

Cancer Cell Biology program - personnel

MOLECULAR RADIATION

Head

Prof. Roger Martin

Senior Research Scientist

Dr Pavel Lobachevsky

Senior Research Officer

Dr Tom Karagiannis

Research Officer

Dr Andrea Smith

Research Assistants

Dr Alesia Ivashkevich
Chloe Pandeli (part-time)

Laboratory Assistants

Amy Distiller
Jai Smith

Honours Students

Katrina Lee (2008–09)
Shanon Loveridge
Haloom Rafehi
Michelle Tang

Summer Scholarship Student

Elizabeth Fletcher

TUMOUR SUPPRESSION

Head

Assoc. Prof. Ygal Haupt

Senior Research Officer

Dr Sue Haupt

Postdoctoral Fellow

Dr Kamil Wolyniec
Dr Gerard Tarulli

Research Assistant

Paul Canham

Postgraduate Students

Ai-Leen Chan
Daniel Brown

Summer Scholarship Students

Simone Woods
Hesham Abdulla

Technical Assistants

Cristina Murphy
Stephanie Munari

UROP Student

Hesham Abdulla

For full information on the research activities of the Cancer Cell Biology program laboratories, visit: www.petermac.org/Research/CancerCellBiologyProgram.

Translational Research

'Effective collaboration between laboratory and clinical researchers is vital for improving the outcomes of patients with cancer. One of the most exciting aspects of being a researcher at Peter Mac is the opportunity to take discoveries from the lab to the clinic.'

Dr Arun Azad, Medical Oncologist and PhD Student, Translational Research Laboratory



Dr Arun Azad

Medical Oncologist and PhD Student
Translational Research Laboratory

Dr Arun Azad is a medical oncologist currently undertaking a PhD in the Translational Research Laboratory at Peter Mac. While undertaking his specialist training in medical oncology, Arun witnessed the emergence of targeted therapies into clinical practice, stimulating his interest in research. Arun's current work involves using novel targeted agents to improve the efficacy of ionizing radiation.



Using basic research, clinical trials and collaboration with industry to maximise the future impact of research findings for cancer patients.

Our translational research aims to foster dialogue and collaboration between Cancer Research and the clinical divisions of Peter Mac, with the ultimate goal of accelerating the application of research findings into clinical practice.

The fusion of an integrated research environment within a dedicated specialist cancer hospital provides unique opportunities to support our translational focus.

Close collaborations between laboratory and clinical researchers facilitates important developments in clinical practice, and ensures our continued leadership role in translating research findings into clinical practice to provide patients with new and better treatment options.

Centre for Blood Cell Therapies

Prof. Miles Prince

Haematology Immunology Translational Research Laboratory

Assoc. Prof. David Ritchie and Dr Paul Neeson

Molecular Pathology

Prof. Stephen Fox and Assoc. Prof. Alex Dobrovic

CANCER THERAPEUTICS PROGRAM

Gene Regulation

Assoc. Prof. Ricky Johnstone

CRC for Cancer Therapeutics

Dr Mark Devlin

Peter Mac/Pfizer Cancer Genetics Project

Dr Karen Sheppard, Assoc. Prof. Pearson, Assoc. Prof. Wayne Phillips

CCV Venture Project

Assoc. Prof. Ricky Johnstone, Assoc. Prof. Ross Hannan, Assoc. Prof. Rick Pearson and Assoc. Prof. Grant McArthur

Translational Research Laboratory

Assoc. Prof. Grant McArthur and Prof. Rod Hicks

Molecular Imaging & Targeted Therapeutics

Prof. Rod Hicks



Director: Prof. Miles Prince

RESEARCH FOCUS

- Development and production of novel cell therapy treatments.
- Innovative regenerative medicine and immunotherapies.
- Cell tracking studies.
- Autologous peripheral blood stem cell transplants.
- Collaboration with the Cancer Immunology program (see pg xx) and the Haematology Immunology Translational Research Laboratory (pg xx).

RESEARCH DIRECTIONS

CBCT's focus is on developing, testing and applying new treatments based on the use of patient cells to control their cancer, and to restore function that has been lost through disease or injury. It does this work in the context of strict government regulation and international standards to ensure patient safety. CBCT also uses novel cell imaging technology to provide unique data on the distribution and function of these modified cells in targeting cancer in patients.

Recent research highlights include:

- First patients treated with autologous T-cells transduced with an anti-Lewis Y chimeric receptor gene. The treatment

was developed at Peter Mac and uses gene-modified cells to treat cancer. Unique in vivo approaches using nuclear medicine imaging demonstrated the function and distribution of these cells.

- Peter Mac's Apheresis Unit achieved NATA accreditation (NPAAC standard HPC-A) and completed audit with no recommendations or conditions.
- Collections, and release for infusion, of haemopoietic progenitor cells reached record numbers.
- CBCT and our commercial partner Cell Therapies successfully tendered to duplicate our local successes in a new facility at the National University Hospital of Malaysia in Kuala Lumpur (HUKM).

Peinert S et al. Gene-modified T cells as immunotherapy for multiple myeloma and acute myeloid leukemia expressing the Lewis Y antigen. *Gene Therapy*. 2010 May;17(5):678-86.

For more information on related research, see:

- Cancer Immunology program (pg xx)
- Haematology Immunology Translational Research program (pg xx)
- Haematology Service (pg xx)

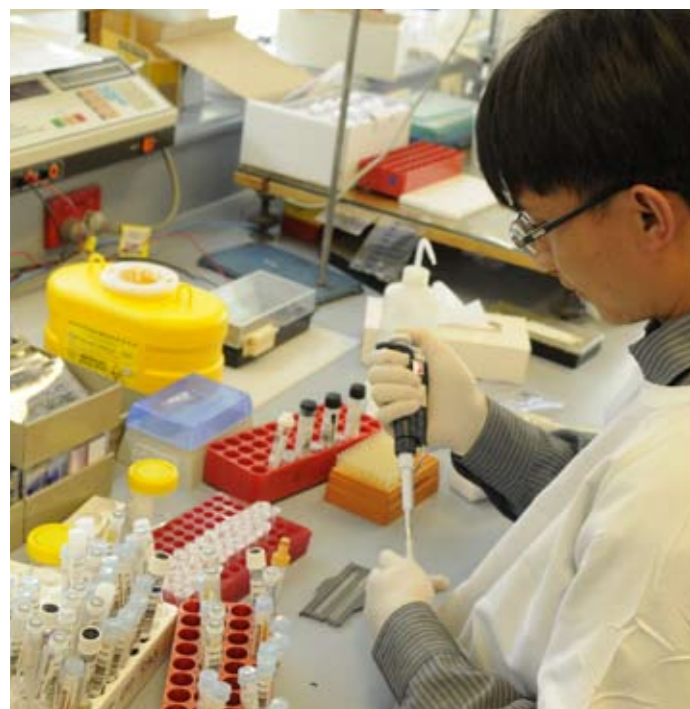
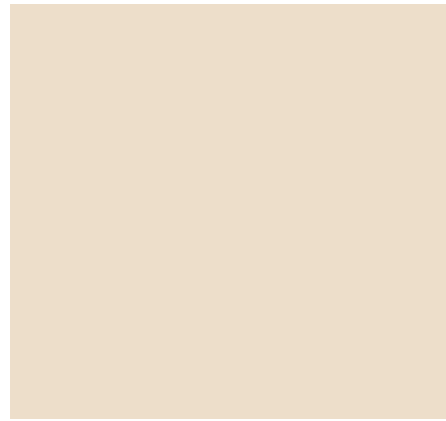


Figure 1: First patients treated with autologous T-cells transduced with an anti-Lewis Y chimeric receptor gene. The treatment was developed at Peter Mac and uses gene-modified cells to treat cancer. Unique in vivo approaches using nuclear medicine imaging demonstrated the function and distribution of these cells. (L-R: Dr Dominic Wall, Dr Michael Dickinson, patient, Prof. Miles Prince, Assoc. Prof. Michael Kershaw).

Haematology Immunology Translational Research Laboratory



Research leaders: Assoc. Prof. David Ritchie and Dr Paul Neeson

The Haematology Immunology Translational Research Laboratory (HITRL) investigates the efficacy of novel immunotherapeutics against human blood cancers. We focus on induction of human immune responses to provide ongoing control over blood cancers.

RESEARCH FOCUS

- Translational research into adapting novel therapeutics to the human system and moving it into phase I clinical trials.
- Testing patient responses to novel therapeutics and adjusting therapy to gain maximum benefit with minimum toxicity.
- Investigation of novel immunotherapy for human multiple myeloma, leukemia and lymphoma.
- Investigation of human immune system responses to multiple myeloma in response to novel immunotherapy.
- Modelling the effect of novel vaccines to multiple myeloma in a humanised mouse model.
- Investigation of graft-versus-host disease in allogeneic bone marrow transplantation.
- Close collaboration with the Cancer Immunology Program (see pg xx).

KEY 2009 RESEARCH ACHIEVEMENT

Peter Mac's Haematology Department conducts a number of clinical trials using novel combination therapies for haematological diseases. During 2009, our laboratory performed five science projects associated with clinical trials for multiple myeloma (MM), myelodysplastic syndrome and lymphoma. The majority of research performed in the laboratory can be grouped into either science projects using direct ex vivo samples from a clinical trial or associated in vitro science projects.

NK cell dysfunction in multiple myeloma

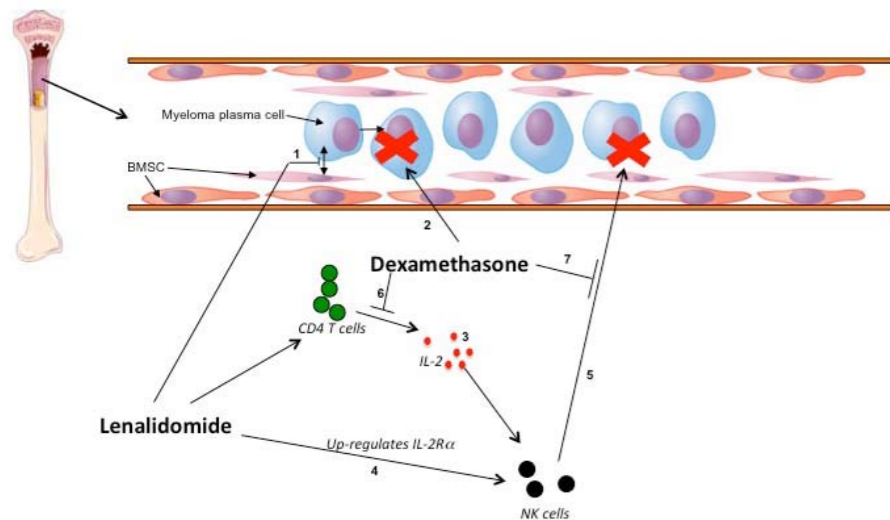
Investigations of the cellular immune response of patients to Revlimid-Dexamethasone therapy has yielded two interesting results. Firstly, a significant increase in PB CD4+ regulatory T cell count occurs from baseline through to cycle 6 and 9 of therapy. Secondly, despite PB NK cell numbers increasing their cytotoxicity function significantly decreased from baseline through to cycle 6 or 9. This was a surprising result, as prior in vitro data suggested Revlimid (Lenalidomide) would amplify NK cell function. To understand why NK cell function was impaired in patients receiving Revlimid-dexamethasone, we first accurately defined the cellular pathways whereby Revlimid (Lenalidomide) amplifies NK cell function in vitro. We showed Lenalidomide induces CD4+ T cells to secrete IL-2, IL-2 binds to the IL-2 receptor on the NK cells, which activated the NK cells and increased their killing capacity. In contrast, dexamethasone specifically decreases IL-2 mRNA and protein production. Dexamethasone abrogates the Lenalidomide-induced increased NK function. These results indicate that concomitant use of dexamethasone with Lenalidomide inhibits the immunomodulatory arm of Lenalidomide.

Peinert S et al. Gene-modified T cells as immunotherapy for multiple myeloma and acute myeloid leukemia expressing the Lewis Y antigen. *Gene Therapy*. 2010 May;17(5):678-86.

For more information on related research, see:

- Cancer Immunology program (pg xx)
- Centre for Blood Cell Therapies (pg xx)
- Haematology Service (pg xx)

Fig 1: The immunological effects of Lenalidomide-dexamethasone are multifaceted. Prior in vitro studies showed that lenalidomide (1) inhibited interactions between myeloma plasma cells (MPC) and bone marrow stromal cells (BMSC), making the MPC susceptible to dexamethasone-induced apoptosis (2). In addition, lenalidomide induced peripheral blood mononuclear cells (PBMCs) to secrete IL-2. We explored this further in a study comprising a clinical trial science project combined with an in vitro mechanism project. We showed that lenalidomide specifically induced CD4+ T cell secretion of IL-2 (3) and upregulated the IL-2R (CD25) on NK cells (4), this contributed to the enhanced NK killing of myeloma cells in vitro (5). In contrast, dexamethasone inhibited CD4+ T cell function (6) and, therefore, abrogated NK-mediated killing of MPC (7). This indicates a change in dexamethasone dose/schedule must occur in order to harness lenalidomide's direct effect on the myeloma cells AND the immune-stimulatory effect.



Molecular Pathology laboratory



Research leaders: Prof. Stephen Fox and Assoc. Prof. Alexander Dobrovic

The Molecular Pathology laboratory aims to perform basic and translational research with the goal of achieving personalised cancer medicine.

RESEARCH FOCUS

- Translational and clinical research into breast, lung, colorectal, urological and haematological cancers.
- Identification of predictive markers enabling appropriate stratification of patients for individualised treatment.
- Development of clinical diagnostics.
- Adoption of novel molecular platforms and methodologies for genetic and epigenetic analysis.

KEY 2009 RESEARCH ACHIEVEMENT

Development and implementation of personalised medicine biomarkers into the clinic.

The era of personalised medicine has now spread from its beginnings in haematology (imatinib) and breast cancer (tamoxifen) to encompass a wide number of tumour types and targets. Personalised medicine involves the choice of drug treatment as a consequence of the presence of a biomarker (often a defined mutation) that indicates the susceptibility or resistance of a patient to a specific drug. We have been working with a number of our colleagues in Cancer Medicine to develop and implement appropriate methodology to detect these predictive biomarkers using blood or tumour biopsies from patients. Our expertise in this area is now nationally and internationally recognised with the result that our diagnostic lab has become the Australian centre of choice to offer statewide or national testing. Tests currently on offer include KRAS, BRAF, EGFR, NRAS, JAK2, NPM and TP53 together with S/FISH assays for ALK, MET and HER2. In addition, we are also offering a comprehensive portfolio of testing for familial cancer genes including BRCA1 and BRCA2 as well as clonality testing and translocation identification for haematological malignancies.

Generali D, et al. EGFR/MAPK/HIF-1 signalling and activated form of ER as markers of resistance and response to primary chemo-endocrine treatment in elderly breast cancer patients. *Journal of Clinical Oncology* 2009; 27: 227-234.

Yan M et al. BRCA1 tumours correlate with HIF-1 phenotype and poor prognosis through modulation of post-translational hydroxylase enzyme profile expression and cellular location. *British Journal of Cancer* 2009; 101, 1168-1174.

Rayoo M, et al. Expression of the forkhead box transcription factor FOXP1 is associated with estrogen receptor alpha, estrogen receptor beta and improved survival in familial breast cancers. *Journal of Clinical Pathology*. 2009 Oct;62(10):896-902

For more information on related research, see:

- Familial Cancer Centre (pg xx)
- Medical Oncology and Early Phase Clinical Phase (pg xx)

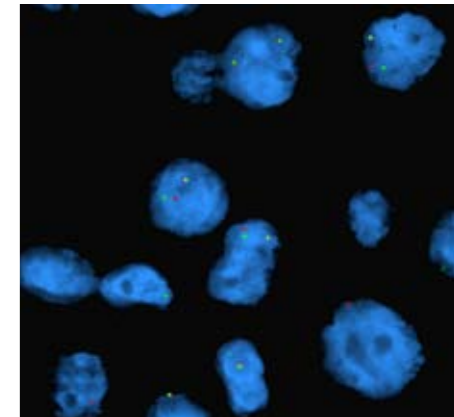


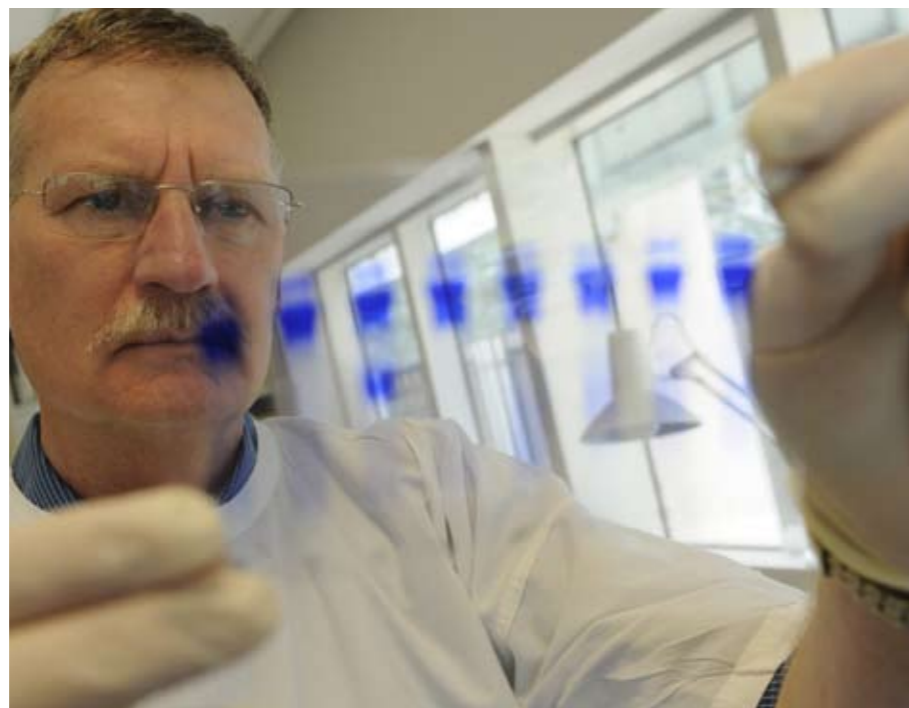
Fig 1: This image is of a lung cancer that has been highlighted with molecular probes to an oncogene called ALK that has split apart from its usual place and has been rearranged to another part of the chromosome. This can be seen by the split or gap between the ALK gene (red) and its usual place (green). Patients with this gene mutation can be treated with targeted cancer drugs.

Cancer Therapeutics Program

Integrating basic research activities, platform technologies, and pre-clinical model systems to discover, develop, characterise and refine novel cancer therapeutics for clinical use.

The Cancer Therapeutics program, combined with the Molecular Imaging and Translational Medicine program, is designed to integrate various basic research activities, platform technologies, and pre-clinical model systems available within the Peter Mac to discover, develop, characterise and refine novel cancer therapeutics for clinical use. Basic research within the program is focused on increased understanding of the biological basis of disease patterns and treatment outcomes observed in the clinic, pre-clinical testing of novel therapeutics, development of imaging methods and biomarker assays to follow treatment efficacy and investigation of cellular pathways involved in response to anti-cancer therapies

Key technologies involved include functional genomics, molecular imaging – PET, CT and optical, mouse models of cancer, and drug development. Scientists and clinicians within these programs use basic research, clinical trials and collaboration with industry to maximise the future impact of research findings for cancer patients.



Gene Regulation laboratory



Research leader: Assoc. Prof. Ricky Johnstone, Pfizer Australia Research Fellow

The Gene Regulation laboratory performs fundamental and pre-clinical research aimed at defining the molecular and biological processes required for anti-cancer drug action and drug resistance, and the mechanisms of interferon signal transduction.

RESEARCH FOCUS

- Basic and pre-clinical characterisation of novel apoptosis-inducing therapeutic agents used alone and in combination.
- Determining the effects of combining novel agents designed to specifically kill breast cancer cells with other agents that stimulate a host anti-tumour immune response.
- Development and use of genetically engineered mouse models of haematological malignancies and solid cancers for pre-clinical studies.
- Use of functional genomics-based screens to identify novel tumour suppressor genes and genes that regulate the apoptotic response to new anti-cancer agents.
- Characterisation of novel signal transduction pathways stimulated by type I and II interferons and the role of interferon signaling in tumour immune surveillance

KEY 2009 RESEARCH ACHIEVEMENT

Combining HDAC inhibitors (HDACi) with the BH3-only mimetic ABT-737.

Histone deacetylase inhibitors (HDACi) are an exciting new class of anti-cancer drugs that have recently been approved by the FDA for the treatment of haematological malignancies. These agents can mediate a wide variety of biological effects such as induction of tumour cell death (apoptosis), inhibition of tumour cell proliferation and activation of immune responses. Any one or more of these activities

may be necessary for the therapeutic effects of the compounds. Using genetically engineered mouse models we have demonstrated that the ability of HDACi to directly kill tumour cells is essential for the compounds to provide a therapeutic benefit. The apoptotic and therapeutic activities of HDACi are blocked by overexpression of Bcl-2 or Bcl-XL and it is well known that these pro-survival proteins are often over-expressed in human tumours. We used the small molecule inhibitor of Bcl-2 and Bcl-XL, ABT-737, to restore sensitivity of lymphomas overexpressing Bcl-2 or Bcl-XL to HDACi. Combining low-dose ABT-737 with HDACi resulted in synergistic apoptosis of tumour cells that were resistant to either agent alone. We demonstrated that ABT-737 and HDACi could cooperate in vivo to reduce the tumour burden of mice bearing lymphoma cells overexpressing Bcl-2, at doses that were well tolerated. These pre-clinical proof-of-principal experiments show that the combination of HDACi and ABT-737 may be a therapeutically attractive approach.

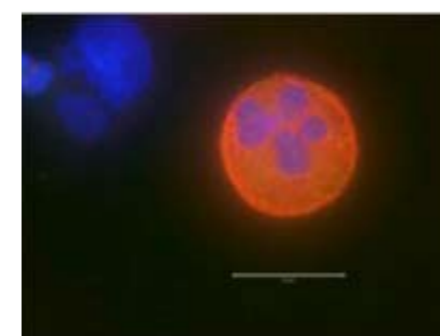
Bots M. and Johnstone RW. Rational combinations using HDAC inhibitors. *Clinical Cancer Research*. 2009 15(12):3970-7.

Frew, A.J., Johnstone, R.W., Bolden, J.E. Enhancing the apoptotic and therapeutic effects of HDAC inhibitors. *Cancer Letters* 2009 Aug 8;280(2):125-133.

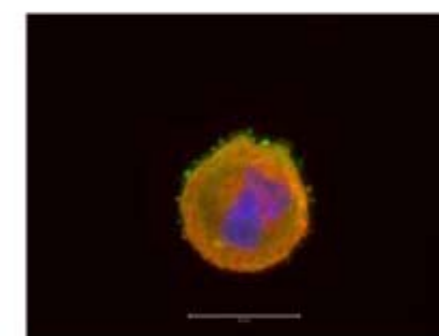
For more information on related research, see:

– Cancer Immunology program (pg xx)

DMSO



Panobinostat 10nM



Romidepsin 1nM

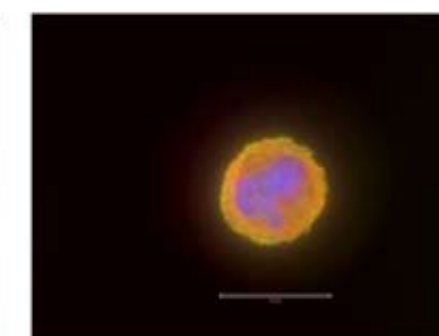


Figure 1: Histone deacetylase inhibitor (HDACi) are a new class of anticancer drug. Thrombocytopenia (low levels of blood platelets) is a major dose limiting toxicity of these drugs. Above are pictures of megakaryocytes, the parent cells of platelets, showing HDACi treatment (pictures on the right) cause increased phosphorylation of the myosin light chain (pMLC) in megakaryocytes, preventing platelet release.

Green = pMLC Red = Actin (cytoplasmic stain) Blue = nucleus.



Research leaders: Assoc. Prof. Rick Pearson, NHMRC Senior Research Fellow and Assoc. Prof. Wayne Phillips

The goal of the Pfizer / Peter Mac Cancer Genomics program is to identify tumour signatures that will guide the use of chemotherapy to cancer patients who are most likely to respond.

RESEARCH FOCUS

- Melanoma and ovarian cancer.
- Screening tumours for drug sensitivity.
- Using genomic, proteomic and metabolomic profiling to obtain a drug predictive signature.
- Functional genomic RNAi screens to identify genes associated with resistance.

KEY 2009 RESEARCH ACHIEVEMENT

PF502 inhibiting ovarian tumour cell proliferation.

We have identified PF502, a Pfizer drug that targets the PI3Kinase pathway, as having a high efficacy in inhibiting ovarian tumour cell proliferation. With this knowledge, we generated a predictive gene signature that was 97 per cent accurate in predicting ovarian cancer cell sensitivity to PF502. In addition, the gene signature provided potential targets for combination therapies in PF502 resistant ovarian cancer.

Cancer develops as a result of multiple gene mutations and individuals with the same type of cancer often have dissimilar genetic defects; these differences underlie the clinical spectrum of disease outcomes, progression and drug effectiveness. One of the major challenges in treating cancer is the selection of the most effective chemotherapy agents for individual patients. To address this challenge we are generating Proteomic, Metabolomic and Genomic profiles of human tumour cells and will use this information to predict drug effectiveness in patients.

As a first step toward achieving this goal, we are screening a panel of human ovarian tumour and melanoma cell lines for their sensitivity to Pfizer drugs that are currently in clinical or pre-clinical trials. From these screens we have demonstrated that PF502 a drug that targets the PI3Kinase pathway shows excellent efficacy in inhibiting ovarian tumour cell growth and proliferation, highlighting it as a potential novel treatment for this cancer. We have also successfully generated a 'gene signature' using a continuous predictor model and principal component analysis based feature reduction that

is 97 per cent accurate in classifying ovarian tumour cells as either resistant or sensitive to this drug. Analysis of this gene signature provided clues into why cells were not responding and gave a clear indication of potential targets for combination therapies in PF502 resistant ovarian cancer.

For more information on related research, see:

- Cancer Genetics and Genomics (pg xx)
- Cancer Immunology program (pg xx)
- Growth Control and Differentiation program (pg xx)

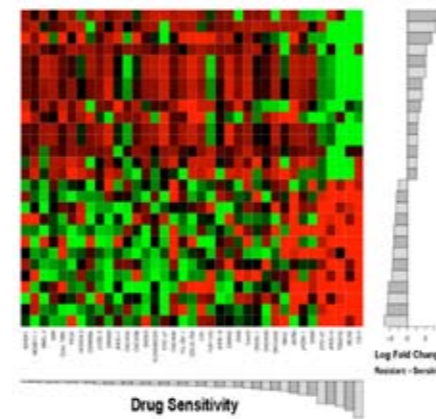


Figure 1: Diagram showing the heat map of the 28 gene signature that was 97 percent accurate in classifying ovarian tumour cells as either resistant or sensitive to a drug that inhibits the PI3Kinase pathway.



Research Leaders: Assoc. Prof. Ricky Johnstone, Pfizer Australia Research Fellow (pictured), Assoc. Prof. Ross Hannan, NHMRC Senior Research Fellow, Assoc. Prof. Rick Pearson, NHMRC Senior Research Fellow and Assoc. Prof. Grant McArthur, CCV Sir Edward Dunlop Clinical Cancer Research Fellow

The Cancer Council Victoria (CCV) Venture Grant Initiative focuses on the identification of novel breast cancer tumour suppressors and genes that regulate sensitivity to cancer therapeutics using whole-genome RNA interference (RNAi) screens.

RESEARCH FOCUS

- RNAi screening to identify novel genes involved in breast cancer onset and the response of breast cancer cells to apoptosis mediated by novel therapeutics.
- Characterisation of the genes identified as novel tumour suppressors and modifiers of responses to cancer therapeutics.
- Development of novel RNA-based functional genomics screening technologies including the use of next generation sequencing.

KEY 2009 RESEARCH ACHIEVEMENT

Functional genomics-based studies to identify novel tumour suppressor genes and genes that regulate chemotherapeutic drug activities.

We have initiated whole genome, functional genomics-based studies utilising the sophisticated RNA interference technology available from the Victorian Centre for Functional Genomics to identify novel tumour suppressor genes and genes that regulate the apoptotic activities of anti-cancer drugs. We have utilised advanced human cell lines developed by Prof. Bob Weinberg that were derived from primary breast epithelial cells and forced to go through stages of malignant transformation through the step-wise introduction of four different genetic elements (SV40 large and small T, hTERT, mutant/active Ras). We have taken these pre-cancerous breast cells expressing hTERT, active Ras and

large T, screened them using our RNAi library and have identified cells that now have the properties of cancerous cells, indicating that a tumour suppressor gene(s) has been inactivated allowing for the transition from normal cell to tumour cell. We have validated the role of eight new potential tumour suppressor genes identified in our screen. Two of these genes (ARL4D and ELMO1) have been previously shown to function in the same biochemical pathway, indicating that this pathway may play a very important role in regulating tumour onset and progression. Further studies are now being undertaken to fully characterise the role of ARL4D and ELMO1 as tumour suppressor genes.

The CCV Venture Grant Initiative is only possible through the support of the John T Reid Charitable Trusts.

For more information on related research, see:

- Cancer Immunology program (pg xx)
- Growth Control and Differentiation program (pg xx)

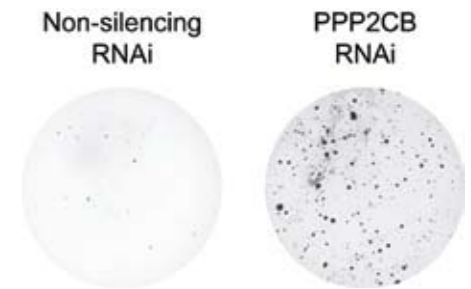


Figure 2: Loss of PP2A function leads to anchorage independent growth. Expression of the catalytic subunit of PP2A (PPP2CB) was attenuated in pre-tumorigenic human mammary epithelial cells expressing the catalytic subunit of telomerase, SV40 large T antigen and oncogenic Ras using a specific RNAi construct. Cells were grown in soft agar for 2.5 weeks to assay anchorage independent growth and stained with MTT to visualise colonies.

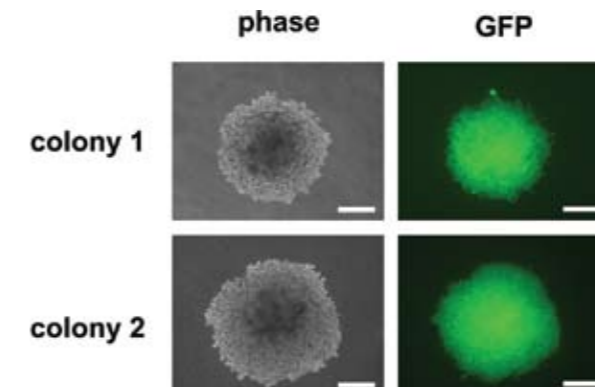


Figure 1: Anchorage independent growth of RNAi construct-transduced mammary epithelial cells. Phase contrast (phase) and fluorescence microscopy (GFP) of two representative colonies of transformed human mammary epithelial cells grown in soft agar for 2.5 weeks. Images were taken on a Leica inverted microscope under 10x magnification. Scale bar 200µm.



Research leader: Dr Mark Devlin

Peter Mac, as a participant in the Co-operative Research Centre for Cancer Therapeutics (CTx), employs a team to help develop small molecules for cancer treatment by integrating in vitro assays, in vivo studies and small animal imaging. The knowledge gained from these studies assists the development of new cancer therapies.

RESEARCH FOCUS

- Investigation of the effects of small molecule inhibitors targeting proteins involved in cell migration invasion and metastasis.
- Identification and validation of biomarkers to predict response to targeted therapeutics.
- The development of non-invasive small animal fluorescent and bioluminescent imaging technologies.

KEY 2009 RESEARCH DIRECTIONS

Peter Mac is well-placed to contribute to the development of new small molecule therapies for cancer through its broad range of activities ranging between basic and translational research programs to its involvement in clinical trials.

The identification of new proteins and the elucidation of the role of these and known proteins in complex cellular signaling pathways involved in cancer is a focus of many researchers at Peter Mac. These proteins, once validated using a variety of genetic and functional screens, have the opportunity to become the focus of proposals put forward to CTx for consideration as drug targets. Once accepted as a project, a multi-disciplinary project team consisting of scientists from various organisations is assembled to advance the project through a series of pre-clinical development milestones. Molecular targets arising from research carried out at Peter Mac are currently the focus of some CTx projects.

Peter Mac has representatives on both the CTx Portfolio Management Group, that helps select and review new and existing projects, and on individual project teams involved in overseeing the day-to-day science. Peter Mac is an important contributor at both a strategic and operational level to the drug discovery and development activities of CTx. Moreover, the guiding principles of CTx and its participant organisations permit commercial-in-confidence information to be shared with researchers at Peter Mac who are not directly involved in project teams, ensuring CTx has access to Peter Mac's cancer-focused expertise, personnel and platform technologies, important to its drug development activities.

For more information on related research, see:
www.cancercrc.com



Research Leader: Assoc. Prof. Grant McArthur, CCV Sir Edward Dunlop Clinical Cancer Research Fellow

As part of the Centre for Cancer Imaging and Translational Medicine, the Translational Research Laboratory investigates the application of novel targeted cancer therapies by integrating cell biology, molecular biology, functional imaging and clinical trials.

RESEARCH FOCUS

- Investigation of inhibitors of protein and lipid kinases using laboratory and clinical studies.
- Identification and validation of tissue and imaging biomarkers to predict response to targeted therapeutics.
- The mechanism of action of therapeutics targeting signalling, cell cycle and cell surface receptors.
- The role of hypoxia in tumour responses to cancer therapies.

KEY 2009 RESEARCH ACHIEVEMENT

Identifying and treating tumour hypoxia – complementary pre-clinical and clinical studies.

Hypoxia (low oxygen) in tumours is known to be an adverse prognostic factor due to hypoxic tumour cells exhibiting increased resistance to chemotherapy and radiotherapy. We are using a highly hypoxic pre-clinical tumour model to investigate the effect of anti-angiogenic therapy with sunitinib on tumour vasculature and hypoxia. In this model, sunitinib treatment results in a decrease in tumour size which is associated with a 'normalisation' of the tumour vasculature as measured by improved perfusion and reduced hypoxia on PET imaging. We are also identifying and validating known and novel endogenous markers of tumour hypoxia in a phase III human clinical trial in head and neck cancer. These studies involve imaging modalities that include PET, ultrasound, immunohistochemistry and ELISA. Our research will inform future clinical trials testing novel therapeutics affecting tumour hypoxia and enhance the treatment options for cancer patients.

Investigating the basis of tumour cell uptake of the positron emission tomography tracer, fluoro-L-thymidine following gemcitabine therapy.

Fluoro-L-thymidine (FLT) is a positron emission tomography (PET) tracer used in the non-invasive imaging of tumour proliferation. We recently demonstrated that the chemotherapy drug gemcitabine induces a 'flare' of FLT uptake into tumour cells in vivo. Using cell based systems we are investigating the basis of this flare, in particular the role of the

nucleoside transporters that take up FLT into the cell, the distribution of the cells in the cell cycle and the activity of thymidine kinase, the key enzyme responsible for trapping FLT in cells. Using a panel of cell lines and cytotoxic drugs with different mechanisms of action and acting at different phases of the cell cycle, results have demonstrated the complexity of the mechanism of the FLT flare, revealing a role for each of the above cellular processes. These studies will provide a greater understanding of what constitutes an FLT-PET signal and will therefore assist in defining the optimal clinical use of this important PET tracer.

For more information on related research, see:

- Molecular Oncology laboratory (pg xx)
- Molecular Imaging and Targeted Therapeutics laboratory (pg xx)
- Centre for Cancer Imaging (pg xx)
- Medical Oncology and Early Phase Clinical Trials (pg xx)
- Gastrointestinal Service (pg xx)
- Head and Neck Service (pg xx)
- Melanoma and Skin Service (pg xx)

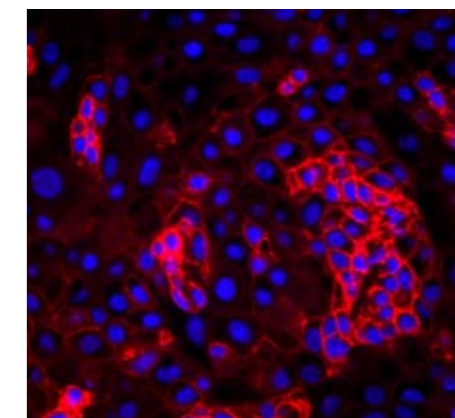


Figure 1: Cancer cells are able to turn on specific genes that enable them to survive in a low oxygen (hypoxic) environment. This image shows cancer cells fluorescently labelled for nuclei (blue) and carbonic anhydrase IX (red), which is a marker of hypoxic cells.

Molecular Imaging and Targeted Therapeutics laboratory



Research Leader: Prof. Rod Hicks

As part of the Centre for Cancer Imaging, the Molecular Imaging and Targeted Therapeutics laboratory uses *in vivo* imaging of tumour biology in models of human cancers to develop new therapies and improved imaging technologies for application in cancer patients.

RESEARCH FOCUS

- Translational research into adapting novel therapeutics to the human system and moving it into phase I clinical trials.
- Testing patient responses to novel therapeutics and adjusting therapy to gain maximum benefit with minimum toxicity.
- Investigation of novel immunotherapy for human multiple myeloma, leukemia and lymphoma.
- Investigation of human immune system responses to multiple myeloma in response to novel immunotherapy.
- Modelling the effect of novel vaccines to multiple myeloma in a humanised mouse model.
- Investigation of graft-versus-host disease in allogeneic bone marrow transplantation.
- Close collaborative links with the Cancer Research Cooperative for Biomedical Imaging Development (CRC-BID).

KEY 2009 RESEARCH ACHIEVEMENT

High-contrast PET of melanoma using (18)F-MEL050

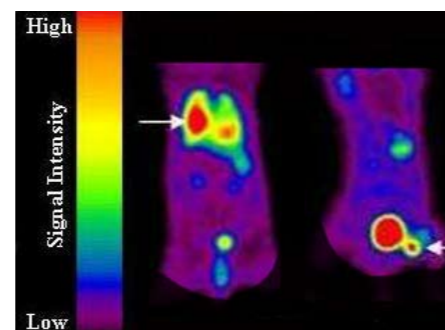
Malignant melanoma is among the most aggressive and invasive tumour types, for which current treatments are rarely effective, making it an important target for improved diagnostic and therapeutic methods. A class of compounds called benzamides (BZAs) have been suggested as possible melanoma imaging agents as these bind tightly and irreversibly to melanin, a pigmented protein found in large amounts in most melanoma cells. Because of this tight binding property, BZAs have the potential to act as 'diagnostic/therapeutic pairs' – that is, when labelled with a PET radionuclide, they can be used for diagnostic imaging of metastatic lesions or recurrences, then labelled with a high energy therapeutic radionuclide for treatment. Past studies have concentrated on BZA analogues labelled with isotopes

of iodine for both imaging and therapy. However, iodine isotopes suitable for PET imaging are virtually unavailable in Australia and very difficult to access worldwide. Together with collaborators at the Australian Nuclear Science and Technology Organisation (ANSTO) and the CRC-BID, we have synthesised a novel BZA compound, MEL050, which can be labelled with 18-fluorine (18F), making it an outstanding candidate as a diagnostic imaging agent for melanoma. We have developed high yielding chemistries for 18F labelling of this compound, which has shown excellent imaging properties in animal models of metastatic melanoma. In addition, we have developed and validated a mouse model of metastatic regional lymph nodes in melanoma using 18F-MEL050 for PET imaging. This new tracer has potential as a highly effective clinical PET imaging agent to improve diagnosis and treatment of metastatic melanoma. First-in-human clinical trials will commence in 2010.

Denoyer D et al. High-contrast PET of melanoma using (18)F-MEL050, a selective probe for melanin with predominantly renal clearance. *Journal of Nuclear Medicine*. 2010 Mar;51(3):441-7

For more information on related research, see:

- Molecular Oncology laboratory (pg xx)
- Translational Research laboratory (pg xx)
- Centre for Cancer Imaging (pg xx)
- Melanoma and Skin Service (pg xx)



Molecular Imaging and Targeted Therapeutics

Figure 1: Imaging melanoma metastasis with an 18F-benzamide (MEL050). False coloured image highlighting lung (left) and lymph node (right) metastases in a cancer model injected with 18F-MEL050 and scanned by PET. The white arrows indicate melanoma metastases.

Translational Research - personnel

CENTRE FOR BLOOD CELL THERAPIES

Director

Prof. Miles Prince

Deputy Director

Assoc. Prof. David Ritchie

Operations Director

Dr Dominic Wall

Managing Director Cell Therapies P/L

Ray Wood

Deputy Production Manager

Kerrie Stokes

Cryopreservation

Peter Gambell
Ayse Mouminoglu

Cell Manipulation

Alannah Evans
Dayna Jackson
Lucy Kravets
Maureen Loudovaris
Tanya Pisanelli
Gillian Treloar
Elise Butler
Valerie Costa
Javier Haurat
Nicole McCarthy
Jude Moloney
Angela Morgan
Gianna O'Donnell

Apheresis

Mel Darby
Jack Parrington

Senior Scientist

Paul Neeson

Senior Research Associates

Prof. Rod Hicks
Dr Simon Harrison
Dr Kirsten Herbert

HAEMATOLOGY IMMUNOLOGY TRANSLATIONAL RESEARCH LABORATORY

Heads

Assoc. Prof. David Ritchie
Dr Paul Neeson

Clinical Collaborators

Prof. Miles Prince
Dr Simon Harrison

Postdoctoral Fellows

Dr Stefan Peinert
Dr Joanne Davis

Clinical Fellow

Dr Hang Quach

Research Assistants

Tsin Tai
Karen Chen
Kellie Tainton
Andy Hsu

Visiting Scholar

Dr Patries Herst

Advanced Medical Science (AMS) Student

Kate Fielding (2008–09)
Reece Cordy (2009–10)

MOLECULAR PATHOLOGY LABORATORY

Heads

Prof. Stephen Fox
Assoc. Prof. Alex Dobrovic

Pathology Research Fellows

Dr Peter Chan
Dr David Westerman

Postdoctoral Scientists

Dr Chelsee Hewitt
Dr Thomas Mikeska
Dr Renato Salemi
Dr Angela Tan

Research Officers

Heather Hondow
Elena Takano
Giada Zapparoli

Research Assistants

David Byrne
Toni-Maree Rogers

Postgraduate Students

Ida Candiloro
Hongdo Do
Katie Huang
Dan Mellor (part time)
Ee Ming Wong
Dr Max Yan

Summer Student

Zi Rong Low (2009–10)

AMS Student

Michael Chung (2008–09)

Cancer Therapeutics program - personnel

GENE REGULATION LABORATORY

Head

Assoc. Prof. Ricky Johnstone

Postdoctoral Researchers

Dr Amber Alsop
Dr Michael Bots
Jessica Bolden
Ailsa Frew
Dr Geoff Matthews
Dr Vanessa Solomon
Dr Inge Verbrugge
Dr Michaela Waibel

Research Assistants

Kellie Banks
Leonie Cluse
Ben Martin
Rachael Ralli
Andrea Reitsma
Ashley Robertson
Kym Stanley

Postgraduate Students

Helen Arthur
Dr Mark Bishton
Jessica Bolden
Ailsa Frew
Nicole Messina
Andrea Newbold
Dr Jake Shortt
Alison West
Adrian Wiegman

Administrative Assistants

Linda Stevens
(Personal Assistant to Assistant Director)

Belinda Kelly
(Personal Assistant to Program)

Laboratory Manager

Jason Brady

PFIZER/PETER MAC CANCER GENOMICS PROGRAM

Heads

Assoc. Prof. Rick Pearson
Assoc. Prof. Wayne Phillips

Chief Investigators

Assoc. Prof. Ross Hannan
Assoc. Prof. Ricky Johnstone
Assoc. Prof. Grant McArthur

Program Manager

Dr Karen Sheppard

Postdoctoral Scientist

Dr Joanna Chan

Research Assistants

Amelia Neilsen
Gwyn Ng
Allen Foo

Bioinformatics Analyst

Jason Ellul

Summer Scholarship Student

Frances Barber

CCV VENTURE INITIATIVE

Heads

Assoc. Prof. Ricky Johnstone
Assoc. Prof. Ross Hannan
Assoc. Prof. Rick Pearson
Assoc. Prof. Grant McArthur

Postdoctoral Fellows

Dr Kathy Jastrzebski
Dr Christine Hauser

Research Assistants

Gregory Leong
Elaine Chilcott

CRC FOR CANCER THERAPEUTICS (CTX) RESEARCH LABORATORY

Scientific Manager

Dr Mark Devlin

Research Assistants

Anthony Natoli
Judy Doherty
Kathryn Visser

TRANSLATIONAL RESEARCH LABORATORY

Heads

Assoc Prof Grant McArthur
Prof. Rod Hicks

Scientific Manager

Dr Carleen Cullinane

Physician Scientist

Dr Ben Solomon

Postdoctoral Scientists

Dr Petranel Ferráo
Dr Kathryn Kinross
Dr Jeanette Raleigh
Dr Titaina Potdevin
Dr Kelly Waldeck

Research Assistants

Ekaterina Bogatyreva
Athena Hatzimihalis
Margarete Kleinschmidt
Anthony Natoli
Richard Young

Technical Assistants

Kerry Ardley
Susan Jackson
Alison Slater
Rachael Walker
Jeannette Valantan

Postgraduate Student

Dr Arun Azad

Advanced Medical Science (AMS) Student

Henry Yao (2008–09)

MOLECULAR IMAGING AND TARGETED THERAPEUTICS LABORATORY

Head

Prof. Rod Hicks

Project Leader

Dr Donna Dorow

Research Postdoctoral Fellows

Dr Delphine Denoyer
Dr Titaina Potdevin

Research Assistant

Laura Kirby

Radiopharmaceutical Chemists

Peter Roselt
Oliver Neels

For full information on the research activities of the Translational Research program, visit:
www.petermac.org/Research/TranslationalResearchProgram

Clinical Research

'I am always inspired by what can be achieved at Peter Mac. The mix of dynamic clinical and laboratory-based researchers with a large number of patients all under one roof makes it a world-class centre for those with inquiring minds'.

Dr Scott Williams, Consultant Radiation Oncologist, Radiation Oncology and Cancer Imaging



Dr Scott Williams

Consultant Radiation Oncologist
Radiation Oncology and Cancer Imaging

Witnessing enormous changes in the treatment of prostate cancer since training as a Radiation Oncologist over ten years ago, Scott Williams has a great understanding of the importance of therapeutic innovation in cancer treatment. Patient responses to different types of radiation treatment form the basis of his clinical research. Scott is driving translational research projects that aim to better understand the mechanism by which radiation works in the individual, potentially leading to better selected therapies and improving cure rates.

