# Dame Roma Mitchell Cancer Research Laboratories

**Senior Staff**
Professor Wayne Tilley
Professor Villis Marshall
Dr Tina Bianco-Miotto
Dr Grant Buchanan
Dr Lisa Butler
Dr Andrew Sakko
Dr Jeffrey Barrett

**Associate staff**
A/Prof David Horsfall
Dr Carmela Ricciardelli

**Scientific staff**
Elisa Cops (RA)
Melissa Lee (RA)
Alexsandra Ochnik (RA)
Marie Pickering (RA)
Margaret Yard (p/time technical assistant)
Michelle Newman (RA)
Helen Hughes (RN)

**Administration Staff**
Leah McFaul (PA)
Susan Macnair (Administrative Assistant)

**PhD Students**
Margaret Centenera
Deborah Marrocco
Eleanor Need
Amelia Peters

**Honours Students**
Miriam Butler
Sarah Carter

**Fellowships that commenced in 2005**

| | |
|---|---|
| Fellowship: | Peter Doherty Post-Doctoral Fellowship |
| Project title: | Protective role of androgen signalling in breast cancer. |
| Candidate: | Dr Tina Bianco-Miotto |
| Source: | NHMRC |
| Funding: | $66,000 p.a |
| Funding period: | 2005-2008 |

**Continuing Fellowships for 2005**

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|---|---|
| Fellowship: | Prostate Cancer Foundation of Australia Research Fellowship |
| Project title: | Dominant negative androgen receptors: a novel approach to the treatment of advanced prostate cancer. |
| Funding: | $100,000 p.a |
| Source: | Prostate cancer Foundation of Australia |
| Candidate: | Dr Lisa Butler |
| Funding period: | 2003-2005 |

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|---|---|
| Fellowship: | The Cancer Council Senior Research Fellowship |
| Project title: | Role of versican in the development of metastatic breast cancer. |
| Funding: | Salary plus $5000 |
| Source: | The Cancer Council of South Australia |
| Candidate: | Dr Carmela Ricciardelli |
| Funding period: | 2004-2006 |

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|---|---|
| Fellowship: | The Cancer Council of South Australia Research Fellowship |
| Project title: | A novel strategy for the treatment of advanced prostate cancer. |
| Candidate: | Dr Grant Buchanan |
| Source: | The Cancer Council of South Australia |
| Funding: | Salary plus $5000 |
| Funding period: | 2003-2005 |

## GRANTS CURRENT IN 2005

### National Health and Medical Research Council

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|---|---|
| Title | Inhibition of estrogen signalling by the androgen receptor (AR): a potential mechanism of suppression of breast cancer cell growth by androgens. |
| Chief investigators: | WD Tilley, LM Butler and Birrell SN |
| Funding period: | 2003 - 2005 |
| Amount: | $123,350 p.a |

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|---|---|
| Title: | Androgen receptor signalling and progression of prostate cancer. |
| Chief investigators: | WD Tilley, LM Butler & VR Marshall |
| Funding period: | 2004 - 2006 |
| Amount: | $151,750 p.a |

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|---|---|
| Title: | Enabling Grant: Australian Prostate Cancer Collaboration (APCC) BioResource. |
| Chief investigators: | J Clements, R Sutherland, G Risbridger and WD Tilley |
| Funding period: | July 2004 – June 2009 |
| Amount: | $420,000 p.a |

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|---|---|
| Title: | Androgen receptor measurements as a tool for staging early prostate cancer |
| Chief investigators : | Horsfall D, Marshall VR, Ricciardelli C and Tilley WD |
| Funding period: | 2005-2007 |
| Amount : | $114,300 p.a |

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|---|---|
| Title: | Barrett's oesophagus and reflux oesophagitis: efficacy of medical vs surgical management. |
| Chief Investigators: | Watson DI, Drew PA, Ruszkiewicz A, Jamieson GG, Bianco-Miotto T and DJ Hussey |
| Amount: | $167,500 p.a |
| Funding period: | 2004-2006 |

**The Cancer Council South Australia**

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|---|---|
| Title: | Versican: a cell motility-promoting proteoglycan pivotal for prostate cancer metastasis. |
| Chief investigators: | Horsfall DJ and Tilley WD |
| Funding period: | 2004-2005 |
| Amount: | $73,967 p.a. |

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|---|---|
| Title: | Prostate cancer cell synthesis of 1,25 dihydroxyvitamin D and cell growth. |
| Chief investigators: | Morris H, May B, Tilley W |
| Funding period: | 2005 |
| Amount: | $84,016 |

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|---|---|
| Title: | Inhibition of breast cancer growth in, and metastasis to, bone using TRAIL therapy. |
| Chief investigators: | Evdokiou A, Butler LM and Findlay DM |
| Amount: | $64,125 |
| Funding period: | 2005 |

**University of Adelaide**

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|---|---|
| Title: | A cohort study of health and aging in North West Adelaide men. |
| Chief investigators: | Wittert G, Marshall VR, Hiller J, Warin M, Taylor A, O'Loughlin P, Tilley WD, Choong C, Wallace J. |
| Funding period: | Sept 2003- Aug 2006 |
| Amount: | $150,000 p.a. |
| Source: | Florey Foundation |

**US Department of Defense**

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|---|---|
| Title: | The role of androgen receptor signalling in breast cancer. |
| Chief investigators: | Tilley WD, Butler LM and Birrell SN |
| Funding Period: | Aug 2003- Jul 2006 |
| Amount: | USD $123,500 p.a. |
| Source: | US Army Medical Research and Materiel Command |

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|---|---|
| Title: | Clock genes: critical modulators of breast cancer risk? |
| Chief investigators: | DJ Kennaway, LM Butler and WD Tilley. |
| Funding period: | July 2004 – June 2005 |
| Amount: | $USD 99,485 |
| Source: | US Army Medical Research and Materiel Command, Breast Cancer Research Program |

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|---|---|
| Title: | Implication of Structural Features of TAU5 in the Androgen Receptor for Prostate Cancer Progression. |
| Chief investigators: | G Buchanan |
| Amount: | USD $49,000 p.a |
| Source: | US Army Medical Research and Materiel Command, Prostate Cancer Research Program (PCRP) |
| Funding period: | 2004-2005 |

**Other**

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|---|---|
| Title: | The role of androgen receptor signalling in the breast: potential disruption by synthetic progestins used in hormone replacement therapy. |
| Chief investigators: | Butler LM, Tilley WD and Birrell SN |
| Funding period: | 2005 - 2008 |
| Amount: | $USD 83,333 p.a |
| Source: | The Susan Komen Breast Cancer Foundation |

**NEW GRANTS STARTING IN 2006**

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|---|---|
| Title: | Disruption of the circadian rhythms of gene expression and the development of breast cancer |
| Chief investigators: | Kennaway D |
| Funding period: | 2006 - 2009 |
| Amount: | $173,333 p.a |
| Source: | US Army Medical Research and Materiel Command congressionally directed medical research programs |

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|---|---|
| Title: | Androgen receptor status as a determinant of breast cancer risk |
| Chief investigators: | Tilley WD, Butler LM, Roder D, Farshid G |
| Funding period: | 2006 |
| Amount: | $76,000 |
| Source: | The Cancer Council South Australia |

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|---|---|
| Title: | Androgen receptor status as a determinant of breast cancer risk |
| Chief investigators: | Tilley WD, Butler LM, Roder DM, Farshid G |
| Funding period: | 2006-2008 |
| Amount: | $34,00 (year 1), $110,00 (years 2 and 3) |
| Source: | The National Breast Cancer Foundation |

**PUBLICATIONS AND PATENTS IN 2005**

1. Shen HC, Buchanan G, Butler LM, Prescott J, Henderson M, Tilley WD, Coetzee GA. GRIP1 mediates the interaction between the amino- and carboxyl-termini of the androgen receptor. Biol Chem. 386:69-74, 2005.

2. Han G, Buchanan G, Harris JM, Ittmann M, Yu X, DeMayo FJ, Tilley WD, Greenberg NM. Mutation of the androgen receptor causes oncogenic transformation of the prostate. Proc Natl Acad Sci USA. 102:1151-1156, 2005.

3. Ricciardelli C, Choong CS, Buchanan G, Vivekanandan S, Neufing P, Stahl J, Marshall VR, Horsfall DJ, Tilley WD. Androgen receptor levels in prostate cancer epithelial and peritumoral stromal cells identify non-organ confined disease. Prostate. 63:19-28, 2005.

4. Makridakis NM, Buchanan G, Tilley WD, Reichardt JK. Androgen metabolic genes in prostate cancer predisposition and progression. Frontiers in Bioscience. 10:2892-2903, 2005.

5. Beekman KW, Buchanan G, Tilley WD, Scher HI. Anti-Androgen Withdrawal Syndromes: Pathophysiology and Clinical Implications. In: Partin AW (Ed) Prostate Cancer: Principles and Practice. Lippincott, Philadelphia, 2005.

6. Beekman KW, Buchanan G, Tilley WD, Scher HI. Beyond first line hormones: options for castration-resistant disease. In: Vogelzang NJ, Scardina PT, Shipley WU, Coffey D (Eds). Comprehensive Textbook of Genitourinary Oncology (Third Edition). Wiley and Williams, Lippincott, Philadelphia, 330-340, 2005.

7. Buchanan G, Birrell SN, Peters AA, Bianco-Miotto T, Ramsay K, Cops EJ, Yang M, Harris JM, Simila HA, Moore NL, Bentel JM, Ricciardelli C, Horsfall DJ, Butler LM, Tilley WD. Decreased androgen receptor levels and receptor function in breast cancer contribute to the failure of response to medroxyprogesterone acetate. Cancer Res. 65:8487-8496, 2005.

## LOCAL, NATIONAL AND INTERNATIONAL COLLABORATORS

### International

Memorial Sloan Kettering Cancer Center
- Professor Howard Scher
- Professor Neil Rosen
- Professor William Gerrald

Fred Hutchinson Cancer Research Center
- Dr Norm Greenberg

University of Southern California
- Professor Ron Ross
- Gerhard Coetzee

Baylor College of Medicine
- Nancy Weigel

### National

The Garvan Institute
- Professor Rob Sutherland

Westmead Institute for Cancer Research
- Professor Christine Clarke

Queensland University of Technology
- Professor Judith Clements
- Dr Jon Harris

### Local

The Hanson Institute
- Professor Howard Morris

The University of Adelaide
- Professor Gary Wittert

Flinders Medical Centre
- Pamela Sykes

## AWARDS/HONOURS RECEIVED

*The Governer's Leadership Foundation of South Australia*
Selected as a participant (one of 30 in SA) in the 2004 experiential leadership program. (Dr Lisa Butler)

*Convener, Australian Society for Medical Research National Scientific Conference*
Couran Cove, QLD, November 2005. (Dr Lisa Butler)

**Fellowships awarded:**

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|---|---|
| Fellowship: | CJ Martin Fellowship |
| Project title: | In vivo regulators of androgen receptor function in prostate cancer |
| Candidate: | Dr Grant Buchanan |
| Source: | NHMRC |
| Funding: | $76,746 p.a |
| Funding period: | 2006-2009 |

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|---|---|
| Fellowship: | RAH/IMVS Florey Fellowship |
| Candidate: | Dr Lisa Butler |
| Source: | RAH/IMVS |
| Funding period: | 2006-2008 |

## INVITED INTERNATIONAL MEETING PRESENTATIONS

*Keystone Symposium on Hormonal Regulation of Tumorigenesis. Monterey*, California, February, 2005. "Androgen receptor in prostate cancer development and progression: New insights and new targeting strategies. Professor Wayne Tilley.

Second Pacific Rim Breast and Prostate Cancer Meeting, Palm Springs, California, April 2005. *" The androgen signalling cascade and prostate cancer"*. Professor Wayne Tilley.

Department of Defence USA, Era of Hope Meeting, Philadelphia, June 2005. *"The role of androgen signaling in breast cancer"*. Professor Wayne Tilley.

Invited speaker, Fred Hutchinson Cancer Research Center, Seattle, June 2005 . *"Androgen receptor function in prostate cancer: New insights into targeted therapies"*. Professor Wayne Tilley.

Invited speaker, Conway Institute of Biomolecular and Biomedical Research, Dublin, June 2005. *"Androgen receptor function in prostate cancer: New insights into targeted therapies."* Professor Wayne Tilley.

Invited speaker, Australian Prostate Cancer Collaboration Seventh Annual Meeting, Sydney 2005. *"Contribution of androgen receptor coregulators to prostate cancer progression"*. Professor Wayne Tilley.

Invited speaker, 6th National Prostate Cancer Symposium, August 2005. "*Androgen receptor function in prostate cancer. New insights into targeted therapies*". Professor Wayne Tilley.

Invited speaker, ComBio, Adelaide, September 2005. *"Androgen receptor in prostate cancer development and progression: new insights and new targeting strategies"*. Professor Wayne Tilley.

Invited speaker, Westmead Millennium Institute, July 2005. *"Androgen receptor function in prostate cancer: New insights into targeted therapies."* Professor Wayne Tilley.

**Breast and Prostate Cancer Research Group, Dame Roma Mitchell Cancer Research Laboratories lay summary:**

Even though breast and prostate cancers currently are the two most common newly diagnosed invasive cancers in women and men, respectively, recent figures from the Australian Institute of Health and Welfare (AIHW) project an approximate 1/3 increase in the number of new cases of both cancers over the period 2001-2001.

The research program in the Dame Roma Mitchell Cancer Research Laboratories, Hanson Institute and University of Adelaide, aims to understand at the molecular and cellular level how breast and prostate cancers grow and escape from hormonal control. This research is essential to develop new strategies for the treatment of both these cancers that are more specific and more effective. Growth of both cancers is initially controlled by sex hormones (estrogens and androgens in women and men, respectively). Current treatments work either by inhibiting the production of estrogens and androgens or by blocking their action in the cancer cells. Unfortunately, not all patients continue to respond to these hormonal treatments, and therefore alternative therapies are urgently required.

Despite the use of androgen ablation therapy (ie castration, LHRH anologs / antagonists) for more than 60 years in the treatment of prostate cancer, it is only recently that the androgen receptor, a protein specifically used by testosterone to affect many processes inside cells, has been implicated in both the disease process and treatment failure. We have shown that genetic alterations (structural changes) occur in the gene that encodes the androgen receptor, and that the resultant receptor variants can promote prostate tumour growth even when testosterone levels are reduced in men by androgen ablation. Importantly, we have recently shown that these altered androgen receptors have the potential to facilitate the development of prostate cancer and its subsequent metastasis.

Our research suggests that new treatments for prostate cancer are required that target the androgen receptor protein, rather than just lowering testosterone levels with androgen ablation. Our research program therefore aims to better understand how the androgen receptor protein controls the growth of prostate cancer cells, and to specifically target this protein to inhibit the growth of prostate cancer cells, while minimising undesirable side effects such as bone loss, impotence and impaired cognitive function. Of particular interest, combining novel androgen receptor targeting agents with traditional androgen ablation strategies results in a marked enhancement of prostate cancer cell death. As many of these novel androgen receptor targeting drugs are either already in clinical use or are currently being evaluated in clinical trials, we have the potential to use these new prostate cancer targeting drugs in combination with conventional androgen ablation in the near future.

In breast cancer, androgens play a protective role, and prior to the development of estrogen receptor antagonists (eg. Tamoxifen), androgens were used to treat breast cancer. However, with the advent of Tamoxifen and, more recently, third generation aromatase inhibitors, the focus of hormonal treatment strategies has been to inhibit estrogen biosynthesis and/or to block out the growth promoting action of estrogens on the tumour – similar to androgen ablation for prostate cancer.

The effectiveness of hormonal therapy for breast cancer is dependent upon a functional estrogen signalling axis in the breast cancer cells. Interestingly, whereas the intracellular mediator of estrogen, the estrogen receptor is expressed in approximately 70-80% of cases, the androgen receptor is expressed in about 90% of primary tumours and a quarter of estrogen-receptor negative metastatic lesions. As androgens have a predominantly inhibitory effect on breast cancer cells, our research has focussed on developing new ways to exploit the androgen signalling axis for the treatment of breast cancer.

One novel approach has been to use active fragments of the androgen receptor to inhibit estrogen receptor function. If successful, this approach would have a distinct advantage over aromatase inhibition in that it would not result in systemic estrogen deprivation which causes bone loss and other undesirable side effects. Additionally, the use of small fragments of the androgen receptor has the potential to circumvent

the masculinising effects of exogenous androgens in women. This research, while in its infancy, is the first step towards understanding the mechanism of androgen suppression of estrogen induced breast cancer cell growth. We envisage that this research will lead to new strategies to complement existing anti-estrogen treatments, especially in women where estrogen therapy is contraindicated (eg. premenopausal women or women with osteoporosis).