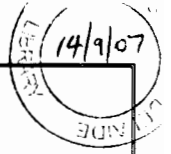


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# **Targeting the Androgen Receptor as a Therapeutic Strategy for Prostate Cancer**

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

by

Deborah Lydia Marrocco B.Sc.(Hons)

Dame Roma Mitchell Cancer Research Laboratories

Department of Medicine

The University of Adelaide and

The Hanson Institute

November 2006

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## Abstract

Prostate cancer is the second leading cause of cancer related deaths in Australian men. Due to the dependence of prostate cancer cells on androgens for survival, androgen ablation therapy (AAT) is the standard therapy for men who have failed treatment for localised prostate cancer. Although initially responsive, most tumours relapse and are typically unresponsive to chemotherapeutic drugs. Recent evidence indicates that the intracellular mediator of androgens, the androgen receptor (AR) continues to play an integral role in maintaining tumour growth in an androgen-depleted milieu following failure of AAT. Therefore treatment strategies aimed at the activity of the AR itself either alone or in addition to reducing the levels of ligand may be more effective in inhibiting the growth of prostate cancer cells.

The objectives of this thesis were to characterise the effects of AR-targeting agents on the growth of prostate cancer cells and to determine whether combining these agents to target the AR at more than one level in the signalling pathway would provide a more complete block of androgen signalling and prostate cancer cell growth. Four agents were analysed for their ability to reduce the levels and/or activity of the AR: the histone deacetylase inhibitor SAHA, the Hsp90 inhibitor 17-AAG, the AR antagonist bicalutamide and AR-specific antisense oligonucleotides. *In vitro* culture of LNCaP human prostate carcinoma cells with each of these agents resulted in reduced AR protein levels and/or activity, inhibition of cellular proliferation and induction of cell death in a dose-dependent manner.

Combinations of low, sub-effective doses of the above agents were tested for additive or synergistic effects on prostate cancer cell growth. Combination treatment with SAHA and bicalutamide, 17-AAG and bicalutamide, or 17-AAG and SAHA, synergistically inhibited proliferation and induced caspase-dependent cell death in LNCaP prostate

cancer cells. The results of this thesis indicate that AR-targeting therapies are effective in suppressing the growth of prostate cancer cells. Furthermore when used in combination, the efficacy of these agents is markedly increased, even at low doses that individually have little effect. The results of this thesis provide a basis for clinical trials of AR-targeting strategies for prostate cancer.