



**THE RELATIONSHIPS BETWEEN EICOSANOID
PRODUCTION AND PRO-INFLAMMATORY CYTOKINES**

by

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A thesis submitted to the University of Adelaide

As the requirement for the degree of Doctor of Philosophy

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31/12/01

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ABBREVIATIONS

The following abbreviations are used in this thesis.

$1\alpha,25\text{-(OH)D}_3$	$1\alpha,25\text{-dihydroxyvitamin D}_3$
AA	arachidonic acid (20:4 n-6)
Abs	antibodies
$\alpha\text{-LNA}$	$\alpha\text{-linolenic acid (18:3 n-3)}$
A	amp (s)
BCA	bicinchoninic acid
BSA	bovine serum albumin
cAMP	cyclic 3', 5'-adenosine monophosphate
$^{\circ}\text{C}$	degrees Celsius
Ca^{++}	calcium
CI	carboxyheptyl imidazole
COX	cyclooxygenase
cPLA ₂	cytosolic phospholipase A ₂
CSF	colony stimulating factor
d	day (s)
Da	Dalton
DAG	diacylglycerol (s)

DHA	docosahexaenoic acid
DPBS	Dulbecco's PBS
DTT	dithiothreitol
ELISA	enzyme linked immuno assay
EP	prostaglandin E receptor
EPA	eicosapentaenoic acid
ERK	extracellular regulated kinases
ETrA	eicosatrienoic acid
FA	fatty acid (s)
FCS	fetal calf serum
g	gram
GSH	glutathione
h	hour (s)
H ₂ O ₂	hydrogen peroxide
IBMX	1-methyl-3-isobutylxanthine
I-BOP	5-heptenoic acid, 7-{3-{3-hydroxy-4-(4-iodophenoxy)-1-{2.2.1}hept-2-yl}-, {1S-1 α ,2 α {Z},3 β (1E,3S*),4 α }
IFN	interferon
IL-1	interleukin-1
IL-1R	interleukin-1 receptor
IL-1Ra	interleukin-1 receptor antagonist
Ig	immunoglobulin(s)
IP ₃	inositol triphosphate
JNK	c-Jun NH ₂ -terminal kinase,

k	kilo
l	litre
LA	linoleic acid
LPS	lipopolysaccharide
m	milli
M	molar
MAP	mitogen activated protein
MeOH	methanol
min	minute (s)
n	nano
NSAID	non-steroidal anti-inflammatory drug
O ₂	oxygen
OA	oleic acid
p	pico
PBS	phosphate-buffered saline
PGA ₂	prostaglandin A ₂
PGE ₂	prostaglandin E ₂
PGF _{2α}	prostaglandin F _{2α}
PGG ₂	prostaglandin G ₂
PGH ₂	prostaglandin H ₂
PGI ₂	prostacyclin I ₂
PKA	protein kinase A
PKC	protein kinase C
PLA ₂	phospholipase A ₂
PLC	phospholipase C

PUFA	polyunsaturated fatty acid (s)
PMA	phorbol myristol acetate
RA	rheumatoid arthritis
RIA	radioimmunoassay
s	second (s)
SD	standard deviation
SKF86002	[5-(4-Pyridyl)-6 (4-fluorophenyl)-2,3-dihydroimidazo (2,1-b) thiazole]
sPLA ₂	secretory phospholipase A ₂
sTNFR	secretory tumour necrosis factor receptor
STZ	serum-treated zymosan
TNF	tumour necrosis factor
TNFR	tumour necrosis factor receptor
TXA ₂	thromboxane A ₂
TXB ₂	thromboxane B ₂

SUMMARY

Rheumatoid arthritis is an inflammatory disease of unknown cause associated with progressive joint damage and functional disability. Current therapy for rheumatoid arthritis is toxic and is associated with a high incidence of side effects.

Recently, the inflammatory cytokine tumour necrosis factor α has been reported to be an important, proximal mediator of rheumatoid arthritis. Antibodies or receptor antagonists for this molecule have been shown to be effective therapy for rheumatoid arthritis. However, such therapy remains expensive, inaccessible for the majority of patients and associated with adverse effects.

The aim of this thesis was to explore alternate strategies that may alter inflammatory cytokine production, particularly tumour necrosis factor α , and therefore provide a possible treatment for rheumatoid arthritis. The focus of the alternate strategies as described in this thesis are the eicosanoids, thromboxane A_2 and prostaglandin E_2 . These strategies are safe, accessible and not associated with significant adverse events.

Alteration of these eicosanoids was shown to modulate tumour necrosis factor α both *in vitro* and *in vivo*. The significance of this alteration of tumour necrosis factor α by these strategies as it might apply to rheumatoid arthritis remains to be tested.

AUTHORS DECLARATION

31/12/01

This work contains no material which has been accepted for the award of any degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

Peter Savas Penglis

31 / 12 / 01

ACKNOWLEDGMENTS

- Associate Professor Michael J James, whose daily presence in the laboratory and ready guidance when needed, combined with a respectful distance to allow freedom to pursue different avenues as part of this thesis, was the ideal supervisor,
- Associate Professor Leslie G Cleland, for his personal and clinical support while working as a registrar attached with his unit, his encouragement to pursue an academic career and in his assistance with grant application. His contribution to reading and marking of this thesis and publications was greatly appreciated, as was the generous spirit in which he performed these time-consuming chores,
- MarieAnne Demasi, for her assistance with experiments and techniques in the laboratory, especially in the first year and for utilising her diagram of COX-1, Figure 3.4,
- Gillian Caughey, for her ready assistance with experiments, and especially for her helpful advice when things went wrong. Her excellent thesis generated some of the ideas for this current one and I greatly appreciated the freedom and generosity in which she shared her findings,
- IMVS Animal House, for their assistance with rabbit injections and collection of PGE₂ antisera (section 2.10),

- Cindy Hall, for her assistance with making the rat chow and advice on animal experiments,
- Ashley Connolly, for using some of his ELISA techniques in measurement of rat TNF α (Connolly 1998),
- To the SA Blood bank for the provision of buffy coats, from which monocytes were prepared,
- To my brother in law and friend, Brad Cowain, for his assistance with computer technology and formatting,
- Finally and most importantly, to my wife, Taryn Cowain, my best friend, for her acceptance and reassurance that enabled this thesis to be a positive and worthwhile experience.