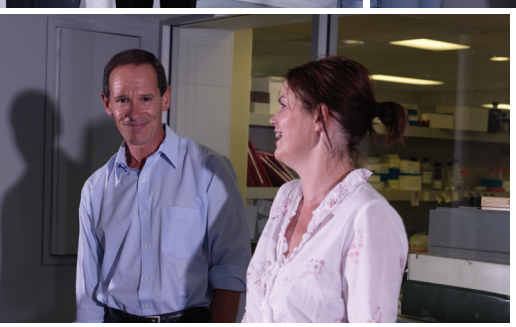
The GO Fund, represented by its CEO Mr Steve Eckowitz, supports Dr Pip O'Brien's ovarian cancer research. Ovarian cancer can even strike very young women, as Georgia is only too aware. Advances in accurate diagnosis of ovarian cancer will aid pathologists and benefit patients by ensuring they receive the most appropriate medicines.







Despite improved survival rates, cancer is still one of the leading causes of death in Australia. It affects one in three men and one in four women before the age of 75

Highlights

Hosting a visit by the Prime Minister of Australia, the Hon. John Howard MP, who officially opened the Australian Cancer Research Fund (ACRF) Unit for Molecular Genetics.

Our work:

- Obtaining a Program Grant from the Cancer Institute NSW to assist with the identification and validation of molecular markers of prognosis and therapeutic responsiveness in prostate cancer.
- Obtaining a Major Infrastructure Grant from the Cancer Institute NSW to enable the use of Garvan's ACRF facility by cancer researchers throughout NSW.
- Identifying an exciting new role for the protein cortactin in breast and head and neck cancers; cortactin sustains the activity of a cell surface receptor that promotes the growth and survival of cancer cells.
- Discovering that the Elf5 transcription factor is a master regulator of mammary development during pregnancy.
- Identifying many new genes regulated by the female hormone oestrogen, and finding that half of them are also regulated by the cancer-promoting gene c-Myc.
- Demonstrating the anti-cancer properties of a novel plant toxin, persin.
- In a collaborative study, developing a novel high-throughput detection assay to screen for abnormal methylation of tumour suppressor genes in cancer.
- Publication of our work on colorectal cancer that showed for the first time that low microsatellite instability identifies a distinct subgroup of stage C colorectal cancer patients with poorer outcome.
- Identifying EDD as a new prognostic marker for early ovarian cancer relapse and which may predict the development of chemoresistance.
- Discovering a new mutation in a steroid metabolising enzyme, CYP17, that is associated with hereditary breast cancer.
- Establishing a specialist pancreatic cancer unit at Bankstown Hospital in Sydney that will centralise the collection of tissue samples.
- Identifying and validating that 2 secreted proteins, neuropeptide Y and macrophage inhibitory cytokine, were overexpressed early in the development of prostate cancer, and were associated with a poor disease outcome.

Cancer Research Program

DIRECTOR: **Professor Rob Sutherland**

Our people:

- Pancreatic Cancer group leader Dr Andrew Biankin was the recipient of the 2005 Cure Cancer National Young Researcher of the Year Award.
- Cancer Institute NSW fellowships were awarded to Andrew Biankin, Maija Kohonen-Corish and Pip O'Brien.
- Senior Research Officer Dr Michelle Henderson was awarded the Macquarie Bank Cure Cancer Research Fellowship.
- Group leader Dr Alison Butt was appointed to the Australian Society for Medical Research Board of Directors.
- Associate Professor Roger Daly, in cooperation with the Australian Society for Biochemistry and Molecular Biology, obtained support from the Australian Academy of Science to hold a Boden conference on cell signalling.
- Group Leader Dr Vanessa Hayes received support from BNP Paribas in recognition of her contribution to cancer genetics.
- Research Assistant Luke Anderson won the 2005 SciArt prize for his photograph entitled 'Looking into the past'. Judges included NSW Art Gallery Director Edmund Capon.
- Dr Susan Clark obtained support, in co-operation with Dr Jean Finnegan from CSIRO, to hold the Sir Mark Oliphant Conference International Frontiers of Science and Technology on "Epigenetic Frontiers of Science and Technology".
- Dr Susan Clark was one of only 20 international participants invited by the Nature Publishing Group to attend the Horizon Symposium on Epigenetics in Maine, USA.
- Cancer Institute NSW scholarships were awarded to Liz Caldon and Rebecca Hinshelwood.
- Dr Maija Kohonen-Corish was awarded specialist accreditation in Molecular Genetics (Part I) by the Human Genetics Society of Australasia.

Cancer can affect many tissues in the body; the word 'cancer' collectively describes more than 100 different diseases. All cancers are different and require different treatments but all are the result of abnormal cell growth and survival.

A large number of genes and proteins regulate cell growth and cell death. Potentially, cancer can be caused by any of them malfunctioning. However, it is changes to certain groups of genes called 'oncogenes' and 'tumour suppressor genes' that underlie most cases of cancer. These changes include mutations in DNA that we either inherit or that spontaneously arise as we get older, and those that exert their effect by influencing protein production in cells without altering the DNA sequence.

Although derived from normal cells, cancer cells have distinctive features that can be exploited to aid diagnosis and treatment. To do this, we need to know much more about the fundamental processes that govern cell behaviours: their division, their survival, and their differentiation into complex tissue structures. With this knowledge, we might be able to stop the formation and early growth of cancers.

As well as basic research into cell and molecular biology, the Garvan's Cancer Program has six translational research groups that study a number of the most commonly diagnosed types of cancer: colorectal (bowel), breast, prostate, pancreatic, lung and ovarian.

Our scientists continue to search for and to discover new therapeutic targets and markers of disease progression that will help clinicians determine the best treatment regimes for their patients.

Basic Cancer Research

Cells respond to signals from the external environment, such as a circulating hormone or a growth factor, by the activation of specific cell surface receptors that transmit a signal to the interior of the cell. The signal may convey a number of instructions to the cell, for example telling it to divide, migrate or alter its metabolism.

One of the ways the signal can be transmitted is via modification of proteins by a process termed phosphorylation, which is mediated by specific enzymes, and by the assembly of protein complexes. Changes in intracellular signalling pathways contribute to many human diseases, including cancer. For example, a high level (overexpression) of a particular cell surface receptor, erbB2, occurs in approximately 30% of breast cancers and is the target for the new breast cancer drug Herceptin.

Fundamental cell and molecular research can shed light on how cancers are formed and how anti-cancer therapies work suggesting new diagnostic and therapeutic approaches.

Cell Cycle Group

Group Leader: Associate Professor Liz Musgrove

Cancer cells have an excess of proteins that drive cellular growth and division. We want to find out how this affects the way they respond to hormonal signals and which of these proteins are important in cancer development

The cell cycle is the process by which cells make a second copy of their DNA and divide to form two genetically identical daughter cells. Cellular reproduction is very tightly regulated in normal cells but in cancer cells it is unrestrained. Female steroid hormones like oestrogen and progesterone strongly influence cellular reproduction in the breast. We are particularly interested in how these hormones act on the machinery that runs the cell cycle and how control over the cell cycle is lost in breast cancer cells.

We are studying two proteins, Id1 and Wt-1, which respond to steroid hormones. We are investigating whether Id1 overexpression in normal breast cells affects how they grow and divide to form duct-like structures. We have found that progesterone-like compounds decrease Wt-1 expression in breast cancer cells and are now testing whether this decrease affects the cell cycle and the ability of the cells to differentiate and make milk components.

In conjunction with researchers in the Steroid Hormone Action Group, we are also searching for new genes that might link oestrogen action with the cell cycle. We have previously shown that c-Myc, a cancer-causing protein, is one such link. We have now screened the whole genome and found many new oestrogen targets, half of which are also targets of c-Myc. While some of these genes are known to control cell growth and division, many are still uncharacterised. Our next step is to determine whether some of the genes we have identified are important in oestrogen action and in breast cancer.

Antioestrogens such as tamoxifen have been widely used in the clinic, leading to significantly improved outcomes for breast cancer patients. However, some patients do not respond to these drugs and many who initially respond become resistant to their effects over time. Since too much c-Myc dampens the antioestrogen response in breast cancer cells, we think that some of our newly-identified oestrogen and c-Myc targets may also affect how cells respond to antioestrogens. Further characterisation of these genes may enable us to understand how resistance to antioestrogens develops and help us identify which patients are most likely to respond to these therapies.

RIGHT:
When cells continue multiplying in the absence of normal restrictions, they form an abnormal mass of cells (tumour).

Steroid Hormone Action Group

Group leader: Prof. Rob Sutherland

Hormone-dependent cancers, including breast, prostate and ovarian cancers, are leading causes of morbidity and mortality in western countries.

The sex steroid hormones oestrogen, progesterone and androgens play an important role in the development and progression of cancers of the breast and prostate. Our research aims to determine and characterise the genes that mediate the actions of these hormones in steroid-responsive cancers, which constitute a third of all newly diagnosed cancers.

One of these genes, EDD, is regulated by progestin and is essential for normal embryonic development. We have shown that EDD interacts with proteins that repair damage to DNA, a critical process that is often deregulated in cancer. These studies have highlighted the role of EDD as an important mediator of the cellular response to DNA damage and cell-cell interactions. In collaboration with the Ovarian Cancer group, we have also shown that overexpression of EDD predicts early disease relapse in ovarian cancer patients, and may be associated with the development of chemoresistance.

Other projects include determining how progestins regulate breast cancer cell growth by interacting with specific 'receptors'. These receptors are frequently overexpressed in breast cancers and we are determining how this may affect the progression of the disease.

Apoptosis Research Group

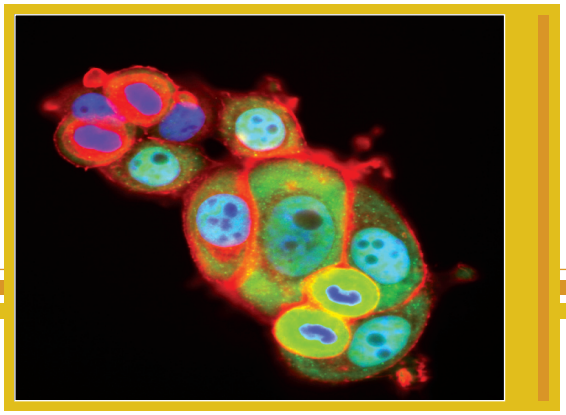
Group Leader: Dr. Alison Butt

The maintenance of normal tissue function requires an exquisite balance between cell division and cell death

Human cancers develop when there is a disruption in the balance between cell division and cell death (apoptosis). Apoptosis, or 'cell suicide' is a tightly regulated process by which old or damaged cells normally self-destruct. Current therapies for the treatment of human cancers, including ionising radiation and chemotherapeutic drugs, kill tumour cells by inducing apoptosis. Thus, understanding how the process of cell death is regulated in normal and cancer cells is an important goal for effective treatment.

Oestrogen not only causes breast cancer cells to proliferate, but it also protects them from apoptosis. In collaboration with researchers in the Cell Cycle Group, we are investigating how this occurs and identifying the genes that regulate this process. This will enable us to understand how these genes may influence the way anti-oestrogens such as tamoxifen can effectively kill breast tumour cells.

Other projects include examining how novel compounds derived from plants induce apoptosis in breast cancer cells. This could lead to their development as new therapies for the treatment of breast and other cancers.



Signal Transduction Group

Group leader: Associate Professor Roger Daly

We want to understand how signals for growth are transmitted within a cell. Once we can speak the cell's language we can intercept the signals and potentially stop the development of cancer.

Our research has focused on three proteins involved in either the transmission of signals within the cell or the regulation of these signalling events: Gab2, cortactin and Grb14.

Gab2 acts as a 'docking platform' at the cell surface, binding and activating other signalling proteins. Following our observation that Gab2 is overexpressed in a subset of breast cancers, we have determined the effects of expressing high levels of Gab2 in normal breast cells. This increased the proliferation of cells and caused misshapen three-dimensional structures to form, suggesting that Gab2 could have a role in breast cancer development. Our next step is to determine whether the expression of Gab2 in breast cancers can identify patients with aggressive disease.

Cortactin regulates the formation of the cytoskeleton, an intra-cellular scaffold that determines cell shape and regulates cell movement. High levels of cortactin are found in some breast and head and neck cancers. Recently we have demonstrated that cortactin prevents the degradation of a cell surface receptor involved in cancer development, prolonging its action in the cell. This discovery identifies a new role for cortactin in cancer development. We now want to identify the mechanism whereby cortactin regulates this receptor and investigate ways to block this effect.

Finally, in collaboration with Steve Hubbard at the Skirball Institute in New York, we have determined how a protein previously characterized by our group, Grb14, inhibits signalling mediated by the receptor for the hormone insulin. This work sheds light on how Grb14 and the related protein Grb10 regulate the growth-promoting effects of insulin and insulin-like growth factors on cancer cells.

Epigenetics Group

Group leader: Associate Professor Sue Clark

We have recently found that cancer cells deactivate large regions of DNA by a biochemical process called methylation. These regions may contain genes that normally prevent the development of tumours. We now need to work out how they do this so we can reverse the process.

The term 'epigenetic' refers to the process that alters the function of a gene from one cell to another without changing the DNA sequence. Processes such as methylation can cause epigenetic changes where small molecules are reversibly attached to the DNA. The extent to which genes are methylated is a means of controlling when and how much of a protein is produced from a gene. Identical twins with the same DNA may even develop different diseases because of epigenetics.

In cancer, the DNA methylation pattern of many genes changes. Genes that regulate normal cell growth - such as tumour suppressor genes - can be 'silenced' by DNA methylation and - oncogenes- can be 'activated" by de-methylation. Our research focuses on understanding the process that triggers abnormal methylation and demethylation between normal and cancer cells. We have developed different methods to detect methylation changes during development and have noticed that epigenetic changes can take place across very large regions of DNA during cancer development. However, we do not know what causes these changes.

Our next step is to compare normal and cancer cells in these regions to understand the mechanism that is involved in triggering this change and leading to the silencing of multiple genes.

Methylation is a reversible process so understanding how it is triggered will open up a whole new area of potential new ways to diagnose and treat cancer.

Development Group

Group Leader: Associate Professor Chris Ormandy

If we can discover the pathways the mammary gland uses in normal developmental processes, we can discover how those pathways go awry in cancer.

Development of the mammary gland occurs in defined stages connected to embryonic and prepubertal life. In women, changes in mammary gland structure and function also occur during pregnancy, lactation and involution of the mammary gland after menopause. Cancer can be considered to be a form of aberrant development.

Prolactin, a hormone produced in the pituitary gland, plays an important role in normal mammary cell proliferation and also stimulates the mammary glands to produce milk. We have developed a model of breast cancer where the loss of the prolactin receptor from the mammary epithelium results in reduced rates of tumour initiation and progression. We have demonstrated that lower rates of cell proliferation caused by the absence of the prolactin receptor at the very early stages of carcinogenesis underlie this observation.

Our hypothesis is that genes that are important in the normal control of mammary gland cell growth and differentiation into specialised tissue could become mutated or dysregulated, resulting in breast cancer. We have focused on genes regulated by prolactin signaling through the prolactin receptor.

We are investigating two key genes, Elf5 and Goblin. Elf5 belongs to a family of proteins that are regulators of many other genes, including many that are responsible for the activation of cell growth and cell death mechanisms. We have shown that Elf5 can replace prolactin-induced mammary cell proliferation and differentiation, making Elf5 a master regulator of this process. We have shown that Elf5 levels change in breast cancer. We are now studying how Elf5 acts in mammary cells in order to better understand its changed role in cancer cells.

Our group was the first to find Goblin, a protein that is expressed in the mammary tissue and is present in high amounts in breast cancer cell lines. We are investigating its role in mammary gland development and cancer.

Translational Cancer Research

Breast Cancer

Group Leader – Professor Rob Sutherland

In women, breast cancer accounts for almost one third of all cancer cases, with a lifetime risk of one in nine.

The Breast Cancer team has developed large tissue banks and patient databases in collaboration with several local and international breast cancer research groups. This material is being used to identify new molecules that are markers of disease subtype, disease progression and response to particular therapies. A major project being conducted with the Cell Cycle and Steroid Hormone Action Groups aims at identifying molecular markers of tamoxifen resistance since loss of response to tamoxifen is a major reason for treatment failure.

We are also conducting collaborative studies with other Institutions to assess the role of new genes in breast cancer. A recent finding with colleagues in Melbourne showed that a protein called LMO4 can cause cancer in mice, promotes cancer cell invasion and predicts poor patient outcome.

Lung and Colorectal Cancer

Group Leader: Dr Maija Kohonen-Corish

One of our big questions is: How do we distinguish the harmful gene mutations from normal gene variation in families with colorectal cancer?

Every time a cell divides, its genetic material must be copied. The DNA in our chromosomes has 3 000 000 000 base pairs, so there is a high chance of copy error or mutation. However, there are cellular proofreading enzymes that search for and correct these errors. If the proofreading enzymes themselves contain mutations, they will be unable to correct copy errors in other genes, which will then be passed on to the daughter cells. Small changes in DNA copying can have major consequences for the cell. For example, if a mutation occurs in genes that control cell division and they escape tight regulation, cancers can develop. Other mutations may have no major effect on the cell.

We have found some new gene mutations in a type of colorectal cancer. These mutations are passed down through families and affect the function of the proofreading enzymes. In collaboration with an international team of researchers we have analysed a large group of these mutations and determined which ones are responsible for colorectal cancer susceptibility and which ones are harmless.

Another focus of our research is lung cancer. Cigarette smoke is a complex mixture of carcinogens and mutagens. It causes genetic alterations to the DNA in the cells of the lung but there is wide variation in the profile of gene mutations between patients. Where these mutations occur determines how and when cancer develops and different mutations will respond to different treatments. The gene profile of each cancer can be identified from surgically removed tumours or biopsies but this is not routinely done in our health system. Our team examines such tumour specimens from a group of patients whose clinical outcomes are already known. Our challenge is to determine which key gene alterations are the most useful for determining prognosis and treatment outcomes. It is anticipated that the work will help stratify appropriate treatments for lung cancer patients.

Ovarian Cancer

Group Leader: Dr Pip O'Brien

The major problem with ovarian cancer is lack of early diagnosis.

Ovarian cancer is the most lethal gynaecological cancer. The poor prognosis is mainly due to an inability to detect ovarian cancer at an early, curable stage and to the lack of effective therapy for advanced disease. Early detection tests and new treatments are vital if we are to improve survival times.

Our research relies on a close collaboration with the Royal Hospital for Women in Sydney, which provides tissue and blood samples from cancer patients. We have used gene expression profiling to identify molecular changes that may be involved in the development of ovarian cancer. Our goal is to use this information to identify molecular markers for use in new diagnostic and therapeutic strategies.

In 2005, we identified a protein called galectin 4 that is specifically expressed in patients with the mucinous type of ovarian cancer. Although relatively rare, mucinous ovarian cancer is often confused with metastases from the gastrointestinal (GI) tract. As ovarian and GI cancers may have widely different outcomes and are treated with different types of chemotherapy, it is vital to make the correct diagnosis. Galectin 4 appears to distinguish between these different cancer types and could be useful in pathological diagnosis by ensuring that patients receive the most appropriate treatment for their cancer.

Correct expression of tumour suppressor genes is critical for preventing unrestrained growth of cells. These genes are often silenced by an epigenetic modification to their DNA called methylation, and this occurs early in the development of cancer. Preliminary evidence suggests that such DNA methylation changes may be detectable in the blood of patients with early stage cancer, including ovarian cancer. In collaboration with the Epigenetics Group, we have identified candidate tumour suppressor genes that are silenced in ovarian cancer by methylation. Our current work focuses on identifying a panel of methylated markers that have potential as diagnostic markers for early stage ovarian cancer.

Sister Anne-Maree Haynes is the face of our prostate cancer research. She speaks to patients and gets their consent to have tissue samples collected.

The HOXB2 protein (see below).

Prostate Cancer

Group Leader: Assoc. Professor Sue Henshall

Every hour, one man dies from prostate cancer.

Photo: Anne-Maree
Caption: Sister Anne-Maree Haynes is the face of our prostate cancer research. She speaks to patients and vgets their consent to have tissue samples collected.

The prostate is a walnut-sized organ that lies close to the bladder and bowel and is only found in men. Its main function is to store and produce seminal fluid. Prostate cancer is potentially curable if detected early and treated while still confined to the prostate gland.

In addition to early detection, it is important to have prognostic markers - clinical and molecular markers that allow patient outcome to be assessed. Our group is concerned with the identification of prognostic markers, as well as markers of therapeutic responsiveness and new drug targets.

We have taken a multidisciplinary approach that utilises expertise from a number of cancer researchers within and outside the Garvan, as well as clinicians and pathologists. A highlight of 2005 was obtaining funding from CINSW to further develop our strong clinical collaborations.

During 2005, the Prostate Cancer Group continued studies aimed at increasing our understanding of the early biology of prostate cancer and identifying genes and pathways whose expression correlate with poor outcome. We have undertaken gene expression profiling of high grade prostatic intraepithelial neoplasia, the premalignant change in prostate cells that precedes invasive prostate cancer by several decades. We have identified patterns of gene expression that are associated with these early morphological changes. Two genes encoding secreted proteins, neuropeptide Y (NPY) and macrophage inhibitory cytokine (MIC-1) were identified and validated in further samples. Increased expression of these proteins was confirmed to occur early in the disease process and increased expression of NPY and MIC-1 was associated with a poorer clinical outcome. These gene products are thus potentially useful diagnostic and prognostic biomarkers for prostate cancer.

Pancreatic Cancer

Group Leader: Dr Andrew Biankin

Recently a gentleman with pancreatic cancer had just one week between diagnosis and death. As a surgeon, researcher and human being, I can't accept these odds. We have to change them.

The pancreas is an organ situated near the stomach that secretes a digestive fluid into the intestine through one or more ducts. It also produces the hormone insulin.

Pancreatic cancer is the fifth leading cause of cancer death in western societies, with a five year survival rate of less than 10%. It attacks people aged in their 60s and begins in the lining of the pancreatic ducts. Pancreatic cancer presents at an advanced stage, so only 10-20% of patients are suitable for surgical treatment. Of these, only one to two in every ten survives.

The treatment and survival of patients with pancreatic cancer has not changed for over thirty years. Yet the outcomes for breast, colon and prostate cancer patients have changed dramatically over the same time period. Understanding of the molecular and cell biology of these other cancers has led to significant advances in their treatment, with a substantial impact on patient outcome. By contrast, knowledge about pancreatic cancer lags behind.

Our projects focus on understanding the role of retinoic acid signalling pathways in pancreatic cancer and defining new diagnostic and treatment strategies that may extend the successful use of retinoids seen in leukemia and skin cancer to pancreatic cancer.

We have found that the HOXB2 protein is an independent marker of poor prognosis in pancreatic cancer, with the potential to be used as a means to select patients for surgery. If the patient's cancer is really aggressive and their chance of survival is low, it may not be worth putting them through the ordeal of invasive surgery. We would like to obtain funding for a pre-clinical trial to see if HOXB2 profiling would be useful in the clinic.

Cancer Genetics

Group Leader: Dr Vanessa Hayes

The sequencing of the entire human genome has opened the door for cancer geneticists to identify genetic markers that influence an individual's risk of developing cancer.

Cancer genetics is the study of the genetic basis of human malignancies. Genetic events may either be inherited, increasing life-time risk of developing cancer, or may be acquired, resulting in tumour progression. We are concerned with the identification and characterisation of genetic variations (mutations) within the human genome sequence that influence individual risk of developing breast or prostate cancer.

Breast cancer tends to run in families, but the known heritable gene mutations (BRCA1 & BRCA2) only account for approximately 20% of cases. We are searching for novel breast cancer mutations in women with a strong family history of breast cancer before 40 years of age. Our studies suggest that multiple genes regulating hormones may be involved in determining familial breast cancer risk.

Colleagues in Melbourne have recruited seventy families from across Australia who do not have mutations in any of the known breast cancer genes. We are sequentially searching through the approximately thirty genes that are regulated by hormones. In one family we found a mutation, which completely destroys the CYP17 protein, involved in regulating hormone production, in all family members with breast cancer. We are now further characterising the role of this mutation.

In contrast to breast cancer, very little is known about what influences a man's risk of developing prostate cancer. Prostate cancer is a disease that affects older men, it is more common in people of European than Asian ethnic background, and the risk increases with every affected father or brother. These observations suggest that heritable gene mutations are likely to play an important role in determining prostate cancer risk.

We know that prostate cancer is regulated by hormones, since males castrated prior to puberty do not develop prostate cancer. More recently, inflammation of the prostate gland has been associated with cancer development. One of our major goals is therefore to identify genes within the pathways of hormone regulation and inflammation, which may be responsible for influencing prostate cancer risk.

These types of studies require large numbers of participants. Our Melbourne collaborators have collected DNA from over 4,000 Australian men. The new ACRF facility enables us to investigate a large number of genes across these large data sets. The project has already identified a number of potential candidate genes that influence prostate cancer risk.

Funding

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National Health and Medical Research Council
St Vincent's Clinic Foundation
GO Fund
Royal Hospital for Women
National Breast Cancer Foundation
BNP Paribas
Cancer Institute NSW
Cancer Council NSW
Boehringer Ingelheim
Association for International Cancer Research
US Department of Defense
Armati Foundation
University of NSW
Cure Cancer Australia
Surgical Research Society
RT Hall Trust
Ted Whitten Foundation
Petre Foundation