

Combinatorial Targeting of the Androgen Receptor for Prostate Cancer Therapy

A thesis submitted to the University of Adelaide in the fulfilment of the requirements for
the degree of Doctor of Philosophy

By

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Abstract

Prostate cancer is one of the most commonly diagnosed cancers in Australian men and is the second leading cause of death from cancer. Since the advent of prostate specific antigen (PSA) testing, more men are being diagnosed with early-stage or organ-confined prostate cancer. At this stage of the disease, surgical removal of the prostate and/or radiotherapy is potentially curative. However, approximately 10-30% of men will progress with metastatic disease despite an initial diagnosis of organ-confined cancer, and 5-10% of men are diagnosed in the first instance with metastatic disease. Given that prostate cancer is dependent on androgens for growth and survival, the current standard of treatment for these men is androgen deprivation therapy (ADT). Despite an initial positive response to this treatment, it is not curative and relapse generally occurs within 5 years. At this stage of the disease, further hormonal manipulations or chemotherapy do not typically significantly prolong survival. It is now well accepted that this relapse is due to mechanisms by which the prostate cancer continues to rely on androgen signalling through the androgen receptor, despite the efficacy of androgen deprivation. Our laboratory and others have shown that clinical agents and molecular methods that target the androgen receptor (AR), as opposed to the androgen, are effective at suppressing growth and inducing death in prostate cancer cells.

The objective of this thesis was to characterise the effects of combining clinically different drugs that modulate levels and/or activity of the AR. The histone deacetylase inhibitor vorinostat and the hsp90 inhibitor 17-AAG were investigated in combination with bicalutamide, an AR antagonist currently in clinical use. Both combinations proved to be significantly effective at synergistically suppressing growth and inducing death in prostate cancer cells *in vitro*, using concentrations of the drugs that are individually sub-effective. Due to factors beyond control, *in vivo* testing did not result in a definitive answer regarding efficacy in a mouse model of prostate cancer.

Microarray profiling revealed a mechanism for the synergistic interaction between vorinostat and bicalutamide, implicating loss of the gene *NFKBIA* as a cause of prostate cancer cell death. Furthermore, microarray analysis showed that combining 17-AAG with bicalutamide reduces the characteristic and undesirable heat shock response associated

with 17-AAG, but also implicated *NFKBIA* in the prostate cancer cell death caused by this combination. These insights provide a basis for further investigation into the role that manipulation of *NFKBIA* could play in future therapeutics, and the potential for the use of 17-AAG in a clinical setting despite the development of new generation hsp90 inhibitors. Overall, the information presented in this thesis builds on the pre-clinical characterisation of two different combinations targeting the AR for prostate cancer treatment, and facilitates clinical testing of these treatment options.

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, 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. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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TL;DR – Thanks everyone, you're all great 😊