mean, I'm sure I had some sort of venture experience, but no actual pharmaceutical industry. [So he was helpful in connecting with big pharma?] Yes. Connecting with big and little pharma, all of that. (interview, 2007b)

As part of their strategic direction, Biota attracted the experienced Hugh Niall, a former vice-president for research and discovery at US biotechnologist Genentech to be chief executive officer with carriage of the all-important relationship with Glaxo. Quirk recalled the hiring process the company had undertaken to find the new CEO:

... [B]y that stage we had Peter Andrews on the board and I remember we all got on a plane. We'd got ourselves a head-hunter from Russell Reynolds, and we all got on a plane and flew to San Francisco to interview about four or five candidates, who they'd rustled up. And so we just sat there. We worked sort of Australian hours in San Francisco interviewing people, and Hugh Niall was sort of outstanding as the candidate .... (interview, 2007a)

Like Reece, Hugh Niall was also based in the USA and had been considering returning to Australia for family reasons. Niall wrote, 'I was contacted by a head-hunter at a time I was considering returning to Australia for personal/family reasons. It seemed like a good opportunity with a product in the clinical phase that was based on good science' (Niall, 2007).

Niall's impression of what the company was like in 1995 was also to describe it at virtual, 'It was a very small company operating mostly in virtual mode – out sourcing its activities and with really only one potential product. There were some very early projects that the company was funding via third parties. Some of these were quite speculative and there was a lack of focus' (Niall, 2007). Niall outlined his strategic approach for Biota's product portfolio at that time; 'I focused the activities of the company into a) those related to Relenza and flu, including second generation anti-flu

drugs and flu diagnostics, and b) projects aimed at finding new drugs for other non-flu viral infections especially respiratory infections, and for cancer' (2007).

## Other Changes

As well as Peter Simpson, a casualty of this period of expansion was Mark von Itzstein. He explained the circumstances contributing to his decision to remove himself from working on Zanamivir and any of Biota's other projects:

So it was roughly that timing, around '95 it would have come to probably an unhappy closure with respect to my relationship with Biota .... At one stage we had engaged with this industry contract on flu, I was particularly interested in para-influenza, I took up a project sponsored by GlaxoSmithKline, nothing to do with Biota and Biota slapped an injunction on me claiming that they owned everything I did with sialidases, irrespective of the organism, which was rather harsh, I thought. So I really felt disturbed, disappointed ... that a company I had produced significant outcomes for would have the audacity to say that you can't do that research which they weren't funding by the way. We [Andrews and Colman and I] all ran into problems but I was the first cab off the rank. I was the first to have a legal injunction slapped on them to stop me doing this research with GlaxoSmithKline and I couldn't believe it. Of course, the universities when they get legal injunctions put ... [on them they don't like it.]

From the corporate point of view I could imagine that if there's any potential for a commercial thing to say they might want to try and grab it but it did a great disservice, in my view to Biota ... I discussed it at great length with Peter Andrews about what the hell are Biota doing because Peter Andrews was on the board at that point in time but Peter Colman had stepped down. That caused me great angst and, in fact, in terms of [my] relationship with Biota it took a spiralling decline where I was not interested. Not interested at all and not interested at all in facilitating anything for them so I was ... [persona non grata.]

... [A]s I said it's the scope of the project and in terms of the project we knew and, in fact, if I recall it was described right around flu, nothing to do with para-influenza. (interview, 2007)

von Itzstein explained the impact this decision had on the project:

I didn't formally say that [I'm resigning] because I had no engagement. I wasn't employed by Biota so I didn't have to say anything to them but it was made well understood that I was not happy with the situation. That project, in

fact, I stopped at Monash. I ceased. GlaxoSmithKline were very kind enough to say ‘Mark, what do you want to do? We’ll give you money anyway.’ So I put a project on that I knew that Biota were not going to be able to touch me. Mind you, having left Monash I had started that same project, the para-flu project here, and we’re making good advances so .... (interview, 2007)

As to why this situation had occurred in the first place, von Itzstein put forward his opinion, ‘I found it very disturbing but from their side, I couldn’t really imagine, [were] they think[ing] oh my God there’s another commercial opportunity that we’ve missed, how do we grab it?’ Moreover, he was also very clear to point out that in his view these projects had little if no relationship whatsoever, ‘By the way, it’s not flu I’m talking about. I’m talking about para-flu so croup in children, for example, so it’s a different disease altogether, a different enzyme altogether’ (interview with von Itzstein, 2007).

Woods (interview, 2008) explained the thinking of the company at the time, ‘Biota believed there was a risk of an overlap of intellectual property between influenza and parainfluenza which had to be protected’.

von Itzstein agreed entirely that in the search for a compound, the VCP scientists were under financial pressures as well as pressures to produce a deliverable compound. And yet it seemed with the benefit of hindsight, many executives in Biota saw the situation as being one of disappointment that Glaxo did not go on to create the oral compound. In their mind, they thought that Glaxo should have kept going. Again, von Itzstein acknowledged this was a quite probable viewpoint many of his colleagues may hold. However as he rightly points out, Biota gave Glaxo a lead compound at the outset of their agreement in 1989, ‘We had delivered right up front already Relenza. That was right at the beginning of the program. Then they funded the program since 1989 till 1995 or whenever it was for that particular program, six years’ (interview with

von Itzstein, 2007). He went on to explain why the program continued for another six years:

We were trying to do two things. One is to say is there anything better with this template that we've missed, so in general terms, making sure that we had a Chinese wall wrapped around the compound itself, that we hadn't missed something. There would be nothing worse than another compound that was a me-too Relenza that would run over us at that point in time. Internally GlaxoSmithKline were running their own program about oral bioavailability. What they did actually do ... was a lot of what was termed combinatorial chemistry so whether it was 10,000 I don't know. ... [W]hat we were all trying to do was to make sure we had the right molecule. You want to have the optimum molecule going forward so it wasn't about disproving. I think it was just saying do we have the right molecule? In terms of the oral story, it's quite logical that they were going to proceed as much as they could. They had three or four team ... I can't quite remember whether it was three or four, chemists working on this project in the UK. A lot of resource but also from a company perspective they understood very well what you needed to do to make a compound more drug like. That wasn't our expertise so, you know.... (interview, 2007)

The process itself was not easy. von Itzstein recalled the numerous heady meetings he had encountered on the trips to London during those years:

From my point of view, for record, I actually found Biota more antagonistic with Glaxo in the early days. In fact, I loathed going to London with Biota. Our meetings started where we just had a joint management science meeting and I loathed that simply because it was so confrontational. Their scientists would be in the room, I would be in the room describing what I was doing, just me with them and the other board members so ... The board and Simpson at the time etc and it was extremely confrontational. Everything that I put up they'd be nitpicking and I thought this is not scientific collegia. I was thinking this to myself. So I said, 'Look, I made a decision that I wanted a science meeting, only scientists please, and we can have our management meeting where you have your management people come in. The science meeting goes first and then we have the management meeting later that day or whenever it happens'. You know, from that day on when that happened the whole mood changed. We'd become such an integrated unit between Glaxo and my own group in the way we were working and the collegiality was fantastic, absolutely phenomenal. (interview, 2007)

As to why the situation arose in the first place, von Itzstein was unsure, but speculated, 'I don't know whether it was the understanding that was the issue. I suspect

it was actually the grandstanding approach. We've got this. No you haven't, and so therefore the whole thing just flowed where we had IP lawyers there questioning this, questioning that ... it was just such a tense horrible non-productive collection at that point in time and there was just this angst and I was caught. I told them that this was just not to go on because we're not constructively doing things for the science but we need to split these meetings which we did' (interview, 2007).

An important point that must be drawn out is one of teamwork and integration of resources. From the time the research commenced at the VCP in 1985 following Biota's IPO and raising of the A\$3 million until the research program with Glaxo was discontinued in 1995, there had been a core group of scientists working on the anti virals. What is particularly important to highlight is that these researchers were not Biota employees. This situation on the one hand was strength from a company resource point of view, but there were others who felt this was also a liability. Such a liability was not only one sided, i.e. from Biota's point of view – at various times it seemed to lack control over the programs, but also from the scientists involved. von Itzstein commented that he did not feel like part of 'Biota'. Rather, he generally felt as though it was Biota that were harassing and bullying him and his scientific team. And when specifically asked about whether he felt connected to the Biota group per se either as a team member or as an employee, he was unequivocal in his reply, 'No, and probably on both counts no and maybe I'm a little bit blinded now because of what's happened over that period of time but certainly never felt a Biota employee, definitely not. That's to my core so to speak. In terms of part of the team, I did feel enthusiasm and I guess in that sense probably when we were particularly flying around the world talking with various companies. So in that sense ...' (interview, 2007).

von Itzstein explained the development process concerning the molecules that

were delivered to Glaxo as part of the agreement:

There were three [molecules]. The very first one [molecule] which people conveniently forget, was based purely on understanding how the enzyme did its job and it was what I call a Volkswagen model. So it was a very weak inhibitor but it was the first compound that went into animals [injected up the nostrils of mice] that demonstrated an effect, weak as it was, but it gave us that glimmer of hope. In fact, for me I said ‘Wow this works, why can’t this, this and this?’ (interview, 2007)

This was a different approach to the work of Palese as von Itzstein explained:

Peter Palese’s work in the US that failed to observe any effect. [It was injected intravenously rather than inhaled] intranasally. So there were three molecules. There was one that was a Volkswagen model, then there was a BMW model. So depending on your car, that was a four-amino compound. Then you pick your next car up, whether it’s a Porsche or a Jag or whatever it may be, Bentley or something like that. [Relenza] was the top [one] in terms of activity ... [So there were] two predecessors but that’s not many ... really in terms of the molecules per se that we thought, here is the logical choice, really in terms of topflight compounds there are only two. [W]ithin the first three years I knew that we had a real opportunity because we were seeing an effect in animals. A big jump to man but at least in terms of saying you can modulate infection using this template ...

So what Peter [Colman] described as his eureka moment with the crystal structure, that was my eureka moment with the compound class, saying ‘something’s been missed’ because we saw this effect. We actually did those experiments, not [in] the animal [though]. The animal experiments were all done by Glaxo so we provided compound to them. What we did was do, obviously apart from the drug design, [was] the synthesis and then the *in vitro* evaluation, so we did the enzyme assays in my group. We had done those experiments back in 1988 in fact.

I would say it’s not a Biota created molecule. That’s my point of difference. [I would say it was a] Biota funded created molecule, yes. To me that’s important because then it’s accurate. It’s [the story of Biota and Relenza’s development] reconstruction that’s occurred, whilst I can understand it’s very tidy and it serves the company extremely well, I think it does a disservice to academics. ... [L]ook, it doesn’t worry me, I’ve got a great career but I’m talking about young people looking at industry saying, you know, this guy was screwed, so that’s the important thing [not to dismisses the role of the university and of the incubator]. Exactly the point and that should never be lost because it’s still a reality today. Not many bright ideas come out of companies actually. (interview, 2007)

## **Developments in Relationship with Glaxo**

In anticipation of the Phase II trials of GG167 that were planned for October 1994, the company established a Scientific Advisory Board (SAB) to provide advice on scientific policy in the September of the same year. GG167's full development Phase II clinical trials began and continued in Australia, NZ and South Africa and further studies were planned for the northern hemisphere (Australian Stock Exchange Announcement, 10 October 1994). It was thought at the time, the trials would be completed by 1995/96, although this was not to be the case. Following the October start date of the trials a report on the study with GG167 in healthy volunteers infected with influenza virus was presented at the 34th InterScience Conference on Antimicrobial Agents and Chemotherapy in Orlando, Florida, USA. The preliminary results suggested that GG167 was effective in the experimental influenza model in human volunteers (Reuters News, 13 October 1994). Continued progress had now become crucial due to the possible emergence of a competitor drug, a second neuraminidase inhibitor developed by US start-up business Gilead Sciences and being commercialised by Swiss-based Hoffman-La Roche.

While Biota was taking decisive steps towards being a 'proper' biotech company, with a SAB, it appeared that GG167 continued to proceed smoothly through development. In September of 1995, GlaxoWellcome's provisional analysis of the effectiveness of GG167 in the northern hemisphere winter Phase II clinical trial showed clear trends in favour of GG167 over placebo; the first indication of the activity of GG167 in patients with naturally acquired influenza (Australian Stock Exchange Announcement, 7 September 1995). This was an excellent milestone in terms of commercial progress.

In addition to the changes happening within Biota during 1995, a major event would happen affecting its licensee. On March 17 1995, a press release was issued with Glaxo Plc saying that the Federal Trade Commission in the United States had effectively cleared its merger worth £9.1 billion (\$14.3 billion) with Wellcome Plc. But Glaxo said the agency told it to divest itself of a migraine drug that Wellcome had in development. The FTC decision, which was expected and followed a similar ruling by the European Commission, cleared the way for the creation of the world's largest prescription drug maker, with more than \$13.7 billion in annual sales. Under an agreement with the FTC, Glaxo would divest itself of rights to 311C90, a Wellcome compound for treating migraine that was in late-stage clinical trials. The agreement would become final after a 60-day period for public comment that is widely considered a formality (Glaxo Press Release, 17 March, 1995).

The first M&A activity seen in the pharmaceutical industry had actually taken place over a decade earlier; between Warner Lambert and Parke-Davis, and according to the Royal Pharmaceutical Society of Great Britain (2007) this event was 'some time in the early '70s'. The next merger occurred in 1987 between Ayerst and Wyeth and the new entity was called Wyeth. Two years later another couple of unions took place: one between Bristol Myers and Squibb, with the new company trading as BristoMyersSquibb, and more importantly Beecham Group Plc and SmithKline Beckam Corporation, who were then known as SmithKlineBeecham. From 1989 until and including 1995, there were 10 more mergers and acquisitions, including that of Glaxo and Wellcome. The impact of the first merger for SKB would later cause speculation as to its significance for Biota and their product Relenza.

At the time of the announcement, it seemed prima facie that the impact of this strategic union would be negligible. Development of GG167 continued – albeit slowly.

However, by the following year the impact of the merger was becoming more apparent. Unfortunately, GG167's trials did not take place as scheduled. Like almost all mergers of with firms of this size, there are challenges, delays and drifts in focus. In this regard, GlaxoWellcome were not exceptional. Whilst it was only a 'year' in the long development pathway, the real cost of the 12 months' loss of time meant that the competitors, Gilead and Roche, were able to pick up the pace and move quickly towards catching the Biota/GW team. Astonishingly, the Biota managers would later watch Tamiflu rocket to market and all but catch Relenza for product launch in 2001. Some in Biota still feel that the consequences of this lack of focus during the merger period were partly responsible for Relenza's ultimate failure to achieve market acceptance. In 2004, almost a decade later, Biota would issue a writ against GSK.

Soon after the appointment of Niall, the results of the phase II clinical trials for GG167 substantiated the preliminary studies, and unlike vaccines, which prevented infections, the results showed that GG167 may be used to treat the infection itself.

The clinical trials of GG167 continued, and there was some speculation as to whether the compound suffered from viral resistance, however in June 1995 (Australian Stock Exchange Announcement, 22 June 1995) the partners, Biota and Glaxo, put out a press release stating that results concerning possible viral resistance to GG167 had no impact on GlaxoWellcome's clinical development program from the drug and that GG167 remained on target for regulatory submissions in 1996/97. By November of that year, Biota announced the estimated filing for the prophylactic use of GG167 and that trials for prophylaxis in high-risk patients use were underway in nursing homes in North America and Eastern Europe. Considering Relenza easily passed Phase 1 clinical trials, which test a compound's toxicity, and proved its antiviral credentials in Phase 2 trials, which test effectiveness and possible side effects on volunteers deliberately

infected with the disease, Glaxo decided to conduct separate Phase 3 trials, which tested for effectiveness in normal clinical situations in Europe, Australia and the US (Shrine, BioWorld Today, 20 March 1996).

The year 1995 was an important one financially for Biota; they had A\$22.95 million cash in the bank by the end of the financial year, the following month in July, they received A\$10,000,000 from exercising options and in November they had raised an additional A\$6,800,000 by issuing a placement (Australian Stock Exchange Announcement, 20 December 1995).

### **Phase III is Underway**

In May 1997, Phase III trials of GG167 began in Australia and continued throughout the winter in NSW, Victoria, South Australia and Queensland. Later the same year, the trials were continued in Europe to coincide with the Northern hemisphere winter. The Australian trial tested Relenza's effectiveness if taken within 36 hours of the onset of symptoms such as aches and pains and high temperature. An increasingly confident GlaxoWellcome decided to test for effectiveness if taken within 48 hours in the US and European trials - a tougher test but one which would give it a clear marketing edge over Roche. Relenza showed clear, positive results in the Phase III trials on 598 people in Europe and Australia, reducing the duration of influenza by 1.5 days in Australia and 2.5 days in Europe. Crucially, these results were statistically significant (Hayden, Osterhaus, Treanor, Fleming, Aoki, Nicholson, Bohnen, Hirst, Keene, Wightma, *New England Journal of Medicine*, 1997).

In September 1997, the *New England Journal of Medicine* published detailed findings of the GG167 study. The article concluded that treatment of influenza A and B with GG167 was 'safe and reduced symptoms if begun early'. As a result of these

positive outcomes, GlaxoWellcome again moved forward with Phase IIb trials in the Northern Hemisphere's winter season (Hayden et al., 1997).

In March 1998, Biota announced that an application to market its influenza drug, Relenza™ had been lodged with the regulatory authorities in Australia. Furthermore, the Biota also advised that it reached an agreement with GlaxoWellcome to receive a royalty of 10% for net sales of Relenza™ in Australia, New Zealand, South Africa and Indonesia, in exchange for the co-marketing rights in those countries.

### **The Product Pipeline**

Biota's search for a product pipeline took it in a number of directions in the period while GG167 was proceeding through clinical trials. In March 1995, the company signed a three-way agreement with the CSIRO and the Federal Government to undertake research to develop an oral therapy for diabetes. Biota and the Federal Government would each contribute A\$1.7 million over 3 years and the CSIRO A\$3 million over 3 years. Biota's contribution comprised A\$900,000 in cash and the remainder in kind over the period of the project. Many people in the company were not necessarily confident this was something that Biota should be venturing in to. However, Colman in particular was excited by the challenge and his colleagues, including Reece (interview, 2007), had high expectations, although were well aware of the difficulties involved, 'You know, I think that was the reason we started the diabetes project at the CSIRO – because of Peter [Colman], I thought well if he can do it once maybe he can do it again. That was a tougher project [though]'.

For various reasons the project did prove to be more challenging. Hence, Reece detailed the circumstances surrounding this collaboration's eventual end:

The whole project was around an oral design rather than an insulin

replacement and see that's a very long drawn[-out] project. I just think that [for] Biota, the costs were getting high and Biota refocused and we just had to sort of get out, just was taking too long ... and just costing too much and there was publication pressures so it just got harder and harder. We shut it – well we didn't shut it, and they kept going. We were contributing, but the CSIRO was paying the large costs. I thought it was a good project because we weren't sharing the whole risk, they were ... putting up a lot of money.

Yes and we had START grants, two START grants supporting it ... – whatever they were called then. So it was well funded by the grant bodies, by CSIRO and we were contributing to it but it was still – it was just very early stage and would take a long time. I don't think – it didn't survive the strategic review of the zone – better get back to our knitting which would turn out to be virus protectors. I think we announced that having had a review we had to focus on virus. (interview, 2007)

Regardless of this funding, there was still a sense of uncertainty about pushing ahead with 'non-influenza' type products from various board members. Woods recalled his feelings on this collaboration at that time:

Well, yes, he [Peter Colman] did have a liking for that. Diabetes is a difficult one because finding the active site – I think there are a couple of active sites and it's not an easy thing to analyse. But we went into that; I think Phil Reece was quite prominent in that and I agreed [to] it. I think we had a few projects which came about because people wanted to get on with some other things, I think. I must say right from early days, I didn't want to push hard at anything. I think it's hard enough to get one project up, let alone half a dozen, and you're going to need lots of money to live with the failures that inevitably occur. (interview, 2007)

Around this time though, there was more tension between some on the Board and senior management. Simpson (interview, 2007) gave the following example, 'Well, there were projects that Peter [Andrews] had in cancer development which he wanted to pursue, and that ended up as the company Alchemia. They sort of fell out over that, had some differences and Peter [Andrews] left'. Andrews himself confirmed this; he had approached Woods and told him about his objections to the way Niall was organising the research projects, however Andrews was quick to point out that he when he

delivered his ultimatum of sorts to Woods, i.e. either Niall goes or he would, he agreed that under the circumstances, it was only proper that it should be he who stood down, given that not more than a year so earlier, he had been part of the interview team that had appointed Niall to the position of CEO.

Another key project Biota ventured into was a research and development collaboration with La Trobe University for a cancer project aimed at reducing the growth of colon cancer cells. Under the agreement, the university would continue with their research with tests on animals with the aim of identifying a lead compound before Phase I trials were started. Biota's part in the deal meant that it would have exclusive worldwide rights to develop any anti cancer compounds that eventuated from the research. Reece discussed the rationale for entering into the partnership:

Hugh [Niall] came on board with very deliberate view to – I mean, I was there to diversify and I had already done something but I was very much of the view that we should stick to structural biology influenza. Hugh wanted to go further afield, he thought well let's have a look at our portfolio so Hugh wanted to add a lot of projects. We ... agreed that was a good strategy and we went out and we added Latrobe Cancer Project .... (interview, 2007)

Reece then discussed the details of the cancer project with LaTrobe:

We took it to a Go/No go decision which is I think the key to any portfolio management. Go/No go decision means that you do sort of five experiments to establish whether you have an opportunity or not. Our criteria were animal models of cancer to see whether these compounds were effective with a suitable toxicity. We did a number of animal studies [pre-clinical] and showed that the therapeutic margin wasn't there. So, we stopped the project. (interview, 2007)

Reece explained that personal networks were again used to facilitate this deal:

I think in this case I spoke to an oncology man. I mean Hugh and I said we should look at the oncology space. So I then spoke to a guy by the name of Bill Denney who I knew from my Parke Davis days and I would say ... the best way of finding people or projects or new opportunities is through networks .... Personal networks. [Although the absolute value of networks is]

hard to quantify.

It doesn't fit with necessarily some of the agenda that let's say some of the societies project. Having said that they serve a role, you know AusBiotech served a role and RSCI serves a role and the various societies and there is no doubt that the BioForum you know, and the ... [others serve a role.]. (interview, 2007)

Specifically Reece talked about the process of utilising networks:

These are individual contacts, so I rang just rang Bill and said, 'we are looking for a project' and he said, 'I am working on this problem that I have seen that has been sent over by this chemist in your backyard [Australia]', what was his name, the LaTrobe chemist, I have forgotten his name. Anyway, he was in LaTrobe as a chemist and he has come back from New Zealand testing and so I went and talked to him. He was interested in licensing ... [We] were going to do the development. We had rights – exclusive rights to develop and commercialise. We ha[d] the options, [it was] a good deal for us, because we had the option of also bringing a third party in to help us in this department. (interview, 2007)

As to the nature of the licenses or deals available to the company, Reece explained the issues involved particularly with regards to bringing in third parties:

It is always an issue because in any deal, the licensee if you like, the academic one, is wanting to know who is going to be commercialising, [and] what share they will get? So are they going to get a royalty? So the challenge in these deals is to agree, you know, [to] a set of royalty rates that are reasonable should Biota commercialise and another set of royalty rates should [a third party do it] – because, I mean, if you just say, well we are going to give you one percent ... [then it's very hard to estimate how big the pie is] ... I mean, most people realise that even today Biota doesn't have the capability – or CSL for that matter, [they] had to go and find Merck as a partner for capital venture – so, you know, the academic group just need to understand what the future is likely to look like if it succeeds. (interview, 2007)

### **In-licensing Activity Continues**

The in-licensing activity of the company was ongoing – with another agreement announced, via a company press release, the following month in May 1997. This deal would involve the Hitachi Chemical Research Centre in Irvine California, USA.

Essentially Biota would contribute scientific and management skills. The press release read as follows:

Mr Jiro Akiba, President and CEO of the Hitachi Chemical Research Centre said: We are very pleased with the exciting discover our research scientists have made concerning new approaches to treating cancer. The mission of our company is to develop our research activities with the goal of relieving people who are suffering from this disease. Therefore, we are very glad to be able to realise our mission by working with Biota as a good partner in developing new pharmaceuticals for cancer.

Our growth strategy is to have a pipeline of pharmaceutical research projects at various stages of development. This project fits very well into the middle of that pipeline. With positive results in animal models of human prostate cancer, it is at a similar development stage to the colon cancer mixed topoisomerase inhibitor project we recently licensed from La Trobe University. Dr Niall said. (Biota Press Release, 12 May 1997)

Biota would provide milestone payments and a royalty on product sales to be shared by Japanese companies. Biota would acquire the worldwide marketing rights outside of Japan and specified countries in East Asia where marketing rights will remain with Nippon and Hitachi. The agreement, structured in incremental steps, so that completion of each development phase must be to Biota's satisfaction before the next phase is begun. However, Wadley summed up the actual ending of that negotiation. '... Hitachi was something that we flirted with and so on and it never went anywhere' (interview, 2007).

Other projects were instigated at this time. In July 1997 Biota formed an alliance with Melbourne's BioMolecular Research Institute (BRI), in the field of structure based drug design, building on the experience and knowledge gained in the development of Biota's influenza therapeutic. As for the this deal with the Bio Molecular Research Institute, Wadley clarified that this 'deal' was really more of a restructuring of various agreements in terms of allowing the respective parties to move ahead with their research following the removal of various patent issues that had been impinging their

freedom to operate, ‘... [T]hat was a little ridgy-ma-didge deal because there was a bit [of a] patent stoush going on as to what they had licensed to us ... in the influenza area and what they were allowed to licence elsewhere. I think we had a lot of negotiations which sort of just – it was a nothing deal’ (interview with Wadley, 2007). Another initiative was announced in February 1998: Biota would work with the Howard Florey Institute of Experimental Physiology and Medicine on the development and commercialisation of a treatment for memory-related disorders, including Alzheimer’s disease. The project came about through Niall’s own connections: ‘Hugh Niall introduced us to that because he was on the board’ (interview with Reece, 2007).

### **The Role of Networks**

Overall, this time in Biota’s history heralded a pattern of picking up deals based on Niall’s pre-eminent networks and connections. Quirk confirmed this:

... Hugh had been at the Florey [Institute, Melbourne]. He had been a professor [there] ... before they – [sold key technology] ... was it epidermal growth factor? [S]omething which Genentech finally got very interested in and bought. They [The Howard Florey Institute] wouldn’t look at us [selling to the Australian biotech industry]. Well, that’s where the pharmaceutical industry was, in a sense, and that’s where their mates were, the people they’d probably been through graduate school or they’d been post-docs together, or they knew each other. So there’s a sort of familiar world. (interview, 2007a)

Moreover, Quirk took care to emphasise the importance of networks, ‘[Networks are v]ital! Absolutely key! Because it’s a shortcut to do I believe what these people are saying’ (interview, 2007a). Wadley also commented on both the importance of Niall’s networks but also the seniority of the players within it, ‘[Niall] had a strong network. I mean I suppose Hugh was of an age group there where the people he had known here at the time were now sort of reaching senior positions in these various

places. And that's how he sort of worked his network. That is how you work your network. Yeah you know that's how we got those projects' (interview, 2007).

However, Quirk also rightly pointed out the downside of networks and the associated reputations of the scientists within them:

Because we had things from Peter Colman and it's that insulin diabetes project, and I looked at that and I thought this is a load of absolute cobblers. And my colleagues on the board said we've got to keep him happy, no, it maybe that's it's a waste of time but blah blah, it's Peter Colman. (interview, 2007a)

Peter Cook, Biota's current CEO, had a somewhat different view of networks:

[In my opinion] there's never any substitute ever for understanding the business sector that you're operating in. Maybe I'm sufficiently old that I don't lapse into terminology that says that's networking. I just put that down to straight industry intelligence. That's what you've got to have. If I'm known to 750 people in the industry does that matter if I'm pig ignorant of what the industry's doing and what are the drivers in the industry? You needed to understand your product attributes and what segment of the market you're going after and how did you get at that. Is that networking? I think networking is too loose a descriptor. We're drug inventors, that's what we do, so we need to understand who's the buyer of that product and which companies are in it and at what stage and what do they pay for that and how do I get them interested in my product as distinct from perhaps the one or two others that are there? I see this as a marketing exercise. I think it's one of the delusions that the market's got. When I say the market, I mean the share market. They run on some pretty loose rules of thumb and the loose rules of thumb are, are products worth more in phase III than it is in phase I? You can't deny that because the product's been de-risked on that process. The problem that they've got is are you the one that's completed phase III because nobody else that actually knows what the market is interested in, is prepared to buy it off you. You have been the one that's actually had to take it through to phase III because nobody else was interested in doing it. So having a phase III result for a product that somebody doesn't want, one of these incremental advantages that nobody can justify, reprogramming their reps for and doing everything else with, why would you do that? There's lots of those. Unfortunately, the investment community is relatively ignorant around the medicine. A general misconception in the marketplace is anti-virals don't work. That's not shared by the medical profession but it's a view. I actually have a shareholder who writes to me 'You guys are right up the creek'. I love shareholders. 'You guys are right up the creek. Everybody knows anti-virals don't work. What are you wasting your time on anti-virals for?' (interview, 2007)

If and networks occur, Cook again shared his thoughts:

Do they consciously network or does the network spontaneously emerge? My argument is this is a spontaneous event. Where I'm going in all of that is, I think that you've got to understand the market and I think that you've got to understand who's the buyer of your product. It isn't an argument about networks and about scientific conferences. Scientific conferences allow you to represent to the very restricted number of buyers what you potentially have got in your pipeline. That's a credibility build. That's a professional endorsement line of logic. It's like a clever advertising campaign. I'm not going to tell you what I'm really doing but I'm going to show you some results that will really whet your appetite and you, as an informed buyer, will know that in fact I couldn't be publishing that information if I didn't know a lot more so it's the [draw card.]

Scientific conferences are part of the advertising and promotion. The networking, I don't think, is relevant. Governments get all hung up about this. Researchers in the area all want to go do spider maps of networks and tell you why Boston's better than bloody Melbourne and all this sort of stuff. It was always a case of who knew the market. It really was. (interview, 2007)

Although Cook mentioned perhaps a special caveat to the networking issue, that of the scientists and their collaborators, 'Scientists always network. That's the nature of western science. It's called peer group review learned journals. That's what they've always done. They always network. Why do people network? People network when they are one of a very limited number of people who are interested in a field' (interview, 2007).

However, in relation to the business makers within the industry, Cook said the following:

... there's buyer seller and the buyer knows very well what's out there in the space that they're looking at. They've got a lot more resources and so therefore they're reasonably well informed. In fact, they'll get up at presentations and talk to you about their dashboards and what's there. Ultimately though this is an argument about power and the issue is that the guy that's further upstream than the guy downstream has ultimately got the power but it's the only point at which you've got the power. The minute you enter into the licensing agreement you transfer power now to the licensee and how you then try and control him is through contractual and authoritarian and legal manners. That's what you do. That's the way the pipeline works. Sure, but the reality is it's got to do with where you sit and the workflow pattern.

The workflow pattern is until we license that's who's exerting it. (interview, 2007)

## **Flu Diagnostic**

With the trials progressing well, Biota and GlaxoWellcome announced a subsequent agreement in March 1996. This would be an adjunct to the core agreement and involved the development and commercialisation of a diagnostic test for influenza. The concept of having a test to indicate the presence of influenza had been toyed with for some time, harking back to the attempted deal with Symex. Driving it was the need for unequivocal diagnosis of the flu to satisfy reimbursement by the various American HMOs. The joint press release dated 8 March 1996 stated:

Biota Holdings Limited today announced an Agreement with Glaxo Wellcome which will facilitate and expedite Biota's development and commercialization of a diagnostic for influenza. Biota and GlaxoWellcome have jointly recognized that optimal use of the influenza therapy, GG167, will be greatly assisted by the availability of a rapid, easy to use diagnostic for the physician's office market. The diagnostic is expected to provide rapid confirmation of a physician's diagnosis so that GG167 can be appropriately prescribed when it becomes available for sale. The drug is currently in phase II human clinical trials worldwide and has an anticipated filing date for a product license at the end of 1997.

Under the agreement with GlaxoWellcome, Biota has exclusive worldwide rights to exploit the intellectual property developed in the GG167 programme for the development and marketing of the diagnostic. Subject to regulatory approvals, the diagnostic and GG167 will be made available in the same markets. GlaxoWellcome will assist Biota with information and test samples from the ongoing clinical trials with GG167 and, subject to availability, will provide certain chemical compounds to Biota.

Biota's diagnostic approach complements GG167 in that it targets the same site on the influenza virus as the drug. Since GG167 is expected to be effective against all medically important strains of influenza virus, Biota's diagnostic is equally expected to bind to and positively detect the same viral strains. Dr. Phillip Reece, Biota's R and D Director who has directed the project since 1993 said: 'Biota's chemists have completed the synthesis of novel compounds with the desired characteristics for the diagnostic and patents have been filed. We believe that our approach is unique in that it incorporates the

most desirable feature designed into the therapy, that is, specificity for all medically important strains of influenza virus. This approach may have distinct advantages over antibody approaches which can be affected by strain to strain variability in the virus’.

Dr Hugh Niall, CEO of Biota Holdings, said today ‘Biota’s work on an influenza diagnostic builds upon years of experience by both companies in targeting the influenza virus. If all goes well our diagnostic will both detect the influenza virus and be predictive of a response to GG167. We have identified several US based diagnostic companies with the necessary technology and experience in physicians’ office diagnostics and are in advanced discussions with our lead candidate to collaborate on this project. We hope soon to move to the next phase and test our reagents in an existing diagnostic device’. (Biota Archives Online)

However, the deal with GlaxoWellcome would not eventuate. GlaxoWellcome decided to collaborate with Quidel, who Biota had previously investigated working with.

In January 1998, Biota announced they had a new partner for their diagnostics business, a Colorado based company called BioStar Inc. Wadley commented on the importance this deal would go on to have – albeit it was not widely known, especially to the shareholders, ‘The diagnostic that we did with BioStar was a beautiful thing because [it was] in a time when ... Relenza wasn’t starting look quite as flash as we’d all hoped it would be. They were great partners. So it meant that diagnostic was sort of putting in a couple of million a year’ (interview, 2007). As to how the deal with BioStar came about, Wadley (interview, 2007) attributes that success to his colleague Phil Reece, ‘Phil found BioStar. BioStar were a down and out little company at the time developing a number of diagnostics. They subsequently got taken over by ThermoElectron’. Specifically it appeared that Biota had this diagnostic development agreement, and at the same time BioStar, who had a history of developing diagnostic tests, was looking to enter the flu arena. Again, Wadley recalled the situation:

We had this diagnostic development agreement with them and part of that deal

was that they would have worldwide manufacturing rights and they would have marketing rights in the US and we would agree a margin. We'd give them the layouts and all that sort of stuff. We paid for the development because they had no money. We barely had any money either but we paid for that and in return that's how the US deal was struck. We had rest of world marketing rights and we employed a consultant, an Australian guy who was based in the US, and he subsequently found us Daichii [Pure Chemical]. And so we did this deal with them which was very good. They paid us a million dollars world marketing rights. So, they would manufacture out of BioStar and Japanese it a little bit and flog it in Japan. We tried other deals with various European diagnostic outfits. But I don't think it turned out. I looked the diagnostic after it had been commercialised if you will. (interview, 2007)

Woods also offered his opinion as to how this deal had come about:

Well, my recollection of that was that Phil Reece, and I was probably initially with him had been chasing it up, the diagnostic idea, for some time. He'd come across technology that BioStar had created for one or two compounds; I forget the names of them now. The idea was to join up with them and see if they could do something using lumina reaction. Well, I went there and saw them, as did others. It looked interesting when I was there. They had these chips which are made out of old Intel chips or silicon and the idea is to get a colour reaction or little blue spot after treating with the appropriate chemicals and mixtures and whatnot, which took not terribly long to do, I think 15 minutes. So that got off the ground .... (interview, 2007)

When prompted about the issue that GlaxoWellcome were indeed being pushed into having a diagnostic for the HMOs, Woods reflected and offered agreement that from his memory this was most likely the case. Moreover, the quality of the test proved divisive amongst various parties, i.e. some people in Biota were insistent that the test should offer the greatest accuracy possible, whilst GlaxoWellcome viewed it differently. They were willing to settle for a simple Yes/No style of diagnostic – with a higher level of tolerance regarding accuracy. Ideally they simply wanted a quick, reasonably accurate indicator that would facilitate the doctor's confidence to go ahead and prescribe a anti-influenza drug:

Yeah, I think that was Phil Reece's department at that stage. He pushed for the

better thing which was the BioStar process. Glaxo didn't want to join up with us, they joined up with somebody else to try and do something similar. (Woods, 2007)

Reece himself talked about his involvement with BioStar, 'BioStar was the one I probably contributed the most to but clearly the Glaxo deal was the most critical deal for Biota ever and continues to be so. Well anyway, Glaxo is still the licensee. It still holds the licence' (interview, 2007).

The two parties then commenced North American clinical trials of the influenza diagnostic. These were conducted at several locations in the US. The trial was designed to assess the performance of the new 15-minute diagnostic for both influenza A and influenza B using several patient specimen types. Later that year the first sales of the diagnostic were made in Australia and in 2000, Biota would go on to record a profit with the diagnostic for the first time of A\$1.7 million.

As for the United States, the diagnostic, which was marketed as FLU OIA, was launched in December 1998. FLU OIA was a rapid (15 minute) influenza diagnostic assay, which detected all strains of influenza. During 1998, Biota's development partner underwent a merger with another US company, ThermoElectron and the new entity was known as ThermoBioStar. The new company would continue to have worldwide marketing and distribution rights in the US and ThermoBioStar would also manage the distribution of FLU OIA in the European Union. The agreement between Biota and ThermoBioStar meant the product was manufactured in the United States that Biota would earn a profit share from sales arising in the US and a royalty based on sales in Europe. As for marketing and distribution, the situation was as follows: in the US it was distributed by ThermoElectron; ThermoElectron had exclusive marketing rights for the product in the US, Europe, Japan and Australia/New Zealand; while Biota had rights in

Asia and the rest of the world (Biota Website, 2008).

During 2002-03, Biota announced plans to expand distribution to new markets and announced they had appointed Daiichi Pure Chemicals Co Ltd as their major distributors in Japan and for Australia, Dade Behring was given distribution rights. The diagnostic would go on to become market leader in the US and was being used by hospitals and in doctors' offices as it provided a accurate test that was considered as sensitive as a 14-day viral tissue culture, but has significant advantages in convenience and cost. Having a correct diagnosis of influenza was considered important because it allowed the physician to appropriately prescribe antiviral therapies, such as Relenza™, and minimise the medical costs associated with unnecessary prescription of antibiotics and in some cases, hospitalisation (interviews with Quirk, 2007a; Simpson, 2007; Wadley, 2007; Woods, 2007).

## **Woods Steps Down**

In 1997, Woods was another one to depart, due both to personal reasons and to his sense that the Relenza project was nearing its conclusion:

There'd been quite a lot of tensions in some of the areas, like BSM. I actually got a bladder cancer which was felt not to be serious at the time and I really wanted to have some time with the family. [My wife had] had a fairly rotten run, I think, with all this gallivanting around. [Me being an] absent husband. Anyway, so after we'd settled down Brian Healey as chairman ... I stepped down as chairman ... I'd been chairman for five years ....

We'd had Hugh in for a while, then we got Brian and also a lady from ICI. Barbara [Gibson]. Yeah, she's a good girl. I was a bit sorry I left early [than I might otherwise have liked to if my health had been better], too early for her, I think she wanted to see a bit more from me. So, we had some good people on board, but I decided one day, look, I've had enough really and I was a little alarmed at the time as to how things were going. So you sort of felt while you hang on here and keep on batting along and doing the best or you give somebody else a go who maybe can pull a bit of something out of the wreckage, if there was going to be any. I didn't sell my shares, I hung on to my shares. (interview, 2007)

As to why Woods was alarmed, he said,

Well, I suppose it was the fact that Windle had left and all the people in Glaxo had left. [That was after the GlaxoWellcome merger, that's right; before the SmithKline [merger]. The research had wound down, VCP research, and I felt it was a time when a lot of it had closed down and there wasn't much that I could do because I wanted to hand over to others anyway. Hugh [Niall] was doing the chief executive job and Brian [Healey] was doing the Chairman's job. I had this scare and so I was a little bit concerned about how it was all going to go. We had I think a fairly indifferent letter from [Sir Richard] Sykes at the time, as well and they'd also slipped up on a year of research. [due to the merger between Glaxo and Wellcome]. No, it wasn't getting easier and my health was deteriorating. That cancer held fairly well for the next four years, but I had to have very major operations. That took me through until 2000, and I guess ever since 2000, there's been a few dramas around. (interview, 2007)

However, reflecting back on that had happened until then, and the motivation underpinning his involvement, Woods also said:

... [O]ne of the things which I think is probably missing today is that it was a bit like playing rugby union in the old days. You sort of played for the honour of the game and you didn't expect much in the way of reward. We didn't take anything much in the way of [financial reward] – apart from the initial thing, which was of course shareholding in BSM; the rest was playful. But during that time the director's fees were nothing and a lot of trips and things hardly met your expenses, that's about all. There wasn't the days of these [the deals of the new generation of biotechs post millennium], I think, outrageous sort of deals that are done. (interview, 2007)

**Table 6: Updated position of Biota - 1997**

Year	Market Cap	Subscribed Capital	Cash	CEO	Development	Projects	Progress	Relenza
1983				1	Biota Pty Ltd	ID phase		
1984								
1985	\$3.0	\$3.0	\$3.0		Biota Holdings	3		
1986	\$3.0	\$3.0	\$2.5				Patents filed for NI	
1987	\$3.0	\$3.0	\$2.0	2				1st active molecule
1988	\$3.0	\$3.0	\$1.6		Takeover bid	2	Vaccine program abandoned	
1989	\$4.6	\$3.0	\$2.7				Glaxo Heads of Agreement	
1990	\$2.8	\$3.0	\$2.7				Glaxo Agreement, angiogenesis abandoned	
1991	\$11.1	\$3.0	\$2.4			2	Diagnostic test – Symex USA	
1992	\$48.4	\$3.0	\$6.9				Lead compound identified	Exploratory development
1993	\$97.7	\$13.0	\$13.9				Symex agreement terminated	Phase I
1994	\$129.3	\$13.0	\$21.8	3	R&D Director appointed			Phase IIa
1995	\$107.1	\$13.0	\$18.4		Biota Labs		Insulin programme	Phase IIb
1996	\$283.5	\$29.5	\$23.0					
1997	\$305.2	\$29.5	\$24.9				Anticancer compound, diagnostic test Biostar USA, RSV programme	

**Source: Quirk (2007b)**

### Strategic Choices

With Relenza inching further to FDA approval, Biota’s pipeline had slowly been expanding into several different areas. Some were showing signs of progress – particularly those positioned in the anti-viral space. This was largely the result of research from its own research labs: the treatment of the common cold, i.e. rhinovirus infections, and for Respiratory Syncytial Virus (RSV) as well as a second-generation anti-flu drug (a long acting neuraminidase inhibitor – LANI), all of which Biota would go on to be involved with. The culmination of these efforts, according to Niall, was that ‘Biota thus became more of a real operating biotech company as opposed to a virtual IP holding company’ (Niall, 2007).

However, by 1999 Niall and his senior management team, Wadley and Reece, spent some time with McKinsey Consulting. Wadley explained:

In about '99 – in about '99 Hugh fixed up some sessions with us, three of us (Reece, Niall, Wadley) to go with McKinsey's they were doing a study. But after the McKinsey thing we then said well you know we don't have the expertise in all these sort of disparate areas. We have expertise in virology, whether that's true or not I don't know but we ... thought we did. So we really then sort of focussed on this rhinovirus program ... and the RSV program that sort of thing. The other things were sort of left to fade away a little bit. And I often wondered whether and still do, although maybe it's paying off now, [whether] those sorts of projects were ideal for a company like Biota in this market.

They're big projects, massively expensive and take along, long time to develop. I mean, if you think about it to write a virus drug. People get their colds four or five times a year or whatever it is. Are you going to be wanting them to pop one pill or one - you know the safety profile for that sort of drug is ... horrific. So I'm just querying really why – if we were based in the US, different financing, different opportunities ... it might have made sense but to me it didn't make sense here [in Australia] [I]t just didn't make sense because investors here, you know were getting pretty pissed off that Relenza hadn't exactly sort of come home for them. (interview, 2007)

So with this renewed focus on the viral area rather than diabetes, Alzheimer's disease and cancer, those projects eventually faded away.

Woods also commented about the matters of portfolio development:

Well, I was never terribly keen about having too wide a portfolio, for a number of reasons, some of which were selfish. Because if you could – as you do normally in business, if you can produce something well and make a good profit out of it and you're still holding much of the equity, you're a hell of a lot better off. Why spend all that equity on things that are more dubious? But as is usual I think with companies with the numbers of common people around, it's a case of Murphy's Law working; work expands to fill the space available. There's a bit of that and everybody gets keen on something new, and you know, let's do it, let's do it, let's raise some more money. As soon as more money's raised I say, there's another 10 per cent down the tube. But you have to have a bit of a combination of that, you can't have it entirely on one thing. I think we're extraordinarily lucky to find something that was very near the mark, and proved finally to be on the mark. (interview, 2007)

Wadley reiterated the importance of networks, but points to the reasons that lead companies to utilising such contacts in the first place and the consequences in terms of the disparate nature or randomness of the projects in licensed at that time:

Well you've got to get what you can get. Basically it was Hugh's network. Hugh was very good with his network. Hugh had – you know he was an old hand. He ... is a very bright man. He knew these people. There were these sort of projects that needed a bit of go about them and ... it was a matter of, perhaps it's an ego trip yeah we could do this, we could do that, we could do anything. But really, you know, it's difficult to fill the pipeline. I mean there's a lot going on in the universities, the CSIRO and so on but you know it's not easy to build your pipeline. So with Hugh's network and it was strictly his network. (interview, 2007)

The cancer project though, would eventually be shut down. The projects that survived were those developed in house:

You know we had quite a good team that was full of ideas. I think both the rhinovirus and the RSV had started in house. I don't they are licensed to anybody. We were actually shit at licensing things in; we were actually pretty shit at licensing things out. We were a pretty arrogant bunch of people. (interview with Wadley, 2007)

As to why this attitude might have prevailed, Wadley speculated and concluded, 'I don't know, I think actually Biota had a lot of difficulty with a lot of its relationships with all sorts of people. And even since, I mean I've been involved from the outside trying to deals with Biota and it's really very difficult' (interview, 2007).

## **The FDA Hearing**

On 24 February 1999, the Food and Drug Administration (FDA) Antiviral Drug Advisory Committee Meeting met in Maryland to hear Relenza's submission. FDA committee meetings can be high drama and are usually deliberately adversarial. As part of the opening address, the following statement was read by Dr Debra Birnkrant from the FDA:

Not only does Zanamivir have a novel mechanism of action, but it depends on the use of a delivery system which is also novel in the area of antiviral drugs. Points related to the use of the delivery system are critical to today's

discussion since appropriate use of the Diskhaler with the Rotadisk™ is crucial to treating this infectious disease with an inhaled product for the proposed treatment period of 5 days.

Moving to the final reason we brought this application to the committee, it represents a departure from the indications we usually present. Generally, we present an application to our committee for a chronic, serious, and life-threatening disease such as HIV or hepatitis B or C. Today we bring an application for a disease which is acute and self-limited in the majority of patients, but one that could potentially infect the entire population and which accounts for a substantial morbidity from a national and international perspective.

Treatment of a disease with the propensity to affect such a large portion of the population is why we granted this application a priority review. This is also in keeping with the Department of Health and Human Services' efforts to reduce the impact of annual influenza outbreaks and coordinate pandemic preparedness for a potential influenza pandemic. (FDA Advisory Board Meeting on the Approval of Relenza – 1999)

In reply and on behalf of the sponsors, GW and Biota, Dr Marc Rubin responded and some of his remarks touched not only on the newness of the drug and its ability to offer patient benefits, but also on the challenges they had incurred along the development pathway:

Well, since Zanamivir was and is the first in its class, in many ways its development really has been a pioneering effort. The design of the clinical development program was very, very challenging. That's clear. There was no road map for us to follow. I think, though, despite those challenges, we've been able to demonstrate antiviral activity and clear clinical efficacy for both flu A and flu B. The proof of concept was first established in the human challenge studies that you'll hear about. Efficacy first was demonstrated in the very large phase II program that enrolled over 2,000 patients, and then in the phase III studies, a global program, enrolling over 1,500 patients.

As can be expected in large global programs with multiple clinical trials, you will see a range of efficacy across these trials today, and Dr Ossi is going to discuss the differences seen, particularly in the North American study. Nevertheless, we believe the weight of the evidence clearly supports a clinical benefit for this drug.

Let me just briefly review some of the important milestones along the way in the development of Zanamivir. In October of 1993, we filed the IND. A year

later, we began the phase II clinical program. In May of 1997, we initiated the global phase III program, and in October of last year, submitted the NDA, which was granted priority review status in December. Of course, this brings us up to today's meeting.

Obviously there has been a great deal of interaction, discussion, consultation with the FDA throughout this process, including agreement on many of the protocol analyses that you'll see us present here today. This has been very, very helpful for us and we're certainly very grateful for all of that interaction.

So, in sum, we believe that the efficacy data, the weight of the data across the phase II and III program which enrolled over 3,500 patients, and the safety data in an even larger number of patients support the proposed indication, which is for the treatment of influenza A and B in adults and adolescents.

That concludes my portion of the presentation. (FDA Advisory Board Meeting on the Approval of Relenza – 1999)

Drs Hayden and Elliott followed with presentations on behalf of GW, each giving informative and professional speeches, which were in turn followed up by a series of questions by the elected panel for the hearing. This panel comprised of leading experts from prestigious research and medical institutions across the US. The panel were rigorous with their questions, but GW were given time for rebuttal later in the afternoon session. The morning was broken up by a short recess and when they reconvened Dr Mike Elashoff<sup>10</sup> commenced his presentation. Systematically he reviewed the data for each of the phase III trial arms and soon it was becoming apparent that the news was not favourable for Relenza; news that no one from GW or Biota had seen coming.

The results of the US study of 990 people showed only a *one-day reduction* in influenza symptoms. However, this reduction was *not statistically significant*.

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<sup>10</sup> Dr Elashoff was an FDA statistician assigned to work on the Glaxo/Relenza application. Elashoff subsequently resigned from the FDA shortly after the hearing in murky circumstances. (see Controversial flu drug approved despite scientist's protests Broadcast: November 7, 2000 | Producer: Christian Côté; Researchers: Cindy Bahadur; Mike Gordon)

Normally, two significant trials are normally enough for the FDA to allow marketing in the US. In arriving at a successful trial outcome, there has been a tradition of the methodology and ‘primary end points’ being set and agreed upon in a consultative fashion by all parties from the outset. For Relenza, this agreed methodology required the trials to show a one-day reduction in the duration of influenza symptoms. Symptoms that lingered or recurred after that alleviation were ignored. However, Elashoff was now attacking the previously agreed end points. Elashoff said, ‘The primary end point ... did not really do justice [to testing the efficacy of Relenza] through the course of their disease,’ he told the committee. ‘[Until now] ... there was no real data to suggest a better way of quantifying efficacy’ (FDA Advisory Board Meeting on the Approval of Relenza – 1999, p. 63).

This was deliberate FDA strategy, with Elashoff undermining the agreed end point to take the heat off the FDA. With the benefit of GlaxoWellcome’s work and the benefit of hindsight, Elashoff criticised the reduction in the duration of influenza symptoms in the Phase III trials. He argued they should have counted the number of days in a 14-day period that patients had influenza symptoms and those days on which their symptoms were alleviated. When the data was looked at from this point of view, Elashoff admitted the drug was still effective in the Australian and European trials, but less so, but that the US trials did not prove efficacy. He said, ‘The largest treatment effect was seen in the smallest study, while the smallest treatment effect was seen in the largest study. Secondly, it was the North American study, arguably the most relevant study for us, that was the one with the smallest treatment effect’ (FDA Advisory Board Meeting on the Approval of Relenza – 1999, p.64).

Following Elashoff’s presentation, questions were again opened to the expert panel; this question arose from Dr Hamilton, and in many ways typified the mood that

had now been set:

Dr Elashoff's presentation brought into sharp focus, for me at least, an issue that has been bothering me throughout the morning, and that is the reliance on this primary endpoint, time to primary endpoint. Flu doesn't just stop in one day, and a difference in one day between the placebo and the active drug treatment is said to be significant in the sense that it reduces global misery somehow and that it translates into a more productive, let's call it, work force. It seems to me looking at the graphs and tables and figures that you showed, the disease doesn't end at the time of the primary endpoint. It lingers. It goes on and on, and so to imagine that that translates into a more productive citizen I find that to be something of a leap of faith. I think it's quite interesting to consider aloud how these different approaches reveal quite different conclusions about the benefits of this drug, and perhaps this will be addressed further.

I would like to ask the sponsors to confirm for me that the endpoints that they selected were, of course, selected prior to the time these studies were performed and they're not the result of some dredging of data that fits their hypothesis. (FDA Advisory Board Meeting on the Approval of Relenza – 1999, p.93)

In response to the question, Dr Elliott from GW replied, 'I'll briefly address that. The analyses we presented were the ones predefined, selected during discussions with the agency during development' (FDA Advisory Board Meeting on the Approval of Relenza – 1999, p.94).

When the meeting reconvened after the lunch session, there was another set of instructions delivered to the panel by Dr Birnkrant of the FDA. She said:

Well, as we continue our discussion and move towards the afternoon deliberations, I just wanted to make a few comments to help us focus this afternoon's discussions. What I'd like you to do is think about the phrase, there's more than one way to look at things. I think this is particularly applicable to influenza, which is a self-limited disease maybe lasting 5 to 7 days, up to 10 days. Think about what type of treatment effect you would actually expect in this type of illness as you deliberate this afternoon, keeping in mind that, for the most part, in patients it's a waxing and waning type of presentation over the course of the 5 to 7 to 10 day period. I think the other thing to keep in mind is that, as Dr Styrt presented this morning, that there are a number of ways to look at things with regard to endpoints for influenza trials, and various types of endpoints have been tried out not only for Zanamivir, but other drugs as well. I also wanted to bring to your attention that years ago, when the protocols were submitted for these clinical studies,

we did agree to certain endpoints with the applicant, GlaxoWellcome.

I also want to raise the point that, as you can see, both the FDA and the applicant did multiple additional analyses, and as you can also see, exploratory analyses can either be more or less reassuring, depending on how you look at things.

I'd now like to just make a couple more comments about foreign data. In our regulations, there's a description as to when and how we can accept foreign clinical data. One of the major ways in which we accept foreign clinical data is if we can apply it to the U.S. population and to U.S. medical practice. To relate that comment to the clinical studies, I just wanted to remind you that the European trial and the North American study followed the same study protocols. In order to use foreign data in a marketing application for the FDA to review and consider worthy, we also have to be able to validate the data, and that would involve an inspection. Lastly, we have to make sure that these clinical trials were conducted according to U.S. standards, which they were. (FDA Advisory Board Meeting on the Approval of Relenza – 1999, p.104)

Such a devastating and un-heralded criticism of an agreed end point was extraordinary for an FDA employee, and brought into question the FDA approach to negotiating the trialing and approval of new drugs. With millions of dollars and market access at stake, companies needed to be sure that the FDA agreed with trial methodologies. The FDA did not honour the end point. The statistician took an idiosyncratic view of the design of the trials and re-opened an issue that had been discussed with and agreed by the FDA years earlier.

However, why did GlaxoWellcome, a global giant with a good track record of shepherding new drugs through the FDA, not see Elashoff's critique coming? Several members of the antiviral committee were openly critical of GlaxoWellcome's submission, presentation and answers to questions. New York analyst Richard van den Broek said, '... if Glaxo Wellcome had proved efficacy in its US trials, the committee meeting would have been short...they just didn't show it worked in the US'.

Elashoff made an even broader attack on neuraminidase inhibitors such as

Relenza, suggesting that on one reading of GlaxoWellcome's data, Relenza caused only a small difference in actual symptoms over time. 'A difference of, say, seven days versus five days [in the duration of influenza] in the European study sounds impressive, like two days less of flu,' Elashoff told the committee. 'But the reality, even in the best study, was one of continued gradual improvement.'

The vote was taken, and the question included a decision regarding both safety and efficacy. The vote returned 4 affirmative votes and 13 negative votes. Of these 13 negatives, most of these panel members of the committee who echoed Elashoff's criticisms, were not with the FDA, but outside specialists in virology, public health and respiratory disease, which the FDA relies on to make an independent assessment. Although, ultimately the FDA makes its own decision and is not bound by the committee's recommendation.

While much was made of the weight the committee put on the US trial above the significant European and Australian results, there were complicating factors, which worked against the committee accepting foreign data. The US patients used twice as many medications such as painkillers and cough syrups, which reduced symptoms, than either Europeans or Australians. The studies in effect supported co-medication, prompting scepticism from committee member Dr Sharilyn Stanley that Relenza was useful in the general US population in reducing influenza symptoms. She suggested GlaxoWellcome focus on at-risk groups. In support of Relenza was Dr John Hamilton of Duke University, who commented: 'I believe [GlaxoWellcome] have demonstrated sufficient efficacy to support their application'. Dr Henry Masur, the chief of critical-care medicine at the National Institutes of Health, said: 'I am impressed at the entire package of the drug discovery program and the drug development'.

However, the committee voted 13 to four against Relenza. While no significant

safety questions were raised, the advisory committee found that GlaxoWellcome had not shown the drug to be effective for the treatment of influenza. Four of the committee members noted that they voted against Relenza reluctantly. ‘I was reluctant in voting no,’ said Dr Brian Wong of Virginia-Connecticut Health Care Systems. ‘I believe that the data we saw ... shows that it is a very promising antiviral, and I think that just a little bit more prospective analysis ... will nail the case’.

The February 1999 meeting was a serious setback in their path to commercial success. It was a shock to both Biota and Glaxo, who had been warned just 30 minutes before the meeting that the statistician was going to take the tack he did. With the FDA announcement in February that it had extended its review period for Relenza by three months, expectations were rising that the drug might be approved in the US at least for ‘at risk’ patients such as the old or the immune-suppressed and could even be more generally available in time for the northern hemisphere winter.

GlaxoWellcome entered into intense negotiations with the FDA and an extra three months were granted to argue their case. The FDA could do anything between approving the drug for sale in the US or rejecting it outright. It could, for example, deem Relenza approvable pending the presentation of evidence in a new form or the conduct of new trials. Evidence gathered in the real-life use of Relenza in Australia this winter would be crucial. Some independent observers were not concerned at the rejection as there was general agreement that it was only a matter of time before Relenza would be approved in the US. Relenza was finally approved by the FDA several months later and Tamiflu was hot on Relenza’s heels with their first FDA approving coming in October 1999 (FDA website)

Biota’s shares, which had risen as the meeting opened, were now in free-fall on the Australian Stock Exchange, plunging from A\$9.10 to as low as A\$3 before

recovering to end the day at A\$4.35. In less than 24 hours, the company's value had been slashed from A\$664 million to A\$320 million and GlaxoWellcome's reputation for guiding new drugs through the FDA was in tatters, while the FDA's bona fides in dealing with drug applications were also under question. All in all, it had been a brutal 24 hours; Wood's later commented that he lost '\$10 million dollars that day!' (interview with Woods, 2008). Burdett Buckenridge Young analyst Michael Carmody valued the company at A\$5.70 based on the value of European and Australian sales and a likely delay - until 2002 was his worst-case scenario - in Relenza's entrance onto the US market. At the time, he said 'The market is a little gun-shy of biotechnology stocks at the moment. They have been reminded that there are risks involved in R&D. Even at Phase 3, there are still risks' (Roberts, Australian Financial Review, 1999). Carmody estimated Biota's revenues from Relenza would peak at A\$60 million in 2007-8. Biota's value was also boosted by other new products in the drug development pipeline and by its development of a rapid test kit for influenza designed to be used by general practitioners in their surgeries.

Wadley elaborated further on the issue of risks, particularly the fact that shareholders in general did not have a good understanding of the overall risk profile of biotechnology companies. '... [O]ne of the things about this business is you haven't even got it [security] when you've got it [scientific proof] because what I'm saying there is, is that you can run through this thing and have your research and development risk and all of what goes with that and this is where Biota shareholders misread it because they thought well 'research risk' is taken care of we've got [a] big brother, we've got this [partner in Glaxo], we've got that and then all of a sudden we've got commercial risk [i.e. the FDA.] ... [T]hat was a painful reminder for them. [And not only the FDA but] then you get a competitor cut across [your research and] you've got

– the commercial risks tak[ing] over where the R&D risks left off’ (interview, 2007).

As well, a window of opportunity was opened for the competitors, the Gilead & Roche partnership; the following year, the FDA approved the sale and marketing of oseltamivir, which became known as Tamiflu. Biota managers blamed the GW team for this fatal error, an assessment confirmed by some of the journalists covering the FDA hearing at the time (see Roberts, Australian Financial Review, 1999). In his opinion, GlaxoWellcome presented themselves in a ‘under-prepared way’ and when the session was over left the hearing feeling rung out, pale and pasty white! Of this Wadley said, ‘Well so they ought to have been. I mean they were bloody arrogant ... the R&D guy ... whatever his name was, I mean he didn’t even go to the hearing ... this guy didn’t even bloody front up at the FDA ... they were pretty blasé about it. And well it was probably the start of the ... [end of Relenza]’ (interview, 2007).

Later in 1999, disappointment was tempered by the fact that Relenza went on sale in Australia in the winter of 1999 and in Sweden and throughout the large EU market by Christmas (Neergaard, 1999). Formulation and packaging was underway at GlaxoWellcome’s Boronia plant. Relenza would go on to be approved for therapeutic use in over 60 countries and for prevention of influenza in eight countries. (Biota Website, Accessed 12 February 2008) And whilst this may have been a difficult period in terms of product development and project fulfilment, one string in the company’s bow was the stability of the management team during this time, ‘And so there was Hugh, Phil and myself and that really was the senior management team for the company for probably about the next eight or nine years’ (interview with Wadley, 2007).

## **2001 Biota Inc Established in USA**

With the marketing clearance of Relenza in Australia, the European Union and the

USA, Biota found themselves in elite company; they were part of a small group of firms that had managed to successfully take biotech research all the way through to commercialisation with the help of their partner, Glaxo and later GlaxoWellcome. The process of partnering in and of itself opened doors for Biota and the Australian biotechnology industry at large. Moreover, Biota realised that the deal with GW had helped raise their profile in the investment community in the USA. The flip side of this profile was Biota's demonstrating of their understanding of the role and importance of the American venture capital markets and their willingness to support projects at an early stage.

With that in mind, in May 2001 Biota established their US subsidiary, Biota Inc. It was based in southern California and its main aim was to allow the company to take full advantage of the physical closeness of potential partners for collaboration. In particular, San Diego was considered to be a hotbed, with over 200 biotech companies and sources of capital. Biota Inc. though took a further step, and instead of being a mere 'shop front' they set up research facilities to continue their work in the broad therapeutic area of infectious disease.

Biota Inc was 88% owned by Biota Holdings Limited (approximately 84% on a fully-diluted basis) and Biota Holdings provided A\$15 million initial equity funding which was used to establish the N-MAX laboratory facilities. The proprietary N-MAX technology allowed the creation of 'nucleotide mimics' novel versions of nucleoside drugs, with the potential for enhanced activity and reduced toxicity. Nucleoside drugs are widely used to treat diseases such as HIV/AIDS, hepatitis C infection, and cancer. AZT (zidovudine), a leading anti-HIV nucleoside drug with sales of around A\$1.5 billion, [in 2003] was the primary target for Biota Inc' research (Biota Press Release, 30 April 2003).

By applying its nucleotide chemistry expertise, and proprietary N-MAX drug discovery technology, Biota's goal was to rapidly discover drugs that have the potential to satisfy unmet needs in multi-billion dollar markets. A market of immediate interest for the company was Hepatitis C Virus infections. Additionally Biota would apply their technology to other chronic viral infections, antibiotic resistant bacterial infections and cancer. At that time Biota's intention was to establish both funded research collaborations with other companies and to develop products for the Biota portfolio. The site was fully operational by mid 2002 (Jones, Valenti and Porter, 2002).

In 2002, Biota entered into a collaboration and licensing agreement with GlaxoSmithKline for the discovery and development of its novel anti-virals for hepatitis C (HCV) and other viruses, however, within two years of the US facility being operational, Biota Holdings made an announcement that Biota Inc had achieved an important breakthrough with the HIV/AIDS drug research program, which the company presented their finding at the *International Conference on Antiviral Research (ICAR)* in Savannah, Georgia, on 28 April 2003. The press release detailing the results stated:

The studies showed that the new compounds were many times more effective than AZT, while having less toxicity. 'The AZT-mimic research has been a remarkable success,' said Biota Group CEO, Peter Molloy. 'In less than a year, Dan Cook's scientific team has demonstrated proof-of-concept for the N-MAX technology and discovered a series of novel compounds that could lead to new treatments for HIV/AIDS.' The lead compound series, referred to as B-108, are covered by the patent applications recently filed by Biota Inc. 'AZT is a good drug and a tough benchmark,' said Dr Cook. 'These results are very promising.' (Biota Holdings Press Release, 30 April 2003)

The same press release also mentioned the early success of Biota Inc's deal with GlaxoSmithKline in terms of generating revenue for the subsidiary. The hepatitis drug discovery program generated A\$2.7 million in revenues for the Biota Inc. in the first

half of 2003.

However, in 2004, Biota Inc. closed down and the equipment, namely the laboratory and scientific instruments were carefully shipped in a sea container back to Melbourne Australia and re-institutionalised in the Notting Hill facility where Biota currently resides (interview with McDonald, 2007). Although one the founders, Woods, had stepped down off the board when the decision to set up Biota Inc occurred, he commented on his reaction to such a decision, ‘I was never very pleased about that, but it was ... after I left. I think it was because there was technology over there, [in] the first place that they wanted, Hugh wanted, and there were people [there]. The main thing was [the] Hepatitis C [project] and also possible HIV interest. They had a variety of processes and people, very expensive people there and seemed like a good idea at the time’ (interview with Woods, 2007).

Andrew McDonald, who was the company secretary at the time said:

Well, I think you’ve got to look at what you’re actually doing. I shut down the US operations ... well, Peter and I certainly worked together on that but, look – I’ll choose my words carefully on this because I think there’s a variety of views on it and a variety of thoughts – but, you know, we simply at the end of the day had a limited number of dollars and we couldn’t afford to fund US research with Australian dollars and starting our other programmes.

What’s been very interesting is since that time I think the results just speak for themselves. Programmes that were languishing and had been starved of funds were now able to receive those funds and, you know, they’ve actually successfully taken forward a number of those into the clinic. Spreading [themselves] too thinly. So, you know, it depends on what you set up and what you’re setting up for. (interview, 2007)

As to the nature of Biota’s international corporate structure, Molloy explained, ‘We keep a business office in Switzerland, in Europe, and we have our business office in the US. We have a business development consultant in Europe and one in the US’ (interview, 2005).

## **Another Attack from the Wild, Wild West**

Along with a new subsidiary, Biota also acquired a new CEO in 2001. New CEO was appointed, Mr Peter Molloy. Hugh Niall's contract had come around for renewal and he had chosen not to take up this option. Molloy had a long history of sales and marketing success in the pharmaceutical industry and was based in the United States. Like Niall, Molloy also came to the company with an impressive network, this time though more involved with key senior managers in pharma organizations in the marketing and business development areas. Like his predecessors, Molloy was also confronted with some large challenges early in his reign. In November 2002, Biota again had the battle lines drawn; Perth-based businessman Farooq Khan wanted to take control of the company. However, at the Annual General Meeting, Biota's board described Mr Khan's bid as 'farcical' and urged their shareholders to reject it. Khan, who owned 9.5% of Biota, wanted to seize control of the company so he can put it back on track. In an interview with Michael Rowland, from the ABC's Business Breakfast on 2 November 2002, Khan said, 'We want to create a new strategic vision for the company. We want to appoint a respected firm of individuals, corporate finance advisors, to come in and look at the assets, see why the market is placing so little value on them and try and create some strategic value.' However, there was much speculation that Khan was merely attempting to raid Biota's cash reserves. Additionally, it was alleged Khan wanted to remove four of the five Biota directors, and was planning to convene an extraordinary general meeting to put the issue to shareholders. Moreover, Khan was apparently not the only shareholder concerned about the company's performance; several others were concerned about Relenza's failure in the market and the resulting plunge in share price from over A\$9 to now below 50 cents. In Biota's defence, Molloy

clarified Biota's commitment by stating, 'We're the company that has the influenza franchise. Many other companies in the world have walked away from influenza. We still think it's a very serious disease that warrants pharmaceutical development.'

### **Moving Anti-virals Forward**

And important part of Biota's influenza franchise was its a second generation anti-influenza program (FLUNET®). Whilst they were making good progress, a development partner was still being sought at this time. However, by October 2003, Biota issued a press release saying they had entered into:

[A] landmark influenza drug agreement with one of Japan's largest pharmaceutical companies, Sankyo Co., Ltd ('Sankyo'). The collaboration and license agreement covers Biota's second-generation influenza compounds (FLUNET™) and a comparable and competitive Sankyo compound (R118958) that is already in human clinical trials. The agreement consummates a Letter of Intent that was executed between the companies on May 23, 2003. (Biota Press Release, 23 October 2003)

The press release continued to explain about the products and the nature of the deal as well as some information about the new partner, Sankyo:

The second-generation compounds are longer acting than any currently available flu treatments. While the existing drugs need to be administered twice per day, the new drugs may only need to be used once or twice a week, potentially making them useful in the prevention of the disease as well as providing a much more convenient treatment.

Under the agreement, Sankyo and Biota will cross-license their relevant patents and pool their new long-acting influenza drugs into a single pipeline of novel products, which will be offered to prospective licensing partners for further development and marketing. Both Sankyo and Biota expect that all future development work on the compounds will be funded by such licensing partners.

The partnership gives Biota shared rights to a long-acting neuraminidase inhibitor that has already completed a Phase I human clinical safety study, whereas Biota's current compounds are still at the preclinical stage. The

development cost to take Biota's preclinical compounds through to the same stage as the Sankyo drug has been estimated at US\$4million. Under the agreement, however, the Biota compounds will not need to be developed immediately, but will be retained as back-up compounds, with the focus on accelerating the pathway to market for R118958.

This is an important partnership for Biota that propels us immediately into human clinical trials, and about 12-18 months ahead of where we would have been with the FLUNET program alone, said Group CEO, Peter Molloy.

It brings together two otherwise competitive programs into a single, robust pipeline of improved influenza drugs, which should be attractive to pharmaceutical companies seeking partnering opportunities. In addition, the agreement effectively combines all the potential partners that Sankyo has been talking to, with those who have shown interest in Biota's drug candidates, giving us a much richer pool of partnership prospects, he said.

The two companies will now form a joint Licensing Committee to conduct the partnering discussions, which will be pursued regionally and worldwide. All licensing revenues, milestone payments, and royalties arising from any partnerships will be shared equally between Biota and Sankyo.

Biota remains confident about the prospects for the new generation of influenza drugs. Despite active vaccination programs, an estimated 100 million people in the US, Europe and Japan become infected annually. In the US alone, a reported 150,000 people are hospitalized each year, and up to 40,000 die from the disease and its complications. In healthcare costs and productivity losses in the US, influenza results in an estimated annual bill of US\$15 billion.

Despite this, total sales of the current twice-daily flu treatments remain modest, amounting to less than US\$300 million worldwide. Mr Molloy noted, however, 'We believe this market has significantly greater potential with an improved, longer acting product.'

Biota pioneered the field of inhaled neuraminidase inhibitors, with its first generation product, Relenza™. FLUNET compounds are also inhaled neuraminidase inhibitors, but represent a significant advance over Relenza, because they are more potent and have a longer residence time in the lung, allowing them to be administered much less frequently. Biota currently has three FLUNET compounds, which are at the preclinical stage of development. (Biota Press Release, 23 October 2003)

As for their research partner, the following details were also issued in the press release:

Sankyo's R118958 compound is also a potent, long-acting inhaled neuraminidase inhibitor, but is significantly more advanced in development than the FLUNET compounds, having already completed a Phase I human clinical study in Europe. Sankyo Co., Ltd is one of Japan's largest pharmaceutical companies, with annual worldwide sales of US\$4.8 billion. Sankyo has a long history of discovering new classes of drugs, including the statin class of lipid-lowering drugs with its discovery of the first statin in the world. Sankyo discovered, co-developed and manufactures pravastatin sodium. (Biota Press Release, 23 October 2003)

One of the key inventors involved, Professor Wen-Yang Wu recalled the nature of the both the initial discovery zanamivir, and how that led to the development of the LANI, 'I remember when we did the discovery work [on Zanamivir], it was the first in the world in that area, in that field. Of course, the drug today is not perfect. So this is why we continue to modify it. [A]fter ... we worked in Biota in 1995/1996, I worked with Phil Reece ... [and] we developed a couple of other things like the LANI product (interview, 2007).

Peter Cook, Biota's current CEO, gave a very detailed account of how and why this deal with Sankyo came in to play:

After about the second or third flu season, neither GSK nor Roche appeared particularly happy about the size of the seasonal market and a lot of the wisdom at that time was there's no point in looking for second generation products. I guess, in part, these products are okay. If we can't build a market for it, there's a market problem that we've got to address and we won't worry about second-generation products until we have understood the market issues. So I think that was the right way to represent the logic.

That put a whole group of companies, including Sankyo, off and they parked their neuraminidase, long acting neuraminidase programs or second-generation neuraminidase programs. One of the other drugs that ended up a casualty in that period of time was BioCryst's peramivir, for example. So BioCryst, a US company, have got a first generation product called peramivir and they abandoned it, parked it, and ceased spending money on it.

When the World Health Organisation basically said to the world's governments you ought to stockpile these products or you ought to get prepared for an avian influenza outbreak lots of these programs got dusted off. One of them that got dusted off was Sankyo's and then Sankyo realised they were standing slam-bang in the middle of our IP so they approached us. They

said 'We don't think we are' and we took a look at it and said 'We think you are'. At this stage we were already in litigation with GSK and we said 'Okay, why would we get involved in another round of litigious activity in a product sector in which it's the second generation stuff? ... This all seems to be too messy'. So we reached what I would describe as a rational commercial outcome with Sankyo. (interview, 2007)

In terms of combining the research programs, Cook talked about each of the company's contributions and original intellectual property:

What we did is we pooled two products and that's why there are two classes of compounds. One of our originality which is the FluNet stuff and [that is] why it's got a different sounding brand and it is called CS8958. How Sankyo have labelled these products is that their active species is R118958 ... But the pro-drug which is what is tested and what you put into the clinical trial is CS8958 so it's 8958. So this is the active species. CS8958 is the pro-drug and so they're different mechanisms of action. One is a pro-drug that's absorbed into the lung cell, gets turned in the lung cell into the active species and is retained there for a long time. It has to be inhaled because it's got to get to the lung cell. Only the lung cell does the transformation.

FluNet are diamers, they're also inhaled but they are long acting neuraminidase inhibitors direct. They are not pro-drugs so to that extent they've got the same mechanisms of action. That's why that deal got done. That was a practical solution to a commercial interest and we liked the idea because, bear in mind at this stage, we were dealing with Glaxo who isn't promoting [Relenza]. The largest market for neuraminidase inhibitors is Japan and Sankyo and now Daichii Sankyo seem to be a very competent company to be able to further that. So we were delighted that that was the reality of it. (interview, 2007)

As to the status of the project, Cook was able to report that, as of 2007, things were progressing strongly, 'In fact, we've informed the market reasonably recently that Daichii Sankyo have completed phase 1. We will do some complementary phase I in westerners because there will be additional work required for western markets over and above what Sankyo or Daichii Sankyo are doing in the Japanese market but it's only ethnically driven. It's not an issue that the Japanese do crummy clinical trials' (interview, 2007).

A new generation of diagnostic kits was also launched in this period. In 2003,

Biota and Inverness Medical (which had acquired ThermoBiostar) released new influenza rapid diagnostic tests, BioStar<sup>®</sup> OIA<sup>®</sup> FLU and BioStar<sup>®</sup> OIA<sup>®</sup> FLU A/B, in the United States. The kits would be marketed by Inverness Medical as part of their BioStar range (Biota Website). Distributors were appointed; for example, Dong Shin Pharma in Korea, which launched a marketing strategy once the kit was approved by the Korean Food and Drug Administration (Biota Release 9 November, 2004) Cook later offered further explanations as to Dong Shin's role as a partner, 'That was just a distribution agreement for the FLU OIA products' (interview, 2007).

In 2004, Biota ramped up another research program, Respiratory Syncytial Virus (RSV). This in part was possible due to the funding they had been awarded in 2003. Biota was the recipient of a A\$2.7 million research and development START grant to advance the RSV program. Using the same three-dimensional structure-based design technology that was used to develop Relenza, Biota was aiming to capture the value of the work on RSV that had started in the late '90s. At the time, they were collaborating with St Vincent's Institute of Medical Research based in Melbourne. Additionally, Biota were using their laboratory resources that they established in 1999; the Structural Biology laboratory at the Institute (Biota website). This type of virus is the most common cause of lower respiratory disease, bronchiolitis and pneumonia in infants and children worldwide.

Molloy was also eager to explain the protracted nature of the research as well as Biota's success to date:

The RSV program that we just announced going into pre-clinical has been a development for five to seven years in research stage. There is a lot of work that is required before you've got something that is of value. The human rhinovirus program has been going since the late '90s I think, so again seven or eight years, that is a long time. Second generation of flu drugs will be into phase one in the next 12 to 18 months. We've been working on those since the mid to late '90s. So what we are seeing now is the fruit of five to seven years

of research activity, turning into pre-clinical candidates that can go into human trials. It is a pretty good batting average, when you have got three programs out of three going forward. There is a very high attrition rate that would normally work against you getting that kind of deliberate yield on your program so Biota has done exceptionally well. (interview, 2005)

Hence with the rhinovirus project going forward with several key compounds identified showing high levels of activity against the virus, a final decision regarding the lead compound to take forward had yet to be made. Several pharmaceutical companies were also showing interest in the project.

With numerous deal activities taking place with Peter Molloy at the helm, he put forward his point of view on the merits of licensing:

I think the two are alternative ways of capturing value<sup>11</sup>. I don't think that by licensing it you are giving stuff away. You are just choosing to take it forward in a different pathway that is less risky. To say that we are going to take it forward ourselves all the way means that you are going to find somebody to fund a bill that is probably A\$150 million, because that is what it is going to cost you. The whole thing could fall over. Who is going to fund that kind of risk in Australia – I don't know anybody who would do that. So you might get it funded in the US and there are companies that try to do that in the US. With the deep pockets over there it is possible they will do it. In Australia it is almost impossible. So I think you have to be realistic and the realistic game in Australia is to find partners to take something forward, generate a success, bring in a revenue stream from that success and then build from there. We should see this as a 20 to 30 year activity, not as a five year plan to bolt together a whole bunch of stuff and then somehow take it to market. Because real value in this sector includes discovery which involves huge bills to get it to market – huge obstacles, huge regulatory obstacles and an enormous risk. (interview, 2005)

On multiple projects, Biota was gaining traction; in early 2005, another press release was issued by Biota, stating that their shared technology with Sankyo, CS 8958, was going on to further development with another company's delivery device, Aerogen's Aeroneb® Go Micropump nebuliser technology. The development work

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<sup>11</sup> licencing or commercialisation by the firm itself

would be funded by a US\$5.6 million National Institutes of Health (NIH) grant (Biota Press Release, 10 March 2005).

However, this deal was later ceased. Cook discussed the details of it:

... these are products that are used once only for treatment and once weekly for prophylaxis, that problem becomes more acute. Also you can't afford to spend \$5 on the inhaler because what do you do? You spend \$5 on the inhaler, use it once and you throw it away. That's \$5 down the drain. So what we needed to do for all these class of compounds [was] ... we needed a better inhaler or a more user friendly type inhaler [but also] which the cost price was sub a dollar and you need to do that to get that right. We started out with Aerogen and that's the deal that you're referring to. They proved to be inflexible and, in fact, we ended up entering into an arrangement with Hovione in Portugal. ... Because the S8958 is co-owned with Sankyo as is our FluNet compounds, this is a joint development agreement between Biota Sankyo and Hovione. So that's the origins of that. We are not, in fact, there's very few people are capable on the planet of actually devising ... getting the mechanics of an inhaler to work right and there's even fewer know how to make them in volume. It's a very difficult area. It's a bit like fuel injection systems on cars. (interview, 2007)

Late in December 2005, Biota announced a collaboration with another US based company, MedImmune of Maryland. The press release read:

As a company strongly committed to successfully developing and marketing anti-RSV therapeutic products, we are excited to expand our RSV research programs through this collaboration with Biota, said JoAnn Suzich, PhD, MedImmune's Senior Director, Infectious Disease Research. Whereas Synagis is an injectable monoclonal antibody approved for RSV prevention in high-risk paediatric patients, the Biota compounds are orally available drug candidates. If successfully developed, these products could expand the RSV market to other susceptible patient groups such as older children, the elderly and individuals with compromised immune systems.

MedImmune is the ideal partner for our RSV program, said Peter Cook, Biota's Chief Executive Officer. This is a world-class deal that provides affirmation of the commercial value of Biota's respiratory anti-virals. (Biota Press Release, 15 December 2005)

### **The Tortoise and the Hare?**

The story of Relenza's development would not be complete if it did not include its

closet competitor – Oseltamivir, also known as Tamiflu. Like Zanamivir, Oseltamivir is a compound that inhibits the operation of the influenza virus neuraminidase enzyme. Oseltamivir must be converted to its metabolite in the liver to become active. The metabolite of Oseltamivir fixes itself to the neuraminidase site on the influenza virus differently from Zanamivir. This can allow the neuraminidase site to mutate but retain functionality thus enabling an influenza strain to become resistant to Oseltamivir but not Zanamivir. Oseltamivir is generally less effective than Zanamivir against influenza B. Oseltamivir was invented by Gilead, and licensed to Roche in 1996. Despite starting nearly six years later, Roche was able to accelerate the drug's clinical development and catch up to GSK, with the result that Tamiflu was launched in North America only two months after Relenza in late 1999. In many other markets, Tamiflu was launched up to three years after Relenza. (Biota vs. GlaxoSmithKline, Back Ground Document, 2007)

In terms of Tamiflu's ancestral links to Relenza, von Itzstein explained the connection:

... [W]e had started the shikimic acid work ... the same substrate with the same material that Gilead had [used to] deliver the drug [Tamiflu]. They were working on a mimetic so it's the same enzyme and so if you superimposed Relenza with Tamiflu there are two differences or three differences in fact. One is that it's a carboxylic so ... it simply mimics Relenza but they added more hydrophobic character to it. What I was trying to refer to is that when we first started we actually started a line of shikimic acid work that was on the same path to make the exact ... well, not the exact same compound. My first interest in that [research] was to say, can we make a carboxylic, take out the oxygen, and as Gilead did, place the double bond in the same position as the transition state. That was what we wanted to do so that's what we were doing in the first instance. I reckon we would have ended up with Tamiflu or something very close to it and certainly by patent covered it off but we didn't. Because the chemistry at that time was pretty difficult and Biota said, 'This is the time when you've got to deliver something otherwise how are we going to get funding?' So I said, 'Okay, I'm going to adjust my resource. I will dump this approach because it's going to take us a long time to get it.' We would have got there but it was going to take us a long time to work through the chemistry where this is working [now]. So I've got lab books that can demonstrate all of that, ... we were working on shikimic acid exactly, because it was obvious that shikimic acid was a good mimic of sialic acid, the

substrate. (interview, 2007)

As much has been written about Relenza, much could equally be said about Tamiflu and its colourful history. However, there are a few key points to outline: (1) Tamiflu is a very close chemical relative of Relenza, (2) its formula allegedly heralded from the labs of the VCP in Melbourne when a publication was issued by Glaxo in the early to mid 1990s, (3) it was approximately five to six years behind Relenza's development, but was approved by the FDA less than 12 months after Relenza, (4) it was in the form of a tablet, (5) it is now the market leader. Phil Reece recalled some early memories he had about Tamiflu, 'Yes, I think I first became aware of Oseltamivir in about 1996 when they presented it at the – I think it was one of the American Virology conferences and you know our deal with Glaxo was in 1990 so that gives you an indication of the time frames' (interview, 2007). Moreover, Reece speculated as to the involvement of the early scientists in the field of neuraminidase in general, 'I think Graeme [Laver] was – involved early on and had a sort of a purest academic approach and a key promotion which was the idea that you should get this information to the public domain. But, on the other hand, you know, there's rumours and I can't substantiate them, that he had – you know was talking to other parties, you know, about commercialising the other approaches ...' (interview, 2007).

Of both the molecule Oseltamivir and Laver's connection with it, Simpson remembered things this way:

Tamiflu was the only molecule in that entire class that had previously been made. So it was the only molecule we couldn't make. So we had a patent over pretty much all the molecules in that class because none of it had been made before, except Tamiflu. Because it had been made previously. ... [T]he real issue was that this ... was a molecule that we couldn't patent so we had to hope that nobody else picked it up. Of course, Graeme [Laver], who knew the

field pretty well, picked up this molecule wasn't patentable. So [he] charged off to Roche with [another company I think he was involved with] ... BioCryst or something like that. Because he was playing cars in garages with a woman ... [from the] ... University of Birmingham, in Alabama ... Her company was trying to do some crystallography. He said let's get the crystallography because I know a compound that'll work and it's not on Biota's patent list. So they played with that, and then [it] went to some mob in Canada who then lost [it] – [and] sent it [the molecule] on to Roche. But we had no great knowledge of what was going on. (interview, 2007)

Seemingly, this chain of events led to the development pathway for Tamiflu being radically compressed. As Simpson commented, 'Yes, it was. Very short! The problem with being short is that you can be short and take shortcuts or you can be very confident about where you're going and run at it real hard. That's exactly what they did' (interview, 2007). In Peter Simpson's opinion, the one factor that the Tamiflu scientists had working for them was the knowledge intrinsically bound up with Graeme Laver – who after all – had been known as 'the father of neuraminidase'. Simpson said:

At the end [of the day] ... they [BioCryst] had the backing of Laver who knew [about the molecule] – because he was doing the crystallography as well. He knew that the active sites were the same [as Relenza's]. He knew that this was just a ... key in a lock. You stick the key in the lock and that's it. It just jumps it up. He knew that – like in our product work, then this had to work too. It's very different when you go into a clinical study thinking, gee, I wonder if this is going to work, to a situation where you're going into a clinical study and you know, with absolute certainty, that it's going to work (interview, 2007).

Wadley (interview, 2007) also made similar remarks, 'He [Laver] was a hooker. He went to everybody. I mean ... he came to us. He went to ... BioCryst'. Gilead was also lucky in having an eager partner in Roche. In terms of the deals both Gilead and Biota negotiated, many were envious of Gilead's royalty percentage:

I think that the Biota Glaxo deal was very good from my point of view, and the Tamiflu, that deal was even better. Because Gilead got 18 per cent royalty. Glaxo was only 7 per cent royalty. They got a milestone payment at tens of millions of dollars upfront. But for Biota, they got a payment plus support for their research for 10 years. So that's also a very good deal, from my point of view, especially at that stage. The condition applies because the specific

circumstances after the deal made, but the Biota/Glaxo deal - by that time, Glaxo needed some new products. If it was one or two years later, maybe they won't be able to get a deal, because when they have thought about it ... Glaxo merged with Wellcome .... (interview with Wu, 2007)

Additionally Wu (interview, 2007) commented on the timing from Roche's perspective, 'The Roche chemical deal was because Roche got really stuck in their pipeline for about five years or whatever. That's when they needed some new projects and Tamiflu was too early, Roche may not have been interested. The timing was right. When everybody knew Relenza, then they wanted [one as well]'.

Wu explained how Tamiflu was related to Relenza, and quickly and adeptly drawing the chemical structure just like he was signing his name:

The compound here [pointing to the diagram he had drawn], that's what we call the side-chain. In Relenza, we call it the hydrophilic side-chain, and because of the side-chain, you can't take it orally. When you take it orally, it won't go to the body. Then you need to modify this, so [you] chop this off or chop this off, [again pointing to the sheet of paper] remove these things and you get a hydrophobic kind of side-chain, and then you get oral bioavailability. (interview, 2007)

Wu discussed the issues in designing a drug that would cover both strains of influenza, A and B, and said:

I would like to see B be the same as A. This is what happened in [the case of] Relenza. But Glaxo said there's no point, because the oral administration, you would take six grams, six and a half grams, [and this is a high dose,] and B is weaker. So they're not interested in [kind of approach.] So they published it [the profile of the compound we had developed with the hydrophobic side chain]. They published it in 1993. Then Gilead chemists and other people [began to become aware ... of the Relenza story, [which] they called a rational [drug] design. [The Gilead scientists ... looked at it [the Relenza molecule design], and it was patent protected, and then they [Gilead scientists] removed the oxygen, so there was no oxygen. That's what it's all about. So that avoided the patent then. So they just changed one oxygen. And they were lucky with the hydrophobic side-chain [that they] eventually they stuck into the crystal structure. They said, okay, let's get into another pocket. They just got another pocket of neuraminidase, and this is why they inhibited it. They don't stick it in the first place when they made this one test, then they found Flu B was ten fold weaker than compound A. So then they decided to go ahead. Then they

made some nice story [about how they] stuck it into the crystal structure. [But the questions is] why is activity there? Because that's a hydrophobic side-chain, and they said that hydrophobic side-chain is not the previous hydrophilic pocket, but another pocket. Do you know what mean? That's all advertisement and marketing. (interview, 2007)

For some of the scientists involved though, their concerns did not rest with the commercial aspects. Wu said:

... Tamiflu the chemical was of a similar level to the compound that we got in 1992. Tamiflu is not just a metabolite issue. The issue is getting to nerves. That's why we've got suicidal use/cases in now more than 20 cases in Japan. At the end of the day, this one will fail. Believe me. From my theory, because that side-chain creates benefits for oral bioavailability as we did before, but it creates nasty side-effects. Do you know what I mean? Because the phobic character fits into your brain. (interview, 2007)

More recently, the FDA has now insisted that both Tamiflu and Relenza carry warnings on their packaging accordingly although Relenza has shown no evidence to be associated with nerve damage in patients.

When thoughts turn back to Relenza and as to which is the better drug, Relenza or Tamiflu, it is not surprising to hear the scientists (von Itzstein in particular) sing Relenza's praises with a passionate conviction:

I believe it is. I say that in all sincerity because in the average seasonal flu issues that we have right now anybody can take Relenza. The beauty in my view, and I always I guess fall back to this scenario, is that Relenza is a drug that's delivered direct to the site of infection, upper, and it does sink down into the lower respiratory chain whereas Tamiflu has to go through first past metabolism. You think about Sinex and Sinutab - remember that ad, maybe you don't - that they had a timer ticking so one chap would take a snort of Sinex and the other would take a Sinutab and, of course, the guy that took the snort had virtually instant relief. So I always thought if I was a marketer that's the marketing strategy I would have used. (interview, 2007)

Irrespective of the sheer scientific technicalities, Wu spoke about this issue in a philosophical style. He said: 'So in the world, you can't win always, but it all depends

about timing. This is why I always say timing is very important. If you have to make a boat, you're waiting for the tide to come. You have to wait for the right wind direction and then you can fly. But the method is how can you make this one with minimal funding? That's the challenge' (interview, 2007).

**Table 7: The Tortoise and the Hare**

	Relenza Glaxo Clinical Trial Calendar		Tamiflu
	Southern Hemisphere	Northern Hemisphere	Roche Clinical Trial Calendar Northern Hemisphere
1992	w	Lead Discovery	
1993	w		w
1994	w	Phase I	w
1995	w	Phase IIA	w
1996	w	Phase IIB	w
1997	w	Phase III	w Lead Discovery Phase I
1998	w	Phase III	w Phase II Phase III
1999	w	July FDA Approval	w Phase III Oct. FDA Approval

Source: Quirk, (2007b)

### The Good Pill?

The next question naturally arises: what if anything could be done once Biota was aware of the situation. Simpson talked about what vague knowledge the company had surrounding the rumours and what in hindsight he would have done if he had still been the CEO of the company:

We sort of did know that something was going on in the background because American companies can't keep anything out of the public domain. So no great issue there. But, by that stage, I'd gone [resigned]. I would have reacted completely differently to the way Hugh [Niall] reacted. Hugh's reaction was to do nothing. My reaction would have been to be very fearful and to exert even more pressure on Glaxo to stop doing this stupid intra-nasal thing ... put it [Zanamivir] in [a] Ventolin [style] of an inhaler [as a delivery device] ...

[Tamiflu], you probably couldn't use [with] an inhaler because you'd have to use more of it. Then you'd run into all sorts of delivery problems. But it was quite good for oral administration. Although the dose is quite high and [you need] a lot more of it. You could have got away with a lower dose [of Relenza using the Ventolin style inhaler]. Relenza would have had less side effects, that sort of stuff. So common sense tells you that, once it became obvious that this was going on, it should have come into base in the oral area. But they didn't. They kept up with this antiquated lunar landing module as a delivery system.

Gilead had ... set themselves a goal. They were going to fast-track this thing. They had seen the *Nature* article they understood the thing. They had Graeme Laver you know. They were very clever to get an oral drug together. That was really to their credit. Their data their data is pretty much the same as ours from the trial. ... [R]emember they could take risks which we or Glaxo couldn't because they could see what we were doing. We were out in front marginally ... We stuffed it up because we missed a year. That was nothing to do with the FDA for us to miss a year - we just had shit data. You know its one of those things. I think the FDA behaved like they did because the data was [shit]. Where was the benefit, one day? If the trial had been ... [better designed].... (interview, 2007)

Wadley shared his thoughts as to why the Diskhaler device was pushed ahead with, as opposed to some other form of 'oral' delivery mode,

... you see ... at the start, for one reason or another, ... [there was] probably a bit of incompetence and that sort of stuff, [and] they'd lost time and so they didn't want to waste [any more time because] they could [see] Gilead coming down the pipe. They [especially] didn't want to waste time getting [money and approval] for a new inhaler. They had this clunky thing which [they] had paid off. So it was mistake begetting another. You know so you [that was the start of the] spiral down. (interview, 2007)

Many in Biota had speculated that the original Diskhalers had been sourced for another project that was subsequently disbanded. So in fact, Glaxo were merely making the most of existing 'useless' inventory. But Biota had little redress as Wadley explained, 'once we'd given up co-marketing rights what were we going to do? We weren't marketing it.... They were way down the track then with an inhaled drug. How it was delivered was really their thing. No, no we had very little input. [Whatever they chose to deliver the drug in], i.e. whatever was appropriate to get the right amount of

compound into the lungs [was up to Glaxo]' (interview, 2007).

Equally, numerous Biota company people had claimed though that the change in direction was indeed Glaxo's fault, or at least Glaxo's doing, in terms of 'pulling the pin too soon' and giving up on the opportunity to further this line of research with the aim of being able to make an orally available compound. von Itzstein voiced his opinion on this particular aspect:

No, no, no. [They don't] understand the science [some Biota people]. I mean, that's okay ... No. I mean, we had opportunity early on to continue work and, of course, by the way ... it's like saying how much more can we explore in terms of the diversity of compound? What happened with the Glaxo story in my view at least is that they had made various substitutions around the sialic acid derivative, dramatic changes where they were still getting good activity but none were delivering oral bioavailability. It had to be more dramatic than that and I had a different view. As I said, at the time when we had initiated the shikimic acid work, it was there to be had [oral bioavailability] and in terms of development I could see that [it was going to take a long time] ... well, I had to make the judgment call then of whether we continued that work ... or not. We hadn't advanced it to a stage that made sense then. (interview, 2007)

Cook also voiced his opinions on then problems with the Diskhaler, 'The key issue, as far as we're concerned is, that when you're dealing with somebody with a chronic disease you can afford to take a little while, while they get used to using the inhaler. When you're dealing with somebody with an acute disease which is what you've got in influenza, the device needs to be a lot more user friendly. The Diskhaler proved to be a bad compromise in our eyes for Relenza and our case in the court is and GSK knew it and GSK chose to do nothing about it is really where that is' (interview, 2007).

The issue of failing to get Zanamivir in to an oral compound has clearly remained a thorn in Biota's side. Some have speculated that part of the problem was that Glaxo had decided much earlier in the process that they were willing to 'live with' it being delivered intranasally as they had some excess inventory that would be able to

be re-used and remarketed as the Diskhaler. This was important as this was proprietary technology owned by Glaxo, and utilising this technology were serve two purposes; (1) save costs in terms of having to buy in or license other technology and (2) save time, as the device had been pre-approved, and (3) Glaxo already had some expertise with atomised delivery vehicles, i.e. their Ventolin ampoules. Wadley explained:

Then of course you had the diskhaler which had been used for something else, asthma or something and it was a sort of clunky thing so there was nothing sexy about that. And there was a report in the UK where some bloody bunch of geriatrics couldn't work the diskhaler or something. You know there was all this sort of stuff. But time was the essence you see and I guess somebody had made a decision to cut costs because they had this thing [that had] already been on the shelf for five or six years or whatever. [These were] not easy [decisions]. But it's a lesson. (interview, 2007)

However, there was some evidence of a counterbalancing perspective, 'Well ... look I don't know. I suspect I thought the diskhaler was actually quite good and I think that the advantages of getting a minimal amount of compound into the lungs which would act straight away was a real advantage. But nobody ever sold it that way' (interview with Wadley, 2007).

### **GSK is Born and Biota Takes It to Court**

In 2000, Glaxo and SmithKlineBeecham merged. On the 5th May 2004, Biota issued a writ against GSK in Supreme Court of Victoria for breach of contractual and fiduciary duties. As was stated in Biota's summary of claim: 'Biota's agreement with GSK obliges GSK to use its best endeavors to develop and commercialise the product. Biota believes that GSK has been and continues to be in breach of these obligations'. Underpinning this claim was, according to Biota's assertion, the alleged decision by the newly merged company that Relenza would no longer be marketed:

Relenza was launched (i.e. first sales reported) in approximately 20 countries

during the 1999/2000 season, including all the major European markets. In Australia, the United States and the major European markets, Relenza was the only neuraminidase anti-viral treatment on the market for a substantial part of the season or the entire season. At the end of that season, Relenza held an average 48% share of the global antiviral market based on sales value across 44 countries. In the US, Relenza's market share was 40%. In January 2000 Glaxo and SmithKlineBeecham announced their merger plans.

In the 2000/01-year, Relenza's sales and market share plunged. Product sales occurred in only a handful of countries, leaving up to 40 countries where the product was or subsequently became registered, but no sales have been recorded by market audits. During 2000 and 2001, Biota expressed concerns to GSK about the fall in sales and an apparent reduction in support for Relenza. This led to extensive discussions between GSK and Biota during 2002 and 2003. In the later stages of these negotiations, Biota became aware of GSK's plans to cancel product registrations in several countries and its apparent decision not to launch the product in a number of countries. Biota independently obtained industry audit data confirming that there were no sales recorded in a large number of countries where the product was registered, and that after 1999/00 promotion of the product was dramatically cutback across all key countries. Finally, the extent of the damage to Relenza became evident after the 2003 flu seasons, which saw the NAI (neuraminidase inhibitor) market grow to an estimated US\$330 million (A\$500 million) worldwide, but saw Relenza's sales fall to a position of only 3% worldwide, and below 1% in the US. By the end of 2004, Relenza had ceased to be promoted or sold worldwide for the treatment or prevention of influenza.

Certainly, there was a considerable discrepancy in the actual sales of the two products. As part of the deal negotiated in 1990, Biota would receive a royalty income of 7% from all Relenza sales from GSK and 10% in the 'Special Territories' which were Australia, New Zealand, Indonesia and South Africa. This was less than the royalty that Gilead received from Roche for Tamiflu, which was tiered from 14-22% depending on sales. Notwithstanding this difference in royalties, Gilead's revenue from Tamiflu was substantially higher (see Table 8.1).

**Table 8.1: Comparison of Royalties Paid to Biota and Gilead**

	<b>FY04</b>	<b>FY05</b>	<b>FY06</b>
Biota royalties on Relenza (A\$)	0.6m	0.1.2m	17.1m
Gilead royalties on Tamiflu (US\$)	44.6	161.6*	364.6

**Source: Biota and Source: Gilead financial releases**

Notes:

- (1) Included US\$80.7m related to dispute resolution with Roche – comprised of \$18.2 million relating to disputed royalties from 2001 to 2003, \$11.8 million relating to the reimbursement of the cost of goods adjustment for 2004, and \$50.7 million relating to the updating of royalties payable to Gilead for the first nine months of 2005 based on current year royalty rates instead of the prior year's effective royalty rate
- (2) Biota receives a 7% royalty on sales of Relenza by GSK (10% in 'Special Territories in Australia, New Zealand, Indonesia and South Africa. Gilead receives a blended royalty on sales of Tamiflu, tiered from 14 to 22% based on Roche's annual net sales.

According to Biota Holdings, Relenza had three important advantages over Tamiflu:

- (1) Relenza is delivered directly to the site of infection in the lungs. Tamiflu must be converted to its active metabolite in the liver before it can be active in the lung.
- (2) Relenza has fewer side effects than Tamiflu.
- (3) There are strong grounds for expecting less viral resistance to Relenza and resistance has already been reported in the clinic with Tamiflu.

Moreover, these points of difference were supported by articles published in *The Lancet*, *The New England Journal of Medicine* and *Nature*. Clearly, from Biota's point of view, they felt that they had a pharmaceutically superior product but it had obviously not been sold as effectively as Tamiflu according to the differences in sales as noted on the Gilead and Biota Financial data releases.

Undoubtedly, contributing to Biota's stance was the recent actions of their competitor; namely, the case Gilead had brought against Roche, claiming a similar failure of Roche with respect to the marketing of Tamiflu. At the end of 2004, Biota lodged an amended statement of claim following a preliminary discovery phase. In response, GSK filed a defence in May 2005. Biota, though, did not recant from their strong stance, instead it listed the Particulars of Loss and Damages outlining losses in range of A\$308 to A\$430 million. Whilst the two companies stood firm, the Victorian Supreme Court mandated that a mediation process be conducted. The mediation occurred on 31 August 2006, and unsurprisingly the parties did not reach a settlement.

Consequently the court set a trial date for April 2008. Six months later, in the March of 2007, Biota increased their statement of claim for damages and loss to over A\$700 million.

With the court case pending, several people have reflected back to earlier times and in particular, some of the challenges encountered along the way. As it is so easy to do with 20:20 hindsight, opinions have been offered as to why things fell apart as they did. Woods did not believe that these developments meant that the original choice of partner was wrong, ‘I think Glaxo, looking back, [were] ... still the logical people. In my day when we joined up with them, they were the best people available and I thought they had the best goodwill around for us’ (interview, 2007). Reece also agreed with this assessment, saying, ‘It happens all the time and I think Relenza in my opinion suffered from being ... associated with a company that went through two mergers’ (interview, 2007).

Molloy also shared Woods’ point of view, and was confident that this could still be the case going forward: ‘[Glaxo] was absolutely the right partner, it was the right deal, it was a good deal and the product got to market. That is an ideal outcome, which is really the end aim. What went wrong was that Glaxo merged with another company and changed direction. They employed new management; they decided to go in a different direction. See, in the industry, we regard it as a normal course of business. The dispute and the litigation, it just gets resolved and frankly there shouldn’t be any lingering hostilities between Biota and GSK after, we should be able to do partnership deals’ (interview, 2005).

## **Bird Flu**

There was another important development that happened in 2005 – for the first time

Governments around the world began stockpiling Relenza for defense against avian (bird) influenza. This was in response to the outbreaks of bird flu in Southern and Eastern Asia. For the first time since Relenza had been launched, it earned revenue for Biota that was greater than that of the diagnostic tests (Quirk 2007b).

However, throughout the formal notices and projections, external factors further complicated Biota's claim against GSK; there was a transmission of H5N1 bird flu to humans and the world once again caught a glimpse of the potential dangers of flu pandemic. Consequently, governments around the globe started to review their existing policies on stockpiling anti-virals. The short of it was that most developed world governments took a positive stance towards maintaining stocks of neuraminidase inhibitors. In particular, Roche made a strategic decision to escalate production of the neuraminidase inhibitor Tamiflu. A press release from the Roche website read:

Roche's global network for the manufacture of Tamiflu includes several Roche sites and more than 15 external contractors located in 10 different countries around the world. These production partners have been selected primarily on the basis of their ability to produce substantial quantities of intermediates and finished materials in accordance with Roche's quality standards in a relatively short time frame. Ampac Fine Chemicals LLC, API Corporation, Clariant, DSM, FIS, Martek, Novasep/Dynamit Nobel, PHT International, PPG Industries, Sanofi-Aventis, Shaanxi Jiahe Phytochem Co and Siegfried Ltd are amongst these production partners. Roche will have increased its production capacity by the end of 2006 and will then have the capacity to produce up to 400 million treatments of Tamiflu annually, significantly exceeding government orders of 200 million treatments received to date. The expansion will be achieved by a further stepwise scale-up of Roche's production network, both internally and together with third parties. It means a ten fold increase over the capacity in 2004 when the decision was taken to increase production, without any firm pandemic orders in place, in order to meet government's needs for pandemic planning.

Moreover, Roche took the step of donating allotments of drug:

In August 2005 Roche donated a rapid response stockpile of 3 million treatment courses of Tamiflu to be used to contain or slow the spread of a pandemic at its site of origin. This was in addition to 125,000 courses of

therapy donated by Roche in 2004, which was used by the WHO in affected countries in Asia. In January 2006 Roche announced the donation of a further 2 million treatment courses, or 20 million doses, of Tamiflu to the WHO for the establishment of regional stockpiles for use in the management of the current avian influenza strain or in the event of a pandemic. These donations will result in a total of 5,125 million treatment courses being available to the WHO to help people affected by a potential pandemic. In 2005 and 2006 Roche donated 15,000 packs to Turkey and 2400 packs to Romania following the emergence of the H5N1 avian influenza virus in birds in these countries. These donations were particularly made.

As far as Relenza was concerned, Glaxo responded by increasing production over 2005 with four plants producing stock. They anticipated they would be able to supply 15 million courses of treatment in 2006. They also issued additional licences globally sales and distribution and there was a focus on government orders. As at March 2006, they had confirmed stockpile orders for 20 million courses of Relenza from France, Germany, US, Australia and Hong Kong. Unconfirmed orders were said to have been from Germany, Holland, Ireland and the US (Biota Investor and Analyst Presentation, March 2006).

### **Biota Appoints New CEO**

In December 2005, Biota issued a press release saying they had appointed their fifth permanent CEO since the company had begun – Mr Peter Cook. Not only would Cook be the CEO, he would also function as the company's managing director. Cook had a distinguished track record in both health care and engineering, working for organizations such as Orbital Corporation Ltd, F.H. Faulding & Co. Ltd and Ansell Australia in senior management positions. Additionally he had sat on the board of Ansell International from 1991 until 1999. Part of the press release read:

Peter Cook is an experienced Chief Executive with a proven track record in building profitable, innovation-based businesses, both locally and internationally. Peter joins us at a very exciting and important phase in Biota's development. We are seeing renewed interest in Biota's ground breaking

influenza anti-viral drug, Relenza, following worldwide concerns about Avian flu and consequent Government stockpiling of anti-virals. In addition, Biota is steadily progressing its product pipeline and expects to commence human clinical trials for three respiratory antiviral drugs over the next twelve months to two years. Biota will be actively seeking licensing partnership opportunities as these clinical trials achieve appropriate milestones. (Biota Press Release, 2 December 2005)

As from Cook's perspective, he described Biota as he found it upon his joining:

What the company was like, I would characterise it by saying that the company was unfortunately - I'm going to say *reeling*. That's not quite the right word. [The company] ... was about to start to emerge from what had been a period of probably about eight years of disappointment ... I think unfairly incidentally, but disappointment to itself and to its shareholders. I say I think that was an unreasonable posture and the reason is when you've been around as long as I have you realise that all companies that are trying to promote innovation - and the biotech space is a particular subset of that but there's plenty of companies that try to get going on innovative aspects and build a business from that innovation, they all get confronted with the fact that the market and the expectations of management and board run away with themselves because of the innovation.

The one that really does the damage is the run away in the hands of the shareholders because they all forget the timetables and the costs and the risks. They bank all the risks. They call them nothing and they then assume ... the whole world as perfection. It's totally analogous to raising your kids. The day you give birth to them they're geniuses and they're going to sort of run the world and everything else and then the reality is, as they grow up, you've got a normal human being is what you've got.

[W]here did I find the company? I found the company going through the gawky teenage years, to keep going with my analogy. There were bits that were starting to look like it was showing promise of budding adulthood and there were still some juvenile parts to it. That's where we were at. There had been some good gutsy decisions made and one of them was to take some action against GSK for the obvious reasons but for the damage that they'd done to shareholder value in the company. That was a fairly gutsy decision so therefore what I found my role was, which is the corollary of this, what was it like? What we had to do is that we had to first of all get the people who were either remaining in infancy or running away on it, get them into balance so that everybody understood really what stage we were at. We were at a transformational stage in the business. We were at a transformational stage where you could see that over the next year or so we would move into profit and positive cash and what did that mean that we needed to do then in terms of either changing the business and, in fact, getting that information out to the market and making sure that the market, again, didn't lose its way? The market struggles a lot with the biotech sector and there's a particular

communication issue that's a problem. (interview with Cook, 2007)

Moreover, Cook explained in more detail what he meant by his statement that the market struggles with the biotech sector:

We talk about the market as if it's a homogeneous whole and, in fact, it's not. [It is] just like every market, you can segment it out. One of the issues that we had in the business at the time that I came in was that we had a high proportion of day tradership holders and they're intrinsically damaging to the business. Why are they intrinsically damaging? ... [B]ecause it's in their interests to maintain volatility in the share price because that's the game they play on. We had to eliminate that and we had to get that volatility out of the share price and we had to get back into making certain that the sustainable shareholder base in the business, the people who are put off by that volatility, were in fact satisfied that in fact they could invest in Biota with confidence and mindful of the risks as to why they were investing and that there were solid reasons for that. So they were the sorts of issues that we had to confront. (interview, 2007)

Although following his explanation about the nuances of biotech investors, Cook was clear to point out that, in his opinion, all companies, whatever their size, have a similar set of objectives and struggles:

... [T]he primary strategy of all businesses should be to survive. Forget any other issue. There is only one driving strategy in a business at all times and that doesn't matter whether you're BHP Billiton or you're NAB or you're a little tiny biotech with a market cap of \$3 million which was where Biota started out, you have to survive to fight another day because when you're dead nothing's going to happen. That's the point at which you've blown all hope that the shareholder's ever got of making money and getting out of it or making money and a return from it. (interview, 2007)

Cook was quick to praise Biota's early management and directors for the course that they had steered the company on, inferring that this strong foundation was largely responsible for Biota's longevity in the market:

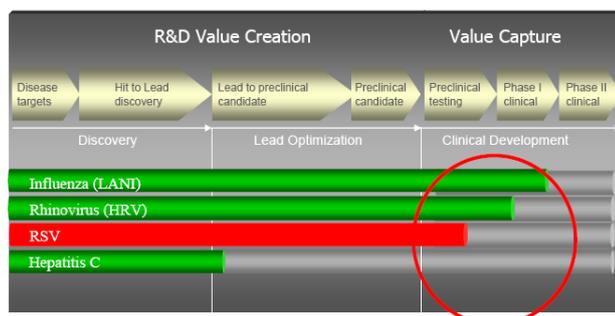
The good bit about Biota was what happened in those formative years, and some people have got a theory on it that says it was essentially because Biota never deviated from actually what it set out to do. It was an anti-viral company. It still is an anti-viral company and it was in small molecules and it never went where the fashion said you might go. It never went where the fast

buck was, that in terms of the core of the business it stuck at delivering what it understood .... (interview, 2007)

Cook indicated that a similar, focused approach was being followed by his management team: ‘... we’ve really only got two products [the LANI and HSV] that we’re actually spending shareholders’ money on and that’s about sticking to the knitting and understanding what you do understand and admitting there’s things you don’t. I think that’s really what’s critical and if I think about it the companies that have survived, they’re not Johnny come latelies. All of those that have got a market cap of around about our size ... [approximately A\$350 million]’ (interview, 2007).

Leading into 2006, Biota’s pipeline looked as follows:

**Figure 9: Biota Pipeline 2006**



**Source: Biota Investor and Analysis Presentation March 2006**

Cook reiterated the importance of trying to balance the costs of managing the project at various stages of development, ‘... the costs are reasonably expensive particularly in the late stage, although everybody thinks they’re in the clinic, they’re actually not. They’re in pre-clinical in that late stage pre-clinical work because that’s where you clock up big money ... Everybody forgets that, in fact, to do appropriate pre-clinical work you’ve been through more than one species of mammal and if those

mammals start to require you to be in primates you spend big bickies and it's a lot more expensive than doing phase Is or phase IIs' (interview, 2007). This means that project management skills are needed within the company, along with a good understanding of the process and an accompanying mindset:

The critical bit is though that when you get into phase I, it means you've done all of that work. Now what you've got to do is you've got to say I've got to project manage big bickies and I've got to make certain that those dollars generate the label claims that we need at some stage in the future. This becomes your shift in terms of what skills you've got to have from drug discovery into all of a sudden being a genius at project management. Things shouldn't fail at phase II and the only issue you should face is am I'm going to get a prophylaxis claim or am I going to get a cure claim or am I going to get a claim that's restricted to over 21 year olds or am I going to get a claim that's down to seven year olds? [The other thing you should consider is] whether there's something screwed up in the PK [pharmacokinetics] in people who are diseased or not. (interview with Cook, 2007)

Cook, naturally linked the relevance of having such skills back to the particular focus of the company, 'Usually in our area - and, again, this is why you play in the space you understand - anti-virals or anti-infectives [as] generally [it is] a lot different from if, for example, you're trying to play around with Alzheimer's Disease or diabetes. We don't understand those disease issues. We don't understand how to do the clinical studies in those. I'm not saying you couldn't learn the skills but it's not what we've cumulatively built. One of the transformations we had to make was to get from drug discovery into project management. That's what we had to do and that's subtle (interview, 2007).

In terms of the nature of the company's diversity of skills and focus of the employees, Cook explained the nature of the transformation that is involved:

You've got to change the structure of your management to a certain extent. Initially we were highly reliant on and highly prized our scientific management team but ... now there is more occurring in the business than just the drug discovery stuff. Whilst everybody ... around here eight years ago would have been [talking about] what structure activity variation we were seeing overnight

from the latest of 700 compounds that we'd synthesised [the conversation] has actually shifted now to more of an issue about – well [other elements of the business], there's extra colour in the conversation. A certain group of people still have that conversation [about the research] but there's another group of people who would be saying so 'we're generating profit, what should we be doing about that?' Another group of people will be having the conversation about how the hell do you design a clinical study to achieve these outcomes when you don't know this and you don't know that and what might be the impact of that and what are the regulators going to say about this? So there's different levels of conversation that occur so the management needs to change, the board needs to change its mindset a little bit and there's a fundamental structure change in the business occurs as you grow up. (interview, 2007)

As part of this process of change, Cook explained the role of using Contract Management Organisations (CMOs):

They're the suppliers of the research activity so they're just part of the supply chain. The project management you've got to do in-house. You don't bring them in-house. You don't buy a clinical trials facility to conduct a clinical trial. You source it but you need competency in-house about what that study should look like and what you can expect out of it. You expect them to bring some expertise to that but you don't let them run it. They're only seeing a particular subset. People who run clinical trial facilities can get really hung up about - I'm going to say that the clinical impact of what they're doing, right, you're not just chasing a clinical impact. You're trying to do a whole bunch of other things. You're trying to make sure that your regulatory package has got enough foundation in it to allow you to do the things that you want. (interview, 2007)

Cook actually explained further what he meant by this, by using an example:

If we were in the influenza space and [as] you know that there are concerns now about Oseltamivir [Tamiflu] and its permeation into the central nervous system through the blood brain barrier, you were likely to get a clinical trial expert who gets all wound up about that, but we may be saying but that's not our market segment. Our market segment is geriatrics because we're interested in trying to get a clinical outcome that's better than vaccinating older people because we know that vaccines only bite about 30% of the time, even if you've got everything else right. You only get antibodies built in 30% of the population. Neuraminidase inhibitors may be a better approach to prophylaxis in that population than a vaccine because of the poor immune systems in those groups of people. That's up to us to form that view and therefore what clinical work we want to undertake. The contract research organisation that might be doing that clinical work or the clinical trials facilitator with that wouldn't know that answer. That's up to you to provide and you've got to make sure that that works all the way through in terms of

your overall project management, the label claim issue at the end of the day. (interview, 2007)

## Licensing Lessons

Molloy felt that whilst Biota may have shown tremendous endurance, as well as skill, with the recent success of their research programs, as a business model for other young biotechs, they were not a good example:

I don't think it [Biota] is an ideal model because I think that the Biota model is seen by many as a rising star that then crashed. I don't think that that is a model that a lot of companies want to follow. I think the reality is that Biota was worth \$700 million and then crashed to \$70 million after Relenza was pulled. Now we are trying to rebuild it, now it is up to \$110/\$120 million, something like that. So we are in the process of rebuilding. But the fundamental business model hasn't changed and that involves discovering drugs, getting them to a stage where you can capture value, deciding carefully about where that stage is going to be based upon your understanding of the market appetite, partnering appetite for each particular type of deal opportunity you have. Then securing the deal and finding a partner that can take it through the more expensive phase of the clinical development, just as GSK did with Relenza, then get it onto the market so that you can generate a royalty stream and become a profitable company from royalties. Then use that royalty stream to fund your transition towards a more integrated pharmaceutical business. (interview with Molloy, 2005)

Clearly one of the key learnings out of the Biota/Glaxo deal was the issue of managing uncertainty. For the companies to follow in Biota's footsteps they would derive benefit from the way the newer deals are structured. Reece explained further:

Normally the agreements are written such that if such an event was to occur [such as a merger or acquisition] then the new entity gets the deal. I mean it changes the dynamics because if you have got a deal which is very simplistic in terms [for example] 20 projects in each company let's say and then they merge and they have got a list of 40 and then they have got to make some decisions. You have got to implement some sort of pruning process to whittle that down and what was not necessarily 20 but let's say 30. Somewhere in between 40 and 20 and then you know the line gets drawn somewhere and various arbitrary criteria – most like arbitrary in my view a lot of the times the NPV calculations are based on assessment of risk from marketing people who

don't necessarily know what the market is going to be for a new therapeutic area. So I mean the biggest risk is rejecting – is throwing things out with the bath water, you know, I think big companies have a tendency to sort of follow the path of least resistance and least risk and so go for the me toos [instead of] something innovative [which] they struggle to put value to ... (interview, 2007)

Cook also commented on the issue of control and how future contracts might be written:

Can you monitor the licensee? You've got to understand that power rests where power rests and you can't fundamentally alter that. That everybody tries to do is to contain the unreasonable wielding of power through authoritarian mechanisms, contractual mechanisms. What I would argue is that the sort of deal which we had with GSK about it was a blanket control which says you will use your best endeavours to develop and market the product, proves to be not particularly helpful during the transformational phases of the program. In other words, if we licensed Zanamivir in 1992 to GSK they got it to market in the year 2000 or '99/2000, in that intervening eight year period we got snippets of information and that's all we got. We were satisfied that, in fact, we had an enforceable position because of this best endeavours clause. In reality what you did is you lost transparency so what I think will happen in future deals is companies such as ourselves will start to put the equivalent on the licensee of what they put on us on our milestone payments. What we'll say is you'll have to deliver this milestone by this date. If not this and this and this happen. You'll have to do this by this date and if not this and this. The trick will be, because it's a developmental program, there's got to be some ability to renegotiate those things. Consulting businesses do this all the time. Consultants start out by saying you've given me the project to do this and I don't know where it's going to go. So what we'll do is we'll deliver the first phase of that study and then we'll nut out what phase II and phase III look like so you can set up a licensing agreement that looks like that.

I don't know whether it is the salient lesson. Ultimately there is no effective control over power and that's a universal statement, social circumstances and everything else. You can put up all of the legal procedures and police forces and everything else but if somebody's armed none of that stops the person pulling the trigger and that's power. All it can possibly do is find and incarcerate that person at the end of the exercise of power because you say you wielded it unreasonably so I think we've got to be realistic. I push back a little bit because [of] the word the salient lesson. A salient lesson is only if you can do something about it and what I'm saying is in absolute terms you can't resist power being wielded. (interview, 2007)

Molloy though took a slightly different perspective:

Handling the partnership [with GSK] over a long period of time, we had a lot of positive and salutary lessons out of that as is evidenced by our lawsuit against GSK. There are a lot of lessons there. It's a company that is taking over the next 12 – 18 months three drugs into human clinical trials so it's really at an advanced stage compared to most companies in Australia, which tend to be at an earlier stage. It's a company that spends 12 to 15 million dollars on each year on R&D, where as the average R&D spend in Australian biotech companies is very modest, spending 1 – 2 million dollars per year. So Biota is a company that is spending very big and hopes to see the results being very substantial. It's also a company that is big in the respect that it has 15,000 shareholders and it has days where its shares traded strongly as Telstra and BHP. So it's certainly a high profile company, much higher profile than it probably deserves given its position, its products and its financials, but good or bad it has a high profile. Given its standing in the industry from a pure financial perspective, probably one of the top 3 or 4 companies and has a market capitalisation of over 100 million dollars and there are very few companies in this sector that have that. (interview, 2005)

Furthermore, Wu expressed another opinion on the issue of control, or rather that of monitoring a licensee:

You can't control [Glaxo]. They lost the monitoring rather than control. You can't control Glaxo. You can monitor them .... You are monitoring their progress, but Glaxo won't listen to you. He [Peter Colman] lost control on the Biota Board and then Biota had their own way. We all try to learn lessons and then make things better later. So from that point of view, Biota made Glaxo pay for the research. That's the way to go. (interview, 2007)

Cook was also clear in explaining the critical importance of licensing to a biotech company:

My test of [whether you have a product/research program of commercial worth] is whether you can license the product. Don't worry [where] in the lifecycle you license the product but if you've licensed the product that gives you two big ticks. Bear in mind that science is a bit of a fickle thing and, in fact, the average shareholder and, indeed, the average employee in this company has no crystal ball about where a drug development program might lead you. What your real vindication is, though, is that if somebody who puts their own money at risk i.e. a licensee, says I can see enough in the science [and that act] ticks the box that says your science is all right, I like the look of that. And secondly, we understand the route to market for this product, because that's what they [the licensee] bring. The licensee ticks off on two critical boxes, (1) is the science okay? We're not saying it's going to happen or it's going to lead to an outcome but is it okay? Yes, it's not smoke and

mirrors, and more to the point, it's not snake oil. And secondly, we can see the route to market. There's a position in the market for a product of this type. So there is two big boxes. We've done that. Really now there's four products in the market or four classes which we've done that one, the diagnostic and any influenza product, Respiratory Syncytial Virus and Hepatitis C. (interview, 2007)

Cook discussed his approach and philosophy to Biota's recent licenses, pointing out that there is much more to licensing than completing the deal:

When you license there's a tendency in the industry to say when I've licensed a product it's all over, sit back and enjoy it. That isn't what happens. What happens is usually an Australian company will license the product reasonably early in the process. The analysts tend to argue that what you're trying to do is to influence the outcome in your favour and that you want to meddle with the processes within - and I'll use the examples of MedImmune or a Boehringer - but in reality you can't do that. But you are interested in what's occurring and you're interested in making certain [that the next phases of development are conducted appropriately] because up to that point in time you're the one that understands your molecule infinitely better than they do [the licensees]. So therefore you want to make certain that the scientific experiments that they undertake are appropriate for your product and that they've got the wisdom of your input on those so you want to remain engaged. We pursue a philosophy and we only license to people who pursue a similar philosophy that says you want to fail early, you want to fail safe. You aren't trying to keep this alive [drug candidate] as long as you can, what you're trying to do is to say this is about efficient use of shareholders' money. So if the product is going to fail you've got to undertake the experiments that fail it right at the front end. [In terms of failing safe I mean] safe in terms of shareholders' money, [you need to] preserve money. [That means being] safe in terms of [the] impact on [patients too] - the earlier you fail the less damage you potentially do to humans on the way through. That's the logic. You can't eliminate the risk but you try in that sense; that is two methods of failing safe. You actually shift from drug discovery [towards] wanting to make certain that, in fact, the right experiments are taken in the right sequence during the rest of the development process. (interview, 2007)

As to the precise nature of the 'licenses' conducted by Biota, Cook elaborated in fine detail, explaining the apparent discrepancy of the terminology used from time to time and some understanding as to why this might be prevalent:

It's one of my little hassles that I have with the Board that they like to use the word collaboration because collaboration implies that we are contributing to it. I happen to like the word license because to me you understand that the

intellectual property of the product has actually changed hands at that point in time. From here on out your relationship changes then because they own the product. It's one of the things, I think, confuses our shareholders immensely because I get shareholders who write to me and say I don't know what the hell you guys are doing but I hope to hell your bloody Relenza lines are flat out making Relenza. You think, you know, this is somebody that's invested in the company and then they tell you they're a long suffering shareholder and you think you haven't even read one annual report that's ever come across your desk or across your table but we contribute to it because the industry does use the word collaboration. To me, who's got a collaboration agreement is Cytopia. That isn't what our relationship is with MedImmune. Our arrangement with MedImmune is, in fact, a licensing agreement.

My Board's view is that a licensing deal would be one in which we outright sold the product - don't worry about the terms of that - that we outright sold the product to another party and we had no further ongoing arrangement with it. That would be a licensing deal. They [the Board] want to insert the word collaboration because under the agreement MedImmune now agree to meet all of the costs associated with our ongoing scientific work. Our Board want to call that collaboration. My view is that's bullshit nomenclature. What it is, is fee for service. We're guns for hire. Why our Board loved the term collaboration because it sounds like you've got this big ongoing relationship with big brother. (interview, 2007)

As far as the process of trying to get licensing off the ground, Cook explained:

... [W]e look at our programs and we say are these licensable and, if so, when is the right time to license them and to whom we should license and we keep that on a continual review. Right now we've only two projects in that issue. There's LANI and there's our rhinovirus program but at various stages if we turn the clock back a couple of years we were doing exactly the same thing around syncytial virus and around hepatitis C as well.

Sometimes you form a view that says, yes, it's licensable but, no, we don't want to do it yet. Sometimes you form a view that, yes, it's licensable but nobody's interested yet because lots of the drugs that we play around with are in what, Jane Ryan - the head of my product development group - wants to call white space. The market isn't interest yet. The timing's not right, yeah. It's not popular. It's not the latest flavour. Other times you get it, that you're really quite early in your development program but the market's hot and, frankly, the very first thing that you've got to do to be able to sell a product is to have a willing buyer. If the market's hot and you've got something then you're bloody silly if you say I'm going to hang around waiting for more money or that I think it will be worth more in the future. How many people do you know that got an offer and then six months later followed the market down? You're stupid if you think that every subsequent buyer that comes into the market didn't know what the first offer was and they're not going to exceed it. It's very rare that you get. ... It's very rare that you get a Dutch

auction running. What we do is that we go through that process and then let's assume that the product's licensable and the market's okay. Then we turn around and we systematically go through this. We say who's in the space and who should be interested? Our object in all of that is to create what Leigh Farrell - the head of business development - calls deal tension. We want to make certain that, in fact, we aren't dealing with a sole bidder. We're interested in generating interest around it so our object is to always end up with two or three term sheets and for us to use those term sheets to try, because we are the minnow .... (interview, 2007)

As to how the deals came about with both Hepatitis C and RSV, Cook suggested:

we farmed it, we created that deal tension and we took what was the best deal for Biota. The best deal, in fact, is a function of multiple things and these are complicated deals. They've actually got to do with what's the upfront, how much of my time are you going to buy, what am I going to contribute to this as the fee for service business, what are the milestones, when do they occur, what's my royalty at the end of the process? So it's a complicated thing so you've got to add up these apples and bananas and somehow or other ... end up with the fruit salad and work out what's the best. (interview, 2007)

## **Recent Deals**

In November of 2006 Biota struck another substantial deal with a large European company, Boehringer Ingelheim (BI). The deal valued US\$102 million, and was centered on a global research collaboration and licensing agreement. Specifically, BI would develop and commercialise Biota's compounds for the treatment of Hepatitis C Virus (HCV) infections. The terms of the deal read as follows:

Under the terms of the agreement, Biota is eligible to receive payments up to US\$102 million based on products achieving certain clinical, regulatory and commercialization milestones, including an initial technology access fee and research support. In addition, Biota would receive royalties on future sales of licensed products marketed by Boehringer Ingelheim. Specific terms of the agreement were not disclosed.

Today's agreement with Boehringer Ingelheim is further validation of Biota's antiviral drug discovery capabilities and our ability to consistently deliver valuable candidates to global pharmaceutical companies' said Peter Cook, Biota's Chief Executive Officer. 'We are delighted to be working with

Boehringer Ingelheim, a premier pharmaceutical company, who is internationally recognised as one of the world leaders in the research and development of antiviral therapeutics.’ Both companies reiterated the importance of this agreement as a joint effort to come one step closer to a potential treatment for HCV infections for which there is a large unmet medical need due to the limited treatment options available. Under the terms of the agreement, Biota is responsible for drug discovery research and Boehringer Ingelheim is responsible for worldwide development of potential compounds and their commercialisation. Biota and Boehringer Ingelheim will be equally represented on the Joint Research Committee to oversee and coordinate the activities of the program. (Biota Press Release, 27 November 2006)

In March 2007, Biota made an announcement concerning the progress of their rhinovirus drug. The HRV drug had successfully completed its phase 1 clinical trial. This included the second stage I, showing human safety and tolerability. The drug was given a code name of BTA798. Consequently the drug was going to progress to stage 2. Peter Cook commented in a Press Release dated 26 March 2007, ‘... a safe and effective treatment of HRV would be a major breakthrough for high risk sufferers of asthma, chronic obstructive pulmonary disease, cystic fibrosis and in patients with compromised immune systems for whom the common cold can trigger events leading to serious illness and hospitalisation.’

In July of 2007, two press releases were issued by Biota: agreements with the VCP and the CSIRO had been reached in relation to finalising the royalties owing on the sales of Relenza. Essentially Biota would pre-pay the royalty rights and the respective institutions would receive a cash payment. A further payment would be triggered should future sales of Relenza meet an agreed target value. Thanks to the stockpiling of governments around the world, in the last quarter of 2007, sales for Relenza reached A\$171.4 million, of which it was estimated that Biota would receive A\$12 million:

This confirms the sustainability of the global stockpiling market on an ongoing

basis. The increase in GSK's sales of Relenza stand in contrast to the decline in Tamiflu sales, as reported by Roche. We expect that GSK will sell its installed capacity over the year. (Biota Press Release, 8 February 2008).

This was significant boost to earnings. (see Table 10 for a full sales history). By the start of 2008, Biota announced that their lead compound from their collaboration agreement with MedImmune had completed Phase 1 clinical trials (Biota Press Release, 8 February 2008).

Additionally, their LANI (CS8958) had completed Phase II enrolments in Japan.

This was a good sign according to Cook:

Early onset of the influenza season in Japan has assisted us in achieving rapid patient enrolment for this study. Enrolment admission to the study was always going to be a critical element in the length of this clinical trial. (Biota Press Release, 11 February 2008)

## **Looking to the Future**

With a market capitalisation value of approximately A\$320 million, Biota are alleging Glaxo owe them damages in the order of over A\$700 million. Recent commentators have intimated that it may be quicker and less painful for GSK to acquire Biota, in a hostile way if need be, to expedite the process and finish the matter once and fall all. Colin Trumble, who had been Biota's first chairman responded to this statement by saying, 'Well, I could never understand why they [Glaxo] didn't do that [buy out or take over Biota] years ago. But evidently, it was against their policy at that time, but you're quite right – that could well be an easy way out for them' (interview, 2007).

Relenza still remains the only Australian drug to be taken all the way from discovery to registration and marketing and is still cited as the world's first example of a viral drug developed from rational drug design techniques; at its height it was approved for sale in 64 countries, including the US, EU and Japan. Although Wen-

Yang Wu gave a delightful summary of his thoughts of what rational drug design really meant:

Some scientists, are very sharp, they've got something - just like Graeme Laver. But you analyse his personality, I can view immediately. He by chance ... got the crystals of neuraminidase. [Wu smiled and whispered again *by chance*]. That's why I said *by chance*. In science, you never talk about that. Dye pigments, when they [were] first developed, the chemist poured the different mixtures down the sink and saw the colour change. Based on that, the German company Bayer was based on these kind of things. But these kind of things was in the 18<sup>th</sup> Century and that was okay. [Before, in the days of research if] I had a great discovery or whatever and I'll say something, but not now. So it's the same thing as Biota's story. Biota happened in the 1980s, but if Biota [was] still selling this kind of story ... [It would have a different ending]. This is why if someone said [Relenza was designed] by totally rational [means then] he himself is not rational. But [even] now [in the new millennium] science is still not rational. Don't be masked by people saying it's rational. No – it's not rational. (interview, 2007)

In terms of achievements, at least three of Biota's key people made mention of the fact that they believed they were most proud of 'making good on their promise of 'delivering' a drug to the market. (interviews with Colman; von Itzstein; Woods, 2007)

Woods put it this way, 'Well, I think probably hanging in there and seeing it through to the point where I really couldn't have contributed much more in an overall sense. It was a pretty trying exercise; there was a lot of pain here and there. [But] I agree with Peter [Colman] that I know also that I couldn't have delivered my part of it without having hung in there and done all the hard yards. I'm pleased that I was able to do that.' (interview, 2007)

And in terms of what if anything he would have done differently, Woods, took a long moment to think and responded:

With hindsight, good hindsight, well let's think. There's a few things I can think of individually, but I think I would've pressed harder with the final research efforts that were made when Glaxo effectively gave up and they didn't try and second template – this is a technical thing – because that's where the game was lost in not having the oral formula. I think the device was appropriate for it being an inhalation thing, but because we didn't have the

technology to have an oral product, it would hang in there and one had to have an inhaled device. I mean, other inhaled devices, I'm sure subsequently approval would have proved better, but at that time, it seemed like a good idea at the time, again. When Glaxo pulled out of the research a bit prematurely – and let's face it, they had spent a lot of money getting to that point. But it really astounds me that they didn't do a bit more and have more skill in developing the oral product, not only Glaxo, but I guess our own people, Mark von Itzstein. It's a case of where do you stop? A huge amount of work was done around the ring with all sorts of things added on, tucked in and taken away, twisted and turned and the various things added. That was the luck of the draw, I suppose, but I think it's a shame that all the technology came from Australia really. It was only that last little thing that was missed and gave the story a little bit of a bizarre ending. But we don't know what the end is. The end never really appears, things go on. ... [The] present story is being driven by stockpiling and things go out of date. You can't use them after their expiry date and by the time a lot of this stuff has to go. (interview, 2007)

Others in the company had their own thoughts about the things which they were most proud of, for example for Richard Wadley it was increasing the shareholding in the company. Woods talked about this too, 'Well, of course, it's become a significant thing because you could always raise money of \$5,000,000 at a time, which had been proved pretty satisfactory in the last few years. Interesting that .... That's a bit of building, what do you call it? Empire building ...' (interview, 2007). Perhaps a final word should be on the tenacity and the longevity of Biota – an achievement perhaps more sterling than all the other accolades, 'In fact, it's really remarkable that it's still got wings to fly with. It's still battling' (interview with Trumble, 2007).

### **The Entrepreneurs and the Scientists**

Like the value of networks within the commercialisation process, it is important to understand the various personalities that come into play in a large-scale project such as developing new human therapeutics. The role of the scientific team is seemingly obvious, but in addition to the scientists there is another vital ingredient; the role of the entrepreneur. In some start-up or spin-out firms (particularly those from universities and

public institutes) the scientist and the entrepreneur can often be one and the same. In Biota's case, with the exception of Alan Woods who had a tertiary education in chemical engineering and lengthy career in business development and commercial aspects of business before his involvement with Biota, there was very little cross over of the roles played by specific individuals. As such, there was a team of scientists and a group of commercial men, including professional Board Members. The net result of having such distinct groups within the business was the need at times to offer and accept the alternate explanations of the other's role and point of view. Practically, this meant getting scientists to understand the business and the entrepreneurs to understand the science. Simpson gave a good account of some of the challenges he encountered, 'Although Colman at the start, didn't want to test the first one that they made. He said 'oh, not comfortable about testing. I think there might be a better compound. What if it doesn't work?' I said 'we'll cover that when we get there. Well, the problem with guys like that is they've spent their entire life doing this. They [will] your scientists - to a certain extent, put it off [doing the test]. The last thing [they] want is 'bugger, it doesn't work' (interview with Simpson, 2007).

It is important also to consider the time frames involved; Biota was a very, very early company in Australia's biotechnology industry. This meant that there was less experience in general terms regarding many of the entrepreneurial functions overall, let alone the scientists demonstrating entrepreneurial activity. Some of those inventors from Biota now consider that they have developed reasonable business skills. Two cases of this are seen with Professors Wu and Andrews:

I'm much more on the entrepreneur side of the fence. I think I'm up to about number 10 company that I've been involved in starting now. I don't intend to stop. I [have] always put my own cash into those sorts of things, to at least whatever degree I can afford. But entrepreneurship is – I don't know what the

best definition of it is, but anyway, that would be my simplest classification, [I am] more than a scientist – these days anyway. (interview with Andrews, 2007)

No. I think I am a scientist, maybe plus a little bit of business minded ... I left Biota because I wanted Australia [to have more than] ... one Biota - Australia needs 10 more successful biotech companies. I think it's the same opinion that Peter Andrews holds. He tried many other initiatives; he tried to establish companies to do things. We are very close from that point of view, because that's life. My whole career I've always made drugs or something to help people. Of course it's for a living, but .... (interview with Wu, 2007)

The challenge is of course for the management of the biotech firm to best assemble their human resources; and to what extent there is an overlap of skill sets is something that most likely needs to be managed on one to one basis. What is still important though is to recruit high profile scientists that are naturally encumbered by their outstanding scientific reputations. Raising capital in the biotech sector is still a difficult business, and quite often this is due investors struggling to understand both the aspects of the science and technology and the associated risks, including the scientific risk as well as the commercial risk. Wen-Yang Wu responded in the affirmative as to the tacit value of the scientific team's reputation, 'Yes, of course [it helps to have an excellent reputation]. Because investors, they don't know anything, [so] ... how can they make the judgment [about the company otherwise]?' (interview with Wu, 2007)

Beyond the everyday 'mum and dad' investors, the institutional and private investors are also partial to projects that have scientific reputation attached to them. Again, Wu (interview, 2007) cited the involvement of the Woods family in terms of its original backing of Biota, 'I think Alan [Woods] really trusted Peter Colman. This is why I think he put the money in....'

Irrespective of the understanding of the science or the foreseeable risks, the fact remains that risk cannot be fully ameliorated. Wu said, 'It's a high risk [the nature of

product development]. A very high risk, because eventually ... you have deal with these kinds of things [science and commercial challenges]. You can't see light at the end of the tunnel' (interview, 2007).

In terms of the teamwork required to get to this outcome, like others such as Nossal, von Itzstein clearly acknowledged the role that his scientific collaborators had played:

That's right so Peter Colman obviously played a role in that as well from the structural point of view. He had a structure there that was still held by patent so nobody had the crystal coordinates at that point in time either for that matter. They weren't published so that was still hot property. I think you need a team that is committed, that is integrated. You don't need people that stick their heads above and say I'm better than the rest. You need to have that sense of collegiality and I think that's exactly what we had and cooperation. I mean, Peter's structural work, without that we couldn't have done what we did. I think the Australia Prize citation reads that beautifully in what Gus Nossal actually put together, 'One without the other couldn't have got anywhere' and that is the hard cold facts, is that we could not have done what we did in getting Relenza to the market. The only regret, of course, is that we didn't get it orally that would compete Tamiflu .... (interview, 2007)

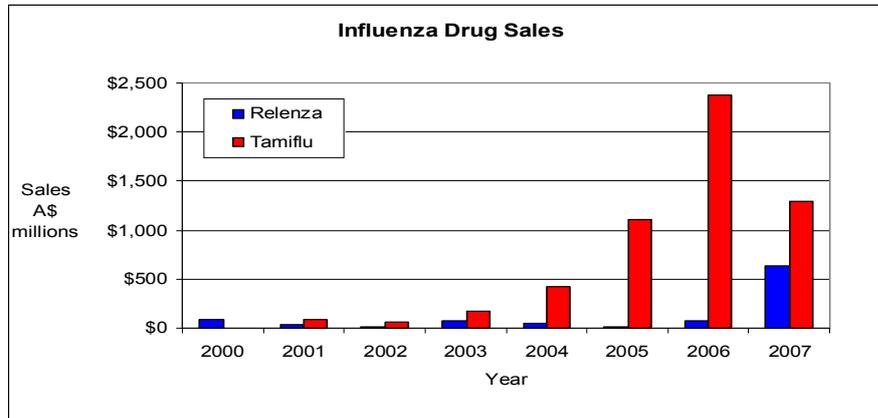
The postscript to the Biota story is difficult to write: for the story is not yet over. The most recent information was released on 8 February 2008, advising shareholders and interested parties as to the state of play for the litigation against GSK. The release said:

... the Victorian Supreme Court has amended the trial timetable for Biota's litigation against GSK as follows: (1) Trial commencement is scheduled to be 4 August 2008 (from 1 July 2008); and (2) Mediation is to occur by 31 July 2008 (from 16 May 2008).

These changes have resulted from extensive Court proceedings between the parties on 31 January, 4 February, 5 February and 7 February 2008, when the Court dealt with outstanding procedural issues. Biota CEO, Peter Cook commented, 'We are pleased that the Court has clarified procedural matters as well as the timetable leading up to mediation and to trial. We believe that the litigation is firmly on track for finalisation. (Biota Press Release, 8 February 2008)

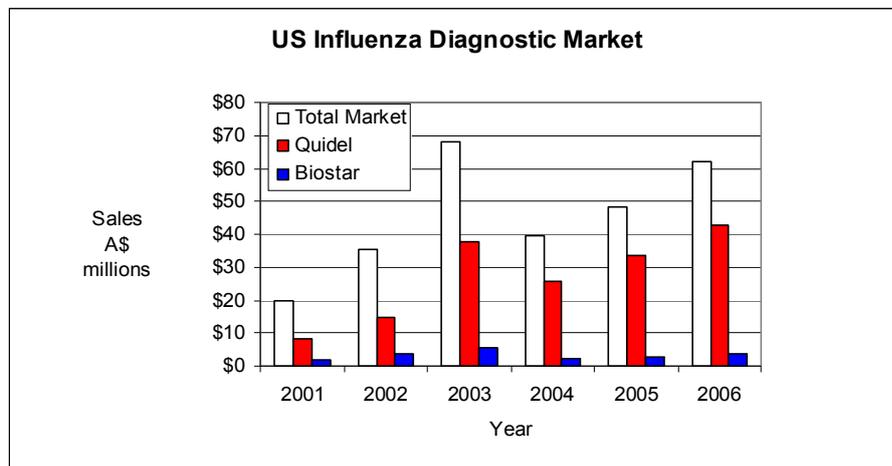
The following tables summarise Biota's position, as well as the market for influenza and Relenza's market share in comparison to Tamiflu.

**Figure 11: Relenza vs. Tamiflu Drug Sales**



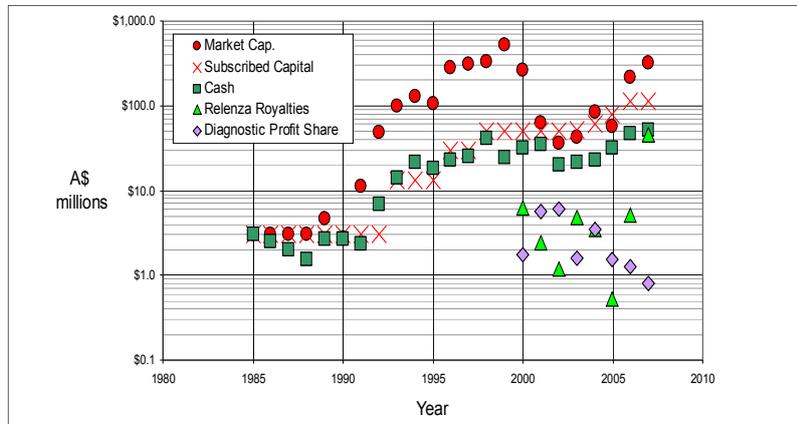
Source: Quirk, (2007b)

**Figure 12: Biostar (Biota collaboration vs Quidel (GSK) Diagnostic Sales**



Source: Quirk, (2007b)

**Figure 13: Financial History of Biota Holdings**



Source: Quirk, (2007b)

**Table 10: Summary of Biota Holdings Position to 2007 – Quirk, 2007b**

Year	Market Cap \$A M	Subscribed Capital	3rd Party Sales	Sales Relenza Royalty	Revenue Diagnostic Profit	Cash	CEO	Development	Projects	Progress	Relenza
1983							1	Biota Pty Ltd	ID phase		
1984											
1985	\$3.0	\$3.0				\$3.0		Biota Holdings	3		
1986	\$3.0	\$3.0				\$2.5				Patents filed for NI	
1987	\$3.0	\$3.0				\$2.0	2				1st active molecule
1988	\$3.0	\$3.0				\$1.6		Takeover bid	2	Vaccine program abandoned	
1989	\$4.6	\$3.0				\$2.7				Glaxo Heads of Agreement	
1990	\$2.8	\$3.0				\$2.7				Glaxo Agreement, Angiogenesis abandoned	
1991	\$11.1	\$3.0				\$2.4			2	Diagnostic Test - Symex US	
1992	\$48.4	\$3.0				\$6.9		CFO appointed		Lead compound Identified	Exploratory development
1993	\$97.7	\$13.0				\$13.9				Symex deal terminated	Phase I
1994	\$129.3	\$13.0				\$21.8		R&D Dir. appoint			Phase IIa
1995	\$107.1	\$13.0				\$18.4	3	Biota Labs est.	3	Insulin program	Phase IIb
1996	\$283.5	\$29.5				\$23.0					
1997	\$305.2	\$29.5				\$24.9			5	Anticancer compound, Diagnostic-Biostar, RSV	Phase III
1998	\$330.1	\$49.5				\$40.6			5	FDA Diagnostic approval	
1999	\$527.4	\$49.5				\$24.7				FDA Relenza approval	Licences
2000	\$259.4	\$49.5	\$95.2	\$6.2	\$1.7	\$32.0	4				Sales
2001	\$63.8	\$49.5	\$57.7	\$2.4	\$5.7	\$35.4		Biota Inc. USA	7		
2002	\$36.1	\$49.5	\$41.0	\$1.2	\$6.1	\$20.3		Takeover bid			
2003	\$41.9	\$52.0	\$75.0	\$4.8	\$1.6	\$21.6					
2004	\$84.3	\$60.4	\$63.7	\$3.5	\$3.5	\$22.9					
2005	\$57.4	\$80.2	\$13.8	\$0.5	\$1.6	\$31.9	5			Biota Inc. closed. Programs moved to Melb.	
2006	\$215.1	\$111.3	\$79.1	\$5.2	\$1.3	\$46.2					
2007	\$323.9	\$111.3	\$641.8	\$44.7	\$0.8	\$52.0					
07Q2	\$171.4			\$12.0							



## **Appendix III**

### **THE CASE OF GROPEP**

#### **The Coming Together of Teams**

Research on growth factors at the Division of Human Nutrition at CSIRO, the Australian Government's scientific and research organisation, commenced in the late 1970s and early 1980s. In those early days, the objectives of the research team, which was led by Dr John Ballard and included Drs Frank Tomas and Geoff Francis as senior scientists, were to obtain sufficient amounts of growth factor preparation that could be used as a treatment for muscle-wasting diseases such as Duchenne muscular dystrophy. John Ballard remarked: '[the] stimulus literally was to ... reverse the wasting of muscular dystrophy, nothing else to do, other than that, ... that was the real stimulus of this work ...' (interview, 2006). Around the same time, scientists in the Department of Biochemistry at the University of Adelaide, including Associate Professors John Wallace, Julian Wells and Rob King, also began work in this area and received a significant national biotechnology grant that enabled them to mechanically synthesise analogues which, at that time, was astronomically expensive to do.

In 1981, collaboration was established between the CSIRO team and their counterparts at the University of Adelaide. Whilst the collaboration was a new venture, the two senior scientists, Wallace and Ballard, were known to each other, having met in the United States many years earlier. Both had excellent scientific reputations, with

John Wallace commenting ‘... I was well aware of his [John Ballard’s] work because of what I was working on in Oxford in 1965/66. I had John’s papers, his PhD publications .... [He] did his PhD at the University of Western Australia and [it was] a spectacular PhD and then he went to the Fells Research Institute in Philadelphia ...’ (interview, 2006). John Ballard also commented on the work he was doing around that time, which involved collaborations with US scholars:

When I went to do my post doc in Philadelphia, I started working with Richard Hansen, and we worked [together] ... in the five years I was in the US but also for 10 years after that [and then] he moved to Case Western Reserve University as Chairman, more or less a little after when I left. Probably five years after I left the US, ... a PhD post-doc of his, Martin Gunn, went to Texas A&M University and Martin and I worked on cell culture, so that’s how we got very much involved with cell culture. (interview, 2006)

### **A Fortuitous Ride Home**

After meeting in 1967 in Atlantic City, both scientists moved to Adelaide within six months of each other; Ballard joined the CSRIO and Wallace took a position with the University as a Queen Elizabeth II Fellow. Closer collaboration was sparked one afternoon when John Ballard placed a call to through asking for a ride home as his car was in the workshop. As the two scientists lived near to each other in the Adelaide Hills, John Wallace gladly gave his friend a lift home. The conversation turned to work and Ballard talked excitedly of an observation he had made in the literature and how he had followed it up with a preliminary experiment. Confirming his friend’s findings, Wallace mentioned what he had read about a researcher in Boston who had observed that milk would cause DNA synthesis in cells in culture. For John Ballard, part of his

interest in purifying IGF1 from milk came about as a result of the fact that in about 1979, the price of foetal calf serum had gone through the roof, and foetal calf serum at that time was still a major source of growth promotents in cultured cells – which without it - the cells would not develop.

According to John Wallace:

[John Ballard] was interested in having a way of controlling not so much DNA synthesis, but protein synthesis and more especially protein degradation, and he was making a big push on what controlled protein degradation at the time and he was looking for something that he could use to control it other than insulin which he knew would work but he didn't feel that was the magic medicine sort of thing. And so anyway I guess my agricultural background came into it then and I said, 'well if it's in milk you can bet your life there's a whole lot more of it in colostrum' and he said 'yeah, you're right' .... (interview, 2006)

In response to Ballard wanting to know where he could get his hands on some colostrum, Wallace told his colleague that he had some friends who lived in the Hills who would probably know how to get it. Through his connections, the two soon had access to some farmers who collected some colostrum for them. As they had expected, the level of protein synthetic stimulant in colostrum was 'off the scale' according to Wallace and they kept 'diluting it so far out to keep it on the scale that it was amazing' (interview, 2006). At that time protein manufacture using recombinant DNA technologies was in its infancy. So, it was a very fortunate finding to be able to use colostrum. Not only was it a very concentrated source of material which was much more convenient for a laboratory to work on than litres of milk, but the farmers were cooperative: and instead of the scientists having to drive up to the Hills every time there was a new calf born, the farmers would put it in their freezers and make a call when

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<sup>1</sup> Insulin-like Growth Factor

they had a couple of gallon cans ready.

These initial conversations led to the founding of the new team that incorporated the cell culture, protein isolations, protein chemistry and animal physiology expertise that was needed for the project. The key strategy was to use muscle cells in culture to screen for growth promoting activities in fractions obtained during the purification of the most abundant growth factors in milk. Once that factor had been purified, it would then either be used in animal trials or would be produced in large amounts by the recombinant DNA techniques that hopefully would be available at the time. In terms of purifying the factors, again serendipity played a role according to Prof. Wallace:

[It was] quite likely during that thawing process there would have been tissue debris there, proteases from the cells and the critical thing was they nicked 3 amino acids off the end terminus of the protein ... we eventually decided [that] was the principal growth factor that was in the milk - which was insulin like growth factor and the fact [was] that [if] you took 3 residues off, one of those 3 [was] a negatively charged residue glutamate and essential for the growth factor to be bound by a binding protein ... so what we effectively did was to make a super active growth factor which was about 10 times more active than the pure IGF molecule. (interview, 2006)

Although the purification and characterisation work took more than 3 years, the outcome was especially worthwhile because it led to the discovery in 1985 of a previously unknown growth factor, des(1-3)IGF-I. The filing of a patent on this factor in 1986 (see Table 1) helped attract substantial grant funding.

**Table 1: GroPep's Patent Achievements**

Patent Title	Application Number	Lodged by	Inventors	Granted in	Commercialised by
Peptide analogues of mammalian insulin-like growth factor-1	PCT/AU86/00246	GroPep	FJ Ballard JC Wallace GL Francis CJ Bagley	Aus USA EU Japan Canada	GroPep
Peptide analogues of IGF-I or IGF-II	PCT/AU88/00485	GroPep	FJ Ballard JC Wallace	Aus USA EU Japan Canada	GroPep
Growth hormone	PCT/AU90/00210	GroPep	JRE Wells	Aus	GroPep

fusion proteins			RM King GL Francis	USA Japan EU Canada	
Growth-promoting agent	PCT/AU91/00303	GroPep	FJ Ballard GL Francis GO Register	Aus USA NZ	GroPep TGR
Method for treating intestinal diseases	PCT/AU91/00031	GroPep	FJ Ballard LC Read	Aus USA Japan	GroPep
Method of administering IGF-1, IGF2, and analogues thereof to birds	PCT/US93/02879	Embrex GroPep US Dept of Agriculture	GL Francis PE Walton FJ Ballard JP McMurtry PV Phelps	S. Africa USA	
Modified Milk Growth Factor	PCT/AU95/00237	GroPep	DA Belford ML Rogers GL Francis GO Register GW Smithers FJ Ballard	Aus USA NZ EU	GroPep TGR
Use of insulin-like growth factor in combination with insulin	PCT/AU95/00422	GroPep Medvet Science	FM Tomas AM Rofe FJ Ballard		PCT Adv Lapsed Date 10/4/97
Method of Selecting Livestock	PCT/AU96/00252	Bunge Meats PRDC GroPep	PC Owens RG Campbell BG Luxford PE Walton		
Method of preventing or treating alimentary tract damage due to chemotherapy or radiation	PCT/AU96/00253	GroPep	LC Read GS Howarth	Aus USA NZ	GroPep TGR
Mammalian milk growth factor	PCT/AU98/00942	GroPep	AJ Dunbar C Goddard DA Belford		
Matrix Binding Factor	PCT/AU00/00292	GroPep	S Humphrys FJ Ballard DA Belford	Aus	
Treatment of damaged connective tissue	PCT/AU01/00503	GroPep	S Humphrys R Woodward		PrimeGro
Compositions and methods for the treatment of skin damage	PCT/AU01/00854	GroPep	TE Rayner AJ Cowin DA Belford		TGR
Bovine factor	PS2820	GroPep			
Treatment of damaged nasal and sinus epithelial tissue	PS2416	GroPep			

**Source: IP Australia Patent Database**

A surprising finding from this first discovery was the realisation that des(1-3)IGF-I was not only a new protein, but the loss of the first three amino acids from the N-terminus of IGF-I increased the potency about 7-8 fold above that of IGF-I. A second

patent filed in 1988 protected this outcome. The result of the CSIRO-University of Adelaide collaboration at this point was, therefore, a couple of bundles of promising IP that needed to be taken to the next stage of development as well as be supported through additional funding.

### **Splicing Proteins and Smashing Bugs**

By 1988, the cross-institutional collaboration had ‘expanded to three different but related research approaches’ (CRC Annual Report 2002 and Historical Review 1991-2002, p. 6), all of which produced further patents. One research stream involved the development of a recombinant DNA method to produce IGF-I and des(1-3)IGF-I in substantial amounts. After a lot of frustration, Julian Wells devised a strategy whereby the coding sequence for the IGF was spliced in an *E.coli* he had engineered to produce pig growth hormone in such a way that a fusion protein of growth hormone and IGF-I was obtained. His team put a cleavage site between the two proteins so that pure IGF-I or des(1-3)IGF-I could be produced. Moreover, by reducing the length of the growth hormone components of the fusion protein, they were able to manufacture an IGF protein with only 13 extra amino acids, which retained the solubility and correct folding properties of IGF-I and also retained the extra potency of des(1-3)IGF-I. This new molecule called LR<sup>3</sup>IGF-I proved extremely useful in mammalian cell culture and remains the backbone of GroPep’s commercial success. A patent covering LR<sup>3</sup>IGF-I and a related growth factor fusion protein was granted in 1990. John Wallace recalled the process they endured and described it as being the brainchild of Julian Wells:

... eventually Julian got the expression system going and because he was making porcine growth hormone and that was ... expressing that brilliantly [producing] huge units - but they wouldn’t express IGF and so Julian had a brainwave one morning riding into work on his bicycle and he came in all excited and he said why don’t we tap the growth factor on the back end of the

growth hormone and sure enough it worked .... (interview, 2006)

Yet, the process was not yet complete as Wallace recalled:

... [it] was silly [because] part of that is in some ways is that you're making 220 amino acids to get 70 at the tail end so Rob King's job then was to tell how many of these 220 amino acids do you need to trick the bugs [bacteria] and it turned out you needed 11 - well 11 was the minimum size that he tried and it worked and then the problem was we really wanted to be able to cut those 11 off cause you don't really want a product with 11 amino acids with porcine growth hormone in there .... (interview, 2006)

Wallace's contribution to the patent continued as he explained what he told his team members: '... well there's a glycine on the end terminus of IGF 1 and if you put in asparagines in front of that you will be able to cleave that with hydroxylamine because that was a bit of chemistry I remembered ...' (interview, 2006).

Geoff Francis, who was one of John Ballard's principal assistants, realised that if he smashed the bugs it was possible to make puree of them and he could spin the inclusion bodies out of the bugs. This was a significant contribution and the research group refined the process of isolating the inclusion bodies efficiently. Such was the team effort involved in this process, they then realised that if they dissolved the inclusion bodies in urea and used any disulphide they would have a linear molecule so they could adjust down the concentrations and they could make it an oxidising environment in which the molecule would fold up. One of Wallace's students, Steve Milner showed that by having the leader peptide on the IGF resulted in nearly a doubling of the efficiency of refolding, meaning it was a good idea to leave it on there while the molecule was refolded; but it could be cut off though if needed, which the team did.

Wallace described how Francis decided to keep a sample of the material before

it was cut off:

... when he assayed it alongside the puree material it was as good if not better and so why are we cutting it off [when] all we're going to do is throw it in a culture medium? ... it [didn't] matter what culture medium it turned out – so he removed the steps in the process so it made the whole thing much more efficient, simpler and cheaper; and it turns out when it's now used in 10,000 litre fermenters in America. The guys over there have told Geoff it's actually better leaving the leader peptide on because it seems to be more resistant to degradation in the process - so it's the lucky model, lucky R3 I think you might call LR<sup>3</sup>! (interview, 2006)

### **A Licence with Genentech and a Single Entity**

The second research stream was galvanised by a licence granted in 1988 to the major US biotechnology company, Genentech, for pharmaceutical applications of des(1-3)IGF-I. The agreement was facilitated by a personal relationship between Dr John Ballard and a manager at Genentech. According to Greg Moss-Smith (interview, 2006), '... I do know there were personal connections in those days and I believe Hugh Niall, who was a senior scientist then I think in Genentech or on his way up the career path there, and John knew each other from earlier days and I think that helped seal the whole exercise ....' Although Dr John Smeaton, the then CEO of Bresa in 1997 later claimed it was his personal link with Hugh Niall that had facilitated the meeting.

Genentech wanted a single entity as a contractual party, instead of multiple institutions relating to the respective inventors and patent holders. As the initial patents had been the result of the work between Ballard and Wallace and their respective research teams at the University of Adelaide and the CSIRO, it seemed as though the only way they could share the intellectual property was accordingly to form a new company. The collaborators therefore decided to set up the company GroPep as Wallace explained:

... forming a company was the only way we could share the IP between

CSIRO and the University because and in fact at that time I was involved with Julian Wells and Bob Symons in a first right of refusal agreement with BresaGen so in actual fact the very first formation was not so much between the University and CSIRO but between BresaTech as it was then. (interview, 2006)

John Ballard also confirmed this:

Genentech signed an agreement with GroPep and no one else, which provided funds to develop this research further ... they were what we usually call upfront payments which are not tied to anything, and an R&D contract, which GroPep then subcontracted to University of Adelaide biochemistry department and to CSIRO, the rest of the money stayed in GroPep as a company and allowed it to get started, and that was about, well I think altogether it was \$1.25 million American dollars at the time, of which about half a million or perhaps a bit less than that stayed in the company and enabled it to pay for its patent costs and all those sorts of things. So that's how it got going. (interview, 2006)

Ballard noted ' ... before the CRC started, that's between 1988 and 1991, GroPep's role [was] what I would describe as a licensing vehicle; it had no staff, other than me, I was employed part time by GroPep and the rest of the time by CSIRO – or strictly I was employed by CSIRO and GroPep paid CSIRO for part of my salary' (interview, 2006). Pushing GroPep forward meant finding a champion and according to his colleague John Wallace '[John Ballard was] a very good scientist as well but he was the driving force behind it. No, I left that to John, he's been a closet businessman since he was at high school. He used to play at the stock market even then' (interview, 2006).

The research funding from Genentech, combined with Australian sources, enabled the Adelaide collaborators to undertake a number of animal studies designed to explore the potential clinical applications of the new growth factors. Genentech also performed research at their end for GroPep; this was a two-way relationship, with Moss-Smith saying:

... But what they [Genentech] did was they went round and used the money they had rather, well, and swept up [to get] everything going ... [even for]

relatively trivial amounts of money as far as they were concerned and in the case of our IGF molecules they did a lot of that work, it was cost based work, did a lot of it themselves but a significant amount of money still flowed back to GroPep and allowed them to actually move on and start developing some of these other things. (interview, 2006)

Frank Tomas at the CSIRO and Leanna Read, initially when she was at the University of Adelaide, and then after she was appointed inaugural Director/CEO of the Child Health Research Institute (CHRI) in 1990, led those animal physiology studies. One surprising outcome of Read's contribution was the discovery that IGF-I and especially the more potent analogues, des(1-3)IGF-I and LR<sup>3</sup>IGF-I, had profound growth effects in all regions of gut. The possibility that one or more of these IGFs could be developed as a therapy for gut diseases led to a fourth patent being filed in 1991. Genentech, however, did not pursue the development of growth factors beyond 1998. As an organisation they decided to move into other areas of research.

### **Cheese Whey Ways in to the Portfolio**

Meanwhile, a third collaborative approach decided to return to sourcing growth factors for dairy products but focusing on cheese whey instead of colostrum:

The Dairy R&D Corporation (DRDC), representing Australia's dairy industry, was keen to identify high value fractions of cheese whey because this by-product of cheese manufacture was produced in vast amounts, yet at the time was more of a potential pollutant than useful product. Within a few months after receiving funding support from DRDC, Geoff Francis ... established a simple and commercially applicable process for isolating a mixture of essentially all the growth factors from whey while removing 99% of other milk proteins. The group's fifth patent filed in 1991 on this invention covered isolation of the material as well as its uses for the treatment of gut diseases, to facilitate wound repair and to support the growth of cells in culture. (CRC Annual Report 2002 and Historical Review 1991-2002, p. 7)

In 1991, The Cooperative Research Centre for Tissue Growth and Repair (CRC) was established with funding from the Australian Government and GroPep as its

commercial arm. Under these new arrangements, both GroPep and the CRC were owned by CSIRO (35.1%), the University of Adelaide (26.4%), The Child Health Research Institute (CHRI) (24.7%) and the Dairy Research and Development Corporation (DRDC) (13.8%). The three collaborations that had underpinned GroPep's formation continued within the institutional framework of the CRC and drew on the resources of the CRC as a whole, with for example up to 100 scientists on average available for research at any one time.

### **The CRC and a Role Change for GroPep**

For GroPep, the establishment of the CRC meant a role change; GroPep had been little more than a trading name that had come about as a result of Genentech's need to have a single firm to negotiate contracts with. But with the beginning of the CRC, GroPep had the central responsibility to maximise commercial opportunities, with aim of the Centre to be financially self-sufficient by 1998 when government funding was due to cease (CRC Annual Report, 1991/92). In the first year of the CRC, GroPep shared premises with a CRC partner, CSIRO; a move that was aimed at encouraging the CRC members to be active in discovery, development and marketing (CRC Annual Report, 1991/2). GroPep slowly began increasing its numbers of part-time employees, and John Ballard oversaw commercialisation efforts. In the first year of the CRC, 0.3 of his position was formally devoted to his role as CEO of GroPep (CRC Annual Report, 1991/2).

GroPep had benefited significantly from their interaction with Genentech and those early years seemed to have provided a solid platform to spring from. Geoff Francis captured the essence of this period in the company's early history when he said:

... I mean basically what we were doing was funded by Genentech, [we] were looking for a number of potential human therapeutic uses for these growth factors or their analogues, and that provided a lot of money into the lab and

enabled us to ... expand our research right across the area of ... insulin like growth factors and also related biological molecules like the binding proteins which became a major focus of John Wallace .... That also provided the support to give us, I guess, enough momentum research-wise to put forward a successful CRC grant application, and that ... was a case of building ... your standing, your capabilities, your credibility and then providing a launching pad for a successful CRC application. (interview, 2006)

## **Marketing Reagents**

In 1991, GroPep began marketing reagents worldwide for sale to other research institutions to use in education and basic research. Initially, a single marketing manager, Paul Walton, was employed in a 0.25 position and the reagents were manufactured through the use of the facilities of the CRC member institutions (CRC Annual Report, 1991/92). Moreover, GroPep marketed the reagents directly, that is they did not use an agent or an intermediary. In 1992, GroPep took over responsibility for manufacturing of reagents from the individual institutions within the CRC, employing two production scientists (CRC Annual Report, 1992/93) and opened a Good Manufacturing Practise (GMP) compliant facility in 1995 (CRC Annual Report, 1994/95). This was the basis for the company's biotechnology reagents. Essentially, GroPep was now able to earn a revenue stream through its small but effective marketing efforts.

Numbers of staff employed by GroPep were still difficult to ascertain precisely, as the nature of the CRC meant there was 'fluidity' between the scientists and their institutions. Geoff Francis recalled those early times when the staff numbers were still small and the resources were modest in terms of sales and marketing: 'by default, yes, I think we all were [marketing people] – well, John and all the principals were involved in it, but I certainly travelled overseas to, you know, sell (interview, 2006)! Also, Francis continued, it was not unusual for them to spend a percentage of their time with GroPep activities and GroPep would pay the corresponding percentage of their wages

back to their original institution, for example, the CSIRO:

[We were selling] ... in the US, and that was while working entirely for CSIRO, which of course, somehow it doesn't fit with CSIRO's charter, but, the reality was that, that's what happened ... eventually of course, a number of us officially became GroPep employees, like 25% of our time- [I guess] ... that would have been about 1995 ... we had to legitimise the relationship so to speak ... In that sense [of the CSIRO being comfortable with the arrangement] I think ... [there] was an uneasy truce ... I mean, we were still in the same building, so all the manufacturing, everything was done out of the CSIRO building. (interview, 2006)

Chris Goddard, who was officially employed at CSIRO from 1994-1996 after having been recruited from Scotland by John Ballard, was also employed on this fractional basis:

GroPep had an arrangement with CSIRO where I think there was 4 or 5 of us where I think GroPep reimbursed CSIRO for half the salary. Yes it was pretty complicated, all the arrangements. My appointment was with CSIRO and I was seconded into the CRC for Tissue Growth and Repair 100%. Now there was a very close relationship between the CRC and GroPep and when I came here ... it became quickly apparent that a lot of the work I would be doing and subsequently did, was underpinning GroPep. (interview, 2006)

**Table 2: GroPep Employees and Sales**

Year	Employees	Sales in \$A
1990/91	No specific information	\$43,000
1991/92	100%: 2, part-time: 5	\$192,000 (expenditure on commercialisation \$101,200; total revenue approx \$400,000)
1992/93	100%: 4, part-time: 6	\$335,000 (expenditure on commercialisation \$85,000; total revenue approx. \$800,000)
1993/94	100%: 4, part-time: 7	\$644,000 (expenditure on commercialisation \$55,000; total revenue approx. \$1.5m)
1994/95	No specific information	\$785,000 (total revenue approx. \$1.6m)
1995/96	100%: 4, part-time: 14	\$941,000 (total revenue \$2.5m)
1996/97	100% GroPep: 7, part-time: 9	\$978,000
1997/98	100% GroPep: 2, part-time: 7	\$2.1 m (exports 90% of sales)
1998/99	100%: 3, part-time: 4	\$2.1 m
1999/00	100%: 2, part-time: 12	\$4.3 m
2000/01	NA	\$5.6 m (total revenue 9.6 m)
2001/02	NA	

**Source: CRC Annual Reports 1991/92-1997-98, GroPep Prospectus**

Facilitating this set-up was the fact that the CSIRO scientists were not

hamstrung by any teaching or academic requirements borne by their university colleagues. Wallace said ‘John handled all that. One of the beauties of the job he had in CSIRO [was] he had a lot of flexibility in the sense he could go when the moment was right and jump on a plane and go to the States and do it, you can’t do that if you’re an academic’ (interview, 2006). This arrangement continued in the early years of the CRC and slowly over a period, GroPep acquired full time staff; for example, in 1997, GroPep still only had a small, dedicated team of approximately 20 employees.

GroPep had acknowledged the importance of marketing and employed managers to help with their products. One of the product managers working for them from 1995-96, Deborah Uzubalis spoke of the significance of the international customers, ‘... 85% of the customers [were] overseas because there’s such a small customer base here in Australia. At that point in time we did have some manufacturing agreements with the FDA [Food and Drug Administration]’ (interview, 2006). She also recalled how some of the initial marketing efforts got off the ground:

When I first started [at GroPep] ... UCLA asked me to do a quote on IGF for them [and] I was pointed to a filing cabinet [that was] in numerical order and it has 600 files in it and I looked at it and [thought] this is ridiculous! It wasn’t even under client name, it was under numerical [order] so you had to rifle through that many. (interview, 2006)

Another part of Uzubalis’s job in the early days was to follow up on the institutions that were using GroPep’s reagents, ‘... researchers were using a lot of insulin like growth factors [at UCLA] so part of my job was to look at which way the research was going ...’ (interview, 2006).

One of the most helpful developments to the reagents business was the construction of a website allowing electronic ordering. Uzubalis described the process of how it came about:

It was primarily because there were a lot of requests coming through for certificate of analysis and certain basic methodology ... you'd get an email and if they [the customer] sent it sometime on the Friday or something like that it was just that the turnaround time was too long [due to the differences in time zones] so my whole idea was if you could actually provide them with the majority of that information on the internet [that would help]. [They also ran a few marketing promotions] ... when we first launched and [customers were] placing orders ... we had ... basically a random discount so to get people used to ordering on line that you placed your order and you'd automatically get this message saying you've received 20% off your order to try and encourage people using the ordering system. (interview, 2006)

### **HyClone Labs is Appointed a Distributor**

As the business began to grow, HyClone Labs in the United States was appointed the distributor of the reagents via a marketing agreement that lasted from 1992 until 1995. With HyClone Labs having exclusive access to market the reagents outside of Australia, in 1993 CSL Ltd signed a marketing agreement for distribution rights within Australia. GroPep and CSL were well known to each other through the small but tight scientific networks in Australia and the partnership flourished. When CSL Ltd bought JRH Biosciences in the USA and formed them as a division of the company in 1995, the marketing agreement was transferred from HyClone to JRH. This would be a worldwide agreement and collaboration and was signed until the year 2000.

The principals offered good support to their distributors, with Francis describing their early involvement, 'we used to accompany those field representatives [of our distributors] with customers and potential customers to give, you know, scientific support for ... selling ... [we were]...product specialists essentially ... (interview, 2006). Another R&D collaboration and marketing agreement, signed in 1995 and lasting until 1999, was notable for the fact that it entailed GroPep acting as the importer, distributor and marketer of growth factor diagnostic kits in Australia for

Diagnostic Systems (USA).

This period of building up the markets for reagents was not accidental, but deliberate and farsighted. It seemed to John Wallace that ‘... John [Ballard] was very well aware of the long lead time to get a pharmaceutical product and he said to hell with that, let’s get something out there that we can sell right away’ (interview, 2006).

Although not joining the company until 1997, Greg Moss-Smith was also able to recall those early years of sales and marketing:

Now GroPep, and this is again a John Ballard visionary manoeuvre, understanding the Australian setting as he did, [realised] in those days, there really was no venture capital – there still isn’t really in my opinion for biotech – and he knew to grow the company you needed products. The only way you were going to make that company [GroPep] grow in a sustainable way was to keep finding things to sell and products were a lot easier to find than inventions ... So the very first thing that was started up [was] the reagent business – and they didn’t make any of those, they [were] all made in the CRC or by other research collaborators – [and] what GroPep did was market them and because we had some molecules in those days that nobody else actually had, they had a capacity to be able to produce recombinant IGFs, in fact nobody’s ever matched that since! ... So at that time GroPep was one of the few sources in the world for this and had excellent contacts in the R&D community in that field through John’s [Ballard] work and in fact the whole team at that stage was very much focused around growth factors, particularly the IGFs, and there was a dozen people tied up with GroPep through its affiliations all working in that field, all publishing in that field, all well connected in that field and so it was a doddle to launch products, those first few products, and they were making like \$½ million in revenues within 2 years which for a little company doing nothing, you know, that’s good and the margins were damn near 100% margin because it was free. So, it was very good and that’s what got it going. (interview, 2006)

Importantly, as Greg Moss-Smith pointed out, GroPep had the benefit of still being supported in kind by the original institutions – this clearly seemed to offer a steady pathway for their business development, as their resources were not heavily drained. Moreover, as Greg Moss-Smith also commented, it gave them access to the scientific inventions being made in the CRC:

GroPep got all their rights from the CRC and GroPep basically agreed to a

invest a very high proportion of its earnings back into the CRC but it also took a share of everything going through so if you like at that point they orchestrated themselves into a position where they were getting most intellectual property benefits without actually bearing much of the cost ... and building up this arsenal of intellectual property and experience. (interview, 2006)

Overall, this period could be labelled as one of an emphasis on new product development: growth factors outside of the IGF/EGF families were focused on with the aim of creating replacements for foetal bovine serum in cell culture products. Expenditure on this in-house R&D expanded three-fold during the 1994-1995 financial year, and exceeded A\$250,000 (CRC Annual Report, 1994-1995).

### **Cell Culture Business**

Five years after GroPep registered their patent, they began to produce their new recombinant variant of IGF-I (LONG<sup>TM</sup>R<sup>3</sup>IGF-I). This product was marketed as a replacement for insulin in cell culture media, and formed the basis of the company's cell culture business. Used by pharmaceutical and biotechnology companies, the product would supplement culture media supporting the growth and maintenance of cells that were engineered to produce therapeutics or vaccines. In 1995, a marketing and distribution agreement was struck with CSL and JRH Biosciences. According to Moss-Smith, the motives for the agreements were as follows, 'as it happened because our [reagent] distributor at that time – a company called HyClone – we weren't happy with them so we were pulling that back ... but by that time ... the product had a little bit of a reputation by then and JRH were interested and I guess that's how they [GroPep] got going' (interview, 2006). This strategic alliance supported the development of new reagents for pharmaceutical cell culture and provided for CSL, via JRH, to exclusively distribute GroPep's pharmaceutical cell culture products.

From 1993 until 2000, this segment of the business underwent rapid expansion and was considered to be the 'core business' for the company, especially in a revenue earning sense. As it was a technology required for the manufacture of many new-generation drugs, industry commentators estimated the market potential was US\$500 million and this would require the development of patented growth factors which would be used by pharmaceutical companies to reduce the need for serum, hormones and other animal derived products that were in use at that time. In 1998, the US Food and Drug Administration (FDA) approved the sale of a new product called Enbrel<sup>®</sup> for rheumatoid arthritis (RA). This drug, globally co-developed by Immunex and American Home Products Corporation but subsequently sold to Amgen for US\$16 billion, is a protein-based drug comprised of human amino acid sequences. Enbrel is thought to interfere specifically with the inflammatory process in RA, which may be driven by Tissue Necrosing Factor (TNF) in patients with RA. Whilst the specifics of the manufacturing process for Enbrel were considered Commercial in Confidence, much was reported in the popular press, for example the *Australian Financial Review*, identified the inclusion of LR<sup>3</sup> in Enbrel's composition; *Business Review Weekly's* Beth Quinlivan reported GroPep's role in Enbrel's manufacture in her article dated 6 September 2001; *The Australian*, 2 February 2002 published an article containing, 'A gene discovered by Wyeth subsidiary Immunex which produces the TNF inhibitor is transferred into Chinese Hampster cell lines. Combined with a special growth factor manufactured by Adelaide company GroPep, it is turned into a miniature Enbrel factory'; as did David Blake from *Shares Magazine* in his article 2 March 2002, 'GroPep's LR3 product is used to make Enbrel. So, when these new facilities are operating, demand for LR3 will increase and the logic of GroPep's acquisition will become visible. LR3 is also incorporated in the manufacture of two other FDA-

approved drugs.’ Investment houses such as Taylor Collison, also made statements regarding GroPep’s role in Enbrel’s manufacture. Colleagues further commented on its possible inclusion, with Prof Wallace remarking:

there were some very fortunate occurrences. Geoff Francis was at a meeting and he happened to share a lunch table with a guy from ... [an American biotech company]. Now [this company] had been around the traps for quite a while trying to get [their] molecule approved and they had to withdraw it because of [some] things like that and it was only when they got talking over lunch that the guy said he had a technical problem and blah, blah, blah and Geoff said ‘oh have you thought of trying this’ and he said ‘no, never heard of it’ and he said ‘well I’ll send you some’ ... and the rest is history. (interview, 2006)

### **Another Collaboration: Cephalon**

Also, during that time, another R&D collaboration and licensing agreement was entered into with Cephalon for the pharmaceutical applications of growth factor analogues.

Moss-Smith commented further about their dealing with Cephalon:

because they had connected the company, this little shell company, to this battery of scientists through the CRC, it gave them a kind of international prestige or presence which they were then able to leverage off and they’ve gone out and built relationships with other companies like Cephalon and done R&D collaborative research with Cephalon and we had a program doing molecule development for Cephalon and things like this and again an awful lot of that actually didn’t come I would say from what I’d call orchestrated business development activity; it came from very much the connections between scientists [for example, Leanna Read from CHRI and John Farah from Cephalon] and who they’d worked with and who they knew.(interview, 2006)

However, Goddard (interview, 2006), who ran the cell culture business from 1996 to 2002, made the point that the deal with Cephalon ultimately did not lead to a commercial payoff: ‘apart from R&D payments, it did not make one cent’.

### **Why Growth Factors and the Agreements**

Research continued with the CRC and involved linkages with domestic and

international firms leading to a range of R&D and co-development. From 1994 through to the late 1990s, GroPep and the CRC were very active exploring all possible applications for their technology. Many of the agreements at this time involved applications for the collaborators' whey growth factors. An R&D agreement was established with Mead Johnson USA, looking at whey growth factor applications in gut disease and polytrauma. However, by 1995 Mead Johnson changed corporate direction with their research when they realised that the application would be more pharmaceutical than nutritional, which was their core business. Yet, they helped GroPep in their search to find a new partner, who would eventually be Nestlé. Other applications of whey growth factors were the treatment of inflammatory bowel diseases, a collaboration with Northfield Labs Australia; a collaboration with FH Faulding (Australia) and Innovative Technologies, UK, for the incorporation of whey growth factor mixtures into wound dressings; and a manufacturing and marketing agreement involving Bonlac Foods, the Dairy Research Laboratory and the CSIRO relating to whey-derived growth factor preparations. The manufacturing technologies group took processes for extractions of growth factors in cheese whey from the lab to pilot plant stage. This was achieved through key improvements to the ion exchange and ultrafiltrations steps. Second generation whey growth factor products were also developed for applications in wound repair and gut disease.

The deal with Bonlac resulted in a marketing office being set up in Kansas City, where JRH Biosciences was headquartered, in July 1995. The aim was to provide a marketing strategy, training and sales support for JRH. When the sole manager heading up the office, Paul Walton, resigned in April 1996, the office was discontinued and technical and marketing support was then offered out of Adelaide. This was partly due to the personal preferences of Walton's replacement, Chris Goddard:

with hindsight, they [the Board] should have sent me to the US, because I had a young family and I would have gone but one of the conditions I would have put on was that I was coming back here because I didn't want to live in the US ... I think the board were nervous that they might lose another one [staff member] and there was still an issue of getting qualified people here. ... I then ran that whole [cell culture] business between 1996 and 2002. (interview, 2006)

Also around that time Smith & Nephew UK, considered world leaders in wound care, signed a license agreement and an R&D collaboration looking into whey growth factors for the treatment of chronic wounds. Greg Moss-Smith regarded this deal as especially significant in the company's development:

I think [it was] the first case where the company had actually built a relationship on a business-only basis if you like, from scratch, and gone out and found somebody who wanted this and we were kind of lucky in some respects because Smith & Nephew had never done anything quite like that before themselves, which was interesting, and they were amenable to it so it meant that we probably got, I know that we got, a more cursory treatment from them, their assessment of what we were doing and why we were doing it and their own understanding of what was going to be required to take the whole thing forward, what I would say would not be 1/10 of what we now expect when we go into a drug company. (interview, 2006)

Then in 1998, Nestlé of Switzerland and GroPep began an R&D collaboration and licence agreement to co-develop whey-derived growth factors for nutritional and gut pharmaceutical applications that would last until 2002. The agreement initially covered an R&D program of pre-clinical trials but included the right for Nestlé to enter into a licence for the eventual marketing of nutritional, nutraceutical or certain oral pharmaceutical compositions covered by GroPep's milk growth factor intellectual property. Mead Johnson had served as the catalyst in terms of finding a new partner in Nestlé following from Mead Johnson's decision to change direction with John Ballard confirming '...[we had been working with Mead Johnson and] it got to the stage that the applications were more pharmaceutical rather than nutritional or nutraceutical and

the BristolMyersSquibb group became involved and they weren't very interested and lots of people were very helpful in trying to get us associated with another entity, you know, really, and that ended up being Nestlé' (interview, 2006).

Goddard summarises the process of deal making in this period as follows:

[I]f you go and have a meeting with someone, [who is] a very busy person, you're trying to talk to them on a technical basis but what you're actually hoping they do is say yes, I'll try that stuff and if I like it I'll buy it, its real simple. And the *quid pro quo* for that is you don't have 3 hours to talk about every single little detail of this, you've just got to get your 3 or 4 points over in a short meeting, hope they like it, do the follow up ... and then go back later when they've actually had a look at it then you can have the next in-depth, then the next in-depth. It's about building relationships and there wasn't anybody else who was going to be able to do that. There was probably, I don't know, at that time maybe 20 ... 25 people in the company, most of whom have never been outside Australia, who had no idea how to sell or make contact, who say they liked international travel but when you said well alright, go - they went oh no, no I really don't want to do that [International business and the associated travelling] - well no it's not glamorous, [but] when you get used to it, its quite good and particularly if you go for a successful period, you feel great but its tiring. (interview, 2006)

Basic research continued to be a high priority over the three-year period of 1994 to 1997, with more joint patents being filed. This included applications for animal health, leading to a co-development agreement and a jointly filed patent with Bunge Meat Industries Australia. MedVet Sciences, a local company, and GroPep co-developed IP covering the synergistic effects of growth factors and insulin and GroPep and Embrex (USA) co-developed a patent on growth factor administration to poultry *in ovo*. As well as this basic research, GroPep negotiated an agreement with Alizyme (UK) that contracted the research and development of Alizyme's proprietary technologies for the treatment of gut disease to the Child Health Research Institute.

### **A Shift to a Project Pipeline Structure and the CRC is Renewed**

However, with the renewal of the CRC funding from July 1997, the Governing Board

spent time throughout the preceding year to ensure that existing cooperative linkages would be best utilised. For example, the CRC had originally adopted a strategy in which research funds were distributed to partners in proportion to their inputs. This allowed resources to be allocated on a contribution basis and dismissed the need for the Centre to make prospective judgements regarding the merits of various projects. Mostly, the system served the CRC well. However, a shift in strategy supported a change to a project pipeline structure. The concept was for a series of research projects that increased commercial relevance and escalated the need for integrated teamwork. Two managers from Cephalon had been part of the impetus for this reorganisation. The process included: discovery, innovation, development and commercially established projects. These projects then sat within the newly re-organised Research Streams, which now totalled five (CRC Annual Report, 1996-1997).

With the success of the CRC to date, the Australian Government renewed the CRC's grant in 1997 for a further seven years. GroPep and Flinders University joined the original partners of the CRC, and GroPep gained exclusive rights to commercialise intellectual property developed by staff in the CRC. In 1997, they advertised for a business development manager, with Greg-Moss-Smith coming on board to fill this role, although Dr Ballard did not become managing director on a full-time basis until 1999.

When asked to think back over those initial deals and the significant contributing factors, Greg Moss-Smith said:

Absolutely, there's no question [that a lot of the success was based on networks and friendships] and in fact the two significant deals that were done, well [I] think the three significant events that had happened to GroPep by that stage - the funding with Genentech had come from personal connections between John and a mate, the funding from Cephalon came from a personal connection between Leanna Read and John Farah and the formation of the CRC was very much a question of a bunch of friends forming together, doing

collaborative R&D for a long time and so those things were very much down to personal relationships. Now some of these were more commercial than others so for example, the movement into Bonlac was very much on a commercial basis, Mead Johnson likewise, I could go into them further, but the point was that personal relationships had been a large part of putting the foundations under the company and lifting to that stage .... (interview, 2006)

Moss-Smith however, commented on one of the limitations as he saw it of the CRC. In his opinion he felt the company had been deluged with a supply of potentially commercially viable products arising from excellent science, but there had been little fine attention to detail regarding much of it:

There was a sort of battery of stuff that was believed to have commercial potential but had never been looked at from a commercial point of view; it had all been coming out really much from just there's good science - here we are making discoveries, and in areas where there are needs these should be valuable but nobody had really stopped to look at what things were valuable and why in any kind of systematic way. (interview, 2006)

Goddard added his thoughts on the structure of GroPep in those earlier years:

The best way I can describe it, you know, it was a nice neat little company which was servicing the CRC. ... [S]ome aspects were quite professional but a lot of it was amateurish. The thing I found difficult and found difficult for a long, long period of time until I joined [GroPep] full time, these split roles don't work for me, they just don't work. So you had a responsibility in the CRC and you had a responsibility in GroPep, there were blurred edges and conflicting things all the time. [In the CRC reports] you'll see that there are big sections on GroPep ... and in GroPep of course there are sections on the CRC, the blurred edges. So there wasn't a focus and in fact as the company developed, it lost even more focus. (interview, 2006)

This lack of focus resulted in a general lack of direction. Goddard (interview, 2006) said, 'There was far too much going on ... far too many projects, there was zero market research, Zero! So projects would get started because ... there was a great one, there was a tendonitis project. Well it ended up as a prime growth product but you

know, because a couple of the Adelaide Crows had got knee problems it was ‘oh there must be a market for this’. It was ridiculous.’

In spite of these challenges though, a highlight for 1997/1998 period was the staggering growth in sales revenue, up to more than A\$2.1 million. Contributing to this increase no doubt was the fact that the first new drug manufactured using this growth factor, Enbrel, was expected to be approved in the US by the FDA in October 1998. Additionally, 12 new products based on the Centre’s research were released by GroPep for sale and for the first time a product catalogue was prepared and distributed to customers worldwide.

### **The Drug Development Business**

A major strategic development occurred in 1998 when the Company established its pharmaceutical drug development business to develop pharmaceutical products through Phase I and II clinical trials. This new division of the firm had come about through its biotechnology reagents business, through which GroPep had access to approximately 7000 researchers globally that were working with tissue growth factors. Seeing this opportunity, GroPep realised this would be a valuable source to in-licence potential candidate drugs. They had also developed a portfolio of products that extended from pre-clinical evaluation through to Phase I and Phase II clinical trials. They were aiming to have five to six products in clinical trials at any one time to maximise the possibility of success whilst keeping trial expenses manageable. This strategy distinguished GroPep from companies that typically developed only one or two drugs and were critically dependent on their clinical success. On the successful completion of the Phase II clinical trials, GroPep intended to on-licence the drug candidates to multinational

pharmaceutical companies for subsequent Phase III clinical trials, regulatory approval and worldwide marketing.

With the drug development business taking shape and gaining good momentum from 1998 onwards and leading up to the year 2000, GroPep had eight products at various stages of development: from lead compounds to pre-clinical testing through to Phase 1 development (see Table 4). Two of these products involved collaborations with other institutions. One of these was with the domestically based International Diabetes Institute. The development of the other drug candidate, PV704, was based on the intellectual property resulting from research into osteosclerosis with growth factors conducted by the Mayo Clinic in the USA. When a surprising finding regarding osteoporosis presented itself, Mayo Medical Ventures and GroPep agreed to co-develop this intellectual property owned by the Mayo. At that time, GroPep had one of their senior scientists working at the Mayo Clinic. The Mayo Clinic had a patent pending on the discovery and GroPep had already developed manufacturing processes for recombinant IGF and IGF-BP. The Mayo scientists began both *in vitro* and *in vivo* bone experimentation but the clinical trials could not commence until pre-clinical studies were completed and IGF and IGF-BP could be manufactured under GMP conditions.

Goddard recalled that this particular deal had come about through personal relationships held between staff at GroPep and the Mayo Clinic. However, he also commented that *prima facie*, the deal seemed lucrative, but a closer inspection of the company's financial statements would most likely have told a different story, 'there was a hell of a lot of money that GroPep spent on R&D on the project. So you look at the [deal] from a profit and loss basis, and they would break even, or they would no more than break-even' (interview, 2006).

GMP was achieved, according to GroPep's 2000 Prospectus document in

February of the same year, with two facilities being opened. The GroPep-Mayo collaboration covered the PV704 program and aimed to co-develop IGF and IGF-BP through pre-clinical trials in order to test the hypothesis that a combination therapy for osteoporosis could be beneficial. The trial work continued until 2002 and negotiations with several major multinational pharmaceutical companies resulted in two companies committing considerable resources to evaluating PV704 in sophisticated animal models. But based on inconclusive results from these studies GroPep, decided to cease investment. However, the Mayo Clinic pursued further development of the technology, and GroPep retained beneficial rights to the relevant patents if the Mayo went on to make progress. According to Greg Moss-Smith, GroPep's reputation had helped facilitate this collaboration, 'again [this deal] came out of the prominence of the CRC and [the reputation of] some of the GroPep staff, particularly John [Ballard], in the area of IGF-1 (interview, 2006).

### **GroPep Finds a Company - PrimeGRO**

GroPep became a founding shareholder in 1999 of PrimeGRO™ Ltd, a company established to commercialise agricultural and veterinary uses of growth factor technology. A correlation was found between blood levels of components of the IGF axis in pigs and the growth performance of their offspring. This led to a new patent covering methods for genetic selection in the pig industry and PrimeGRO was established for the commercialisation of this discovery as a joint venture through Bunge Meat Industries and the PRDC. GroPep was positioned though, to remain firmly along the lines of developing human therapeutics, hence the establishment of PrimeGRO to capitalise on agricultural and veterinary products.

With a strong pipeline having been built up from 1988 until 1999, the

overarching strategy for the company heading into 2000 was to continue building a successful biopharmaceutical company that generated significant profits from selling growth factors and on-licensing drugs based on growth factors to the pharmaceutical industry. The company stated in their 2000 Prospectus that there were three inter-related objectives: (1) achieve strong growth in revenue and profits from cell culture media products and develop new cell culture products to meet the needs of the pharmaceutical industry, (2) maintain a leading position in growth factor R&D and in-license new discoveries for development as candidate drugs, (3) use the cash flow to fund development of up to six pharmaceutical drug candidates at any one time so as to maximise the prospects of a success while keeping development costs manageable. Additionally the Company's lead growth factor, LR<sup>3</sup>, was used in the production of three approved drugs marketed by pharmaceutical companies and was being evaluated in the manufacturing processes of 50 drug candidates under development by 25 pharmaceutical companies.

Moss-Smith felt that one of the reasons GroPep was able to move into drug development was because of their manufacturing ability, stating:

We would never have been able to do drug development if we had not built the knowledge of how to manufacture products. We would have been like every other biotechnology company and not able to make our own product, not being able to get anyone else interested in the product either and you would have stalled out. Most small drug biotechs stall out as they can't make their own molecule and they can't get anybody else to make it either because nobody is interested at that stage. (interview, 2006)

Undoubtedly the hub and spoke arrangement of the CRC had afforded GroPep the use of resources not usually available to such small spinout firms. In addition to the fluidity and transferability of the team of scientists, GroPep was also able to commandeer manufacturing facilities in the very early days of the CRC, prior to the

establishment of their own sites. At times, space was rented from other local South Australian biotechs, i.e. MedVet, who were known to GroPep via their links with the Royal Adelaide Hospital and the Institute of Medical and Veterinary Sciences (IMVS).

At this time, too, there was a need for the senior scientists associated with GroPep to resolve the increasing tension between their research and commercial identities, as Geoff Francis recalled:

... it was a good deal for them [CSIRO], but ... eventually ... there became a point of credibility and [in] particular, I guess, due to liability issues that eventually [came in] '98 ... [when] GroPep was starting to grow, it was employing more people, it was ... generating [more] ... cash inflow, and of course, the key individuals, including myself, were offered share options in the company and of course that was totally anathema to CSIRO, there's no way [that would have been OK ...]. (interview, 2006)

On the same day in 1998, three senior CSIRO staff – Geoff Francis, Chris Goddard and David Belford – resigned to take up full-time employment with GroPep. Chris Goddard (2006) confirmed that they felt this move had been forced upon them by CSIRO, which advised them that they would not be able to take up an option scheme offered by GroPep.

## **The IPO**

The late 1990s seemed to be a promising period for the company. The cell culture business was moving forward, as was the reagents division, and Dr Geoff Regester, who joined the company in 1998 with a view to overseeing projects that he had worked on in the early nineties as a post-doctoral student and then later became in charge of GMP manufacturing, commented, 'In those times, there was a lot of good R&D floating around thanks to the CRC. We had a lot of research in house so we didn't really have to in-license. In that sense, the CRC was the vehicle. But the CRC was coming to an end

and I guess they [GroPep's management] sensed that' (interview, 2006) so with the buoyant stock market conditions and building on the strength of the previous decades, GroPep successfully launched its business on the Australian Stock Exchange in 2000. John Ballard also confirmed that one of the impetuses for pushing forward with a stock listing was to:

provide equity - the shareholders couldn't sell their shares, they had their shares in this company but they couldn't do anything with them, because there wasn't any market, and the IPO was just a logical way to do that, and there was a special arrangement with the Child Health Research Institute that they were allowed to sell some shares at the IPO, no one else was allowed to, that was agreed because they needed the money. (interview, 2006)

In preparation for the Initial Public Offering (IPO), a new building consisting of multiple GMP suites and laboratories was constructed at the Thebarton campus. This was intended to house GroPep's manufacturing capabilities, which it had been acquiring over the previous decade, as well as accommodate the research scientists and the company administrators: in total, 56 employees were relocated to the site. The building was important in terms of gearing up for scale in manufacturing and ability to meet new market demands including the FDA and TGAs regulations but also because it provided GroPep a sense of its own corporate identity.

The Biological Reagents division was also keeping pace with the changes. Sales of growth factors, binding proteins and antisera were making significant contributions to sales and more importantly achieving their overall plan of being financially independent. As such, 16 new products developed from within the CRC were added to GroPep's product catalogue in one year. A consequence of this growth meant improving marketing techniques; promotion material was distributed via email to over 7000 potential customers, and of the orders received that year, nearly half of those were through the GroPep online ordering system via their website. (CRC Annual Report,

1999-2000)

### **Making Scientific Progress**

The company was making good scientific progress, with drug candidates for four clinical conditions undergoing human trials and a number of others at earlier stages passing their respective milestones. Two products progressed to Phase II trials and the remaining trials were due to commence before the end of the year 2000. The next year, 2001, GroPep successfully completed a new Phase IB clinical trial at the Peter MacCallum Cancer Institute in Melbourne for a chemotherapy side-effect treatment with their PV701-WGFE product. A pre-clinical development was begun of a treatment for recurrent miscarriage and other unexplained infertility conditions in humans was (PV903) that had been in-licenced from researchers from the University of Adelaide and the Queen Elizabeth II Hospital. The initial connection between the inventors of PV903, Drs Kelton Tremellon and his supervisor, Dr Sarah Robertson, came through a personal friendship, with Tremellon commenting, ‘Sarah ... knew someone at GroPep, had a meeting there and it snowballed from there’ (interview, 2006). PV903 is an immune medication based on, as Tremellon explained, ‘a theory that one of the causes of women having lots of miscarriages is their immune system attacking the baby’ (interview, 2006).

However in order to proceed with clinical trials, an agreement had to be made with OSI Pharmaceuticals in the USA to acquire the IP rights that existed between the University of Adelaide and OSI. The IP rights for PV903 were owned partially by OSI, who also agreed to provide clinical grade drug substance of transforming growth factor beta or TGFb and the relevant drug safety information package. Specifically the TGF Beta 3 patent was held by OSI, but the University of Adelaide held the right to use

TGFb. By having access to these materials via the agreement, GroPep estimated it would shorten their product development phase by two to three years (GroPep Annual Report, 2001). Tremellon explained some of the journey of the product to date in terms of other deals that he had tried to negotiate with Pharmacia:

They [Pharmacia] didn't have a local R&D presence - that may have been an impediment. The actual drug component of PV903 is TG (Growth Factor) Beta and a reason why Pharmacia might have been interested, [is] they saw synergies with a product that they had. (interview, 2006)

All of these activities were supported with an underlying cash flow from cell culture products. In 2006, Goddard calculated that over the years, the JRH earned A\$50 million for the company, with a 70% margin. Continuing their marketing collaboration, a second deal was entered into with JRH/CSL in 1998, bringing the period covered by the deal up to 2002. But this second agreement was revised again in 2000, at the instigation of JRH/CSL, who wanted a further extension of the time period so it covered 10 years (i.e. until 2010). Goddard (interview, 2006) explained the reason for this lay in the fact that the customers for cell culture are using it for their own drug development programs, so the final product containing the cell culture, if it eventuates, will not be on the market for about a decade.

The JRH/CSL Ltd and GroPep strategic alliance was supported by a grant awarded under the Australian Government's START program. The agreement with JRH therefore included any future growth factors identified, patented and manufactured by GroPep. Under the agreement, CSL was to promote market acceptance of growth factors and would be responsible for the development and implementation of a sales promotion campaign with GroPep providing marketing and technical support. GroPep would obtain appropriate Therapeutic Goods Administration (TGA) registration of the

growth factors and CSL was responsible for obtaining registration in all other relevant countries. Goddard voiced the opinion that the JRH/CSL deals were central to the success of the company, 'If you're talking about important deals, they're deals which provide revenue streams, and the only one that's ever provided any revenue stream other than R&D money is the CSL deal. There hasn't been another one' (interview, 2006).

### **GroPep Finds Another Company – TGR BioSciences**

GroPep was a foundation shareholder of TGR BioSciences Pty Ltd, who incorporated two years after their 1999 birth from the the CRC and by the time TGR incorporated in 2001, GroPep were strongly embedded in this new start-up. This connection to TGR was important for two reasons: first, it provided a foundation of extensive scientific and management expertise as well as over 10 years experience in the discovery, development of the novel bioactives that had arisen from the CRC, that would give rise to the ongoing opportunity for commercialisation exploitation, and second, with the CRC's end in sight (the funding would cease in 2002) it provided a vehicle for the integrity of their hard work during the years of the CRC to be maintained – rather than stopped altogether.

With the IPO approaching and the need to be financially productive for shareholders, and to capitalise on the strategic decisions made the previous year in 1999 with the establishment of PrimeGRO, GroPep signed a deal for the development of a new manufacturing process with Alpharma Inc, a United States based specialist pharmaceutical company with global leadership positions in products for humans and animals. PrimeGRO was formed to commercialise some of the animal health technologies discovered from the CRC. GroPep intended to use its proprietary

technology to develop manufacturing procedures for new veterinary products that would then be manufactured and marketed by Alpharma's Animal Health Division. The arrangement was seen as an excellent opportunity to share the risk of developing a process technology that had application in GroPep's pharmaceutical development business, and to diversify their revenue base without shifting focus from pharmaceutical product development.

Around the time the CRC had been renewed, there was a decided emphasis in terms of trying to pursue a more managerial orientation. Greg Moss-Smith himself acknowledged his contribution to the company at that time, 'When I joined the company as business development manager I had a primary responsibility for this partnering stuff they wanted to do with the CRC and basically trying to ship all the intellectual property into some kind of commercial framework ...' (interview, 2006). In describing those years leading up to the IPO, Moss-Smith also reflected:

The company itself went through quite a lot of re-organisation over those periods of time ... prior to the float [there was] a general lack of experience in general management. I was the only person in the company who had come from other companies and worked primarily in a company background and everybody else had come through from the kind of internecine warfare of CSIRO related organisations. People have ideas about management but there was no strong experience of general management and I think the management team really struggled with how to impose management disciplines and the desire to cut across those to get things done at different times and it really was a difficult time for the company and all small companies go through this transition to professional management and we were trying to do that and really were struggling with it. (interview, 2006)

GroPep's organic development from the Genentech deal and subsequently the CRC had resulted in a three 'silo' type arrangement. In Greg Moss-Smith's opinion, this was not without its difficulties for the company at that time. He reflected on this:

It really was a very confused organisation I think. We were at this point where we had essentially organised divisionally, we had research products

coming up through Geoff [Francis], we had industrial products coming up through Chris [Goddard] and we had pharmaceutical products and drug development basically coming up through me and David Balfours as a medical director of it. Then somehow or another I was also working across the whole lot when it came around to any kind of transactional stuff [and overseeing intellectual property management] and the company was strapped for resources and so there was always the desire to manoeuvre around people to get the job done. [We had to ask ourselves] ‘what’s the next most important thing to get done sort of thing?’, but there was very little assessment of what the company could actually do with those resources. (interview, 2006)

According to Moss-Smith, who shared some insight into the emotional challenges felt by staff at that time, the company went through a period of struggling to gain traction leading up to and immediately after IPO:

Were we actually making any progress because we had all these different things we were trying to do, where we were actually focusing where it counted? Sometimes we were and we’d make progress, other times we weren’t and couldn’t and we wouldn’t make progress and then we’d spin our wheels in the mud and that was all adding up to not going where we wanted to go. The company had gone IPO by that stage; we still had that divisional approach to a large extent in management. It was very difficult to organise [management] functionally ... to get anything done that way you always found yourself in a situation where you wanted something [but] you had to go and rob somebody of it if you like to get it done and of course that creates all its own management issues. (interview, 2006)

Importantly, a large contribution to this state of flux was the relationship between GroPep and the CRC. The CRC had offered many positives and successes, as Moss-Smith recalled, ‘... they orchestrated themselves into a position where they were getting most intellectual property benefits without actually bearing much of the cost and indeed a trivial amount of cost at that time and building up this arsenal of intellectual property and experience’ (interview, 2006). But the union was encumbered by contractual obligations: GroPep was not in a position to make strategic choices regarding the products they commercialised. Rather, all products discovered from

within the CRC were put into the commercialisation basket, and GroPep was obligated to take these inventions through to market, as Moss-Smith explained, ‘There was this cupboard full of stuff [inventions] and GroPep had obligations, not just a right, but an obligation to try and commercialise all of that stuff as best it could and it was pretty much an impossible task because there were too many different things to be done ...’ (interview, 2006).

This put pressure on GroPep to develop its linkages and commercial partners. As Moss-Smith mentioned, he felt that this had been a primary factor in his offer of employment by GroPep in 1997, ‘... my job was to get all this other stuff in drug development and licensing moving. I think that was really [what] John saw [as] that’s what they couldn’t get done because there was nobody who knew how to do it. That’s why he hired me [but] that isn’t why I joined the company’ (interview, 2006).

Beyond utilising the networks and friendships already established, GroPep was strained to take a forward step in its development by showing it was now able to negotiate deals based on the virtues of their technology. Moss-Smith said, ‘it required us to build relationships with companies whom we had never worked with before at all, and [we] didn’t have anybody who knew them at all. And it required us to sell those technologies on their merits so we had to prove that they were worthwhile, which was something that hadn’t really been an issue up to that point’ (interview, 2006). Table 4 summarises the abundance of deals negotiated in the first decade of the company’s evolution.

**Table 4: Collaborations Between GroPep, Partner Firms and Organisations<sup>2</sup>**

<b>Year Started</b>	<b>With Whom</b>	<b>Nature</b>	<b>Content</b>
Pre 1988-1998	Genentech, USA	R&D Contract and Licencing agreement Provided up front payments	Pharmaceutical uses of growth factor analogues
c. 1992	Genentech, USA	R&D	Evaluation of IGF in a primate (CRC Annual Report, 1993-1993 p. 21)
1992-1995	Mead Johnson, USA	R&D and Product Development	Whey growth factors for gut disease and polytrauma
1993-1998	Cephalon, USA	R&D and Licencing agreement	Pharma applications of growth factor analogues
1994-1998	Bonlac Foods, Aust	R&D – clinical trials to GroPep for PV701 in with Bonlac Manufacturing – done by Bonlac and Marketing agreement	Whey-derived growth factor preparations
1992-1995	HyClone Labs, USA	Marketing Agreement for reagents in US	Commercialisation of growth factor analogues in industrial cell culture
1993-1995	CSL, Aust	Marketing Agreement for reagents	Commercialisation of growth factors in industrial cell culture
c. 1994	AMRAD Operations, Aust	Contract research	Research for wound healing
c. 1994	Inovax Ltd, Aust	R&D collaboration	Application of Inovax's technology for the delivery of growth factors
c. 1994	Celtrix Pharmaceuticals Inc	R&D collaboration	Research on growth factors to treat oral mucositis
c. 1994	Immunex, USA	R&D collaboration	Research on the use of GroPep's growth factors to support the growth of cells in bioreactors
1995 – ongoing	JRH Biosciences, USA (division of CSL)	Worldwide marketing agreement and collaboration	Commercialisation of growth factors in industrial cell culture
1995-1999	Diagnostic Systems Labs (USA)	R&D collaboration Marketing agreement for importing and distribution	Growth factor diagnostic products
1995 – ongoing	Bunge Meat Industries, Aust	Co-developing IP and patent filing	Methods to select livestock
1994-1996	MedVet Sciences, Aust	Co-developing IP and lease of MedVet's facilities. Patent filed in joint names.	Synergistic effects of growth factors and insulin
1994-1996	Northfield Labs, Aust	Collaboration	Whey growth factors and milk proteins for treatment of inflammatory bowel disease
c. 1995	BresaGen, Aust	Marketing agreement	Cross-marketing arrangement for certain products
1995-1997	Embrex, USA USDA	Co-developing of joint patent with Embrex and US Department of Agriculture	Growth factor administration to poultry <i>in ovo</i>

<sup>2</sup> This table does not include scientific linkages of the CRC.

c. 1996	Cephalon Inc.	R&D collaboration	Extension of development of novel growth factors and to include effects on nerve growth in the renewed Centre.
1995	JRH Biosciences (acquired first by CSL and then Sigma-Aldrich)	Collaboration	Co-development to design and manufacture of a range of growth factors and related proteins as well as the use of novel whey-derived factor. Replaced by a second agreement in 2000. Initiated by GroPep staff visiting the US. i.e. Goddard, Ballard and Read.
c. 1996	USDA Livestock and Poultry Sciences Institute, USA	Collaboration	Collaboration on chicken IGF between Dr John McMurtry at USDA and the IGF group has been in operation for several years. Extension of research to contract manufacture animal hormones by GroPep.
1996-	FH Faulding, Aust & Innovative Technologies, UK	Collaboration	Incorporation of whey growth factor mixtures into wound dressings
1997-1999	Alizyme, UK	R&D of Alizyme's IP contracted to CHRI	Application of Alizyme's proprietary technologies for the treatment of gut diseases
1997-2000	Smith & Nephew, UK	Licence agreement R&D collaboration	Whey growth factors for treatment of chronic wounds.
1998-2002	Nestle, Switzerland	Licence agreement and R&D collaboration Covers an R&D program of preclinical trials but includes the right for Nestle to enter into a licence for the eventual marketing by Nestle of nutritional and certain oral pharmaceutical compositions covered by GroPep's milk growth factor intellectual property.	Enteral applications of whey derived growth factors.
c. 1997	Mayo Medical Ventures, USA	Co-develop IP owned by Mayo. Beneficial rights for GroPep to develop products resulting from further research by Mayo.	Research program for treatment for osteoporosis. Covers PV704 program.
c. 1997	Aerogen, USA	Co-development	Improved manufacturing processes for IGFs
Late 1990s	International Diabetes Institute, Aust	GroPep to sponsor clinical trials of IGF-I as a topical treatment for diabetic neuropathy.	Covers PV705 program.
c.1998	Fish Research and Development Corporation, ACT	Research Collaboration in the form of support	Support to help GroPep design, manufacture and evaluate fish growth factors and antibodies for the aquaculture industry.
2001	PrimeGRO, Aust	Co-development of IP	
2001	OSI Inc., USA	Agreement to acquire IP rights	IP rights for PV903

	Uni of Adelaide, Aust	between OSI and Uni of Adelaide and GroPep. OSI to provide clinical grade drug (transforming growth factor beta or TGFb) and drug safety info package that will shorten product development by 2-3 years	
2000	Alpharma Inc., USA	Manufacturing for product development that will be manufactured and marketed by Alpharma, US.	Share the risk of developing a process technology that has application in pharmaceutical development business, and diversify revenue without shifting focus pharmaceutical product development.
2003	Campina, Netherlands	Out-licensed its rights to WGFE Allowed company to use aspects of GroPep's WGFE technology to manufacture and sell nonpharmaceutical oral products in return for fees, royalties and patent-related expenses.	
2003	Program for Appropriate Technology in Health, USA	Contract manufacture collaboration between Vaccined Solutions Pty Ltd and LaTro Uni.	Malaria Vaccine Initiative to develop vaccines for clinical trials.
2002	TGR Biosciences Pty Ltd, Aust	License of Technology of 6 patent families	GroPep will receive royalties of more than 10% on TGR's commercialisation of the technology
2002	Biomedical Australia	Purchase of facility and IP for A\$11 million, divided into A\$7 million for the CMO assets including land, buildings, plant and equipment and A\$4 million for the IP portfolio	Royalty revenue received. Parts of the IP portfolio are being sold.

### Expanding Manufacturing – Acquiring Biotech Australia

With the IPO being formalised 2000, and now as a profit earning entity, according to their Press Release dated 20 February 2002, had decided it needed to expand manufacturing capacity in order to meet market requirements for its existing products. Additionally, according to the same press release the worldwide sales of protein drugs exceeded A\$36 billion in 2000, had a projected growth rate of 20% and there were more than 100 such drugs possibly using or requiring cell cultures on the market. Examples of such drugs included Epogen, Enbrel, Herceptin and Remicade. A series of

market research reports carried out within the industry during 2001 and 2002 had identified a shortage in production capacity that was expected to become a crisis as the number of drugs under investigation in clinical trials rapidly expanded (Press Release, GroPep website, Wednesday 20 February, 2002). As an example of the conclusions made in these reports, a J.P. Morgan Equity Research paper in March 2001 stated: ‘We estimate that the demand for manufacturing capacity will exceed current capacity by a factor of four by 2005’. Although many pharmaceutical companies and contract manufacturers were expanding their capacities, it would take up to 4 years from beginning the construction of the plant and its accreditation by national regulatory agencies such as the FDA in the US. At that time, there was already an acute shortage of capacity limiting the sales of Enbrel. Furthermore, under the arrangements with CSL, GroPep was required to purchase a specified minimum amount of LONG<sup>TM</sup>R<sup>3</sup>IGF-I – hence continuity of supply had to be ensured.

When an opportunity to acquire a manufacturing business, Biotech Australia (BA), presented itself: these market developments along with an attractive purchase price, facilitated the negotiation. The acquisition of Biotech Australia meant that GroPep could project future requirements at least at the minimum level with a four-fold greater production capacity by 2004 at the latest. This had been expected to cost A\$5.5 million (Press Release: GroPep website, Wednesday 20 February, 2002), however the acquisition of the Biotech Australia facilities made that expenditure unnecessary. GroPep had a second GMP facility in Adelaide used to manufacture protein drugs for the Company’s clinical trials program and should any of these drugs prove successful during the trialing process, the much larger scale facility acquired from Biotech Australia could also have been utilised for the production of the drugs for marketing, thus avoiding the need to license an external manufacturer.

In February 2002, GroPep announced completion of the acquisition of the assets of Biotech Australia in Roseville, NSW, to provide an expansion and diversification of the Company's revenue. Since early 2001, BA had repositioned itself as a contract-manufacturing organisation (CMO) providing expertise, equipment and facilities suitable for developing and manufacturing protein drugs for biotechnology and pharmaceutical companies worldwide. The intellectual property acquired included a series of patents, licences and contracts that covered technologies developed or accessed by the BA group. Royalty revenue was received and projected by GroPep management to increase substantially whilst other parts of the IP portfolio were in the process of being sold. The A\$11 million paid by GroPep was divided into A\$7 million for the CMO assets, including land, buildings, plant and equipment, and A\$4 million for the IP portfolio. Some of these rights were intended to be transferred to a US biotechnology company and most of the rest commercialised through another US company that specialised in diagnostic products. GroPep projected revenue of A\$15 million from this IP purchase and expenditure of A\$8.3 million.

The equipment acquired through the acquisition included fermenters as well as all control and manufacturing equipment needed to operate these facilities. GroPep offered employment to 35 Biotech Australia staff who were trained in the marketing, manufacturing and quality program components of the CMO business. This gave GroPep a total of 110 staff, the largest it had ever been in its history. However, the rationale for the acquisition quickly began to unravel. Bob Finder, a later CEO of the company, felt that fundamentally, the problem stemmed from the fact that GroPep did not have sufficient knowledge of contract manufacturing to do sufficient due diligence prior to the acquisition.

Two key manufacturing opportunities under negotiation during the acquisition

process were delayed by customers to the extent that GroPep could not expect them to provide earnings as early as anticipated. This had a significant negative effect on the Company's cash flow in financial year 2002-03 and without the anticipated revenues; the costs were beyond the resources of GroPep. As a consequence, they decided to vacate and sell the site located in Sydney's North Shore with the sale process completed by 2003. The challenges for GroPep didn't stop there: following the below expectation result of the Biotech Australia acquisition there was a profit downgrade.

On 17 April 2002, GroPep released a statement to the press advising there had been a change in senior management, 'GroPep Limited announces that its Board has terminated the Managing Director, Dr John Ballard's contract of employment 14 months before the date on which his employment was due to expire.' The statement continued on to say, 'The Company has before it a number of strategic issues which go beyond the tenure of Dr Ballard's employment contract.' There had in fact been disquiet for some time about the leadership of the company, with some board members believing that it was time to make a transition to a professional manager. In particular, there was a feeling that John Ballard was having trouble letting go of the CRC and adjusting to GroPep's independence. Geoff Francis commented on the role his friend and mentor, John Ballard, had played in the company's development, 'It must be [said], and whatever happens along the way, there is one immutable absolute fact - there would be no GroPep without John Ballard' (interview, 2006). Francis spoke of his approach to the change of leadership, 'And the thing is, that, you know, in the life of a company, you know, the entrepreneurial brilliance of the founder can become a liability ... I've heard John say that himself ...' (interview, 2006).

## Refocusing

As well as having to deal with a financial loss resulting from the sale of the Biotech Australia facilities and property during 2002 and 2003 and the lack of permanent senior leadership, The CRC reached the end of its funding period on 30 June 2002 and the participation of GroPep, along with other partners, was completed by the end of the year, meaning the company would no longer invest resources directly in discovery research. According to the Company's 2002 Annual Report, this was the most difficult year in GroPep's history. Moss-Smith commented on the challenges at that time:

we kind of stacked on 106 employees and they were coming from an organisation that had been in terminal decline for the best part of a decade and from a different site, luckily not overseas but that was the only thing that wasn't difficult about it, and somehow we were supposed to stitch all this together and it didn't work and became very apparent very quickly that it wasn't going to work. Anyway ... we stripped that all out again and basically pulled the company back to about 65 people at that stage and then rebuilt from there. (interview, 2006)

Chris Goddard was appointed acting CEO and was confronted with the need to make some tough decisions:

The board charged me and Grant Rumble, the then company secretary and CFO, to look at the books, [they] wanted to know where we at and so when Grant and I had a real good look at everything it was not great. Not a pretty picture so we did the obvious which said ... this [BA facility] has to go and jaws dropped at that board meeting. Oh but we've only just bought it, yeah, but it's got to go! You are allowed to get divorced a month after if you've chosen the wrong partner. So, we did it and part of that was going round to the shareholders. So what they'd done is they'd gone to a secondary raising and they'd raised more money at A\$1.80 a share ... the profit share price went to about 70 or 80 cents so these guys over in Sydney and Melbourne where they'd raised A\$3½ million bucks from to put into the BA were spewing ... Richard and I went round and you know, bent over the desk and got belted like buggary. So yeah that was my first experience at going round to professional investors, get my head kicked in every meeting. So yeah that was a good education I can tell ya. I reckon I did an MBA on the job every single aspect of an MBA on the job in about 8 months. Oh but to be honest I was too naïve to realise what was going, no I knew what was going on, I just

worked through it and I just worked and worked and worked until we got it. (interview, 2006)

Bob Finder nevertheless stressed that ‘[t]here was some good that came out of the Biotech Australia acquisition’ (interview, 2006).

There was some good that came out of that. The malaria vaccine project that we ended up working with PATH and the Bill Gates Foundation was quite a success for the company and showed our abilities on that process development side of things ... I think it also ... led to a lot of changes into the total management organisation [of the company]. I mean, you see so many little companies go through that. (interview with Finder, 2006)

Following the decision to close the Sydney site and the disposal of the Biotech Australia assets by 2003, the on-going business was consolidated to Adelaide. The company had decided to concentrate on increasing growth of the cell culture products business as well as focus on the drug development business on to a smaller number of higher quality, higher value projects related to core competencies. This meant some hard decisions about which research to fund, as Moss-Smith and Goddard explained:

... we had a big clean out of all the things which we had not been able to successfully shut down before then and I think we shut down 14 – it’s wrong to call them projects because most of them weren’t actually projects they were more things that wouldn’t go away – there were 14 of those which we shut down at that time and left us still with 6 and we shut down another 3 in the subsequent year [2004] after that so it was a big shakeout and we had learnt a lot in terms of what kind of products you wanted to pursue and what could be turned into a product and in fact that we’re actually only going to be interested in products was part of that break through. (interview with Moss-Smith, 2006)

[We killed of lots of projects and] we ended up with five that were still going and then subsequently killed another one because it wasn’t working. (interview with Goddard, 2006)

### **Working Towards Independence – Winding up of the CRC**

GroPep were working steadily towards independence and were anticipating the windup

of the CRC. They were now able to leverage off their good reputation for their reagents and Moss-Smith explained the situation:

We managed to keep that [reagents segment of the business] growing about 15% a year which [was] pretty good. We [had] a worldwide reputation for the supply of IGF molecules and related reagents and everybody working in that area [knew] us, whether they [could] afford to buy our products was something different. (interview, 2006)

GroPep continued with its in-licensing opportunities, although further development of the whey-derived growth factor compositions did not proceed beyond current commitments. GroPep actively sought development partners for both the PV701 mucositis and PV702 venous ulcer programs as the results of the Phase Ib trial for the mucositis project were expected in late 2002. Patient enrolment into the venous ulcers clinical trial continued throughout 2002/2003 and the manufacture of drug substance for the osteoporosis project to provide preclinical investigational materials for ongoing third party evaluation studies continued in into the following year, 2003. Moss-Smith discussed why these trials lurched on:

... we couldn't have stopped what we were doing anyway because we were already committed to clinical trials, we had [a] product in two clinical trials at that time – or in fact we had three at that time in that product – so you can't just pull the pin on the clinical trial and shut it down and walk away - people have done it but it has incredible ramifications with the R&D community and if you ever want to work with those people again, forget it and you will have upset every one of those ethics committees and R&D institutions and it will stain you for life so we still had to see them through and they were long trials and they were expensive trials. That happened essentially immediately prior to the float and so we knew going into the float that we were committed to seeing these products out and there was always the question that if we got a good result from those trials it could affect the result of those trials because two of them were Phase II that would we pursue them anyway kind of thing and I guess my view was that we couldn't, they could never be products but it's hard to argue down if you've got a positive Phase II result you'll make them into a product and it was really quite a salutary lesson about the ground has shifted around us and we were in a position where we could not respond at that time, we had to see it through. (interview, 206)

Behind the need to stop this work was an unforeseen event, with Moss-Smith commenting:

... I guess the disappointing thing about that [having to stop the trials] was that we were at the point where we had achieved this milestone and the commercial evolution of the company getting it ready to be a drug development company it kind of unwound as well almost simultaneously because the whole regulatory regime shifted against these natural product extracts because that was the outbreak of mad cow disease ... and all of a sudden this thing which the CRC and GroPep had bid a lot on really in my opinion couldn't even be a drug and it had already been tried in other industrial applications and cell culture so while it might be able to be turned into something like a cosmetic or something else like that it was apparent to my mind it couldn't be a drug, it wouldn't get past regulators and we didn't even know how to specify it adequately to fit a new regime so the obstacles to its development as a drug were I thought astronomical but I wasn't able to convince people of that at the time .... (interview, 2006)

Hence, with the CRC windup in 2002, GroPep decided stop any further research development and to license six of its patent families to TGR: they included the Whey Growth Factor Extract technologies: PCT/AU91/00303 'Growth promoting agent', PCT/AU95/00237: 'Modified milk growth factor', PCT/AU96/00253: 'Method of preventing or treating gut damage', PCT/AU98/00942: 'Mammalian milk growth factor', PCT/AU01/00854: 'Methods and Compositions for the treatment of skin damage', PCT/AU03/00714: 'Bovine TIMP-2 Insulin-like growth factor technology', and PCT/AU91/00031: 'Method for treating intestinal disease'. This raised A\$3 million from two separate agreements with venture capitalist Nanyang Innovation Fund (managed by Nanyang Ventures) to fund further clinical development of WGFE (PV701) as a treatment for oral mucositis, and GroPep would receive royalties of more than 10% on TGR's commercialisation of the technology. At the same time GroPep's shareholding shrunk from 20% to 12%. Among the rights licensed to TGR was GroPep's oral mucositis product technology – PV701.

An out-licensing deal was reached in December 2003 between GroPep and

Campina Melkunie B.V – a multinational dairy products manufacturer based in the Netherlands – concerning the Whey Growth Factor Extract (WGFE) portfolio. It was the result of an ongoing court battle over the patent rights to the technology. Campina had been awarded the patent in Australia and GroPep filed action against them stating they already owned the IP and they had been issued with an existing patent. This action was decided in favour of GroPep. However, a decision was made to licence WGFE rights to them, meaning that GroPep had now out licensed all of its rights in WGFE and terminated all internal development work on natural extract products. The agreement allowed Campina to manufacture and sell nonpharmaceutical oral products in return for fees, royalties and patent-related expenses. Campina, one of Europe’s biggest dairy companies, had annual turnovers at that time in excess of €3.7 billion.

Resulting from the acquisition of Biotech Australia in the previous year, a project called Program for Appropriate Technology in Health (PATH) had been part of the original purchase deal and as part of the contract GroPep needed to tie up those loose ends and act to honour the terms of the agreement. Hence, in 2003, a contract manufacturing deal was negotiated with partners involved in PATH who were working on a malaria vaccine initiative (PM0103). The researchers were based in the United States, and were aiming to develop vaccines for clinical trials. Collaborators included Vaccine Solutions Pty Ltd, the commercial arm of the CRC for Vaccine Technology and LaTrobe University. The work was focused on developing a manufacturing process for the antigens. The project was a fee-for-service contract encompassing two major milestones. The first of these was completed in August 2003 and at the beginning of the second milestone, GroPep received an upfront payment of A\$3.8 million. The major activities associated with the second milestone involved manufacturing the drug substance for a Phase I trial that was completed in 2005.

In terms of consolidating and moving forward after a short but difficult period in 2002, the Company achieved a turnaround in financial performance to record a profit of A\$0.4 million during the second half of the financial year in 2003. Behind this result was the restricted cash outflows to less than A\$0.5 million and the focus on a research and development program of fewer, high quality projects and reduced net expenditure to A\$1.5 million or 14% of revenue. This meant a gross research and development expenditure of A\$3.3 million that was A\$1.9 million lower than 2001-2002. Clinically, there were some positive outcomes for GroPep: they successfully completed a Phase IB clinical trial of PV701 for oral mucositis and following the trials, GroPep sought to find a partner to help fund the further trial work required. However, with no partner forthcoming work was suspended for several years, and PV701 was eventually out-licensed to TGR in 2005. GroPep did however finish recruiting patients into the Phase II trial of PV702, their treatment for chronic venous ulcers. Sales maintained good growth, as did the profits from the cell culture business, with A\$6.2 million and A\$3.8 million respectively. And the US granted a key patent covering the active ingredient for PV903.

**Table 4: Summary of GroPep’s Portfolio Development until end 2006**

<b>Product</b>	<b>Partner</b>	<b>Stage of Development</b>
PV701 - Oral Mucositis		A Phase 1a trial showed PV701 to be well tolerated and safe when administered to the oral cavity of healthy adult volunteers. Recruitment into a Phase Ib trial at the Melbourne-based Peter MacCallum Cancer Institute started in 2002. The trial involved administration of PV701 mouthwash. The results, announced in February 2003, confirmed the safety and tolerability of PV701 in patients with cancer. GroPep needed to access external funds to continue Phase II clinical trials that would be in the order of A\$10-15 million and the Company sought partnership to continue development. In 2005, PV701 was licensed to TGR Biosciences Pty Ltd, which will continue product development.

PV702 - Venous Ulcers		Pre-clinical data generated by GroPep and its research partners demonstrated that PV702. Initial safety and tolerability in humans was demonstrated in a Phase 1 clinical trial where PV702 was applied to leg ulcers. In 2005, PV702 trials were discontinued after a Phase II clinical trial indicated that the drug did not improve wound healing. The trial involved 106 patients across 10 Australian sites with patients randomised to treatment with either PV702 or a placebo.
PV704 - Osteoporosis	The Mayo Clinic, USA	The collaboration was terminated in 2003. Although pre-clinical studies yielded encouraging data in some animal models of osteoporosis, the results were not significant enough to warrant GroPep's ongoing involvement. Further work is being carried out at the Mayo Clinic and GroPep retains residual rights should the product be commercialised in the future.
PV705 - Diabetic Neuropathy	International Diabetes Institute (IDI), Australia	Clinical development of this product was based upon the successful demonstration by the IDI of the effects of insulin across the skin when the drug is applied in a similar manner to IGF-1. The Phase I clinical trial conducted by the IDI was completed in 1999. A Phase II trial was completed, but results were not uniformly positive. However, the tests were sufficiently encouraging to support further studies initially directed at optimising the formulation and delivery of IGF-I. Additional product development studies undertaken by GroPep in collaboration with the Department of Nuclear Medicine and Bone Densitometry at the Royal Adelaide Hospital did not yield a formulation that promoted sufficient uptake of IGF-I across the skin. GroPep announced the cessation of the project in March 2002 and began searching for partners with an interest in transdermal delivery of proteins to divest the IP to.
PV707 - Treatment for Burns		PV707 was administered topically to burn wounds and had the same active ingredient as PV701 and PV702. The cell culture, <i>in vitro</i> skin closure and preclinical animal experiments reported for PV702 had similar relevance for PV707 and was shown to increase the repair of a partial thickness skin wound in pigs. The Phase I trial completed for PV702 was also applicable for this product. A Phase II trial using skin graft donor sites as a model for burn wounds was initiated at the Burns Unit of the Royal Adelaide Hospital and Concord Hospital. Ethics and regulatory approvals were obtained in December 1999. As part of its rationalisation of clinical projects, GroPep terminated the trial in June 2002. At this time, 44 burn patients had been treated with PV707 and placebo. Following site closure, the available data was tabulated, analysed and reported in accordance with ethical and regulatory requirements.
PV801 - Treatment of Tendon Injuries		GroPep announced in 2001 successful pre-clinical studies in horses showing dramatic improvement in tendon repair after administration of IGF-I. In 2002, the Company planned to initiate clinical trials in humans, however, a feasibility study indicated that the incidence of the injury similar to that generated for the pre-clinical studies was not sufficient to warrant further clinical development. PrimeGRO Limited is now developing this for veterinary application.
PV802 - Short-bowel Syndrome		The active ingredient in PV802 is IGF-1, which had been demonstrated to facilitate post-surgical gut adaptation and attenuate absorption defects in animal models, and therefore may enable a shift from TPN to oral feeding. However, in 2002 a review of operations determined that this project would not be continued because the market size was insufficient to justify further development work.

PV903 - Recurrent Miscarriage	IP licensed from OSI Pharmaceuticals & University of Adelaide	A\$2.5 million AusIndustry R&D Start Grant in December 2001. In 2002 the major activities for this project centred on developing and manufacturing a stable PV903 formulation ready for use in the clinic. Batches of PV903 were manufactured for Australian and overseas research facilities to conduct further pre-clinical experiments and toxicology studies. The Company began partnering negotiations with a pharmaceutical company established as a global franchise in infertility and women's health. In 2003, a Phase Ia clinical trial was due to begin. However, it was delayed to allow additional pre-clinical tests to provide further evidence to support the proof-of-concept, and to determine the optimum dose and formulation to be used in the trial. There were a limited number of laboratories throughout the world that could perform this type of work. GroPep collaborated with Professor Clark at McMaster University in Canada, an expert in this field, who conducted pre-clinical studies in 2005. The results led to the decision by GroPep to conduct a Clinical Research Study in healthy women, followed by a Phase Ia clinical trial. Recruitment for Phase I clinical trial began in January 2006 with the trial to commence in mid-February 2006 with objectives to determine safety/tolerability and preliminary efficacy. The results are expected during 2nd half of 2006. A key patent was granted providing US exclusivity through to mid-2020.
PV905 - End-stage Liver Disease		A review of operations in 2002 determined that the project would not be continued because the market size was insufficient to justify further development work.
PM0103 - Malaria vaccine	Program for Appropriate Technology in Health, USA & Vaccine Solutions	A process development and manufacturing project that aims to produce a malarial vaccine. The first milestone, to develop a robust manufacturing process for two antigens, progressed rapidly and was completed in 2003-2004. The second milestone was completed in August 2005 under current Good Manufacturing Practice (cGMP) conditions, allowing the partners to formulate a vaccine for the clinical trial.
PP0102 - Psoriasis/ Asthma	NSAHS	In-licensed technology and exclusive worldwide rights from the Northern Sydney Area Health Service in 2002 and began formulation and methods development tasks in 2003-2004 for treatment of mild to moderate psoriasis and investigate its safety and efficacy in humans. In May 2005, GroPep filed a new International Patent Application on the use of the drug for the treatment of asthma. The Company was awarded an AusIndustry R&D Start Grant for 3 years towards the psoriasis application in December 2004. However, they decided to stop work on this indication, in December 2005 and sought a mutual termination of the grant. In 2005, GroPep said it would continue to undertake a market feasibility assessment for the use of the drug in asthma and the application of Tcell Peptide technology.

## A New Managing Director

Management stability seemed to be returning with the employment of a new managing director in September 2002, Mr Bob Finder. He had a long history of general management, in the US and Thailand as well as Australia, as the company's press

release dated 2 September 2000 detailed: ‘Robert Finder brings extensive experience in pharmaceutical manufacturing, project management and research and development to GroPep. He has significant and successful turn around experience in biotechnology, pharmaceuticals and chemicals. Bob is a seasoned professional manager with a strong track record in the pharmaceutical industry.’ Bob Finder’s pharmaceutical background was a novelty for GroPep and his experience led him to pinpoint what he saw as some weaknesses in the company he joined:

Probably the biggest weakness was the lack of understanding of quality systems, quality control, quality assurance. The people that they had in the quality groups were actually academia types that they had – who had really good intentions, but ... One thing that – in the pharmaceutical industry, one of the key things and it’s really hard to get people to understand good manufacturing practices and the TGA and the FDA and regulatory process. If you haven’t come up through that system and spent years at it, then it is really, really hard to just develop that on your own. So, that was a key weakness. One of the other weaknesses was – again, it’s this home grown, the sales and the business development. A lot of that was home grown people, out of the organisation. There were just a few people that had real experience in sales and commercial. So typical of, I think, a lot of biotech companies, were they have very energetic leaders that form the company, that have an academia background. They’re R&D types. But they don’t have some of the practical experience in sales and marketing and they don’t have the quality control that you have in pharma. I mean, when I joined the company, we didn’t have a single person on the board that had been in the pharmaceutical industry. We [had] very few of our 60 folks, here in the company – we had very few that actually had been real pharmaceutical experience. (interview, 2006)

This assessment was backed up by Goddard (interview, 2006), who argued that there was too much of a temptation on the part of some employees to be ‘just so focused on the science’ at the expense of being commercially ‘savvy’.

Due to his pharmaceutical background and professional management expertise, Finder’s appointment as Managing Director signalled a changing of guard in some respects. The main changes he instigated ranged across organisational structure,

corporate governance, financial discipline and management style. Moss-Smith explained the organisational restructuring at that time:

When Bob [Finder] arrived he basically reorganised everything on a functional basis so we got rid of divisionalisation and while we do actually still report on a divisional basis in our books and Annual Report that's not how we run the company, we run the company very much on a functional basis of the general executive, which brings together the functions and the report proofing to Bob. (interview, 2006)

Finder aimed to improve functional performance by bringing in new personnel to oversee production quality (critical not just for the integrity of the research program, but also to enable regulatory approval down the track), defining the responsibilities of the separate sales and marketing team and organising R&D in the form of projects, instead of the previous pipeline approach.

As well as these functional innovations, Finder made changes to the board, bringing in two directors with extensive pharmaceutical experience. As a result, he felt that 'our board, as it sits today [i.e. 2006], is really good' (interview with Finder, 2006). Finder also brought in new faces to improve financial accountability, notably a Chief Financial Officer (Anthony Mitchell) with whom he had previously worked at Mayne Pharmaceuticals. Part of Mitchell's role was to accompany Finder on meetings with key investors, in which they sought to regain the confidence of the investor community:

Every six months or so, Tommy Mitchell and myself would go out. We would have 40 to 50 – I'm serious – 40 to 50 one-on-one meetings with different investors. It took one to two years for people to believe our story. Normally, you wouldn't put that type of effort, I think, unless you were trying to turn around. But what ended up being is that GroPep got a fairly high level ... presence with these investor groups in Melbourne and Sydney that you normally wouldn't see. (interview, 2006)

From the company's first collaboration with Genentech in 1988 until around the time of the IPO, world-class scientists with outstanding vision and insight into the

industry had populated GroPep. However this vision had been harnessed to the CRC and in most respects GroPep had been a servant to the CRC. Geoff Francis confirmed this point, ‘... the CRC really was the research focus, GroPep didn’t have a research focus, it was just a servant of the rest of us, it was like a commercial shell, it was just our servant’ (interview, 2006). The IPO and the need to now be answerable to shareholders, heralded new challenges for GroPep. Dr Tremellon had also observed this shift and said, ‘At the time [prior to 2001], the people running it were mostly scientists whereas now they’re mostly management’ (interview, 2006). Francis commented on this new approach from a strategic point of view – being the company’s chief scientist:

And now of course these days I’ve moved [into a different role within the company], like everybody else around me at GroPep, [we] have moved very much into the area [of approaching commercialisation] of, ‘well that’s an interesting bit of research, but can we use this to create value, and create value in a way that returns benefits to health and benefits to our shareholders. You have to take a slightly tailored view of how you, you know, how you manage that. (interview, 2006)

## **Profits and Performance**

The company went on to achieve a record profit of A\$1 million and operating cash flow of A\$3.8 million in 2004, and began a A\$3 million facility upgrade to support their rapidly growing cell culture business. The strong financial performance continued in 2005 for GroPep with a record growth in net profit before tax of A\$3.1 million, more than triple that reported in 2004. Also, success continued for the cell culture products business with marketing arrangements transferred from CSL Limited to Sigma-Aldrich Corporation (USA) by CSL’s sale of its JRH Biosciences subsidiary in January 2005. Besides the change of ownership, all other aspects of the agreement, which was originally established in 2000 and is planned to continue until 2010, remain unchanged. CSL was to pay GroPep US\$1 million per annum over the remaining six years of the

agreement with equal half yearly instalments over this period.

GroPep continued to remain focused on high quality projects. Capitalising on a A\$2.5 million AusIndustry R&D Start Grant awarded in December 2001 to develop IP licensed from OSI Pharmaceuticals and the University of Adelaide, GroPep worked on ramping up the development and manufacturing of a stable PV903 formulation ready for use in the clinical trials. As Tremellon explained, some of the pre-clinical work was contracted to other labs; for example, the toxicology was ‘done in the UK, as we don’t have that sort of lab here’ (interview, 2006). Batches of PV903 were manufactured for Australian and overseas pre-clinical experiments and toxicology studies and the company began partnering negotiations with a global pharmaceutical company interested in infertility and women’s health.

In 2003 a Phase Ia clinical trial for PV903 was due to begin but was delayed to allow additional pre-clinical tests to provide further evidence to support the proof-of-concept, and to determine the optimum dose and formulation to be used in the trial. There were a limited number of labs throughout the world that could perform this work so GroPep collaborated with Professor Clark at McMaster University in Canada, an expert in this field, who conducted pre-clinical studies in 2005. The good results led to starting a Phase Ia clinical trial. Recruitment for the Phase I trial began in January 2006 and commenced in mid-February 2006 with the objectives to determine safety/tolerability and preliminary efficacy. The results were expected during the second half of 2006 and a key patent was granted providing US exclusivity through to mid-2020.

With six of their eight original drug compounds now defunct, GroPep continued to in-license technology. This time they negotiated the exclusive worldwide rights from the Northern Sydney Area Health Service in 2002 and were awarded another R&D Start

Grant for A\$3.4 million in December 2004, covering a three-year period. This technology had potential for broader applications in the treatment of inflammatory autoimmune diseases such as dermatitis, rheumatoid arthritis and asthma. GroPep decided to manufacture and formulate the peptide as a topical treatment for mild to moderate psoriasis and investigate its safety and efficacy in humans; in addition, in May 2005 they filed a new International Patent Application on the use of the drug for the treatment of asthma. Unfortunately, work was stopped on the psoriasis indication in December 2005 and the company sought a mutual termination of the grant, but they continued with their feasibility assessment for the use in asthma.

The remaining two original compounds, PV701 and PV702 both met their fate, with PV701 at least going onto to a new life by being out-licensed to TGR, but PV702 was unceremoniously stopped due to poor results in its Phase II trial involving 106 patients indicating that it did not improve wound healing. In reality, only one of the original eight projects remained alive – PV701. This result clearly demonstrated the fragile, lengthy, speculative and risky nature of the drug development process. The company's pipeline at the start of 2006 had just two projects: PV903 and PP0102. GroPep had implemented clear and stringent criteria that drug candidates had to meet to be included in its stable:

We said we had to have a clear path to regulatory approval, through the FDA. It had to bring substantial improvement, in health, to humans. Those were the key things. So, some of the projects fell out, because they didn't have A\$500 million potential ... Like the milk cheese whey products [PV701]. There wasn't a clear path that we could go through the FDA. Since that, we've spun that off to TGR. They're looking at it as a nutritional. To get those through, as an approved drug, would be extremely difficult, but they may be able to go through a nutritional path. We weren't willing to go – our company wasn't focused towards nutritional products. It was through approved human therapeutic drugs. (interview with Finder, 2006)

These activities ultimately aimed at claiming GroPep's legitimacy in the biotech

value chain. GroPep's current position as an organisation is clearly in terms of adding value to the commercialisation chain. Geoff Francis elaborated on this: '... [with respect to the inventor] we're the big pharma ... we're minding, adding value, to this research and then we're going to pass it on to ... a bigger pharma ...' (interview, 2006). Similarly, Moss-Smith saw GroPep's value proposition as part of a longer chain, with the core capabilities for early stage drug development consisting of 'the quality systems that actually do that [allow us to have credibility and transparency], we have sufficient control and do our development work to a standard that enables us to prove that what we are saying is true is in fact true and not just might be true depending upon which end the wind was blowing from' (interview, 2006). In his view, this is the only viable role for a niche player in the industry:

the biotechs that don't realise that's actually their role are the ones that burn out. The ones that think their role is only as a source of innovation [and their] job is to go and do more and greater and bigger and better R&D are the ones that are never able to get a foundation under their work and not able to move it on unless they happen to be such as sexy field that pharma will take it anyway. (interview with Moss-Smith, 2006)

### **When Research Isn't Research**

GroPep had moved a long way from their origins of discovering and patenting scientific inventions, with Geoff Francis explaining, '... well strictly speaking we don't do any R&D ... which does require something that looks an awful lot like research at certain times but it's more about solving problems to bring about successful clinical trials, but that's a long way between, you know, the start of the CRC and of course the present day ...' (interview, 2006). The challenges facing GroPep have consequently moved on: mostly according to Francis, it is about handballing the product to the next team member hoping they don't drop the ball:

[Is it an issue passing it on?] Absolutely not! When can we do it, how soon can we do it, and how much money are we going to make out of it, and ... are we sure they're [big pharma] going to do it properly, are they committed to this product because for us it's a very important thing, we've had it for say five years, from our branch, we've put five years of investment into it [that's what we are concerned with.] (interview, 2006)

From the wider view of the external scientific community, it seems GroPep has continued on with its pathway of refocusing and consolidation with Tremellon noting 'GroPep [has a] product, they're not burning cash. For a while, they were spread too thinly, they invested in a manufacturing plant in NSW. They've become more focused on their core activities. I'm really impressed with GroPep, their management and the people there. Very professional, never had [a] bad experience with them' (interview, 2006).

Moss-Smith encapsulated the key skills and learnings up to this point:

For this company ... the capacity to be able to make a molecule or to be able to make the assay as required to tell if things are working right, [having] those sorts of capabilities have been essential to company's progress. I think we've learnt other ways of doing things since but at the time they were certainly essential and I would say still represent a major part of the company's capability. (interview, 2006)

Leaving the CRC behind and standing independently as a profitable, listed Australian biotech required the company to consider some serious questions concerning their sustainability. Moss-Smith discussed the issues that faced GroPep in last two years:

We had this issue ... that neither of our business areas was really going to give us a short term growth rate that we would want to be able to keep pushing up the stock price and at the time the market was flattening out, GroPep held its valuation quite well but the whole market was fanning out, the biotech bubble had definitely deflated. (interview, 2006)

The dilemma of short-term sustainability versus long-term profit has continued

to plague GroPep's management. Moss-Smith described what he considered to be the key issues underpinning the strategic tension facing GroPep:

... I have always [held the view that] the company's greatest value would come from success in drug development but because we've always had profitable businesses in the other areas there's always been this tension about what would happen and how it would happen and I don't think anybody really felt that research of products was ever going to be a really big business. (interview, 2006)

Moss-Smith was well balanced though in his assessment of the challenges of maintaining such a business within the company's portfolio:

It's the sort of business where you can keep growing if you keep adding new brands but we found [out] ourselves that when you go to launch a new product that is outside of your existing portfolio, outside your existing scientific range [we struggled] to get traction of those markets. There's a lot of money you've got to spend to shift into a whole new area of molecules when you don't have reputation. So the only way you can really do that, and if you look at the other research catalogue companies, is [to] buy another brand [that] already has that presence when they bring it in. So what you end up with is diminishing margins but a bigger business and I guess since we'd made the decision to concentrate, we kind of had a couple of goes at trying to broaden out from where we were and every time the basic result of not making ground so we cut back and we focused pretty much on where we are with IGF. (interview, 2006)

The sentiments expressed by Moss-Smith have materialised most recently in the form of a proposed new strategic direction for GroPep. A press release dated Thursday 29 June 2006 flagged potential changes:

The report [by Ernst & Young] clarified and reinforced several initiatives which have been under consideration by the Board. Chief among these were the possible divestment of GroPep's Biopharmaceutical Development division and the possible sale of the Company in its entirety. The Board is of the view that shareholder value is not being maximised at present through the existing business model, whereby profits and cash flow generated from GroPep's Biological Products division are invested in biopharmaceutical research and development. With its lead infertility drug PV903 nearing completion of a Phase I clinical trial, GroPep has developed its biopharmaceutical research and development activities to the point where it believes that this division should support a stand alone business case for the commercialisation of its projects. Accordingly, the Board advises that it has

retained eG Capital to examine the possible divestment of the Company's Biopharmaceutical Development division – most likely through a spinout from GroPep or a trade sale. GroPep's Biological Products division, particularly its growth factor products for Cell Culture, is a highly successful and profitable business with excellent long-term growth prospects. GroPep is committed to maximising shareholder value from this business [and believes it will be best] if the Company focuses primarily on the development and expansion of its Biological Products business, either in its present form or under a new corporate or ownership structure.

The longer-term profitability of the company was forecast to continue with net cash reserves of approximately A\$12 million as at 31 December 2005 and a net profit before tax estimate for 2005-06 of approximately A\$4.0 million compared to a net profit before tax of A\$2.7 million in the 2004-05, showing an increase of around 45% and a net profit before tax for the 2006-07 financial year to be approximately A\$5.4 million, an increase of 35% over the 2005-06 (Press Release, GroPep website, Thursday 29 June 2006). The same press release did caution investors of an anticipated short-term decline in demand for cell culture products in 2006-07, however volume is expected to upturn in the long term:

GroPep believes that its leading product, LONG<sup>TM</sup>R3, will be used in commercial production in the future by a number of new pharmaceutical products currently in the late stages of clinical trials. The Company expects to launch a new liquid formulation of LONG<sup>TM</sup>R3 during the first half of 2007. The product will be much easier for customers to use and can be customised to meet the specific handling requirements of individual major customers. This is expected to further embed our product in customer production processes and improve our competitive position. (Press Release, GroPep website, Thursday 29 June 2006)

### **A Danish Invasion – Novozymes Acquires GroPep**

Another significant milestone, the acquisition of the company, in a A\$96 million takeover offer from listed Danish biotech company Novozymes, was announced on 14 August 2006 on the company's website via a Press Release:

GroPep and Novozymes A/S have reached an agreement under which Novozymes will acquire all of the issued securities in GroPep. It is intended that the Proposal will be implemented via Schemes of Arrangement between GroPep and its share and option holders. The Proposal is expected to be completed by the end of 2006, subject to satisfying all relevant conditions. Commenting on the Proposal, the Chairman of GroPep, Mr Richard England, said today 'The Board of GroPep is pleased with this Proposal and has concluded that it is the most effective means of maximising shareholder value. The price of A\$2.05 per share provides all of GroPep's shareholders with the opportunity to realise cash for their investment at a substantial premium to recent trading prices.' GroPep's Chief Executive Officer, Mr Bob Finder, said the Proposal will generate significant benefits for the shareholders, customers and employees of GroPep. He added that Novozymes is a leading global bioindustrial manufacturer that will bring extensive management, research and marketing capabilities to enhance GroPep's market access and boost development of our product portfolio.

This acquisition then represents a new phase in the internationalisation of GroPep. The company had been formed to enable a licensing agreement with Genentech and successfully sold to the world's scientific community in subsequent years and now was the target of an international acquisition. Clearly, the firm had been through many transformations in its history. Goddard gave a précis of how he saw these transitions impact the organisation:

[In terms of having different division that spend money and earn money – that can cause tension] but see that's not where the tension comes from. The tension for that comes from the shareholders, not internally. Internally people are reasonably comfortable or were but the more time [or], the longer you go without having a success in the drug development side of the business, the more difficult it is to justify it because you're burning 5 million bucks a year of shareholders money and what could they do with that? Well they could quite honestly argue why haven't you put 3 people over there where you're markets are? See what GroPep has not done still and what it finally realised it should do was split it in to 2 different companies. So, you end up with investors in one company who have certain goals and aims and investors in another company with certain goals and aims. Whereas we are now right at this moment, we have things that are at the same stage that biological products have and we have things that are at the same stage and money and revenue that CSL have. That's interesting, CSL have gone backwards into the model that we had but the difference there is that their revenue's are monstrous compared to ours. (interview, 2006)

In general terms, the decision to be acquired was welcomed by GroPep's management, and moreover, it was considered to be strategic:

The strategic review said we will continue to be [multiple divisions] and the argument for that was if drug development is successful it will dwarf the other one division and there were lots of arguments put forward and lots of debate as to the sort of business model [we should have] .... The argument was 'why don't you ditch the drug development and watch the share price go up?' Well just to go back to prove to yourself that that is true. We put out an announcement earlier this year where we said we are going to divest the R&D business; if you read it carefully, that's what it says. And the share price over the next few weeks climbed to A\$1.89 from about A\$1.50. Proof and then we didn't do it, it went back down again to A\$1.14. If you look back through all of the announcements we've made this year and you'll see a pattern ... Now of course 3 of us knew about Novozymes, the rest of the people we were dealing with had no idea. One of the three things we said we'd said; we'd sell the company in its entirety so we were completely honest, but one of the others was divest the drug development and over the next weeks or days the share price went up and climbed to its highest point its been since John [Ballard] was fired and then it went back down again to about A\$1.40 until we announced the Novozymes deal and then it went up to A\$2.02 Because they've offered A\$2.05 so all the shares that are trading now are all arbitrages. We were making 5 cents in 2 and a half months, so they're making 2½% sheer profit, in 2½ months you multiply that up by 5 and you get a much better return on your investment than most other places. So that's where we are. (interview with Goddard, 2006)

From Goddard's point of view, he saw the motivation for the acquisition as being:

Well they [Novozymes] are primarily buying this business for the cell culture part of it and anybody who says anything else is deluding themselves. So that's one thing and what they intend to do with that is they're going to put it into a division which'll have Long R3, albumin and transferron, which are the 3 key ingredients you need to make cells grow in the absence of serum. And they'll do that by putting together some sort of division, which includes GroPep, Delta and part of Novazyme that exists already. And now what they'll do is they'll have a look at the reagents business and see what they can make of that and they'll have a look at the drug development business and see what they can do with that. (interview, 2006)

Mr Sven Licht, the business unit manager in charge of the GroPep acquisition explained the strategic position of Novozymes:

Until we were de-merged, most of our IP was all related to enzymes, so there wasn't actually a lot of outside enzymes – of course, there was some general IP but not a lot – and that is changing also now as we try to expand into this new field. So, in this process we were looking at a lot of different things and one project that we were running was making recombinant albumin. That was an in-house project and that was making recombinant albumin for cell culture media where we knew that people would use extracted albumin and we knew there was an interest. If we could produce it cheaply enough that could be of interest.

Now, out of that, during the course of this, we also looked at other opportunities in this field to see what else is there. If you look at the cell culture media, actually got 90% of the proteins – and remember we are becoming primarily focused on recombinant proteins and peptides. So if you look at the cell culture media and you want to provide for mammalian cell lines, you see, you want to provide proteins that are used in the media. Eighty to ninety percent of these proteins are either albumin, transferrin – which is used to transfer the iron to the cells – or insulin or IGF-1, so LR3 from GroPep. The only one that actually came on the market was the LR3 and the insulin – insulin actually from NovoNordisk, quite interesting. But the other ones, the transferrin and the albumin, they were not commercially available in the quantities and the prices that the industry wanted. We had our own project on albumin and then there was a company called Delta Biotechnology in the UK, who were the only company actually really selling recombinant albumin but in a different grade and a completely different price range than we were looking at for the cell culture media. But they also had a project on making recombinant transferrin, so we said, this company's interesting. (interview, 2007)

On GroPep's side of the fence, they saw Novozymes situation as being one of needing room to grow, 'Novozymes is about US\$5 billion cap and over a billion dollars of sales. They still dominate that enzyme business. There's not much more room for them to take market share. The business is only growing at about five per cent a year' (interview with Finder, 2006). Finder remarked at the commitment Novozymes makes to R&D, '... they're a very science-driven company. They spend, for an industrial company, they spend about 15 per cent of their sales back in R&D, which is extremely high. That's typical in pharmaceuticals. But not in industrial' (interview, 2006).

The next steps in the process involved a discussion between an American investment banker and the Danish executives. The banker was aware of GroPep's presence in the market and suggested that Novozymes should review them, 'we have this GroPep and they make this IGF-1 analogue for cell culture media. Okay, now all of a sudden we can pull the strands together, we can do our own project combined to an acquisition and make a shift in the marketplace. We will actually try to do something that has not been able to be done before. So, to create a complete package to the industry in terms of recombinant animal-free components; making it possible it do what the cells actually want, so the actual proteins are transferrin and insulin, but not from an animal source, and that's what the industry was looking for. So that was the starting of it and that came back in ... summer 2005 when we saw the idea coming to us' (interview with Licht, 2007).

Very positively though for GroPep, was when Novozymes followed through on the advice of the American banker, GroPep was perceived to be 'world leader in cell culture. We didn't approach Novozymes. They approached us' (interview with Finder, 2006).

This idea turned into something tangible when two Novozyme's employees decided to pay a visit to GroPep in Australia as part of a larger Asian trip, 'So they came to GroPep and said, "hello, we are Novozymes and this is what we want to do in the cell culture media area." It was an extremely open book approach to them in terms of our vision; very unusual, I think from an acquisition point of view' (interview with Licht, 2007).

From that point, things snowballed quickly and smoothly according to Licht, 'they clicked on right away and they were nodding all around the table and they really

liked it' (interview, 2007). Licht credits this with the fact that it fitted GroPep's already acknowledged strategic plan:

GroPep, remember, were two things; it was the ingredients for the cell culture media and it was in also the drug development. Our primary interest was cell culture ingredients not the drug development. They were also thinking about should they split it up. The board actually were considering whether they should try to de-merge also; sell off, spinout, do something because they could see they were sort of jeopardising, actually, the structure of the organisation and they didn't give the drug development maybe the right focus in terms of a biotech platform in that way it's been valued versus a commercial ongoing business with the growth factor a business wants. (interview, 2007)

Another important factor that facilitated the acquisition was the approach taken by Novozymes, 'we also have what we call triple bottom line, which is important also for acquisitions and we look very much about the management and that's why also we liked GroPep, because it clicked with our thinking. [It was a good cultural fit too] ... very much so. It's also because Novozymes is not a very tough company as an acquirer. We are not good in slashing and taking the assets or taking the spoils, you know' (interview with Licht, 2007). As to their preferred way of dealing with mergers and acquisition, Licht explained, 'What we are good at is collaborating with people and then people grow and, given the opportunity, grow even more. We push them, of course – people get a lot of push from here but it's positive reinforcement rather than their necks are tied. So, we really need often the local management with that in the acquired companies' (interview, 2007).

GroPep felt the process had gone well overall, 'So it took over ... a little bit over a year from when they first met with us till ... the shareholders voted. It was a long process. They did it extremely thoroughly, with due diligence. They ... they had something like 70 to 90 people involved in the due diligence and 30 of them were actually here' (interview with Finder, 2006). As did the Novozymes team, who saw the

collaboration as being attractive ‘... because with the combination of their [GroPep’s] activities we could create something that was unique in the marketplace; an offering that didn’t exist, a position in the value chain for the mammalian cell lines ... we could ... latch onto the growth of monoclonal antibodies without taking the risk of being a biotech drug development company, because what you do is try to add solutions and products into an industry with a growth of maybe 15-20% per annum but you don’t take the risk of one development project’ (interview with Licht, 2007).

Licht discussed the potential deal breakers though, from Novozyme’s point of view:

We talked very much about their physical distance and the setup being down there [in Australia] and it was a problem, it was probably one of the major problems. Other ones that got a bit hefty was that this was the first acquisition we did of a listed company. Up until then we primarily have been acquiring – and we still are primarily acquiring – privately owned companies or non-listed companies or carve-outs from other companies or whatever, kind of thing. So this was a first and, until now, only sort of listed company that we have been acquiring and that created, of course, some issues about is the price higher for a listed company than a privately owned company? Is the price too high? What kind of competition are you up against in terms of getting the deal? Should you do it as, in Australia, this system of Scheme of Arrangement versus a classical way of doing it? We actually decided to go for a Scheme of Arrangement because we interpreted this with our consultant as the one with the least risk for us in terms of speed and timeliness of it, whereas the GroPep people, they thought it was a bit odd that we selected that. They thought it would be much better to do a classical, just bidding kind of offer on shares. We were afraid that then you will have counter-bids. It could inflate the price and you would never know where you were. We preferred to have a system – we knew the system, we knew this is the time where a decision is made and that’s it. (interview, 2007)

What this approach amounted to was Novozymes desire to be in control of the process, ‘We felt that we were more in control this way than the other way. We might be wrong, but that was our interpretation of it. Another thing that was important for us was always to look for change of control because in GroPep their main distributor was Sigma-Aldrich and there was a change in control in the contract. That was crucial for us

to ensure that they were not stop-lock us in any way or form in the dealing – that was a major issue for us – so I think that was enforced’ (interview with Licht, 2007).

Beyond the cell culture business, there was speculation as to what would become of the drug development division of the company. Goddard speculated ‘I suspect they’ll flog it off, I don’t think they’ll close it, I think they’ll try and maximise what they can from it but that’s just a personal opinion, I’ve got no idea. They also have what they’ve acquired here as well as a whole set of expertise and I think they’ll use that and I think some people will perhaps be moved to other parts of the organisation’ (interview, 2006). And in response Licht said, ‘We also ... had a bigger discussion ... about the drug development side, what should we actually do with it? Should we stop it completely? Should we sell it off? What shall we do with it? There was a lot of discussion back and forth as to whether we wanted to do it because it was this issue’ (interview, 2007).

At the time of writing, there had been some progress in terms of the physical collaboration between the companies and how they would manage the perceived primary problem of geographical distance, ‘but the physical distance actually was an issue and it is today, in terms of how we collaborate, but it is not a problem, you see. Now, just in there in the office next door, they’ve got two from Australia sitting there. We have people come here ever so often to work for a short or longer while, so we are dealing with the physical distance but it’s cumbersome and it’s expensive’ (interview with Licht, 2007).

Licht also offered some key learning for Novozymes out the process:

Another thing we did wrong was the usual that we always do wrong and that is saying you should never, ever close an acquisition during summer breaks. We have done it several times in the US ... [and for GroPep] that was New Year Australian summer break. It was announced in August as a deal but it was not closed until December. So I think there’s a lot of learning. I can give

you – we have a list of learnings, actually, that we could do better ....  
(interview, 2007)

### **Closing Vs. Parking**

For the remaining projects, there was some consolidation on that front. However, as to their long-term viability, there was still a level of speculation, principally due to the uncertainty facing the organisation at that stage. Moreover, the terminology itself was challenging – with Licht preferring to say the projects had been parked not closed:

Maybe I should turn around and say there's a difference in closing and parking. Now, because GroPep is under another kind of regime, there are opportunities to park and figure out what do you want to do with the assets – can you create more value and in what form? We think, what do we do with the company, you know. Other unplanned issues – no, there were not major ones. Of course, we do the usual things; we looked at what's going on, the financials and forecasts – there was a lot to do with the forecasting of the systems and the market growth and what should we do now, but nothing that we couldn't sort of detail with. The future role as our Australian subsidiary, that's basically in two ways. It's still the production site for LONG R3 IGF-1. It is an area we are building up in our capabilities to support cell culture ingredients, so to understand actually mammalian cell culture lines. So, what we're trying to build is a competency around mammalian cell culture lines. Try to say, if you take this and that and that component into the ingredient what happens and how do you optimise the different cell line and all that stuff. Another thing that we are doing is we will most likely also use some of the resources there for some other projects that we are in, development projects – could be in different areas. Of course, there is an issue in terms of what will the future bring? We don't know. Novozymes is constantly changing; we are building, in the first instance, our plan is to build even more in China, so large scale facilities and, again, we will be trying very much to utilise the biopharmaceutical skills of GroPep, former GroPep, known now at Novozymes Adelaide. (interview, 2007)

GroPep's staff were expected to provide ongoing contribution to their new owner, Novozymes, however the financial contribution of the company was not disclosed with Licht saying:

... I can say that in terms of the experience of the people, it's [GroPep] really high skilled people and that has, to the full extent, lived up to our expectations. Whether from a business perspective whether it's above or

below I will not tell you. In terms of other outcomes, there was a clear feeling that we should take a much more diligent decision in terms of the drug development side and we changed that, actually, because when we got into the process of learning the capabilities, we were, 'hey, we can use this for many other things than just the portfolio down there.' So, yeah, people again. We had an antimicrobial peptide project running in Denmark; people from Adelaide are supporting this as well now. So it's non-ending, this networking. Very much blending skills into the right way of functioning. That's why Chris [Goddard] is now moving to Denmark to head up our entire pharmaceutical drug development ... you've got super people. It's part of us realising that competence is the people and the fit – cultural fit, if you want to say it that way – it was ideal in many way for us. (interview, 2007)

And beyond simply parking projects, Licht was quick to say that as a company, Novozymes was well aware of the problems of shutting doors prematurely on projects, '... that's one thing that you could argue that we are very careful about, not slamming the doors. We have our finance people in our organisation quite high up in the system, who actually want us to close down the stuff you don't want, whereas a lot from the business development side and new areas say, hang on, let's now see what's in the bag. Even our board of Novozymes, when we presented Delta and GroPep to them said, 'guys, now be careful you don't cut away good science – we are a science-driven company' (interview, 2007).

### **What's in the Bag?**

GroPep's future as a part of Novozymes remains largely unknown at this point in time, 'It still remains to be seen in terms of the projects and what they have in the bag' (interview with Licht, 2007). Considerations by the senior management team in charge of the acquisition are obviously taking a holistic approach to their decision-making as Licht indicated:

I mean, you should never say never, but for the time being there is no specific plans to say we're going to slash and dice it away and move the money in the container. That would be a pity because you will not utilise actually the skills

that are down there [in Australia]. You will – again, if you think about it in the way that we’re thinking: people are the skills. We acquire people, we don’t acquire what’s in the drawer – we do both, of course, but ....

With biotechnology, you actually need to make sure that you handle it properly. That’s one thing. The other thing you have to be aware of, if the activities become too small down there [in Australia] then people will leave the company. (interview, 2007)

Yet as Licht pointed out, managing the situation is not without its challenges: fundamentally, the *people* are scientists. It is well known that what motivates others, such as business people and entrepreneurs, is quite different from that which motivates the scientists:

You have the other side, when we acquired Delta Biotechnology. One of the problems we had there was the lack of sense of urgency because they were very much in the scientist role. They didn’t – they had this ongoing business, they were earning a lot of money, enough money to sustain them but ... [it was a case of] Let’s go and have a cup of tea and read the newspaper every morning. Whereas you come [along] and say, now boom, boom, and you’re pushing all the time, because we are much more on the entrepreneur side of this, if you are saying this word here. So I think it’s a challenge – if we take it in this context here – if you acquire a company of scientists to ensure that they get the entrepreneurial experience but don’t lose the science because the science is for the future as well. (interview, 2007)

The early approach taken by the new management bode well for the legacy of GroPep and their IP to take on a sense of longevity. It is exciting to see that from a little spinout company in 1988, that many great things remain yet to be seen.



## Appendix IV

### THE CASE OF CYTOPIA

#### Discovering the Drug Target

In 1989, Andrew Wilks, a molecular biologist at the Ludwig Institute for Cancer Research at the Royal Melbourne Hospital, found two members of a new class of enzymes that his colleagues jokingly christened Just Another Kinase 1 (JAK1) and Just Another Kinase 2 (JAK 2). Wilks described the process he used to find his new kinases:

The original discovery, the actual process of discovery started in about 1989. There was a new technology [published] ... and the ink was [literally] still drying on the journal paper. When I saw it, it was called thermo-chain reaction and subsequently the guy who invented this technology won the Nobel Prize, Kary Mullis. But it was a way of amplifying DNA out, specific DNA. I was working at the Ludwig Institute at the time, I had a small group there, and we were nesting in the Walter and Eliza Hall Institute. What basically transpired was that as I applied this technique to look for some of the receptors for colony stimulating factors that were actually being studied at the Walter and Eliza Hall Institute, the technique worked incredibly. I got probably the paper I'm most proud of out of that. What was in the paper was the discovery of a number of different proteins and these proteins were kinases or enzymes basically that put a phosphate group onto other proteins, and that's a signal within the cell that is a state of activation really. Basically this phosphorylation process was part of what's called signal transduction. In fact, all drugs work on signal transduction one way or another. They are kind of key enzymes and they become quite well validated targets in Glivec and a bunch of other drugs .... (interview, 2007)

For Wilks it was a bit of a whirlwind, '... the journal arrived on the Wednesday. On the Friday I was doing the experiment, on the Saturday – [I was] working the weekends in those days – I realised that the rest of my life was about to change because

the experiment had worked and I got this big band of DNA that had been amplified ... I cloned the DNA and I sequenced everything and there were dozens to hundreds of these new kinases' (interview, 2007).

His result was staggering, not only to himself, but also to many other scientists: in fact, it became a revolutionary process that many other people adopted:

It's extraordinary popular .... Ironically, as we started working with them it became clear that these were in fact part of the process inside a cell that is triggered by a cytokine like GM-CSF and G-CSF. Because of that, lots of pathologies, lots of inflammatory pathologies, but also lots of cancer related pathologies, are related to over-production of cytokines. Looking back, it's kind of an obvious deduction that this might be a good drug discovery target. (interview with Wilks, 2007)

The commercial potential of the JAKs was recognised early on. An article on the discovery noted that 'Multinational pharmaceutical companies are lining up to negotiate with the Ludwig Institute for Cancer Research ... for the rights to develop drugs based on the JAK kinase discovery' (Sweet, 'The "I'm all right JAK drug"', SMH, 19 August 1995, p. 7).

In 1991, the Ludwig Institute lodged a patent cooperation treaty (PCT) covering the technology Wilks had discovered. Simultaneously, the resources allocated to work in this field grew enormously, 'Well the patent went in 1991. What happened was in that band of DNA there were so many sequences, my lab went from about four people to about 30 people. Not quite overnight, but in a year to 18 months' (interview with Wilks, 2007).

Approximately two years later, Wilks 'fell into the idea' of starting up a company. As he explained, he was inspired by other scientists of his acquaintance who had been involved in start-ups:

At the same time a number of my friends were starting companies in the States. I'm skipping now to about 1992 to when a lot of this stuff had become

clear. In 1992 a chemical company called Sugen - S stands for Schlessinger, U stands for Ullrich [started up]. Schlessinger and Ullrich were two incredibly famous scientists who started a company. They were starting to work on kinases, EGF receptor for example. Iressa and Herceptin - these were products that Axel Ullrich, specifically [commercialised]. [They were] the inventors of that. Around '93-'94 the idea blossomed that I have a patent on a potential drug target, some of my mates are starting companies using their drug targets, why don't I start a company? (interview, 2007)

Wilks though, readily confesses to his naiveté in terms of the degree of difficulty in starting a company in the Australian biotechnology context, 'I hadn't realised how incredibly hard it was in Australia. I fell in with a rather bad crowd ...' (interview, 2007). The proposed vehicle for setting up the company with his IP was a syndicate, which at that time was positioned as a tax advantage for investors for highly speculative products, as is consistent with early stage biotechnology research and development:

With a vastly increased valuation on the IP, you could generate tax deductions for people who wanted to invest in technology. On the one hand it was entirely fictitious as a way of generating money, but on the other hand a lot of good techniques or a lot of companies rode the back of that sort of thing. For a couple of years I looked into working with certain groups, I won't say who they are, to set up one of these syndicates. Around about 1996 we almost got the forms in and they stopped the system, I think it was 1996. So we were kind of at square one. (interview with Wilks, 2007)

And whilst he conceded at the time it was disappointing, with 20:20 hindsight it is more a sense of relief Wilks describes than anything else, '... [A]t least I'm not in jail now which is a nice thing! I know a lot of people that are getting probed by the IRS and all of that. But the idea was already really quite well fleshed out. There were good targets; there were ideas about how you might get the chemistry to discover drugs ...' (interview, 2007). Hence, the change in legislation put pay to Wilks's plans at that time, with the government ending a period in Australian investment history known as the Syndication Schemes.

As part of his attempt to get his company off the ground, Wilks himself prepared a business plan – but found he was on a steep learning curve: ‘The first business plan I wrote, I went to see a venture capitalist, who I won’t name’ (interview, 2007). Upon showing it the investor he was promptly told, “‘it’s a great NHMRC grant but it’s not a business plan, mate”, and they were right of course’ (interview with Wilks, 2007).

Around the same time, about 1996–1997, Wilks was introduced to two men, Kevin Healey and Nicholas Mathiou. At the time they were working for a company called Vision Systems in one of its consulting divisions named Invetech, but they would go on to found their own consultancy, Insight. This introduction was facilitated by a mutual colleague, as Wilks explained:

One of my friends who is now a professor in Peter Andrews’s old department in the IMB [Institute of Molecular Biology], Paul Alewood, is a good friend of Kevin’s. Kevin’s really very skilled at picturing science in a commercial context and so, unlike a lot of the other VC people I went to see, Kevin got it very quickly. He used to be a proper scientist as well. (interview, 2007)

This introduction was fortunate in numerous respects: (1) Healey had a good understanding of the science and expressed a certain amount of confidence in Wilks’s work, (2) Mathiou and Healey helped Wilks to produce a business plan and (3) Healey utilised his connections with the investment community to help Wilks take further steps in terms of creating his business:

They helped revamp the business plan and turn it into a proper business plan. He hooked me up with an investment bank, it’s an increasingly long story, and so off I trooped with the investment bank and Insight were left way behind. With some of the people in the investment bank we re-wrote the business plan, not entirely, but the nugget was still there but we sort of cut out some of the old technology that we didn’t want now and put some new technology in ... really to try and bring in the idea.

[The investment bank] had another company in the States which was largely based on natural products and here in Australia we had some synthetic

chemistry ideas and some natural products ideas and there was this synergy there in terms of natural product sources. Could we, not join the companies together, but package them together to sort of leverage it off each other to get the funding done? So, off we went on the world tour in the United States, San Diego and San Francisco. (interview with Wilks, 2007)

As part of his world tour, the group visited investment banks in Switzerland. Wilks describes this process as somewhat surreal at times: '[We would visit] Swiss banks which don't look like banks but knock on the door, the door opens, we go in. [It was] very strange stuff. A different world; very strange places' (interview, 2007). But in the end, nothing eventuated from a year of meetings, planning and travelling: 'In the end what happened was the other company fell out with the investment bank and the whole thing just cut apart' (interview with Wilks, 2007).

Meanwhile though, the Ludwig Institute still formally employed Wilks. They naturally were growing more aware that Wilks was spending more and more time on this commercial enterprise than on his duties at the Ludwig. As a result, they suggested that Wilks needed to make a decision about the future of his employment. Wilks explained things from the Ludwig's point of view, 'The Ludwig said "well look, you can't actually hold equity in a company based on your technology and still stay at the Ludwig because there's a conflict of interest"' (interview, 2007). Wilks did not share this point of view: 'There isn't [a conflict]. Or well, at least it's a surmountable conflict of interest' (interview, 2007). The Ludwig gave Wilks six months to consider his position, after which he would have to 'pick one. So, on December 31<sup>st</sup> '1996 I said, okay I'm going to start the company, and of course there were tears in the lab' (interview with Wilks, 2007). Despite this initial dismay upon news of his departure, Wilks maintains that his decision was actually positive for the lab that he left behind: 'Actually the lab did incredibly well; I was probably holding them back thinking about

it. So all these young scientists ... either sank or swam and some of them swam and they've done incredibly well' (interview with Wilks, 2007).

This sequence of events meant Wilks was now unemployed. He explained the significance of this decision to him on a personal level:

But I was now without a job, start of '97 and, at the same time, I had the opportunity to go to this investment bank to get the money up. Anyway, that all turned to ashes August that year and there was then what my wife calls the baked bean years which was no money, nothing. She was a post doc in a lab and was supporting us on that so it was really spiraling downwards. We had bought this nice house in South Yarra; just the whole thing was just a shambles. (interview, 2007)

With these personal challenges confronting him, Wilks said at the time he considered returning to a 'proper' scientific job, but the options there were not clear-cut either: 'I couldn't go back to the Ludwig because that was just all over so where would I go ... ? I'd have to start again writing grants and all this sort of thing. So it was quite a difficult time ...' (interview, 2007).

Wilks shared some of the personal challenges he faced during this early period of the company's history when on one occasion he had to renew his passport. As part of the process he was asked to write down his occupation. He realised he was unsure just what to write at that moment in time:

I'm not a scientist, I used to be a scientist, I'm not a scientist. I'm not a businessman; I haven't been very good at that. Not sure. What have I actually done that's earned money? And there were two things that I'd done. I'd written a book, a text book, which is on the shelf there. So [I] could have been an author. And I'd also won a prize in a chess tournament. I came sixth in the Australian Lightning Chess Tournament. Was I a chess professional? (interview, 2007)

'And, in fact, I didn't have the money to renew my passport ... for a while. Which is kind of a suicide thing to do because you need a passport for travel? Anyway, Medica came to the rescue in the end. They actually dipped in to support me and pull

me through until the money came in. That probably took three or four months all up. So they actually took the risk on me and it could have all fallen away' (interview with Wilks, 2007).

At the same time, he was fortunate on another front. Whilst Wilks was the named inventor on the patent, it was his employer, the Ludwig Institute, that legally owned the intellectual property, as is customary in these kinds of organisational arrangements. However, the Ludwig institute was prepared to favour his moral claim to the IP despite being courted by some large multinationals: 'the Ludwig held the licences for the technology for me and fought off a couple of other suitors, big pharma suitors to take these patents. So they were good enough not to do that and screw me over with cutting the IP from under me. [T]hey could have done that though if they wanted. It was their IP. It's my patent, but I'd given it to them for a dollar' (interview with Wilks, 2007).

Besieged by seemingly unpalatable choices, Wilks was feeling rudderless and approaching the end of his tether. He then described the next crucial event to take place in Cytopia's development pathway, '... and so re-enter[ed] the Insight boys who were now Medica Holdings ... I called them up and literally said, so you got any money? They said, well actually no, but what we are going to do is float this baby, so we're going to put it on the ASX. So, what we'd like to do is include Cytopia into a funding strategy, raise some money and have you part of our three investee companies (interview with Wilks, 2007).

As far as the company Cytopia was concerned, though, it did not formally exist at this point; it was nothing more than a series of business and scientific plans. Wilks did proudly explain though the origins of the name Cytopia, 'it's kind of a Greek/Latin approximation. So Cyt means cell, so cytokines are things that work on cells, make

them grow and remember cytokine is the word which it originally came from and opia means *all things*. It means *all things cytokine*' (interview, 2007).

## **The Founding of Medica**

Medica Holdings launched as a Pooled Development Fund in August 1997 and now they had agreed to invest in Cytopia. How Medica came to being is an equally complicated story. Dr Kevin Healey, a PhD in science, began working in the field of life sciences as a consultant as part of the company Vision Systems in the late 1980s. Vision Systems was involved in advising various biotechs in terms of knowledge and investment, but invariably, Healey explained that some companies they were able to help and others they watched fall by the wayside.

Some time later, Nicholas Mathiou joined Healey as a colleague. Mathiou had a strong finance background and was employed for these skills. According to Healey:

Nick came in a bit later into the business strategy group having a finance background because we were, I think, seen as being too technical, so we wanted to beef up the financial capability of the company and Nick came in as really someone who was excellent on analysis of companies and did a number of M&A reviews. We sort of worked together quite a bit on various assignments and decided that we'd like to branch out and start our own consulting business focused on technology commercialisation. (interview, 2007).

Mathiou also recalled their initial connection, '[Kevin and I were working] in the business strategy and technical group there [at Invetech]. It was actually commercialising technology. It was part of the Vision Systems Group which was, until recently, listed on the ASX. But Kevin and I both sprang from there to set up Insight Advisors – that was our equivalent, if you like, but with a slight difference. We took on projects on a success fee as opposed to just purely fee for service' (interview, 2007).

With Nicholas being based in Brisbane and Healey having a high degree of flexibility over where he lived at that time, the pair made the decision that Healey would relocate from Melbourne to Brisbane to start up Insight. Healey also had contacts in the industry already; for example, he knew Professor Peter Andrews from Bond University. In fact, his friendship with Andrews extended back over a much longer period, ‘Well, I knew Peter when he was at the pharmacy clinic in Victoria and Perth. You know, [we] go way back, and [I knew] his number two, Paul Alewood, who is now sort of deputy head of the IMB [Institute of Molecular Biology]’ (interview with Healey, 2007). In terms of reconnecting with his colleague upon his move to Brisbane, this came about in about 1996 – 1997 when Andrews asked him to do some consulting work at the institute that Andrews was working for at that time, the 3D (Drug Design and Development) Centre where Andrews had joined after he resigned from Bond University. The 3D Centre was the predecessor to the IMB. Healey explained, ‘one of the outcomes of doing the technology audit of Peter’s 3D Centre was that I saw a number of opportunities that I felt couldn’t get funded adequately in the university setting because they really needed commercial development funding’ (interview, 2007). Also noteworthy was that at that point in time, the universities were also unskilled and unorganised in terms of identifying and capturing technology potential. As Healey said, UniQuest was around but effectively not doing very much:

They had some idea – I mean, they were toying with a ceramic spinout but nothing had happened in the life sciences. Basically in my report I suggested to Peter [Andrews] that there were at least a couple of spinouts and one became Xenome, that we started up later on, and the other became Protagonist, which we ended up not funding for financial reasons but they got money from Start-Up Australia eventually. Then in the process Alchemia came to light and the prospectus for that, and I said to Peter I wouldn’t mind being able to fund some of that and I was willing to go out and try and raise some cash. I mean, why would he say no? (interview, 2007)

The outcome was that out of their first venture, Insight, the pair realised they could set their sights higher and in essence this was how Medica was spawned. This meant trying to put together a plan to raise money – not a simple thing to do on any occasion, least of all during a national (and partly international) economic crisis, i.e. the Asian financial crisis of 1997. Healey detailed the events surrounding Medica's gestation:

So I went back to Nick and I said, Nicholas, there's an opportunity here if we can raise some funds through a vehicle to get a piece of the action in some of these start ups and play a major role in the companies going forward. That's easier said than done in those days, because in 1997 that was the year of the Asian meltdown and the October crash. It was a pretty horrible financing period but I knew a couple of stockbrokers in Melbourne that I'd worked with on the other deals from an advisory point of view and they liked the idea. Then we chose a Pooled Development Fund [PDF] as a structure that was fairly clean and had [tax] advantages for the shareholders. Being a fairly clean shell sort of set up, transparent to the investors, I went and talked to these stockbrokers who had some [possible investment funds] – there was no concept at that stage of raising money from the public, but they had some high network clients who were sick of being taxed on capital gains and biotech really is a capital gains area and I don't expect dividends for quite a while. (interview, 2007)

Pooled development funds were a structural option for financing firms for over a decade in Australia and only ceased to exist as recently as June 2007. Most recently, according to Healey (interview, 2007), 'the Government's introduced legislation for venture capital limited partnerships which, if you look really closely, the rules are almost the same as the PDFs. You get a tax benefit immediately, though. But there hasn't been any set ups yet'.

Given the partner, Healey and Mathiou were realistic in their expectations of both timing and money, the plan was to, 'raise about half a million dollars then, when the time was right, to try and raise [more] money from the public. [The A\$500,000] ... that was just really to fund a prospectus and all the legal work to get the float up later

on' (interview with Healey, 2007). Healey also called on some of Andrews's network in terms of getting a feel for the market, 'Peter suggested I go talk to Alan Woods, who obviously did well out of Biota and David Bull' (interview, 2007). Medica was launched in August 1997.

For Mathiou and Healey this meant committing significant funds alongside another investor. Healey described the initial investment structure:

with Alchemia ... because another investor was also interested in coming in [to the group], we had to commit to come in alongside Start-Up, who also funded it on day one. Start-Up Australia ... was ATG [Australian Technology Group] in those days. So, we had to commit half a million to Alchemia and we had a schedule of investments up to about A\$2.1 million over an 18 month period. We never thought we'd have to shove in the half a million that we'd just raised but the time came – I think it was December '98 or January '99 – and we only had that half million in the bank and we had committed to invest half a million in Alchemia. So the prospects for us was to let that half million go into Alchemia or lose the investment opportunity. In hindsight – we put it in obviously, but it was a bargain at the time. Even though Start-Up thought they'd screwed us. Start-Up's first investment into Alchemia was at a much lower valuation than we had to come in at. So, they got a much better deal but for us it turned out to be the catalyst that got the whole company off the ground.

Then I think six months later we were due to put another half million but we didn't really have that half million because the market conditions had been so bad, so we went back to the original seed investors and they wrote out cheques again for another half million ... That all went into Alchemia again and at this stage Nick and I hadn't had a salary for a year.

So we still didn't have any cash. We had another million to put into Alchemia the following January, so that would have been January '99, I think, just before our float. We managed to raise that again. They [the University of Queensland] weren't able to put funds in at that stage. Alchemia wasn't really a spinout of the University of Queensland. It was more or less a private start up by Tracey [Ramsdale] and Peter [Andrews]. (interview, 2007)

Mathiou explained that while they felt the two of them could bring a powerful combination of skills to the table – 'we've got Kevin's scientific commercialisation bent and my financial commercialisation bent' – they did not find it easy to get funding for Medica: 'We've certainly got a set of experiences which are, you know, highly

unique in the Australian market. But trying to convince investors that that's worth something is the difficulty for everyone in Australia, actually' (interview, 2007). Healey and Mathiou did not feel they were in a position to pay themselves a salary in this early period: 'Well, Andrew talks about his lean years but they weren't as lean as he makes out because Nick and I mortgaged our houses to pay him a consulting fee to keep him alive while we went out and raised cash, it was nerve wracking. Very nerve wracking' (interview with Healey, 2007). Mathiou also talked of the tough times Healey and himself faced early on, 'Look, the first two years getting Medica up we didn't draw a salary, not a cracker. So, you know, that's tough times' (interview, 2007).

On top of the stresses associated with raising finances, Healey also explained the challenges of physically setting up Alchemia:

I think [the home of Alchemia] was Tracey's [Ramsdale] spare bedroom ... when we started Alchemia we actually had to develop everything from scratch. We had portable, prefabricated laboratories on a CSIRO site at Long Pocket in Brisbane. [We paid] token rent for the site. We brought in the prefab labs. [We had] to kit them out ourselves, though. That's one thing that really pissed me off about Government in those days. They could have really helped start-ups by helping with infrastructure, and they still don't, except for South Australia. It does. (interview, 2007)

Healey speculated that in Victoria and Queensland, a series of corporate failures has meant that 'Government's very afraid to help private companies at all, being seen to pick winners and help them – they're very shy of it still' (interview, 2007). For the older companies again such as the ones who had started in the mid to early 1980s, Healey said this:

Look, the thing that helped companies – I mean, Circadian was first ... I think, '83 [was the nature of investment and the environment]. That was Leon Sherry who was privately wealthy setting up a listed fund to go into biotech. He'd had a few failures and he'd started up Metabolic. Then '86, '87 really there was major change in Victoria when the Cain Government got in. He believed strongly that technology was going to save the state and they made it very easy for companies in the technology field to get money – too easy, in fact. So

there was the Victorian Investment Corporation and there was VEDC and they all put money into various companies including Biota and, as it turns out, Vision Systems. (interview, 2007)

Specifically in relation to government schemes, Healey painted a detailed picture of the investment and economic landscape around that time:

Well, there were a few Government things that happened. VIC was one but the other was the Federal MIC Scheme. It was more the financial markets and just the lack of experience of investment markets with biotech. Like, there wasn't a long list of tried and true either high networks or institutions that had been in biotech and made money. So you had the unique situation where, you know, the Alan Woods' [one of two major private investors in Biota in 1985] of this world didn't mind chipping in because they'd made some money in biotech but there wasn't a long list. Most of the other money that we raised came in from contacts of the brokers that I knew. A large investment came through a personal contact, Mark Rowsthorn who now heads up Asciano. Now Mark I've known for 20-odd years and sailed with him and his father all over the world just about, and he's put in, I don't know, up to a million – I'm not too sure how much altogether – but recently put in another 8 million. ... You know, when you've got 7 or 800 million in the bank you can afford to spray it around a bit. (interview, 2007)

In terms of how he came to decide in investing in Wilks's technology, Healey did concede that there is a certain benefit in being a trained scientist as he was. Specifically, he said, 'It shortcuts a lot of due diligence, because I think you can do all the due diligence you like on an investment but if it doesn't pass the smell test and your gut feel you're still never going to invest in it ... we didn't do an awful lot of due diligence because I just felt that they were right, you know, the right investments' (interview with Healey, 2007).

A key consideration in making an investment decision was the integrity of the intellectual property, although it transpired out that the JAK kinases were not as clear-cut in terms of ownership as what it first appeared:

We would use a patent attorney to get a final opinion but I would do the initial strafing around to see whether it looked murky or not murky. If it looked murky then we'd employ an attorney. If it looked squeaky clean then I usually

didn't bother. [But] it's not always black and white. Sometimes you don't find out under many years later. Sometimes it's not the patent at all, it can be – well, a classic case is the JAK2 patent that we licenced from the Ludwig. I mean, the chances are that that's worthless because of court cases that have happened in the kinase area. At least, there was a case between Merck and Integra in the US which was basically could you use a proprietary drug to screen your own compound against, even if something else happened – which is the case in JAK2, we have the patent – and the US Supreme Court upheld the fact that you could – providing that the data was necessary for the FDA and drug registration – you could use anything you liked basically, whether it was patented by someone else or not. So we know that people are infringing the JAK2 patent but we're reticent at the moment, until they get a bit more advanced, to take any action because it would just cause a major financial issue for us to challenge them at this stage. (interview with Healey, 2007)

With regards to their own situation concerning their IP, Healey said, 'JAK3 is in the public domain, but we've certainly got patents on the molecules and that's the best protection you can get, anyway' (interview, 2007). He also explained some of the challenges by offering an example of Alchemia:

Well, if you take Alchemia for an example. Well, you know the chemical structure roughly of a sugar means that when you try and add two sugars together it can join together in about 25 different ways. If you try and join two amino acids together to make a peptide, it can only join in two ways. So, sugar chemistry is a hell of a lot more complicated. Alchemia came up with the trick of being able to control how two sugars join together so that you only ended up with one product. So what you would call the platform technology patents are all about how you do that and they're pretty protective and no one else has come up with better chemistry to circumvent those patents. But then what you do is, if you use those patents that cover the platform to create a product then you can patent the product as well. So you build up a suite of patents around being able to do it and then what you've actually done and then the applications of what you've done, so you get a good suite of patents around it.

Well, in the case of Cytopia, we don't – I mean, we do have patents on the targets but, as I say, the strength of those is dubious – so we have to build a suite of patents around the molecules that actually hit those targets and try and protect the chemistry patch so that other companies can't design around our molecule. [We are] constantly [trying to protect them], all the time. (interview, 2007)

Kevin Healey also pointed out that the evaluation of investment opportunities involved above all an assessment of the key scientists involved in the venture:

you back the people to a certain extent. Tracey [Ramsdale from Alchemia] had no experience at all in commercial biotech. I mean, she came into the 3D Centre to do a PhD in molecular modelling and has never really had a commercial job. So, with that background, stepping into a start-up and really feeling her way and learning on the job, she's done an amazing job of getting there. (interview, 2007)

From Healey's point of view, Wilks's decision to resign from the Ludwig Institute was decisive. It evidenced not just belief in his scientific discovery, but also their willingness to commit to the risk of commercialisation:

[O]ne of the reasons that we ultimately didn't invest in Protagonist was that it wanted to remain incubated in the IMB building. We just felt that if the researchers and the principal of it aren't committed enough to jump out and take a risk then that's not the sort of investment we want to make. That [Wilks] was willing to leave the Ludwig, take the risk – and it was a reasonable risk for him because he had a good career and a good group – that was worth backing. (interview with Healey, 2007)

Healey gave a recent example as to how this still forms part of his 'smell test' technique:

... well someone offered a technology to me yesterday that's within – I won't say which institution – but the first question I asked was, who's the product champion, who's really pushing to get this off the ground? Oh, I'll have to check, which automatically says to me that it may be a good idea but there's no one pushing it, it's not going to fly. ... [I]f it's good intellectual property – which is a product platform, not a single product – and there was someone really championing it and, you know, it had freedom to operate in the space it was in and it was in good markets then, you know, we would look in on it very favourably. (interview, 2007)

Healey was quick to point out that throughout the 1990s, one reason why networks, contacts and his 'smell test' was so widely used was 'because there were no experienced biotech managers around in the late '90s. Some people would argue there's still not' (interview, 2007).

Legally speaking, Cytopia was registered as a proprietary limited company with the Australian Securities and Investment Commission in July 1998. Wilks said, ' ... the

actual first day when we first lifted a pipette in anger was 1999' (interview, 2007). As part of its foundation IP, Cytopia obtained an exclusive licence giving it worldwide rights to the JAK proteins from the Ludwig Institute for Cancer Research (LICR).

For Healey and Mathiou, the next critical step was the listing of Medica on to the Australian Stock Exchange. Healey highlighted how and why this occurred:

The IPO of Medica came in March '99 and that was basically the last roll of our dice – Nicholas and I, that is – to try and raise a substantial amount of cash, so we went for A\$8 million. The markets had been cracked but there were signs that they would recover in '99 and we were the first successful float in '99. That was on the back of backing of one of the directors of ANZ [a leading Australian commercial bank] who'd liked the story all along. He'd finally got his other directors to say, yeah, we'll get behind it, and basically found us A\$8 million from retail investors in the last couple of days of the campaign. We did manage to get one or two institutional investors but it was mostly mums and dads. We had Telstra in it at that stage, Telstra Superannuation.

[Healey agreed it was very much a process of grabbing a bag and hitting the pavement and selling.] I mean, I did road-shows, [saw] all the stockbrokers. Hammered on the door of institutions that ANZ introduced us to, so I think we had AMP come in, in the early days, Telstra. We had money from Seafirst, which was John Calvert-Jones and they were there for quite a while. I think they traded in the highs of the biotech boom, so they made some money. (interview, 2007)

When it came to the point of taking Medica to an initial public offering (IPO), two biotech firms: Alchemia and Cytopia, as well as three potential investments: Xenome; Cytokine Mimetics and Cytopia Research listed as part of the prospectus:

... what happened was that as part of the review of the 3D Centre there were two companies: one ultimately became Protagonist, [which was] Xenome and, obviously, [the other was] Alchemia. We [Healey and Mathiou] wrote a prospectus saying that these were going to be the investments ... the investors knew what they were getting.

There were three investments that looked pretty good. In fact, I think we had two others in there – Cytopia and, no, we took the other one out, I think – they were the four. [T]he way that we sold it to our investors was that you can spread your risk by investing into lots of different companies or you can spread your risk by investing into a manager, if you like, that knows the area and then we'll spread it out amongst a number of companies. So each of the

companies we chose to invest in had platform technologies. They weren't like a one product company Biota. [It was a deliberate strategy to chose platform technologies] because the thought was that if it's got an underlying platform and one of the products fall over – which it did several times with Alchemia – that there'll always be another product to push through. I mean, in the case of Cytopia it was a kinase platform that we developed. Xenome had a conotoxin screening system and Protagonist had a technology based on molecular modelling to select leads that could mimic cytochromes. So each of them had multiple opportunities but they were extremely early.

As to what motivated him to go out and 'sell' the concept of Medica, Healey simply said, 'it's something that we just put all our faith in and really believed in it. We knew that we had some strong backers; that it was never going to be able to fund all three companies from high network money' (interview, 2007). The United States financial markets had not hit Healey's radar at that stage, and he characterised them as 'just a total unknown [and] even five years later you would have struggled to make money in the US – and it's still the case. It does happen now, which is good, but it's still rare' (interview, 2007).

Although, with hindsight, Healey could barely believe how the IPO came off at all:

I still don't [know] – when I look back I just think, how did anyone put money into this? I mean, Cytopia, for example, was just an idea. There was nothing – no products. Andrew [Wilks] had discovered the JAK kinase, or JAK2, and it was a target that we liked from the Ludwig Institute. Yet as a start up, I mean, there was no staff, there was no equipment and there was no product. It was just a thought that kinases were going to be up and coming new targets and we believed in Andrew's ability as a scientist to get the whole show rolling, which he did quite well. (interview, 2007)

Although the IPO of Medica had been successful, the managers could not stop there. Additional round of funding were required, as Healey explained:

We did various funding rounds in Medica to keep raising money for further investments. But in the boom of 2000 and 2001 it became obvious that everything was getting overvalued because people just couldn't [wait] – it's a bit like the mining boom now – people couldn't wait to get money into a

biotech stock because everything was going gangbusters, the NASDAQ Index was 5000+. (interview, 2007)

In May 2000 Medica raised A\$6.2 m in a rights issue. Among others, the purpose of the rights issue was ‘to bring its drug discovery programme at Cytopia closer to commercialisation’ (Medica Annual Report, 2000, p. 11). By this stage, Cytopia’s research program was ramping up and regular capital injections would be vital.

### **The Engine Room**

Mathiou saw Cytopia as having an independent destiny almost immediately: ‘I always viewed it as a company from the day we listed, which was March ’99 ... From that day when a fair whack of dough got committed to Cytopia, it pretty much was from then’ (interview, 2007). Right from the start, the decision was made to seed the board with experienced and credible directors who as a group, provided a range of skills:

One of the initial directors, I guess, was a strong contributor of funds. Yeah, Mark Rowsthorn – you know, a business builder and one who’s very astute from a business point of view. We got Geoff Vaughan on board, in particular because of his background with the TGA [Therapeutic Goods Administration] and the regulatory environment, which is an area we need to keep a strong eye on. John Hasker was brought on. He had, at least in an Australian context, experience in the chemicals area ... and he was an experienced chair, so he joined us. You know, not everyone we sought did join but they were feathers in our cap, as I see it, at the time. So, we did look for the right person for us at that time .... (interview with Mathiou, 2007)

Wilks was quick to point out that Cytopia was not going to be profitable overnight: ‘But I mean, we were all one, philosophically, that this was going to be a long term prospect, that we would build an engine room, kind of a pipeline device that would create new compounds so that we could push through’ (interview with Wilks, 2007). In the early years, there were still few Australian companies to model

themselves on, but there was ‘a lot of “eyeing off” of what kinase pioneers in the US were doing, such as Ligand and Sugen’ (interview with Healey, 2007).

Initially, the ‘engine room’ consisted of a small team working in rented lab space in St Vincent’s Hospital:

We started off with seven or eight people and then it got a bit bigger, 12 people. We were located in the jail ward of St Vincent’s Hospital ... It’s not exactly the maternity ward, it’s not very pleasant. We had low cost real estate. One of my academic colleagues, a chap called Dick Cotton, who was a director of something ... with the disturbing name of Mutation Research Centre, he had some extra lab space and we [used it]. [Using this kind of low cost space was] just incredibly important for companies like ours. A private company ... [We] took that lab space for rent, basically. That helped him, freed him up to spend more money on the research. We actually lived very well with those guys for a couple of years. Then we started to get big. We were very successful with start grants and things like that. (interview with Wilks, 2007)

Fuelling this engine room was Healey and Mathiou’s tenacity in getting cash raised for Cytopia. These funds were very important in trying to establish a critical mass for Cytopia in terms of staff numbers to push their technology forward. After the capital raising in May 2000, additional funds were raised in the next six months with the financial reports ending 2001 stating that Medica had raised A\$7.1m for its various investment activities (Medica Annual Report, 2001). Additionally Cytopia received a A\$2 million START grant to develop a drug candidate for Hormone Refractory Prostate Cancer (Medica Annual Report, 2001) and this research resulted in three patent applications to protect the discovery of several drug candidates (Medica Annual Report, 2002).

As for Wilks’s involvement at the start of the company, he said he was wearing both his management cap and his white scientific lab coat:

I was doing both. When you start a company like that there is no better manager than the scientist to run the company. It’s a scientific company; you want a CEO or a CFO that can control you to some extent. But it’s all about

realising the vision that's in the scientist's mind. Certainly, Kevin and Nicholas were sufficiently indulgent of me that I was allowed to do that. And, in fact, I can tell you what is out there in this company, it's my vision [pointing to the laboratory outside of his office] but there are a lot of other people that actually built the thing. It's the best drug discovery engine in Australia. I've got absolutely no doubt about that. The quality of the people, the things that we can do is just fantastic. And that's largely the indulgence of Medica as an investor in the company that has allowed us to do that. And we will survive long-term. (interview, 2007)

The company was going forward with the key people playing to their strengths:

Kevin, of course, had two other companies to look after so he was on the Board of all those companies. He was based in Brisbane although he came down a fair amount. So we used to share a CEO role but he would also do business development and I would do the science side of things. Nicholas just did the books and stuff. We had someone, my secretary, who was my secretary at the Ludwig as well. She did the HR type stuff. So everybody doubled up and did lots of different jobs.

But the team started to grow. We got these grants. We built the engine room. We acquired a team from the Ludwig Institute that did computational chemistry. Now that's completely unheard of in a biotech. It's just a stupid idea unless you know what you're doing. (interview with Wilks, 2007)

In terms of acquiring the staff, Wilks (interview, 2007) was forthright about his approach, 'I stole them basically'.

Mathiou elaborated upon his role in Cytopia and Medica:

I was finance director, if you like – CFO and company secretary and Andrew was the CSO. We used to meet formally monthly, in a formal reporting way that a normal business would operate, but we rolled up the sleeves down there constantly, essentially almost fulltime employees of it. So, whenever a collaboration was involved I was involved. First instance, I was involved in preparing the budgets, involved in preparing the aspects of the business plan, operation plan, etc. So it was, yes, we were executives of it.

Kevin and I at Medica Holdings had an executive assistant and then Andrew had an executive assistant and we had a financial controller. That pretty much was the overhead, if you like. We had several scientists heading up different divisions of the company who managed their programme underneath them and their people underneath them, but with the overall research and development programme being managed by Kevin, Andrew and myself. (interview, 2007)

The early years were not completely smooth sailing; Mathiou recalled a particularly tense period when a contraction in staff numbers was necessary:

There was a stage, after Bin Laden hit the towers and all the capitals flooded out of biotech investment and the riskier end of town, where a few people had to be laid off because we just simply didn't have the capital to continue the programmes, you know. The programmes had to shrink and we had to manage within the given set of capital. It's a horrible, traumatic event but it does focus people's minds (interview, 2007).

## **Early Deals**

In 2001, Cytopia entered into a deal with a US based firm called Chemicon. This was the first international licensing arrangement that Cytopia had entered into, and indeed the first out-licensing deal it had finalised. However, Healey describes this arrangement as, '... a pretty minor deal just basically to get some value out of an area that we were never going to progress' (interview, 2007). As to how it came about, personal contacts again played an important role:

We had good contacts with their people in the US because there was an Australian who was product manager for that range of chemicals and screening tests. So, Leanne Daly, who was living over in California at the time, was a good friend of Andrew Wilks as well and they were a supplier to us. (interview with Healey, 2007)

According to their Annual Report for the 2001-2002 financial year, the deal was worth approximately A\$82,000. Healey also explained the impetus for this move:

So they basically were trying to build up a kit of kinase screens and we had the wherewithal to basically provide them with enzyme and all the detail. We did several deals with Chemicon; one was basically on antibodies to the JAK kinases which are used for research and we got an upfront fee for that and a very good split of the sales revenue. Then we agreed another agreement to provide enzymes. In the end we taught them how to do it themselves because it was a bit of a distraction for us but, you know, it brought in – I don't know in total – but hundreds of thousands a year which paid for a couple of people. (interview, 2007)

The next agreement was research collaboration entered into with the Ludwig Institute, Queensland Institute Medical Research (QMIR) and Sloan-Kettering Institute for Cancer Research in 2002. As part of the agreement, Cytopia would have first rights to commercialise any IP resulting from the collaboration. Healey explained that the collaboration had come about due to the technology ownership of the partners:

[It was a] a collaboration where we had one piece of jigsaw puzzle for the group. Sloan-Kettering had done some work on the F gene, I think it was, and Ludwig had another part of the [IP] – [the] peptones, I think, that bound to it and had some anti-cancer activity. We had the molecular modelling component which would, in theory, allow us to improve the peptones or convert them into small molecules that might become drugs. We completed successfully in the first part of the programme but it didn't progress from weakly active peptides into hugely active peptides and it was just, I think it was terminated or they're just carrying on in the research level, so it wasn't any big deal. I mean, the big deal for us was getting recognised by two world-leading institutions as being good enough and important enough to take part in their research. That was, you know, newsworthy at the time but it wasn't any kind of big deal for us. (interview, 2007)

As for his involvement in the deal, Healey said, 'Well, I got involved again after the scientists had agreed it was a good idea. I just got in to make sure that the agreement was sensible and that the IP was protected and that we weren't giving stuff away' (interview, 2007).

Another early deal was with the New York based company, Myomatrix. The collaboration, announced in late 2003 involved the companies working on breakthrough treatments for heart failure and hypertension. Myomatrix had worldwide exclusive rights to develop and commercialise therapies for certain cardiovascular diseases by inhibiting a kinase target and their research was approaching testing in animals (PR Newswire Press Release, 15 December 2003).

## Doing Deals

From a business point of view, Healey talked about some of the challenges involved when attracting partners:

[Road shows for partners are very different from road shows for fund raising, very different; you have to speak a totally different language. I mean, if you put Andrew [Wilks] in front of an investor they would turn off. But on the partnering with pharma companies there's credibility because he discovered the JAK kinases, and all the big pharma who are interested in JAKs as a target recognise that he was number one in the field, and I think they've been impressed with the platform that Cytopia's built up in being able to screen the drugs against kinase targets. Because there are 500 different kinases, you screen one molecule and you want to screen it against as many as possible to see what that molecule does and so you build up a matrix of potential leads. (interview, 2007)

There were various options that Cytopia explored in order to make contact with potential partners. One traditional forum was the networking opportunities at scientific conferences Healey said, 'I think going to a single conference doesn't help much but, when you've been to three or four and the Amgen guys invite you to their cocktail parties because they know you and they want to see what the latest is, that's when it's really starting to help' (interview, 2007). As well, Cytopia managers attended business partnering forums:

I think we initially started out just by attending things like the Bio conference in the US, Bio-Europe, where you get an opportunity to meet – you get a half hour meeting with pharma companies and they've got their licensing gatekeepers there. It either fits what they're looking for or it doesn't. I think the first two or three times we did it we were so early stage we shouldn't have bothered, but it – no, I shouldn't say we shouldn't have bothered because we did learn a lot. In fact, one thing we did learn was that they weren't interested in JAK2, they were interested in JAK3, so we came back and put chemists onto JAK3 and that led to our deal with Novartis. So getting out there and getting the feedback's pretty important. But we found it to be much more effective when we found contacts within the pharma companies that we could go in there and present where you weren't distracted by conference meetings. These licensing gatekeepers, they see 25 companies a day and you get lost in the noise. Late stage is pretty exciting. So we did a mixture.

[And] it's a waste of time [approaching the subsidiaries; you need to speak to the parent firms ....] We sort of did it backwards. We would – well, if you give Merck as an example. Well, so we had some very good contacts in Merck because our chairman knew the – well, he wasn't the CEO, he was the president of something over in New Jersey – so that gave us good entrée. But I got to know some of the licensing gatekeepers through the bio meetings and they were pretty interested in what we were doing because they had a JAK programme and at one stage had asked us for a sublicense to keep working in the field – we said no. But they were very good between, they had a – I'm just trying to think of his name now, based in Sydney. But they wanted us to keep in touch with the Sydney group but the action was always at the New Jersey end. [They] have a chief medical licensing officer or something. Graham McDonald was the last one, he's just stepped down. So we ... always kept Graham up to speed and whenever the Merck guys in New Jersey made a foray into Australia, there'd be Graham and a couple of the other New Jersey people there. So he was always kept informed but you would never have gone to Graham first because all he can do is just ship it off and see what they do, but you can't – it was just too passive for us. (interview with Healey, 2007)

It was clear though; having the scientific founder present in these stages of discussion was absolutely essential in the process:

I'd say [it was] more than a benefit [in having Wilks there], he was an essential component and in most of the early meetings it's all about the science. Once you get past the credibility of the science and then you start to talk about structure of the deal, then that's when I would really play a bigger part. But most of the early meetings I'd sit back and let Andrew talk his head off, basically – well, talk their heads off, which he is quite capable of doing. (interview with Healey, 2007)

### **The Move to a New Building**

In its third year, the company had grown to such a size – to approximately 23 full time employees – that it required a move to a new facility. Hence, in 2002 Cytopia moved into the Baker Heart Research Institute. Although they had to invest some money into the move, overall it seemed like a great outcome with the staff excited to be housed in the 'fabulous new facility' as Wilks (interview, 2007) put it. The new laboratory was estimated to have cost A\$5.5 million (Australian Stock Exchange Company Announcement, 15 September 2002). Overall, the year was capped off with Cytopia

receiving a BIF grant from AusIndustry that rounded out the financial figures for the year-end very nicely (Medica Annual Report, 2002). And whilst Cytopia was growing its staff, it is important to remember that Medica still only employed three people, as Healey explained, '[We had] twenty-two, three, that sort of number – 24. [But that was all Cytopia]. If you add on the Medica staff, there was only ever three of us. [Me, Nicholas and] just an assistant' (interview, 2007).

As he had done previously, Wilks credited this huge move, both physically and psychologically, to Medica's patient approach:

And, again, Medica saw the vision. At that time I was compulsively controlling about [how] I wanted to control all the parts of the process of discovery, from the protein to the screening to the chemistry to the computational chemistry. That way, I figured, you could quality control every step and, indeed, that's correct. [I could do that actually b]ecause everyone's within a couple of hundred yards of each other. And it's very expensive to do it. (interview, 2007)

Healey confirmed that he was in favour of keeping drug discovery capabilities in house, not just due to quality considerations but as a means of safeguarding intellectual property:

The discovery part of it I think you've got to keep in-house because there's so much IP tied up in your chemistry that you really just don't want others getting a lead from it. When we do outsource chemistry we always buy components, we never buy finished molecules, so that there's certain IP protection in what we actually do with those components afterwards. The building blocks – we buy building blocks.

Well, I mean, everyone these days goes to China and India for cheap chemistry but I think they're taking a huge risk. The quality can be okay but the IP protection and, you know, staff leave and think they can take everything with them. But it's also the [case that] you might give somebody – like, you might have cheap chemistry in China. You might give somebody an idea and they'll deliver what you ask for but, meanwhile, they've thought of a tremendous idea of their own, which is a branch of your chemistry that you haven't protected, and off they go selling that to Syngene in the US or something.

We outsource pre-clinical studies and clinical work – I think most people would do that – but as the company grows, we will also build up our own internal clinical management expertise. (interview, 2007)

Andrew McDonald, who became CEO in 2006, agreed with the in-house strategy and mentioned a third reason: the importance of obtaining commitment from staff:

It's building a business, you know, and how many businesses really work on a true outsource model? Yeah, well, let's face it, this business is about people, it's about IP – now, they're your two big assets in this business and I don't like outsourcing people as a general rule; you use them as the icing on the cake but not the cake. You need those people, you need the dialogue with them, you need the buy in. (interview, 2007)

Wilks provided some insight into the strength of the experience that has been developed in house, and which is augmented through contracting arrangements:

In fact, at different stages in the process, you would contract different activities and maintain in-house other activities. Now we have a very strong chemistry team and we have no problem contracting out other chemistry. So effectively, while we have 20 people in chemistry, we have 30-odd people doing chemistry for us. So once you have a strong hand you can enhance it a lot by doing stuff outside.

From a position of weakness where you don't have any internal capability or skill base it's actually quite a dangerous thing to do I think, unless you've got the right sort of collaborator. But we understood that entire process ourselves. We'd done the basic research, we knew how to make the protein, we knew everything about all this stuff. It cost us money to do that but the control was quite important at that time. And it's turned us into the company that we are. We are somewhat unique in the size of the organisation that we have ... with close to 50 staff [in 2007]. (interview, 2007)

For example, Cytopia had to look outside the company to access highly specialised expertise in crystallography. Wilks, who due to his training at the Ludwig Institute, was committed to rational drug design and wanted to crystallise JAK2 in order to then design inhibitors for this drug target. Wilks found a collaborator in Jamie Rossjohn at Monash University, and in 2004 the pair was successful in winning an

ARC Linkage grant worth A\$2.5 million – the largest such grant ever to have been awarded – that covered the costs of the crystallography. Because of this collaboration, ‘we were the first in the world ... to crystallise JAK2’ (interview with Healey, 2007). However, the molecular modelling that is central to rational drug design was built up in-house: ‘whereas some people would buy a software package off the shelf and use that and have one molecular modeller, we have three people just writing software’ (interview with Healey, 2007). As a result, Cytopia has proprietary software, Chemaphore, that it claims accelerates the process of drug discovery.

This does not mean that Wilks insists on an in-house capability under all circumstances. He explained that ‘Cyt2pia [sic], my next company, will be somewhat more geographically spread out. Look, contracting costs you more money but gives you more flexibility’ (interview, 2007).

Cytopia could point to research milestones being reached. In Medica’s 2003 Annual Report, Cytopia reported ‘exciting results’ from the animal testing of its lead molecules (p. 6). However, the research was still at an early stage so additional funding was sought. Again, grant money would line their coffers; this time through winning A\$1.7 million to support their research program targeting kinases to treat Chronic Pulmonary Disease (Cytopia Annual Report, 2002-2003). During the same time period, Cytopia’s parent company, Medica, invested a further A\$3 million in Cytopia (bringing its total investment to A\$9.8 million). Medica raised a further A\$3.25 million in that same financial year 2002-2003.

### **Medica Changes Identity**

July heralded changes to the structure of Cytopia and Medica Holdings. In a press release issued to the Australian Stock Exchange, ‘Medica Holdings officially became

Cytopia (ASX: CYT) this week, as it took the next big step from being a biotech investment company to a biotech company in its own right' (Australian Biotechnology News, 21 July 2004). This move was agreed to at an Extraordinary General Meeting in June 2004, after which Medica changed its name to Cytopia Ltd and moved to acquire all the minority shareholdings in Cytopia Pty Ltd, which was renamed Cytopia Research Pty Ltd (Cytopia Annual Report, 2004), with the new Cytopia Ltd retaining Medica's stakes in Xenome and Alchemia. Healey explained the process of tidying up the agreements and structural arrangements binding the companies together:

[we had to get an agreement to acquire 100% of the shares, including the ones that Andrew [Wilks] had, and then he would be issued shares in the parent company, Medica. So all the holders of shares in Cytopia Research, including the staff options, got converted into shares or options in the parent and all of a sudden they had listed stock instead of unlisted stock. (interview, 2007)

Wilks (interview, 2007) summed up the motive behind this move as being dissatisfaction with the Medica model: 'It's a shocking business plan being publicly listed and a venture capital organisation. You just can't win. You had to go through it to find that out, but it's not a good business plan'. One reason for this was a lack of investment opportunities:

Medica were actually going to have this rolling [plan], start a company every year, approach ... But the truth is that Kevin [Healey] is actually pretty picky, so a lot of the technology that came across his desk he would just see through and reject. It's actually very hard to find one good company a year you want to start. So there's a shortage of supply .... (interview with Wilks, 2007)

Another reason for deciding that a listed PDF was 'a flawed model' lay in the fact that:

you can't control the market situation that you have to raise cash in. I mean, in an ideal situation you would be adding value to your investments that would be reflected in your share price; you would be raising capital with an ever-increasing share price. But then when NASDAQ dropped from 5000 to 2200, which it did in one day, it become impossible to raise capital and then you get

under pressure. So when the market's determining the price of the cost of capital it's very difficult to run a listed investment company. If we had been private it wouldn't have been an issue. The truth is that every investment, every listed investment company has the same problem and it's reflected in their share price, so the market automatically discounts a listed investment vehicle by about 30-40%. So if you look at biotech capital – Circadian and Medica as it was, there's been one of two other consistent storywriters off the top. So it was a choice between then continuing to raise cash and then spread the investments around and bringing other investors into Cytopia and copping a dilution. Whereas we had the choice. We owned about 89% of Cytopia and Andrew Wilks owned the rest, so we had a choice of bringing in a venture capital player or just grabbing 100% of Cytopia. Given that the model, the listed investment vehicle model, wasn't delivering value to shareholders, we felt much better to become a biotech company. (interview with Healey, 2007)

Mathiou agreed that the timing – the contraction that occurred in the stockmarket – forced their hand:

There was one period of contraction which occurred soon after that event and, indeed, that probably was the trigger that changed the strategy of Medica. We had, in essence, four cash burning companies and insufficient capital to provide for the four and we had to focus on, we thought, the best of the group. Medica itself, the holding company [was the fourth company]. Pretty much and we needed to figure out what was the best way and what gave us the best chance to raise capital going forward. Our view was that being a investment firm listed on ASX was not the best way and it would be very difficult to raise capital as that, so we thought we had a much better chance of raising capital as a pure biotech play. We also thought that we could sell down, eventually, some of the other assets we had; for instance Alchemia's, Xenome, etc, which could provide the capital that Cytopia needed. It was essentially of necessity. Would we look like we are today but for that event? Probably not. If we had another boom at that time we probably would have raised a swag of capital and, you know, Medica would have a broad portfolio of opportunities today. So it did change the strategy of the company. (interview with, 2007)

Mathiou was very pragmatic about having to relinquish the Medica strategy: 'when a bunch of external events occur, well, you can stick to your current strategy and wither or you can change strategy and thrive. We think we did that, we did the latter. We weren't head in the sand, what are we going to do now, we changed tack and we're up and running. I can say if we didn't change tack we probably wouldn't be around, so

that's probably the case' (interview, 2007). Fortunately, the way Medica had been structured made the transition process easier:

One of the other critical differences between us, as Medica, and other investment companies that were listed – especially biotech capital – was that we had an internal management structure, as opposed to being a fund manager with a separate trust which holds the cash for the investors. It's quite different and that meant that it was much easier to do the merger of Medica and Cytopia Research to become the new entity. So the new entity had 100% of Cytopia, in theory, and owned all the shares in Alchemia and Xenome and we ultimately sold off Xenome and Alchemia to fund Cytopia. So that was good, non-diluted funding. (interview with Healey, 2007)

The stake in Xenome was sold in 2004, Alchemia in 2006.

The metamorphosis of Medica into a biotech company meant that Melbourne was now the company's base. Mathiou did not want to make the move so he decided that this was an appropriate time for him to step down from the board. Like everything else, the move was well planned: 'we implemented a succession plan over some time. Actually, it took quite a while though, to implement' (interview, 2007). The succession plan involved the appointment in August 2005 of a CFO, Andrew McDonald, who was recruited from Biota. McDonald was to take over from Kevin Healey as CEO in June 2006.

In the 2004 annual report, the restructured company's strategy was set out.

Among its goals were to (p. 5):

- (1) Develop our cancer drug candidate [CYT997] to proof of efficacy (Phase II) stage in humans with our own resources;
- (2) Seek a major pharma partner to accelerate and broaden the development of our core JAK kinase program;
- (3) Implement a partnering strategy that allows Cytopia to build a clinical development capability while at the same time bringing in early revenues to enable later stage development of selected candidates;
- (4) Seek to acquire synergistic technologies or products or, companies with technologies or products, capable of growing our drug development pipeline and

(5) Expand the company’s operations and investor activities into major markets.’

Overall, the plan was ‘to expand the clinical pipeline to a point where we have multiple development candidates ... ’ (Cytopia Annual Report, 2006, p. 5). By the end of the 2005-2006, Cytopia felt that it could report it had delivered on this goal and had achieved a ‘maturing pipeline’ (p. 9). The result, Healey (interview, 2007) explained, is progress on multiple fronts: ‘when you’re in the kinase patch, because there’s so many of them, you really have to look at your development and discovery work as a matrix’. Cytopia was able to physically represent their R&D work via a diagram they presented on their website:

**Figure 1: Cytopia’s Product Pipeline**

Drug Target	Indication		Market Rights	Lead Optimization Efficacy Data	Preclinical	IND/Ethics Approval	Phase I	Phase II
	Cancer	Non-Cancer						
CYT997	✓ (PO)		Cytopia					
CYT997	✓ (IV)		Cytopia					
JAK3		✓Transplant	Novartis					
JAK3		✓RA	Novartis					
JAK2		✓MPD	Cytopia					
JAK2	✓		Cytopia					
JAK2		✓PH	Cytopia					
FMS	✓		Cytopia					
FMS		✓Inflammation	Cytopia					

IV Intravenous PO Oral RA Rheumatoid Arthritis MPD Myeloproliferative disease PH Pulmonary Hypertension

**Source: Cytopia Website 2007**

### **CYT997 Committed for Development**

CYT997 was a novel, orally active drug that was aimed at significantly inhibited growth in cancerous tumours without adverse effects. In the 2004 Annual Report, Cytopia reported that in further animal testing this drug candidate CYT997 had been

found to be ‘very potent’ (p. 9). The company had commenced preclinical toxicology evaluation of CYT997 and stated that ‘Cytopia has committed to the development of CYT997 as a broad acting anticancer drug candidate’ (p. 10).

By November the same year, Cytopia put out a press release announcing that ‘... CYT997 has been accepted by Cancer Research UK into its clinical trial program, allowing Cytopia direct access to leading British oncologists and world-class clinical trial facilities’ (Cytopia Press Release, 22 November 2004, p. 1). In April 2005, an announcement was made that Cytopia had received approval to begin phase 1 clinical trials for CYT997 (Cytopia 2005 Annual Report, p. 6). It was hoped that the drug would be effective against solid tumours. CYT997 is a totally synthetic molecule and considered to be technically ‘cytotoxic’, although its mechanism of action was to disrupt microtubule formation by interaction with tubulin. CYT997 was Cytopia’s first drug to reach the stage of clinical trials. Early in 2005, an Investigational New Drug (IND) Application was lodged with the FDA and several months later the Phase I dose escalation study in cancer patients began at the Royal Brisbane Women’s Hospital with the aim of the trial aimed at determining safety, tolerability and dose-limiting toxicities up to a maximum tolerable dose. The details included taking 30 patients into a trial where they would receive 24 hour intravenous infusions three weekly for up to six cycles of chemo. Additionally, Cytopia applied for approval to conduct a Phase I trial for the oral administration of CYT997 where the objectives of the trial would be similar to that of the intravenous study. Later in 2005, Cytopia was awarded a A\$3 million grant over three years to help with the clinical trial process. In 2006, enrolment and dosing for the oral CYT997 began in December whilst the intravenous trial continued with good results. A press release in May 2007 said that CYT997 was going to be continued to be supplied to patients on compassionate grounds while an important

milestone, dose-limiting toxicity had been reached on a patient. If another patient showed symptoms of maximum dose toxicity, this would be considered to the maximum dose profile and the trial would be considered completed as per the trial protocol (Cytopia Half Yearly Announcement, 17 May 2007). Late in 2007, a special announcement was made that CYT997 was moving into Phase II trials. Up to 24 multiple myeloma patients would be enrolled in the trial to be conducted at the Alfred Hospital in Melbourne. These patients suffered incurable cancer of plasma cells of the bone marrow as well as solid tumours. The trial was to single arm, tow stage design with an interim analysis after 14 patients and the interim data to be release in the spring of 2008. This study was the first of many Phase II trials for CYT997, with the next trial tipped to be for CYT997s oral administration (Cytopia Press Release, 3 December 2007).

### **Myomatrix Acquisition – JAK2 in Pulmonary Hypertension Moves Forward**

In January 2005, Cytopia then found themselves in a position where by they purchased the IP from another company, Myomatrix for US\$625,000. As a consequence of this, Cytopia then set up a US subsidiary, Cytopia Inc. The details of the acquisition, according to the Cytopia 2005 Annual Report, were:

- (1) The two founders of Myomatrix, Dr Shreefal Mehta and Dr Larry Zisman, came on board
- (2) Myomatrix's licence was transferred to Cytopia Research
- (3) 'We are pleased to report that our New York-based laboratories are fully operational ...' (p. 10).

As to how Cytopia found themselves in this position, Healey explained:

Purchasing the IP was a result of being a Pool Development Fund. But the way that came about was that these guys that had founded Myomatrix had a

licence from the University of New York upstate to develop JAK2 inhibitors for the cardiovascular area – they'd done some work that showed that, on a very crude inhibitor, that it might have some promise. But they also ran into our patent so they knew of us and they didn't have any chemistry capability, they were basically on the clinical side. So we had a chat to them and we agreed to do a little exploratory bit of research to see whether or not our much-improved JAK2 inhibitors would also work in the models and they did quite well, so at that stage we decided to bring that in-house. We couldn't acquire the company or merge with the company because Cytopia was by that stage a pooled development fund and pooled development funds are forbidden to merge or buy existing shares of companies. So, we had to find a sneaky way around the PDF rules, which we did, and that was basically to buy the assets of the company into Cytopia Research and then there was a share swap, which meant that there wasn't an acquisition as such. But we brought that in-house because we just felt, you know, for not much money really we had a whole new therapeutic area that we could put our JAK2 inhibitors into that we were developing, anyway, so in a sense it was a no-brainer. We've done quite a few animal models now with our JAK2 inhibitors and they do show some interesting activity in models of cardiomyopathy and pulmonary hypertension. We took on the two key staff members; one was Larry Zisman, who is a cardiologist, and another guy, Shreefal Mehta, who is more the entrepreneur who really kicked it off and we've now got him doing business development for us in the US. (interview, 2007)

However, by 2007 Cytopia decided to shut down its research lab in the US: 'Why? We've got to a stage where we were looking to out-licence that programme, but strategically it's hard to justify three people sitting in a lab in upstate New York when I've got the majority of operations here. It's just commonsense. Do you really want to invest heavily in labs there? No' (interview with McDonald, 2007).

In terms of its role in cardiovascular disease, the JAK2 molecule was also undergoing investigation through a collaboration with the Baker Heart Institute in Melbourne, specifically being testing in the area of heart failure (Cytopia 2005 Annual Report, p.10):

Yeah, and I think it means since that – when you're in the kinase patch, because there's so many of them, you really have to look at your development and discovery work as a matrix. For example, our FIMS programme now came out of a side branch of the JAK2 programme. If we hadn't have been screening FIMS we never would have found it, so you can't just look at your own target. Most of the companies out there are doing that. Now you've got

Insight Pharmaceuticals and Exelixis and Aztechs and a few others. (interview with Healey, 2007)

The annual report also explains: ‘We have been very active during the year with of JAK2 program, talking to partners regarding a collaboration to develop, and take forward to market, inhibitors for the enzyme’ (p. 5). They elaborate later in the report: ‘We believe that the [JAK2] cardiovascular program is now better placed to be driven forward with a partner who can contribute specialist expertise, including drug delivery and formulation, and the necessary funding required to take the program further. Accordingly, we have reduced our US-based research operations and are seeking appropriate collaboration partners ...’ (p. 6). In this year, they announced the cessation of PDF status (Cytopia Annual Report, 2005).

A recent press release said:

Cytopia has demonstrated that CHF [congestive heart failure] pathology can be prevented by a JAK2 inhibitor in an animal model of CHF, while maintaining normal haemodynamic function. These early data indicate that a JAK2 inhibitor might play a significant role in treatment of human CHF. Further animal efficacy studies with highly potent and specific inhibitors of JAK2 are ongoing. The company anticipates progressing a drug candidate to formal preclinical development late in 2008. (Cytopia Press Release, ‘Cytopia at a Glance’, 2007)

## **JAK2 - MPD**

The 2007 Cytopia website covered JAK 2s role in myeloproliferative diseases (MPD). MPDs are a series of diseases where there is over-production of particular cells within the blood stream, including polycythemia vera (PV) and essential thrombocythemia (ET): both relatively rare, but highly debilitating disorders for which there are limited and poorly efficacious therapeutic options. PV causes patients to have excess

production of red blood cells in the body, which can lead to life-threatening conditions such as haemorrhage, thrombotic events (e.g. stroke) and enlargement of the spleen.

To develop this inhibitor Cytopia entered in R&D collaborations with the Royal North Shore Hospital in Sydney and the Mayo Clinic in Cleveland Ohio, US to conduct the pre-clinical trials. The most recent report on JAK2 for MPD (identified as CYT387) came from a company press release issued in January 2008 said:

There are few pharmaceutical treatments for MPD patients and consequent unmet clinical need. Progressive disease can lead MPD patients to develop leukemia or myelofibrosis. Over 95% of patients with PV and about 50% of patients with two related MPDs, essential thrombocythemia and primary myelofibrosis, possess a genetic mutation which causes over-activation of the enzyme JAK2. Cytopia is developing selective and potent inhibitors of the JAK2 enzyme to block excessive activity.

The data obtained in these studies show that Cytopia's compounds block the mutant JAK2 enzyme and thereby inhibit, in the case of PV, the over-production of red blood cells. Additionally, when normal human cells were tested in the same assay, Cytopia's JAK2 inhibitor showed a possible therapeutic window with a greater potency inhibition of disease cells. Extensive screening against a panel of 73 kinase enzymes indicates that CYT387 possesses selectivity for JAK2, potentially minimising off-target toxicity. Dr Pardanani of the Mayo clinic said: 'In *ex vivo* studies, we have seen encouraging preliminary results with Cytopia's compounds including the inhibition of erythroid colony growth from PV patients harboring the JAK2 V617F mutation.' Cytopia's Research Director Dr Chris Burns stated: 'This data is important validation that our selective JAK2 inhibitors stop the proliferation of mutant cells from patients with these diseases at clinically achievable doses.' (Cytopia Press Release, 30 January 2008)

## **JAK2 – Cancer Progress**

One of the cancers that JAK 2 is being investigated for is acute lymphoblastic leukaemia (ALL). This disease is predominate in childhood and has a poor prognosis.

Cytopia's website stated:

JAK 2 and its related biochemical pathways are now known to play a key role in the proliferation of cancer cells, particularly those in haematological malignancies such as acute lymphoblastic leukaemia. Again, Cytopia's anticancer JAK2 programme is well advanced, with formal drug development

expected to commence in 2008. (Cytopia Press Release, 'Cytopia at a Glance', 2007)

### **The FMS Projects: CYT 645 for Cancer and Inflammation**

CYT645 is a potent and selective small molecule inhibitor of c-FMS, a kinase enzyme intimately involved in both the growth and spread of cancer. C-FMS also plays a role in many inflammatory disorders, including rheumatoid arthritis and inflammatory bowel disease. Late in 2006, Cytopia issued a press release advising that after extensive research internally, CYT645 would move into a formal development programme that included animal studies; scale-up chemistry and pre-clinical toxicology studies aimed at filing and IND with the FDA. The projected timing of this was 9 to 12 months and Phase I trials would start at the end of 2007 or early in 2008 (Cytopia Press Release, 17 November 2006). Besides rheumatoid arthritis, another significant role of CYT645 was thought to be in the treatment of osteoporosis and well as inflammatory bowel disease.

Cytopia's website said:

CYT645, a potent inhibitor of the enzyme FMS, blocks the function of cells known as osteoclasts which cause destruction of bone, in a process known as resorption. The bone protecting activity of Cytopia's compounds is an important addition to the anticancer properties of the compounds and augers well for beneficial patient outcomes in a clinical setting. (Cytopia Press Release, 'Cytopia at a Glance', 2007)

CYT645 was also showing benefits for the inhibition of cancer growth and tumour spread, over current oncology therapies, namely that of Pfizer's blockbuster drug Glivec™:

Importantly the activity of CYT645 is significantly greater than the blockbuster drug Glivec™, another known inhibitor of FMS, as well as another FMS inhibitor from GlaxoSmithKline. (Cytopia Press Release, 'Cytopia at a Glance', 2007)

## **JAK3 Program and Novartis**

In its 2005 Annual Report, Cytopia reported that, 'We believe it is to Cytopia's advantage to partner this project so that we are able to accelerate the pace of development. In the coming year we expect to partner this program with a pharmaceutical company' (p. 12). A major announcement was made via a press release issued on June 5 2006 by Cytopia saying they had signed a 'global licence and R&D collaboration with Novartis to develop orally active, small molecule therapeutics targeting JAK3 kinase for the prevention of transplant rejection and the treatment of multiple indications in autoimmune disease such as rheumatoid arthritis' (Cytopia Press Release 5 June 2006). The deal involved:

Both companies will contribute expertise and intellectual property relating to JAK3 inhibitors for the purpose of bringing compounds into the clinic. Novartis will assume responsibility for product development and commercialisation. Cytopia has retained co-promotion rights for Australia and New Zealand.

Under the terms of the agreement Cytopia will receive payments from Novartis of approximately A\$13 million over three years including an up front payment and research funding. Over the life of the agreement, Cytopia may become eligible to receive development, regulatory and sales milestones which could total approximately A\$274 million if an agreed number of multiple indications are successfully commercialised. Cytopia will also receive royalties on product sales. (Cytopia Press Release 5 June 2006)

Mathiou described the Novartis deal as a 'true collaboration', in the sense that :

'... they have access to ours [IP] and we have access to theirs' (interview, 2007).

Healey (2007) explained the background to the deal:

The thing that led to the deal with JAK3 was that JAK3 is a hot target for transplantation and that is a big area of Novartis. They knew that Pfizer were in the patch, in fact they had a Phase I drug already. So Novartis could either sit back, do it internally and try and generate a JAK3 inhibitor, but they scoured the world for a bit of a leg up to see who was maybe ahead of them and they decided that we were ahead of everybody else. That's basically when

we really were just very early stage ... [But] if they let the opportunity go either Pfizer might buy it up or someone else. It was quite interesting because three months after we announced our deal with Novartis, Wyeth announced their deal with Pharmacoepia. You know, we knew that we were competing with Pharmacoepia for Wyeth because we talked to all of them – we were out there negotiating with about five pharmas and we all knew they wanted something and Novartis got our deal.

The situation therefore allowed Cytopia to build some ‘deal tension’; Healey recalled that ‘Even within six weeks of signing the Novartis deal we had another huge pharma company thinking about just buying us up ... buying the whole programme without any due diligence – just buying out JAK3 programme. ... [I]n the end the offer didn’t materialise because they decided six weeks was too short. But the fact that they actually had another look and talked about it was pretty interesting’ (interview, 2007).

At the same time, Mathiou pointed out that Cytopia’s possession of desirable technology was far from coincidental:

We saw the market opportunity. We went to develop something that we saw that people out there in the world hitherto hadn’t been able to achieve. We achieved it and then went to various parties we identified that we thought would be interested in the intellectual property we developed. So, in that particular case it really was market pull, if you like, as opposed to just simply technology push. There was an issue that we solved that no one else was able to solve hitherto and that is a highly specific JAK3 inhibitor. It’s very easy to inhibit JAK3 but also inhibit the other JAKs 1 and 2. It’s very difficult to get a molecule, in essence, inhibiting JAK3 alone and that’s what we cracked, at least in pre-clinical – it hasn’t got to clinical yet, it’s not drug-like yet – but nevertheless we were able to crack it and that’s what attracted Novartis. (interview, 2007)

McDonald explained why the deal was seen to be a good fit, and how it has brought Cytopia more than the immediate up-front and milestone payments, allowing increased headcount, from Novartis:

They’ve got the expertise in clinical development, in particular. We’ve got the kinase expertise, so we understand the target well – not that they don’t understand it but we bring something special to the table there. So, you put that together and to make it work you’ve got to be open ....

We had an early stage asset. At the end of the day they gave us a real going over. We had some hard times in that but you've got to again remember, we weren't in the strongest of positions there. I think we did a damn good job of it, and to end up with what we did – in fact, when I came across [to Cytopia from Biota], my criticism of the deal or a proposed deal, I said, look, this is just too early and we're going to get done over like a dinner. We didn't; we came away with what was a great deal and actually unlocked value where people traditionally would have allocated absolutely no value. So, you know, I think we were very smart ultimately in what was achieved there. Can we do it again? I think we can.

For one swallow, a supper does not make. So, you don't profess to be experts but, equally, as we go through other discussions and separate deals, you become smarter and you become better along the way. We've, actually, just earned some street cred, so when we go out and talk with partners they know we've had a deal with Novartis, they know we've been through the wringer and they know that we're a little bit smarter about what's expected. (interview, 2007)

Healey provided insight into the different phases of the negotiations, which a commenced with a presentation at Novartis headquarters in Basle:

We ... got invited into Basle to present, they call it the full oncology team, transplant team – immunology and oncology – and we had a follow-up meeting about four months later in Boston. Then it was clear after that that they wanted to enter formal due diligence and so they sent a team out here a couple of weeks later, hauled over everything. By and large were pretty complimentary but found a few faults that we fixed as soon as we could, but they were just to do with databases, how well it was easy to pull out data and things like that. Then term sheets happened about another four months later ... [W]e'd sent them a term sheet and they'd returned one which, obviously, was totally different to what we wanted. Then we had a face to face [meeting in San Francisco] and then it was an issue of arguing over each point, you know what's included in the licence and who'd do what and how much up front and what the milestone payments. You'd argue over every single thing and you had to produce your data to show that it was reasonable or unreasonable. We did that in a day.

But then we walked away from that thinking, well, that's the deal done and then we got their draft agreements which were totally at odds with what we thought we'd gone away agreeing. Then you'd have a lawyer-fest which, I must say, wouldn't be as long typically but this deal was very complicated for various reasons and not least of which it was an all-in deal where it wasn't just us doing research for them, it was us working with their researchers to achieve an end. Even if their chemistry gets to market, we still get all our milestone payments and so it was a complicated deal. We had to separate JAK2 from

JAK3 in the deal, so that made it a little bit more complicated than it could have been. (interview, 2007)

Mathiou credited his partner Healey for being the driving force behind the successful deal with Novartis: ‘That’s all Kevin, in the sense of, you know, driving, negotiating and executing on that deal’ (interview, 2007). Healey delayed stepping down as CEO until the agreement was finalised. But Healey also noted that Andrew Wilks’s involvement was crucial in the early phases of the negotiations and when more technical issues were at stake, ‘particularly how you isolate JAK3 from JAK2. We wanted to keep JAK2 squeaky clean so we could licence it elsewhere later’ (interview, 2007).

From Novartis’s perspective, due diligence was particularly important given the nature of the collaborative arrangement:

... a big chunk of that [the Novartis deal] wasn’t negotiating the contract, a big chunk of that was them doing their due diligence as well, on the company. Because it was a collaborative approach, they had to satisfy themselves of not only the voracity of the intellectual property that existed but also our ability to deliver on the research and development programme they were suggesting. (interview with Mathiou, 2007)

Healey added his perspective on why the negotiations were so time consuming:

in terms of financial [content] there’s always a general template; there’s an upfront fee for access to the licence and then there’s various milestones which are typical and there’s industry averages and everybody knows what they are and then that can go up or down depending on how unique the technology is, how advanced it is. But then the complicating issues are things like what happens on termination of the deal and where does the IP lie and they’re the issues that prove to be the hardest to agree, not the financials. I think we were happy with the financials nine months before we did the deal. That took over 18 months from start to finish. It’s amazing, really. Eighteen months is a long time in chemistry. You wonder what you lose competitively .... (interview, 2007)

In the meantime, Cytopia decided that, in light of the ongoing negotiations, it could shift more of its scientific resources into other programs: 'I think if you had all the resources in the world you'd just keep steaming on the chemistry but we had a number of targets we wanted to progress. So once we felt the JAK3 deal was going to go ahead, even though there was a risk it could still fall over, we put more of our chemistry onto JAK2, so it was a balance' (interview, 2007).

However, the upside of the lengthy negotiations was that the two sides were able to develop a high degree of respect and trust:

with Novartis we had formed an incredibly good relationship with their scientists through the process of just getting credibility and doing all the due diligence. I'm still friends with – in fact, I've got a call in this afternoon to the guys I worked with at Novartis because they want to see what I'm doing. You know, it's that sort of relationship built up and I think that that also was responsible for how the deal got structured in the end and we would have preferred that. If we had Wyeth saying that they wanted the deal rather than the Pharmacopeia deal, we would want to have had that same kind of feeling but we didn't ... you know, now I can call the CEO of Novartis if I need to. That's good. (interview with Healey, 2007)

The Novartis deal also indicated how the relationship between biotech start-up and big pharma was shifting. In the 1990s, there was a definite trend among big pharma to want later stage deals. However, more recently, i.e. the last three or four years, has seen a trend back towards earlier stage agreements:

over the last ten years a couple of things have happened. They concentrated on M&A activity, which I think resulted in a lot of dysfunctional R&D activity, which has resulted in a dearth of pipeline. The other thing that's happened is that they're being attacked by generics, as a lot of their existing drugs come off patent. So, those factors in combination have resulted in pharmaceutical companies seeking aggressively molecules external to their activities to fill the pipeline. Now, the type of stuff they're looking at is affected by the generic play ... What you've seen is they're now accepting of the fact that a broad portfolio of earlier stage external deals overall is a better play than a narrower portfolio of later stage external deals and they're coming right back to early stage deal making. If you have a look at Cytopia's deal –and that was pre-clinical – and for a pre-clinical deal to have A\$274 million worth of milestone

payment attached to it is a stunning result relative to what you could have got ten years ago. (interview with Mathiou, 2007)

### **Selling Off Alchemia**

Shortly after the Novartis deal had been announced, a further press release was issued stating that the 14.4 million shares that Cytopia owned in Alchemia were sold off to ‘domestic institutional investors ... for a total consideration of A\$15 million’ (Cytopia Press Release, 7 July 2006). Underpinning this sell off was the need to raise cash to support their pipeline.

### **Sustaining the Company Into the Future**

As to measuring success, McDonald agreed with the comments of his former colleague at Biota, Richard Wadley, that it may be best to use a measure such as ‘length of time the firm can manage to operate and stay open’ (interview, 2007). Healey was very proud of the way in which Cytopia has managed its finances: ‘... when most people look at Cytopia they can’t believe how far we’ve got for the expenditure over the years. We’ve been reasonably frugal. Having said that, we haven’t held back when we needed something ...’ (interview, 2007). However, as McDonald pointed out, Cytopia is still ‘undercapitalised’, particularly compared to US biotechs with a similar profile. The financial position of Cytopia is summarised in the table below:

**Table 1: Summary of Cytopia's Financial Position 1998-2007 – A\$**

Financial Year	Licensing Revenue	Other Income	R&D Expense	Other Expenses	Net Profit (Loss)
98/99		233,191	-365,717	-636,528	-769,054
99/00		330,197	-1,083,746	-1,136,004	-1,889,553
00/01		517,956	-1,907,020	-1,650,602	-3,039,666
01/02	82,432	1,383,134	-3,413,906	-1,853,487	-3,801,827
02/03	72,292	1,306,768	-4,490,740	-1,229,069	-4,340,749
03/04	36,129	1,627,414	-4,254,154	-1,721,855	-4,312,466
04/05	70,572	4,741,432	-6,857,835	-3,073,681	-5,119,512
05/06	448,634	7,907,390	-8,474,927	-4,293,457	-4,412,360
06/07	4,404,517	2,841,604	-9,310,094	-2,883,287	-4,947,260

**Source: Cytopia Annual Reports 1998-2007**

McDonald contrasted companies like Biota and Cytopia, which have multiple products padding out their pipelines, with that of single product companies. He is actively seeking to build out Cytopia's pipeline, beyond its current four programmes, and has employed a business development manager who is seeking external opportunities, whether they be partnerships or M&As. In planning Cytopia's growth, he found comparison with its US peers to be instructive:

It's interesting, we looked last year, just inwardly thinking about our strategy and where it was going. I sat back to look at some of the US companies that are of sort of similar ilk to us – looked at those biotech companies, cancer-focused, small molecule focused, etc, so, you know, broad profiling – and the factors that were common to all of those is that they had a multitude of programmes, between four and 14 programmes are running, plus more to feed the pipelines. They usually had the integrated capability in-house; they use collaborations to help but by-and-large a lot of it was done in-house. They had major partnerships, one or more of them. Lastly, they had significant amounts of capital and capital to back them for a reasonable amount of time. They spend hard, they spend fast and they try and get the results in the shortest period that they can. Sometimes it's quick and loose but, because they play a volume game, they can afford to do that. (interview, 2007)

McDonald portrayed growth as a careful balance between focus and flexibility:

You'll look back over our annual reports ... and you will see how – and this is what all biotechs do – you keep yourself flexible. You give yourself – you know, we all talk about cancer, autoimmune diseases. We leave so many

things open knowing that we have to be flexible, and we do that for a reason. But we've sat back and looked and thought to ourselves, well, let's get serious, what is it we're good at, what do we want to do? So, we looked at it, and not just as a therapeutic strategy but as an operational and commercial strategy. It's pretty easily summed up now; we're cancer focused – it doesn't mean that we won't look at other indications, in fact, with the JAKs on target, they're actually quite rich targets and they yield opportunities in different areas, but this helps us focus. So if we look at JAK2, we have cancer opportunities, we've been concentrating on the MPDs, which is still where the focus is, but cancer is really our game; our lead compound is cancer. We then have said, well, that makes sense, so we would look to partner out very late in life to pharma to help us unlock the value points. With our earlier programmes that are non-cancer, we'd look to partner early and bring in the other expertise that we don't have and to help us build. (interview, 2007)

McDonald has also focused on trying to recruit new people, particularly scientists with experience in a commercial environment. He has been particularly keen to attract talent who have worked in the US and who 'have actually done the hard yards that can see the problems before others see them' (interview, 2007):

We've got new people on board. ... [W]e've been recruiting actively in the last 12 months or so – I'd like to have more on board – but, yeah, I've started looking in different places for our scientists. We've got a mix – we bring some in from institutions and academia but we've been bringing in people, looking in the US, bringing in commercial skills, bringing in people that have been through it. We've just appointed a head of chemistry, first instance, and brought him in from – he was from [Rygol] in the US, been there for 30 years, hard biotech veteran and a damn good chemist to boot. It's just been great. He's brought in skills and people are setting up – in conjunction with us - setting a new culture here, they're looking at him going, okay, I understand but isn't this exciting, there's new things we can do. And he's challenging them. It's good. (interview with McDonald, 2007)

This process of sourcing new talent also extends to the board, for which Mathiou and Healey built in a renewal process:

I expect the Cytopia board to keep changing over time, over the next few years in particular. The company has evolved, people get older, you need new people. We set up a nomination committee, we call it, within the group and annually reviewed the board; its composition, who we need, the skill set, etc, and continually assess it annually. (interview with Mathiou, 2007)

Mathiou and Healey have also been part of this renewal process, although Healey remains a board member.

One reason why an injection of new talent was seen as necessary at this stage lay in the fact that key programs were progressing from discovery to development:

You know yourself; the rubber hits the road when you take things into the clinic. You can get away with a heck of a lot when you're in early research; you can promise a lot, you can hide a lot, you can come up with all sorts of exciting animal models and the like. But it's only when you get compound into the clinic and suddenly – that's a really interesting inflection that I find – because suddenly you've moved from your mass of people internally to just a few people internally who run those, coordinate those programmes. You've got much more outsourcing of responsibilities – you still want to keep the drive internally – but it's a completely different approach and it's quite analytical. The issues that you're dealing with are partially science, they're largely commercial issues. (interview with McDonald, 2007)

The transition to 'largely commercial' issues brings up the question of balancing science and business, a perennial concern for biotech companies.

## **Science and Entrepreneurship**

Healey had numerous thoughts about the challenges of blending scientists and entrepreneurs together, '... how long have you got?' was his opening statement. He then gave examples of his working relationship with Andrew Wilks:

I mean, if you talk about the relationship between Andrew and I, I was in control of the money and he was in control of the science. He was like a kid in a candy shop and it's like any parent telling their kid you can't have those lollies and so there's tension all the time. Then you've got to – I think entrepreneurs are less egotistic than scientists, who can be prima donnas sometimes, not mentioning any names. It's basically the tug of war between what a scientist thinks is a good idea versus how much cash there is in the bank. (interview, 2007)

The 'tug of war' is no surprise given that, as Mathiou explained, 'It's the nature of the beast for particularly the guys who love the early stage stuff; it's all about

discovery, it's not about necessarily delivering an end product' (interview, 2007). Mathiou and Healey both recalled the 'constant battle' they had in getting the scientists 'to do excellent science but also focus on doing it quickly, doing it for the lowest cost possible and doing it in the most appropriate riskless manner. Because all that adds value and, if they don't deliver that sort of equation, capital becomes a problem' (interview with Mathiou, 2007). Healey added: '... when is a lead good enough to become a candidate? A scientist will always want to make one better. I'd say the relationship I've had with Andrew has been extreme but a very good one – probably a bit like Costello and Howard<sup>1</sup>. But at least I let him take over' (interview, 2007).

Wilks, too, was somewhat exceptional as a scientist, not just in terms of his decision to leave the security of a research career, but also because he has continued to seek out business opportunities: 'I've started other companies as well. So, I've had a company in China that I run a chemistry capability and there is another Cy2pia coming along at some point in the future. I know where my strengths are though and they are very much in the science area. I would say there are weaknesses in some of the other areas that are part of being an entrepreneur; structuring finance and that kind of thing' (interview, 2007).

Wilks pointed out that 'scientists have to be entrepreneurial as well' (interview, 2007) and in fact, a commercial environment is likely to stifle this innovation:

It's intriguing that, as a scientist, you're probably more entrepreneurial as an academician than as a commercial scientist. Because I think it's all about creativity and invention and ... in academic research. In commercial research, we're much more focussed on goals and timelines and things like that. There's really not much flexibility for self-indulgence in terms of the experiments that you do. So not much margin to do entrepreneurial experiments in commercial research. Kind of an interesting ... [You're playing with somebody else's money usually.] That's right. And that's as it should be. There's a balance to be struck. And in Cytopia that balance has moved from, essentially, carte

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<sup>1</sup> Peter Costello – the ex Federal Treasurer and John Howard – the ex Australian Prime Minister

blanche on day zero to really very structured, project driven, milestone driven, budget driven stuff that we do today. And there's a natural progression that every company has to have from the former to the latter. And you're never sure you've got the balance right until it's too late. But it's probably a good idea to keep both of those things in your mind and focus on how to maintain the entrepreneurial science in the presence of the entrepreneurial business side of things. (interview with Wilks, 2007)

McDonald saw his role as introducing a cultural shift that recognises the different drivers operating in a commercial environment:

Within the institutions, within some of these semi-commercial institutions there is a culture which is very different [to commercial firms]. ...Well it's where they've [the scientists have] come from, from the university system, isn't it? ... Gee, I've been here a year therefore my pay must go up. Now, what grade am I? You know, there was great disquiet at Biota when we tried to drive out the old CSIRO categories of wages. I said, listen, we're going to introduce performance bonuses. No, no, we like that structure; we need to know how we're measured. I said, well, guess what, if you really feel good about that then perhaps you should be working at CSIRO but you're not and it's a different culture. We're going to reward people on their efforts and if you perform and can actually do what we need we're going to look after you. Equally, if you don't perform and you don't feel comfortable in a high risk environment, where delivery on timetables is critical and you don't get a chance to play with the science that excites you but the science that drives us, then maybe this isn't the place for you.

It's not as – you know, I make these comments and people think, geez, he's having a shot at them, and it's not but you have to consider the different drivers. They don't have profit [targets] – they do have more commercial targets, they have to think back to their owners; their owners are the Government, our owners are private individuals and they're individuals who are hungry for return on their capital. [In the past they were remunerated differently even in the institutions, as far as the universities, it was about publications] ... publish or perish.

Come into this environment and the driver is different. We ... want publications to the extent that people see us. We don't want to publish our IP, we don't want to put things out in the market which are going to prejudice our commercial ... But people sort of don't see it this way and you have to – you know, I was just dealing the other day with someone here who was getting hot under the collar about inventorship and we've moved away from that. I said, I'm sorry but, look – I didn't use these words – but the company owns the IP and we want to see you recognised if you are a true inventor, great, but we're just not going to put you on because there's a whole raft of commercial issues that we have to deal with down the track.

Well, you name them on patents according to the rules. If they've been true inventors you put them on, whereas in the scientific world everyone goes on. It's not to say that it's wrong but we take a fairly careful, legalistic view, if you will. If you're an inventor and you've contributed to the process then you're nominated on the patent. If you're not, we find ways of recognising people but it's not through necessarily the traditional, academic means.

It's been really interesting to watch the penny drop with the people at Biota over time and Biota – just to make comments for the time we were there – I looked at how that company had grown and I think it really came into its commercial being more in the last six or seven years, since 2000. Yeah, look, it's just time, it's just growth; it's just promoting the right sort of culture. Here, I think we're still – you know, when I came along to Cytopia I felt like I'd stepped back about three or four years from Biota, and that was exactly what it was. (interview with McDonald, 2007)

Furthermore, McDonald argued that part of this cultural shift involves moving away from the hierarchical management style of the laboratory:

Where there's science leading, everything gets led from the top, and that's okay but you've also got to start empowering people and making people accountable down the track. You tend to see in many of the biotechs every decision coming from – and I mean every decision, whether it's about the science or anything else – coming from a science perspective and there's not, it takes time to develop a culture where you're willing to trust people down the tree to make key scientific decisions, and yet that has to be a hallmark of a company. If you're growing a commercial entity then you do need to have people accountable and able to deliver at a range of levels. You need to motivate, you can't have it all from the top. Again, why? Manage your risk.

You've got to stand back and, I think, again, you come up with your strategy and all these things are the way a commercial company approaches them. You establish your strategy, put it into place and then everything's got to fit around that the same way ... I take the view that there is absolutely no one in this company that is indispensable, and that applies to anyone from me down. There isn't any single person in this company, as we grow, that the company would fall over if we lost tomorrow. Would it hurt? Would it give us a lot of grief losing some of the key people? Absolutely, and I don't mean that we do not value our people at all. Again, I come back to just managing risk within the business, and get you find that people grow the environment. When you pass out accountability to people – responsibility and accountability and make them accountable for things – and you pass that down, it's great to watch people that are empowered. They think, I can actually make decisions now and not be second-guessed on them. It doesn't come without its price but most people actually like that. People actually like certainty. People like to understand that they've got a focus and a direction. Like to understand what it is – and if you set hopefully the right strategy then they've got that clear and

they then, if they've got something to focus on, really get the bit between their teeth. But if they find things flip flopping, and biotech isn't particularly good at this over time. Because of the opportunism you think, I'll go this way, and then suddenly something changes and I'm that way, and it often leaves people thinking, gee, I'm not quite sure where exactly we're going. The companies that have survived and have grown get rid of that; they start to develop a certainty. You don't eliminate the opportunistic opportunities but, at the same time, you've got more structure around it. (interview, 2007)

The following tables and figures summarise Cytopia's key internal and external networks and position.

**Table 2:Key Relationships**

<b>Date</b>	<b>Partner</b>	<b>Type of agreement</b>	<b>Content</b>
Aug 01	Chemicon	Licencing	'Under the agreement, Chemicon* will receive exclusive rights to market for research purposes Cytopia's patented range of antibodies to a family of proteins involved in controlling immune diseases such as rheumatoid arthritis as well as certain cancers.' (Australian stock exchange company announcement 13 August 2001) Entered into a second agreement which extended the range of kinase antibodies being commercialised (Annual Report 2002). *Serologicals Corp (now part of Millipore).
Apr 02	Ludwig Institute for Cancer Research's Melbourne Branch, Sloan-Kettering Institute for Cancer Research, New York Queensland Institute for Medical Research	Research collaboration	'Cytopia's computational biology group together with Sloan-Kettering Institute scientists, will model the receptor/ligand structure based on X-ray crystal data produced by Sloan-Kettering. Cytopia will also design and evaluate potential inhibitors in silico prior to producing a selected range of compounds for laboratory testing. The Ludwig Institute and the Queensland Institute for Medical Research (QIMR) will evaluate peptide and small molecule inhibitors, initially in purified receptor and cell-based tests and subsequently, in animal models of melanoma. 'Cytopia has been granted commercialisation rights in the form of a 'first option to licence new technology from the collaboration subject to it funding any patent applications'. (Australian stock exchange company announcement 8 April 2002)
Jul 02	IBM	Licence	Supplying the hardware needed to run its Chemaphore drug discovery platform.
May 03	Children's Cancer Institute Australia for Medical Research (CCIA)	Research collaboration	CCIA performed in vitro tests on Cytopia's compounds for Acute Lymphoblastic Leukaemia (ALL) (Press Release 28 May 2003)
Jan 03 Jun 06*	Myomatrix Therapeutics	Initially a research collaboration,	Collaboration to develop JAK2 kinase inhibitors for cardiovascular targets including heart failure

		followed by an acquisition*	and hypertension. Myomatrix has a licence to technology demonstrating that JAK kinase inhibitors can potentially cardiac hypertrophy in animals. Myomatrix acquired in Jan 2005.
Nov 04	Cancer Research UK	Research collaboration for CYT997	CYT997 has been accepted by Cancer Research UK into its clinical trial program, allowing Cytopia direct access to leading British oncologists and world-class clinical trial facilities. Cancer Research UK's New Agents Committee (NAC) reviewed CYT997 and "... assessed CYT997 for originality, potential therapeutic benefit and likelihood of clinical success", Dr Wilks said. "The NAC's recommendation to accept CYT997 for clinical development independently verifies the enormous clinical potential of CYT997", he added. (Press Release 22 November 2004)
c. 04	Monash University's Department of Biochemistry and Molecular Biology	Research collaboration	A\$3.6 m 3-year drug discovery project to determine the 3D structure of Cytopia's drug discovery targets through X-ray technology. Supported by A\$1.2m Linkage grant (Cytopia 2004 Annual report).
Jun 06	Novartis	Licencing and R&D Collaboration	Development of JAK3 inhibitors. 'Under the terms of the agreement Cytopia will receive payments from Novartis of approximately US\$9.5 million over three years including an up front payment and research funding. Over the life of the agreement, Cytopia may become eligible to receive development, regulatory and sales milestones which could total approximately US\$205 million if an agreed number of multiple indications are successfully commercialised. Cytopia will also receive royalties on product sales.' (PR Newswire 5 June 2006) The Novartis deal is discussed in the 2006 annual report: 'We believe that this deal is the largest ever announced by an Australian listed biotech company' (p. 5). 'This is also the first biotech collaboration deal that Novartis has entered into with an Australian based company. Our geography can often be a hurdle to attracting the interest of global pharmaceutical companies'.
Nov 07	Barwon Health, Aus	Research collaboration for CYT645	Research collaboration with a leading osteoporosis expert to study the effects of Cytopia's FMS inhibitors
Nov 07	RNSH, Sydney Mayo Clinic, Cleveland Ohio	Research collaboration for CYT387	Cytopia has collaborated with leading laboratories in this field including the Royal North Shore Hospital in Sydney, Australia and the Mayo Clinic in Cleveland, USA to study the effects of its JAK2 inhibitors in pre-clinical studies on MPD patient cells. Cytopia's lead JAK2 inhibitor compound CYT387 has demonstrated potent activity in cells isolated from patients with myeloproliferative disorders (MPDs). (2007 Annual General Meeting, Chairman's Address)

Dec 07	The Alfred Hospital	Research collaboration for CYT997	Cytopia will proceed with a Phase II clinical study assessing its lead anti-cancer drug in up to 24 multiple myeloma patients conducted at the Alfred Hospital in Melbourne. It will investigate the activity of CYT997 in patients with relapsed or refractory multiple myeloma. (Press Release 3 December 2007)
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**Source: Cytopia Annual Report 2007**

**Table 3: Relationship Activity**

Country	No of relationships
USA	8
Canada	2
Scotland	2
England	1
Germany	1
China	1
Japan	1
Taiwan	1
Australia	15

**Source: Cytopia Annual Report 2007**

**Table 4: Cytopia's Product Pipeline**

Compound	Stage	Market rights
<b>CYT 997</b>		
Cancer PO	Phase I completed	Cytopia
Cancer IV	Phase I	Cytopia
<b>JAK 3</b>		
Transplant	Lead optimisation efficacy data	Novartis
RA	Lead optimisation efficacy data	Novartis
<b>JAK 2</b>		
MPD	Preclinical	Cytopia
Cancer	Lead optimisation efficacy data	Cytopia
PH	Lead optimisation efficacy data	Cytopia
<b>FMS</b>		
Cancer	Preclinical	Cytopia
Inflammation	Preclinical	Cytopia

**Source: Cytopia Annual Report 2007**

**Key**

RA- Rheumatoid Arthritis; MPD – myeloproliferative disease; PH – pulmonary hypertension; FMS – functionalised mesoporous silica

## Financials

In 2007 Cytopia had an operating loss \$4.9m, revenue \$5.6m (from licence fees and investment income); a cash balance of \$14.1m, which was estimated to be enough to last them until 2009 financial year. Cytopia's staff numbers are tablisted below. Unfortunately these numbers are estimates as they appear in a bar chart.

**Table 5: Staff Levels**

Year	No of staff
2001	21
2002	30
2003	26
2004	26
2005	31
2006	34
2007	49

**Source: 2007 annual report**

## McDonald Joins the Team - 2005

Andrew McDonald stressed the importance of fully understanding the nature of the global biotech industry – in order to be able to contextualise Australian spin-offs like Cytopia:

I think you have to think firstly about which sector we're discussing, and I think there's a global biotech sector that sets trends and you look at the US market and, arguably, the European market, but more primarily the US. It's a far more mature market, a far more advanced market and, whilst we think we're very similar, I think there's a range of whole drivers, particularly Government funding, that is much stronger in the US than it is here in Australia. Well, it's [US market] is more organised, there's more capital in it, there is more expertise, more commercialisation expertise. You have a much stronger VC capital market that playing in that space so, as a result I think it's a sector that has largely grown up and I'd probably characterise it as not only mature but it's a lot more of a professional sector and all of the attendants that surround it, such as the analysts and like. You can talk with an analyst in the US and they know their stuff; they know the science, they know the companies, they understand the commercial issues. That's a rare to find – I'm not saying you won't find it – but there's very few people here that are good commentators on the sector.

So you come back to the Australian sector and it's interesting. A company like Biota ... it is 22 years old now and people tend to forget that; there's a few companies around and they've had to put in the hard yards. Those companies have started off pretty much the same way we've started off. I think there's some subtle differences but by and large they've started off with early stage research, and that's a really gutsy call because it's a long gestation period to take drugs all the way through. I think if you go back to the late '90s is really when the sector started to come alive here in Australia, so Biota was one of the pioneers in this area, there was Amrad – or Zenyth as they ended up. They were more the forerunners, if you will, of the sector. But it started off with early stage research, got people excited, attracted capital – and not necessarily what I would term intelligent capital, either – it's capital that enthused about an opportunity rather than a sound business proposition. So they've put in the long hard yards and, again, Biota was the only company that's ever taken a drug all the way through from discovery through to the market, so let's not comment on how they should have gone. But nonetheless, it's there, successful, and it's growing, they've just taken a long time to do it.

Cytopia is probably a very similar category [to Biota]. We started off, as you know, we floated in '99. Cytopia itself had started earlier than that and, of course, Cytopia was Medica – the guys [Wilks, Healey and Mathiou] probably explained this to you, how the investments occurred. But I think it's fair to settle early stage – and it's easy to sit back down with the benefit of hindsight – but you go, well, of course it was going to take seven or eight years to get a drug through into the clinic and yet, had the investors and the people that came to look at that company at the start really thought hard about it, they probably would not have invested. So they've come on and expected things to happen very quickly. Of course, this whole sector is largely about management expectations; you want to get the excitement in, you want to attract the capital but it's a long haul and the other – I sort of refer to it as almost the dirty little secret in biotech – the fact is that most of us fail.

It depends on where you start; it depends on the area in which you wish to play into. But I think it's fair to stay in terms of a successful drug to the market, it's not that you can't unlock value along the way, but the attrition rate and the failure rate is rather high. (interview with McDonald, 2007)

McDonald also commented on the fact that like many biotechs before Cytopia, they too went to IPO early in their organisational development, 'Cytopia launched into the public market, as many biotechs do, because it's the only route. We've got a poor VC market, there are VCs around and they are funding, but by and large there's not many options for small biotechs. The only option is to go to the public market to attract capital and to grow your company from that point' (interview, 2007). As to the nature

of the investors, he explained it was a combination of institutional and domestic investment:

There was a focus, obviously, in the large end of town, you want to bring in big licks and capital and mum and dads are normally aren't going to put that money in. So, it was typically a register that comprised large institutions and they certainly had expectations of the company. Now some of the things I'm going to comment here, I wasn't around at the time so I'm giving you my views probably from afar as opposed to being involved with the company. Without doubt there was a large core of institutions the came onboard. There was Merrill Lynch, there was a whole raft of investors that came on in the serious capital raisings but, I think it would be fair to say, just lost interest along the way. Expectations of partnering deals, expectations of getting drugs into the clinic and, when you stand back and look at things in the cold, hard light of day, it's a long haul. We know that as a sector but we don't want to talk about that – we don't like to talk about that openly because nothing turns an investor off more than hearing it's going to take three times as long.

So I think the journey that we've had here, once you launch as a biotech company into the commercial sector, and you suddenly have shareholders and owners of the company who have expectations – you've got your mum and dad giving a dollar of their money, and they're essentially wanting more than a dollar back in some sort of time period. Some have expectations of it quickly, some more knowledgeable ones have expectations that it's going to be longer, but the risk reward says they expect much bigger up-kicks and upturns for their money. So, you know, they're going to expect to be in there six or eight years, they don't expect a 10% return over that time, they want a lot bigger pick up. I think that the challenge for all biotechs is managing that process from the early days where the companies do not raise enough money. They typically will get funding for a year to two years, they've usually overshot or oversold the expectations and what they think they could achieve in that time. So you're out with your cap in hand to the market in a reasonably short period of time and people are going, where are your milestones, what have you hit, what have you done? I think it's interesting when you look at many of the new companies coming onboard these days. It's not unlike the States whether people are realising that start up biotechs, it's almost impossible – well, not quite impossible but it's a real tough haul, so many companies are now looking to buy in a programme that's in a reasonably advanced stage and look to leverage it up and bring their skills and experience to bear, and the closer it is to the clinic and the real value point for them, of course, the more attractive that proposition becomes. Again, investors have that very short-term time horizon. (interview with McDonald, 2007)

McDonald was critical of the fact that very few companies should have to be in a position where by they are forced to go an initial public offering:

Arguably, none of us – I’m sorry, very few of us – in the sector should be on the public market. [If we could avoid going to IPO we would, and] What you would do, what you need here is significant capital, you need *patient capital* – and I’d be surprised if you haven’t heard that from others. But if we had long term, private, patient capital, we have no expectations other than to our owners that we can honestly and wholesomely give them a strategy. I say again honestly, because there is a process as you go through this that’s not dishonest, but I’m not too sure it’s being totally open with people. We know, because we’re all good people who understand the sector – well, hopefully we are – that we know it’s going to take a long time, and yet we always are promising things that are a struggle to deliver.

That’s the other interesting challenge in running a business like this. I come very much from a commercial world – I started in science, I spent most of my life in a commercial setting, a non-science setting, and then I found my way back into science in the last six or seven years and it’s interesting. I look to bring my skills to merge the commercial aspects, the people aspects. All the other aspects are the science and we all know science is unpredictable. You have to be understanding of that and accepting of it. What I know is that I don’t have to be understanding or accepting of other things I can control and manage, and that’s the challenge. As many of the biotechs go through this evolutionary change moving from educational institutions, they have to bring in commercial skills and thinking, and that happens in a variety of ways. But until you can bridge that gap and have the right focus and really have people understand what the true drivers are, then ultimately you’re going to be lucky to make it. You might do partnering and you might manage to play pass the parcel – you’ve built up to the value and you’ve on sold it or licenced it out to someone, and that’s a good outcome in itself. But if your goal is to build up a sustainable company, you want to have a company that can keep on delivering and you have to recognise the risk profile of what you do. It’s inherently risky business, and that’s okay, you therefore manage that risk accordingly. You cannot manage risk when you’re running only one project, it’s a binary outcome; it either works or it doesn’t work. And guess what, it happens.

... when we go out and talk to investors, you know, I want to be able to play an educating role and yet it’s an absolutely turnoff. Investors don’t want to hear about risk, they don’t want to hear about attrition, they don’t want to hear about sensible timelines; they just want the results and they want them as quickly as they can and you have to manage around those expectations. (interview, 2007)

McDonald contrasted the Australian investment community to that of the United States, explaining there was some important differences in terms of private and patient capital:

They do [have private and patient investors] and a lot of them are public. It's a different market, though; they start off with their capitalisation typically, you know, seven, ten times what we would raise here. We have biotechs here who will go out and raise A\$3 or A\$4 million to start. That same biotech in the States would raise US\$20- 30 or 40 million. So they are well-capitalised, they raise money frequently in big licks and from knowledgeable investors. The investors come in, they look at the work they're doing, the indications they're playing into. They look at the people and they make, I call them just sound, commercial investments. A lot of it in the Australian sector still remains, you know, I talked about intelligent investing – and it's not to bring emotional terms into it – but many of the people investing do not understand. Yes, we go around, we walk to potential investors; I'd have to say the majority of them would be lucky to spell cancer let alone understand what it does. I don't mean that in a derogatory sense.

It is a challenge and yet, you know, they're usually the people willing to stump up and put their money in. They actually manage their risk – if you think about what they do and what we do, they manage their risk everyday. They look, they balance out their portfolio and it's those people who have had a successful approach in doing that, and that's the sort of things that we should be doing in our business. So we look, over time, to build a portfolio out. We need to, I guess, crawl before we can walk. (interview, 2007)

From a global point of view, Mathiou shared his thoughts on the issue of generics, research and manufacture:

Undeniably [China and India are important in the market] but, you know, they've been incredibly clever, as I see it. In a very strategic sense they are targeting generics aggressively. Why? Because there is no intellectual property issue because the drugs are off patent and they're the cheapest manufacturers in the world, so they have a cost advantage. They're making a fortune, at the minute, out of the generic revolution that's emerging. There's going to be US\$40 billion worth of drugs coming off patent over the next five years and that's US\$40 billion worth of – well, US\$20 billion worth of revenue stream going to generic manufacturers in China and India. That's going to fund other activity. That's going to fund the industry there, so they're real competitors. (interview, 2007)

As for their role in discovery research, Mathiou also saw them playing a limited role, ' ... we dealt with laboratories over there [southern and eastern Asia], in particular to get cheap chemistry – much cheaper than we could manage here. But you would only give them certain aspects to make and they'd provide you that product and then you

would combine it with other chemistry into the molecule you want locally. So, you were never really, truly giving away your intellectual property position to them. But, clearly, one of the major valuable things that a biotech has is the strength of its intellectual property at any point in time, so you don't want to put that at risk' (interview, 2007).

However, Mathiou was clear to state that in his opinion he would take that approach to protection IP with any prospective partner or supplier, 'With anyone in the world you'd take a similar approach; for anyone external to your organisation you take a similar approach. But they do have their issues in relation to enforcing intellectual property over there but I understand they're trying to improve that. To the extent they do that they'll benefit, but we'll see how we go' (interview, 2007). Additionally, the very concept of IP and freedom to operate is also contributing difficulty to the commercialisation process right across the board, '[Getting freedom to operate is] very, very difficult and it's becoming more so because just of the enormity of applications and research. The enormity of the research that's occurring now, which is resulting in backlogs of intellectual property applications, etc, worldwide – it's becoming a minefield. But, if you do discover something and you get to a patent stage, and if you've had appropriate advice that ties up the area particularly well, you're better placed. Is it a stone cold guarantee you'll be successful? Absolutely not! Is it a requirement to be successful? Absolutely yes! So, it's just part of the equation and you do as best as you can' (interview with Mathiou, 2007). Cytopia's way of managing this task was to ensure their scientists were across the technology, but Mathiou explained that the company also employed intellectual property specialists.

Networks according to Mathiou are, 'very important and you've got to continually build them. You know, you just don't wake up in the morning and say, I've

got something to sell, I'll just cold call a few people and get it away. You are building relationships constantly and it's from those relationships that most deals get started and developed and ultimately closed' (interview, 2007).

Mathiou discussed the challenges facing the Australian scientific and biotech community. In particular in relation to the scientists moving between academia and the commercial world:

I think they'd cope particularly well if there was available capital. The big difference between the US and Australia, as I see it, is the scale they're able to obtain because of vastly more efficient venture capital markets over there. A start up over there can raise A\$20 million to kick off with the next round 50. The equivalent in Australia is two to kick off with the next round five. Now that doesn't give scientists huge levels of comfort and, you know, it really is difficult and, in my view, until we get a vastly more efficient venture capital market in Australia it's going to be a problem. But that, I see, is one of the major differences. The quality of science in Australia is internationally competitive, I've got no doubt. There might be the not-invented-here syndrome from the US, but I think they're waking up and I think they do realise that the quality of the research coming from Australian research institutes is of the highest order, so that's not the issue.

### **Healey's Future Directions**

Whilst there had been a succession plan in place for Nicholas Mathiou in terms of stepping him off the board and management of Cytopia, Healey remained on the board in late 2007. Rather than showing signs of slowing down or taking a well-earned rest, Healey and Mathiou were still in full flight in terms of getting another company off the ground – a more traditional venture capital company – amongst other things. Healey gave more details of his activities:

Yeah, I'm still on the board of Cytopia but I've taken up the chairmanship of a company called Bio-Link, which is more of a commercialisation partnering vehicle, a bit like [Burrell] in the US. We just opened an office in Melbourne. But I'm up and down like a yoyo there [from Sydney to Melbourne]. I've joined the board of a company in Adelaide, actually called Nidor, which is a diagnostics company coming out of the Women's and Children's Hospital. They're incubated within the hospital at the moment. But we're just going

through a venture capital round so they'll probably spin out and go to the tech park after that. Nicholas and I are trying to get a more conventional venture capital fund together but it takes so long. [The change in the legislation to the PDFs is probably determining the structure but the idea really is just to have a more – because Medica wasn't a conventional fund – we just want to try our hand with a more straight up and down VC fund with an external manager rather than the internal manager and maybe do a number off it. (interview, 2007)

In the 2006 annual report they state that this willingness to actively seek acquisitions 'remains unaltered' (p. 6).

### **Why Universities Get Commercialisation Wrong**

Their experiences to this point led Mathiou to verbalising his observations on the nature of the university research and commercialisation approach:

One of the major mistakes, in my opinion, that universities and transfer offices throughout Australia make is that you think you need science. One of the major things, in my experience, that you actually need is finance and business acumen. Science is just one part of the equation. [You need other things that are] completely different. [You need] project management, in particular ... in the sense that you do start with a good bit of science – and you need that to get cracking – but you're obviously undertaking significant research and development programme that requires project management. You're collaborating with a large number of groups, often, externally who have particular skill sets that you can't afford or you don't use frequently enough to develop in-house, so you're constantly collaborating and that requires a skill set in project management. So, you know, it's a question of doing the right thing – that is your strategy – but it's also a big chunk of doing things right. Implementing on it and, you know, you do need significant project management skills or call them research and development programme skills or whatever you would like. But in our world, project is the research and development programme. (interview, 2007)

As for the ability of young start-ups or spinout firms to actually employ these skills Mathiou speculated about this. On the one hand he took a strong stance that they were needed but equally as to whether the scientists could be morphed into these roles

more out of financial necessity and then perform adequately he was unwilling to say if this was possible:

I think at the start up level you just can't afford it. That's the problem, you know, there's just not enough money to go around and it becomes difficult to do that in terms of employing people with the appropriate skill set in Australia, from a business point of view and a financial point of view. The other thing I can say, too, is that there's a very competitive marketplace out there for those types of people at the minute. They're more inclined to join Macquarie or Babcock & Brown or some financial institute that pays them handsomely, than find their way into a risky start up biotech. So, they're just not around. If anyone's saying they're employing the right people at the start up stage, I think that's palaver, personally. That's just because they're not around. If a scientist's telling you that they're thinking they're hiring the people with the relevant skill set but can I suggest that they're not picking up people with the relevant skill set because they're not around. As you get bigger they become more and more available, yes.

As for the likelihood that with the maturity of both the biotech and the pharma industry, along with the accompanying mergers and acquisitions, there could be an excess of staff also known as 'pharma refugees', Mathiou was again unsure as to whether this particular group of people would even have the skill set. It depends. A lot of them, if they've come from large biotech or pharma are used to a different world. You know, they're dealing with science that's far more advanced, they're dealing with infrastructure that is big business, there's infrastructure in place. [Money's not usually an object] ... and it's a different skill set. Do they have a place in the world? Absolutely. When Aussie biotechs go beyond proof of concept and start getting into the clinic and you start needing their skill set to sell to large pharma or large biotech, by way of example. But would they know actually how to run an early stage Aussie biotech from an Australian base? No, no chance. (interview, 2007)

Like, Healey and Wilks, Mathiou too was heavily involved in 'selling' the company. Of his role in this process he said, 'I was involved in the road show] on and off, absolutely. It just depended on the circumstances but through our time absolutely. We were constantly – at the Medica level – selling all the companies beneath it. Obviously the more attractive our investments, the more attractive our stock and that improved our ability to get the capital into our company to provide the investments. So, we were constantly presenting to high wealth individuals and institutional individuals the story' (interview, 2007).

Moreover, he gave a very good insight into the deal negotiated between Cytopia and the Ludwig Institute around the time Cytopia was listed on the ASX, ‘In relation to looking at IPO and ... due diligence of the licence for the JAKs with the Ludwig, I was involved]. Absolutely! And look, they [the Ludwig] were good. Andrew [Wilks] came to us with sort of an idea and a handshake from the Ludwig that, should he achieve certain parameters, they’d facilitate the licence to the intellectual property. So, you know, Andrew’s done particularly well because he didn’t have an agreement – he didn’t have a written agreement or even an option or anything – he just had a relationship with the Ludwig and we went from there. But, you know, a strong relationship and one which panned out to be particularly good’ (interview with Mathiou, 2007).

Trust and contracts seem to be juxtaposed, but Mathiou put it this way, ‘There’s no doubt that, you know, the best contract is the one that is unbelievably detailed and lucid and covers all the bases but which then gets put in the drawer and never taken out of the drawer again’ (interview, 2007). As to how often this scenario managed to appear in Mathiou’s experience he said, ‘[It happens] fairly often, particularly in cases that you mentioned, where the relationship is good. But, unless you have exceptional agreements in place, you will not go through the due diligence process successfully. So, you can’t attract capital, venture capital in particular, if your agreements aren’t ironclad and appropriate, it just won’t happen. So you need to go through the process and, once again, if anyone has told you there that a handshake is good enough, well, they’ve never had to raise capital for a biotech in their life’ (interview, 2007).

As to Cytopia’s business model, of employing research in house, Mathiou was unsure as to its popularity within the broader biotech community:

I don’t know but let me put it this way; for stuff that we do frequently and that is highly valuable to us, we keep in-house. For stuff that we use sporadically or periodically, where other skill sets are better than what we could create with

our given dollar internally are elsewhere, we go elsewhere. But there is certain parts of our research, in particular the drug discovery engine room, which we constantly keep in-house for intellectual property protection issues, but also because that's what we do. You don't outsource something that you do frequently to someone else. Why pay their overhead and profit margin, etc. It just doesn't make sense. (interview, 2007)

There were very definitely [other companies], quite a few companies who'd be interested in this space. The idea was to get as many attracted to the opportunity as possible to get the best possible deal. [Deal tension] that's it. You can present what you've got in conferences, and that might get a few scientific people interested, but the thing is, you've got to go direct to the team, the licensing team in particular of a pharma company, and explain what you've got and why they should really look at it. (interview, 2007)

## **IP Management**

McDonald discussed in detail Cytopia's approach to managing its intellectual property:

IP is still critical, you take huge care with it and it's not and it doesn't come from a publish or perish mentality. If we keep in-house everybody here understands the need for that. We're clever about how we do it now; we now have a patent strategy, whereas before it was a bit of a scattergun. It's no criticism, it's just simply an evolution. Biota has done the same thing. As you start to grow up, you start to realise that you need the disciplines around you. You can't patent every drug you've got in every jurisdiction – well, you can but you can't afford it. JAK3 as a target it's not patented. It really isn't patentable as a target so we just have our NCE patents and they stand us in extremely good stead, thanks very much. We protect that very, very carefully. (interview, 2007)

McDonald talked about the issue of looking for ways in which to cease programs yet as the same time have enough different projects on the boil that you could attract shareholders, 'You know, you should always be searching for the experiments that are going to kill your programme within reason, and if it makes it through you've got yourself a good candidate' (interview, 2007).

McDonald agreed with his colleague Mathiou, about the importance of having project management skills. Of this he said, 'I think that it's a really salient point, though. One of the biggest things that I see missing internally in biotechs here

[Australia] is project management, where it's actually needed through the early stage process. Being able to kill off programmes, being able to make sound decisions rather than keeping programmes alive. [Emotions were agreed as part of the reason that programs were not disbanded, but also] the fact that if you're only running one programme and you kill it off, what have you got left? Yet, from your owners' perspective, that's exactly the decision you should be making' (interview, 2007).

From Wilks's perspective, he explained how and why some of the patents were dropped off some of the targets that were initially patented:

A number of those targets we had patents on. Some of them we let lapse. Some of them were either [sequenced] simultaneously, or we were later in terms of characterising the full sequence, so they came off the JAKs; JAK1 and JAK2, JAK,3 a bunch of these .... JAK3 though, was actually discovered.

JAK3 is another family member, we actually discovered it, [but] we didn't patent it. [JAK 3] ... was subsequently uncovered looking at cells from the lymphoid series, T cells and B cells. JAK3's the program that we've now partnered with Novartis. (interview, 2007)

Cytopia's full suite of products and their current patent status are tabled below.

**Table 6: Cytopia's Patent Suite**

Patent Title	Application Number	Lodged by	Inventors	Earliest Priority Date Granted in:
Receptor-type tyrosine kinase-like molecules	PCT/AU93/00210 WO93/23429	Ludwig Institute for Cancer Research, Switzerland	Steven Alan Stacker Christopher Martin Hovens Andrew Frederick Wilks	11/05/92 PL2358 Australia
A novel protein tyrosine kinase	PCT/AU93/00560 WO94/10197	Ludwig Institute for Cancer Research, Switzerland	Andrew Frederick Wilks Andrew Stewart Runting	30/10/92 PL5581 Australia
Immuno-interactive molecules-I	PCT/US95/01727 WO95/21865	Ludwig Institute for Cancer Research, NY USA	Andrew Frederick Wilks Steven Alan Stacker Robert Brenchley Oelrichs	10/02/94 PM3793 Australia
An immuno-interactive molecule which binds the (TIE) 2/TEK receptor extracellular domain	PCT/US95/01743 WO95/21866	Ludwig Institute for Cancer Research, NY USA	Andrew Stewart Runting Andrew Frederick Wilks Steven Alan Stacker	10/02/94 PM3794 Australia

Assay, receptor proteins and ligands	PCT/US95/16753 WO96/20403	Ludwig Institute for Cancer Research, NY USA	Steven Alan Stacker Andrew Frederick Wilks	23/12/94 PN0300 Australia Serial 705793 is a Divisional of this Application
Recombinant vascular endothelial cell growth factor D (VEGF-D)	PCT/US97/14696W O98/07832	Ludwig Institute for Cancer Research, NY, USA and Helsinki University Licensing Ltd., OY Finland	Marc G. Achen Andrew F. Wilks Steven A. Stacker Kari Alitalo	23/08/96 PO 1825 Australia 23/08/96 60/023751 USA 11/11/96 PO 3554 Australia 14/11/96 60/031097 USA 05/02/97 PO 4954 Australia 10/02/97 60/038814 USA 19/06/97 PO 7435 Australia 01/07/97 60/051426 USA
Protein kinase signalling	PCT/AU02/00088 WO2002/060927	Cytopia Pty Ltd	Atkin, Julie Fantino, Emmanuelle Wilks, Andrew Frederick	30/01/01 Australia
Methods of inhibiting kinases	PCT/AU02/00089 WO2002/060492	Cytopia Pty Ltd	Burns, Christopher John Wilks, Andrew Frederick	30/01/01 Australia
Protein kinase inhibitors	PCT/AU03/00629 WO2003/099796	Cytopia Pty Ltd	Bu, Xianyong Burns, Christopher John Wilks, Andrew Frederick	23/05/02 Australia
Kinase inhibitors	PCT/AU03/00628 WO2003/099811	Cytopia Pty Ltd	Bu, Xianyong Burns, Christopher John Wilks, Andrew Fredrick	23/05/02 Australia
Pyrazine-based tubulin inhibitors	PCT/AU2003/0016 61WO2004/052868	Cytopia Research Pty Ltd	Bu, Xianyong Burns, Christopher John Wilks, Andrew Frederick	13/12/ 02 Australia
Nicotinamide-based kinase inhibitors	PCT/AU2003/0016 66WO2004/054977	Cytopia Research Pty Ltd	Burns, Christopher John Kling, Marcel Robert	13/12/02 Australia
Tubulin inhibitors	PCT/AU2004/0016 89WO2005/054199	Cytopia Research Pty Ltd	Burns, Christopher John Fantino, Emmanuelle Harte, Michael Francis Sikanyika, Harrison Sims, Colette Gloria Wilks, Andrew Frederick	3/12/003 Australia
Azole-based kinase inhibitors	PCT/AU2004/0016 90WO2005/054230	Cytopia Research Pty Ltd	Bu, Xianyong Burns, Christopher John Wilks, Andrew Frederick	3/12/03 Australia

Selective kinase inhibitors	PCT/AU2005/0000 22WO2005/066156	Cytopia Research Pty Ltd	Bu, Xianyong Burns, Christopher John Kling, Marcel Robert Styles, Michelle Leanne Treutlein, Herbert Rudolf Wilks, Andrew Frederick Zeng, Jun	12/01/04 Australia
Retrometabolic compounds	Provisional Patent No. 2007906387	Cytopia Research Pty Ltd	Not Given	22/11/07 Australia