
Our
Research
Peter MacCallum Cancer Centre
RESEARCH REPORT 2010

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Front cover: Dr Mark Shackleton, Pfizer Australia Research Fellow, Head, Melanoma Research laboratory and medical oncologist, Melanoma Service. Below left: Dr Jamie Lopez, Cancer Immunology program. Below right: Dr Claire Milton, Cancer Cell Biology program.

Contents

As the largest cancer research site in Australia, Peter MacCallum Cancer Centre is a major contributor to advances in cancer diagnosis and treatment.

The co-location of a sophisticated research facility and a world-class cancer hospital creates a highly synergistic combination. With researchers and clinicians working side-by-side, Peter Mac has made significant contributions to basic research, translational research and clinical trials.

CEO's report

2010 was a busy and challenging year for research at Peter Mac. We continued to win competitive grants; our staff distinguished themselves in many ways; we streamlined our research governance framework and we worked hard to strengthen our partnerships with other research organisations and to reach out to the community.

In addition, a lot of passion, energy and time were devoted to articulating a vision for the research facilities to be incorporated into the Comprehensive Cancer Centre to be built in Parkville.

As a major focus in 2010, our research staff continued collaborating with colleagues from Melbourne Health, the Ludwig Institute for Cancer Research (Parkville Branch) and The University of Melbourne in advising on the research facilities that will form part of the Victorian Comprehensive Cancer Centre (VCCC). We finished the year with the three bidding consortia having submitted their formal responses to the Request for Tender that had been issued mid-year. Our research staff worked closely with the Department of Health's Project Team and with the three consortia in working through many and varied design options. Whilst very time consuming, this was also a very stimulating and rewarding process—in which our research staff have a clear interest.

At the time of writing, we await a decision on the procurement method. Building work is due to be completed in late 2015.

Our research staff also contributed strongly to the strategic discussions sponsored by the Victorian CCC Joint Venture; a group comprising the four Parkville building partners (as above), plus the Walter and Eliza Hall Institute of Medical Research, The Royal Women's Hospital and The Royal Children's Hospital. This group is charged with enhancing collaboration amongst the seven independent members to produce better outcomes for cancer patients treated at the new facility…and beyond.

Professor Joe Trapani took up his appointment as Executive Director Cancer Research at the beginning of January 2010, succeeding Professor David Bowtell, who returned to full-time research having completed his second five year term in December 2009. Professor Trapani was well supported during a year of strategic, funding, space and other operational challenges by Assistant Directors: Associate Professors Ricky Johnstone and Grant McArthur; Chief Operating Officer: Mary Harney and the Group Leaders. I am very grateful for all their support, advice and guidance.

Highlights during the year included the opening of the Victorian Centre for Functional Genomics in Cancer (supported by a $2.5m grant from the Australian Cancer Research Foundation) and the establishment of both the Melanoma Research laboratory, as part of the Cancer Therapeutics program, and the Tumour Angiogenesis program. Considerable energy was also devoted to further strengthening our focus on translational research.

A number of Peter Mac researchers and clinician-researchers were honoured, or published significant articles, in 2010—in particular, Professors Mark Smyth, Joe Sambrook and Joe Trapani; Associate Professors Grant McArthur, Danny Rischin and Scott Williams and Dr Mark Shackleton, amongst others. Dr Hollie Pegram was awarded the 2010 Peter Mac Postgraduate Research Medal.

Craig Bennett
Chief Executive Officer

Introducing our new Director

Professor Joseph A. Trapani
Executive Director, Cancer Research

New Director, new directions

Following an extensive international search, Professor Joe Trapani was appointed the Executive Director Cancer Research at Peter Mac in January 2010, succeeding Professor David Bowtell, Director for the previous ten years. Already established as a familiar face in the wider Melbourne Research community, Joe began his role as Director of Research in his eleventh year at Peter Mac. He had previously been Deputy Director Research and co-head of the Cancer Immunology program at Peter Mac (with Professor Mark Smyth) since 2000, and Chief Operating Officer Research Division from 2003–2008.

Joe is the first Research Director to also be a clinician, having received his medical degree at the University of Melbourne in 1977. He was Registrar in the Professorial Medical Unit at The Royal Melbourne Hospital in 1981, and from 1982 to 1985 completed his PhD in the Department of Pathology at The University of Melbourne (UoM) and The Royal Melbourne Hospital. Joe completed his physician training (FRACP) in Rheumatology in 1985.

Among Joe's research interests are the cellular and molecular biology of cancer cell death induced by the immune system, the immunopathology of viral and auto-immune diseases and adoptive immunotherapy of cancer. Joe first became interested in how the immune system defends us against viruses and malignancy while working as a post-doctoral fellow at the Sloan-Kettering Cancer Institute, New York in the late 1980's. Here, Joe discovered and characterised a number of the genes and proteins used by killer lymphocytes to eliminate virus-infected and cancerous cells. He found that one protein (perforin) forms pores in the target cell and provides access for other proteins (granzymes) to enter and trigger cell death through apoptosis. Joe returned to Melbourne in 1989 with the support of a Wellcome Trust Senior Research Fellowship and spent the next decade building his research group at The Austin Research Institute, before moving to Peter Mac. With his colleagues, Joe also devised novel ways of harnessing the power of killer lymphocytes and adapting their use to vaccines for killing cancer cells. Joe's team in the Cancer Cell Death laboratory has further identified a rare group of children with inherited defects of perforin function and shown that they are abnormally susceptible to leukaemia.

Joe has received many personal awards and prizes including the 2008 National Health and Medical Research Council Award for Research Excellence and the 2009 GSK Research Excellence Award, which he shared with long-term collaborator Mark Smyth. Joe was an NHMRC Senior Principal Research Fellow from 2003 until 2009, and has been Chief Investigator on a highly successful NHMRC Program Grant that was first awarded in 2003 and only recently renewed until 2016. Joe also holds honorary Professorial appointments at both UoM and Monash University. Joe's research interests remain the immunopathology of viral diseases, apoptosis induction by cytotoxic lymphocytes and cancer immunotherapy. He has authored more than 230 research papers, reviews and book chapters on these topics, including papers in *Nature, Science, Immunity* and *Nature Medicine*. Joe Trapani is also a member of the Executive (Board) of the Cancer Council Victoria and contributes to many peer-review bodies in academia and industry. Joe and his wife Dr Vivien Sutton, also a Peter Mac researcher, have two teenage children, Sarah and Nick.

Director's report

'The next decade holds the promise of many more targeted therapies and the hope that ultimately, cancer therapy will be individualised according to the molecular profile of that patient's own disease. This will mean people living longer and fuller lives with cancer, a greater hope of total cure and an overall reduction in the impact of many cancers on patients and their carers.'

Professor Joseph A. Trapani MBBS, FRACP, FFSc(RCPA), PhD

In January 2010, I was greatly honoured to commence a five year term as the third Executive Director of Research at Peter Mac.

When offered the appointment, my excitement and enthusiasm were tempered by the high responsibility that goes with inheriting such a vibrant and high-achieving division: more than 430 laboratory, translational and clinical researchers collectively ranked amongst the very strongest cancer research institutions in Australia.

The renaissance of research achievement at Peter Mac clearly dates to Peter Mac's move to its East Melbourne campus in 1994, with the appointment of Professor Joe Sambrook as the inaugural Director of Research. A number of key recruitments, coupled with strong philanthropic support and Joe's outstanding vision led to significant growth in peer-review grant and fellowship funding, and the rebirth of Peter Mac as a significant player on the Australian cancer research scene.

Under Professor David Bowtell's superb leadership from 2000–2009, the Research Division underwent a decade of sustained growth, with the establishment of several new and sophisticated research programs such as Cancer Genomics and Immunology and the founding of Platform Technologies to rival the best in the country. Remarkably, an independent assessment of the impact of cancer research publications between 1981 and 2006 (ISI) saw Peter Mac ranked third nationally, only narrowly behind The Garvan Institute but still some distance behind The Walter and Eliza Hall Institute. This achievement was all the more impressive when one remembers that Peter Mac's research productivity had only blossomed over the final decade of the 25 year assessment period.

The next five years hold the promise of further achievement, but on a landscape vastly different to that of recent years, and in the face of unprecedented opportunities and challenges.

In 2015/16, the whole of Peter Mac will move into its new, expanded, purpose-built home in Parkville, as part of the VCCC initiative. The course we set now, and our capacity to adapt to change will ultimately determine whether Peter Mac can ascend to the pinnacle of laboratory, translational and clinical research achievement in cancer on an international basis, for the benefit of cancer patients and their carers.

A recurrent theme in this report is that the recent massive technological achievements in molecular medicine and genomics find us at the dawn of personalised diagnosis and treatment for many cancers.

There is genuine optimism that within the foreseeable future, many cancers will be managed as chronic diseases, rather than fatal conditions. Peter Mac's unique structure, with a thriving cancer laboratory complex embedded within an iconic specialist cancer hospital, presents a generational opportunity to propel Peter Mac and the VCCC more broadly to a position of international leadership.

Director's report (cont.)

As the new Director, I face two major strategic challenges: to maintain and where possible augment the momentum of research achievements of the past 15 years, and to place the Division of Research laboratory achievements ever-more into the clinical context, to maximise translational opportunities and outcomes for patients.

The challenge will be to achieve these aims with minimal space available for further expansion at East Melbourne, and in the face of significant and diverse financial risks. Most importantly, Government funding agencies must find a way to fund the indirect costs of research incurred when hospital-employed researchers win peer-review grants. Quite remarkably, not a single dollar of indirect cost funding flows to the health care sector at present.

To realise our many opportunities, I propose the following:

- As the first clinician to be appointed Executive Director Cancer Research, I firmly believe that Research Division must expand and enhance its links with clinical colleagues at Peter Mac.
- The Research must communicate its achievements and its aspirations more effectively to the entire Peter Mac community, including the Peter Mac Foundation, on whose support we so strongly rely.
- Planning for our move to Parkville must involve a genuine desire to maximise collaboration with VCCC partners. Designing and building a first class physical facility must be balanced by the desire to maximise collaborative opportunities, while maintaining independent governance for all VCCC members.
- Peter Mac's strong record in post-graduate teaching must be extended to encompass more clinician/researchers taking higher degrees, while our profile in undergraduate teaching must also be enhanced.

I look forward to reporting on these aims and aspirations over the coming several years.

MAJOR ACHIEVEMENTS IN 2010

Australia Fellowship awarded to Professor Mark Smyth

In January 2010, Federal Parliamentary Secretary for Health, Mark Butler announced that Professor Mark Smyth (below) had been awarded a $4m Australia Fellowship from the NHMRC. This 'super' award provides personal Fellowship support as well as funding for Mark's research program over the next five years. This extremely prestigious award recognises biomedical researchers of the very highest calibre in terms of the originality and impact of their research. In Mark's case, the Australia Fellowship recognised his superb and sustained work linking the function of the immune system with the genesis and spread of cancer cells.

Professor Mark Smyth

Recruitment of Dr Mark Shackleton and opening of the Melanoma Research laboratory

Dr Mark Shackleton returned to Melbourne following a highly successful post-doctoral fellowship at the University of Michigan, to establish the Melanoma Research laboratory (pg 65) within the new Cancer Therapeutics program. To support his repatriation, Mark was awarded an Innovation Fellowship from the Victorian Endowment for Science Knowledge and Innovation (VESKI) to study melanoma skin cancer progression and explore potential new therapies. Dr Shackleton is a medical oncologist who has pioneered novel techniques for isolating and growing the very cells that underpin the development of malignant melanoma. These new technologies will underlie our efforts to identify novel molecular targets that will form the basis of new therapies for melanoma patients.

Later in 2010, Dr Shackleton was once again honoured with the award of the Pfizer Senior Research Fellowship, a five-year $1m award that provides salary and research funding support.

Recruitment of Associate Professors Steven Stacker and Marc Achen and establishment of the new Tumour Angiogenesis program

In July 2010, around 20 staff and postgraduate students relocated from The Ludwig Institute for Cancer Research, (Parkville Branch) to establish Peter Mac's new Tumour Angiogenesis program (p 58), under the leadership of Associate Professors Achen and Stacker (pictured below). Marc and Steven are highly respected and internationally recognised researchers whose research covers the range of lab-based cell biology through to pre-clinical cancer models and advanced human clinical trials. Tumour Angiogenesis is the process by which tumours generate the new blood vessels they need to secure nutrients and oxygen from the blood stream. Marc and Steven are developing new drugs to interfere with this process, to halt local tumour growth and especially its spread through both blood vessels and lymphatic channels. Marc and Steven jointly hold a NHMRC Program Grant, and each is also supported at a senior level through the NHMRC Fellowship Scheme.

Associate Professors Steven Stacker and Marc Achen

Refreshment of research programs in the Cancer Research Division

Along with establishment of the Tumour Angiogenesis program, the Cancer Therapeutics program was formalised with the appointment of Associate Professors Grant McArthur and Ricky Johnstone as joint Program Heads, and the opening of the Melanoma Research laboratory. This brought the number of formal research programs at Peter Mac to six, the others being Cancer Immunology, Cancer Cell Biology, Cancer Genetics and Predictive Medicine and Cancer Cell Growth and Proliferation. The close integration of these programs and the research of their clinical colleagues aims to maximise the translation of research into clinical trials, and ultimately changed practice in cancer care.

Building closer ties with Peter Mac clinicians and clinical researchers

An area of particular focus for me has been to maximise links with the clinic, to capitalise on Peter Mac's unique governance structure that lends itself to rapid research translation. I have been greatly encouraged by the positive response of Divisional Directors Professor John Zalcberg, Professor Gillian Duchesne and particularly, newly appointed Executive Director Cancer Surgery, Professor Alexander Heriot.

In 2010, I initiated a series of three research retreats, the aim of which was to maximise collaboration and identify new initiatives that would involve lab-based and clinical researchers working in tandem. The three themes were: Genetics and Genomics, Cancer Therapeutics (broadly defined) and Tissue Architecture/Inflammation and Metastasis. One or two senior, external clinician/researchers facilitated each retreat. Each was strongly attended, with broad cross-divisional representation. I look forward to presenting a number of the initiatives distilled from this excellent process in due course.

Consolidating research operational support at Peter Mac

A further major initiative has been to establish a formal Office of Cancer Research (OCR) at Peter Mac. The purpose of an OCR is to provide broad operational support for research across the whole of Peter Mac, to facilitate grant submission and financial management, research governance and ethics, the mentoring of junior researchers and to foster cross-divisional collaboration. Ms Mary Harney, Chief Operating Officer Research Division was confirmed as interim Director of the OCR during the year.

A number of senior Peter Mac clinician researchers were appointed as honorary Group Leaders within the Research Division during 2010. These included Professor Stephen Fox, Director of Pathology, Professor Rod Hicks, Director Cancer Imaging, Associate Professor Penny Schofield, Senior Research Fellow Supportive Care Nursing Research and Dr Gillian Mitchell, Director Familial Cancer Centre.

Strengthening undergraduate and postgraduate teaching

Peter Mac Research Division has historically enjoyed a strong relationship with the Department of Pathology at (UoM), dating back to the 1940s, when Sir Peter MacCallum was Head of Department. In conjunction with the current Chair of Pathology, Professor Paul Waring, senior Peter Mac clinicians and clinician/researchers underpin a new, third year undergraduate course in Molecular Oncology. Peter Mac Group Leader, Associate Professor Rob Ramsay coordinates this exciting new 12 lecture series with Professor Waring. Peter Mac's research laboratories also supported the projects of 12 BSc honours students enrolled in Pathology or other UoM departments.

At the postgraduate level, Peter Mac continues to host around 60 higher degree students, mostly through PhD candidature. The Research Division is a potent focus for attracting clinicians wishing to undertake higher degrees, with medical oncologists, pathologists and surgeons all strongly represented.

Communicating our research aspiration and achievements

Raising the profile of research within Peter Mac, amongst our colleagues at other institutions and in the public arena is critical for continued success in fundraising and for reinforcing Peter Mac's leadership in cancer treatment and research. Guided tours of the research laboratories have enabled many Peter Mac staff to learn of our research capability, or to support the wonderful fundraising efforts of our colleagues in the Peter Mac Foundation.

In October, the second annual Peter Mac public lecture was held at the Melbourne Town Hall, moderated by media personality Dr Sally Cockburn. Professor David Bowtell and Dr Gillian Mitchell (pictured below) gave fascinating and accessible presentations that outlined cancer as a 'disease of the genes', and identified genetics as the key to future rapid diagnosis and personalised cancer care. The winners of an essay competition for Victorian secondary school students were presented with cash prizes and certificates.

At the Peter Mac annual general meeting in November, Dr Hollie Pegram, who performed outstanding PhD studies with Associate Professor Mike Kershaw and Dr Phil Darcy (Immunotherapy laboratory, pg 29) was presented with the 2010 postgraduate research medal.

2010 also marked the launch of a new quarterly newsletter *Forefront* that outlines recent research achievements across Peter Mac.

Dr Gillian Mitchell

Success in NHMRC project and fellowship funding

Of 38 applications for Project Grant support, 16 (42 per cent) were funded, representing about double the national success rate. Of the 22 grants that were not funded, 12 scored in the '5' category: these are grants that qualify easily on quality but receive no support because of insufficient funds. All in all, this meant that 28 of 38 grants (74 per cent) scored 5 or above, which is absolutely outstanding and a testament to the mentoring that all applicants receive from Peter Mac colleagues prior to submission.

Director's report (cont.)

INDIVIDUAL RESEARCH AWARDS

- Dr Mark Shackleton and Associate Professor Penny Schofield (pictured below) received awards for Research Excellence from the NHMRC ('Top ten projects').

Dr Mark Shackleton and Associate Professor Penny Schofileld

- Mr Tony Lupton, Cabinet Secretary of the Parliament of Victoria opened the ACRF Victorian Centre for Functional Genomics in Cancer. Support for this cutting edge resource was centred on a $2.5m grant from the Australian Cancer Research Foundation (ACRF), together with grants from the Victorian Government and the Peter Mac Foundation. The VCFG in Cancer is a national resource in cancer genomics and houses various research platforms including robotically-controlled RNA knockdown technologies and next generation DNA sequencing to rapidly decipher cancer genomes.
- Dr Scott Williams was awarded a highly prestigious research grant from the Prostate Cancer Foundation, USA. Scott, who has established study collaborations with a number of Research laboratories, also received a five year clinician researcher Fellowship from the Victorian Cancer Agency.
- Professor Joe Sambrook, inaugural Director of Research at Peter Mac was presented with a life-time achievement award by Monash University, in recognition of his stellar research career and countless contributions to research leadership and peer-reviews.
- Associate Professor Grant McArthur was a major contributor to a paper published in *Nature* that described clinical efficacy of a BRAF inhibitor that is revolutionising care in advanced malignant melanoma. This ground breaking work offers new hope for countless sufferers of this devastating disease. A further paper describing results of the clinical trials was published in the prestigious clinical journal, *The New England Journal of Medicine*.
- Peter Mac was announced as part of a breakthrough international project that has uncovered a genetic mutation connecting ovarian cancer to endometriosis. Peter Mac Program Head in Genetics and Principal Investigator in the Australian Ovarian Cancer study, Professor David Bowtell described the findings as a potent example of the power of the new DNA sequencing technologies to find critical genes that control ovarian cancer growth.
- Members of the laboratory of Professor Joe Trapani (Cancer Cell Death laboratory, pg 26) were featured as principal authors in a publication in *Nature* that described the crystal and electron microscope structure of perforin, a key protein involved in the elimination of virus-infected and cancerous cells by the immune system.
- Dr Andreas Moeller was awarded a prestigious Early Career Fellowship from the National Breast Cancer Foundation.

2010 has been a challenging but highly invigorating and successful year for Peter Mac researchers.

I am greatly indebted to the Board and Senior Management of Peter Mac for their continual support of research, and to the Peter Mac Foundation whose tireless efforts continue to provide the philanthropic support that underpins our every effort and achievement.

Finally, I thank our generous donors, our funding agencies and particularly our dedicated researchers and postgraduate students whose stellar achievements promise so much in alleviating cancer suffering.

Professor Joseph A Trapani
MBBS, FRACP, FFSc (RCPA), PhD
Executive Director Cancer Research

Clinical research overview

Through dedication to reducing the burden of cancer in Australia for over 60 years, Peter Mac has earned an international reputation for excellence and innovation in cancer research, treatment and patient care.

As Australia's only public hospital solely dedicated to cancer, Peter Mac is in a unique position to drive developments in cancer research, underpinned by a vibrant clinical research program integrated with a sophisticated laboratory cancer research facility.

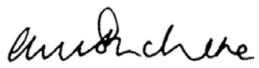
The geographical and functional intertwining of the basic science and clinical research programs, supported by clinician scientists working across both areas and close interaction between the scientists and clinicians, provides the ideal synergistic environment to facilitate translational research. This is pivotal in the development of new therapeutic approaches and individualisation of cancer care.

Clinical research is embedded within the 11 tumour streams that deliver clinical care. The streams are underpinned by specialist laboratories and enabling technology and interdisciplinary research platforms, all with research programs that function both independent of and integrated with the tumour streams. The four divisions, Cancer Medicine, Cancer Surgery, Radiation Oncology and Cancer Research, complete the matrix.

It is difficult to select research highlights of the year due to the plethora of successes. However collaborative translational research leading to the identification of a novel molecular target for non-small cell lung cancer, and the clinical demonstration of the therapeutic benefit of an inhibitor of mutated BRAF gene in malignant melanoma, must be considered to be a couple of the highlights of 2010.

As we plan towards the development of the new Peter Mac at Parkville, we have opportunities to plan for the continued growth and development of our clinical research—research that is pivotal to the development of new directions in treatment.

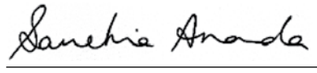
We take this opportunity to thank all our researchers for their contributions to clinical research and congratulate them on their leadership and achievements in 2010.



Professor Gillian Duchesne
Executive Director, Radiation Oncology and Cancer Imaging

Associate Professor Alexander Heriot
Executive Director, Cancer Surgery

Professor John Zalcberg OAM
Executive Director, Cancer Medicine



Professor Sanchia Aranda
Executive Director, Cancer Nursing

Peter Mac strives to lead the charge in discovering more about cancer, ultimately leading to a goal where more cures are possible.

Peter Mac plays an extremely important role in the community as the only public hospital in Australia solely dedicated to cancer. Even more unique is the integration of an extremely strong research program that is internationally renowned.

Peter Mac delivers care through a multidisciplinary model across 11 tumour streams. The provision of care is closely integrated with the largest cancer research team in Australia.

Peter Mac's key research strengths include that:

- It is one of the few hospitals in the world with the benefit of having its own integrated cancer research programs and laboratories, providing the opportunity to lead the way in translational research in cancer.
- Its research program continually drives improvements in all aspects of treatment and clinical care.
- It provides a multidisciplinary tumour stream-based and holistic model of care—experts from all fields come together to provide the best treatment possible at all stages of a patient's illness, across the full spectrum of cancers.
- It has a pre-eminent academic program, with internationally renowned researchers and clinical researchers.
- It has specialised equipment and technology, enabling highly complex research and treatments.

Peter MacCallum Cancer Centre
2010–2015 Strategic Plan

OUR VISION

The best in cancer care—accelerating discovery, translating to cures.

OUR MISSION

As Australia's only public hospital solely dedicated to cancer, as a national leader in multidisciplinary cancer care, and a national and international leader in laboratory, clinical and translational research, Peter Mac:

- Is dedicated to providing care across all clinical services to improve the outcomes for individual cancer patients, and reduce the impact of cancer on our community.
- Through its dedicated focus to cancer and the critical mass of its services, provides specialist treatment in rare and complex cancers to ensure that all Victorian patients, regardless of where they live, will have access to the expert care they require.
- Ensures that discoveries progress to increasing the cancer knowledge base that then translates to the development of the best cancer treatments.
- Provides the best in educational opportunities resulting in the training of the best cancer clinicians for today and the future.

OUR VALUES

We strive for **Excellence** ensuring that clinical practice is evidence based, patient centred and is provided by qualified and experienced staff that are accountable and appropriately credentialled.

We strive to ensure that **Innovation** is fostered by supporting research and a learning culture.

Adhering to the strongest ethical standards to ensure a culture of openness, mutual respect and trust, **Compassion** is at our core.

About research at Peter Mac

Peter Mac's research goal is to alleviate the impact of cancer on the community through innovative research and through collaboration and contribution to national and international cancer research programs.

OUR KEY RESEARCH STRATEGIC DIRECTIONS

Research and innovation to cure or control cancer

Key core components within this research strategic direction include:

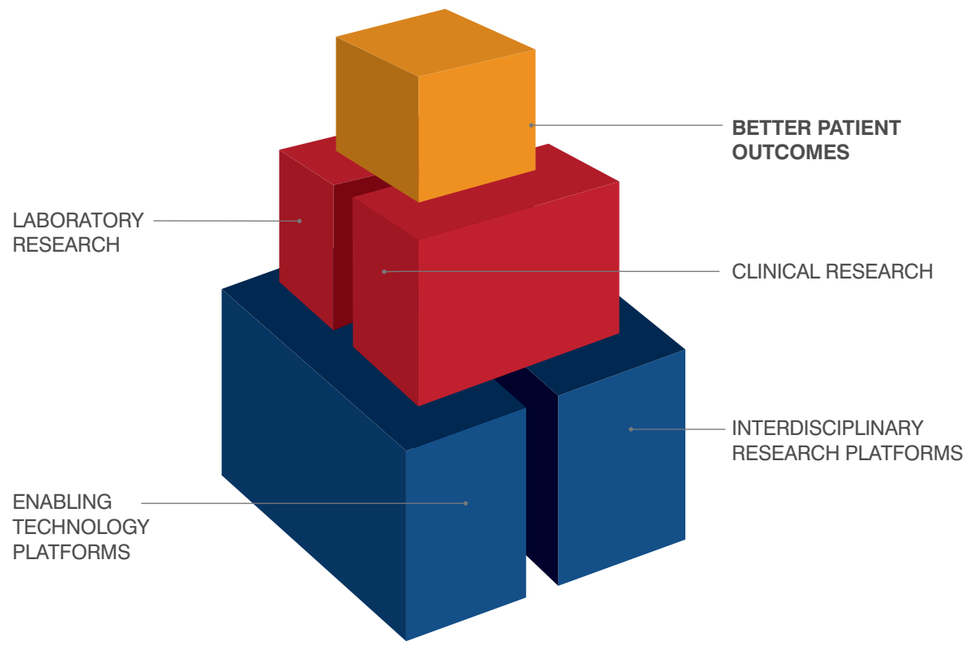
- A pre-Parkville Strategy, with a focus on growth and development of collaborative relationships and platform technologies pre-2015.
- Developing Peter Mac as a leading centre for innovative research and treatment, including further developing personalised medicine approaches (e.g. genomics), and responding to innovative opportunities to develop all laboratory, translational and clinical research programs.
- Further develop the laboratory/clinical interface, including resources to enable Peter Mac to lead in the development of translational research programs across all clinical services, and a structure to support further development of tumour stream-based research.
- Continuing to develop and enhance Peter Mac's clinical research capacity and profile.

PETER MAC RESEARCH MODEL

The model below is representative of both the structure of research at Peter Mac and of the structure of this report.

Our laboratory, clinical and translational research is supported by an extensive base of enabling technologies and interdisciplinary research platforms that underpin our nationally and internationally recognised research.

With this breadth of expertise and resources available, we aim to drive the translation of our laboratory and clinical research into best clinical practice and better patient outcomes.



Cancer research at a glance

Powerful trends in genetics, molecular therapeutics, imaging, and personalised medicine will shape the future of cancer service delivery. As a specialist cancer centre and with a strong disease focus in our research, Peter Mac is exceptionally well placed to translate research findings into clinical practice and to help devise the most beneficial and cost-effective new approaches to cancer management.

Our cancer research program is underpinned at all levels by a belief in the importance of developing a deep understanding of the processes that control cancer cells, and employing this knowledge in the clinic to develop rational, evidence based protocols that improve cancer outcomes.

Patient care at Peter Mac is modelled around tumour-specific clinical services, provided by multidisciplinary teams of surgeons, radiation oncologists, medical oncologists, specialist nurses, allied health and other support staff. Our clinical services are underpinned by a strong research program that extends from basic laboratory research through to translational research programs and clinical trials of new cancer treatments. In addition, we support a growing program of research in supportive care and palliative care.

Our laboratory, clinical and translational research is supported by an extensive base of enabling technologies and interdisciplinary research platforms that underpin our nationally and internationally recognised research.

LABORATORY CANCER RESEARCH

Cancer Research is home to over 420 laboratory-based scientists and support staff including over 100 postgraduate, honours and advanced medical science students.

Our laboratory-based translational research programs are conducted across 27 laboratories, organised into collaborative research programs:

- Cancer Cell Biology (Associate Professor Rob Ramsay)
- Cancer Genetics and Genomics (Professor David Bowtell)
- Cancer Immunology Research (Professors Joseph Trapani and Mark Smyth)
- Cancer Therapeutics, incorporating Molecular Imaging and Translational Medicine (Associate Professors Ricky Johnstone and Grant McArthur)
- Growth Control and Differentiation (Associate Professors Ross Hannan and Rick Pearson)
- Tumour Angiogenesis (Associate Professors Marc Achen and Steven Stacker).

Our laboratory programs are supported by nine core technology platforms, from advanced microscopy facilities through to sophisticated functional and molecular genomic facilities.

CLINICAL AND TRANSLATIONAL RESEARCH

Our clinical and translational research is embedded within the 11 tumour streams that deliver clinical care, and is underpinned by interdisciplinary research platforms all with research programs that function both independent of, and integrated with, the tumour streams.

Over 200 clinician researchers across Peter Mac are involved in clinical trials and clinical research. These include medical, radiation and surgical oncologists, and staff from allied health, nursing and supportive care, physical sciences, imaging and radiation therapy, statisticians and research nurses.

Over 200 clinical trials were active at Peter Mac through both the Clinical Trials Unit (CTU) and through trials coordinated by the Centre for Bioinformatics and Clinical Trials (BaCT).

FELLOWSHIPS AND AWARDS IN 2010

- 15 senior fellowships (NHMRC and others)
- 13 NHMRC career development and postdoctoral awards
- 8 clinical research fellowship awards (CCV, VCA)
- 13 new scholarships awarded to postgraduate students in 2010.

RESEARCH OUTPUT

Our scientific excellence, underpinned by grant successes, is evident in the strong impact of our research publications.

PUBLICATIONS TYPES AND QUANTITIES

Publication type	2010
Original research articles	291
Reviews	63
Editorials and comments, letters, author replies	59
Book chapters	12
Total	**425**

Metrics

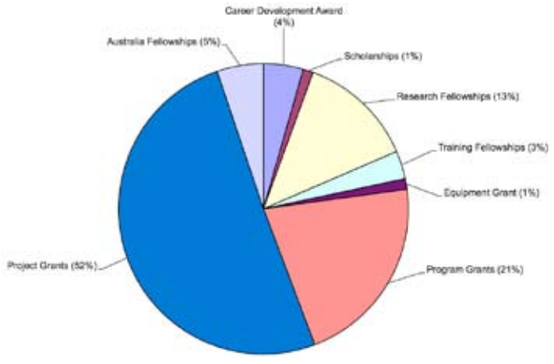
PUBLICATIONS

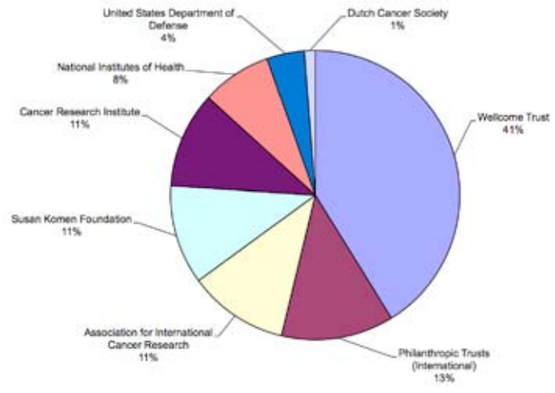
In 2010, the cancer research of Peter Mac was published in a range of international peer reviewed journals, including:

Publication	Impact Factor	2009	2010
New England Journal of Medicine	52.59	1	4
Cell	29.89	2	1
Science	29.75	-	1
Nature	28.75	1	4
Nature Reviews Cancer	29.54	-	2
Lancet	28.64	2	2
Nature Reviews Immunology	28.30	1	-
Nature Medicine	26.38	1	-
Nature Immunology	26	-	1
Nature Genetics	25.56	3	2
Cancer Cell	23.86	1	2
Immunity	19.27	3	-
Journal of Clinical Oncology	17.79	14	16
Nature Cell Biology	17.62	1	-
Journal of Clinical Investigation	16.92	2	-
Journal of the National Cancer Institute	15.68	2	2
Lancet Oncology	12.25	2	6
Gastroenterology	11.67	2	1
American Journal of Human Genetics	11.09	1	-
Blood	10.90	9	5
Gut	10.02	1	-
Total (JIF>10)		49	49

GRANTS

With a budget of over $40m annually, the excellence of our research is reflected in our success in obtaining competitive funding to support our research endeavours. We continue to achieve more than double the national average for success in grants from the (NHMRC), and are proud of the success of our researchers in obtaining competitive funding from national and international organisations.





Research/Cancer Matrix

LABORATORY	PLATFORM TECHNOLOGY								CANCER TYPES										
	Transgenic Models	Microscopy	Next Gen Sequencing	Flow Cytometry	VCFG	Bioinformatics	Tissue Bank	Micro-array	All Cancers	Breast	Gastro-intestinal	Gynae-oncology	Haematology	Head & Neck	Lung	Melanoma & Skin	Neuro-Oncology	Sarcoma	Uro-Oncology
1.1 Cancer Immunology Progarm																			
1.1.1 Cancer Cell Death	•	•	•	•	•	•	•	•	•	•	•		•			•			
1.1.2 Cellular Immunity	•	•		•		•	•	•	•	•	•		•		•	•		•	•
1.1.3 Immune Signalling	•	•	•	•		•	•	•	•				•						
1.1.4 Immunotherapy	•	•		•			•	•	•	•			•		•	•		•	
1.1.5 Haematology Immunology Translational Research	•	•		•			•						•						
1.2 Cancer Genetics Program																			
1.2.1 Cancer Genetics and Genomic	•	•	•	•	•	•	•	•	•	•	•	•							
1.2.2 Sarcoma Genetics and Genomics	•	•	•	•	•	•	•	•										•	
1.2.3 Surgical Oncology	•	•	•	•	•	•	•	•		•	•	•							
1.2.4 VBRC		•	•	•	•	•	•	•		•		•							
1.2.5 kConFab			•			•		•		•	•	•						•	•
1.3 Growth Control and Differentiation Program																			
1.3.1 Growth Control	•	•	•	•	•	•		•	•	•		•	•			•			•
1.3.2 Molecular Oncology	•	•	•	•	•	•	•	•		•	•	•	•		•	•	•	•	
1.3.3 Protein Chemistry	•	•	•	•	•	•	•	•		•		•	•			•			
1.4 Cancer Cell Biology Program																			
1.4.1 Cell Cycle and Cancer Genetics	•	•	•	•	•	•	•	•	•	•					•				•
1.4.2 Cell Cycle and Development		•	•	•	•	•		•	•	•	•	•				•			•
1.4.3 Cell Growth and Proliferation		•	•						•	•	•	•		•		•		•	•
1.4.4 Differentiation and Transcription	•	•	•	•		•	•			•	•								
1.4.5 Epithelial Stem Cell Biology	•	•		•		•	•	•	•			•			•	•			
1.4.6 Metastisis Research	•	•		•	•	•	•	•	•	•									
1.4.7 Molecular Radiation Biology	•	•		•						•	•			•	•				•
1.4.8 Tumour Suppresion	•	•		•	•	•	•	•	•	•	•		•						•
1.5 Tumour Angiogenesis Program																			
1.5.1 Tumour Angiogenesis	•	•		•	•	•	•		•										
1.6 Cancer Therapeutics Program																			
1.6.1 Gene Regulation	•	•	•	•	•	•			•	•	•		•		•	•			•
1.6.2 Melanoma Research	•	•		•			•									•			
1.6.3 Molecular Imaging and Targeting Therapeutics	•	•		•					•							•			
1.6.4 Translational Research	•	•		•		•	•		•					•	•	•			
1.6.5 Pfizer/Peter Mac Cancer Genomics program	•	•	•			•						•				•			
1.6.6 CCV Venture			•	•	•					•									
1.6.7 CRC for Cancer Therapeutics	•	•		•					•	•	•								

Interdisciplinary Matrix

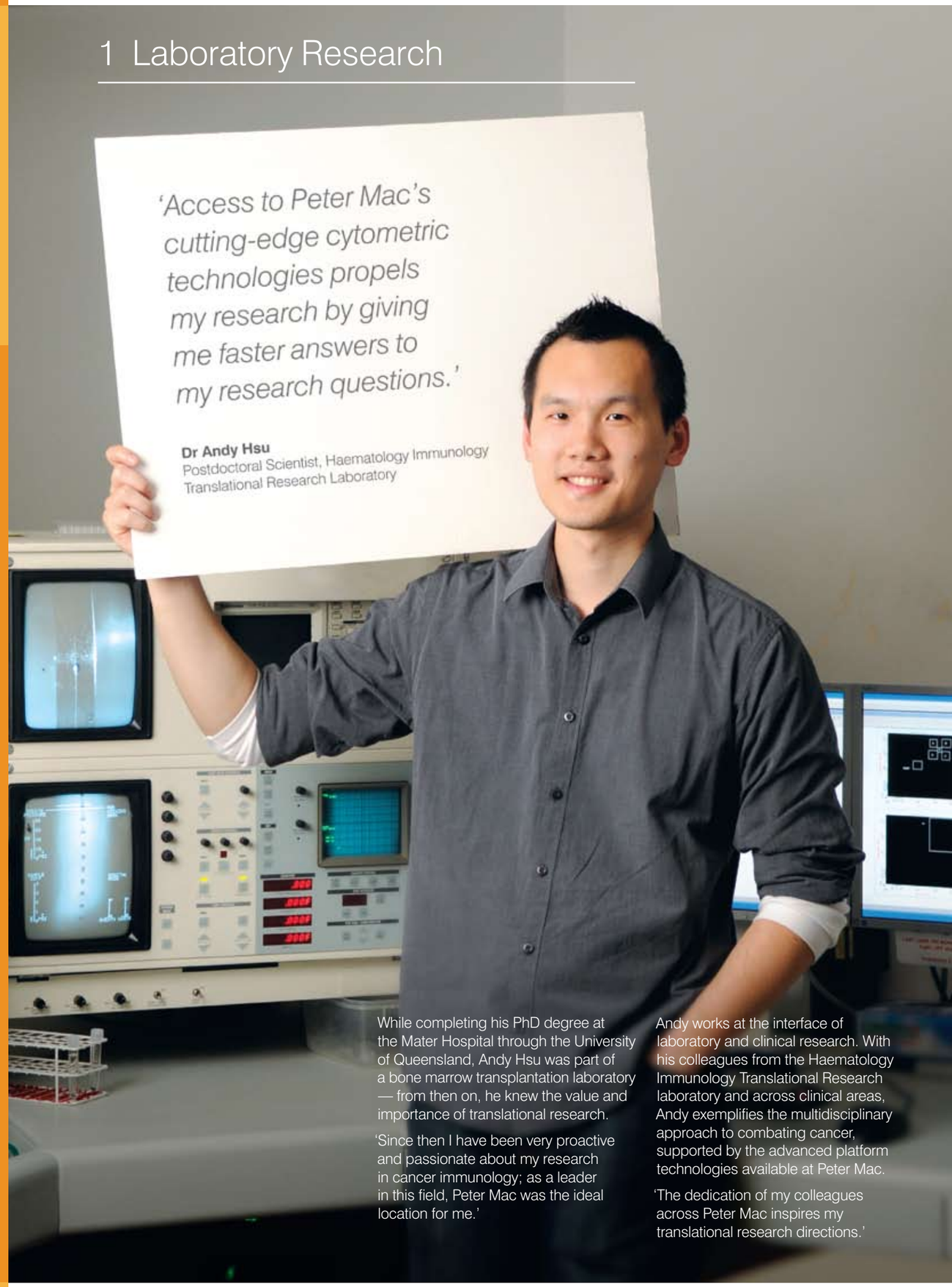
INTERDISCIPLINARY RESEARCH PLATFORMS	CANCER TYPES											
	All Cancers	Breast	Gastro-intestinal	Gynae-oncology	Haema-tology	Head & Neck	Lung	Melanoma & Skin	Neuro-Oncology	Paeds/ Late Effects	Sarcoma	Uro-Oncology
3.2.1 Centre for Blood Cell Therapies					•							
3.2.2 Centre for Cancer Imaging	•	•	•	•	•	•	•	•	•	•	•	•
3.2.3 Centre for Biostatistics and Clinical Trials	•	•			•	•						
3.2.4 Clinical Trials Unit	•			•	•		•	•			•	
3.2.5 Clinical Psychology	•	•				•						
3.2.6 Familial Cancer Centre	•	•	•	•								
3.2.2 Infectious Diseases	•				•							
3.2.3 kConFab Follow-Up		•		•								
3.2.4 Molecular Pathology laboratory	•	•	•		•	•	•					•
3.2.5 Nursing and Supportive Care	•			•			•				•	
3.3.1 Nutrition	•		•		•	•	•				•	
3.3.2 onTrac@ PeterMac	•				•						•	
3.3.3 Pain and Palliative Care	•											
3.4.1 Pharmacy	•											
3.4.2 Physical Sciences	•	•					•		•	•		•
3.4.3 Radiation Therapy	•	•	•	•		•	•		•	•		•
3.4.4 Social Work	•			•						•		

Recent research highlights with impact on cancer care

- Establishment of the use of PET as a global standard technique for the staging and response to treatment in lung and head and neck cancer
- Efficacy of tirapazamine in hypoxic tumours such as head and neck
- RANKL as a novel therapeutic for large cell cancer in bone
- BRAF inhibitors in melanoma: world first clinical trials
- The establishment of Imatinib as a global standard of care for dermatofibrosarcoma protuberans
- New methods of diagnosing cancers of unknown primary (CUP)
- Establishment of HDACi as a standard of care in cutaneous T cell lymphoma
- Identification of PI-3 kinase as an important oncogene in several cancers including colon and ovarian
- Identification of molecular markers that distinguish various types of stomach and ovarian cancer
- Identification of cell size regulation as important in cancer causation
- Realisation that the immune system is an important regulator of cancer development, particularly leukaemia/lymphoma
- New methodologies for diagnosis of hemophagocytic lymphohistiocytosis
- Demonstration that stromal cells in ovarian cancer are not genetically mutated
- Accurate definition of stem cells in skin
- Leading practice in the application of brachytherapy in prostate cancer
- Leading practice in eliminating movement as a confounder in delivery of radiotherapy
- The development of the world's first radio-protector molecules
- World's best practice in management of the psycho-social aspects of adolescent cancer (onTrac@Petermac)
- p16 as a prognostic marker in head and neck cancer
- ALK inhibitor in lung cancer: world first clinical trials
- Use of radiotherapy in lymph node metastases from melanoma
- The discovery of new breast cancer genes that will explain the cause of these cancers
- Development of highly efficient and clinically relevant models of human melanoma progression
- Translation of research patients into effective targeted therapies for breast, ovarian and prostate cancers

Laboratory Research

1



While completing his PhD degree at the Mater Hospital through the University of Queensland, Andy Hsu was part of a bone marrow transplantation laboratory — from then on, he knew the value and importance of translational research.

'Since then I have been very proactive and passionate about my research in cancer immunology; as a leader in this field, Peter Mac was the ideal location for me.'

Andy works at the interface of laboratory and clinical research. With his colleagues from the Haematology Immunology Translational Research laboratory and across clinical areas, Andy exemplifies the multidisciplinary approach to combating cancer, supported by the advanced platform technologies available at Peter Mac.

'The dedication of my colleagues across Peter Mac inspires my translational research directions.'

1 Laboratory Research

Working at the interface between basic biology and clinical cancer care, our scientists are committed to reducing the impact of cancer on people.

With 27 integrated research laboratories embedded in a world-class cancer hospital and researchers and clinicians working side-by-side, we have established an outstanding reputation for excellence in cancer research.

A focus on translating our laboratory research into clinical practice underpins our strategic research directions. Working in an integrated environment delivers unique opportunities for medical advances to be developed and tested, and for clinically oriented questions to guide research agendas. This has a profound effect on the understanding of cancer biology, leading to more effective and individualised patient care, in effect, research from 'bench to bedside' and back again.

Cancer Immunology program
Cancer Cell Death laboratory
Cellular Immunity laboratory
Immune Signalling laboratory
Immunotherapy laboratory
Haematology Immunology
Translational Research laboratory

Cancer Genetics program
Cancer Genetics and Genomics laboratory
Sarcoma Genetics and Genomics laboratory
Surgical Oncology laboratory
VBCRC Cancer Genetics laboratory
kConFab

Growth Control and Differentiation program
Growth Control laboratory
Molecular Oncology laboratory
Protein Chemistry laboratory

Cancer Cell Biology program
Cell Cycle and Cancer Genetics laboratory
Cell Cycle and Development laboratory
Cell Growth and Proliferation laboratory
Differentiation and Transcription laboratory
Epithelial Stem Cell Biology laboratory
Metastasis Research laboratory
Molecular Radiation Biology laboratory
Tumour Suppression laboratory

Tumour Angiogenesis program
Tumour Angiogenesis laboratories

Cancer Therapeutics program
Gene Regulation laboratory
Melanoma Research laboratory
Molecular Imaging and Targeting Therapeutics laboratory
Translational Research laboratory
Pfizer/Peter Mac Cancer Genomics program
CCV Venture Grant Initiative
CRC for Cancer Therapeutics

Peter Mac Fellow Dr Jane Oliaro is a postdoctoral scientist in the Cancer Immunology program. Using the latest confocal, electron and time-lapse microscopes, Jane's research involves imaging immune cells: understanding how we can activate a type of immune cell, called a T cell, to mount an immune response to clear infected and cancerous cells.

With her colleagues in the Immune Signalling laboratory, Jane hopes to further understanding of immune cell development and determine the processes that are disturbed in cancers such as leukaemia.

'By using the microscopy facilities at Peter Mac I can image, in real time, cells communicating with each other, growing and killing cancer cells, and monitoring the movement of molecules within individual cells.'

1.1 Cancer Immunology program

Harnessing the power of the immune system to fight cancer

The Cancer Immunology program performs internationally recognised work on cancer immune surveillance and chemo/immuno-therapy, defining key cells and molecules that constitute an effective response to tumour.

Immunotherapy is of increasing interest as an approach to arrest cancer at a much earlier stage. Strategies range from vaccines that mobilise the immune system *de novo* (active immunotherapy), to administering preformed biologicals such as monoclonal antibodies (mAbs), cytokines, or exogenously activated immune cells (adoptive immunotherapy).

The program has recently strengthened its focus on haematological cancers, greatly strengthening links with Peter Mac's Division of Cancer Medicine.

Current and future efforts are directed at understanding the fine balance between the developing tumour microenvironment and the immune system, the key molecules that link innate and adaptive immunity and promote lasting memory to tumour antigens, and the molecular pathways that underpin the signalling of anti-tumour interferons.

Complementing these approaches is the development of genetically enhanced T cells for adoptive immunotherapy, whose potency and specificity have rapidly moved this strategy into phase I clinical trials.

The Immune Signalling laboratory (led by Dr Sarah Russell) is part of the Cell Polarity program, and is making important discoveries about the polarity of immune cells and the structural network that controls immune cell synapse, migration, division and effector function.

The Gene Regulation laboratory (led by Assoc. Prof. Ricky Johnstone) in the Cancer Therapeutics program is closely linked with the Cancer Immunology program, collaborating in a program of chemo-immunotherapy in breast cancer.

Cancer Cell Death laboratory
Prof. Joseph Trapani

Cellular Immunity laboratory
Prof. Mark Smyth

Immune Signalling laboratory
Dr Sarah Russell

Immunotherapy laboratory
Assoc. Prof. Michael Kershaw and Dr Phil Darcy

Haematology Immunology Translational Research laboratory
Assoc. Prof. David Ritchie and Dr Paul Neeson

For immunology research conducted within associated programs:

- Gene Regulation laboratory

  Assoc. Professor Ricky Johnstone (See Cancer Therapeutics program, pg 62)

- Haematology Service (pg 86)

1.1.1 Cancer Cell Death laboratory

Research Leader: Prof. Joe Trapani, Executive Director Cancer Research

We investigate immune mechanisms of defence against viral pathogens and cancerous (transformed) cells. Understanding these processes will help to better understand molecular mechanisms that govern the immune system; identify genetic predisposition to haematological malignancies; design novel therapeutic approaches to prevent life-threatening complications of bone marrow stem cell transplantation.

RESEARCH FOCUS

- Investigation of molecular mechanisms behind cytotoxic lymphocyte-induced apoptosis of cancer cells.
- Understanding the structure, mechanism and genetics of a key regulator of cytotoxic lymphocyte activity, perforin.
- Development of cytotoxic lymphocyte suppressors based on targeted inhibition of perforin function by novel compounds.

KEY 2010 RESEARCH ACHIEVEMENT

The crystal structure of perforin monomer and the three-dimensional reconstruction of the entire perforin pore

Natural killer cells and cytotoxic T lymphocytes accomplish the critically important function of killing virus-infected and neoplastic cells. They do this by releasing the pore-forming protein perforin and granzyme proteases from cytoplasmic granules into the cleft formed between the abutting killer and target cell membranes. Perforin, a 67-kilodalton multidomain protein, oligomerises to form pores that deliver the pro-apoptopic granzymes into the cytosol of the target cell. The importance of perforin is highlighted by the fatal consequences of congenital perforin deficiency: autosomal recessive immunoregulatory disorder, familial haemophagocytic lymphohistiocytosis (type 2 FHL). In the past, we characterised many of those mutations and also defined some of the key aspects of perforin mechanism of action.

In collaboration with colleagues at Monash University and Birkbeck College (London) we have now resolved the X-ray crystal structure of monomeric murine perforin, together with a cryo-electron microscopy reconstruction of the entire perforin pore. Not only did these studies support our earlier work, but they also allowed the elucidation of the mechanism of perforin pore formation, which remained one of the most puzzling secrets of cytotoxic lymphocyte biology for well over two decades.

Perforin turns out to be a thin 'key-shaped' molecule, comprising an amino-terminal membrane attack complex perforin-like (MACPF)/ cholesterol dependent cytolysin (CDC) domain followed by an epidermal growth factor domain that, together with the extreme carboxy-terminal sequence, forms a central shelf-like structure. A C-terminal C2 domain mediates initial, Ca-dependent membrane binding. Most unexpectedly, however, electron microscopy reveals that the orientation of the perforin MACPF domain in the pore is inside-out relative to the subunit arrangement in ancestral homologous bacterial CDC. These data reveal remarkable flexibility in the mechanism of action of the conserved MACPF/CDC fold and provide new insights into how related immune defense molecules such as complement proteins assemble into pores.

These studies now provide a valid framework for the rational design of modulators of perforin function, which may potentially be used to alleviate undesirable outcomes of cytotoxic lymphocyte activity in autoimmune diseases, such as Type I Diabetes and cerebral malaria.

Reference: Law RH, Lukoyanova N, Voskoboinik I, et al. The structural basis for membrane binding and pore formation by lymphocyte perforin. Nature. 468: 447–451, 2010.

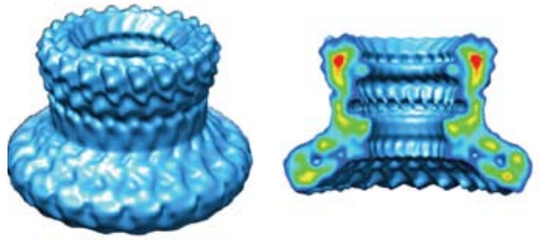


Figure 1: A cryo-electron microscopy reconstruction of a perforin pore (from Law, Lukoyanova, Voskoboinik I, et al. The structural basis for membrane binding and pore formation by lymphocyte perforin. Nature. 468: 447–451, 2010).

1.1.2 Cellular Immunity laboratory

Research leader: Prof. Mark Smyth, NHMRC Senior Principal Research Fellow

The Cellular Immunity laboratory undertakes basic and pre-clinical research in cancer immunology, with a view to combining new cancer immunotherapies with current first line cancer therapies.

RESEARCH FOCUS

- Basic studies of the role of immunity in the tumour microenvironment.
- Immunosuppressive pathways that prevent tumour regression.
- The biology of natural killer (NK) cells and NKT cells.
- Translational studies designing and testing new combination immunotherapies pre-clinically and clinically in cancer patients.

KEY 2010 RESEARCH ACHIEVEMENT

CD73 as a novel therapy in primary cancer growth and metastasis

It is becoming increasingly apparent that one of the difficulties of inducing clinically relevant cancer immunotherapy is the tight regulation associated with immune responses.

One of the most important regulatory processes that restricts immune activation is the accumulation of extracellular adenosine in tissue. It has been observed that extracellular adenosine is a potent immunosuppressor that accumulates during tumour growth. One of the sources of extracellular adenosine is through the activity of CD73, an ecto-enzyme that catalyses the dephosphorylation of adenosine monophasphates into adenosine. CD73 is normally expressed on endothelial cells and subsets of leukocytes, and is induced in response to cellular stress such as hypoxia. Importantly, CD73 is overexpressed in various cancer cell types, including breast cancer. We hypothesised that blocking the activity of CD73 would decrease the level of extracellular adenosine in the tumour microenviroment, break immune tolerance to the tumour and promote immune-mediated tumour cell destruction.

To investigate CD73 as a potential target for anticancer strategies, we performed proof-of-concept studies investigating the therapeutic potential and mechanism of action of monoclonal antibody (mAb)-based therapy against CD73. We found that anti-CD73 mAb therapy could significantly delay primary mammary tumour growth in immune competent mice. Furthermore, we observed that anti-CD73 mAb therapy significantly reduced the number of lung metastases. The anticancer activity of anti-CD73 mAb therapy against primary tumours was essentially dependent on the induction of adaptive anti-tumour immune responses. Knockdown of CD73 in 4T1.2 tumour cells confirmed the immunosuppressive effect of CD73. However, anti-metastatic activity was observed in both immune competent and immunodeficient mice. Using selective adenosine receptor antagonists, we demonstrated that activation of A2B adenosine receptors promoted 4T1.2 tumour cells chemotaxis.

In conclusion, our study identified tumour-derived CD73 as a novel mechanism of tumour immune escape and tumour metastasis, and established the proof-of-concept for therapeutically targeting CD73.

Reference: Stagg J, Divisekera U, McLaughlin N, et al. Anti-CD73 antibody therapy inhibits breast tumour growth and metastasis. Proc. Natl. Acad. Sci. USA 107:1547–1552, 2010.

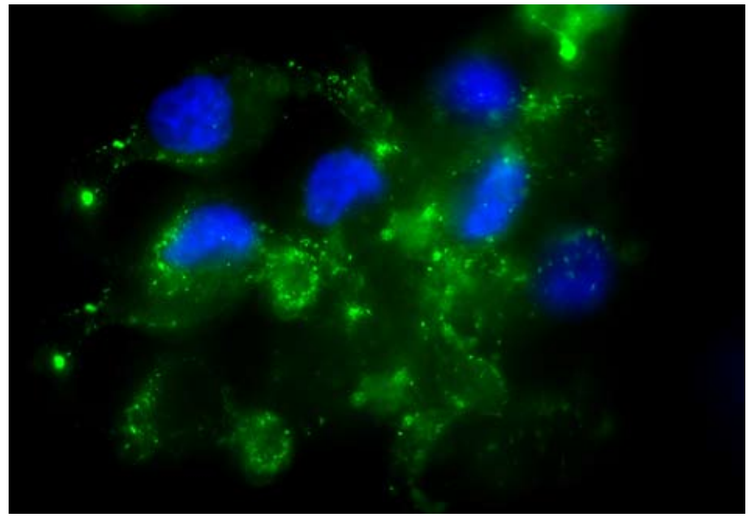


Figure 1: In our study, we identified CD73 expression on tumour cells as an important mechanism of tumour immune evasion. The image represents CD73 expression (in green) detected by immunofluorescence microscopy on MDA-MB-231 human breast cancer cells.

1.1.3 Immune Signalling laboratory

Research leader: Dr Sarah Russell,
ARC Future Fellow

Health depends upon each cell in our body conforming appropriately to its prescribed fate—dying, proliferating or altering its characteristics to remain in an appropriate ratio to all other cells. Cancer occurs when cells ignore the signals that usually control fate, and to combat cancer we need to understand exactly how these signals work. We have recently found that asymmetric cell division, in which the two daughters of a dividing cell inherit different properties from their parent cell, controls the fate of blood cells.

RESEARCH FOCUS

- Map lineage pedigrees of developing hematopoietic cells to elucidate how fates such as death, proliferation and differentiation affect immune cell development and are altered in leukemia.
- Determine how asymmetric cell division determines the fate of blood cells.
- Determine whether alterations in asymmetric cell division lead to or alter leukemia.
- Determine how asymmetric division of blood cells is regulated, and develop means to disrupt or promote asymmetric cell division.

KEY 2010 RESEARCH ACHIEVEMENT

From chaos to order: new approaches to quantifying the behaviour of rapidly moving blood cells

The most effective way to study cell fate decisions and their influence on development and cancer is by a technique called lineage tracing, in which the daughters, granddaughters and subsequent generations of a cell are tracked, processes such as cell division, death and differentiation are monitored for each cell, and lineage pedigrees assemble. The power of this approach is perhaps best illustrated by lineage tracing in the model organism, c. elegans, which led to an explosion of knowledge, much of which has impact in the clinic.

These studies rely on time lapse microscopy to 'watch' the behaviour of cells over time, and similar studies have not previously been possible in blood cells due to technical difficulties related to the dynamic behaviour of blood cells. We have recently made some key technical breakthroughs that now enable us to perform such lineage tracing. These breakthroughs come from our interactions with physicists and engineers in our sister laboratory (also run by Dr Sarah Russell) at Swinburne University. Firstly, we manufacture 'cell paddocks' which contain the blood cells in the field of view—these paddocks allow long term imaging of hematopoietic stem cells, developing and mature immune cells, and leukemic cells. Secondly, we have developed systems for fluorescent tagging of the cells, and of proteins within the cells, which enable us to monitor cellular and molecular behaviours. Thirdly, we have developed custom software which not only automatically tracks and quantifies these behaviours, but can assemble the data in the form of pedigree trees.

Together these tools provide an extremely powerful new way of studying how fate decisions are managed in blood cells, and we hope that our findings with this approach will provide a new platform of knowledge form which to determine how cancers arise, and how they can be treated.

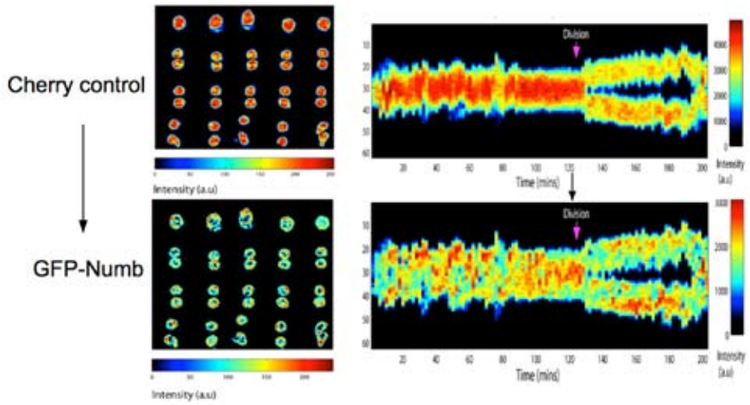
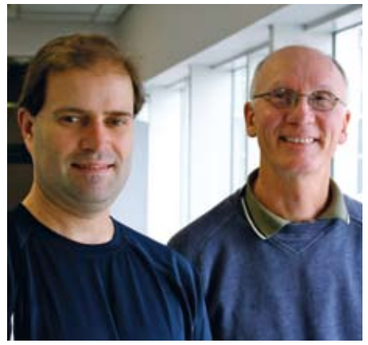


Figure 1: Tracking divisions during T cell development. We have established new software methods with which to track migrating cells and quantify aspects of their behaviour, fluorescence, orientation and morphology. In this instance, we identify cells at the time of division, and automatically create a montage of time lapse images of the cells (left panels) in which the orientation is fixed *in silico* against an axis that we define. From these images, numerous attributes can be quantified and plotted over time, such as the summed fluorescence along the axis of division as shown in the right panels. In this instance, Kim Pham and Raz Shimoni have analysed the polarity of a fate determinant called Numb in dividing thymocytes.

1.1.4 Immunotherapy laboratory



Research leaders: Dr Phillip Darcy, NHMRC CDA Research Fellow and Assoc. Prof. Michael Kershaw, NHMRC Senior Research Fellow

The Immunotherapy laboratory focuses on pre-clinical development of novel immune therapies for cancer with the aim of translating the most effective treatments into the clinic.

RESEARCH FOCUS

- Anti-cancer gene design.
- Testing of various gene-modified immune system cells to eradicate cancer in pre-clinical animal models.
- Development of novel combination therapies against cancer.
- Translation of basic research discoveries into clinical practice.
- Molecular construction of genes for enabling T cells to recognise and respond against cancer cells.
- Use of Toll-like receptor agonists and immune agonist antibodies for cancer therapy in mice.

KEY 2010 RESEARCH ACHIEVEMENT

Genetically modifying white blood cells to destroy cancer

Adoptive immunotherapy is a very promising approach to cancer therapy. This form of therapy involves taking a sample of blood from patients, activating T cells from this blood in the laboratory and growing them to large numbers before injecting them back into the patient. This form of therapy has been used very effectively in clinical trials to induce tumour regression in patients with melanoma and those with some lymphomas. To make this form of therapy suitable for other types of cancer, like breast cancer, we have genetically modified T cells to express a receptor on their surface that enables recognition and response against tumour cells.

Using gene-modified T cells we have shown in the past that this form of therapy can cause regression of some cancers in mice. However, our previous therapies were performed in immunodeficient mice that lack expression of tumour antigens on normal tissues of the body. This is not the case in patients, with tumour antigens being expressed on some normal tissues including vital organs. Therefore, it has been difficult to gauge the safety of the adoptive T cell approach in mice up to now.

Recently, we have used transgenic mice that express a human tumour antigen, called Her-2, on some of their normal tissues including breast and brain. We have generated mouse cancers expressing human Her-2 and used these in mice along with adoptive transfer of gene-modified T cells, to see if we can cause regression of established cancer safely without causing damage to normal breast and brain.

Using this approach in this new strain of mouse, we have demonstrated that established cancer metastases in the lungs of mice can be eradicated using T cells. This effect was achieved in the absence of damage to normal tissues.

Reference: Wang LX, Westwood JA, Moeller M, et al. Tumour ablation by gene-modified T cells in the absence of autoimmunity. Cancer Res. 70:9591–8, 2010.

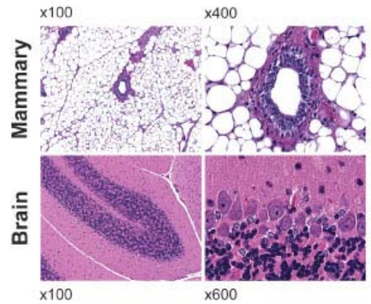


Figure 1: Adoptive transfer of gene-modified T cells into tumour-bearing mice does not cause damage to normal breast and brain tissue. Top: Microscopic views of breast tissue from mice that received gene-modified T cells for cancer treatment. Bottom: Brain tissues appear normal with no evidence of destruction by T cells.

1.1.5 Haematology Immunology Translational Research Laboratory

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

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 adapting novel therapeutics to the human system and moving it into phase 1 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 of 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.

KEY 2010 RESEARCH ACHIEVEMENT

Myeloma immunogenic death

This is an ongoing project examining whether a rational combination of novel therapies can induce both myeloma cell death and simultaneously promote an endogenous immune response to myeloma.

Evidence to date indicates that tumour cells can display signature molecules on apoptotic bodies or release them from necrotic cells; these molecules incite dendritic cell (DC) maturation. DC maturation, following endocytosis of tumour cell apoptotic bodies, leads to display of tumour-derived peptides to antigen-specific T cell and induction of the endogenous response. However, data to date also indicate many drugs used for conventional therapy of myeloma are toxic to the immune system (e.g. Dexamethasone), making the induction of a myeloma-specific immune response impossible.

We are using combination therapy with a dose of the proteasome inhibitor (bortezomib), that does not inhibit dendritic cell (or other immune system cells) function, with a TRAIL-R1 agonistic antibody (Mapatumumab). This novel combination therapy, termed low dose bortezomib-Mapa (or LTB-Mapa), induced apoptosis of myeloma cells. We demonstrated (by live video microscopy and flow cytometry) that LTB-Mapa-treated myeloma cells form apoptotic bodies which are rapidly endocytosed by autologous immature DCs (iDCs). Interestingly, these myeloma cell apoptotic bodies inhibit iDC maturation, either constitutive iDC maturation or that induced by the TLR4 ligand lipopolysaccharide (LPS).

Subsequent studies examined the potential for induction of myeloma-specific T cell responses to LTB-Mapa induced myeloma cell apoptosis. Thus, there was no increase in myeloma-specific T cells when autologous DCs pulsed with LTB-Mapa killed myeloma cells were used to prime T cells. This is likely due to suppression of iDC maturation by myeloma-derived cytokines (e.g. VEGF, IL-6 and IL-10), a topic for ongoing investigation. Nonetheless, there was a significant increase in induction of myeloma-specific T cells when the DC endocytosis of myeloma apoptotic bodies occurred in the presence of LTB-Mapa. Subsequent studies are now examining the mechanism whereby this could occur.

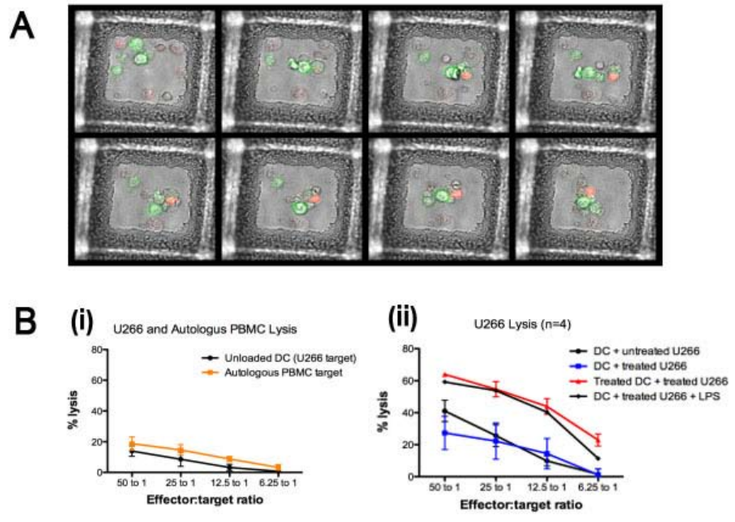


Figure 1: Combination LTB-Mapa therapy induces myeloma immunogenic death. (A) Immature monocyte-derived dendritic cells (CD11c, green) rapidly phagocytose apoptotic U266 cells (pre-treated with 1nM bortezomib and 0.12mg Mapa). pHrodo-labelled U266 cells fluoresce bright red when they pass into endosomes of pH≤5. (B) U266 myeloma-pulsed iDCs induce increased numbers of myeloma-specific CD8+ T cells and NK cells compared to controls (i) when combination LTB-Mapa was present at the priming phase of the CTL culture (ii).

Cancer Immunology program – personnel

CANCER CELL DEATH LABORATORY

Head
Prof. Joseph A. Trapani

Peter Mac Fellow
Dr Ilia Voskoboinik

Senior Research Officer
Dr Vivien Sutton

Research Officers
Dr Daniella Brasachio
Dr Amelia Brennan
Dr Magdalena Hagn
Dr Jamie Lopez

Research Assistants
Kylie Browne
Annette Ciccone
Susie Roczo
Kevin Thia
Sandra Vershoor

Postgraduate Students
Desiree Anthony
Jenny Chia
Olivia Susanto

Advanced Medical Science (AMS) Student
Wei Zhen Yeh (2009–10)

Executive Assistant to Professor Joseph Trapani
Diana Motion

CELLULAR IMMUNITY LABORATORY

Head
Prof. Mark Smyth

Research Officers
Dr Daniel Andrews
Dr Nikola Baschuk
Dr Nicole Haynes
Dr Stephen Mattarollo
Dr Christophe Paget
Dr John Stagg
Dr Trina Stewart
Dr Michele Woei Ling Teng

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Dr Michael Dickinson
Saar Gill

Advanced Medical Science (AMS) Student
Reece Cordy (2009–10)
Joanna Loh (2010–11)

CANCER IMMUNOLOGY PROGRAM

Administrative Assistant
Belinda Kelly

Laboratory Manager
Jason Brady

As an academic clinician, Alex heads Peter Mac’s Gastroenterology Service. As a researcher, Alex and his team in the Cancer Genetics and Genomics laboratory investigate upper gastrointestinal cancer — particularly Barrett’s Oesophagus, oesophageal adenocarcinoma, gastric intestinal metaplasia and gastric cancer — through research encompassing a number of disciplines and collaboration with partners in Japan, Singapore, South Korea and the UK.

Alex is committed to translational research that aims to realise clinical benefits for patients at-risk-of or diagnosed with gastrointestinal cancer.

‘As a clinician, compassion and caring for patients are guiding principles; as a scientist, knowledge and scholarship are my goals. Together, these principles guide me at Peter Mac.’

1.2 Cancer Genomics program

Using sophisticated highthroughput genomic technologies to improve our understanding of cancer

The Cancer Genomics program seeks to use sophisticated high throughput genomic technologies to improve our understanding of the biology of cancer and to advance the clinical management of cancer patients, through the development of individualised approaches to treatment.

Research in the program focuses primarily on breast, upper gastrointestinal, prostate, ovarian, and sarcoma cancer types, and involves some of the largest familial and population-based cancer cohorts in the world.

These studies address questions of general importance to solid cancers such as genome-wide genetic and epigenetic changes during tumourigenesis; as well as more specific questions including inherited susceptibility to cancer, prediction of response to therapy, gene status linked to treatment and survival, the use of molecular profiling for accurate cancer diagnosis, and screening surveillance to improve detection and clinical management.

The program includes internationally recognised, large-scale national molecular and epidemiological studies into breast, ovarian and sarcoma cancer, notably in the research conducted by the Australian Ovarian Cancer Study, kConFab familial breast cancer consortium and the International Sarcoma Kindred Study, and in key collaborations with national and international researchers.

Cancer Genetics and Genomics laboratory
Prof. David Bowtell

Sarcoma Genomics and Genetics laboratory
Assoc. Prof. David Thomas

Surgical Oncology laboratory
Assoc. Prof. Wayne Phillips

VBCRC Cancer Genetics laboratory
Prof. Ian Campbell

kConFab
Ms Heather Thorne

1.2.1 Cancer Genetics and Genomics laboratory

Research Leader: Prof. David Bowtell

Our laboratory focuses on the molecular characterisation of ovarian and gastric cancer, cancers of unknown primary, and on understanding the role of the Siah E3 ligases in angiogenesis and cancer progression.

RESEARCH FOCUS

- Genomic characterisation of human ovarian and gastric cancer.
- Coordination of the Australian Ovarian Cancer Study cohort.
- Development of a molecular diagnostic for cancers of unknown primary.
- Biochemical and functional characterisation of Siah E3 ligases in cancer models.
- Development of novel small molecules targeted to the Siah proteins.

KEY 2010 RESEARCH ACHIEVEMENT

Amplification of cyclin E1 drives treatment failure in women with serous ovarian cancer

Surgery followed by a combination of carboplatin and taxol form the mainstay of treatment for women with ovarian cancer. About 70 per cent of those with the most common histotype, high grade serous cancers, have a durable response to chemotherapy. However, the tumours of a significant fraction of women are resistant to primary treatment, with a rapid return to growth soon after the end of chemotherapy. Previously we demonstrated that amplification of the 19q12 chromosomal locus is the most important chromosomal copy number change associated with primary treatment failure. In our latest work, we have shown that CCNE1, which encodes CyclinE1, is a driver oncogene within the 19q12 locus. Knockdown of CCNE1 results in cell cycle arrest and attenuation of clonogenic survival specifically in cells with amplification of 19q12, demonstrating an oncogene addiction of these tumour cells. CyclinE1 interacts with cell cycle kinases, including Cdx2, providing a therapeutic approach to inactivating the protein complex using small molecule inhibitors of kinase function. Approximately 20 per cent of high grade serous cancers have amplification of the 19q12 locus.

CCNE1 gain is present in cells prior to chemotherapy, so it must provide a selective advantage to their growth, independent of treatment. To better understand how CCNE1 amplification interacts with other mutations, we mapped chromosomal aberrations that correlated with 19q12 gain. Amplification of 20q11, involving the cell cycle protein TPX2, was highly correlated with CCNE1 gain, suggesting that genes in the 20q11 locus form part of a mutational network that controls the growth of this poor prognosis tumour.

Our studies with CCNE1 are typical of much of the current work in our laboratory where we aim to develop useful diagnostic and therapeutic approaches, but also seek to understand the molecular wiring and biological processes that drive the growth of tumour cells.

Reference: Etemadmoghadam D, George J, Cowin P, et al. Amplicon-dependent CCNE1 expression is critical for clonogenic survival after cisplatin treatment and is correlated with 20q11 gain in ovarian cancer. PLoS One 5, e15498, 2010.

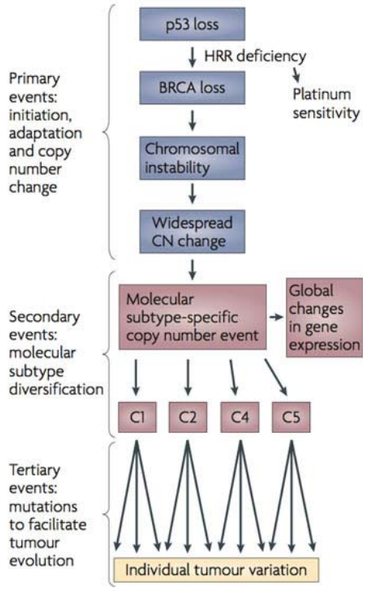

Figure 1: Model outlining the stages of the initiation and progression of high-grade serious ovarian cancer. Our recent genomic studies in ovarian cancer have led us to a model of the molecular evolution of high grade serous cancers, initiated by p53 loss and BRCA loss, deficiency in homologous recombination repair (HRR), chromosomal instability and widespread copy number (CN) change (Bowtell, 2010, Nature Reviews Cancer 10, 803-08).

1.2.2 Sarcoma Genomics and Genetics laboratory

Research Leader: Assoc. Prof. David Thomas, VCA Clinical Researcher Fellow

The Sarcoma Genomics and Genetics laboratory undertakes translational research into the inherited and somatic genetic causes of sarcoma. Our research program is founded on the Australasian Sarcoma Study Group (ASSG), a national cooperative research group which acts as a conduit for early phase clinical research arising from basic discoveries. We have a broad interest in cancers that affect adolescents and young adults.

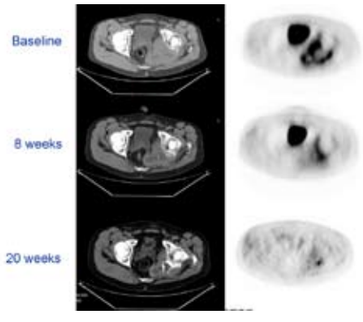

Figure 1: Positron emission tomographic images demonstrating metabolic response to denosumab treatment of a patient with recurrent i schial Giant Cell Tumour of bone.

RESEARCH FOCUS

- Germline and somatic genetics of sarcomas, focusing on osteosarcoma and liposarcoma.
- Animal models of osteosarcoma and liposarcoma.
- Translational and clinical research in sarcoma.
- Research into adolescent and young adult cancers.

KEY 2010 RESEARCH ACHIEVEMENTS

The highlight of the year was the final publication of the results of a phase 2 study using denosumab in patients with unresectable giant cell tumour of bone *(Lancet Oncology)*. This study established a new paradigm for treatment for such patients, and has generated considerable interest from the clinical community caring for patients with sarcomas. The overall response rate on this study was an astonishing 86 per cent, with clinical benefit commonly reported. The eventual role of denosumab in sarcomas remains an active subject for research.

The International Sarcoma Kindred Study, led by Dr Mandy Ballinger, has begun to generate research outcomes. Over 300 families have now been enrolled onto this study across five national centres, with recruitment well exceeding projected rates. International involvement has extended to India, France, Italy, USA and the UK. Initial data suggest a strong heritable component to sarcoma, and an unexpectedly high incidence of what appear to be de novo mutations in the tumour suppressor, TP53. We have also begun to undertake deep sequencing of unexplained high risk families, in order to identify the causal mutation.

We have almost completed a definitive study of the molecular structure of a key molecular feature of liposarcomas—neochromosomes. These studies have been led by Mr Dale Garsed in collaboration with Dr Tony Papenfuss at WEHI. Neochromosomes are supernumerary or marker chromosomes observed in more than 80% of well-differentiated liposarcomas, however their structure and oncogenic properties are not fully understood. We used next-generation sequencing of neochromosomes and their derived transcriptome to comprehensively map molecular variations associated with well-differentiated liposarcoma.

We have a long-standing interest in the molecule Wnt inhibitory factor-1 (WIF1) as a tumour suppressor in osteosarcoma. In studies performed by Dr Maya Kansara, ecombinant WIF1 protein suppresses tumour growth in a mouse model of osteosarcoma. We are investigating the mechanism by which this occurs to determine the clinical potential of this molecule.

To investigate the role of the immune system in the development of osteosarcoma we are undertaking a systematic screen using a radiation model (45Ca) of osteosarcoma and knockout-mice deficient in immune cells or cytokines to investigate the role of these molecules in osteosarcoma development and progression. These studies are giving insights into potential immunomodulatory targets for the treatment of osteosarcoma.

Recent work in the laboratory includes development of a syngeneic mouse model of osteosarcoma using cell lines derived from our radiaocarcinogen model. The tumours that arise from these cell lines are currently being characterised. This mouse model will form an invaluable tool for investigation of potential therapeutics in osteosarcoma as well as understanding the development and progression of this disease.

Reference: Thomas DM, Henshaw R, Skubitz K, et al. Denosumab in subjects with giant cell tumour of bone: results from a phase 2 study. Lancet Oncology, 11:275-80, 2010.

1.2.3 Surgical Oncology laboratory

Research Leader: Assoc. Prof. Wayne Phillips

The Surgical Oncology laboratory uses molecular and cellular approaches to understand the development and progression of gastrointestinal cancers and to identify new treatments.

RESEARCH FOCUS

- PI3-kinase signalling pathway.
- Links between Barrett's Oesophagus and the onset of oesophageal adenocarcinoma.

KEY 2010 RESEARCH ACHIEVEMENT

The role of *PIK3CA* mutations in tumour development

Mutations in the PI3K gene, *PIK3CA*, are found at high frequency in many human cancers, particularly colorectal and breast tumours. *PIK3CA* mutations are common in many human tumours including breast cancer.

Our laboratory has developed a novel mouse model in which we can target expression of the common *PIK3CA* mutation *PIK3CA^{H1047R}* to specific tissues. The mutant protein is expressed only at normal levels and only in cells that normally express *PIK3CA*, thus replicating the physiological scenario of a spontaneous mutation occurring in the endogenous *PIK3CA* gene. By targeting the *PIK3CA^{H1047R}* mutation to the mammary gland of the mouse we have demonstrated enhanced proliferation of epithelial cells lining the mammary ducts and increased ductal branching during mammary gland development. These mice do eventually get mammary cancers but not for over 12 months. This long latency period suggests that *PIK3CA* mutation alone is not sufficient to induce tumourigenesis and that a 'second hit' (an additional mutation) in another gene is likely to be required for tumour development.

Our studies are now focussing on identifying these secondary events that cooperate with *PIK3CA* mutations to induce progression to cancer in the mammary gland. We are also extending our studies to other cancer types by using this model to target the *PIK3CA^{H1047R}* mutation to other tissues. In addition, our model will be a valuable tool for the pre-clinical testing of new anti-cancer therapies that target the PI3K pathway.

Reference: Loi SB, Haibe-Kains F, Lallemand V, et al. PIK3CA mutations associated with gene signature of low mTORC1 signalling and better outcomes in estrogen receptor positive breast cancer. PNAS, 107: 10208-13, 2010.

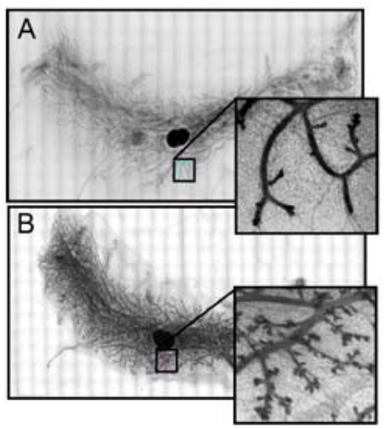

Figure 1: Whole mounts of the developing mammary gland from (A) wild type and (B) *PIK3CA* mutant mice at 12 weeks of age showing the increased ductal branching induced by expression of the *PIK3CA^{H1047R}* mutation.

1.2.4 VBCRC Cancer Genetics laboratory

Research leader: Prof. Ian Campbell, NHMRC Senior Principal Research Fellow

The major focus of the Victorian Breast Cancer Research Consortium (VBCRC) Cancer Genetics laboratory is the identification of genes involved in the predisposition, initiation and progression of breast and ovarian cancer.

RESEARCH FOCUS

- Identification of genes involved in breast cancer predisposition through next generation sequencing.
- Genome-wide genome copy number analysis of breast ductal carcinoma *in situ* identify markers of disease progression.
- Next generation sequencing and function screens to identify driver genes of ovarian tumourigenesis.
- Integrated genomic analysis to identify genes involved in breast and ovarian carcinogenesis.

KEY 2010 RESEARCH ACHIEVEMENT

The building of a major cohort to investigate issues in breast cancer epidemiology and biology

The VBCRC Cancer Genetics laboratory uses an integrative genomics approach to investigate genes involved in breast and ovarian cancer, whereby data from several genome-wide array-based platforms are combined to more rapidly define the critical cancer-causing genes. A key focus of the laboratory is familial breast cancer, where the majority of familial risk is yet to be attributed to genetic variants. We are continuing to apply next generation sequencing to identify these genes. The ability to identify disease-causing mutations in high-risk breast cancer families has broad implications for those affected, in terms of risk assessment and management, as well as treatment.

A major new initiative during 2010 has been the establishment of Lifepool cohort. Headed by Ian Campbell, Lifepool is a collaboration between Peter Mac, BreastScreen Victoria, University of Melbourne School of Population Health and The Royal Melbourne Hospital.

lifepool
Australian women finding answers

This unique cohort will recruit 100,000 Victorian women and support a range of research into breast cancer and other important women's health issues. Eventually it is anticipated that Lifepool will expand to include recruitment through BreastScreen services in other states. This long-term cohort study will integrate clinical follow-up, epidemiological information and molecular profiling of breast tumours detected through BreastScreen.

Lifepool will perform nested case-control studies on patients diagnosed with breast cancer to better understand how factors such as mammographic density, genetics and gene expression is associated with breast cancer risk and behaviour. By combining the information provided by such a large group of women, Lifepool will support a range of studies on prevention, screening and treatments aimed at reducing the impact of breast cancer. Lifepool has been made possible through a $5m grant from the National Breast Cancer Foundation Collaborative Grant scheme for Breast Cancer Research, and in partnership with Cancer Australia.

1.2.5 kConFab

Research Manager: Heather Thorne

The Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer (kConFab) brings together geneticists, clinicians, surgeons, genetic counsellors, psychosocial researchers, pathologists and epidemiologists from all over Australia and New Zealand. They believe the causes and consequences of familial predisposition to breast and ovarian cancer can be understood only by a national effort at both the basic and clinical levels.

RESEARCH FOCUS

- Germline screening for the known genes such as BRCA1, BRCA2, ATM, CHEK2, PALB2 implicated in the causation of breast and ovarian cancer, and a gene discovery search for new cancer susceptibility genes.
- Development of predictive risk models to determine which mutation carriers are at risk of developing breast or ovarian cancer and at what age.
- Use of fresh normal and tumour tissue collections for the isolation and identification of stem cells that may be involved in cancer development.
- Delivery of clinically significant research mutation test results back to the clinic and family.
- Translation of basic research discoveries into clinical practice, such as new targeted therapies like the PARPi inhibitors.
- Development of a resource to promote collaborative basic, translational and clinical research into familial breast, ovarian, prostate and pancreatic cancer.

KEY 2010 RESEARCH ACHIEVEMENTS

The unique kConFab biospecimen and data resource has become of increasing value to Australian and international breast, ovarian and prostate cancer researchers alike, as seen from the number of approved projects using this resource and from its contribution to the number of high profile publications. In addition to facilitating basic and clinical research, kConFab has been instrumental in networking with the Familial Cancer Centres around the country to recruit high-risk multiple breast, ovarian and prostate cancer families for research, and has played a key role in translating its research findings to ensure high quality, standardised clinical care throughout Australia. This has been achieved by the organisation of annual scientific meetings that provide the Family Cancer Clinics with a unique opportunity to meet and optimise clinical practice, enabling the identification of individuals and families who carry pathogenic breast, ovarian and prostate cancer predisposing mutations (genetic faults) and rapidly translating research findings made by kConFab into clinical practice.

In recent times kConFab played an increasing role in clinical trial activity. Examples of this activity include the IMPACT study, which is determining the utility of prostate cancer screening and new biomarker discovery amongst men from mutation positive families, assisting with a carboplatin chemotherapy trial for BRCA1 *and* BRCA2 mutation carriers, and more recently PARP inhibitor studies.

Researchers and clinicians using the kConFab biospecimen and data resource have contributed to a large number of prominent national and international studies in the past 12 months, including:

- The first large Genome-Wide Association Studies (GWAS – published in *Nature Genetics*) to identify risk modifier SNPs in breast cancer.
- Identifying novel moderate — to high-risk breast cancer predisposing genes that are likely to be incorporated into clinical practice over the next few years, using next generation sequencing technology
- A stem cell breast cancer research program has gained international recognition through kConFab's supply of prophylactic mastectomy specimens and tumours that led to the discovery of an intrinsic defect in luminal progenitor cells, which appear to be the target cell that gives risk to *BRCA1*-associated breast cancer (*Nature Medicine*, 2009).

Reference: Antoniou AC, Wing X, Frederickson ZS, et al. A genome-wide association study identifies a 19p13 locus that modifies the risk of breast cancer in BRCA1 mutation carriers and is associated with hormone receptor-negative breast cancer in the general population. Nature Genetics, 42: 885–892, 2010.

Cancer Genomics program – personnel

CANCER GENETICS AND GENOMICS LABORATORY

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Dr Prue Cowin
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Executive Assistant to Prof. David Bowtell
Linda Stevens

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Dale Garsed
Sophie Young

VCA Translational Research in Sarcoma Project

Project Officer
Anna Tarasova

International Sarcoma Kindred Study

Project Manager
Mandy Ballinger

Research Administrator
Faina Zlatsin

Research Assistant
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Australasian Sarcoma Study Group

Executive Officer
Dr Sally Whyte

Project Officer
Sophie Gatenby (to Aug)
Charelle Byrne (from Sept)

SURGICAL ONCOLOGY LABORATORY

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VBCRC CANCER GENETICS LABORATORY

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Sally Davis
Clint Johnson
Joyce Lin
Wen Qiu
Manasa Ramakrishna
Georgie Ryland

kCONFAB

Research Manager
Heather Thorne

Executive Director
Prof. Joe Sambrook (to July)
Prof. Stephen Fox (from August)

Research Assistants
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Lana Djandjgava
Dragana Prodanovic
Danni Surace
Kylie Scott
Johanna Stoeckert
Dr Amber Willems
Lynda Williams

Data Manager
Eveline Niedermier

1.3 Growth Control and Differentiation program

Amee George is a postdoctoral research fellow at the University of Queensland currently working on a collaborative project in the Growth Control laboratory at Peter Mac. Her research focuses on understanding the mechanisms by which G protein-coupled receptors (GPCRs) hijack other growth factor receptor signalling pathways. By piecing together the highly complex signalling networks involved in this process, Amee hopes to better understand the subsequent implications for cellular growth and malignant transformation.

1.3 Growth Control and Differentiation program

Understanding protein chemistry, signal transduction, cell biology and how these processes affect differentiation and cancer cell growth

The Growth Control and Differentiation program brings together three groups with extensive and complementary expertise in areas ranging from proteomics and protein chemistry, through signal transduction and cell biology to the regulation of gene transcription and protein translation.

A major focus of our work is in understanding the mechanisms of regulation of ribosome biogenesis, and protein translation, and how these processes impact on differentiation and are corrupted in tumour cells. This is a critical area of cancer research as accelerated cell growth and increased protein synthesis due to increased levels of functional ribosomes are major features of tumour formation and progression. Conversely, cellular differentiation is associated with reductions in these processes and often antagonises carcinogenesis. A number of current projects employ state-of-the-art biochemistry, molecular and cell biology to characterise the basis of the regulation of these fundamental processes.

The program has recently made ground-breaking discoveries linking signalling via the key PI3K/AKT/mTOR and c-MYC growth control pathways to the regulation of ribosome synthesis and function. We aim to use this knowledge to develop novel therapeutic approaches that target differentiation, cell cycle and cell growth. In addition, together with the Cancer Therapeutics program (pg 62), we have established models of a range of tumours including ovarian and prostate cancer and lymphoma. These systems are being used to investigate novel applications of targeted therapeutics and the program is ideally poised to translate discoveries on fundamental aspects of cancer growth control into the clinic. In particular, we have developed a completely new strategy for the treatment of cancer based on disruption of RNA Polymerase I (Pol I) and we have collaborated with Cylene Pharmaceuticals to develop the world's first small molecule selective inhibitor of Pol I transcription CX-5461. We plan to begin the first-in-human trials with this drug at Peter Mac in cancer patients in 2012.

This work represents a major scientific advance and paradigm shift in our understanding of one of the most fundamental and universally conserved cellular functions, ribosome biogenesis. We predict it will have major impact on the fields of cell biology and cancer.

Growth Control laboratory
Assoc. Prof. Ross Hannan

Molecular Oncology laboratory
Assoc. Prof. Grant McArthur

Protein Chemistry laboratory
Assoc. Prof. Rick Pearson

1.3.1 Growth Control laboratory

Research Leader: Assoc. Prof. Ross Hannan, NHMRC Senior Research Fellowship

The focus of the Growth Control laboratory is to understand the molecular basis of the regulation of the ribosomal gene transcription by RNA Polymerase I, and how dysregulation of this process contributes to the process of malignant transformation.

RESEARCH FOCUS

- Epigenetic mechanisms regulating ribosomal gene transcription by RNA Polymerase I.
- Basic mechanisms underlying cell growth control.
- Dysregulation of ribosome biogenesis during cancer.
- Functional screens for novel tumour suppressors in breast cancer.

KEY 2010 RESEARCH ACHIEVEMENT

Is dysregulation of ribosome biogenesis a necessary step in malignant transformation?

The MYC-family of oncogenes plays a prominent role in cancer and has been implicated in the regulation of ribosome assembly and function. We were the first to demonstrate that c-MYC can regulate transcription of the ribosomal RNA genes (rDNA) by RNA Polymerase I (Pol I) through upregulation of the essential Pol I transcription factor UBF.

Interestingly, upregulation of rDNA transcription is a frequent event during malignant transformation, leading us to propose the provocative hypothesis that the oncogenic potential of MYC is directly related to its ability to modulate rDNA gene transcription. We have tested this hypothesis in a transgenic model of B-cell lymphoma (Eμ-MYC) in which the malignancy is dependent on overexpression of c-MYC. This model is associated with a robust upregulation of rDNA transcription and increased expression of the rDNA transcription factors UBF and Rrn3.

vRNA interference mediated knockdown of UBF or Rrn3 expression in Eμ-MYC lymphoma cells reduced rDNA transcription to the level in wild type B-cells. This resulted in a proliferative disadvantage of the lymphoma cells, both due to rapid cell death. To establish whether this heightened dependence on rDNA transcription could be exploited as a therapeutic target for c-MYC driven cancer, we collaborated with Cylene Pharmaceuticals to test a 'first in class' small molecule inhibitor of Pol I (CX-5461) in this model. Treatment of the animals with CX-5461 delayed sacrifice due to disease of transplanted Eμ-MYC tumours, which was accompanied by a period of complete remission with no identifiable tumour cells in the peripheral blood. Importantly, death of malignant B-cells in response Pol I inhibition occurred rapidly via apoptosis and was not due to ribosome insufficiency.

These data provide the first evidence that dysregulation of rDNA transcription is required for MYC driven cancer and is a therapeutic target for treatment of malignancy. Ongoing studies are exploring the molecular mechanisms responsible for the selective therapeutic effectiveness of inhibiting Pol I transcription in Eμ-MYC lymphomas.

References: Sanij E, et al. UBF levels determine the number of active ribosomal RNA genes in mammals. J Cell Biol. Dec 29;183(7):1259–74, 2008.

Sanij E, Hannan RD. The role of UBF in regulating the structure and dynamics of transcriptionally active rDNA chromatin. Epigenetics. Aug;4(6): 374–82, 2009.

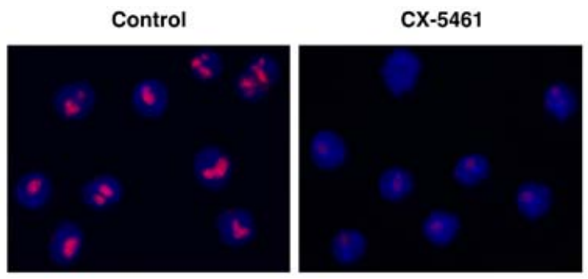

Figure 1: Fluorescent *in situ* hybridisation (FISH) analysis of ribosomal RNA (red) in Eμ-MYC lymphoma cells. rRNA synthesis is significantly reduced after 1hr treatment with 100μM CX-5461. Nuclei were visualised by DAPI (blue).

1.3.2 Molecular Oncology laboratory

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

The Molecular Oncology laboratory investigates new targets for cancer treatment that control cell growth, division and differentiation.

RESEARCH FOCUS

- The interaction between the MYC oncogene and the PI3K pathway in regulating cancer progression and maintenance.
- Fundamental mechanisms of regulation of cell growth by MYC.
- Targeting of CHK1 kinase for cancer treatment.
- Targeting of BRAF Kinase for cancer treatment.
- Targeting of retinoic acid receptors for the treatment of acute myeloid leukaemia (AML).

KEY 2010 RESEARCH ACHIEVEMENT

CHK inhibitor therapeutics display efficacy as single agents in MYC-driven lymphomas

CHK proteins function as effectors of cell cycle checkpoint arrest following DNA damage. Small molecule inhibitors of CHK proteins such as PF-0477736 are under clinical evaluation in combination with DNA damaging chemotherapeutic agents.

We examined the effects of CHK inhibitor treatment on lymphoma cells with inherent DNA damage due to MYC-driven replication stress. Eμ-myc murine lymphoma cells showed a dramatic increase in the extent of DNA damage within an hour of treatment with PF-0477736. We observed extensive caspase-dependent apoptosis and subsequent cell death *in vitro* and *in vivo*. Apoptotic cell death was preceded by accumulation of DNA damage and a DNA damage response (DDR). In all cases, the level of DNA damage following treatment was the most consistent indicator of sensitivity to various CHK inhibitors.

We propose that inhibitors of CHK can act in a synthetically lethal manner in cancers with replication stress as a result of these cancers being reliant on a CHK-mediated DDR for cell survival. Our results suggest that CHK inhibitors would be beneficial therapeutic agents in MYC-driven malignancies.

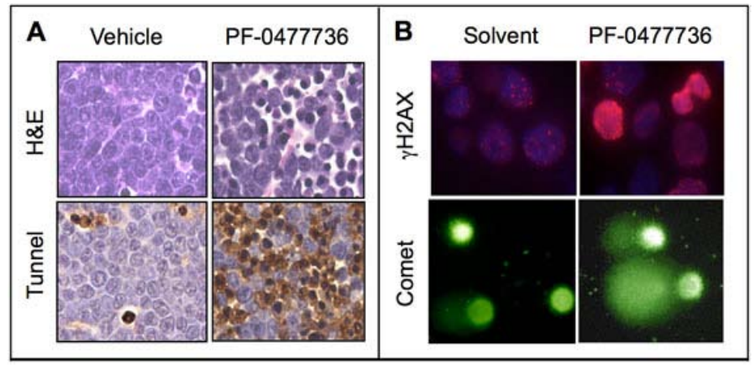

Figure 1: Eμ-myc lymphoma cells following PF-0477736 treatment. A: Lymphoma sections stained with H&E and the Tunnel assay showing CHK inhibitor induced apoptotic cell death. B: Stained lymphoma cells displaying CHK inhibitor induced DNA damage by γH2AX staining and the Comet assay.

1.3.3 Protein Chemistry laboratory

Research leader: Assoc. Prof. Rick Pearson, NHMRC Senior Research Fellow

The major focus of the Protein Chemistry laboratory is to understand the molecular basis of the regulation of the PI3K/Akt/mTOR/S6K signalling pathway, and to use this knowledge to address how deregulation of this process may contribute to cancer.

RESEARCH FOCUS

- Understanding of the signal transduction pathways underpinning cell growth control.
- Biochemical and cell biology analysis of the role of deregulated cell growth in cancer.
- Cell biology and genomic research into the pathogenesis of ovarian cancer.
- High throughput functional screens to identify novel genes important in breast and ovarian cancer.

KEY 2010 RESEARCH ACHIEVEMENT

The role of the P13K/AKT signalling in cancer

The importance of deregulation of mTOR/S6K signalling in cancer became clear when it was shown to be a major downstream mediator of signalling via the PI3K/AKT axis that is deregulated in a high proportion of human tumours. Indeed, small molecule PI3K and mTOR inhibitors are showing promise as anti-cancer agents in clinical trials. Thus, the second major theme of our research is to understand the mechanisms by which PI3K/AKT signalling contributes to cancer and to gauge the contribution made by the mTOR pathway and uncontrolled growth signalling.

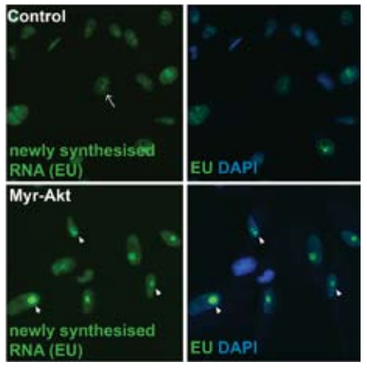

Figure 1: Akt increases rDNA transcription. (A) BJ-Tert cells labelled with EU, which incorporates into newly transcribed RNA, exhibit high EU signal in the nucleolus (arrow) marking the site of rDNA transcription. Nucleolar EU intensity is higher in Myr-Akt expressing cells compared to control cells reflecting enhanced rDNA transcription (arrowheads).

The Protein Chemistry laboratory and other groups have shown that this pathway is activated in over 65 per cent of ovarian cancers and our research aims to take a range of complimentary cell biology, biochemical and genomic approaches to characterise the role of activation of the pathway in tumorigenesis and to identify key pathways that also contribute to the development of ovarian cancer. It is hoped that these studies will provide a basis for generation of new therapeutics useful for second-line treatment of this cancer.

In 2010, we have used specific inhibition of AKT to show it is necessary for rDNA transcription independent of mTORC1 signalling. Furthermore, expression of constitutively active AKT revealed AKT is sufficient to drive ribosomal RNA synthesis, ribosome biogenesis and cell growth independent of growth factors. AKT cooperates with c-MYC to hyper-activate rRNA synthesis and ribosome biogenesis identifying the AKT/mTORC1/MYC network as a master controller of cell growth. Consistent with this concept, AKT activity is required for maximal activation of rRNA synthesis in MYC driven lymphoma cells. Importantly, AKT inhibition results in reduced rDNA transcription that is associated with reduced lymphoma cell viability and apoptotic cell death.

These data strongly implicate decreased ribosome biogenesis as a fundamental component of the therapeutic response to AKT inhibitors in malignant disease. This work was the subject of an invited oral presentation entitled 'AKT cooperates with c-MYC to control ribosome biogenesis and growth via mTORC1-dependent and independent pathways' by Assoc. Prof. Rick Pearson at the OzBio2010 conference in Melbourne in September 2010.

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Dr Elaine Sanij

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GROWTH CONTROL AND DIFFERENTIATION PROGRAM

Laboratory Manager
Katrina Wilson

1.4 Cancer Cell Biology program

Sue and Ygal Haupt were brought together by an interest in biological research. Research experience at the Weizmann Institute and the Hebrew University in Israel resulted in a milestone discovery delineating how the most important tumour suppressor p53 is controlled. Their recruitment to Peter Mac two years ago brought us their internationally recognised expertise to lead this field of research which has far reaching clinical implications, including the development of new approaches to anti-cancer therapy. Their relocation closes a personal circle in their family; Sue's father, Dr. John Moody, while working in India in the 1950s, was visited by his former pathology professor — Sir Peter MacCallum, and accepted his invitation to bring back to Australia his expertise in treating oral cancers.

1.4 Cancer Cell Biology program

Utilising multidisciplined approaches to explore the cross-talk between cancer and surrounding cells, factors influencing cell growth, differentiation, survival and senescence, with a strong focus on the genetic control of cancer spread

The Cancer Cell Biology program is the most diverse program of research at Peter Mac. The program spans developmental to tumour biology and connects investigators working with flies, mice and primary tissue from cancer patients.

The program focuses on the high incidence epithelial-derived tumours such as breast, prostate and colon. As tumours arise amid, and in communication with, surrounding normal cells and the extracellular matrix, attention to the stromal and immune environment is an important area of investigation. These non-tumour elements play a central role in promoting tumour growth and metastasis.

Epithelial cells demand tight, ordered connections with their neighbours and disruptions to these interactions affect cell polarity and these mark early events in the transformation process. Similarly, pathways that have been employed across evolution that control the size of organs also seem to be targeted early in tumourigenesis. Much interest in the properties normally attributed to stem cells such as self-renewal, impeded differentiation and extended proliferative capacity have captured the attention of cancer biology. Several program members have long standing interests in stem cell biology and accordingly have applied their laboratories to address these properties.

Recent advances in our ability to study the growth, proliferation and invasion of epithelial tumour cells have come from approaches that allow three dimensional cultures of mammary, intestinal and skin cells. These have provided new opportunity to examine cells from mice that have been genetically manipulated on a gene by gene basis or by introducing agents that interfere with endogenous gene function on a whole genomic scale.

Exploiting these insights will be central to how tumours can be effectively and selectively targeted as well as how normal tissue can be spared adverse and lasting damage. Agents that are aimed at addressing this direct clinical need are also being developed within the program. One of the most exciting developments that is impacting the Cancer Cell Biology program is the heightened interaction with clinical researchers across Peter Mac. Structured and informal meetings around tumour streams are now common place, opening opportunities for clinic investigators to spend more time in laboratories and for researchers to refocus their investigations within the program.

Cell Cycle and Cancer Genetics laboratory
Dr Patrick Humbert

Cell Cycle and Development laboratory
Assoc. Prof. Helena Richardson

Cell Growth and Proliferation laboratory
Dr Kieran Harvey

Differentiation and Transcription laboratory
Assoc. Prof. Rob Ramsay

Epithelial Stem Cell Biology laboratory
Dr Pritinder Kaur

Metastasis Research laboratory
Assoc. Prof. Robin Anderson

Molecular Radiation Biology laboratory
Assoc. Prof. Roger Martin

Tumour Suppression laboratory
Assoc. Prof. Ygal Haupt

Cell Polarity/Tissue Architecture Program
- Cell Cycle and Cancer Genetics (Dr Patrick Humbert)
- Cell Cycle and Development (Assoc. Prof. Helena Richardson)
- Immune Signalling (Dr Sarah Russell, see Cancer Immunology program pg 28)

1.4.1 Cell Cycle and Cancer Genetics laboratory

Research leader: Dr Patrick Humbert, NHMRC CDA Research Fellow

The Cell Cycle and Cancer Genetics laboratory investigates the fundamental role of tissue organisation and asymmetry on cancer progression, with the aim of identifying novel therapeutic strategies.

RESEARCH FOCUS

- Cell biology and genetic analysis of cell polarity protein function in 3D epithelial cell culture models.
- Generation and analysis of Genetically Engineered Mouse Models (GEMMs) to investigate the role of polarity proteins in cancer progression and organ development *in vivo*.
- Analysis of cell polarity proteins and gene alterations in human cancers.
- Large Scale RNAi functional screens to identify effectors of Scribble function.
- Collaborative analysis of tissue polarity in cancer and development with the Russell and Richardson laboratories.

KEY 2010 RESEARCH ACHIEVEMENT

An extensive cell polarity network suppresses the oncogenic functions of Ras through regulation of sustained MAPK signalling

Scribble is a core polarity regulator first identified in Drosophila and shown to have important roles in the regulation of tissue architecture and cell proliferation. In addition, Scribble loss cooperates with activated oncogenes Ras or Notch to give rise to invasive and metastatic tumours in Drosophila.

Our laboratory has recently shown that loss of the mammalian homologue of Scribble can similarly cooperate with activated H-Ras to drive invasion of mammary epithelial cells in 3D organotypic culture. Conversely, we also observe suppression of Ras-mediated cell transformation phenotypes through ectopic expression of Scribble, including loss of polarity, invasion in 3D culture and importantly, anchorage independent growth.

How Scribble regulates oncogenic Ras signalling is currently unknown. We have conducted an unbiased large-scale, functional genomics screen to identify the genetic requirements for Scribble to suppress Ras-driven cell transformation, combining RNAi technology with Next Generation Sequencing. We have screened approximately 20,000 shRNA constructs from the Open Biosystems human genome-wide miR30-based lentiviral shRNA library, utilising the well defined soft agar anchorage independent colony assay.

Through this approach, we have identified more than 100 candidate genes that were significantly enriched in our selected sample sets, identifying them as important regulators and effectors of Scribble's tumour suppressive functions in mammalian systems. We have subsequently performed both primary and secondary validation experiments for a number of key targets, confirming not only their requirement for the inhibition of Ras-driven oncogenesis by Scribble but also their ability to cooperate with oncogenic Ras to drive invasive phenotypes *in vitro*. The top ranked hits are also independent predictors of outcome in breast cancer patients. One common function of these top hits appears to be the regulation of sustained MAPK signalling.

1.4.2 Cell Cycle and Development laboratory

Research leader: Assoc. Prof. Helena Richardson, NHMRC Senior Research Fellow

The Cell Cycle and Development program uses the model organism, the vinegar fly, Drosophila, to dissect the mechanism by which cell polarity (shape) regulators and Extra Cellular Matrix (ECM) proteins affect signalling pathways to promote the hallmarks of cancer—increased cell proliferation, survival, prevent differentiation and induce invasion. We also are examining how cell polarity regulators cooperate with oncogenes in tumourigenesis, and are carrying out screens to identify small molecule inhibitors of tumour growth in vivo.

RESEARCH FOCUS

- Mechanism by which cell polarity regulators, including the junctional neoplastic tumour suppressor genes, lgl/scrib/dlg, affect cell proliferation, survival and tumourigenesis.
- Role of the extracellular matrix protein Sparc as an invasion/metastasis-suppressor.
- Modelling cooperative tumourigenesis in Drosophila—epithelial and paediatric brain tumours:
  - The mechanism of cooperation of cytoskeletal regulators with oncogenic Ras in tumourigenesis — role of JNK signalling.
  - The mechanism of cooperation of BTB/POZ domain Zn finger proteins in cooperation with polarity mutants.
  - Building models of paediatric brain tumours in Drosophila, and investigation of the cytoskeleton in tumourigenesis.
  - Screening for anti-cancer drugs using Drosophila cancer models.

KEY 2010 RESEARCH ACHIEVEMENT

The RhoGEF/Rho-family/JNK pathway is an important driver for cooperative tumourigenesis in *Drosophila melanogaster*

To identify novel genes that cooperate with Ras^{V12} in tumourigenesis, we carried out a genome-wide screen for genes that when overexpressed throughout the developing *Drosophila* eye, enhanced Ras^{V12}-driven hyperplasia. Amongst the Ras^{V12}-cooperating genes identified were Rho-family GTPases, *Rho1* and *Rac1*, and their regulators, *RhoGEF2* and pbl (Ect2 homolog).

In a clonal setting, which reveals genes conferring a competitive advantage over wild-type cells, *Rac1*, an activated allele of *Rho1* ($Rho1^{V14}$), *RhoGEF2* and *pbl* cooperated with Ras^{V12}, resulting in reduced differentiation and large invasive tumours. Expression of *RhoGEF2* or *Rac1* with Ras^{V12} upregulated Jun kinase (JNK) activity, and JNK upregulation was essential for cooperation. However, in the whole tissue system upregulation of JNK alone was not sufficient for cooperation with Ras^{V12}, whilst in the clonal setting JNK upregulation was sufficient for RasACT-mediated tumourigenesis.

JNK upregulation was also sufficient to confer invasive growth of Ras^{V12}-expressing mammalian MCF10A breast epithelial cells, but did not affect proliferation in culture.

These differences highlight the context dependent nature of JNK in cooperative tumourigenesis. We also found that $HER2^{+}$ human breast cancers (where human-epidermal-growth-factor-2 is overexpressed and Ras signalling upregulated) show a significant correlation with a signature representing JNK pathway activation. Our genetic analysis in the *Drosophila* whole tissue system revealed that Rho1 and Rac are important for the cooperation of RhoGEF2 or Pbl over-expression, and of mutants in polarity regulators, Dlg and aPKC, with Ras^{V12} in the whole tissue context.

Collectively our analysis reveals the importance of the RhoGEF/Rho-family/JNK pathway in cooperative tumourigenesis with Ras^{V12}. This research has important implications for understanding and developing novel therapeutic approaches to combat Ras-mediated human cancers.

Reference: Brumby, et al. Genetics 2011.

Upper image: Identification of Novel Ras-Cooperating Oncogenes in Drosophila melanogaster: A RhoGEF/Rho-Family/JNK Pathway Is a Central Driver of Tumorigenesis. Brumby AM, Goulding KR, Schlosser T, et al. Genetics. 2011 May;188(1):105-25. Epub 2011 Mar 2.

Lower image: Lgl, the SWH pathway and tumorigenesis: It's a matter of context & competition! Grzeschik NA, Parsons LM, Richardson HE. Cell Cycle. 2010 Aug 15;9(16): 3202-12. Epub 2010 Aug 10.

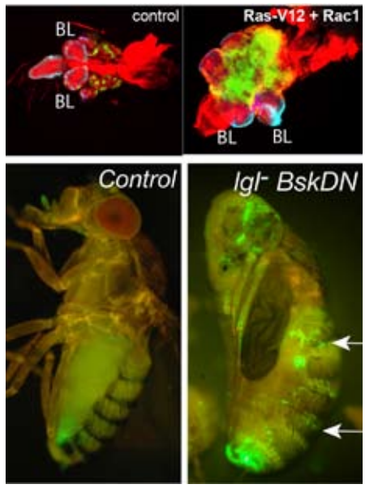

Figure 1: Top Panels: Cooperation of Rac1 with Ras^{V12}. Clones are marked by GFP (green). Rac1 + Ras^{V12} clones massively overgrow and invade between the brain lobes (BL), relative to wild type control clones in the developing eye.

Bottom Panels: Blocking JNK in lgl mutant clones results in an invasive phenotype. Clones are marked by GFP (green). When JNK is blocked using a dominant negative transgene (BskDN) in lgl mutant clones the mutant tissue overproliferates and becomes highly invasive, as evidenced by GFP+ tissue throughout the body of the developing fly.

1.4.3 Cell Growth and Proliferation laboratory

Research leader: Dr Kieran Harvey,
Viertel Senior Research Fellow

The Cell Growth and Proliferation laboratory studies mechanisms that control organ size during development, and how deregulation of these processes contributes to human cancer.

RESEARCH FOCUS

- Developmental organ size control in the vinegar fly, Drosophila melanogaster.
- Functional characterisation of the Salvador-Warts-Hippo tumour suppressor pathway in Drosophila.
- Investigation of the Salvador-Warts-Hippo tumour suppressor pathway in human cancer.

KEY 2010 RESEARCH ACHIEVEMENT

The Salvador-Warts-Hippo organ-size control pathway controls regenerative tissue growth

During tissue regeneration, cell proliferation replaces missing structures to restore organ function. Regenerative potential differs greatly between organs and organisms; for example some amphibians can re-grow entire limbs whereas mammals cannot. The process of regeneration relies on several signalling pathways that control developmental tissue growth, and implies the existence of organ size-control checkpoints that regulate both developmental, and regenerative, growth.

The Salvador-Warts-Hippo pathway limits tissue growth by repressing the Yorkie transcriptional coactivator. Several proteins serve as upstream modulators of this pathway including the atypical cadherins, Dachsous and Fat, whilst the atypical myosin, Dachs, functions downstream of Fat to activate Yorkie.

Using Drosophila melanogaster imaginal discs we found that Salvador-Warts-Hippo pathway activity is repressed in regenerating tissue and that Yorkie is rate-limiting for regeneration of the developing wing. We found that regeneration is compromised in Dachs mutant wing discs, but that proteins in addition to Fat and Dachs are likely to modulate Yorkie activity in regenerating cells.

Our findings reveal the importance of Yorkie hyperactivation for tissue regeneration and suggest that multiple upstream inputs, including Fat-Dachsous signalling, sense tissue damage and regulate Yorkie activity during regeneration.

Reference: The Salvador/Warts/Hippo pathway controls regenerative tissue growth in Drosophila melanogaster. Grusche FA, Degoutin JL, Richardson HE, et al. Dev Biol. 2011 Feb 15;350(2):255-66. Epub Nov 25, 2010.

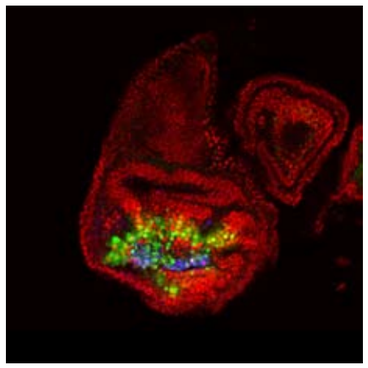

Figure 1: Tissue injury is induced in cells marked in green through expression of a pro-death gene, leading to apoptosis of some cells, marked by staining for Caspase 3 in blue. Remaining cells of the tissue can regenerate the missing structures. Our laboratory has shown that the Hippo pathway, whose output is shown in red, is important for this regenerative response.

1.4.4 Differentiation and Transcription laboratory

Research leader: Assoc. Prof. Rob Ramsay,
NHMRC Senior Research Fellow

The Differentiation and Transcription laboratory investigates mechanisms of transcriptional control of differentiation and carcinogenesis in epithelial tissues. These include gastrointestinal, mammary, epidermal and neurogenic tissues. We are particularly interested in stem and progenitor cell regulation in these compartments.

RESEARCH FOCUS

- Gastrointestinal epithelial tissue homeostasis and early events that initiate cancer.
- Mammary development, stem cells and carcinogenesis.
- Control of transcriptional elongation.
- Chromosome stability, radiation responses and DNA Repair.
- Translation of basic research discoveries into new therapies and vaccines.

KEY 2010 RESEARCH ACHIEVEMENT

The role of Myb in the regulator of stem and progenitor cell populations

The laboratory had previously proposed a direct role for Myb in regulating stem cells in the GI. The most evident GI stem cell gene is Lgr5 which we have now confirmed is a direct Myb target.

When Myb is mutated profound stem cell recovery defects are marked.

These defects are most severe when mice are subjected to radiation exposure. The second unanticipated discovery is that when we delete Myb, specifically in the mammary gland, tumourigenesis is essentially ablated without any lasting effect on mammary gland function. This is of considerable note, as our observation suggests there is a critical Myb-dependent window that affects mammary cancer. This may speak to the epidemiological data in women that suggests that some key events in setting up mammary cancer occur in or around puberty. Finally, we have a strong interest in chromosome cohesion mediated by proteins that hold chromatids together during mitosis. One of these, Rad21, is very important in this function and we now have confirmed that it is over-expressed, and is of prognostic significance in breast cancer.

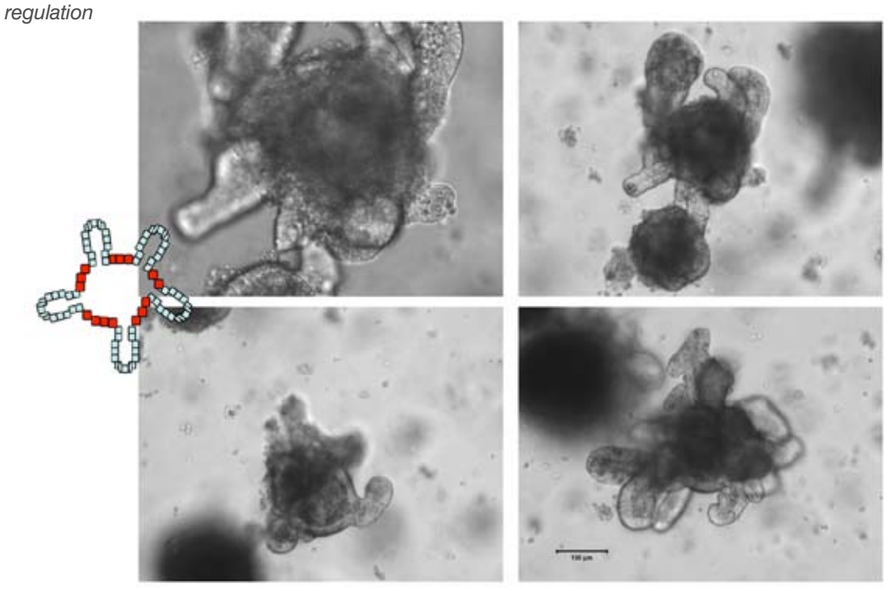

Figure 1: Growing the gut in plastic dishes. Recent advances in the culturing of small intestinal (SI) stem cells are serving the DT lab in their study of signalling pathways that affect stem cell function and cancer development. Images show organoid cultures at different times of culture and the cartoon indicates the position of the crypt-like structures (blue cells) that feed into the red region that ultimately form villi. Thus the organoids have all the cell types of the SI epithelium including the stem cells.

1.4.5 Epithelial Stem Cell Biology laboratory

Research Leader: Dr Pritinder Kaur,
NHMRC Senior Research Fellow

The Epithelial Stem Cell Biology laboratory studies the role of skin stem cells and their microenvironment in tissue renewal and carcinogenesis. The benefits of this research to patients include a greater understanding of the mechanisms by which the mesenchymal microenvironment promotes normal tissue replacement which will be useful in designing tissue regenerative therapies; and how the microenvironment can be hijacked to achieve cancerous growth. Knowledge gained in the latter aspect is being used to develop better diagnostic tools for patients with aggressive epithelial cancers including ovarian and head and neck cancers.

RESEARCH FOCUS

- Tissue reconstitution ability of epidermal stem cells and their cycling progeny.
- Role of pericytes in homeostasis, tissue repair and cancer.
- Molecular profiling of epidermal stem cells and their progeny.
- Molecular and cellular cross-talk between the epidermis and dermal microenvironment during homeostasis and cancer.

KEY 2010 RESEARCH ACHIEVEMENT

Dermal pericytes can act as cancer associated fibroblasts

Cancer associated fibroblasts (CAFs) are a heterogeneous population of cells with a broadly similar phenotype, but with the common ability to promote cancer growth. We have studied the role in cancer progression of a particular stromal cell type: the pericyte. Pericytes are wellknown to stabilise blood-vessel endothelial cell function both during homeostasis and tumour-associated angiogenesis.

We have demonstrated a novel role for these cells as CAFs. Specifically, ovarian cancer patients carrying the pericyte gene signature are predisposed to having a higher risk of relapse and lower overall survival, suggesting that pericyte involvement is a strong predictor of recurrent cancer and mortality. Importantly this high-risk patient group was distinct from the groups identified by an angiogenic signature, suggesting a more direct role for pericytes in increasing tumour growth. Consistent with this, co-injection of an ovarian cancer cell line (OVCAR-5), with pericytes resulted in accelerated tumour-forming ability *in vivo*. Pericytes were also able to enhance the intrinsic migratory and invasive capacity of OVCAR-5 cells *in vitro*.

Taken together, these results suggest that CAFs can originate from pericytes and the genes they express may be useful prognostic tools in predicting patient survival. Current work is aimed at identifying the cellular and molecular events by which pericytes contribute to tumour development. The data obtained will assist in developing potential targets for anti-cancer therapy.

Metastasis, or the spread of cancer

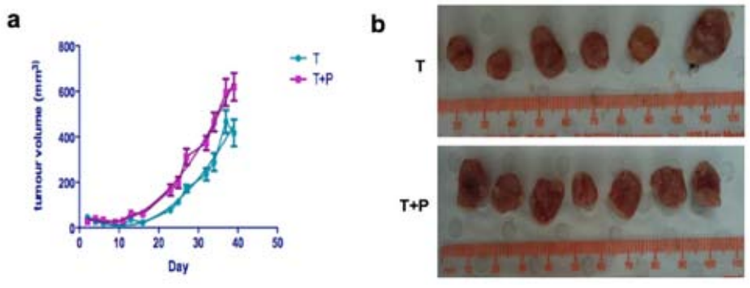

Figure 1: Pericytes promote promote the growth of OVCAR-5 tumours *in vivo*.
(a) Co-injection of ovarian cancer cells (OVCAR-5) cells with cultured pericytes p4 (T+P) at a 10:1 ratio results in accelerated tumour growth compared to ovarian cells alone (T) in a subcutaneous xenograft model in nude mice with time taken to reach a volume of 200 mm3 being 7 days earlier (n=3; 15 mice per group). (b) Representative images of tumours excised from mice at end point of experiment.

1.4.6 Metastasis Research laboratory

Research leader: Assoc. Prof. Robin Anderson,
National Breast Cancer Foundation Career Fellow

to other organs in the body, is a major cause of cancer related deaths. Our research aims to identify the molecular events that control metastasis to enable the development of new therapies that prevent metastasis from occurring or that kill secondary tumours before they cause organ failure and death.

RESEARCH FOCUS

- Development of animal models of tumour growth and spontaneous metastasis.
- Identification of genes that control the process of metastasis.
- Development of molecular targeted therapies to prevent or treat metastatic disease.

KEY 2010 RESEARCH ACHIEVEMENT

A functional genomics screen implicates a novel class of molecules in breast cancer metastasis

For almost 50 years after the discovery of DNA, it was universally accepted that large regions of the genome amounted to 'junk DNA,' exhibiting neither transcription nor function. It has recently become apparent that transcription of the human genome is far more pervasive than originally thought. There is now virtual consensus on the existence of a novel class of transcripts known as long non-coding RNAs (ncRNAs).

Numerous approaches have revealed an abundance of transcripts with low or no protein-coding potential, many of which exhibit temporal and tissue-specific expression patterns, are highly conserved across species and have demonstrable functionality in a variety of contexts. ncRNA transacts transcriptional and post-transcriptional regulation, guides chromatin-modifying complexes to repress gene expression and has recently been found to associate with enhancer regions to promote transcription of genes nearby. Not surprisingly, emerging evidence implicates aberrantly expressed ncRNA in the development of diseases, including cancer.

Dr. Richard Redvers in our laboratory has further developed a model of spontaneous breast cancer metastasis, isolating many independent sublines representing a wide spectrum of metastatic capacity and sites of distant dissemination. Using these lines, he has recently completed a functional genomics screen to identify genes regulating the spread of tumour cells to lungs and bone. Significantly, a long ncRNA was the most upregulated transcript *in vivo* in tumour cells (311-fold, p=2.82x10-4) derived from the metastatic cohort. Importantly, his screen also revealed a role for numerous other long ncRNAs whose functional role in metastasis has yet to be determined.

Clearly, this novel class of molecules represents an important area of metastasis research that we and others are only just uncovering. Ongoing research will focus on the underlying mechanisms of action of these potential modulators of metastasis, with the potential to uncover new therapeutic strategies for patients with advanced breast cancer, whose prognosis is currently very poor.

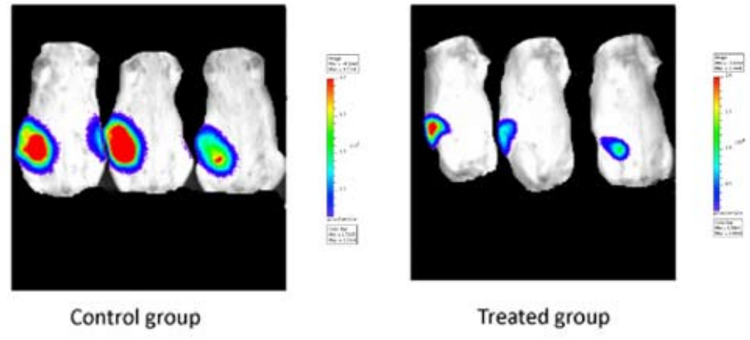

Figure 1: Measurement of breast cancer growth in the mammary glands of mammalian models with or without treatment with a new experimental compound designed to inhibit primary tumour growth and metastasis. The tumour cells have been engineered to express luciferase which releases light when the enzyme substrate, luciferin, is injected into the models.

1.4.7 Molecular Radiation Biology laboratory

Research leader: Assoc. Prof. Roger Martin

In two separate approaches to improving radiation treatment of cancer, the Molecular Radiation Biology laboratory is developing a topical radioprotector to protect normal tissues, and a strategy to target radioactivity to tumours.

RESEARCH FOCUS

- Continuing development of a new class of DNA-binding radioprotecting drugs, exemplified by the initial lead methylproamine, to identify improved radioprotectors, in a program of research supported by a Licensing Agreement with Sirtex Medical.The new analogues are being evaluated as topical radioprotectors.
- Design and synthesisi of minor groove-binding DNA ligands labelled with Auger-emitting isotopes, evaluated for DNA breakage efficacy and cytotoxicity.
- Preparation and evaluation of conjugates of the labelled ligands with tumour targeting proteins, both *in vitro* (cytotoxicity) and *in vivo* (distribution in tumour-bearing mice).

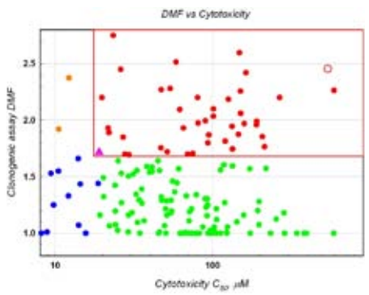

Figure 1: Each of more than 150 new methylproamine analogues has been assessed by clonogenic survial assays, generating a pair of values for each drug. One of these values is a dose modification factor (DMF), derived from the increase in survival conferred by the drug, at the optimal concentration, after a radiation dose of 12Gy. A DMF value of 1 corresponds to null radioprotective activity; <1 to radiosensitisation. The other value is a measure of cytoxicity — an estimate of the drug concentration (C50) corresponding to a decrease in survival of un-irradiated cells by 50 per cent after a one-hour exposure. The green triangle depicts the values for methylproamine, the first lead drug. The red circles correspond to the 41 drugs (as of December 2010) that are both less cytotoxic (lower C50) and better radioprotectors (higher DMF). The 'target zone' is the top right-hand corner of the diagram, so on this basis, the most promising analogue depicted by the open red circle. The experiments were done with a cell line derived from human keratinocytes.

KEY 2010 RESEARCH ACHIEVEMENT

Development of new DNA-binding radioprotector drugs

During 2010,the laboratory made good progress in the project aimed at developing new radioprotecting drugs that could be applied to normal tissues to reduce the side effects of cancer radiotherapy.

Starting with the lead drug methylproamine, more than 150 new analogues have been designed, synthesised and evaluated. The initial evaluation, using cultured cells, provides data for radioprotective activity and cytotoxic activity. Mapping these values on a graph, in which each data point represents one analogue, provides a visual indication of progress. Increasing radioprotective activity is reflected in the vertical dimension, and cytotoxicity reduces from left to right. It is immediately apparent that more than 40 drugs are both better radioprotectors and less cytotoxic (red symbols), than methylproamine (green triangle). One recent analogue (open red circle) is particularly promising. Some of the new analogues have been shown to protect mouse oral mucosa after topical application.

Attention is now focused on formulating strategies to improve the efficiency of delivery of such drugs to basal cells in oral mucosa, after topical application.

1.4.8 Tumour Suppression laboratory

Research Leader: Assoc. Prof. Ygal Haupt, NHMRC Senior Research Fellow and VESKI Fellow

The Tumour Suppression laboratory studies the regulation and function of tumour suppressors, with the aim to explore new therapeutic strategies based on restoration of tumour suppression in cancer cells.

RESEARCH FOCUS

- Identification of key determinants of regulation of the tumour suppressors p53 and the promyelocytic leukemia (PML) protein: implication to the treatment of lymphomas.
- Definition of the regulatory mechanisms and function of mutant forms of p53.
- Investigation of the involvement of the E6AP-PML axis in cancer development, with a focus on prostate cancer.
- Identification of novel pathways of cellular stress response using functional screen and mouse models for cancer.
- Exploration of the regulation of cellular aging (senescence) and its link to tumour suppression.

KEY 2010 RESEARCH ACHIEVEMENTS

Involvement of the E6AP/PML axis in cancer development

The laboratory has recently identified a new regulatory pathway of tumour suppression. We found that the E3 ligase E6AP controls the protein stability of PML, a major known tumour suppressor. We have demonstrated in mouse models for cancers that aberration in the regulatory axis of E6AP/PML promotes cancer development, and that inverse correlation between E6AP and PML is associated with poor survival of patients with prostate cancer.

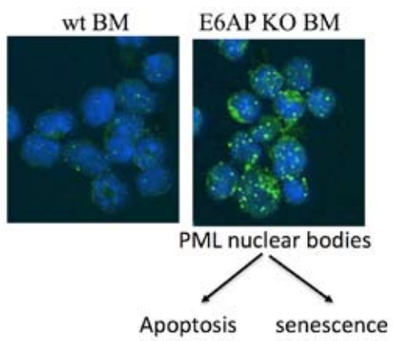

Figure 1: Immunofluorescence staining of freshly isolated bone marrow cells for PML.

The nuclear dots represent the PML nuclear bodies, structures that regulate cell death and cell aging (senescence). We found that in cells lacking the E3 ligase E6AP, the levels of PML and PML nuclear bodies increased significantly leading to enhanced growth suppression.

Interplay between mutant p53 and PML in cancer development

Mutations in p53 are found in nearly 50 per cent of human cancers. Certain mutations in p53 provide a 'gain of function', including the induction of chemoresistance, and enhanced proliferative and metastatic potential, thereby making them attractive therapeutic targets. We have recently identified physical and functional interaction between PML and mutant p53. A loss of PML and acquisition of mutant p53 correlates with poor survival of prostate cancer patients, and of mice in animal models.

Use of copper ionophores to selectively target cancer cells

Prostate cancer cells accumulate high levels of copper. We have taken advantage of this phenomenon and used copper ionophore, clioquinol, that transport copper into cells, to selectively kill prostate cancer cells. This provides a proof of principle for this therapeutic approach, which we will test in animal models.

Cancer Cell Biology program – personnel

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Head
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Dr Helen Pearson
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Tanja Schlosser

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Ryan Galea
Lorey Smith

Technical Officer
Olivia Cakebread
Samantha Williams

CELL CYCLE AND DEVELOPMENT LABORATORY

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Felix Grusche
Ashesha Sinha

Honours Students
Lucas Dent

Summer Scholarship Student
Kiryu Kee-Long Yab

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Yan Yuqian

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Ryan Cross
Suh-youn Ko

Summer Scholarship Student
Ryan Cross (2009–10)

Scholar
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Visiting Postgraduate Student
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Dr Normand Pouliot

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Christina Restall
Kathryn Visser

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Yuan Cao
Rachel Carter
Nicole Kusuma
Yu Rebecca Miao
Nimali Withana

Summer Scholarship Student
Lauren Burton

AMS Student (2010–11)
Chloe Georgiou
(The University of Melbourne)

Sabbatical visitor
Dr. Gunbjørg Svineng

Visiting Postgraduate Student
Yvonne Smith

MOLECULAR RADIATION BIOLOGY

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Visiting Scientist
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Dr Kamil Wolyniec

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Joel Greaney
Stephanie Munari
Cristina Murphy
John Daly Rayner

1.5 Tumour Angiogenesis program

Tumour angiogenesis is the process by which tumours generate the blood vessels they need to secure their blood supply and survive. Tumours also recruit lymphatic vessels (lymphangiogenesis) which can facilitate metastatic spread, the most lethal aspect of cancer. Under the supervision of Associate Professors Steven Stacker and Marc Achen, Steve Williams uses siRNA from Peter Mac's Functional Genomics facility to screen the genome and to identify molecules that can be targeted therapeutically to block lymphatic metastasis.

Determining the molecular mechanisms that regulate the formation of blood vessels and lymphatic vessels during normal development and tumourigenesis

Heads of Tumour Angiogenesis program: Assoc. Prof. Marc Achen, NHMRC Principal Research Fellow, and Assoc. Prof. Steven Stacker, NHMRC Senior Research Fellow

The Tumour Angiogenesis program was established at Peter Mac in July 2010. The program is led by Associate Professors Marc Achen and Steven Stacker, highly respected and internationally recognised researchers whose work covers the range of lab-based cell biology through to pre-clinical cancer models and human clinical trials. Marc and Steven jointly hold a NHMRC Program Grant and each is supported at a senior level through the NHMRC Fellowship Scheme.

Research conducted under the Tumour Angiogenesis program is focused on growth factors, cell surface receptors and signalling pathways that regulate growth and differentiation of endothelium and other cell types associated with the vasculature in solid tumours.

We aim to use this information to develop therapeutics that block tumour angiogenesis and lymphangiogenesis, and thereby restrict the growth and spread of cancer. This information will also be used to develop diagnostics for applications in cancer and other human diseases.

RESEARCH FOCUS

- Large-scale genomic screens to determine the signalling pathway networks in endothelial cells.
- Development of discovery platform for predictive biomarkers of clinical response and resistance to anti-neovascular agents.
- Characterisation of lymphatic vessel subtypes and their relationships to human disease.
- Determining the role of proteases in the regulation of vascular endothelial growth factors and formation of tumour stroma.
- Development of mouse models to understand human lymphatic disorders and disease.
- Structure-function analysis of vascular endothelial growth factors and receptors.
- Characterisation of the role of novel growth factor receptors (e.g. the Ryk receptor) in human cancer, and development of modulators of their function.

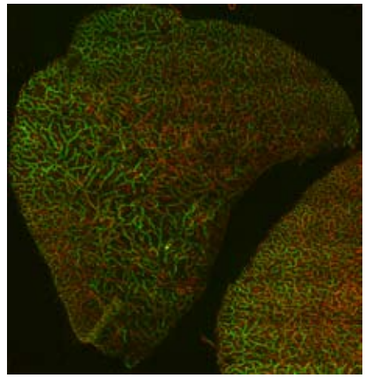


Figure 1: Lymphatic and blood vasculature of a mouse ear: whole-mounts of the ear were performed to immunostain the lymphatic endothelial cells, using the LYVE-1 marker (green), and the blood endothelial cells, using the CD31 marker (red).

KEY RECENT RESEARCH ACHIEVEMENTS

The Tumour Angiogenesis program has been involved in the discovery and characterisation of growth factors and receptors involved in promoting human cancer. We have also generated specific reagents and inhibitors to allow the development of therapeutics and diagnostics for application to human diseases including cancer. These discoveries include:

- Cloning and characterising novel members of the vascular endothelial growth factor (VEGF) family.
- Identifying VEGF-D as a key mediator of tumour lymphangiogenesis and metastasis via lymphatic vessels.
- Developing inhibitors of VEGF-D for use as anti-cancer agents.
- Using adenoviral delivery of the VEGF-D gene to prolong the patency of vascular access grafts and treat cardiovascular diseases.
- Generating VEGF-D antibodies; such antibodies are now used in the first blood-based diagnostic test for lymphangioleiomyomatosis (LAM), a devastating neoplastic disease effecting women.
- Advancing our understanding of lymphatic biology through the characterisation of new molecules and pathways associated with lymphatic endothelium.
- Defining the roles of novel growth factor receptors and their role in Wnt signalling.

1.5 Tumour Angiogenesis program – overview

Research into the molecular control of blood and lymphatic vessel formation started in the program over 15 years ago with the initial cloning of growth factor receptors involved in angiogenesis. These receptors (e.g. VEGFR-2 and Tie-2) were a starting-point to understand the control of angiogenesis in the context of developmental biology and cancer.

At the time it was evident that other receptors and ligands must exist to mediate the array of different functions served by specialised vessels in different organs of the body, and by vessels which form in response to human diseases. Using techniques of gene discovery combined with specialised bioassays for endothelial growth factors, new members of the VEGF family were isolated. The cloning and characterisation of VEGF-D (Achen *et al., Proc. Natl. Acad. Sci. USA*, 1998), and the demonstration that this soluble growth factor activates both VEGFR-2 and VEGFR-3 on blood vessels and lymphatics opened new doors for understanding the biology of the vasculature. Combined with the discovery of a related growth factor, VEGF-C, in the laboratory of Professor Kari Alitalo in Helsinki, Finland, a subfamily of VEGFs capable of driving the formation of new lymphatic vessels was identified. These findings opened the way for studies in the field of lymphangiogenesis (the formation of new lymphatic vessels) and importantly, the role of lymphangiogenic signalling in human disease.

Our interest in tumour biology and the function of vessels in the metastatic spread of cancer led us to examine the role of VEGF-D in the growth and spread of cancer. We demonstrated that VEGF-D induces both new blood vessels and new lymphatic vessels in a tumour. Further, VEGF-D promoted the spread of the primary tumour to regional lymph nodes, whereas tumours that did not express VEGF-D grew slowly and never spread to lymph nodes (Stacker et al, *Nature Medicine*, 2001). These experiments showed the importance of the lymphangiogenic growth factors for the metastatic spread of tumour cells.

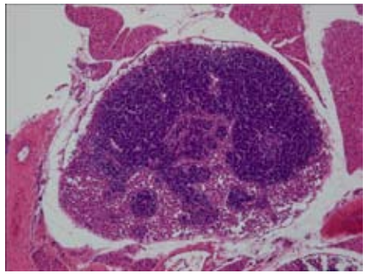
This work was further validated in human cancer patients by studies which correlated the expression of VEGF-C and VEGF-D in primary human tumours with disease outcome and measures of metastasis. To directly address whether VEGF-D was responsible for the formation of new vessels and the spread of tumour cells, we also developed a monoclonal antibody to VEGF-D which blocked its interaction with both of its receptors, VEGFR-2 and VEGFR-3 (Achen *et al., Eur. J. Biochem*., 2000; Davydova et al., J. Mol. Biol., 2011). The successful inhibition of both primary tumour growth and metastasis with this antibody was the first demonstration of an anti-metastatic approach based on inhibition of a lymphangiogenic growth factor (Stacker *et al., Nature Medicine*, 2001).

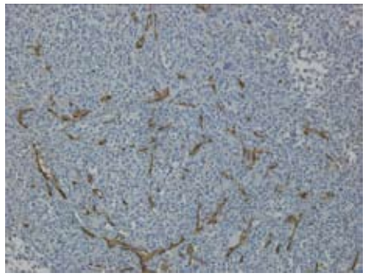
Detailed biochemical analysis of the VEGF-D polypeptide in our program revealed two protein domains which can be cleaved to generate the fully bioactive growth factor (Stacker *et al., J. Biol. Chem.,* 1999). These studies not only confirmed how the activity of VEGF-D could be regulated *in vivo*, but showed that it is similarly regulated to VEGF-C, and indicated potential avenues to target the protein via the proteases that release its fully bioactive domain (McColl *et al.*, J. Exp. *Med.,* 2003; McColl et al., *FASEB J.,* 2007).

In 2006, a family of patents generated in our program, describing the *VEGF-D* gene, inhibitory VEGF-D antibodies and therapeutic and diagnostic approaches for cancer and other diseases based on these reagents, was acquired by Circadian Technologies (an Australian publicly-listed company) for development primarily in the area of cancer. A phase I clinical trial testing an antibody to VEGFR-3 (a receptor for VEGF-D) in cancer was initiated in 2011. Companies have taken licenses to discoveries from our program to examine the therapeutic potential of the *VEGF-D* gene in angina, foetal growth restriction and peripheral vascular disease, and for prolonging the patency of vascular access grafts.

Some of the resulting studies have now progressed to clinical trials in the USA and Europe.

Since relocating to Peter Mac in 2010, our program has continued with advances in the development of the first blood-based diagnostic test for LAM which utilises antibodies to VEGF-D. LAM is a debilitating, progressive and often lethal neoplastic lung disease effecting women of child-bearing age. The diagnostic test, developed from intellectual property generated in our program, is aiding in the diagnosis of LAM, and is an excellent example of the translation of our scientific discoveries for the benefit of patients.





PC3 cells (prostate tumour cells) endogenously expressing VEGF-C and VEGF-D were implanted as xenograft tumour to study the lymphogenous spread of prostate tumour cells to regional lymph nodes. (work of Tara/Maria). Top: Metastasis of PC3 cells have been observed in an axillary lymph node. (40% of the lymph node was invaded by tumour cells, shown by H & E staining). Bottom: IHC of LYVE 1 has shown lymphangiogenesis within a PC3 cells induced tumour.

Tumour Angiogenesis program – key publications & personnel

PROGRAM PUBLICATIONS

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Stacker SA, Vitali A, Caesar C, et al. A mutant form of vascular endothelial growth factor which lacks VEGFR-2 activation but retains the ability to induce vascular permeability. J. Biol. Chem. 274:34884–34892, 1999. (cit.=67)

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PERSONNEL

Program and Group Heads
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Assoc. Prof. Steven Stacker

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Dr Rae Farnsworth
Dr Michael Halford
Dr Tara Karnezis
Dr Maria Macheda
Dr Sophie Paquet-Fifield

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Sally Roufail
Dr You-Fang Zhang

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Dr Sidney Levy
Steven Williams

Casual Research Assistant
Katie Ardipradja

Surgical Associate
Dr Ramin Shayan

After obtaining a PhD in Pharmacology from The University of Melbourne, Mark Devlin worked in a variety of roles focused on academic-based drug discovery and development. He then joined Peter Mac in 2008 to head the CRC for Cancer Therapeutics (CTx) Translational Research Laboratory.

Mark conducts his research as part of a larger, multidisciplinary drug discovery and development team, involved in the development and validation of target-specific biomarkers, *in vitro* functional assays and *in vivo* cancer models. These proof-of-concept studies provide an important foundation for further development towards new targeted therapies for cancer.

1.6 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 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, genetic and genomic basis of cancer onset.
- Development and clinical responses to treatment.
- Pre-clinical testing of novel therapeutics, development of imaging methods and biomarker assays to follow treatment efficacy.
- Investigation of molecular pathways involved in response to anti-cancer therapies.

Key technologies involved include functional genomics, next generation sequencing, 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
Assoc. Prof. Ricky Johnstone

Melanoma Research laboratory
Dr Mark Shackleton

Molecular Imaging and Targeted Therapeutics laboratory
Prof. Rod Hicks

Translational Research Laboratory
Assoc. Prof. Grant McArthur

Pfizer/Peter Mac Cancer Genomics program
Assoc. Profs. Rick Pearson and Wayne Phillips

CCV Venture Grant Initiative
Assoc. Prof. Ricky Johnstone

CRC for Cancer Therapeutics Translational Research laboratory
Dr Mark Devlin

1.6.1 Gene Regulation laboratory

Research leader: Assoc. Prof. Ricky Johnstone, NHMRC Senior 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.
- Determination of 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 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 signalling in tumour immune surveillance.

KEY 2010 RESEARCH ACHIEVEMENT

Defining the molecular mechanisms of action of anti-cancer agents

We determined that regulated basal expression of Type I interferon (IFNβ) production by c-Jun is necessary to maintain the levels of transcription factor STAT1 within cells and 'prime' cells for subsequent responses to IFNγ and other cytokines that utilise STAT1.

These studies have provided important information regarding the fundamental molecular mechanisms of IFN signalling and the complex molecular and biological interplay between Type I and II IFNs.

We used syngeneic pre-clinical models of human solid cancers to demonstrate that the HDACi panobinostat can sensitise tumour cells to apoptosis mediated by the anti-mouse TRAIL receptor antibody MD5-1. We showed that the combination of panobinostat and MD5-1 can eradicate tumours grown subcutaneously and orthotopically in immunocompetent mice, while single agent treatment had minimal effect. However, escalation of the dose of panobinostat to enhance anti-tumour activity resulted in on-target gastrointestinal toxicities that were fatal to the treated mice. Given that clinical studies using HDACi and activators of the TRAIL pathway have been initiated, our pre-clinical data highlight the potential toxicities that could limit the use of such a treatment regimen.

For more information on related research, see:

- Cancer Immunology program (pg 24)

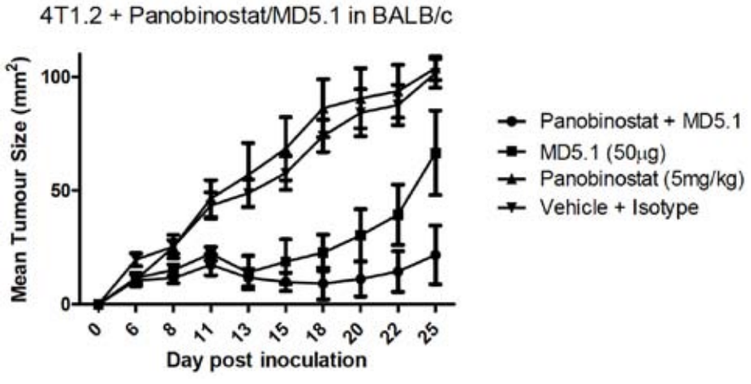


Figure 1: Mammalian models with established subcutaneous mammary carcinomas were treated with an agonistic monoclonal antibody to DR5, a pan histone deacetylase inhibitor or a combination of both, the latter treatment causing regression and/or long term cures with no toxic side effects.

1.6.2 Melanoma Research laboratory

Research leader: Dr Mark Shackleton NHMRC CDA Fellow

Newly established in 2010 following the recruitment of medical oncologist and VESKI Fellow Dr Mark Shackleton, the Melanoma Research laboratory aims to identify molecular mechanisms that drive melanoma initiation and progression.

OVERVIEW

In Australia, melanoma causes the second most years of lost productive life of any cancer. Our research program aims to identify ways to reduce the incidence of melanoma and to improve the outcomes of patients with established disease.

We underpin molecular studies of melanoma development and progression with detailed biological investigations, using *in vivo* models. Our main focus is currently on studying the growth of human melanomas using *in vivo* models that are highly permissive for revealing the malignant potential of human cancer cells. The *in vivo* assay we use is remarkably efficient, allowing tumour formation from single melanoma cells and providing a unique vehicle for studying human cancer biology.

Through identifying tumours that vary in their abilities to propagate disease, we aim to identify molecular determinants of melanoma growth and metastasis. Our close links with the Melanoma Unit at Peter Mac and the Melbourne Melanoma Project provide us with clinically annotated human tumour specimens that have been kindly donated by patients for study. This enables us to link our laboratory findings directly to patient characteristics and outcomes.

RESEARCH FOCUS

- Elucidating mechanisms of melanocyte development and transformation.
- Identifying mechanisms of melanoma progression and metastasis.
- Developing clinically relevant models of melanoma biology and treatment.

2010 OVERVIEW

Since our genesis in January 2010, the Melanoma Research laboratory has been successful in attracting independent funding for our research and in establishing key and logistically complex *in vivo* assays that form the basis of our work. Initial developments focused on restructuring of the laboratory space and on acquisition of major equipment items, including a new FACS Aria II cell sorter through support from the Peter Mac Foundation and the Flow Cytometry facility. The first research staff appointments were made in March/April and experimental work commenced in May. Key to the development of our program has been the building of relationships with the Melanoma Unit at Peter Mac, the Victorian Biobank and the Melbourne Melanoma Project. These relationships provide us with fresh melanoma tumor tissue from patients in a way that enables translation to the clinic of findings from in vivo disease modelling.

References: Quintana E, Shackleton M, Sabel MS, et al. Efficient tumour formation by single human melanoma cells. Nature. Dec 4;456(7222):593–8, 2008.

Quintana E, Shackleton M, Foster HR, et al. Phenotypic heterogeneity among tumorigenic melanoma cells from patients that is reversible and not hierarchically organised. Cancer Cell. 18: 510-523, 2010.

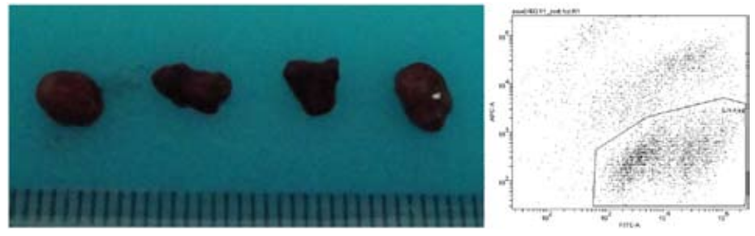


Figure 1: Pieces of melanoma tumour obtained freshly at surgery from a Peter Mac patient who consented to donate tumour tissue for research. The specimen was taken immediately and freshly to Pathology. Peter Mac pathologists separated parts of the tumour not required for clinical management and gave them to staff from the Victorian Biobank for initial processing and forwarding to the Melanoma Research laboratory. As a result of such co-ordination, the total time from surgical removal of the tumour to its delivery to the lab was only 30 minutes. Melanoma cells were then dissociated from the tumour, stained to enable identification of dead and contaminating cells, and evaluated by flow cytometry (dot plot shown to right, enclosed region indicates melanoma cells).

1.6.3 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

- Targeting molecular pathways involved in metabolism, amino acid transport and apoptosis for cancer imaging and therapeutic monitoring.
- Developing novel agents and technologies for imaging melanoma, neuroendocrine cancers and lymph node metastasis.
- Imaging receptor activation and hypoxia in tumours to guide therapeutic intervention.
- Developing advanced chemistries and automation procedures to produce radiopharmaceuticals for clinical cancer applications.
- Participating in clinical trials of new treatments and imaging modalities to enhance translation of research finding to clinical practice.

KEY 2010 RESEARCH ACHIEVEMENT

Imaging cancer with radio-labelled amino acid derivatives

Cancer cells have a high demand for glucose and other nutrients in order to support their rapid growth and proliferation. Since the 1980s, the high glucose consumption of tumour cells has been exploited to image cancers by Positron Emission Tomography (PET) using the glucose analogue fluorodeoxyglucose (^{18}FDG). However, despite its proven usefulness in cancer management, ^{18}FDG has some limitations, in particular for brain tumour imaging. Indeed, glucose is also the preferred source of energy for normal brain cells which, therefore, have a high uptake of ^{18}FDG. In addition to high glucose utilisation, cancer cells require high amounts of amino acids for the protein production necessary to maintain their continuous proliferation. Thus, radio-labelled amino acid derivatives are another type of metabolic probes that can be used as alternative to ^{18}FDG imaging.

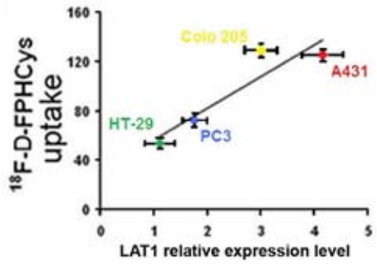


Figure 1: 18F-D-FPHCys uptake into cancer cells correlates with expression of amino acid transporter subclass LAT1.

Until now, these imaging agents have been labelled with the PET isotope carbon (^{11}C) which has a very short half-life of 20 minutes, making transport and multi-centre trials impractical.

To overcome this limitation, we, together with collaborators at the Australian Nuclear Science and Technology Organisation (ANSTO) and the Cooperative Research Centre for Biomedical Imaging Development (CRC-BID), have developed a novel methionine analogue, ^{18}F-D-FPHCys, labelled with ^{18}Fluorine which has a significantly longer half-life (109 minutes). ^{18}F-D-FPHCys has shown excellent imaging properties in animal models of human tumours. This tracer has great potential to become an effective clinical PET imaging agent and improve the localisation and characterisation of cancers, in particular brain tumours. First-in-human clinical trials will commence in 2011.

Our pre-clinical work in developing new imaging tracers in association with the CRC for Biomedical Imaging Development has moved into the clinical domain with commencement of human studies of Mel050, a highly specific melanoma imaging agent.

1.6.4 Translational Research Laboratory

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.
- Understanding of the mechanism of action of therapeutics targeting signalling, cell cycle and cell surface receptors.
- Understanding of the role of hypoxia in tumour responses to cancer therapies.

KEY 2010 RESEARCH ACHIEVEMENT

BEZ235 targets the DNA damage response leading to radiosensitisation and senescence

Activation of the phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway confers resistance to ionising radiation. Therefore, pharmacological inhibition of signalling through the PI3K/mTOR pathway is a promising strategy for enhancing the cytotoxicity of radiation.

In this project, we are investigating the therapeutic consequences of combining a novel PI3K/mTOR inhibitor (BEZ235) with radiation. Treatment with BEZ235 cause significant radiosensitisation as evidenced by clonogenic survival assays in a panel of human cancer cell lines including non-small cell lung cancer cells. Importantly, BEZ235 also reduces tumor growth following radiation treatment of tumour xenografts *in vivo*. The enhanced radiation response produced by BEZ235 coincides with delayed repair of radiation-induced DNA double-strand breaks (as measured by γ-H2AX immunofluorescence) and the induction of accelerated senescence (terminal growth arrest) *in vitro* and *in vivo*. BEZ235 also exhibits potent inhibition against a key DNA repair protein, DNA-dependent protein kinase (DNA-PK). Significantly, DNA-PK knockdown using either a selective pharmacological inhibitor (KU57788) or small interfering RNA replicates the effects of BEZ235 on DNA repair and senescence, suggesting that DNA-PK is a key therapeutic target of BEZ235 following radiation. Using p53-inducible cells, we also demonstrate that functional p53 is required for BEZ235 to induce senescence in irradiated cells.

We conclude that BEZ235 modulates DNA double strand break repair and promotes p53-dependent accelerated senescence after radiation by inhibiting DNA-PK. These data highlight that DNA-PK is an attractive therapeutic target for enhancing tumor radio-sensitivity and identify accelerated senescence as an important determinant of outcome when DNA-PK inhibitors are combined with radiation.

For more information on related research, see:

- Molecular Oncology laboratory (pg 43)
- Molecular Imaging and Targeted Therapeutics laboratory (pg 66)
- Centre for Cancer Imaging (pg 110)
- Medical Oncology and Early Phase Clinical Trials (pg 82)
- Gastrointestinal Service (pg 84)
- Head and Neck Service (pg 87)
- Melanoma and Skin Service (pg 89)

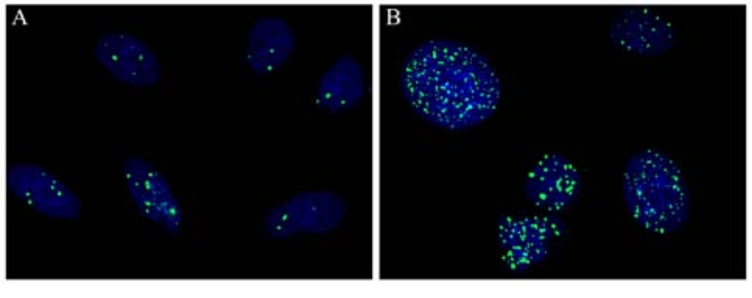


Figure 1: γ-H2AX immunofluorescence in cells after treatment with radiation alone (A) and radiation plus BEZ235 (B). Note increased staining with addition of BEZ235. γ-H2AX (green), DAPI – nuclear staining (blue).

1.6.5 Pfizer/Peter Mac Cancer Genomics program

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

- Screening tumour cells for drug sensitivity, focusing on melanoma and ovarian cancer.
- Using genomic and proteomic profiling to obtain a predictive signature of drug response and gain insight into drug resistance.
- Functional genomic RNAi screening to identify genes associated with resistance to specific drugs and to enable rational development of novel combinational drug therapies.

KEY 2010 RESEARCH ACHIEVEMENT

- Ovarian cancer included as one of the tumour types selected for clinical trials of PF502 (PI3Kinase/mTOR inhibitor), with potential targets for combination therapies in PF502 resistant ovarian cancer identified.

One of the major challenges in treating cancer is the selection of the most effective chemotherapy agents for individual patients. To address this challenge, the aim of the Pfizer/Peter Mac Cancer Genomics Program is to generate Proteomic and Genomic Profiles of human tumour cells, correlate these with response to targeted therapies and use this information to predict drug effectiveness in patients.

We have successfully screened 35 Ovarian cell lines and 100 Melanoma cell lines with drugs that are currently pre-clinical or in clinical trials. We have successfully generated a 'gene signature' that is 87% accurate in classifying cells as either resistant or sensitive to PF502, a drug that targets the PI3 kinase pathway. In addition we have identified potential mechanisms that confer drug resistance.

These studies have led to the inclusion of ovarian cancer as one of the tumour types selected for PF502 clinical trials and also identified potential targets for combination therapies in PF502 resistant disease.

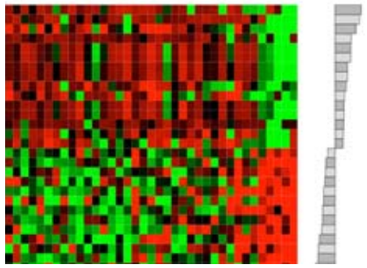


Figure 1: Heat map of the 28 gene signature that was 87 per cent accurate in classifying ovarian tumour cells as either resistant or sensitive to PF502.

For more information on related research, see:

› Cancer Genetics and Genomics laboratory (pg 34)

› Cancer Immunology program (pg 24)

› Growth Control and Differentiation program (pg 40)

1.6.6 CCV Venture Grant Initiative

Research Leaders: Assoc. Prof. Ricky Johnstone, NHMRC Senior 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 2010 RESEARCH ACHIEVEMENT

Identification of novel putative tumor suppressor genes

We have validated the role of eight new potential tumour suppressor genes identified in our initial RNAi-based functional genomics 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. We have shown that altered activity of the ARL4D/ELMO pathway affects the biological activity of breast cancer cells and have identified the biochemical processes that are involved.

The CCV Venture Grant Initiative was supported by the John T Reid Charitable Trusts, through the Cancer Council of Victoria.

For more information on related research, see:

› Cancer Immunology program (pg 24)

› Growth Control and Differentiation program (pg 40)

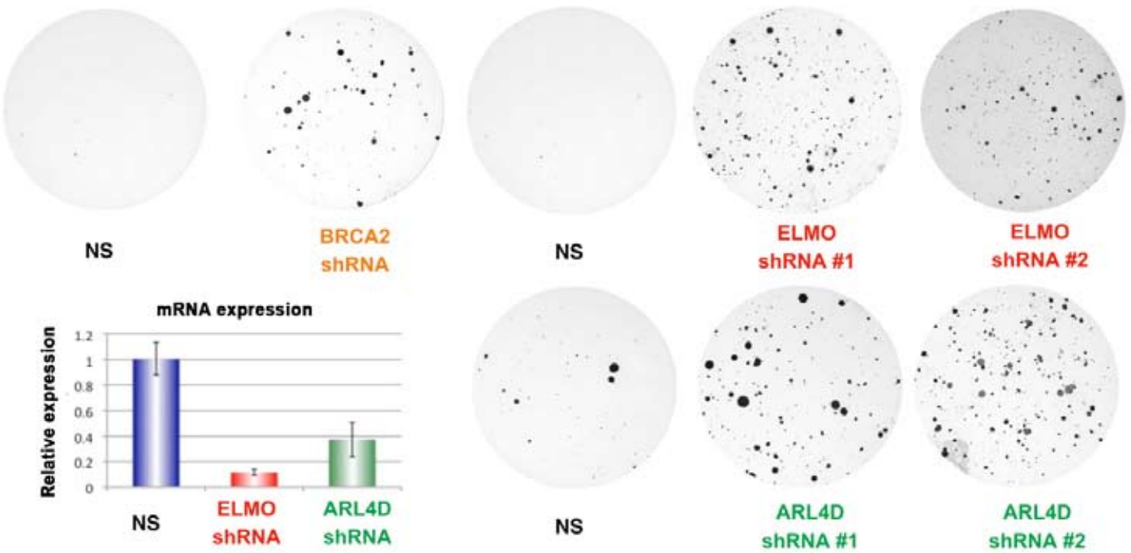


Figure 1: Knockdown of ARL4D and ELMO1 confers anchorage independent growth in HMEC-LTR cells.

1.6.7 CRC for Cancer Therapeutics Translational Research laboratory

Research leader: Dr Mark Devlin

As a participant in the Co-operative Research Centre for Cancer Therapeutics(CTx), Peter Mac 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.
- Development of non-invasive small animal fluorescent and bioluminescent imaging technologies.

KEY 2010 RESEARCH ACHIEVEMENT

Progression of a major CTx project to the late lead optimisation phase of development

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

The identification of new proteins and the elucidation of the role of these and known proteins in complex cellular signalling 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 multidisciplinary 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 is an important contributor at both a strategic and operational level to the drug discovery and development activities of CTx. We have 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. Moreover, the guiding principles of CTx and its participant organisations permit commercial-inconfidence 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

Cancer Therapeutics program – personnel

GENE REGULATION LABORATORY

Head
Assoc. Prof. Ricky Johnstone

Postdoctoral Researchers
Dr Amber Alsop
Dr Michael Bots
Dr Ailsa Frew
Dr Nicole Haynes
Dr Geoff Matthews
Dr Jessica Salmon
Dr Vanessa Solomon
Dr Inge Verbrugge
Dr Michaela Waibel

Research Assistants
Kellie Banks
Leonie Cluse
Ben Martin
Christina Neff
Rachael Ralli
Andrea Reitsma
Ashley Robertson
Kym Stanley

Postgraduate Students
Helen Arthur
Mark Bishton
Katrina Falkenberg
Nicole Messina
Andrea Newbold
Jake Shortt
Alison West

Honours Student
Marcus Lefebure

Executive Assistant
Linda Stevens

MELANOMA RESEARCH LABORATORY

Head
Dr Mark Shackleton

Research Assistants
Pacman Szeto
Elisha Wybacz

Summer Scholarship Students
Jessalyn Sukamto
John Yek

MOLECULAR IMAGING AND TARGETED THERAPEUTICS LABORATORY

Head
Prof. Rod Hicks

Project Leaders
David Binns
Dr Carleen Cullinane
Dr Donna Dorow

Research Postdoctoral Fellows
Dr Delphine Denoyer
Dr Titaina Potdevin

Research Assistants
Laura Kirby
Richard Young

Radiopharmaceutical Chemists
Dr Oliver Neels
Wayne Noonan
Dr Peter Roselt

Postgraduate Student
Dr Damien Kee

TRANSLATIONAL RESEARCH LABORATORY

Head
Assoc. Prof. Grant McArthur

Co-head
Prof. Rod Hicks

Scientific Manager
Dr Carleen Cullinane

Physician Scientist
Dr Ben Solomon

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

Research Assistants
Ekaterina Bogatyreva
Athena Hatzimihalis
Margarete Kleinschmidt
Richard Young

Technical Assistants
Kerry Ardley
Susan Jackson
Alison Slater
Rachael Walker
Jeannette Valentan

Postgraduate Student
Dr Arun Azad
Dr Damien Kee

PFIZER / PETER MAC CANCER GENOMICS PROGRAM

Scientific Manager
Dr Karen Sheppard

Project Leaders
Assoc. Prof. Rick Pearson
Assoc. Prof. Wayne Phillips

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

Postdoctoral Scientists
Dr Joanne Chan
Dr Richard Tothill

Research Assistants
Patricia Bukczynska
Allen Foo
Amelia Neilsen
Gwyneth Ng

Animal Technician
Kerry Ardley

Bioinformatics Analyst
Jason Ellul

CCV VENTURE GRANT INITIATIVE

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

Postdoctoral Fellows
Dr Christine Hauser
Dr Kathy Jastrzebski

Postgraduate Student
Gregory Leong

Summer Scholarship Student
Maria Selvadurai

CRC FOR CANCER THERAPEUTICS

Scientific Manager
Dr Mark Devlin

Research Assistants
Judy Doherty
Anthony Natoli
Kathryn Visser

CANCER IMMUNOLOGY PROGRAM

Administrative Assistant
Belinda Kelly

Laboratory Manager
Jason Brady

2

2 Clinical and Translational Research

Assoc. Prof. Declan Murphy moved to Melbourne in January 2010 to take up appointments as consultant urological surgeon at both Peter Mac and The Royal Melbourne Hospital, and Director of Outcomes Research at the Australian Prostate Cancer Research Centre, Epworth Richmond.

Trained in all aspects of open and endoscopic urology—with particular interest in laparoscopic and robotic-assisted surgery—Declan has a strong academic background and has published extensively in the field of minimally-invasive urology for the management of prostate, renal and bladder cancer.

Declan is also leading the establishment of the first Academic Robotic Cancer Surgery Program in Victoria's public health system, available to patients at Peter Mac. This will provide our patients with better treatment options and better outcomes—an excellent example of translating research developments into clinical practice.

Developing novel, evidence-based approaches to cancer care and cure, and providing patients with new and better treatment options by participating in cutting-edge research studies.

Based on the principle that cancer patients are best treated under the care of a multidisciplinary team focused on a particular type of cancer, Peter Mac has 11 'tumour streams'. The philosophy of these tumour streams is to provide integrated patient-focused care, based on evidence-derived treatment protocols, in a supportive and compassionate environment.

This clinical service model has led to a focus on research efforts along site-specific tumour lines. This scope is wide-ranging, from early phase clinical studies which allow our patients access to novel anti-cancer drugs to international randomised controlled trials designed to answer key clinical questions in cancer care.

Our clinical and translational research aims to drive the translation of our laboratory and clinical research into best clinical practice: to improve cancer survival, provide new diagnostic and treatment options, and reduce the impact of cancer on patients and their carers.

Division of Cancer Medicine
Prof. John Zalcberg, OAM

Division of Cancer Surgery
Assoc. Prof. Alexander Heriot

Division of Radiation Oncology and Cancer Imaging
Prof. Gillian Duchesne

TUMOUR STREAMS AND MEDICAL ONCOLOGY RESEARCH

Medical Oncology and Early Phase Clinical Trials
Assoc. Prof. Danny Rischin

Breast Service
Assoc. Prof. Michael Henderson

Gastrointestinal Service
Assoc. Prof. Michael Michael

Gynae-oncology Service
Assoc. Prof. Kailash Narayan

Haematology Service
Prof. John Seymour

Head and Neck Service
Assoc. Prof. June Corry

Lung Service
Prof. David Ball

Melanoma and Skin Service
Assoc. Prof. David Speakman

Paediatrics and Late Effects Service
Dr Greg Wheeler

Sarcoma
Prof. Peter Choong

Uro-oncology Service
Dr Farshad Foroudi

OVERVIEW

The Division of Cancer Medicine comprises Medical Oncology, Haematology, Pathology, Pharmacy, Pain and Palliative Care, Psychiatry, Allied Health, Centre for Blood Cells Therapies, Clinical Trials Unit and the Centre for Biostatistics and Clinical Trials.

Staff all work in multidisciplinary teams—regarded as a best practice model. With a focus on evidence-based practice, all staff members are committed to clinical research and improving treatments for patients. Cancer Medicine is also committed to ensuring that patients receive optimal supportive care (including psychosocial care).

The research conducted is closely linked to the affiliated clinical and basic science programs, including strong links with the Immunology and Cancer Therapeutic laboratory programs.

Notable research achievements representative of the breadth of translational research within Cancer Medicine are outlined in the following highlights and in the tumour stream and medical oncology sections (pg 82).

Figure 1: Registered Nurse Laura Pyszkowski and Research Nurse Carrie Donohoe with a patient in the Chemotherapy Day Unit. Joint appointments between the divisions of Cancer Medicine and Cancer Research help facilitate early drug development research, while close cooperation with the Translational Research laboratory permits bench to bedside research, and opportunities to return to the laboratory to explore observations made in the clinic.

2 Cancer Medicine

Executive Director: Prof. John Zalcberg OAM

RESEARCH HIGHLIGHTS

Clinical trials into high-risk cutaneous squamours cell carcinoma (CSCC) of the head and neck

Under the leadership of Peter Mac's Assoc. Profs. Danny Rischin and June Corry, and coordinated by the Trans-Tasman Radiation Oncology Group (TROG), this trial is a first for looking at new treatment strategies for CSCC, the second most common form of non-melanoma skin cancer. Involving researchers from across Australia and New Zealand, and led by study co-chairs from Medical Oncology and the Head and Neck Service at Peter Mac, this clinical trial is emblematic of the layered collaborative relationships that are fostered to strengthen cancer research, underpinning improvements in cancer care.

Haematological translational research

Pursuing a broad and varied clinical and translational research program, incorporating Peter Mac initiatives, cooperative group trials—particularly those of the Australasian Leukaemia and Lymphoma Group (ALLG)—and pharmaceutical industry studies, our clinician researchers facilitate important links with relevant oncological groups nationally and internationally.

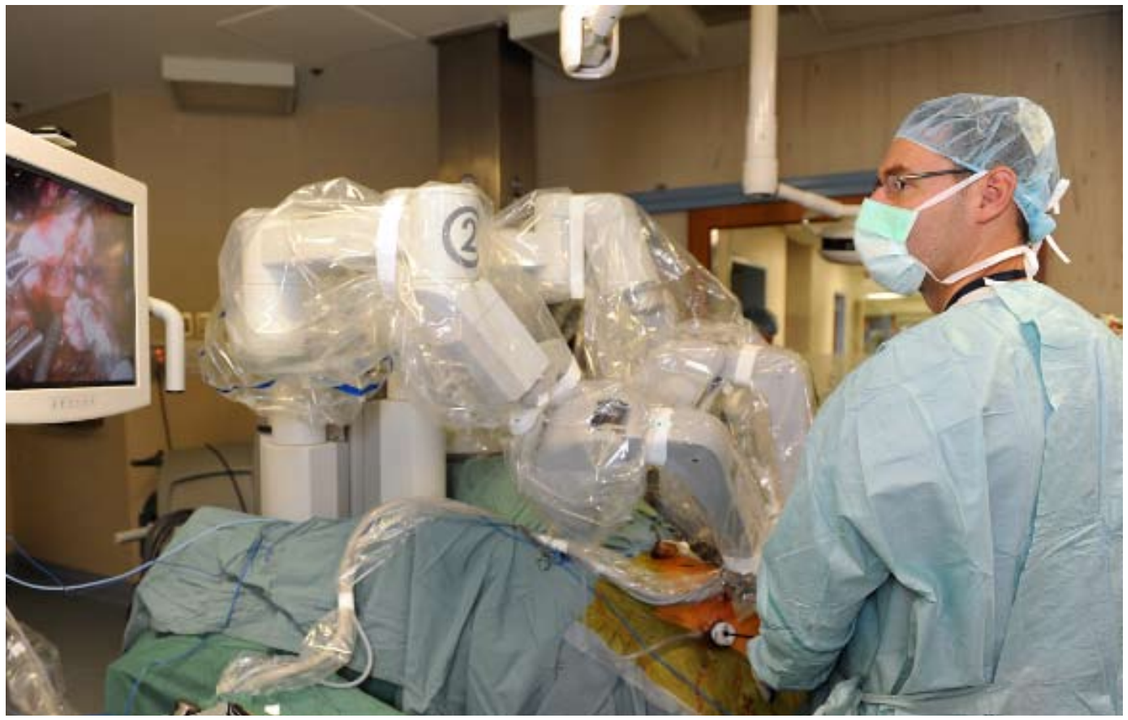
They lead studies for the early phase development of novel therapeutics, including clinical investigations into therapies for multiple myeloma, leukaemia and lymphoma.

Collaborative familial cancer studies investigating BRCA gene mutations in ovarian cancer

A collaborative genotyping study between the Familial Cancer Centre (FCC) and the Australian Ovarian Cancer Study (AOCS), both based at Peter Mac, is determining the number of women presenting with ovarian cancer who have BRCA gene mutations. The findings of this study are providing insights into the mechanisms underlying the development of ovarian cancer, and have the potential to change the way women with ovarian cancer are selected for BRCA genetic testing.

Also under Cancer Medicine are the departments of Pathology, Clinical Psychology, Nutrition, Occupational Therapy, Physiotherapy, Social Work and Speech Pathology; each with their own thriving programs, working together as interdisciplinary research platforms to support the entirety of Peter Mac's clinical and translational research.

2 Cancer Surgery



OVERVIEW

The Division of Cancer Surgery is committed to providing high quality healthcare and optimal outcomes for all patients and their families. We strive to ensure that the model of care is evidence-based, safe, efficient and effective. Surgical Oncology is committed to ensuring that the services we provide for our patients are the most effective available. We continually monitor and evaluate our processes, redesign our services and implement changes where required so that patient safety and clinical effectiveness become part of our every day routine as we continue to work toward achieving the most appropriate surgical service profile for Peter Mac.

The research conducted is closely linked to the affiliated clinical and basic science programs, particularly in the following areas: gastro-oesophageal, colorectal cancer and lower gastrointestinal, breast, melanoma, head and neck, hepatobiliary, clinical trials and basic science (with a focus on Barrett's Oesophagus and the PI3-kinase signalling pathway).

Cancer Surgery is committed to a research focus in all its activities and encompasses a wide area of research activity. This includes, though not limited to, the clinical science and technical aspects of surgery and anaesthesia, the evaluations of outcomes after surgical management, an understanding of tumour behaviour, particularly when relevant to the discipline of surgery, and an understanding of pre-malignant disease and those at genetically high risk of development of cancer. In addition, a variety of laboratory-based programs in basic oncological science are conducted, in particular, utilising molecular and cellular approaches to understand the development and progression of gastrointestinal cancers and to identify new treatments.

Cancer Surgery has successfully implemented fortnightly translational research meetings to allow cross fertilisation of research ideas among clinicians and research scientists, leading to greater collaboration and improved quality research. We also actively encourage and support junior medical staff to conduct clinical research projects, undertaking full time research within the division.

Notable research achievements which are representative of the breadth of translational research within Cancer Surgery are outlined in the following highlights and in the tumour stream achievements.

Figure 1: The da Vinci© Surgical System progressed through trial phases in 2010 in preparation for its launch in 2011.

2 Cancer Surgery

Executive Director: Assoc. Prof Alexander Heriot

Acting Executive Director
Assoc. Prof. Michael Henderson
(Until Oct 2010)

Executive Director
Assoc. Prof Alexander Heriot
(From Oct 2010)

RESEARCH HIGHLIGHTS

Initiation of the academic robotic surgery program

In 2010, robotic surgery was introduced to Peter Mac with the installation of a da Vinci© Surgical System, a first for a Victoria public hospital. The da Vinci© system was delivered as part of the Academic Cancer Robotic Cancer Surgery Program directed by Assoc. Prof. Declan Murphy, who has been awarded a two-year grant from the Victorian Policy Advisory Committee on Technology to enable a detailed evaluation of the clinical and health-economic impact of using this technology within the public hospital system. This research evaluation of robotic surgery will assess all aspects of the utilisation of robotic surgery, including oncological outcome, quality of life, and health economics and the impact on society.

Aberrant epithelial-mesenchymal hedgehog signalling characterises Barrett's metaplasia

In collaboration with researchers at Johns Hopkins University, Baltimore, USA, the Surgical Oncology laboratory recently demonstrated that the hedgehog signalling pathway, a key pathway important for the normal development of many organs including the gastrointestinal tract, may play an important role in Barrett's Oesophagus, a benign precursor to oesophageal adenocarcinoma. This study revealed that the hedgehog pathway is aberrantly activated in Barrett's Oesophagus compared to normal oesophagus, and that activation of this pathway in mouse oesophageal cells in a novel 3-D *in vivo* tissue reconstitution model resulted in morphologic changes and expression of columnar genes, reminiscent of Barrett's Oesophagus. This work highlights the translational research program between the Division of Research and Cancer Surgery.

Reference: Wang DH, Clemons NJ, Miyashita T, et al. Aberrant epithelial-mesenchymal Hedgehog signalling characterises Barrett's metaplasia. Gastroenterology. May;138(5):1810-22, 2010.

OVERVIEW

The Division of Radiation Oncology and Cancer Imaging comprises Radiation Oncology, Physical Sciences, Radiation Therapy Services and Diagnostic and Molecular Imaging. Our integrated research efforts range from basic science in cancer biology and physics, through translational research using molecular biological and imaging methods to clinical trials of innovative treatment strategies.

Radiation Oncology and Cancer Imaging is a rapidly evolving discipline. Consequently, to ensure patient treatments implemented at Peter Mac are based on world's best practice and enable Peter Mac to be actively involved in clinical research, the department is structured into ten specialist clinical units that focus on the various types of cancer.

Our focus of is to enhance the treatment of cancer patients, using radiotherapy, both as a single modality and in combined modality therapy with novel chemotherapy and targeted therapy agents.

Significant change and increase of complexity of radiotherapy treatment technology is enabling further refinement of brachytherapy and external beam radiotherapy methods, the development of image guided radiotherapy and patient motion management, use of novel 'diagnostic imaging devices' to assess the impact of organ motion on planning dosimetry and target volume assessments. Increased integration of imaging into the radiotherapy process is a key focus.

The research efforts continue to grow, particularly at the satellites, with increasing emphasis on multidisciplinary team programs. As well as radiation oncologists, we have a very active group of radiation medical physicists and radiation therapists who are increasingly involved in collaborative projects. Much of the research is investigator-initiated and multidisciplinary, and is increasingly attracting peer-reviewed funding.

Major areas of research include the successful program assessing the utility of molecular imaging in staging, biological characterisation and treatment and response assessment, together with the development of clinical dose escalation and body stereotactic irradiation approaches using PET/CT defined target volumes and gated acquisition of target volumes and with gated therapy delivery.

We are also actively involved in clinical trials. We have strong links with the Trans Tasman Radiation Oncology Group (TROG) and have recently become a member of the Radiation Therapy Oncology Group (RTOG), one of only three groups outside of North America. We have affiliations with Melbourne University, RMIT, Monash and Wollongong Universities and there are collaborations with both applied and basic research.

Figure 1: Recipient of the 2010 Prostate Cancer Foundation of America Creativity Award, Assoc. Prof. Scott Williams is investigating if better use of radiation therapy can more effectively treat prostate cancer.

2 Radiation Oncology and Cancer Imaging

Executive Director: Prof. Gillian Duchesne

RESEARCH HIGHLIGHTS

Our research achievements are highlighted below, in the tumour stream research and in the Enabling Technology Platforms sections.

Radiation therapy in prostate cancer

Scott Williams was awarded a Prostate Cancer Foundation of America Creativity Award, to conduct research aiming to provide new insights into how to optimally treat prostate cancer with radiation therapy.

PET imaging and tumour response

PET imaging is being used in the assessment of tumour volume and response to radiation in lung cancer patients, which involves staff working in all disciplines including imaging. Our PET program has influenced the management of lung cancer worldwide, with six papers cited in the *American Society of Clinical Oncology* lung cancer treatment guidelines; our criteria for response assessment after chemoradiation in non-small cell lung cancer (NSCLC) have now been widely adopted by clinicians worldwide.

Gated Radiotherapy

Gated Radiotherapy is Improving the delivery of radiotherapy to tumour volumes which move with respiration. This research aims to assess and detect the range of tumour movement with respiration and delivery of radiotherapy only when the tumour is present within the target zone. This approach, known as gated treatment delivery, aims to improve the dose delivered to cancerous cells whilst minimising the effect to healthy tissues.

Managing organ deformation and patient compliance

This is being studied via the implementation of a structured patient preparation program for daily radiotherapy for men with localised prostate cancer.

eLearning

A Victoria-wide web based electronic learning (eLearning) program has been developed for Image Guided Radiotherapy. This program brings together all Victorian Radiation Oncology departments in creating and utilising this resource.

Recent treatment results for Peter Mac chemoradiation patients with NSCLC show that the use of PET/CT for patient selection and treatment planning has led to survival that is among the best ever reported anywhere in the world.

2.1 Medical Oncology and Early Phase Clinical Trials

Head: Assoc. Prof. Danny Rischin

The Department of Medical Oncology runs a large clinical research program that includes clinical trials of cancer therapeutics from early phase trials (with a focus on targeted therapies) to definitive phase III trials, studies exploring the clinical relevance of new biologic findings, supportive care research including survivorship and psycho-social interventions, adolescent and young adult oncology research and familial cancer research including risk management and chemoprevention.

RESEARCH FOCUS

- New drug development and early phase clinical trials focused on targeted therapies.
- Establishing benefit of new therapies in phase 2 and 3 clinical trials including investigator initiated cooperative group trials.
- Supportive care research including survivorship.
- Familial cancer including risk management and chemoprevention.

2010 RESEARCH ACHIEVEMENTS

Members of the department gave a number of significant presentations at the American Society of Clinical Oncology Annual Meeting. Assoc. Prof. Danny Rischin gave an oral presentation on the prognostic significance of human papilloma virus and p16 status in patients with oropharyngeal cancer treated on a large international phase 3 trial and Assoc. Prof. David Thomas reported on the activity of denosumab for the treatment of giant cell tumour of bone in an oral session.

Peter Mac investigators were co-authors on two of the most exciting trials with new drugs presented at the meeting:

- Assoc. Prof. Grant McArthur on the phase 1 trial of a BRAF inhibitor which has shown significant activity in melanoma.
- Dr Ben Solomon on a phase I study of a drug that inhibits the ALK receptor which has shown very promising activity in patients with ALK positive lung cancer.

Publication highlights included a population-based cohort study of over 3,000 breast cancer patients which examined the association between reproductive risk factors and death. Women who had had a full-term pregnancy within two years prior to their breast cancer diagnosis had a 2.75 times higher death rate (Phillips et al. Cancer Epidemiol Biomarkers Prev 18: 1792–1797, 2009).

In another study Peter Mac investigators found that the Australian general public wants to be informed about expensive anti-cancer drugs as potential treatment options, even if they are not willing or readily able to pay for them (Mileshkin et al, J Clin Oncol Dec 1;27(34):5830-7, 2009).

Kelly Phillips won the award for best oral presentation by a consultant at the Medical Oncology Group of Australia (MOGA), 30th Anniversary Annual Scientific Meeting for her work on *Breast Cancer Prognosis In BRCA1 and BRCA2 Mutation Carriers: An International, Prospective, Population-Based Cohort Study*.

Grant highlights included a survivorship project in bowel cancer survivors led by Assoc. Prof. Michael Jefford funded by Cancer Australia/Beyond Blue and the Victorian Cancer Agency (VCA); a NHMRC project grant led by Assoc. Prof. Michael Michael to investigate genomics and functional imaging to predict pharmacokinetics and pharmacodynamics; translational cancer research grants from VCA in melanoma led by Assoc. Prof. Grant McArthur and in sarcoma led by Assoc. Prof. David Thomas.

2.2 Breast Service

Head: Assoc. Prof. Boon Chua

The Breast Service is actively progressing a strategic planning and service development framework to establish national and international leadership in research-driven multidisciplinary clinical programs for optimal patient outcomes.

Our strong and diverse research program, which encompasses laboratory, translational and clinical research, draws on the collective academic strengths of our members in collaboration with other leading Peter Mac researchers and major national and international clinical trials groups.

RESEARCH FOCUS

- Breast cancer genetics.
- Breast cancer prevention.
- Early stage breast cancer.
- Locally advanced breast cancer.
- Metastatic breast cancer.
- Survivorship issues.

2010 RESEARCH ACHIEVEMENTS

A phase 3 study of radiation dose escalation and fractionation schedules in non-low risk ductal carcinoma *in-situ* (DCIS) of the breast

This is a TROG (Trans Tasman Radiation Oncology Group)-led trial in collaboration with the Breast International Group, NCI Canada Clinical Trials Group (NCIC CTG), European Organisation for Research and Treatment of Cancer (EORTC), UK Breast Intergroup and International Breast Cancer Trials Group (IBCSG). This active trial aims to individualise radiation therapy for women with DCIS of the breast and is underpinned by an international translational research program that investigates the biological profiles of DCIS predictive of a high risk of invasive breast cancer recurrence.

A phase 3 study of regional radiation therapy for early breast cancer

This study evaluates if regional nodal irradiation in addition to whole breast radiation after breast conserving surgery and systemic therapy improves overall survival for early breast cancer. The first results of the study will be presented at the American Society of Clinical Oncology Annual Scientific Meeting in 2011.

Randomised trial of accelerated partial breast irradiation (RAPID)

This active trial evaluates if partial breast irradiation using external beam 3D conformal radiotherapy is as effective as the more protracted conventional whole breast irradiation after breast conserving surgery for early breast cancer. If confirmed, partial breast irradiation will improve convenience of care for patients and radiotherapy resource utilisation.

International randomised controlled trial to compare targeted intra-operative radiotherapy with conventional post-operative radiotherapy after conservative breast surgery for women with early stage breast cancer (TARGIT)

The study showed that a single fraction of intra-operative radiotherapy targeted to the tumour bed (partial breast irradiation) is equivalent to standard post-operative whole breast radiotherapy after breast conserving surgery in women with early breast cancer, in terms of local control. The first results were published in *The Lancet* in 2010.

For more information on related research, see:

- Familial Cancer Centre (pg 114)

- kConFab Follow-Up Project (pg 116)

2.3 Gastrointestinal Service

Head: Assoc. Prof. Michael Michael

The Gastrointestinal Service is a multidisciplinary therapeutic program for patients with upper and lower gastrointestinal cancers. Our research focus is directed, from the institutional to international level, towards the evaluation of new therapeutic strategies to provide optimal individualised care for our patients.

RESEARCH FOCUS

- Translational and multi-modality approaches of surgery, radiation with chemotherapy and/or biological agents in the treatment of all gastrointestinal (GI) malignancies, in particular rectal, gastric and anal cancers.
- Predicting the efficacy of chemoradiotherapy through genomic approaches in rectal and oesophageal cancers.
- Phase 1 to 3 studies of new drugs and novel combined modality regimens.
- Participation in national and multinational phase 2–3 clinical trials
- Predicting chemotherapy drug handling, toxicity and efficacy by functional imaging, pharmacogenomics (normal host tissues and tumour tissues) with the aim of individualising treatment. In particular in colon cancer and gastrointestinal stromal tumours (GISTs).

2010 RESEARCH ACHIEVEMENTS

The Gastrointestinal Service aims to optimise and individualise the treatment of GI malignancies through several research initiatives:

The evaluation of novel combined modality therapies with the commencement of novel chemoradiotherapy trials for rectal cancer

This involves the evaluation of novel combinations of agents to both optimise the control of local disease and micro- and macroscopic metastatic disease as well as increasing radiosenstisation in rectal cancer.

The evaluation of functional imaging and pharmacogenomics in several settings to predict prognosis, tumour response and normal tissue toxicity for several malignancies to systemic and combined modality therapies

These will hopefully enable us to individualise therapy (agents used and treatment intensity) to increase tumour control, whilst reducing toxicity and to improve patients overall survival. Specific work is being carried out in oesophageal cancer, colorectal cancer and anal cancers.

Technological evaluation

The evaluation of novel technologies such as Robotics, IORT, stereotactic radiotherapy to optimise local treatment of GI malignancies.

These have led to several ongoing trials supported by research funding and postgraduate research fellows.

The program has been supported by competitive grants from post-graduate research scholarships, the NHMRC and Cancer Australia as well as industry support.

2.4 Gynae-oncology Service

Head: Assoc. Prof. Kailash Narayan

The Gynae-oncology Service is a multidisciplinary program with a research focus directed at understanding and improving the management and treatment of gynae-oncology patients.

RESEARCH FOCUS

Assessing and improving the treatment of:

- Cervical cancer.
- Endometiral carcinoma.
- Ovarian carcinoma.

2010 RESEARCH ACHIEVEMENTS

Nurse led interventions

Peter Mac's Gynae-oncology Service is dedicated to developing and delivering improved supportive care. Led by Prof. Penny Schofield, behavioural researcher, a national study into the role of nurse led interventions supported by trained cancer peers is underway. Recruiting patients nationwide into a process of education and support, this study is unique in that it includes peer support from carefully chosen long-term survivors, offering them a role in supporting newly diagnosed patients on their journey through cancer treatment.

Adjuvant systemic chemotherapy in cervical cancer treatment

The OUTBACK randomised phase 3 study being developed by Dr Linda Mileshkin and Assoc. Prof. Kailash Narayan aims to assess the value of additional adjuvant systemic chemotherapy for patients who have completed definitive chemo-radiation treatment for locally advanced cervical cancer. This trial will be run internationally through the Gynaecologic Cancer Intergroup and led by the Australia New Zealand Gynaecological Oncology Group (ANZGOG) in collaboration with the NHMRC Clinical Trials Centre.

Adjuvant chemotherapy in endometrial cancer

The PORTEC 3 study aims to assess the role of adjuvant chemotherapy for patients receiving post-operative radiation treatment for high risk endometrial cancer; Peter Mac is the highest recruiting site to this large international study which is supported by a grant from the NHMRC. Dr Linda Mileshkin is the study chair for the Australia New Zealand Gynaecological Oncology Group (ANZGOG). Dr Pearly Khaw is the radiation oncology lead for the study who is working with TROG to perform quality assurance for the study.

If positive, OUTBACK and PORTEC 3 will change the standard of care for women with high-risk endometrial and cervical cancers.

The value of PARP inhibitors in treatment of ovarian cancer

Several open studies are assessing the value of PARP inhibitors in the treatment of women with relapsed ovarian cancer. These targeted agents are particularly effective in women known to have a genetic predisposition to ovarian cancer due to a BRCA1 or BRCA2 mutation. Their value is also being assessed in women with sporadic ovarian cancer. In addition, our patients participate in phase 1 trials open through of Cancer Medicine.

2.5 Haematology Service

Head: Prof. John Seymour

The Haematology Service conducts a broad range of clinical and translational research studies focused on patients with haematologic malignancies — on pathogenesis, supportive care and the enhancement of long-term quality of life. Key conditions on which we focus include multiple myeloma, non-Hodgkin lymphoma, chronic lymphocytic leukaemia and the myelodysplastic syndromes.

RESEARCH FOCUS

- Novel therapies for multiple myeloma, and their immunologic basis of activity.
- Early phase development of novel therapeutics, particularly monoclonal antibodies and epigenetic therapies.
- Enhancing the efficacy and safety of nucleoside analogue combination therapies in indolent lymphoproliferative disorders.
- A state-wide referral centre for the management of cutaneous lymphomas and investigation of novel therapies for these diseases.
- A recognised centre of excellence for management of myelodysplastic syndromes and myeloproliferative disorders, including the development of novel treatments such as Jak-2 inhibitors.

2010 RESEARCH ACHIEVEMENTS

The focus of our research is improving our understanding of disease pathogenesis, improving treatments, enhancing supportive care, and enhancing the long-term health status of patients with haematologic malignancies. We have pursued a broad and varied clinical and translational research program, which incorporates our own initiatives, cooperative group trials—particularly those of the Australasian Leukaemia and Lymphoma Group (ALLG)—and pharmaceutical industry studies.

At every opportunity we seek to enhance translational research productivity and collaborate with laboratory-based research colleagues, particularly in the Cancer Therapeutics, Cancer Immunology, and Haematology Immunology Translational Research laboratory programs.

2010 was very successful, with more than 30 international conference presentations, and 52 peer-reviewed publications by the medical, nursing, and laboratory staff of the Haematology, Service including numerous influential reports:

- Detailed exploration of the mechanism of action of immunomodulatory drugs revlimid and thalidomide used in multiple myeloma, and the detrimental effects of the commonly used corticosteroid agent dexamethasone.
- Presentation and publication of the first study demonstrating the benefits of maintenance treatment with the monoclonal antibody Rituximab as part of the initial chemo-immunotherapy treatment program for patients with follicular lymphoma.
- Confirmation of the superior therapeutic activity of the hypomethylating agent azacitidine over conventional therapies in elderly patients with acute myeloid leuekaemia.
- Confirmation of the activity of the immunotoxin conjugate deileukein diftotox in cutaneous T-cell lymphomas, in a study which supported the licensing of this agent internationally.
- Demonstration of the activity of the epidentic agent romidepsin in patients with T cell lymphomas, which are very difficult to treat with conventional agents.
- Early phase development of novel therapeutics. This high priority area of research includes the following clinical investigations:
  - A co-ordinated suite of ongoing studies into novel therapies for multiple myeloma.
  - Ongoing trials of the novel pro-apoptotic agent ABT263 in patients with chronic lymphocytic leukaemia.
  - Optimising therapeutic approaches for indolent lymphoproliferative disorders.
  - Exploration of the novel Jak-2 inhibitor SB15158 in myeloproliferative disorders.

For more information on related research, see:

› Cancer Immunology program (pg 24)

› Cancer Therapeutics program (pg 62)

› Haematology Immunology Translational Research Laboratory (pg 30)

2.6 Head and Neck Service

Head: Assoc. Prof. June Corry

Peter Mac's Head and Neck Service is the largest in Australia and offers comprehensive diagnostic and treatment services to cancer patients throughout Victoria. Patient care is provided by an experienced multidisciplinary team of radiation oncologists, medical oncologists, surgeons, diagnostic radiologist, nursing, radiotherapists, social workers, dietitians, dental oncologists and speech pathologists. A key feature of our service is expertise in the complex and technically challenging planning of head and neck radiotherapy treatment. We also offer expertise and on-site delivery of concurrent chemo-radiotherapy and, when appropriate, the availability of novel agents through phase I/II studies.

The Head and Neck Service has a strong international profile based on its published record of clinical research, which underpins optimal patient care.

RESEARCH FOCUS

- Improving clinical outcomes for head and neck cancer patients.
- Investigating novel head and neck cancer treatments with a focus on hypoxia.
- Minimising treatment side-effects with a focus on Intensity-Modulated Radiation Therapy (IMRT).

2010 RESEARCH ACHIEVEMENTS

Peter Mac's Head and Neck Service has 25 clinical research projects currently in progress. Some examples of institutional, national and international collaborations include:

Trans-Tasman Radiation Oncology Group study on Post-operative concurrent chemo-radiotherapy in high risk cutaneous squamous cell carcinoma of the head and neck

This study is the first looking at new treatment strategies for high risk skin cancer. Study co-chairs are Assoc. Prof. Sandro Porceddu, and Assoc. Profs. Danny Rischin and June Corry from Peter Mac. The primary objective of the trial is to determine, in patients who have undergone surgery with curative intent for high-risk cutaneous squamous cell carcinoma (CSCC) of the head and neck, whether there is a difference in time to loco-regional relapse between patients treated with post-operative concurrent chemo-radiotherapy (consisting of Carboplatin) and patients treated with post-operative radiotherapy alone.

Radiotherapy with Humidification in Head & Neck Cancer (RadioHum)

A randomised Phase III trial of TROG in collaboration with Fisher and Paykel Healthcare. This study uses simple humidification aiming to reduce the severity and duration of patients painful mucositis. Study principal investigators are Dr Andrew McCann (NZ) and Dr Tsien Fua from Peter Mac.

A Phase I/II Study of Cetuximab, Carboplatin and Radiotherapy in patients with locally advanced head and neck cancer

This study focuses on a unique group of head and neck cancer patients not previously studied—those unable to have cisplatin treatment. Study co-chairs are Assoc. Profs. Danny Rischin and June Corry.

IHN01 Study—Randomised study of cisplatin-RT ± nimotuzumab

A collaboration with Singapore National Cancer Centre (NCC), this is a study intensifying adjuvant treatment after surgery using a new biological drug in addition to chemotherapy and radiotherapy. Study principal investigators are Prof. Khee Chee Soo (Singapore NCC) and Assoc. Prof. June Corry.

2.7 Lung Service

Head: Prof. David Ball

Peter Mac's Lung Service promotes and facilitates clinical, translational and supportive care research directed at improving outcomes for patients with lung cancer and other thoracic malignancies.

RESEARCH FOCUS

- Molecular imaging and prognostic factors.
- Development of novel therapies for non-small cell lung cancer.
- Symptom palliation.
- Psychosocial research.

2010 RESEARCH ACHIEVEMENTS

The CHISEL randomised trial

A Cancer Australia funded trial comparing conventional radiotherapy (33 treatments) with hypofractionated stereotactic radiotherapy (three treatments) for stage I peripherally located lung cancers. This is now a collaborative national study of the Trans-Tasman Radiation Oncology Group (TROG) and the Australasian Lung Cancer Trails Group. This study may lead ultimately to the availability of an effective non-surgical treatment option for patients with early stage lung cancer. Work on Quality Assurance for the CHISEL Trial was presented by Natalie Clements at the 52nd Annual meeting of the American Association of Physicists in Medicine in Philadelphia, USA.

FLT PET study

A study of tumour cell kinetics during radical radiotherapy using the novel tracer FLT was completed in 2010, with NHMRC funding secured by Dr Sarah Everitt to continue this work into 2011.

4D PET/CT

The influence of 4D PET/CT on radiotherapy planning is under investigation.

SAFRON study

A pilot study of single dose stereotactic radiotherapy for patients with secondary lung cancers is being led by Dr Shankar Siva. The cancers will be studied using perfusion CT to determine if the tumour killing effect of this treatment is achieved through an effect on its blood supply.

FGFR1 amplification in squamous cell carcinoma

This project, conducted in conjunction with St Vincent's Hospital and international collaborators based in Cologne, Germany, has identified overexpression of a factor (FGFR1) in a common type of lung cancer which may make the cancer susceptible to inhibition of FGFR1. This is the first time a factor of this type has been detected in patients with squamous cell carcinoma. This study was funded in part by the Peter Mac Foundation, and published in *Science Translational Medicine* in December 2010.

Chemotherapy studies

Peter Mac's Lung Service has a number of active chemotherapy studies, including:

- The Canadian led BR29 randomised study of chemotherapy with and without AZD 2171.
- A phase 3 study of chemotherapy and crizotinib in patients with ALK mutations.
- The GATE study of erlotinib and gemcitabine in elderly or poor performance status patients.

2.8 Melanoma and Skin Service

Head: Assoc. Prof. David Speakman

The Melanoma and Skin Service undertakes translational and clinical research in melanoma and non-melanoma skin cancer with a focus on integrating research with multidisciplinary care of patients with skin cancer.

There have been significant developments in the treatment options for patients with advanced skin cancers, and we are in the fortunate position of being at the forefront of the newest agents to control this disease.

RESEARCH FOCUS

- Evaluation of novel therapeutics in melanoma.
- Integration of molecular analysis of melanoma with clinical care.
- Targeted therapies in skin cancer.
- Role of radiotherapy in melanoma and other skin cancers.

2010 RESEARCH ACHIEVEMENTS

The Melbourne Melanoma Project

This is a tissue banking and database program with the potential to unlock the further molecular secrets of melanoma and with significant potential to develop improved therapeutic strategies for management by identifying specific targets related to melanoma. We have expanded the range of local therapies to combat locoregional disease with the use of photodynamic and microwave therapies and focused laser along with the standards of surgery and radiotherapy for patients in whom progressive disease has a high impact on their daily lives and routines.

BRAF inhibitors in melanoma treatment

The Melanoma and Skin Service has been involved in trials of PLX4032—a highly promising BRAF inhibitor to combat melanoma in its more advanced stages. This work provides the strongest light yet for patients with progressive disease, and we continue to be involved in first-line trials of this agent (see Clinical Trials Unit, pg 112).

Sentinel Lymph Node Biopsy

The focus of our Surgical Oncology team remains centered around the ever-evolving role of Sentinel Lymph Node Biopsy. We continue to participate in the MSLT 2 International Multi Centre Trial regarding the ongoing management of patients with positive Sentinel Lymph Nodes in Melanoma. The unit has also presented significant data on the role of staging, in particular with PET scans in stage 3A disease,
and also in patients with high risk primary lesions. We continue to investigate ways to avoid the morbidity of radical lymphadenectomy.

For more information on related research, see:

- Clinical Trial Unit (pg 112)
- Translational Research Laboratory (pg 67)

2.9 Paediatrics and Late Effects Service

Head: Dr Greg Wheeler

The Paediatrics and Late Effects Service is contributing to developments in a number of institutional, national and international clinical and translation trials into the treatment and clinical outcomes of children with cancer.

RESEARCH FOCUS

- Understanding and improving the treatment of children with cancer.
- Cooperative research into childhood brain tumours.
- Novel supportive care interventions for children undergoing radiotherapy.
- Physical and psychology health of the 'survivors' attending the clinic.

Our main research focus is to participate in international cooperative group studies. Our portfolio of local studies is also expanding.

2010 RESEARCH ACHIEVEMENTS

Peter Mac's Paediatrics and Late Effects Service is developing guidelines and protocols that will, over the next few years, result in the development of research protocols. We are also developing an important network of supportive care projects to investigate the effects of the process of radiotherapy on children. These projects include music therapy, information books and video creation.

Recent local protocols, guidelines and collaborations have started to bear fruit, with two Public Health Care Awards and a VCA Supportive Care Research Capacity Building grant awarded in 2010. Further research initiatives are being developed in both technical and supportive care fields so that we may better care for children as they undergo radiation therapy and subsequently throughout their lives.

We remain committed to participation in the Children's Oncology Group Cooperative trials in conjunction with The Royal Children's Hospital and the St Jude Meduoblastoma consortium in the SJMB03 study. This study investigates the genetic makeup of tumours related to treatment outcomes and cognitive effects of treatments of patients with newly diagnosed childhood brain tumours known as medulloblastoma, supratentorial primitive neuroectodermal tumour (PNET), or atypical teratoid rhabdoid tumour (ATRT).

2.10 Sarcoma Service

Head: Prof. Peter Choong

The Sarcoma Service provides access to leading treatments through an active clinical trials program, and supports basic and translational research programs in osteosarcoma and liposarcoma, and adolescent and young adult cancer.

RESEARCH FOCUS

- The identification and characterisation of a novel tumour suppressor gene in osteosarcoma, Wif1 (see Sarcoma Genetics and Genomics laboratory, pg 35).
- The role of the immune system in osteosarcoma.
- Clinical trials of denosumab in Giant Cell Tumour of bone, and of antiangiogenic agents in soft-tissue sarcoma.
- Understanding inherited cancer risk in sarcoma families.

2010 RESEARCH ACHIEVEMENTS

The Australian Sarcoma Study Group(ASSG)

The ASSG, a national cooperative aiming to facilitate access to leading treatments through translational and clinical research, is hubbed at Peter Mac. The group's chief aim is to develop and coordinate cohesive clinical trials and basic research while still focusing on community education and patient advocacy of sarcomas. In the last 18 months, Peter Mac has enrolled over 250 patients on the national sarcoma-specific clinical database.

The Rainbows for Kate International Sarcoma Kindred Study

Sarcomas are uncommon cancers that disproportionately affect young people with a high mortality and significant morbidity. The Rainbows for Kate International Sarcoma Kindred Study (ISKS) is creating a resource to investigate the familial aspects of adult-onset sarcoma. After 12 months, we have over 400 fully consented participants across five states, above the projected rate, and we expect to meet the national target of 600 index cases within three years. We are now opening sites in India, France and New Zealand, making this a global study. Early data confirm powerful underlying genetic factors present in families with sarcoma. In the coming years the ISKS resource will be invaluable in elucidating these factors and improving outcomes for those families affected by sarcoma.

The Livestrong Young Adult Alliance Osteosarcoma Meta-analysis

In collaboration with co-operative oncology groups internationally, we have conducted the world's largest meta-analysis of outcomes for patients with curable osteosarcoma. This study, involving over 4,000 patients from 26 clinical trials, has shown that there are important gender- and age-related differences in side effects and treatment response for patients with osteosarcoma.

Denosumab and Giant Cell Tumour(GCT) of bone

Peter Mac has played a key role in the development of denosumab in GCT, resulting in a lead author publication of the first clinical study in *Lancet Oncology* in 2010. Denosumab has shown remarkable biological and clinical activity in GCT, and is now being explored in follow up studies.

Sarcoma Service Nursing highlights

Regular nursing education forums, held in conjunction with staff at St Vincents Hospital, begun in 2010. These forums focus on the medical and psychosocial care of sarcoma patients undergoing multimodal therapy between Peter Mac and St Vincent's.

For more information on related research, see: Sarcoma Genetics and Genomics laboratory (pg 35)

2.11 Uro-oncology Service

Head: Dr Farshad Foroudi

The Uro-oncology Service is a multidisciplinary clinical unit offering treatment for all forms of uro-oncology malignancies. Our Service offers tertiary care including all forms of surgical management, radiation oncology techniques and systemic therapy. We have links to co-operative research groups and laboratory based research.

Our Service is also involved in a number of supportive care programs and patients are offered co-ordinated care.

RESEARCH FOCUS

- Multidisciplinary care.
- Nursing interventions and supportive care.
- Image guided and adaptive radiotherapy.
- Testicular cancer.
- Prostate, bladder and renal cancer.

2010 RESEARCH ACHIEVEMENTS

The research of Peter Mac's Uro-oncology Service is aimed at improving the clinical outcomes of patients. Through surgical innovations we aims to reduce perioperative stay and pain as well as shorten the time needed to return to work. Developments in radiation oncology should have the dual benefits of reducing toxicity in terms of surrounding normal tissues as well as the improving local control. Involvement in multiple clinical studies will help provide the basis of future therapies.

Recent research highlights include:

- The introduction of robotic surgery to Peter Mac with the installation of a da Vinci© Surgical System, a first for a Victoria public hospital. The da Vinci© system was delivered as part of the Academic Cancer Robotic Cancer Surgery Program directed by Assoc. Prof. Declan Murphy, who has been awarded a two-year grant from the Victorian Policy Advisory Committee on Technology to enable a detailed evaluation of the clinical and health-economic impact of using this technology within the public hospital system.
- Assoc. Prof. Scott Williams continues to alead a project that brings together unique data from Peter Mac's excellence in imaging, biology, external beam radiation and brachytherapy fields to provide new insights into how to optimally treat prostate cancer with radiation therapy.

Clinical and Translational Research – personnel

CANCER MEDICINE

Prof. John Zalcberg, OAM

CANCER SURGERY

Assoc. Prof. Alexander Heriot

RADIATION ONCOLOGY AND CANCER IMAGING

Prof. Gillian Duchesne

BREAST SERVICE

Chair
Assoc. Prof. Boon Chua

Medical Oncologists
Dr Ian Collins, Fellow
Dr Prudence Francis
Dr Marisa Grossi
Dr Sandra Harvey (Breast Cancer Genetics and Survivorship Fellow)
Dr Ross Jennens
Dr Gillian Mitchell
Assoc. Prof. Kelly Phillips

Radiation Oncologists
Dr Jill Ainslie
Dr Michelle Bishop
Dr Steven David
Dr Roslyn Drummond
Dr Mary Dwyer
Dr Tracie Gleisner
Dr Bronwyn King
Dr Chen Liu
Dr Claire Phillips
Dr Phillip Tran

Surgical Oncologists
Assoc. Prof. Michael Henderson
Miss Jane O'Brien
Miss Cathie Poliness
Miss Anita Skandarajah
Assoc. Prof. David Speakman
Miss Chantel Thornton, Fellow

Pathology
Prof. Stephen Fox
Dr Catherine Mitchell

Cancer Imaging
Prof. Rod Hicks
Dr Alexander Cochet, PET Fellow
Dr Kate Moodie
Dr Brooke Sawyer

Familial Cancer Centre
Dr Gillian Mitchell

Medical Physicist
Prof. Tomas Kron

Radiation Therapists
Katie Davidson
Brigid Moran
David Willis

GASTROINTESTINAL SERVICE

Chair
Assoc. Prof. Michael Michael

Deputy Chair
Mr Bruce Mann

Medical Oncologists
Dr Alex Boussioutas
Assoc. Prof. Michael Jefford
Prof. John Zalcberg, OAM
Dr Alan Zimet

Radiation Oncologists
Dr Julie Chu
Dr Trevor Leong
Assoc. Prof. Sam Ngan
Dr Kirsty Wiltshire

Surgical Oncologists
Mr Simon Banting
Mr Cuong Duong
Assoc. Prof. Sandy Heriot
Mr Craig Lynch
Assoc. Prof. John Mackay
Mr Bruce Mann
Mr John Spillane
Mr Ben Thomson

Anatomical Pathologists
Dr Bill Murray (Head)
Dr Catherine Mitchell

Nuclear Medicine Physicians
Prof. Rod Hicks
Mr Michael Hoffman
Dr Grace Kong
Dr Kate Moodie

Radiologists
Dr Nick Ferris

Surgical Oncology laboratory
Assoc. Prof. Wayne Phillips (Head)

Postgraduate Students
Dr Charles Pilgrim
Dr Henry To

GYNAE-ONCOLOGY SERVICE

Chair
Assoc. Prof. Kailash Narayan

Medical Oncologist
Dr Linda Mileshkin

Radiation Oncologists
Dr David Bernshaw
Dr Pearly Khaw
Dr Bronwyn King

Brachytherapist
Sylvia van Dyk

Visiting Fellow
Dr Joanne Alfieri

HAEMATOLOGY SERVICE

Chair
Prof. John Seymour

Consultant Haematologists
Dr Kate Burbury
Dr Dennis Carney
Dr Simon Harrison
Dr Kirsten Herbert (CCV Fellow)
Dr Henry Januszewicz
Prof. Miles Prince
Assoc. Prof. David Ritchie
Dr Stephen Ting
Dr David Westerman
Assoc. Prof. Max Wolf

Research Fellows
Dr Michael Dickinson
Dr Amit Khot

Nurse Coordinators
Odette Blewitt
Sharna Debham
Catherine Grima
Kristen Houdyk
Trish Joyce
Yvonne Panek-Hudson

Clinical and Translational Research – personnel

HEAD AND NECK SERVICE

Chair
Assoc. Prof. June Corry

Medical Oncologists
Assoc. Prof Danny Rischin
Dr Annette Lim
Dr Ben Solomon

Radiation Oncologists
Assoc. Prof June Corry
Dr Andrew Coleman
Dr Ieta D'Costa
Dr Tsien Fua
Dr Chen Liu
Dr Mark Lee

Surgical Oncologists
Mr Sorway Chan
Mr Stephen Kleid
Prof. Andrew Sizeland

Dietitian
Nicole Kiss

Nurse Coordinator
Wendy Poon

Psychology/Psychiatric Service
Annabel Pollard
Kate Neilson
Dr Jeremy Cooper

Radiotherapy Charge
Sue Walsham

Speech Pathologist
Louise Dobbie

Translational Research
Assoc. Prof. Alex Dobrovic
Richard Young

LUNG SERVICE

Chair
Prof. David Ball

Medical Oncologists
Assoc. Prof. Michael Michael
Assoc. Prof. Linda Mileshkin
Dr Ben Solomon

Radiation Oncologists
Prof. David Ball
Dr Belinda Campbell
Dr Steven David
Assoc. Prof. Michael Mac Manus
Dr Nikki Plumridge
Dr Mark Shaw
Dr Greg Wheeler
Assoc. Prof. Andrew Wirth

Thoracic Surgeons
Mr Phillip Antippa
Mr Gavin Wright

Respiratory
Assoc. Prof. Lou Irving
Dr Renee Manser

Cancer Imaging
Prof. Rod Hicks

Psychosocial
Assoc. Prof. Penny Schofield

Nurse Coordinator
Mary Duffy

Structural Imaging
Dr Brooke Sawyer

Physicists
Prof. Tomas Kron
(Principal Research Physicist)

Assoc. Prof. Annette Haworth
(Clinical Research Physicist)

Radiation Therapists
Yolanda Aarons
Dr Sarah Everitt

Radiologist
Assoc. Prof. Eddie Lau

Nuclear Medicine Physician
Dr Michael Hofman

Statisticians
Assoc. Prof. Richard Fisher
Alan Herschtal

Radiation Oncology Fellow
Danny Duplan

Radiation Oncology Registrar
Dr Shanker Siva

Research Manager
Virginia Tuckwell

Study Coordinator
Deborah Cruickshank

Research Division
Assoc. Prof. Alex Dobrovic

MELANOMA AND SKIN SERVICE

Chair
Assoc. Prof. David Speakman

Medical Oncologists
Dr Ben Brady
Dr Damien Kee
Assoc. Prof. Grant McArthur
Dr Mark Shackleton

Radiation Oncologists
Dr Vanessa Estall
Dr Andrew Hui
Dr Mark Lee
Dr Mathew Seel

Surgical Oncologists
Mr Felix Behan
Mr Simon Donahoe
Assoc. Prof. Michael Henderson
Mr Miki Pohl
Mr John Spillane

Pathologist
Dr Sarah Swain

PAEDIATRICS AND LATE EFFECTS SERVICE

Chair
Dr Greg Wheeler

Radiation Oncologists
Dr Kate Cardale
Dr Mary Dwyer

Radiation Therapists
Katie Davidson
Julia McAlpine
Brigid Moran
David Tongs
David Willis

Nurse Coordinators
Priscilla Gates
Natalie Goroncy
Frances Ness
Jessy Thambiraj

Music Therapist
Pip Barry

Neurologist
Dr Richard Stark

SARCOMA SERVICE

Chair
Prof. Peter Choong

Surgical Oncologists
Assoc. Prof. Michael Henderson
Mr Gerard Powell

Consultants
Assoc. Prof. Samuel Ngan
Assoc. Prof. David Thomas
Dr Jayesh Desai
Dr Ken Khamly
Dr Sarat Chander
Dr Julie Chu

Paediatric Oncologist
Dr Lisa Orme

Australian Sarcoma Study Group
Dr Sally Whyte (Executive Officer)
Dr Mandy Ballinger (Project Manager, ISK Study)

URO-ONCOLOGY SERVICE

Chair
Dr Farshad Foroudi

Radiation Oncologists
Prof. Gillian Duchesne
Dr Sarat Chander
Dr Farshad Foroudi
Dr Keen Hun Tai
Assoc. Prof. Scott Williams

Urologists
Assoc. Prof. Laurence Cleeve
Mr Jeremy Goad
Assoc. Prof. Declan Murphy

Medical Oncologist
Assoc. Prof. Guy Toner

Nursing
Mary Leahy (Coordinator)
Katherine Schubach

Research Radiation Therapists
Daniel Pham
David Tongs

Anatomical Pathologist
Dr Catherine Mitchell

Diagnostic Radiologist
Dr Colin Styles

Research Fellow
Suki Gill

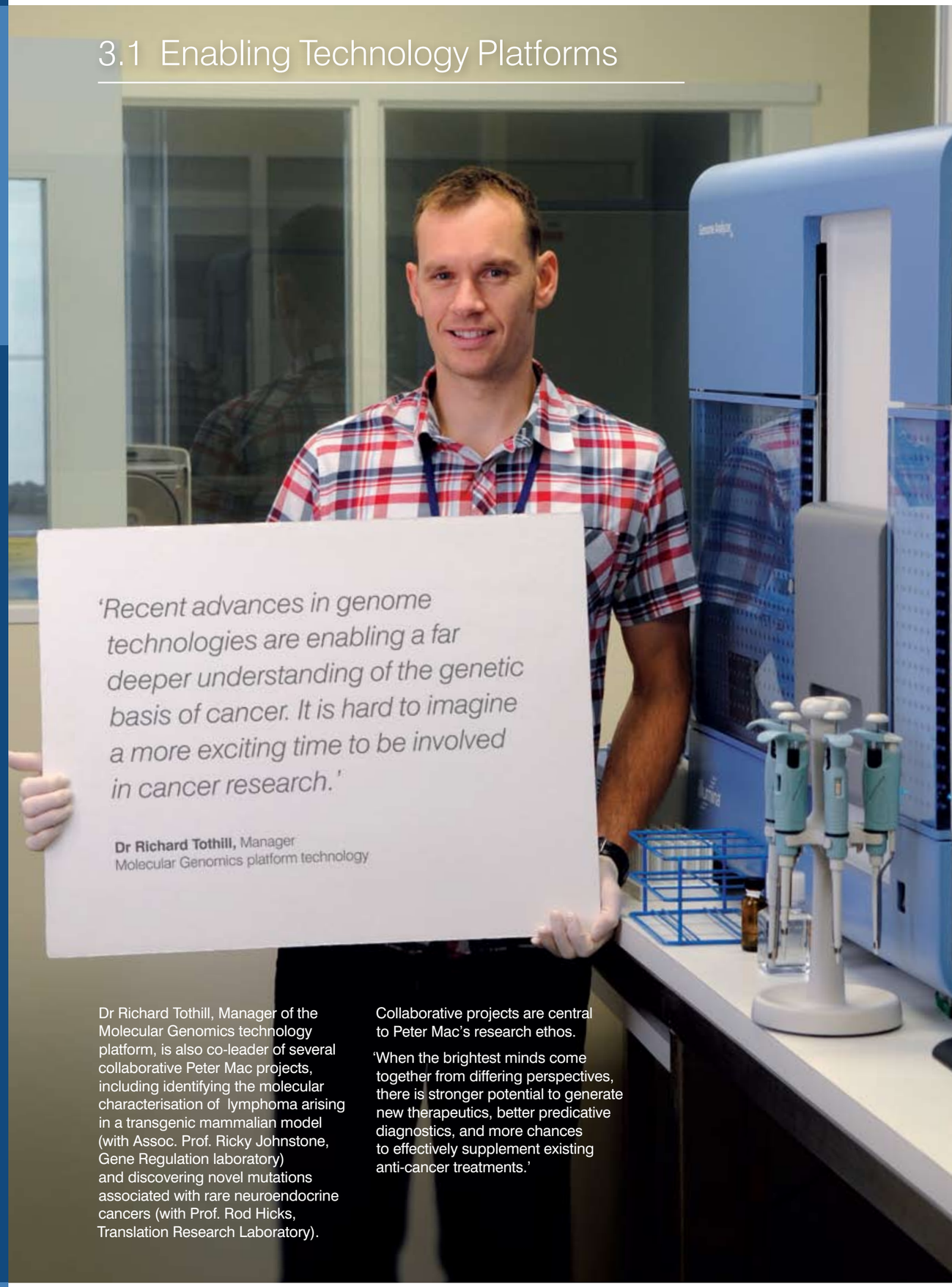
Statistician
Alan Herschtal

3 Enabling Technologies and Interdisciplinary Research Platforms

3

Across Peter Mac, there is a breadth of expertise and resources that form the foundations of our laboratory, clinical and translational research, facilitating and identifying new research directions and achievements.

3.1 Enabling Technology Platforms



Dr Richard Tothill, Manager of the Molecular Genomics technology platform, is also co-leader of several collaborative Peter Mac projects, including identifying the molecular characterisation of lymphoma arising in a transgenic mammalian model (with Assoc. Prof. Ricky Johnstone, Gene Regulation laboratory) and discovering novel mutations associated with rare neuroendocrine cancers (with Prof. Rod Hicks, Translation Research Laboratory).

Collaborative projects are central to Peter Mac's research ethos.

'When the brightest minds come together from differing perspectives, there is stronger potential to generate new therapeutics, better predicative diagnostics, and more chances to effectively supplement existing anti-cancer treatments.'

3.1 Enabling Technology Platforms

Our enabling technologies are the backbone of our laboratory research, providing the cutting-edge technology needed to facilitate research, and the expertise to identify, import and develop vital new resources.

An extensive enabling base of platform technologies and interdisciplinary research completes the research structure that underpins our nationally and internationally recognised research.

With a focus on developing and implementing advanced technologies, our enabling research platforms are led by experienced specialists and supported by highly trained teams who help drive our key scientific directions and fulfil our strategic focus.

Functional Genomics facility
Dr Kaylene Simpson

Molecular Genomics facility
Dr Richard Tothill

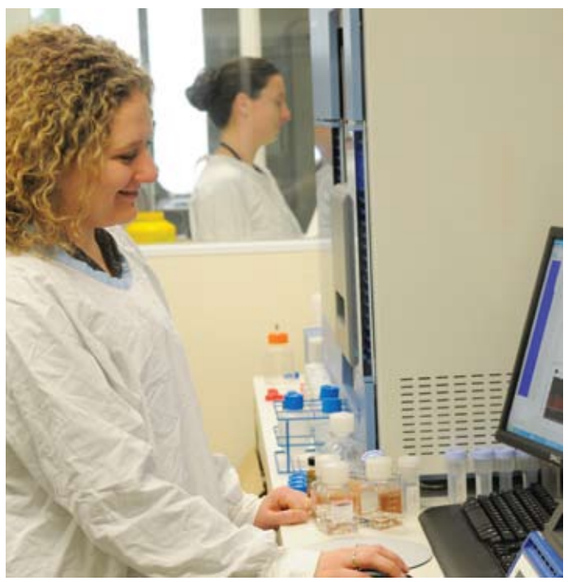
Bioinformatics facility
Dr Gian Sberna

Flow Cytometry facility
Ralph Rossi

Microscopy facility
Sarah Ellis

Media and Laboratory Services facility
Lara Sekhon

Tissue Bank facility
Sam Cauberg



3.1.1 Functional Genomics facility

Head: Dr Kaylene Simpson

The Functional Genomics facility provides cutting edge, high-end technology infrastructure and expertise to enable researchers to analyse gene function using high throughput RNA interference approaches.

OVERVIEW

The Functional Genomics facility houses the Victorian Centre for Functional Genomics and the Australian Cancer Research Foundation Victorian Centre for Functional Genomics in Cancer. The facility offers unprecedented access to evaluate the function of all the genes in the human and mouse genomes by using gene knockdown technology.

The ability to assess the function of each gene in the human genome will allow researchers to discover genes that play critical roles in disease states, such as cancer. Open to medical researchers Australia-wide, we provide expertise in the use of high throughput technologies and unparalleled access to RNAi interference reagents and imaging technology.

The Functional Genomics facility enables researchers to perform unbiased gene discovery experiments using RNA interference that would otherwise be impossible to do in a regular laboratory.

The application of this technology is limited only to the imagination of the researcher and, as such, the facility is dedicated to assisting researchers meet their goals. Our team provides critical advice on experimental design, assay development, high throughput workflows, ongoing instrument training and support and bioinformatics analysis of data.

The facility currently operates three main platforms;

1) A lentiviral-based short hairpin microRNAi (shRNAmir) strategy, enabling the shRNA sequences to be delivered to human cell lines and primary cells using a viral infectivity approach. Such an approach allows for short or long term gene knockdown. Human and mouse genome-wide viral pools or boutique gene family collections are available.

2) Synthetic siRNAs (short interfering) in the form of SMARTpool reagents (four sequences targeting one gene in a single well) are transiently transfected into cell lines and analysed 72-96 hours later. The functional effects of gene knockdown are evaluated at the cellular level using high throughput microscopy or by using a fluorescence plate reader for overall measurement of cell survival or reporter gene expression. Following the primary screen, validation libraries comprising the individual SMARTpool sequences arrayed in single wells are then interrogated to create a subset of gene 'hits' that are high confidence and suitable for more detailed biochemical and molecular analysis. We house human and mouse genome-wide SMARTpool and individual siRNA libraries.

3) Synthetic microRNA screening reagents, allow parallel over-expression and knockdown of all the individual human miRNAs currently encoded in the human genome. Cell transfection protocols follow a similar process as for siRNAs and permit short term assays (generally inside one week).

The high-end instruments that we house, all of which are fully automated and bar code reader enabled, include:

- Cellomics ArrayScan VTi microscope.
- BioTek 406 for liquid handling and cell dispensing.
- BioTek Synergy 4 plate reader which reads absorbance and fluorescence and has a monochromator to measure assays at any wavelength, kinetic assay option, luciferase reading and low volume DNA quantitation.
- Calliper ALH3000 liquid handling robot for library management and transfection.
- Liconics 220 tower incubator.
- Velocity 11 Plate Loc automated plate sealer.

Over the course of this year, the Functional Genomics facility has welcomed a large number of users and two genome-wide siRNA screens were initiated, whilst many are in the assay development phase. A number of high profile researchers in the field visited PeterMac, presented a seminar and held discussion time with members of the facility. Dr Simpson initiated the inaugural RNAi Australia meeting in July and also co-organised the Australian High Content Screening meeting, both of enormous relevance to the facility.

For more information on the Functional Genomics facility, visit:

www.petermac.org/Research/ACRFCentreforFunctionalGenomicsinCancer

3.1.2 Molecular Genomics facility

Head: Dr Richard Tothill

The Molecular Genomics facility at Peter Mac provides state-of-the-art facilities and expertise in the use of next generation sequencing, microarray technologies and associated instrumentation to facilitate genetic/ genomics related cancer research.

OVERVIEW

Next generation sequencing is a revolutionary genomics platform that has a number of applications including DNA resequencing, transcriptional profiling and epigenomics. The sequencing core offers PCR clean laboratory space and access to all reagents and equipment required for library preparation, while the sequencing process itself is based on a fee-for-service model. Alternatively, users have a full service option, starting with submission of nucleic acids taken right through to data output.

The microarray laboratory also provides access to necessary microarray instrumentation as well as complete Affymetrix microarray services to both internal and external researchers.

The facility is committed to protocol development, provision of reagents for new methodologies and is continuously surveying the genomics technology arena for new genomics related technologies, tools and products, facilitating their introduction into Peter Mac to ensure our research remains internationally competitive.

The Molecular Genomics facility principally offers access to the Illumina GAIIx sequencing platform, and Affymetrix microarray platform but also supports other microarray platforms including Agilent.

A significant amount of development work was invested in the next generation sequencing facility during 2010 including the development of a fully integrated LIMS system for pipeline sample submission, processing and data management and development of robotics protocols for automated sample preparation.

The core facility generated more than 500 gigabases of sequence data during 2010. Principal application for the sequencing instrument was targeted resequencing from cancer samples using hybridisation enrichment strategies, epigenomic profiling (ChIP-seq, MeDIP-seq) and transcriptome profiling (RNA-seq).

One large project funded by the Peter Mac Foundation involved collaboration of more than ten laboratories with the aim to sequence 250 cancers across more than 500 genes of interest. This work was completed in 2010 with data made available to researchers through a web-based database also developed within the Molecular Genomics facility.

Other notable research projects included: a VBCRC funded project from the VBCRC Cancer Genetics laboratory focusing on a genome-wide screen for mutations predisposing to breast cancer in kConFab family cohorts, a study searching for novel cancer genes in ovarian cancer (VBCRC Cancer Genetics laboratory pg 37) and a project focusing on the mapping of the ribosomal transcription factor UBF in mouse fibroblasts (Growth Control laboratory, pg 42).

More than 900 Affymetrix microarrays were processed through the facility in 2010, with completion of several studies including a large pharmacogenomics study in ovarian cancer as part of the Pfizer genomics program. Demand for microarrays remains strong with an increase in interest from external providers following advertising of the facility through the Victorian Platform Technologies Network (VPTN).

For more information on related research, see:

- Cancer Genetics program (pg 32)
- Cancer Therapeutics program (pg 62)
- Growth Control and Differentiation program (pg 40)

For more information on the Molecular Genomics facility, visit: www.petermac.org/Research/MicroarrayandNextGenerationDNASequencing

3.1.3 Bioinformatics facility

Head: Dr Gian Sberna

The Bioinformatics facility provides statistical and computational support for the analysis of high-throughput biological data including, but not limited to, DNA microarray and next generation sequencing data.

OVERVIEW

The Bioinformatics facility at Peter Mac provides statistical and computational support for researchers to analyse and interpret the results of their biological data, including gene expression and genotyping microarray data, next generation sequencing data and high throughput siRNA screening data. The analysts in the Bioinformatics facility work closely with experimental scientists and clinicians to ensure the biological assumptions and subsequent translational relevance of their studies are fully considered when building or selecting an appropriate analysis model.

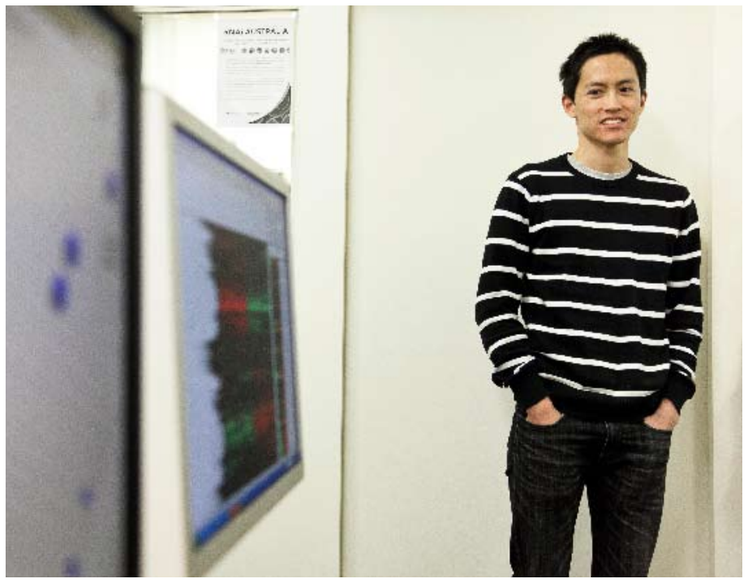
The Division of Cancer Research currently operates an Illumina GAIIx sequencer and also has access to further next generation sequencing instruments offsite. These platforms produce large-scale amounts of data that require advanced bioinformatics analysis.

We have subsequently placed a substantial focus on meeting this sharp rise in the demand for bioinformatics support by recruiting additional personnel, expanding computational capacity and establishing strategic collaborations with external bioinformatics and high performance computing groups.

We also provide and maintain computer workstations with commercial and open source bioinformatics specialty software packages. Workshops are regularly held by core staff for training in the use of these software packages. The use of these workstations and bioinformatics consulting services are cost recovered.

For more information on the Bioinformatics facility, visit: www.petermac.org/Research/Bioinformatics

Picture courtesy of Bio21 Cluster



3.1.4 Flow Cytometry facility

Head: Ralph Rossi

The Flow Cytometry and Cell Sorting facility provides investigators with access to state-of-the-art equipment and expertise in all aspects of flow cytometry and cell sorting for the analysis and separation of cell populations stained with fluorescent compounds.

OVERVIEW

The aim of the Flow Cytometry facility is to give researchers access to, and offer support with, the modern cytometric technologies that enable them to conduct their work. Our facility provides professional consultation and technical assistance with samples, appropriate instrumentation, data analysis capabilities and data interpretation.

The major areas of support are:

- Sorting samples that are brought to the facility.
- Technical assistance with protocols.
- Advice on instrumentation.
- Data interpretation.
- Education and tutorials.

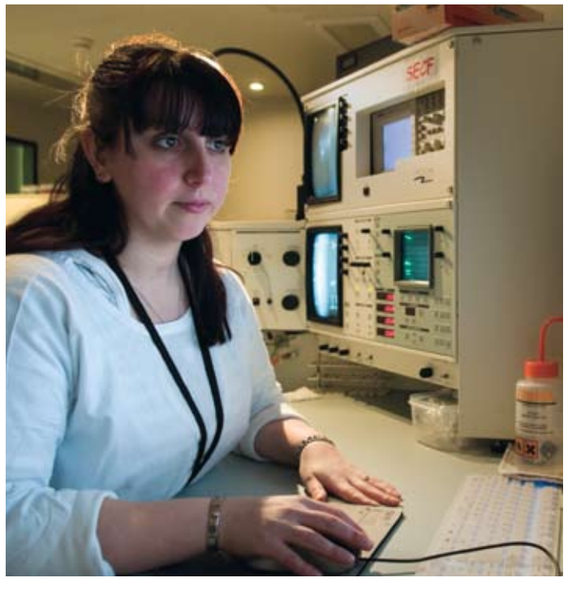
CAPABILITIES AND ACTIVITIES

As the biological sciences become increasingly technologically dependant, it is important to have sufficient technology to allow researchers to conduct their work in a competitive manner with other leading institutes. Peter Mac's Flow Cytometry facility achieves this; our services are used heavily by most Peter Mac researchers, contributing to a large variety of innovative research projects dedicated to advancing the understanding of how cancer occurs and how it can be prevented or treated.

Assistance provided by the Flow Cytometry facility includes simple screening and sorting of transfected cells, complex multiparameter analysis and sorting, and cell function assays. There is a strong demand for sorting with an emphasis on low frequency populations. Education and training is an important component of the facility and tutorials and one-to-one advice are provided on a regular basis.

This facility incorporates eight instruments: three cell sorters (two Vantage SE Divas, and an Aria2 Sorp model), an LSR2, two Canto2s, an Automacs magnetic cell separator and a Luminex 200.

Both of the Diva sorters have been configured to have maximum flexibility in the scope of work that they can perform. The Aria2 is a special order product that has a maximum capability of 17 parameter aquisition; additionally it can perform high speed sorting, large particle sorting and has a FSC PMT detection option that allows detection of microparticles. The LSR2, is capable of more complex analysis and includes a plate reader, while the other analysers conduct simpler work. The Automacs Magnetic cell separator (Miltenyi Biotech, Germany) is an adjunct to the other sorters. This instrument allows the separation of magnetically labelled cells. This technology is ideal for quick separations where very high purity is not required. The Luminex 200 is a bead-based multiplexing instrument and is used in fields such as genetic disease diagnosis, immunodiagnostics applications, gene expression, protein analysis and drug discovery.



3.1.5 Microscopy facility

Head: Sarah Ellis

The Microscopy facility is a world-class facility, providing sophisticated microscopy equipment and software supported by technical expertise to facilitate research integral to a wide range of cancer research projects.

OVERVIEW

The Peter Mac Microscopy facility was developed in 1999 as the Microscopy Research and Imaging Core by merging the existing electron microscopy/histology facilities with the optical microscopy facility. Laser capture microscopy was added in 2001. The core has enlarged through the purchase of new equipment funded by competitive grants. We are now recognised as a world-class facility encompassing all aspects of biological optical and electron microscopy.

The aim of the Microscopy facility is two-fold: to provide researchers with a dedicated research histology facility, sophisticated microscopy equipment and software to facilitate their research, and to educate, train and supervise researchers using the facility. In addition, the Microscopy team advises researchers on imaging and sample processing and conducts regular tutorials and workshops. By organising regular trials and evaluations of newly developed microscopes and software, we ensure that Peter Mac researchers have access to the latest technology.

Currently the Microscopy facility houses microscopes and equipment to facilitate a wide range of cancer research projects, including four confocal laser scanning microscopes, six wide-field microscopes, a transmission electron microscope (TEM), a laser capture microscope, and digital recording and analytical software for each microscope. Three of the microscopes, two confocal and one wide-field, are dedicated to the capture of live cell data through the addition of gas-controlled, heated environmental chambers, motorised stages, and specialist objectives. A complete array of ancillary equipment required for the processing of tissues and cells for both optical and electron microscopy is also provided; for histology work this includes a tissue processor, embedding centre, auto-stainer, coverslipper, rotary microtomes, and immunostainer, and, for electron microscope, high pressure freezer, ultramicrotomes with cryoattachments, freeze substitution system, and immunostainer for electron microscopy grids.

The excellence of the Microscopy facility is well-known throughout Australia, resulting in extensive collaborations between Peter Mac and leading medical research institutes and universities. We aim to maintain our reputation and to continue to meet the current and future needs of researchers by continually updating our equipment and extending our knowledge base.

KEY 2010 RESEARCH ACHIEVEMENT

In 2010 we evaluated a number of newly released equipment including a slide scanner for the automated imaging, analysis, and archiving of sections on slides. We also evaluated four different confocal microscopes. With the exciting addition of three new research laboratories to Peter Mac, the demand for confocal microscope usage has outstripped supply. As a consequence we are purchasing a new confocal to add to our suite of microscopes. The new confocal will be commissioned in early 2011.

Histology has also experienced an increase in workload and we have increased the EFT of several staff members to cope with this. We are also endeavouring to increase our range of services offered to introduce new technologies to researchers.

3.1.6 Media and Laboratory Services facility

Head: Lara Sekhon

The Media and Laboratory Services facility provides an essential service to Cancer Research, serving the needs of Peter Mac laboratory researchers by supplying high quality liquid and solid media and sterile laboratory ware in a cost efficient manner under strict quality control.

OVERVIEW

The Media and Laboratory Services facility is separated into two areas: Media Kitchen and Laboratory Services.

The Media Kitchen maintains a cost effective, consistent and reliable store of commonly used sterile media and buffers for Cancer Research and the Department of Pathology.
The facility supports the needs of individual research groups who may have a specific media or buffer stock maintained for them and Media Kitchen staff can also supply specific non-stock requests on demand.
The facility steam sterilises all Cancer Research liquids and retrovirus linen and maintains the x-ray developer and water ultra filtration unit.

Laboratory Services provides a convenient and consistent system of cleaning, dry heat and steam sterilising and returning of reusable laboratory items to Cancer Research across all laboratories and to the Department of Pathology.

For more information on Media and Laboratory Services, visit:

www.petermac.org/Research/MediaandLaboratoryServices

3.1.7 Tissue Bank facility

Head: Sam Cauberg

The Tissue Bank facility at Peter Mac is one of four consortium members of the Victorian Cancer Biobank providing scientists with high quality, ethically-collected human tissue samples for research studies.

OVERVIEW

Tissue Bank facility offers researchers centralised access to a broad collection of ethically-collected human tissue and blood derivatives from more than 17,000 donors.

In 2010, 855 specimens from 1098 consenting donors were added to Peter Mac's collection of tissue samples. The figure below details the number and breadth of specimens banked in 2010 for each cancer type.

Donors provide broad consent for their biospecimens to be used in unspecified future research. This includes consent to access medical record information enabling the Tissue Bank facility to provide up to eleven years clinical follow-up data on individual specimens. Consequently, the ability to provide clinical outcome data together with the breadth of the specimen collection (across ten of the 11 main tumour streams, including rare tumour types) sets our bank apart from other tissue banks in Australia.

The Tissue Bank facility also supports clinical trial activity and project-specific requests. Researchers make a single application to the Victorian Cancer Biobank to access services or specimens held in tissue banks across the partner sites: Melbourne Health, Austin Health, Southern Health and Peter Mac.

The Tissue Bank facility also offers a digital slide scanning service; scanned images can then be viewed, analysed, shared and archived across multiple sites.

The Victorian Cancer Biobank resource of readily available tissue has been crucial for researchers securing major research grants from bodies such as NHMRC and international funding agencies such as US Department of Defense.

For further information on the Victorian Cancer Biobank please visit www.viccancerbiobank.org.au

For more information on the Tissue Bank facility, visit: www.petermac.org/Research/TissueBankCore

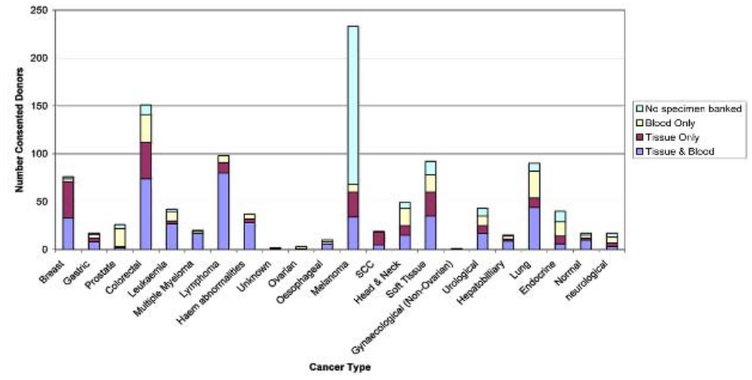


Figure 1: Specimens banked from Consenting Donors 2010

Enabling Technology Platforms – personnel

FUNCTIONAL GENOMICS FACILITY

Head
Dr Kaylene Simpson

Research Assistants
Katrina Gouramanis
Kai Syin Lee
Yanny Handoko
Daniel Thomas
Kate Gould

MOLECULAR GENOMICS FACILITY

Head
Dr Richard Tothill

Research Assistants
Aga Borcz
Aidan Flynn
Tim Holloway

BIOINFORMATICS FACILITY

Head
Dr Gian Sberna

Bioinformaticians
Jason Ellul
Jason Li

FLOW CYTOMETRY FACILITY

Head
Ralph Rossi

Senior Flow Cytometrist
Ralph Rossi

Cytometrist
Sophie Kotsakidis

MICROSCOPY FACILITY

Head
Sarah Ellis

Research Assistants
Leah Adolf
Stephen Asquith
Judy Borg
Agnes Gany
Dhanya Menon
Basia Pryzbylowski
Matthew Reardon
Karin Sedelies
Claire Tan
Simon Yoong

MEDIA AND LABORATORY SERVICES FACILITY

Head
Lara Sekhon

Media Kitchen
Helen Braun
Menka Kyriakou

Laboratory Services
Emily Breninger
Elzbieta Gajewska
Graham Heffernan
Suh-youn Ko
Paul McPherson
Patrick Murray
Nicole Robb
Belinda Whitby

TISSUE BANK FACILITY

Head
Samantha Cauberg

Tissue Bank Scientists
Paul Pinto Correia
Jeremy Hoglin
Rhonda Mawal
Kimberly Ong
Amanda Ross

Resource Enhancement Scientist
Kylie Scott

Data Managers
Leanne Bowes
Samara Rosenblum

3.2 Interdisciplinary Research Platforms

Assoc. Prof. Penny Schofield is the Research Director of the Nursing and Supportive Care Research Department at Peter Mac. Nursing and Supportive Care Research (N&SC Research) is firmly embedded across each of Peter Mac's tumour streams and Penny leads a multi- disciplinary program of supportive care research that assesses and improves the quality of life for patients who are undergoing and completing cancer treatment.

Penny develops and tests evidence-based psycho-educational programs that can be readily adopted into clinical practice, and the rigorous assessment of quality of life outcomes in clinical trials of novel therapies for cancer.

3.2 Interdisciplinary Research Platforms

Our interdisciplinary research platforms are the foundation upon which clinical medicine is practised.

The research conducted by our interdisciplinary research platforms is crucial to our cancer care; it is the source of new approaches to difficult management issues, involves managing patients according to world best practice, delivers state-of-the-art diagnostic and treatment options, and strives to improve treatment outcomes.

The multidisciplinary nature of our clinical services has facilitated a valuable multidisciplinary focus in our research, with all clinical and allied health professionals in all areas of the hospital engaged in important collaborative research. The scope is wide-ranging, from early phase clinical studies which allow our patients access to novel anti-cancer drugs to international randomised controlled trials designed to answer key clinical questions in cancer care.

Centre for Blood Cell Therapies
Prof. Miles Prince

Centre for Cancer Imaging
Prof. Rod Hicks

Centre for Biostatistics and Clinical Trials
Assoc. Prof. Dina Neiger

Clinical Trials Unit
Shannon Uren

Clinical Psychology
Annabel Pollard

Familial Cancer Centre
Dr Gillian Mitchell

Infectious Diseases
Assoc. Prof. Monica Slavin

kConFab Follow-Up
Assoc. Prof. Kelly-Anne Phillips

Molecular Pathology laboratory
Prof. Stephen Fox
and Assoc. Prof. Alex Dobrovic

Nursing and Supportive Care
Prof. Sanchia Aranda

Nutrition
Janelle Loeliger

onTrac@Peter Mac
Dr Lisa Orme

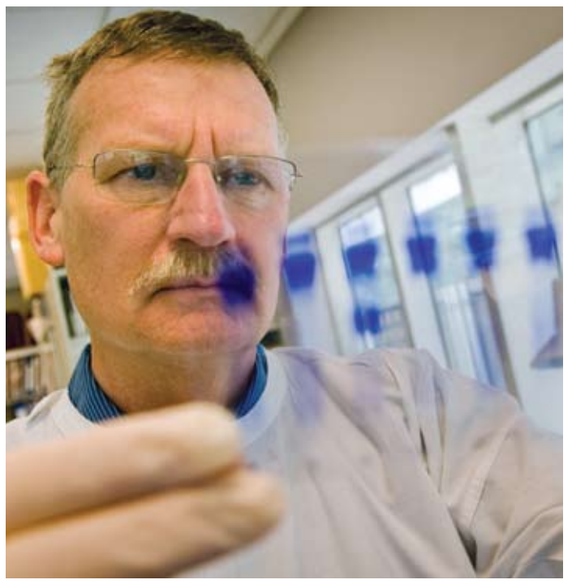
Pain and Palliative Care
Dr Odette Spruyt

Pharmacy
Sue Kirsa

Physical Sciences
Jim Cramb

Radiation Therapy
Aldo Rolfo

Social Work
Alison Hocking



3.2.1 Centre for Blood Cell Therapies

Director: Prof. Miles Prince

The Centre for Blood Cell Therapies (CBCT) provides standard of care treatments for cancer patients via two collection sites and a central processing facility in East Melbourne. The centre manufactures cell and tissue-based treatments arising from both our own discoveries and the discoveries of our clinical and commercial partners.

Through Cell Therapies Pty Ltd, the commercial interface for the CBCT, we expedite the translation of cellular therapy research from the bench into the clinic and in some cases through to standard of care therapies.

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 (pg 109) and the Haematology Immunology Translational Research Laboratory (pg 30).

RESEARCH DIRECTIONS

The Peter Mac CBCT focuses 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. We do 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:

- Expanded cell tracking program to include the use of 19F and nano-Fe materials on Peter Mac's 3T MRI machine.
- For the second year in a row Peter Mac's Apheresis Unit achieved NATA accreditation (NPAAC standard HPC-A) and completed audit with no recommendations or conditions.
- Cell Therapies entered into a collaboration agreement with National University Hospital of Malaysia in Kuala Lumpur (HUKM) and successfully trained HUKM staff in cGMP compliance and quality systems management.
- Secured a TGA manufacturing license (a world first) for a commercial client using mesenchymal precursor cells.
- Secured a number of subsidies for both Peter Mac and outside researchers to progress their activities up to regulatory compliance for clinical trials.

For more information on related research, see:

- Cancer Immunology program (pg 24)
- Haematology Immunology Translational Research laboratory (pg 30)
- Haematology Service (pg 86)

3.2.2 Centre for Cancer Imaging

Head: Prof. Rod Hicks

The Centre for Cancer Imaging is a consultative and research oriented service, providing advice on the best test or combination of tests to answer specific needs to cancer patients and their management team, and to integrate the results of those tests into multidisciplinary management selection and planning.

The Centre applies its experience and research in the use of multi-modality correlative imaging to provide advice on the best test or combination of tests to answer the specific needs of cancer patients and their management team.

RESEARCH FOCUS

- Improvement of diagnostic paradigms for cancer staging.
- Establishment of optimal timing and tracer combinations for therapeutic response assessment to novel molecular targeted therapies.
- Development of novel PET imaging agents.

RESEARCH DIRECTIONS

An initial report detailing the safety of the combination of radiosensitising chemotherapy with peptide receptor radionuclide therapy using Lu-177 octreotate was published in 2010; Peter Mac has pioneered this approach internationally.

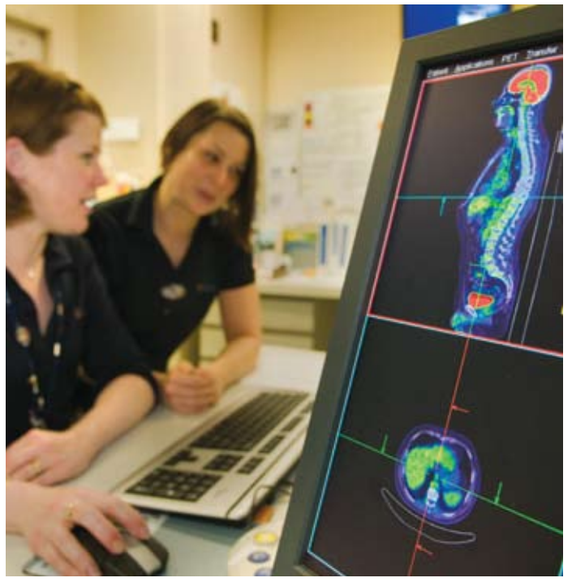
Reflecting ongoing developments in this field, the Centre for Cancer Imaging was successful in achieving a Victorian Cancer Agency Translational Research Grant. This grant of almost $1.6 million over three years will accelerate discoveries regarding the genetic drivers of neuroendocrine cancers and our understanding of new treatment targets to improve patient outcomes. The research will involve a close collaboration with the medical physics, genomics and medical oncology groups at Peter Mac. The Royal Children's Hospital and RMIT University in the pre-clinical imaging domain. This research aims to provide insights into potential therapeutic targets for neuroendocrine cancers.

Other research projects conducted in 2010 include:

- New trials looking at radiation dose and quality of life outcomes in neuroendocrine tumour (NET) patients.
- Our pre-clinical work in developing new imaging tracers in association with the CRC for Biomedical Imaging Development has moved into the clinical domain with commencement of human studies of Mel050, a highly specific melanoma imaging agent.

For more information on related research, see:

- Cancer Therapeutics program (pg 62)



3.2.3 Centre for Biostatistics and Clinical Trials

Director: Assoc. Prof. Dina Neiger

The Centre for Biostatistics and Clinical Trials (BaCT) is a leading Australian coordination centre for clinical trials in oncology, providing a full range of services to clinical trials and other clinical research projects, including assistance with protocol development, study design, database design, randomisation and registration services, management of data, central trial coordination, statistical analysis, interpretation and reporting of data.

Through a continuing commitment to high quality research, BaCT contributes to improved outcomes for patients currently participating in specific clinical trials as well as for cancer patients in the future.

The centre is home to the Operations Office of the Australasian Leukaemia and Lymphoma Group (ALLG) — Australasia's leading clinical trials and translational research group in haematological malignancies.

RESEARCH FOCUS

BaCT has expertise in all phases of clinical trials as well as specialist diagnostic trials and treatment planning studies with the research focus on:

- Provision of high quality biostatistical and data management support to cooperative oncology groups and researchers at Peter Mac.
- Collaboration in clinical trials, including phase 1 trials, translational research programs and supportive care.
- Biostatistical and clinical trial methodological research.

BaCT staff have specific expertise in the design, conduct, analysis and interpretation of cancer clinical trials as well as retrospective studies, and are experienced in the analysis of other clinical and laboratory research data. The trial centre supports approximately 100 phase 1 to 3 trials involving over 5,500 patients.

Trial centre statisticians are actively involved in research into statistical methods applicable to clinical trials and the analysis of medical data, as required by clinical projects.

RESEARCH DIRECTIONS

- BaCT successfully applied for a continuation of Cancer Australia funding support of clinical research trial development services to the ASSG from 1 July to 30 June as part of the Cancer Clinical Trials Development Unit (CTDU). Established in July 2008, CTDU is a collaboration between the NHMRC Clinical Trials Centre and BaCT, providing expert advice, support and trial development services for the newly established multi-site, collaborative national cancer clinical trials groups.
- BaCT staff collaborate in the international phase 3 head and neck trial (HEADSTART) with Assoc. Prof. Danny Rischin and Prof. Lester Peters as principal investigators. The results of this trial have demonstrated the critical importance of radiotherapy quality on the outcome of chemo-radiotherapy in head and neck cancer. The trial has also generated many studies, involving BaCT, into the role of markers in head and neck cancer using data from blood and tissue samples obtained from the marker sub-study component of the phase 3 trial.
- BaCT is working with Assoc. Prof. Jane Turner (UQ, Medicine) and Beyond Blue on the PROMPT (Promoting Optimal Outcomes in Mood through Psychosocial Therapies) study, a multi-centre randomised controlled trial to evaluate the effectiveness of a systematically-introduced brief psychosocial intervention in cancer services to reduce anxiety and depression, which affects up to one-third of cancer patients. There is limited detection of distress by clinicians and most centres do not systematically identify patients who are distressed. Even when implemented, screening for distress is not always supported by defined clinical referral pathways. There is also limited access to specialist psychosocial service providers. The trial will take advantage of an eCRF system introduced by BaCT last year, improving efficiency by facilitating on-line data entry and multi-site system access.
- BaCT staff currently manage a multi-site, international, randomised phase 3 study investigating radiation doses and fractionation schedules in non-low risk Ductal Carcinoma In Situ (DCIS) of the breast. The DCIS study has grown considerably since international collaboration was introduced in 2008. BaCT staff currently manage 70 active sites globally (more than double the original number of Australian sites) across Singapore, New Zealand, Canada and Europe. The number of active sites is expected to reach 110 by the end of 2011, following introduction of new collaborative groups, including the International Breast Cancer Study Group (IBCSG), the Scottish Cancer Trials Breast Group (SCTGB), and the Ireland Cooperative Oncology Research Group. The increase in site activation since international collaboration has contributed to an almost three-fold increase in the total annual accrual in 2010. International collaboration initiated the development of a web-based randomisation system, which was released globally in June 2010.

3.2.4 Clinical Trials Unit

Manager: Shannon Uren

Under the auspices of the Division of Cancer Medicine, the Clinical Trials Unit (CTU) underpins clinical research across cancer types. The unit is involved in the co-ordination and management of clinical trials, providing a key service to both internal and external bodies. With a focus on Ph I, II and III trials and the provision of ongoing education and support to clinician investigators and trial participants and their carers we are the largest single oncology clinical trials unit in Victoria. With more than 180 active clinical trials currently underway, growth of our unit has been rapid.

RESEARCH FOCUS

Our clinical research program covers prevention, diagnosis and management and extends from early to advanced stages of disease. Our research includes investigations of novel treatments or new approaches in medical oncology, haematology, radiation oncology and surgery. The end goal of all our work is improved outcomes for our patients.

RESEARCH DIRECTIONS

In 2010, Peter Mac's CTU was involved in over 180 active clinical trials, including the following:

- A phase 1 study in the oral AKT Inhibitor GSK2110183 in Haematological malignancies.
- Playing a key role in the development of MUC1 Dendritic Cell Vaccine (CVac) for Epithelial Ovarian Cancer Patients.
- Playing a key role in the development of PLX4032/ RO5185426 a BRAF inhibitor molecule in melanoma from phase 1–phase 3, including the follow-on phase 1 study of RO5185426 in combination with GDC-0973. Peter Mac staff developed sophisticated molecular screening tests to identify patients with mutations in the BRAF gene that allowed Peter Mac to join with cancer centres in the USA to lead the development of a new class of anticancer treatment that has established a new way of treating melanoma.
- Playing a key role in the development of PF-02341066 in ALK positive Non-Small Cell Lung Cancer from Phase 1–Phase 3.
- Phase 1 studies in LY2874455, ABT-199 & NPI-0052.
- A Pilot Study—LITTVAC in Multiple Myeloma. The LITVAC study is unique in its approach to treating patients with an incurable malignancy of the blood called multiple myeloma. The immune investigations are generating some very new findings that are being using to design further therapies for patients. The LITVAC study has been extended to look at the effects of higher doses of lenalidomide and no steroid on the myeloma and the immune system, to inform optimum combinations for future studies.

For more information on related research, see:

- Haematology Service (pg 86)
- Lung Service (pg 88)
- Melanoma and Skin Service (pg 89)

3.2.5 Clinical Psychology

Head: Annabel Pollard

The aim of Clinical Psychology is to be a national centre of excellence in clinical interventions, research and implementation of specialist evidence-based psychological and psychiatric care for people with cancer and their families.

RESEARCH FOCUS

- Develop and drive the implementation of an overarching psycho-oncology research strategy.
- Facilitate statewide and national research collaborations.
- Drive the clinical application of evidence-based improvements in psycho-oncology care.
- Raise the awareness of psycho-oncology as a collaborative field of research.
- Keep abreast of and disseminate information about new developments and resources.
- Develop education and training opportunities for clinical researchers.
- Contribute to national advocacy efforts related to survivorship research issues.
- Seek external funding to sustain and grow our clinical interventions and research program.

RESEARCH DIRECTIONS

Our overarching aim is to focus on research that has the potential to improve the psychological and clinical outcomes for people with cancer and their families. Our current research program seeks to establish and develop evidence-based improvements in the psychological care of patients such as effective psychological interventions.

The research program is explicitly collaborative. Aiming to build knowledge and understanding of psychological issues across the organisation, our research program involves working directly with patients through collaborative projects with the multidisciplinary teams in the Head and Neck (pg 87) and Breast (pg 83) tumour streams.

Head and Neck Study

We are involved in a three-year prospective observational study of people with head and neck cancer. The study has highlighted the incidence of psychological morbidity (anxiety and depression and quality of life) in patients undergoing treatment for head and neck cancer.

The Breast Cancer Survivors' Healthy Lifestyle Study

A Randomised Controlled Pilot Study To Test The Effects of a Behavioural Intervention (Theory-Based Information and Advice) on Uptake of Physical Activity in Breast Cancer Survivors. This study has highlighted the effects of a psycho-behavioural intervention on uptake of exercise in breast cancer survivors.

For more information on related research, see:

- Breast Service (pg 83)
- Head and Neck (pg 87)

3.2.6 Familial Cancer Centre

Head: Dr Gillian Mitchell

The Peter Mac Familial Cancer Centre (FCC) is a comprehensive cancer genetics centre with a commitment to clinical service and research. The FCC provides cancer risk assessment, genetic counselling and genetic testing, medical advice and management as well as psychological support to individuals and their family who have concerns about their personal and/or family history of cancer. Our aim is to reduce the morbidity and mortality from cancer associated with hereditary cancer syndromes.

RESEARCH FOCUS

Our research portfolio covers many aspects of familial cancer with a particular emphasis on:

- Finding new cancer predisposition genes.
- Evaluating new technology for genetic testing.
- Investigating new cancer treatments targeted to the mutated genetic pathway.
- Streamlining the care and follow up of families at risk.
- Investigating the wider impact of hereditary cancer syndromes and their management on the psychosocial functioning of individuals as well as their wider family.

RESEARCH DIRECTIONS

Our research is focused on finding better ways to identify people at risk of hereditary cancer syndromes and then reduce the morbidity and mortality associated with these syndromes.

Recent research highlights include:

- Understanding that the clinical information we hold on our patients is a rich resource for familial cancer research while reducing the burden of research fatigue on our unique group of patients. We have developed an integrated clinical/research database, transferring all paper records into an electronic format, permitting rapid interrogation and data queries and speeding up the time taken to complete our research projects.
- Developing an FCC consumer research group to help us set a research agenda that is responsive to our patients' and their families' needs, evaluating research proposals and helping us draft the patient information documents associated with specific projects.
- Holding a Research Strategic Planning Day in November involving the FCC, molecular pathology, representatives from tumour streams and the Division of Research. Its purpose was to ensure close collaboration across these groups that will result in effective translation of research from the research labs into the clinic and for the clinical needs of the FCC patients to drive future laboratory research directions. The success of this day leads us to hold one or two such meetings per year from now on.

3.2.7 Infectious Diseases

Head: Assoc. Prof. Monica Slavin

The Department of Infectious Diseases and Infection Control aims to minimise the impact of community and healthcare-associated infections in patients and healthcare workers. Our services involve preventing and managing infections among immunocompromised patients and we provide care across outpatient, ambulatory care and inpatient settings. In addition to patient clinical care, we perform epidemiological surveillance, outbreak management and policy development. We also conduct research on prevention and treatment of infections.

RESEARCH FOCUS

- Development of local and national evidence based clinical guidelines for the management of the immunocompromised patient.
- Development of epidemiological tools for the surveillance of infections in cancer patients.
- Study and report on the outcomes of infections in cancer patients, including newly emerging infections such as influenza H1N1 (swine flu).
- Study of the clinical, molecular and infection control factors associated with healthcare-associated infections, including infection due to multi-resistant organisms in the immunocompromised patient.
- Development of new strategies for improving outcomes of infection in cancer patients.

RESEARCH DIRECTIONS

Antimicrobial Stewardship – Guidance DS®

Antimicrobial therapy plays an important role in the prevention of adverse patient outcomes related to underlying immunocompromised diseases or their treatment. Electronic decision support tools are a necessary and important way of optimising clinical practice, preventing antibiotic resistance, auditing prescribing practices and monitoring the use of restricted antimicrobial agents. Guidance DS® — a computerised clinical decision support system — involves electronic real-time monitoring of inpatient prescribing of restricted antimicrobials.

Febrile Neutropenia Guidelines

Consensus and evidence based guidelines for the treatment and management of febrile neutropenia were developed in collaboration with specialists from haematology, oncology and pharmacy.

Randomised Control Trial (RCT) for Invasive Aspergillosis

This RCT is evaluating an early treatment strategy for invasive aspergillosis in high risk haematology patients. This national study in bone marrow transplant recipients and patients undergoing treatment for acute leukaemia is comparing an early diagnostic strategy based on serological testing and PCR to the standard empiric antifungal therapy approach.

Our research group comprises infectious diseases physicians who have appointments across multiple institutions. We are therefore able to perform high quality clinical research projects that influence care of patients across haematology/oncology units across the state.

All current Infectious Diseases projects focus on best practice and surveillance.

For more information on related research, see:

- Pharmacy (pg 122)

3.2.8 kConFab Follow-Up Project

Head: Assoc. Prof. Kelly-Anne Phillips

The kConFab Follow-Up Project researches the clinical consequences of having a hereditary predisposition to breast cancer and the non-genetic factors that might modify cancer risk. Data on the risk management behaviours and outcomes of kConFab participants are collected every three years. The Follow-Up Project is funded separately from the kConFab core.

RESEARCH FOCUS

- Prospective evaluation of the effect of non-genetic potential risk modifiers such as risk-reducing surgery, chemoprevention, reproductive factors, exogenous hormones, alcohol, cigarettes and exercise.
- Prospective determination of penetrance of BRCA1 and BRCA2.
- Evaluation of prevalence and predictors of use of various cancer risk management strategies, including risk-reducing surgery, chemo-prevention and cancer screening.

KEY 2010 RESEARCH ACHIEVEMENT

Prospective Study of Adequacy of Risk-Reducing Salpingo-oophorectomy in Australasian BRCA1/2 Carriers and Women at High Familial Risk of Ovarian Cancer

This study is the first to report on the adequacy of risk-reducing gynaecologic surgery undertaken in Australian women at high familial risk for ovarian cancer. Such surgery should include removal of both ovaries and fallopian tubes, and the removed tissue should all be submitted for pathology examination to ensure that undiagnosed cancer, that might require additional treatment, is not present. The study was prompted by anecdotal reports of high risk women receiving inadequate surgery. We reviewed the surgical and pathology reports of 201 high risk women who underwent surgery between 1998 and 2008. We showed that 9 per cent of women had inadequate surgery and 77 per cent had inadequate pathology. Women were most likely to have adequate surgery if they were operated on by a specialist gynaecologic oncologist (rather than a general gynaecologist or general surgeon), and if they were younger. Reassuringly, the adequacy of the surgery performed seemed to have improved over time. We are now working with peak bodies to ensure that our results are disseminated to women and surgeons, so that the adequacy of risk-reducing surgery and pathology can be further improved.

Reference: Kiely BE, Milne RL, Burnham L, et al. Prospective Study of Adequacy of Risk-Reducing Salpingo-oophorectomy in Australasian BRCA1/2 Carriers and Women at High Familial Risk of Ovarian Cancer in the Kathleen Cuningham Consortium Foundation For Research Into Familial Breast Cancer (kConFab) (2011). Familial Cancer, published online 22 March 2011, DOI 10.1007/s10689-011-9435-0

For more information on related research, see:
- kConFab (pg 38)
- Breast Service (pg 83)

3.2.9 Molecular Pathology laboratory

Heads: Prof. Stephen Fox and Assoc. Prof. Alex 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 cancers including breast, lung, colorectal and urological cancers and haematological malignancies.
- 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 2010 RESEARCH ACHIEVEMENT

New Risk Factor for Developing Breast Cancer

The risk factor involves a special type of alteration (DNA methylation) of the BRCA1 gene. This study has been published in *Cancer Prevention Research*, where it also featured in an editorial.

Women with mutations in the BRCA1 gene are predisposed to breast cancer. The DNA methylation modification is known as an epimutation. It is not a mutation but it acts to turn off the BRCA1 gene leading to the loss of its protective function against breast cancer.

The study involved women diagnosed with breast cancer before the age of 40 years for whom BRCA1 mutations had not been identified. The epimutation was found in the blood of some women with breast cancer, especially those who develop the same type of breast cancer that develops in women with a BRCA1 mutation. Factors that triggered epimutations that stopped the gene BRCA1 from doing its usual job of preventing breast cancer seem to cause the same proportion of early-onset breast cancers (10 per cent) as do inherited faults in this gene. In about three to four per cent of young women, their BRCA1 gene has been made less capable of preventing breast cancers, placing them at a 3.5-fold increased risk of breast cancer.

The discovery of this epimutation in the peripheral blood indicated that it was present in many tissues of the body. This is highly significant for the understanding of mechanisms of breast cancer development as it could drive the development of breast cancer in the same way as a mutation. Many questions remain unanswered, in particular what triggers this epimutation and whether women carrying this risk factor can reduce their risk by dietary or pharmacological intervention. Testing for this risk factor will be unavailable until answers to these and other questions are known.

Reference: Wong EM, Southey MC, Fox SB, et al. Constitutional methylation of the BRCA1 promoter is specifically associated with BRCA1 mutation-associated pathology in early-onset breast cancer. Cancer Prevention Res. 2011 4:23–33.

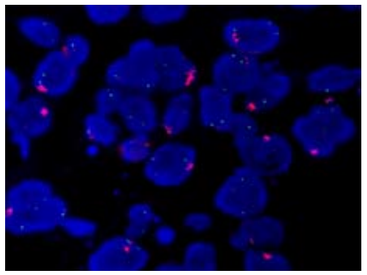


Figure 1: Poorly differentiated adenocarcinoma of the oesophagus illustrating amplification of the MET gene (red) in relation to chromosome 7 centromere (green) by fluorescent in situ hybridisation (FISH) in formalin fixed paraffin embedded (FFPE) tissue.

For more information on related research, see:
- Familial Cancer Centre (pg 140)
- Medical Oncology and Early Phase Clinical Trials (pg 82)

3.2.10 Nursing and Supportive Care

Head: Prof. Sanchia Aranda

The Department of Nursing and Supportive Care Research group develops, evaluates and disseminates new knowledge about nursing and supportive care for people affected by cancer. We are committed to the application of evidence to practice, education and policy. Our team works in collaboration with cancer clinicians, managers, educators and researchers both within Peter Mac, nationally and internationally. These collaborations ensure that our research program is relevant to patients, carers and health professionals, is at the cutting edge of international innovations in cancer supportive care and is translated into practice.

RESEARCH FOCUS

The focus of our research is to improve outcomes for people affected by cancer by:

- Actively engaging with people affected by cancer and clinicians involved in their care to identify gaps in supportive care service provision.
- Developing and testing innovative and sustainable supportive care interventions applicable across the illness trajectory.
- Supporting rigorous assessment of quality of life in cancer trials.
- Developing and testing innovative models of care focused on enhancing self-management capacity of people affected by cancer.
- Developing and validating new supportive care research measures.

KEY 2010 RESEARCH ACHIEVEMENT

PENTAGON: Peer and Nurse support Trial to Assist women in Gynaecological Oncology

Radiotherapy for gynaecological cancer (GC) has numerous potentially distressing side effects which impact on psychosocial functioning and intimate relationships. Distress associated with diagnosis and treatment can be ameliorated by comprehensive preparation for treatment and addressing informational, physical and psychosocial needs during treatment.

The initial objective of PeNTAGOn (Principal Investigator: Assoc. Prof. Penelope Schofield) was to develop, refine and pre-test an innovative intervention package combining tailored specialist nursing consultations with a telephone-based peer support person (a GC survivor), to ensure its relevance and acceptability to patients and clinicians. A three-stage process for developing complex interventions, based on UK Medical Research Council (MRC) Framework (2008), was used: (1) problem definition; (2) refining the intervention: evidence-based content, complexity and tailoring, delivery and dose, and integrity; (3) pre-testing the intervention with qualitative interviews to finalize the intervention.

Drawing on extensive literature reviews, consumer input, and the MRC guidelines, this novel program was developed and tested throughout 2009–10. Two intervention manuals (the *Nurse Intervention Manual* and the *Peer Intervention Manual*) were drafted based on identified unmet needs and best available evidence for self-care. The *Nurse Intervention Manual* specified the content of patient consultations to provide tailored information, self-care coaching and multidisciplinary team care-coordination. The *Peer Intervention Manual* described the content of phone calls to patients that provide psychosocial support and encourage adherence to the self-care plan. Intervention sessions are delivered at critical time-points in the illness trajectory: pre-, mid-, end- and post-treatment. Both intervention manuals were refined by clinician and consumer review. Peers and nurses were rigorously trained and the intervention pre-tested with six patients who provided qualitative feedback.

This unique intervention was well-received by consumers and multidisciplinary clinicians, and found to be relevant, acceptable, feasible and useful. The final package addresses key physical, functional, psychological, sexual, informational and social needs of patients that arise at critical points in the illness trajectory.

In November 2010, we were awarded $1.13m in NHMRC funding for a national, multi-site trial of PeNTAGOn (2011–14). This randomised controlled study will test the effectiveness of the intervention to reduce psychological distress, informational and psychosocial needs, symptom distress, psychosexual difficulties and vaginal atrophy; and improve patient preparation for treatment and quality of life. This novel and timely research to meet patients' psychological and supportive care needs could have economic benefits, and is potentially transferable to a range of treatment settings and types of diseases, such as diabetes or cardiovascular disease, across Australia. If this intervention is successful, the proposed research program has the potential to transform health care practices nationally and internationally.

3.2.11 Nutrition

Head: Janelle Loeliger

The Depaertment of Nutrition continues to provide nutritional support and advice to patients in both the inpatient and outpatient settings at East Melbourne, at Box Hill and Moorabbin satellites and for up to 100 tube-fed patients at home at any one time. Our team consists of dietitians, nutrition assistants and secretarial support. We aim to be recognised as one of Australia's leading oncology nutrition centres.

Nutrition is involved in the education and training of dietetics students, as well as running a strong continuing professional development program supporting dietitians outside of Peter Mac in nutritional management in oncology. We prioritise maintaining and improving the quality of our services and play a significant role in clinical research.

Current research projects underway in our department include:

- Inpatient malnutrition strategy.
- Development of an evidence-based nutrition care pathways for different tumour streams.
- An integrated cancer services partnership project between Loddon Mallee and Western Central Melbourne Integrated Cancer Services.
- Development and implementation of guidelines for gastrostomy tube insertion in head and neck cancer patients.
- Malnutrition strategy for Chemotherapy Day Unit patients.

RESEARCH FOCUS

- Striving for excellence and ensuring that our clinical practice is evidence-based.
- Provision and improvement of patient care through innovation, collaboration and education.

RESEARCH DIRECTIONS

Our research is linked to the multidisciplinary tumour stream teams we work closely with, and in 2010 our research directions included:

- Permanent implementation of the Malnutrition Inpatient Strategy into usual care.
- Ongoing development and completion of evidence-based care pathways for all tumour streams that map evidence-based dietitian interventions and frequency of intervention.
- LMICS/WCMICS partnership project 'Improving care for regional cancer patients through collaboration between Integrated Cancer Services to support and mentor regional health professionals', a funded mentoring project for dietitians and speech pathologists in head and neck and upper GI cancers.
- Jenelle Loeliger's and Nicole Kiss' work as members of the dietitian committee developing the National Evidence Based Guidelines for the Nutritional Management of Head and Neck Cancer.
- After two years of research, publishing *'Oncology nutrition: the essential resource for the nutritional management of cancer'*, an educational manual targeting dietitians which aims to provide guidance for the nutritional management of oncology patients.
- Extensive audit of malnutrition prevalence in Peter Mac's Intensive Care Unit.
- Participation in the inaugural Australasian Nutrition Care Day Survey — providing malnutrition prevalence data in acute care settings across Australia and New Zealand.

Reference: The Nutrition Department Peter MacCallum Cancer Centre. Oncology Nutrition: an essential resource for the nutritional management of cancer. Peter MacCallum Cancer Centre: 2009.

3.2.12 onTrac@Peter Mac

Acting Head: Dr Lisa Orme

OnTrac@PeterMac is Victoria's first and leading Adolescent and Young Adult (AYA) cancer service, bringing together research and clinical service development. Located at Peter Mac, this specialist multidisciplinary team offers specialised, age appropriate care to AYAcancer patients treated within adult hospitals. The team includes a medical and paediatric oncologist, psychologist, social worker, education advisor, music therapist, education and training officer and research officer.

This unique service model is based on the integration of research and clinical service development offering young people access to the most current cancer therapies and clinical trials whilst providing the most comprehensive developmentally targeted psychological, social and emotional support.

The mandate of the onTrac@PeterMac Service is to provide:

- clinical care and support for young people undergoing cancer treatment
- secondary consultation service to healthcare professionals, young people and the wider community
- professional development, training and education program
- medical and psychosocial translational research and data management.

RESEARCH FOCUS

OnTrac@PeterMac is committed to undertaking internationally outstanding clinically-focused research aimed at influencing health care and health policy in the field of adolescent and young adult oncology.

RESEARCH DIRECTIONS

Cancer during adolescence and early adult life is one of the most under researched areas within oncology. Assumptions about the best way to manage the care of the AYA patient are based on studies conducted with other age groups and are not appropriately targeted towards the specific needs of the AYA population. This practice is assumed to be contributing to the issues associated with this age group. Addressing this practice is one of the central goals of onTrac@PeterMac.

Over the past five years, onTrac@PeterMac has become a world leader in AYA evidence-based cancer research. The team has developed and implemented a number of world-first studies both collaboratively and independently which will be able to inform both national and international AYA care. Below are some of the studies being lead by onTrac@PeterMac throughout 2010:

- AYAPK Study: evaluating the effect of gender on the pharmacokinetics (PK) of doxorubicin in AYA's newly diagnosed with osteosarcomas, Ewing sarcoma or Hodgkin lymphoma.
- Patterns of care and experience of care for adolescents and young adults with cancer.
- An exploratory study into oncology specialists understanding of the healthcare preferences of young people living with cancer.
- The role of PET/CT in the staging, evaluation of response to treatment and surveillance of disease recurrence in bone and soft tissue sarcoma of children and young adults.
- A patient management platform for cancer care: eCanCare: A collaborative study with the Department of Nursing and Supportive Care at Peter Mac.
- *Transitions: An exploratory Study into Survivorship of Adolescents and Young Adults with Sarcoma.*

For more information on related research, see:

- Sarcome Genomics and Genetics laboratory (pg 35)
- Medical Oncology and Early Phase Clinical Trials (pg 82)
- Sarcoma Service (pg 91)

3.2.13 Pain and Palliative Care

Head: Dr Odette Spruyt

The Department of Pain and Palliative Care conducts research aimed at improving quality of life, pain and symptom control and end of life care for patients with cancer.

RESEARCH FOCUS

Pain and Palliative Care is focused on projects which directly improve patient care through better integration of palliative care across all of cancer care, to ensure symptom control is optimised not only at the end of life but throughout the cancer trajectory.

RESEARCH DIRECTIONS

Pain and Palliative Care aims to improve the evidence base for palliative care through the conduct of clinical trials, pharmacovigilance monitoring, development of validated assessment tools, participation in national quality improvement activities such as PCOC, reflective case reports, clinical audits and evaluation of the impact of palliative care in cancer care.

We have a current project implementing end of life care pathways across four WCMICS sites and a project conducted on behalf of the Department of Health to conduct a literature review on palliative care pain indicators and develop an implementation plan for these indicators to be incorporated into quality assurance in cancer care and palliative care. We also aim to promote the development of palliative care in oncology in the developing world and evaluate the impact of clinical mentorships.

Current clinical trials include:

- A randomised, double blind control trial of megestrol acetate, dexamethasone and placebo in the management of anorexia in people with cancer.
- A randomised control trial of oral risperidone, oral haloperidol, and oral placebo with rescue subcutaneous midazolam in the management of delirium in palliative care inpatients.
- A randomised double blind placebo controlled trial of infusional subcutaneous Octreotide in the management of malignant bowel obstruction in people with advanced cancer.
- A two-stage trial of antiemetic therapy in patients with cancer and nausea not related to anti-cancer therapy. Study 1: A randomised open label study of guideline-driven targeted antiemetic therapy versus single agent antiemetic therapy.
- A two-stage trial of antiemetic therapy in patients with cancer and nausea not related to anti-cancer therapy. Study 2: A randomised controlled double blind study of methotrimeprazine or ondansetron versus placebo with rescue antiemetics (best supportive care) in patients with refractory nausea.
- Multi-site cluster randomised controlled trial comparing the severity of constipation symptoms experienced by palliative care patients receiving usual care compared to those diagnosed and managed according to the usual pathophysiology.

3.2.14 Pharmacy

Head: Sue Kirsa

The Pharmacy at Peter Mac provides medicines management support for patients and staff, focusing on ensuring medicines use by Peter Mac patients are safe, effective and efficient.
The Pharmacy conducts high quality research that will contribute positively to the drug therapy outcomes of our patients.

RESEARCH FOCUS

- The Pharmacy is actively involved in a number of research activities relating to drug therapy, many of these involve collaborations within Peter Mac and with national collaborative groups.
- Particular focus includes medication safety, pharmacokinetics and pharmacodynamics, drug stability, pharmacogenomics, adverse drug reactions and chemotherapy drug dosing.
- Research experience includes clinical and practice-based research with self-initiated projects, competitively funded initiatives and supervision of undergraduate and postgraduate students.

RESEARCH DIRECTIONS

The key focus of the Pharmacy's research work is on improving the efficacy of medicines. Research has mainly centred on formulating, rolling out and then auditing medicine use following evidence-based guidelines. Through the robust methodology of literature review, clinician practice survey and consensus meetings, we contribute to the formulation of nationally consistent approaches to medicine management: reducing practice variation, aligning practice with evidence and ultimately improving patient outcomes.

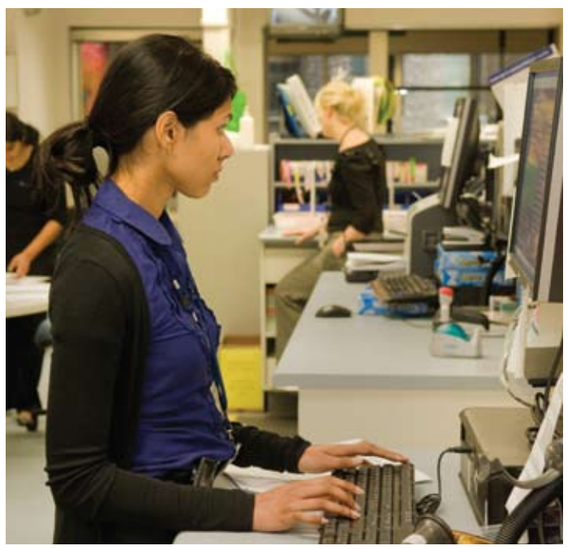
Current research projects include:

- Pharmacogenomics (Personalised Medicine)
  - Identifying predictive and prognostic biomarkers and the development of genotyping assays.
  - Preventing or overcoming chemotherapy resistance with posaconazole (p53 resistance) (Senthil).
- Pharmacotherapeutics
  - Preventing DVTs in cancer patients through effective thromboprophylaxis strategies (Verna).
  - Using Azol antifungals in prophylaxis against systemic mould and fungal infections effectively in severely immunocompromised patients.

Other audits and roll out of clinical practice guidelines have similar aims on a local scale—providing support for clinicians to provide evidence based care to our patients and providing feedback to clinicians about how closely our practice aligns with evidence.

For more information on related research, see:

- Infectious Diseases (pg 115)
- Molecular Pathology laboratory (pg 117)



3.2.15 Physical Sciences

Head: Jim Cramb

The Department of Physical Sciences comprises medical physicists, who provide a range of services underpinning the planning and delivery of radiotherapy treatments. These include equipment commissioning and quality assurance, development and enhancement of treatment techniques, fundamental and clinically oriented research, involvement in clinical trials and teaching. Medical physicists play a key role at our main campus at East Melbourne, and also at each of Peter Mac's four satellite centres.

Our Biomedical Engineering section is primarily responsible for the testing, maintenance and quality control of patient-related equipment. The team also contributes to the design and development of special-purpose radiotherapy equipment for both external beam radiotherapy and the treatment with implanted radioactive sources (brachytherapy).

RESEARCH FOCUS

Most of the Physical Sciences research projects are directly aimed at improving patient care in radiotherapy. However, there are also external collaborations including both applied and basic research.

In 2010, the research focus of the Physical Sciences team was on the development of new techniques and technologies for radiotherapy delivery. A particular emphasis was the introduction of these techniques into the clinic via clinical trials, both in-house and on a national level through TROG.

RESEARCH DIRECTIONS

- Continuing research into and development of imaging modalities, in particular to allow for or correct for organ movement during radiotherapy treatment.
- Development of a protocol to use a hand-held ultrasound scanner to confirm bladder volume prior to radiotherapy treatment for post-prostatectomy patients.
- Development of a software tool to analyse data from clinical trial benchmarking exercises. This application provides quantitative assessment of variations in contouring treatment volumes and organs at risk.
- Involvement in multiple clinical trials including advice on QA activities for trials using IMRT techniques, and participation in international discussion on global harmonisation of quality assurance standards in clinical trials.
- Assessment of the benchmarking data for the 'RAVES' (Radiotherapy Adjuvant Versus Early Salvage) clinical trial for post-prostatectomy patients.
- Investigation into ways to minimise out-of-field doses in radiotherapy of brain lesions in children.
- Development of mathematical models based on radiobiological models and functional imaging, with the objective of improved treatment of prostate cancer (Cancer Australia funded project).
- Assessment of radiation dose outside of the treatment field with the aim to determine and minimise risk of secondary cancer induction due to radiotherapy. This is part of an NHMRC funded project.
- Development of a technique for extracranial stereotactic radiotherapy treatments for small lung cancers as part of a Cancer Australia funded clinical trial (CHISEL). This involves also work on motion management.
- Development of a method for credentialing of centres for participation in a clinical trial employing adaptive radiotherapy for bladder cancer (BOLART—funded through NHMRC).
- Commencement of support for research activities in nuclear medicine and medical imaging as it pertains to radiotherapy treatment planning.

3.2.16 Radiation Therapy

Head: Aldo Rolfo

Significant change and increase of complexity of radiotherapy treatment technology is enabling further refinement in our radiotherapy methods, the development of image guided radiotherapy and patient motion management; use of novel 'diagnostic imaging devices' to assess the impact of organ motion on planning dosimetry; and target volume assessments. Increased integration of imaging into the radiotherapy process is a key focus.

The research efforts throughout Radiation Therapy continue to grow, particularly at the satellites, with increasing emphasis on multidisciplinary team programs.

RESEARCH FOCUS

Radiation Therapy research crosses all types of cancer, with a focus on the appraisal and improvement of radiotherapy techniques as a single and combined modality including:

- 4D PET imaging
- 4DCT imaging
- SBRT
- Gated Radiotherapy
- managing organ deformation
- PET and tumour response
- Adaptive Radiotherapy.

RESEARCH DIRECTIONS

Many of the clinical trials being undertaken within the department are part of TROG. Clinical trials of innovative treatment strategies include:

- NHMRC Project Grants:

- 'A multi-centre feasibility study of online adaptive radiotherapy for muscle invasive bladder cancer', 2010–12.
- 'Analysis of low radiation dose outside of the treatment field delivered to cancer patients undergoing radiotherapy', 2010–12.
- 'RAVES - 2009–13, with University of Newcastle
- 'Phase 3 trial comparing adjuvant versus salvage radiotherapy for high risk patients post radical prostatectomy 2008–11.
- 'Determination of unwanted radiation dose outside of the radiotherapy treatment field', 2008–10.
- 'A prospective single arm trial of involved field radiotherapy alone for stage I-II low grade non-gastric marginal zone lymphoma', 2007–11.
- 'A randomised phase 3 study of radiation doses and fractionation schedules in non-low risk ductal carcinoma *in situ* (DCIS) of the breast', 2007–11.
- Cancer Australia, DoHA & Prostate Cancer Foundation of Australia: 'Translation of clinical and functional imaging data to brachytherapy treatment optimisation for prostate cancer', 2010–12.
- Victorian Cancer Agency (VCA) Supportive Care & Palliative Care Capacity Building Grant: 'Evaluation of the psychosocial impact of a novel intervention that aims to reduce anxiety and aid coping in paediatric radiotherapy patients by producing a short DVD about their treatment experience', 2010.
- Peter Mac Foundation Grant: 'Bladder volume surveillance using ultrasound volumetric imaging for the post-prostatectomy patient undergoing radiotherapy treatment', 2010.
- Cancer Australia Priority-driven Collaborative Cancer Research Scheme: 'A randomised trial of stereotactic versus conventional radiotherapy for inoperable stage IA non-small cell lung cancer', 2009–11.
- VCA Platform Technology Grant: A Victoria wide Web based electronic learning (eLearning) program for Image Guided Radiotherapy', 2009–10. The key research strategy was based around the use of high quality imaging available now on the radiotherapy treatment machine. This involved better targeting of the tumour and avoidance of normal health tissues. A specific example being the use of imaging for bladder cancer to reduce the radiation dose to healthy tissues. This area of research examined the dose reduction achievable to healthy tissues when an image guided adaptive treatment plan is used. In a study of 27 patients, 25 received significantly less dose to these tissues which correlated with reduced side effects.
- VCA Clinical Trial Funding (Tumour Stream): 'A prospective study investigating the impact of serial PET/CT scans on the radiation therapy treatment of patients with lung cancer', 2008–10.

3.2.17 Social Work

Head: Alison Hocking

The Department of Social Work Department provides social work, music therapy and language services to patients and their families at Peter Mac.

Social workers are members of multidisciplinary teams across all clinical services, providing psychosocial assessment and care planning.

Our Language Services staff arrange interpreting services for Peter Mac patients to ensure they are able to communicate with staff and receive the information they require in the language of their preference.

RESEARCH FOCUS

Research activities focus on:

- Patient focused psychosocial priorities in treatment and survivorship
- Social Networks, including caregivers
- Workforce development and sustainability.

Current research projects focus on:

- Family/caregivers
- Gender
- Multiculturalism
- Social Work interventions and innovative service delivery methods
- Vicarious trauma of practitioners.

RESEARCH DIRECTIONS

Following the commencement of the research collaboration between Social Work and The University of Melbourne in 2009, we have progressed research activities under the Collaboration of Social Research in Cancer Care. We are currently in discussions with national and international partners to develop other joint research initiatives.

Social Work as part of Allied Health at Peter Mac, is also engaged in partnering with Allied Health at St Vincent's Health in the Older Persons with Cancer Project. Supported by a grant from the Western and Central Melbourne Integrated Cancer Service (WCMICS), the project, is entitled 'Can we improve the care of older people with cancer (OPWC) through targeted supportive care assessment, capacity building and partnerships with sub acute ambulatory care service?'

The general aim of this project is to improve the care of OPWC at St Vincent's and Peter Mac by testing the feasibility of a geriatric screening assessment (GSA) with supportive care pathway and addressing the learning needs of sub-acute ambulatory care service staff to meet the needs of OPWC. The project will thus propose an improved supportive care pathway for OPWC.

3.2 Interdisciplinary Research Platforms – personnel

CENTRE FOR BLOOD CELL THERAPIES

Director
Prof. Miles Prince

Deputy Director
Assoc. Prof. David Ritchie

Operations Director
Dr Dominic Wall

Clinical Apheresis Director
Dr Simon Harrison

Quality Manager
Martin Bleasdale

Managing Director Cell Therapies P/L
Ray Wood

Business Manager
Dr Wendy Chung

Cryopreservation
Peter Gambell
Ayse Mouminoglu

Cell Manipulation
Kerrie Stokes
Elise Butler
Carmen Chong
Valerie Costa
Kate Dunster
Alannah Evans
Javier Haurat
Lucy Kravets
Maureen Loudovaris
Nicole McCarthy
Jude Moloney
Angela Morgan
Tanya Pisanelli
Gianna O'Donnell
Gillian Treloar
Dimitrios Tsiavos
Lezly Penalver
Gabby Workman
Sichong Zhou

Apheresis

Mel Darby
Jack Parrington

Senior Scientist
Dr. Paul Neeson

Senior Research Associates
Prof. Rod Hicks
Dr Kirsten Herbert

CENTRE FOR CANCER IMAGING

Head
Prof. Rod Hicks

Research Officer
Dr Annette Hogg

Research Imaging Specialists
Assoc. Prof. Eddie Lau
Dr Kate Moodie

Research Coordinator and Clinical Trials Specialist
David Binns
Jason Callahan

Radiopharmaceutical Chemists
Dr Oliver Neels
Dr Peter Roselt

Radiopharmacist
Peter Eu

Research Coordinator
Elizabeth Drummond

Nuclear Medicine Technologists
Silvana Breglevska
Melanie Crowther
Emily Hong
Val Johnston
Mick Thompson

Nuclear Medicine Physician
Dr Michael Hofman

Nuclear Medicine Specialist
Dr Grace Kong

Nuclear Medicine Registrar
Tom Barber

Analytical Chemist
Dr Wayne Noonan

Visiting Scientist
Nicolas Aide

Radiologists
Dr Robin Cassumbhoy
Dr Churata Dagia
Dr Nick Ferris
Dr Catherine Mandel

Honorary Nuclear Medicine Physician
Dr Rob Ware

Research Fellow
Jean-Mathieu Beauregard

MRI Supervisor
Noelene Bergen

Research Project Leader
Dr Donna Dorow

Research Officers
Dr Delphine Denoyer
Dr Kathryn Kinross

Research Assistants
Laura Kirby
Richard Young

Advanced Medical Science (AMS) Student
Ashray Gunjur (2009–10)
Francis Wong (2010–11)

CENTRE FOR BIOSTATISTICS AND CLINICAL TRIALS

Director
Assoc. Prof. Dina Neiger

Clinical Trials Program Manager
Marianne Hundling

Development and Project Manager
Paul Fahey

Biostatisticians
Marnie Collins
Mathias Bressel
Gaelle Dutu
Assoc. Prof. Richard Fisher
Emma Link
Alan Herschtal

IT
Jenny Beresford
Linas Silva

Trial Centre Data Managers
Ruth Columbus
Linda Cowan
Juliana Di Iulio
Kylie Gillberg
Bereha Khodr
Michael Kornhauser
Narmatha Kuru
Poppy Kypreos
Ania Matera
Bev McClure
Teresa Morgan
Christina Phassouliotis
Larissa Popowski
Christine Russell
Caroline Sardjono
Janani Sivasuthan
Janey Stone
Marijana Vanevski

Administration
Robert Hannah
Ditas Sioco
Julie Umek

Australian Leukaemia & Lymphoma Group (ALLG) Operations Office
Melissa Benedict
Cristina Conesa
Megan Ellis
Megan Sanders
Delaine Smith
Janey Stone
Dilu Uduwela

CLINICAL TRIALS UNIT

Unit Manager
Shannon Uren

Research Nurse Consultants (Team Leaders)
Allison Lamb
Heike Raunow
Sam Ruell

Research Nurses
Glenda Burke
Duncan Colyer
Jill Davison
Rebecca Doherty
Carrie Donohoe
Karena Hanlon
Rosetta Hart
Jo Hawking
Kate Khamly
Amanda Marshall
Sharyn Meadows
Michele Mortos
Carmela Rooney
Gillian Shilton

Study Coordinators
Fareda Fazli
Sophie Katsabanis
Katrina Parente
Anita Sridhar
Diane Strong
Vicki Walcher

Clinical Trials Nurse Specialist
Danielle Harvey

Office Manager – Administrative Team Leader
Tenille Gaylard

Junior Study Coordinator
Nicole Roylance

Administrative Assistant
Rachael Brooking

Data Assistant
Gens George

Ethics Submission Coordinators
Sarah Bascomb
Hayley Pritchard

CLINICAL PSYCHOLOGY

Head Clinical Research Fellow
Annabel Pollard

Clinical Staff Undertaking Research
Dr Ann Boonzaier
Dr Kate Neilsen

FAMILIAL CANCER CENTRE

Director
Dr Gillian Mitchell

Geneticists
Assoc. Prof. Paul James
Dr Alison Trainer

Clinical Research Coordinators
Kate Drew
Rebecca Driessen
Joanne McKinley
Sarah Sawyer

Medical Oncologist
Dr Yoland Antill
Assoc. Prof. Sue-Anne McLachlan

Medical Oncologist and Geneticist
Dr Marion Harris

Gastroenterologist
Assoc. Prof. Alex Boussioutas

Psychiatrist
Dr Daina Rumbergs

Genetic Counsellors
Shauna Buscombe
Linda Ciccarelli
Lucinda Hossack
Alexandra Lewis
Mary-Anne Young

Genetics Nurses/Coordinators
Morgan Murphy
Mary Shanahan

Research Assistant
Katrina Reeve

Data Manager
Chris Michael-Lovatt

Postgraduate Students
Kathryn Alsop
Ashley Crook
Lauren Plunkett

INFECTIOUS DISEASES

Head
Assoc. Prof. Monica Slavin

Senior Researcher
Dr Karin Thursky

Research Assistants
Dr Iain Abbott
Vivian Leung

Postgraduate Students
Dr Michelle Anada-Rajah
Senthil Lingaratnam
Dr Leon Worth

Visiting Fellow
Dr James Koh

KCONFAB FOLLOW-UP PROJECT

Principal Investigator
Assoc. Prof. Kelly-Anne Phillips

Project Coordinator
Prue Weideman

Research Fellow
Dr Sandra Harvey

Research Assistants
Kate Lucas
Lucy Stanhope

MOLECULAR PATHOLOGY LABORATORY

Heads
Prof. Stephen Fox
Assoc. Prof. Alex Dobrovic

Pathology Research Fellows
Dr Peter Chan
Dr Max Yan

Postdoctoral Scientists
Dr Chelsee Hewitt
Dr Thomas Mikeska
Dr Renato Salemi
Dr Angela Tan
Dr Ee Ming Wong
Dr Stephen Wong

Research Officers
Heather Hondow
Elena Takano
Giada Zapparoli

Research Assistants
David Byrne
Toni-Maree Rogers

3.2 Interdisciplinary Research Platforms – personnel

Postgraduate Students
Ida Candiloro
Hongdo Do
Katie Huang

Dan Mellor (part time)
Dr Max Yan

Summer/AMS Student (2010–11)
Zi Rong Low (The University of Melbourne)

NURSING AND SUPPORTIVE CARE

Director of Cancer Nursing Research
Prof. Sanchia Aranda

Deputy Director of Cancer Nursing Research
Assoc. Prof Meinir Krishnasamy

Director of Strategy and Development
Assoc. Prof. Penelope Schofield

Senior Clinician Researcher
Dr Donna Milne

Senior Supportive Care Researcher
Dr Sibilah Breen
Dr Jessica Faggian

Statistician
Dr Karla Gough

Consultant Medical Oncologists
Assoc. Prof. Michael Jefford
Dr Linda Mileshkin

Research Operations
Fiona Hewitt
Cherry Horan

Clinician Researchers
Michaela Brindas
Lisa Demosthenous
Tracey Dryden
Mary Duffy
Catherine Grima
Suzi Grogan
Allison Hatton
Lynette Joubert
Trish Joyce
Nicole Kinnane
Mary Leahy
Rebecca McMillan
Andrew Murnane
Cathie Pigott
Mary Shanahan
Kath Schubach
Lisa Sheeran
Kathy Watty

Researchers
Rachid Annab
Carl Baravelli
Rebecca Bergin
Lara Dolling
Matt Holmes
Dr Sarah Kofoed

Kerryann Lotfi-Jam
Kerith Sharkey
Anna Ugalde
Eva Yuen

Postdoctoral Fellow
Dr Carrie Lethborg

Postgraduate Students
Jenny Anderson
Anna Boltong
Mary Duffy
Priscilla Gates
Miranda Goh
Chi-Yin Kao
Kerryann Lotfi-Jam
Anna Ugalde

AMS Students (The University of Melbourne)
Kelvin Koay (2009–10)
Simon Wu (2010–11)

Undergraduate Research Opportunities Program (UROP) Student
Desmond Chee (2010–11)

Research Consumer Advisors
Diana Black
Katie Emma Burrell
Annemarie Charles
Wal Crellin
Dorothy King
Debbie Lee
Dean Lynch
Helene O'Neill
Sylvia Penberthy
Vigneswara Rajah
Ian Roos
Barbara Shaw
Beryl Shaw
Christine Thom
David Wenzel
Claire Wilkinson
Leonie Young

Support Volunteers
Tamara Anghie
Tia Field
Melinda Grant
Georgia Mills
Bernadette Kelly
Sue Rowsthorn

NUTRITION

Head
Jenelle Loeliger (Malnutrition Inpatient Strategy Project Manager)

Dietitians
Gen Francis
Amanda Hill
Belinda Hodgson (Malnutrition Inpatient Strategy Project Co-Manager)
Amber Kelaart
Nicole Kiss
Vivian Kong
Tracey Martin
Sally Muir
Fiona Rezannah
Hannah Ray

Nutrition Assistants (Malnutrition Inpatient Strategy)
Stephanie Acosta
Angela Harris
Chloe Schibeci
Pauline Tsang

ONTRAC@PETER MAC

Acting Director
Dr Lisa Orme

Director
Assoc. Prof. David Thomas

Manager
Kate Thompson

Research Coordinator
Lucy Holland

Research Assistant
Gavin Dyson

Senior Clinician
Ilana Berger

Adolescent and Young Adult Research Fellow
Dr Rachel Conyers

Adolescent Psychologist
Dr Felicity Sleeman

Victorian and Tasmanian AYA Clinical Trials Officer
Deb Howell

Education and Vocation Advisor
Nicole Edwards

VCA Fellow, onTrac@Peter Mac
Assoc. Prof. Lynette Joubert

PAIN AND PALLIATIVE CARE

Head
Dr Odette Spruyt

Consultant
Dr. Natasha Michael

Study Coordinator
Elaine Mills

Research Nurse
Indy Khera

Project Co-ordinators
Alex Brando (PCI)
Di Saward (LCP)

PHARMACY

Director
Sue Kirsa

Deputy Director
Dan Mellor

WCMICS Project Officer
Senthil Lingaratnam

Postgraduate Student
Dan Mellor

PHYSICAL SCIENCES

Director
Jim Cramb

Principal Research Physicist
Prof. Tomas Kron

Senior Research Physicist
Assoc. Prof. Annette Haworth

Senior Physicists
Paul Roxby
Chris Fox
Dr Jim Hagekyriakou

RADIATION THERAPY

Director Radiation Therapy Services
Aldo Rolfo

Radiation Therapists
Yolanda Aarons
Therese Chesson
Robyn French
Brayden Geary
Rebecca Height
Felicity Height
Belinda McInnes
Richard Oates
Daniel Pham
Maria Portillo
Cate Sproston
Fiona Wightman

Charge Radiation Therapists
Brent Chesson
Alison Cray
Katie Davidson
Dr Sarah Everitt
Cathy Markham
Karen McGoldrick
Andrea Paneghel
Josh Rudolph
Mike Sproston
Ann Thompson
David Tongs
Sylvia Van Dyk
David Willis

Head of Planning, Radiation Therapy Services
Julie Miller

Head, Education and Development Unit, Radiation Therapy Services
Kate Wilkinson

SOCIAL WORK

Head
Alison Hocking

Senior Research Fellow
Assoc. Prof. Lynette Joubert

Senior Social Workers
Elizabeth Ballinger
Denise Beobich

Social Workers
Annette Betheras
Hamlata Bhana
Jennifer Burn
Catherine Coppolino
Elizabeth Dillon
Tegan Murnane
Lucy Pollerd
Elena Schiena

Music Therapists
Dr Clare O'Callaghan
Christine Mesarich

Language Services Coordinator
Kerrie Dunn

4

4 Education and Learning

Ever since her first laboratory experience with the CSIRO at age 15, Katrina Falkenberg has wanted to work in medical research. Now a PhD student at Peter Mac, Katrina's research is driven by an innate curiosity to understand cancer at a molecular level as well as a desire to improve treatment options for patients. Access to Peter Mac's sophisticated equipment allows Katrina, with her team in the Gene Regulation laboratory, to define the molecular and biological processes required for anti-cancer drug action and drug resistance.

Encouraging and training medical researchers of the future

Dr Caroline Owen, Education and Communications Officer, Cancer Research

Our Research Education program is underpinned at all levels by a belief in the importance of developing a deep understanding of the processes that control cancer cells, and employing this knowledge in the clinic to develop rational, evidence-based protocols that improve cancer outcomes. Using state-of-the-art facilities, we are focused on supporting the next generations of basic translational researchers who will improve cancer diagnosis, treatment and care.

In supporting Cancer Research at Peter Mac, our Research Education program provides excellence in scientific research training and support for all laboratory researchers and students as they develop expertise in new technologies, and help drive new discoveries that lead to changes in research and clinical practice.

Our postgraduate PhD and DMedSc/MD students and our postdoctoral scientists contribute significantly to the success of Peter Mac, and we are proud of the outstanding, motivated and enthusiastic staff and students who are an important part of our internationally recognised research team. Supporting the teaching and learning needs of the next generation of research scientists and clinician-researchers at Peter Mac is a high priority, and we strive to foster a collaborative and enabling environment that encourages and supports our young researchers as they develop their potential for future leadership in health and biomedical research.

The Cancer Research Education program is supported by full-time Education and Communications Officer, Dr Caroline Owen, who coordinates all aspects of student and staff education and career activities across Cancer Research and affiliated clinical areas, and liaises with affiliated universities and research institutes.

4.1 Cancer Research Education Program

- Seminar programs
- Student training program
- Research awards
- Peter Mac Postdoctoral program
- Community and school outreach activities

4.2 Clinical Research Education and Training Programs

- Specialised Certificate in Clinical Research (Oncology), The University of Melbourne
- Clinical Research Methods in Radiation Oncology
- Seminars in Oncology program

4.1.1 Seminar programs

Promoting recent advances in the rapidly changing technologies used in medical research is an important aspect of our development of the next generation of researchers. At Peter Mac, we host seminar activities designed to assist the professional development of scientists at all levels.

The weekly Research Seminar Series provides opportunities to hear about advances in cancer research at Peter Mac and external organisations. Staff and students also participate in weekly laboratory meetings and research hub seminars. These seminars provide Peter Mac researchers with the opportunity to discuss their research with broader expert audiences while also assisting them in developing presentation and discussion skills to increase their breadth of science knowledge and build confidence. We also host seminars and workshops designed to broaden the professional development of our scientists and students, and we organise an annual Topics in Cancer Seminar series to provide an opportunity for students and scientists to expand their understanding of key aspects of cancer research.

2010 POSTGRADUATE SEMINAR SERIES: TOPICS IN CANCER

Date	Presenters	Topics in Cancer
4-May	Drs Amber Alsop, Kylie Gorringe, Mark Shackleton	*How do cancers progress?*
18-May	Drs Trina Stewart, Michele Teng, Dan Andrews	*Cancer and immune regulation*
8-Jun	Drs Trina Stewart, Linda Berry, Nicole Haynes	*Immunotherapy of cancer*
22-Jun	Drs Kathy Jastrzebski, Kaylene Simpson, Megan Astle	*RNAi screening and cancer*
29-Jun	Drs Petranel Ferrao, Mark Devlin, Amber Alsop	*Molecular targeted therapeutics/small molecule inhibitor drugs in cancer treatment*
13-Jul	Drs Kathryn Kinross, Nathan Godde, Geoff Matthews	*Mouse models in cancer research*
27-Jul	Assoc Prof Grant McArthur	*Targeting oncogene addiction in clinical trials*
10 Aug	Prof Rod Hicks	*Imaging as a platform technology in translational research*

2010 PROFESSIONAL DEVELOPMENT WORKSHOPS

Date	Presenters	Topic
30-Mar	Peter Mac student participants and facilitators	*Prism and Endnote workshop*
6-Apr	Peter Mac student participants and facilitators	*Statistics workshop*
6-Jul	Yovanna Adamis (The University of Melbourne), Dr Luke Lambeth and Dr Edwin Hawkins (Peter Mac).	*Student Careers Seminar*

2010 PETER MAC RESEARCH SEMINAR SERIES

Date	Speaker	Institute	Topic
25-Feb	Prof. Miles Prince	Peter Mac	*Translational research in haematology at Peter Mac*
4-Mar	Assoc. Prof. Michael Ryan	La Trobe University	*Assembly of mitochondria in health and disease*
11-Mar	Prof. John Hopper	The University of Melbourne	*From tumour-type to phenotype: a new paradigm for breast and colorectal cancer genetics services that will save lives*
18-Mar	Assoc. Prof. Kathy Belov	University of Sydney, NSW	*The genetics of Devil Facial Tumour Disease (DFTD)"*
25-Mar	Assoc Prof. Anthony Jaworowski	Burnet Institute	*HIV: from AIDS to chronic inflammatory disease*
14-Apr	Dr Axel Kallies	The Walter & Eliza Hall Institute of Medical Research	*The transcription factors Blimp1 and IRF4 jointly regulate differentiation and function of effector regulatory T cells*
21-Apr	Prof. David Ashley	Children's Cancer Centre, the Royal Children's Hospital, Melbourne	*Epigenetics of childhood cancer*
28-Apr	Assoc. Prof. Carola Vinussa	The John Curtin School of Medical Research, The Australian National University	*The Roquin pathway in RNA regulation and autoimmune disease*

4.1 Cancer Research Education program

2010 PETER MAC RESEARCH SEMINAR SERIES (CONT.)

Date	Speaker	Institute	Topic
5-May	Dr Matthew McCormack	The Royal Melbourne Hospital	*Identification of Precancerous Stem Cells in a mouse model of T cell Leukemia*
12-May	Prof. Julian Rood	Monash University	*Role of clostridial toxins in human disease*
19-May	Prof. Terry Speed	The Walter & Eliza Hall Institute of Medical Research	*Combining matched gene expression and transcription factor binding sites: some lessons from an experiment with ERbeta*
27-May	Prof. Wolfgang Weninger	Centenary Institute for Cancer Medicine and Cell Biology, NSW	*Visualising the orchestration of skin immune responses in real time*
3-Jun	Prof. Peter Currie	Australian Regenerative Medical Institute, Monash University	*Modelling muscle growth and disease in zebrafish*
10-Jun	Prof. Anne Kelso	WHO Collaborating Centre for Reference and Research on Influenza, Melbourne	*Flu shifts backwards: the 2009 pandemic*
17-Jun	Prof. Leann Tilley	La Trobe Institute for Molecular Science	*Super-resolution optical microscopy and electron tomography of malaria parasites*
24-Jun	Dr Darren Saunders	Garvan Institute of Medical Research, NSW	*Illuminating molecular pathways through integration of functional genomics and proteomics*
8-Jul	Prof. Ashley Bush	Mental Health Research Institute	*Alzheimer's disease and cancer*
15-Jul	Dr Jake Baum	The Walter & Eliza Hall Institute of Medical Research	*The molecular mechanics of malaria parasite motility and host cell invasion*
22-Jul	Prof. Richard Harvey	Victor Chang Cardiac Research Institute, NSW	*Cardiac-resident MSC-like stem cells: definition and origins*
29-Jul	Prof. Levon Khachigian	Centre for Vascular Research, University of NSW	*Transcriptional control in vascular dysfunction*
5-Aug	Prof. Alpha Yap	Institute for Molecular Bioscience, University of Queensland, QLD	*Epithelial interactions: cadherins, signalling and the actin cytoskeleton*
12-Aug	Prof. Melanie Wakefield	Cancer Council Victoria	*Tobacco control in Australia: where have we come from and where are we going?*
19-Aug	Prof. John Quackenbush	Dana-Farber Cancer Institute and the Harvard School of Public Health, Boston, USA	*Network and state space models: science and science fiction approaches to cell fate predictions*
26-Aug	Dr Ben Solomon	Peter Mac	*ALK gene rearrangements: A new target in non-small cell lung cancer*
2-Sep	Dr Robert Vonderheide	Abramson Family Cancer Research Institute, University of Pennsylvania School of Medicine, USA	*Cancer immune surveillance and immunotherapy in solid tumours: strategies for stepping on the gas and cutting the brakes*
9-Sep	Prof. Peter Howley	Harvard Medical School, USA	*HPV and cancer: regulation of viral oncogene expression*
16-Sep	Prof. Peter Vischer	Queensland Institute of Medical Research, QLD	*Genome-wide association studies and the problem of 'missing heritability'*
23-Sep	Prof. Christophe Marcelle	Australian Regenerative Medicine Institute, Monash University	*Neural Crest regulates myogenesis through the transient activation of NOTCH'*
30-Sep	Dr Stuart Tangye	Garvan Institute of Medical Research, NSW	*Lessons for human knock-outs: what primary immunodeficiencies can tell is about immune regulation'*
7-Oct	Assoc. Prof. Penny Schofield	Peter Mac	*Sex, death and transformation: Improving outcomes for people affected by cancer*
14-Oct	Prof. Peter Gunning	University of NSW	*Deconstructing the cytoskeleton and identification of the actin filaments which drive cell proliferation in normal and cancer cells*
21-Oct	Dr John Silke	La Trobe University	*The TNF uncertainty principle — and lessons for other signalling pathways*
4-Nov	Assoc. Prof. Steven Stacker	Peter Mac	*Lymph angiogenesis*
11-Nov	Prof. Sam Berkovic	The University of Melbourne	*On the origin of epilepsies*
18-Nov	Prof. Jonathon Carapetis	Menzies School of Health Research, Northern Territory	*Priorities in Aboriginal health research*

4.1 Cancer Research Education program

2010 SPECIAL SEMINARS AND TECHNICAL WORKSHOPS

Date	Speaker	Institute	Topic
27-Jan	Dr Nikola Baschuk	University Hospital of Cologne, Institute for Medical Microbiology, Immunology & Hygiene, Germany	*Immune surveillance of cancer—molecular and translational aspects of Cytotoxi Effector: Target Cell Interactions*
9-Feb	Amy Rappaport, Katie McGukin	Cold Spring Harbor Laboratory, New York, USA	*MLL/AF9 is required for the maintenance of aggressive acute myeloid leukemia in mice(AR)* *Inducible, transgenic RNAi targeting essential genes in mice (KM)*
10-Feb	Dr Jon Karpilow,	Thermo Fisher Scientific	*Using RNAi screening to Identify host and pathogen genes that are relevant to viral infection*
13-Apr	Xose Fernandez	European Bioinformatics Institute, EMBL Outstation, Cambridge, UK	*Bioinformatics Services at EBI: An Introduction to EBI with a focus on gene expression analysis* *How the EBI is riding the tsunami: next generation sequencing*
25-May	Assoc. Prof. Bill Matsui	John Hopkins Sidney Kimmel Comprehensive Cancer Centre, Baltimore, USA	*Cancer stem cells in Multiple Myeloma: basic biology and clinical translation*
25-May	Dr Axel Kallies	The Walter & Eliza Hall Institute of Medical Research	*The transcription factor Blimp1 Is a context specific B cell tumor suppressor*
11-May	Paul Ramadge	Editor-in-Chief, The Age	*The media and science — a new relationship*
6-Sep	Dr Stephen Laderman	Agilent Laboratories	*Advanced measurement technologies for personalised cancer medicine*
14-Sep	Assoc. Prof. Han van der Loo	Cincinnati Children's Research Foundation, USA	*GMP manufacturing at the Cincinnati Children's Hospital translational cores*
14-Sep	Dr Yuri Nikolsky	GeneGo Inc	*Functional analysis of OMICs Data in breast cancer*
29-Sep	Dr Gianfranco de Feo	Sequenom	*Translating biomarker research to human health"*
1-Oct	Dr Roderick Beigersbergen	Netherlands Cancer Institute	*The powers of RNAi in cancer discoveries*
6-Oct	Assoc. Prof. David Granville	University of British Columbia, Canada	*Granzyme B: A multi-functional protease in inflammation and disease*
11-Oct	Dr Grzegorz Popowicz	Max Planck Institute for Biochemistry Martinsried, Germany	*p53 interaction with Mdm2 and its implications for the activity of the therapeutic drugs, the nutlins*
14-Oct	Prof.John Scott	University of Washington School of Medicine, USA	*Cell signalling in space and time*
8-Nov	Prof. Ze'ev Ronai	NCI Cancer Centre, Sanford-Burnham Medical Research Institute	*The ubiquitin ligase Siah2 in hypoxia and tumourigenesis*
7-Dec	Dr Luke Dow	Cold Spring Harbor Laboratory, New York, USA	*Transgenic RNA interference defines new roles for the Adenomatous Polyposis Coli tumour suppressor*
13-Dec	Dr Laura Johnston	Columbia Medical School, New York, USA	*Homeostatic mechanisms during organ growth*

4.1.2 Student Training Program

Student teaching and learning are key activities in Cancer Research, and the attraction of high-quality students to undertake Doctor of Philosophy (PhD), medical doctorates (MD or DMedSc) and honours programs in our laboratories continues as a priority. In 2010, we welcomed 12 new honours students, 12 new PhD students and two DMedSc students to our team.

Cancer Research is home to approximately 100 students throughout the year, including postgraduate, honours and advanced medical science students. In 2010 we also provided research placements for four international postgraduate students and for undergraduate students associated with our Summer Vacation Research Program, undergraduate work experience and Biomedical Science (Pathology major) research projects undertaken in our laboratories.
The Cancer Research team at Peter Mac also offers opportunities to TAFE and secondary school students to undertake short-term work placements in our laboratories.

Our comprehensive student program includes mentor programs, dedicated student scientific review committees, onsite workshops and seminars, an annual retreat, and community and outreach opportunities.

Our postgraduate, honours and AMS students contribute significantly to the success of Peter Mac. We warmly congratulate the following students who successfully completed their studies at Peter Mac in 2010.

CLASS OF 2010

Doctor of Philosophy (The University of Melbourne)

Amos S, Enhancing lymphocyte trafficking for adoptive T-cell therapies. Dr M. Kershaw.

Everitt S, The utilisation of PET/CT for assessing therapy naïve tumour growth, radiation therapy target volumes and cellular response in Non small Cell Lung Cancer. Assoc Prof M. MacManus, Prof T. Kron and Dr M. Schneider-Kolsky.

Grusche F, The regulation of tissue growth in Drosophila melanogaster during development and regeneration. Assoc. Prof. H. Richardson, Dr K. Harvey, Dr T. Brumby.

Lin J, Effects of ribosomal protein hypomorphs on cell growth and proliferation in Drosophila melangaster. Assoc. Prof. R. Hannan, Assoc. Prof. R. Pearson and Dr L. Quinn.

Pegram H, Gene modification of multiple leukocytes for cancer immunotherapy. Dr P. Darcy,Dr M. Kershaw.

Qiu, W, Cellular, molecular and genetic characterisation of breast and ovarian cancer associated fibroblasts (CAFS). Assoc. Prof. I. Campbell, Dr I. Haviv.

Wiegmans A, The biomolecular actions of HDAC inhibitors. Assoc. Prof. R. Johnstone.

Bachelor of Science (Honours) (The University of Melbourne)

Barber F, Development of a functional genomic screen for novel modulators of drug resistance in ovarian cancer. Assoc. Prof. R. Pearson, Dr K. Sheppard.

Cameron D, Developing a screen for novel regulators of RNA Polymerase I transcription. Dr M. Astle, Assoc. Prof. R. Hannan.

Cross R, Myb and its involvement in development and tumorigenesis. Prof. R. Ramsay, Assoc. Prof. R. Anderson.

Dent L, Novel regulators of the Hippo tumour suppressor. Dr K. Harvey, Dr C. Poon.

Devlin J, Investigating the role of AKT signalling in c-MYC driven tumorigenesis. Assoc. Prof. R. Pearson, Dr K. Hannan.

Fund I, The role of signalling and polarity proteins in asymmetric cell division of T lymphocytes. Dr J. Oliaro, Dr S. Russell.

Halse H, Siah2 ubiquitin ligase dependent communication between breast cancer tumour cells and the immune system. Dr A. Moeller, Mr C. House.

Kapadia N, Investigating receptor mediated delivery of Iodine-125 labelled DNA ligand to the DNA of tumour cells. Dr P. Lobachevsky, Assoc. Prof. R. Martin.

Ko SY, Pathways that regulate intestinal crypt cell fates and impinge upon cancer. Assoc. Prof. R. Ramsay, Dr J. Malaterre.

Lefebure M, Novel combination treatments against multiple myeloma. Assoc. Prof. R. Johnstone, Dr G. Matthews.

Munforte L, *In vitro* evaluation of the combination of a new DNA-binding radioprotector with a radical scavenger. Dr P. Lobochevsky, Dr A. Smith.

Woods S, A role for E6AP in the regulation of p53 under stress conditions. Assoc. Prof. Y. Haupt.

Advanced Medical Science (AMS) (The University of Melbourne)

Cordy R, Novel combination immunotherapies induce immunogenic cell death in human myeloma cells. Dr P. Neeson, Assoc. Prof. D. Ritchie.

Gunjur A, The patterns of progression and pseudo-progression for glioblastoma multiforme patients treated with the 'Stupp Protocol'. Assoc. Prof. E. Lau, Prof. R. Hicks.

Koay K, Understanding health information in the oncology setting. Assoc. Prof. P. Schofield, Assoc. Prof. M. Jefford.

Yeh WZ, Investigation of differential allelic expression of the human PRF1 gene. Dr I. Voskoboinik, Prof. J. Trapani.

4.1 Cancer Research Education program

STUDENTS IN PROGRESS

Scholarships to support training

APA: Australian Postgraduate Award
ASCC: ASCC Postgraduate Scholarship
CASS: CASS Foundation Scholarship
CCV: Cancer Council Victoria Postgraduate Scholarship
CRIS: Cancer Research Institute Scholarship
CSL: CSL Postgraduate Scholarship
EGIPS: Egyptian Government International Postgraduate Scholarship
EQUITY: Equity State Trustees
FUSRS: Flinders University Student Research Scholarship
LaTrobe: La Trobe University Postgraduate Scholarship
LF: Leukaemia Foundation Scholarship
MFS: Melbourne Faculty Scholarship
MGS: Monash Graduate Scholarship
MIRS: Melbourne International Research Scholarship
MRS: Melbourne Research Scholarship
NBCF: National Breast Cancer Foundation Scholarship
NHMRC: NHMRC Postgraduate Scholarship
Peter Mac: Peter Mac Research Laboratory or Grant Funding
RACS: Royal Australasian College of Surgeons
SUT: Swinburne University Postgraduate Scholarship

PhD in Progress

Ackora D, Pathways regulating asymmetric cell division and binary cell lineage fate in the intestine. Dr J. Malaterre, Assoc. Prof. R. Ramsay, Ministry of National Education Scholarship, Republic of Turkey.

Alsop K, Genotypic and molecular analysis of ovarian cancer. Prof. D. Bowtell, Dr G. Mitchell, CCV.

Azad A, Enhancing the efficacy of ionising radiation with the dual PI3K/mTOR inhibitor BEZ235. Assoc. Prof. G. McArthur, Dr B. Solomon, NHMRC.

Bearfoot J, Identification of microRNA genes involved in breast and ovarian tumourigenesis. Assoc. Prof. I. Campbell, Assoc. Prof. W. Phillips, Assoc. Prof. A. Dobrovic, MRS.

Bishton M, Investigations into Histone Deacetylase Inhibitor induced Thrombocytopenia. Prof. R. Johnstone, Prof. M. Prince, Peter Mac.

Brown D, Regulation and function of mutant p53. Assoc. Prof. Y. Haupt, Dr P. Humbert, APA.

Bruhn M, Role of SGK3 in tumourigenisis. Dr K. Sheppard, Assoc. Prof. R. Hannan, FUSRS.

Burrows A. The contribution of stromal caveolin-1 to breast cancer metastasis. Assoc. Prof. R. Anderson, NHMRC.

Bywater M, Regulation of ribosome biogenesis during lymphomagenesis. Assoc. Prof. G. McArthur, Assoc. Prof. R. Hannan, NHMRC.

Candiloro I, Somatic DNA methylation and cancer predisposition. Assoc. Prof. A. Dobrovic, Dr T. Mikeska, MFS.

Cao Y, BMP4 — a metastasis suppressor gene in breast cancer. Dr R. Anderson, Dr B. Eckhardt, MRS.

Carpenteri S, Pathways regulating asymmetric cell division and binary cell lineage fate in the intestine. Assoc. Prof. R. Ramsay, Dr P. Darcy, LaTrobe.

Carter R, Integrin ss3 as a therapeutic target for breast cancer metastasis to bone. Dr R. Anderson, Dr N. Pouliot, NBCF.

Chan AL, Regulation of Promyelocytic Leukaemia (PML) by E6AP in human cancers. Assoc. Prof. Y. Haupt, Assoc. Prof. D. Thomas, MRS.

Chan C, NK cells in Tumour Immunosurveillance. Prof. M. Smyth, Dr D. Andrews, LF.

Cheasley D, Investigations of Myb target genes and regulation within stem/progenitor cell populations of the intestine. Assoc. Prof. R. Ramsay, APA.

Chee L, Differentiation therapy of acute myeloid leukaemia: combining RARAgonists and G-CSF. Assoc. Prof. G. McArthur, Dr P. Humbert, CSL.

Chia J, Investigating the molecular basis of perforin dysfunction that leads to atypical Haemophagocytic Lymphohistiocytosis (HLH) or other primary pathologies. Prof J Trapani, Dr I. Voskoboinik, CCV.

Chong L, Investigating Olt-4 in skin. Dr P. Kaur, Dr H. Schluter, Peter Mac.

Chow M, The role of inflammasome in cancer initiation and tumour immunogenicity. Prof. M Smyth, Dr A. Moeller, CRIS.

Conyers R, Creation of an *in vivo* model recapitulating amplification of MDM2 and CDK4 in human Liposarcoma. Assoc. Prof. D. Thomas, Dr M. Kansara, MRS.

Davis S, Integrated Genomic Analysis and Functional Characterisation of Novel Oncogenes in Ovarian Cancer Prof. I. Campbell, Dr K. Gorringe, Dr K. Simpson, APA.

Do H, Genetic and epigenetic mechanisms determining responses to therapy in non-small cell lung cancer.Assoc. Prof. A. Dobrovic, Prof. S. Fox, Peter Mac.

Duong C, Generating highly responsive T cells with tumour homing ability for use in the adoptive immunotherapy of cancer. Assoc. Prof. K. Kershaw, Dr P. Darcy, APA.

Ellis S, *In situ* protein and molecular characterisation of the hemopoietic stem cell niche. Dr S. Nilsson, Dr I. Bertoncello, Peter Mac/ ASCC/CASS.

Elsum I, The role of Scribble in oncogenic signalling and tumourigenesis. Dr P. Humbert, Assoc. Prof. H. Richardson, CCV.

Falkenberg K, Targeting epigenetic enzymes for the treatment of cancer. Assoc. Prof. R. Johnstone, Dr K. Simpson, APA.

Galea R, The role of the Scribble/Discs Lager polarity complex in development and tumourigenisis. Dr P. Humbert, Assoc. Prof. H. Richardson, APA.

Garsed D, Uncovering the molecular basis of well-differentiated liposarcoma. Assoc. Prof. D. Thomas, Assoc. Prof. Y. Haupt, MRS.

George J, Integrated analysis of distinct molecular profiles of tumour data. Prof. D. Bowtell, Assoc. Prof. G. Smyth, APA.

Hare L, Investigating the role of PIK3CA mutations in colorectal cancer. Assoc. Prof. W. Phillips, APA.

Huang K, Epigenetic mechanisms in benign and malignant breast cancer. Prof. S. Fox, Assoc. Prof. A. Dobrovic, MRS.

Huynh D, CSF-1/c-fms signalling in intestinal biology and cancer. Assoc. Prof. R. Ramsay, LaTrobe.

Johnson C, Molecular profiling of breast ductal carcinoma in situ. Prof. I. Campbell, Dr E. Thompson, APA.

Khoo P, Investigation of pathways that act downstream of scribble and Rho GEF2 in cooperation with oncogenic RAS in a Drosophila cancer model. Assoc. Prof. H. Richardson, Dr P. Humbert, Dr T. Brumby, MRS.

Koh SY, Role of Proteases and PARs in Barrett's Oesophagus and Oesophageal Adenocarcinoma. Assoc. Prof. W. Phillips, Dr N. Clemons, MIRS.

Kusuma N, Targeting of Laminin-10 in breast cancer metastasis. Dr R. Anderson, Dr N. Pouliot, NHMRC.

Lee R, Biochemical analysis of AKT3 specific signal transduction. Dr R. Pearson, Assoc. Prof. R. Hannan, APA.

Leong G, Identification and characterisation of novel tumour suppressor genes involved in breast cancer. Assoc. Prof. R. Hannan, Assoc. Prof. R. Pearson, Assoc. Prof. R. Johnstone, NHMRC, NBCF.

Messina N, Role of STAT1 in Interferon signalling and immunity. Assoc. Prof. R. Johnstone, Dr C. Clarke, CRIS. Miao, YR, The role of Myb in mammogenesis and breast cancer. Assoc. Prof. R. Ramsay, Dr R. Anderson, MRS.

Newbold A, Mechanisms of histone deacetylase inhibitors. Assoc. Prof. R. Johnstone, NHMRC.

STUDENTS IN PROGRESS (CONT.)

Ngiow SF, Immune suppressive pathways in cancer: mechanisms and applications. Prof. M. Smyth, Dr M. Teng, Malaysian Government Scholarship.

Pasam A, Mechanisms and role of polarity proteins in T cells. Dr S. Russell, Dr P. Humbert, MRS.

Pham K, Investigating polarity proteins in thymocytes—a potential role in asymetric cell division? Dr S. Russell, Prof. M. Gu, NHMRC.

Pilgrim C, Predicting chemotherapy induced hepatic injury on clinical, genetic and imaging parameters following treatment of colorectal carcinoma. Assoc. Prof. W. Phillips, Dr C. Duong, MRS/RACS.

Quin J, Mechanisms regulating ribosomal gene transcription. Assoc. Prof. R. Hannan, Dr E. Sanij, APA.

Ramakrishna M, Identification of novel ovarian cancer genes using a cross-platform, integrative genomics approach. Assoc. Prof. I. Campbell, Dr K. Gorringe, CCV.

Ryland G, Next generation sequencing of candidate ovarian tumour suppressor genes. Assoc. Prof. I. Campbell, Dr K. Gorringe, MGS.

Saad M, Biological characterisation of human phosphatidylinositide 3-kinase Mutations. Assoc. Prof. W. Phillips, NHMRC.

Sacirbegovic F, The role of polarity proteins in T cell function. Dr S. Russell, Dr P. Humbert, MRS.

Sceneay J, The contribution of non-malignant cells to breast cancer progression. Dr A. Moeller, Prof. D. Bowtell, Prof. M. Smyth, Equity.

Shimoni R, The computational microbioreactor: Analysing asymmetric cell division in immune cells. Dr S. Russell, Prof. Min Gu. SUT.

Shortt J, Therapeutic inhibition of the phosphatidylinositol-3 kinase/mammalian target of rapamycin pathway in Myc driven models of B-cell neoplasia. Assoc. Prof. Ricky Johnstone, Assoc. Prof. Grant McArthur. LF.

Sinha A, Control of organ size during development and disease. Dr K. Harvey, Dr C. Milton, MFS.

Smith L, Characterisation of the signalling network through which Scribble exerts its tumour suppressive function. Dr P. Humbert, Dr I. Haviv, APA.

Susanto O, Signalling pathways in cytotoxic lymphocyte-induced cell death. Dr N. Waterhouse, Prof. J. Trapani, CRIS.

Turkel N, Characterisation of a novel drosophila oncogene. Assoc. Prof. H. Richardson, Dr T. Brumby, Peter Mac.

Wang L, Gene-modified leukocytes for cancer therapy. Assoc. Prof. M. Kershaw, Dr P. Darcy, APA.

West A, The role of HDACi in anticancer immunotherapy. Prof. R. Johnstone, Prof. M. Smyth, NHMRC.

Withana N, Contribution of tumour derived cysteine cathepsins to breast cancer metastasis to bone. Assoc. Prof. R Anderson, Parker, NHMRC.

Wong C, Inhibition of Siah ubiquitin ligase in breast cancer. Dr A. Moeller, Prof. D. Bowtell, CCV.

Wood P, Molecular analysis and therapeutic targeting of the PI3K/AKT/mTOR pathway in paediatric neuroblastoma. Assoc. Prof. G. McArthur, Assoc. Prof. D. Ashley, MRS.

Yassin M, Elucidating the molecular basis for hematopoietic cell fate determination by asymmetric cell division. Dr S. Russell, Dr P. Humbert, APA.

Young S, Molecular analysis of myxoid liposarcoma. Assoc. Prof. D. Thomas, Dr K. Kansara.

Yuqian Y, The role of sister chromatid cohesion in colon biology and carcinogenesis. Assoc. Prof. R. Ramsay, Dr H. Xu, Dr J. Malaterre, MIRS.

Doctor of Medical Science/ Doctor of Medicine in progress (The University of Melbourne)

Dickinson M, Biological and clinical effects of epigenetic agents for haematological disease. Assoc. Prof. D. Ritchie, Prof. M. Prince, Peter Mac.

Handolias D, Molecular analysis of the PI3K pathway in epithelial ovarian cancer. Assoc. Prof. G. McArthur, MRS.

Kee D, Novel molecular and imaging characteristics of human skin cancers. Assoc. Prof. G. McArthur, Prof. R. Hicks, MFS.

Khamly K, Tumour hypoxia and response to preoperative radiotherapy in soft-tissue sarcomas. Assoc. Prof. D. Thomas.

Yan M, The impact of the tumour microenvironment on breast cancer prognosis and treatment. Assoc. Prof. A. Dobrovic, Prof. S. Fox, NHMRC.

MPhil in progress (The University of Melbourne)

Arthur H, Molecular and biological characterisation of interferon mediated signal transduction pathways and genes that respond to interferon. Assoc. Prof. R Johnstone, MRS.

To H, A genetic study of Barrett's Oesophagus and Oesophageal Adenocarcinoma using next generation sequencing. Assoc. Prof. W. Phillips, Mr C. Duong, RACS.

Tran T, PI3K pathway alterations in gastric cancer. Assoc. Prof. W. Phillips, Dr C. Duong, MRS

Advanced Medical Science(AMS) in progress (The University of Melbourne)

Georgiou C, Breast cancer brain metastasis: characterisation of a syngeneic mouse model for preclinical treatment evaluation of histone deacetylase inhibitors. Dr N. Pouliot, Assoc. |Prof R. Anderson.

Lin D, Establishment and characterisation of an immunocompetent mouse model for osteosarcoma. Dr M. Kansara, Assoc. Prof. D. Thomas.

Loh J, Mechanisms of inducing immunogenic cell. Dr P. Neeson, Assoc. Prof. D. Ritchie.

Low ZR, Analysis of gene methylation in CLL for potential therapeutic targets. Assoc. Prof. A. Dobrovic, Dr T. Mikeska.

Wong F, The clinical impact of F-18 FDG PET/CT in the assessment of cutaneous malignant melanoma. Assoc. Prof. E. Lau, Prof. R. Hicks.

Wu S, Discussions of Chronic Myeloid Leukaemia and Imatinib Adherence with Patients and Health Professionals. Assoc. Prof. P. Schofield, Assoc. Prof. J. Seymour.

4.1 Cancer Research Education program

4.1.3 Peter Mac Research Postgraduate Student Society

The Research Postgraduate Student Society is a student-run organisation that coordinates educational and social events for research students throughout the year. The main goal of the student society is to provide a welcoming and supportive environment for students during their undergraduate and/or postgraduate studies at Peter Mac. In this regard, the student society not only supports scientific achievement at Peter Mac but also builds a strong social and interactive network. In 2010, students organised and facilitated several professional development workshops to support graduate study. The 2010 committee was Nimali Withani, Alison West and Dan Brown, who we thank for their hard work throughout the year.

The Research Postgraduate Student Society committee coordinates the annual student retreat, which serves as a forum for undergraduate and postgraduate students to discuss scientific ideas, career opportunities and develop professional skills, as well as allowing students to interact in a relaxed environment; the 2010 retreat was held in Torquay. Over two days, the students participated in a communication workshop and seminar discussions on topics related to the research process and career issues. A panel of guest speakers provided excellent career advice and prompted very productive discussions. Our industry supporters set up a tradeshow, to allow the students the opportunity to develop their communication skills within a supportive environment.

We sincerely thank Jenni Metcalfe and Cathy Sage who ran the communications workshop, and the guest speakers who very generously gave their time to talk to the students, including Dr Brett Kennedy (Illumina), Dr Clara Gaff (VCCC), Dr Clarre Scott (WEHI), Dr Richard Hekker (CSIRO), Ross Dickins (WEHI), and Dr Mark Devlin and Assoc. Prof. Rob Ramsay from Peter Mac. We would like to acknowledge the sponsorship of our industry supporters for the retreat in 2010: Miltenyi Biotec, Lonza Australia, Quantum Scientific, Bio-Rad Laboratories, Biocabinets Australia, Beckman Coulter Australia, Becton Dickinson and Company, GeneWorks, Integrated Sciences, Jomar Bioscience, Sigma-Aldrich, Stemcell Technologies and Genesearch, Illumina, Interpath Services, Life Technologies, Qiagen, Thermo Fisher Scientific, DKSH Australia, and MNX.

4.1.4 Research Awards

It is a great reflection on research at Peter Mac that we have so many talented young research scientists and students at work in our laboratories, some of whom were recipients of the following research awards.

2010 PETER MAC POSTGRADUATE RESEARCH MEDAL

Peter Mac's Postgraduate Research Medal aims to promote excellence in cancer research by PhD and medical doctorate students at Peter Mac, and is judged in consideration of the international impact of the basic, translational or clinical cancer research. Accompanying this prestigious medal is a plaque and a prize of $1,500.

The 2010 medal was awarded to Holly Pegram from the Immunotherapy laboratory, in recognition of her scientific research into the utilisation of Natural Killer (NK) cells for cancer immunotherapy. Immunotherapy is a promising strategy for the treatment of cancer and Holly's research findings have important implications for enhancing the use of NK cells in adoptive cell transfer immunotherapy. In congratulating Holly on her research achievements, we also acknowledge the achievements of the other applicants. The competitive nature of the medal selection process reflects the high calibre of research that continues to be undertaken at Peter Mac.

2010 MILLER FAMILY TRAVEL FELLOWSHIPS

In 2010, the Miller family generously donated funding for international travel fellowships for three of our young researchers, designed to provide opportunities for them to develop and build on their career pathways. The 2010 Miller Family Travel Fellowships were awarded to postgraduate students Jenny Chia from the Cancer Cell Death laboratory and Andrea Newbold from the Gene Regulation laboratory, and to postdoctoral scientist Dr Amelia Brennan from the Cancer Cell Death laboratory. These young scientists used these awards to present their research at international conferences and to visit and speak at international research laboratories. We sincerely thank the Miller family for its generosity in providing support for these awards.

2010 NICOLE LUNDIE UNDERGRADUATE STUDENT PRIZE

The Nicole Lundie Undergraduate Student Prize is awarded annually to the most outstanding honours student who has undertaken their research project at Peter Mac. The award is made in honour of Nicole Lundie, in memory of her exceptional academic achievements, and her passion, drive and commitment to science.

The 2010 award was a particularly competitive process, with a very strong group of applicants. The 2010 prize was awarded to Marcus Lefebure who conducted his Honours project in the Gene Regulation laboratory under the supervision of Assoc. Prof. Ricky Johnstone and Dr Geoff Matthews. Marcus continued this research with a PhD project to analyse the activities of histone deacetylase inhibitors (HDAC) and other small molecule therapeutics to treat multiple myeloma, supported by a Leukaemia Foundation scholarship.

The selection panel also highly commended Ivan Fung who undertook his Honours project in the Immune Signalling laboratory, under the supervision of Dr Jane Oliaro, and Lucas Dent who undertook his Honours project in the Cell Growth and Proliferation laboratory under the supervision of Drs Kieran Harvey and Carole Poon.

This award is sponsored by the Geelong Lions Club of Breakfast Group, the Lundie family, donations made in memory of Nicole Lundie, and Cancer Research at Peter Mac. We would like to thank the Lundie family and the Geelong Lions Club of Geelong Breakfast Group for their ongoing support of this award.

2010 HAROLD MITCHELL TRAVEL FELLOWSHIPS

The Harold Mitchell Travel Fellowship program at Peter Mac recognises two outstanding young researchers by awarding them travel support to develop and build on their career pathways. The 2010 Travel Fellowships were awarded to postgraduate student Nimali Withani from the Metastasis Research laboratory, and to postdoctoral researcher Dr Helen Pearson in the Cell Cycle and Cancer Genetics laboratory. These travel awards provide valuable career and collaboration opportunities for the young scientists and Peter Mac. We thank the Harold Mitchell Foundation for its generous ongoing support of this program.

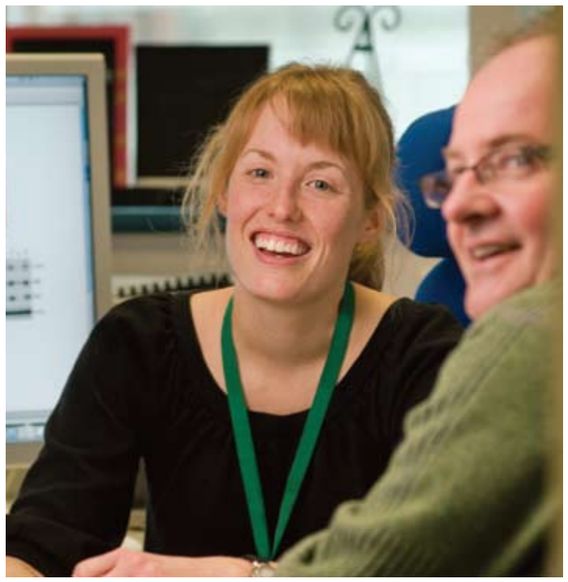
4.1.5 Peter Mac Postdoctoral program

Postdoctoral researchers undertaking research at Peter Mac have the opportunity to work with Australia's top cancer research scientists, in facilities designed to encourage interaction and collaboration locally and overseas and to build successful research careers. The postdoctoral experience is a time when these early-career scientists develop their scientific and technical skills and gain experience in other skills needed for a professional career. The career development of postdoctoral scientists is a key focus of Cancer Research.

Our postdoctoral scientists play a crucial role in facilitating the Cancer Research Education program, undertaking roles as mentors and scientific committee members of our Student Advisory Committees, providing them with the opportunity to support the next generation of scientists while also furthering their own supervising experience.

Postdoctoral scientists also lead Peter Mac outreach activities, participating in workshops and seminars to build new research and education links with school and community groups. In 2010 many of our postdoctoral scientists took leadership roles in the development and presentation of seminars and workshops for our school outreach activities: Bringing Science to Life program and the VCE Biology Lecture Series. Our early career scientists also assisted with presentations and visits by school and community groups.

Cancer Research has an active postdoctoral society that coordinates social and career development activities throughout the year. In 2010, the society was led by Drs Geoff Matthews, Linda Howland and Jamie Lopez. This society provides a nurturing environment for postdoctoral scientists throughout their time at Peter Mac, providing opportunities to build an interactive network of science and industry links that will benefit their future careers, through the organisation of seminars, workshops and social activities.



4.1 Cancer Research Education program

4.1.6 Community and School Outreach Activities

ANNUAL SIR PETER MACCALLUM PUBLIC LECTURE

In October 2010, members of the public and the Peter Mac community gathered for the second annual Sir Peter MacCallum Public Lecture: Cracking the Cancer Code. Developed as an event to help celebrate the achievements and vision of Sir Peter MacCallum, the public lecture provided a community education opportunity. On a warm spring evening, 3AW's Dr Sally Cockburn welcomed the enthusiastic audience — attendance was up by over 50 per cent on the inaugural 2009 event.

In the elegant Swanston Hall at Melbourne Town Hall, Professor David Bowtell and Dr Gillian Mitchell gave informative, entertaining and passionate presentations, updating the community on the recent history and exciting future of cancer genetics and individualised patient care.

The two half-hour talks took the audience from the laboratory into the clinic, a structure that echoed the on-site collaboration between basic and clinical research that defines Peter Mac as unique among Australian public hospitals. Feedback from the event was overwhelmingly positive, highlighting the value of the annual Sir Peter MacCallum Public Lecture as a key communications platform for Peter Mac Cancer Research. We thank Dr Sally Cockburn and the City of Melbourne for their support of this event.

RESEARCH LABORATORY TOURS: MELBOURNE OPEN HOUSE

In 2010, Peter Mac again joined the Melbourne Open House program by opening its doors to the public for tours of the research laboratories and radiation therapy bunkers. Throughout a very busy day, many curious Melburnians and visitors took the chance to glimpse the inner workings of our iconic research facility. Guides and demonstrators fielded a broad scope of queries posed by an interested and informed public.

Tours groups were shown examples of our important research by our own volunteers. The 20 tours that ran over a total of five hours were all at capacity, demonstrating the enthusiastic support Cancer Research receives from the wider community. We would like to thank the Peter Mac researchers who generously donated their time to make the day such a smooth success.

SCIENCE IN SCHOOLS: VCE BIOLOGY LECTURE SERIES

This annual VCE Biology Lecture Series has been designed to complement the VCE biology curriculum, and to provide an opportunity for students to revise and develop a better understanding of the topics by placing them within the context of cancer research. Held at Peter Mac, the lectures were attended by students from a range of Victorian public and private secondary schools.

- 'Signalling molecules and drug design' (Prof. David Bowtell)
- 'Apoptosis and cell death' (Dr Ilia Voskoboinik)
- 'Differentiation and transcription' (Assoc. Prof. Rob Ramsay).

SCIENCE IN SCHOOLS: PETER MAC BRINGING SCIENCE TO LIFE PROGRAM

In 2010 we continued our school science program, with 20 students from a range of public and private schools attending three days of science activities. Spread across three months, the program was open to science students in Years 10 to 12, and provided a valuable opportunity for them to experience real science in action. The students attended an external science or research site in the morning, before coming to Peter Mac for the afternoon, during which they heard about our research activities in talks provided by our young scientists. The students then met with our young researchers to participate in laboratory science activities.

We thank the following groups who supported this program by opening their laboratories to this group of students: CSL Limited at Bio21 (Molecular Biology Research groups); Swinburne University (Biomedical and Biotechnology laboratories); and the Bionic Ear Institute. We would also like to thank the Inner Melbourne VET Cluster (IMVC) for its generous support in administering this program for us. For further information about IMVC, visit: www.imvc.com.au.

SCIENCE IN SCHOOLS: PETER MAC CANCER ESSAY COMPETITION

With the view to reaching a wider audience of schools and students, in 2010 we launched the Peter Mac Cancer Essay Competition, open to all Victorian secondary students in Years 10 and 11. Complementing the topic of the annual Public Lecture, the 2010 theme was 'The human genome: cracking the cancer code'. Students were invited to submit essays in scientific or creative categories. All entries were assessed for their scientific and creative merit, and a shortlist of finalists was compiled. All finalists were invited to attend the Annual Sir Peter MacCallum Public Lecture for the awarding of prizes. We are grateful to the Geelong Lions Club Breakfast Group, who has been an ongoing sponsor of a student prize at Peter Mac and generously sponsored a prize in this new essay competition.

At the conclusion of the lecture, honorary guest Dr Peter MacCallum joined Paul Austin from the Geelong Lions Club Breakfast Group to award prizes for the 2010 Peter Mac Cancer Essay Competition. First prizes were awarded to Anna Gruen from Melbourne Girls' Grammar School (creative essay) and Zoe Calulo-Chan from MacRobertson Girls High School (science essay). Five runners-up were awarded, reflecting the depth and quality of the essay entries. The runners up for the scientific essay were Yuan Mei Wan (Presbyterian Ladies College) and Katie Punshon (St Leonard's College), and for the creative essay were Stephen Wong (Overnewton Anglican Community College), Nicole Da Cruz (MacRobertson Girls' High School) and Brooke Walter (Billanook College).

4.2 Clinical Research Education and Training Programs

The research strengths which underpin Peter Mac's reputation as a national and international leader in clinical and basic research also present a range of challenges related to the differing needs of researchers, and therefore their differing education and training requirements.

In 2010 a review of clinical research education and training was undertaken by Dr Caroline Owen with the assistance of many of our busy clinician researchers and research managers. This review provides the foundation for further development of training opportunities for our clinical researchers as they all work to maximise the potential and translational impact of our cancer research. One thing that was strongly evident during this review process was the passion for excellence in care, and passion for leading clinical research to translate to better treatment options and outcomes for our patients.

With our multidisciplinary team approach to clinical care, teams of researchers are brought together with a common focus—to conduct significant research that leads to the development of better models of care and improvements in treatment options and outcomes. These multidisciplinary teams make significant contributions to the welfare and treatment outcomes of our patients, and the structure of the team can also impact on the research conducted in that area.

Multidisciplinary teams help drive research and build research momentum, utilising the expertise across the team to develop a range of research directions related to clinical observations. Research naïve personnel within these teams are introduced to research within a supportive team environment, which then provides the opportunity for them to develop research interest and skills by involvement in these activities. Such research momentum is reliant on leadership and mentoring within the team, which is particularly strong in some clinical areas.

The range of clinical expertise in the multidisciplinary teams can result in a breadth of skills, and in a great variety in the research readiness in the clinical staff within the different disciplines, related to the amount of research incorporated into the training programs of the disciplines. Peter Mac strives to improve the research education of our clinicians and further support them as they lead new research directions into clinical practice, treatments and outcomes.

While much of the research training conducted at Peter Mac occurs within a largely informal structure including mentoring, seminars and workshops, and supervised research activities, there are several key areas where more structured programs have been developed for both internal and external audiences, and which form a basis for the development of further clinical education programs.

Specialised Certificate in Clinical Research (Oncology)

The Specialised Certificate in Clinical Research (Oncology), The University of Melbourne, was developed in partnership with Peter Mac, and is coordinated by Assoc. Prof. Michael Jefford from Cancer Medicine.

Designed to provide a better understanding of all types of research conducted in oncology as well as an understanding of the essential components and features of successful research activities and research careers, the course content is largely delivered by Peter Mac clinicians and researchers. It is designed for people currently working in oncology or other health services—attendees include oncologists in training, clinical trials nurses, project coordinators, radiation therapists, pharmaceutical personnel, sales specialists, registrars and allied health workers. Peter Mac's involvement in the delivery of this clinical research course is further evidence of our leadership in supporting and educating the next generation of researchers.

Clinical Research Methods in Radiation Oncology

The Clinical Research Methods in Radiation Oncology program was developed at Peter Mac to address the need for clinical research training for radiation therapists, but its audience has broadened to also include allied health professionals, physicists, nurses, study coordinators and radiation oncologists.

This program is in two modules—an introductory program delivered across two days, and an advanced program delivered across three days. The program is delivered by Peter Mac staff, with all discussions using an oncology context. These modules address key research topics including clinical governance and ethics, statistics, research design and methodologies, project management and scientific writing.

More than 60 Peter Mac staff completed the course in 2009–10. In 2010, it also ran as an external program with 56 attendees from across Australia and New Zealand.

4.2 Clinical Research Education and Training Programs

Seminars in Oncology

In 2010, Cancer Surgery developed a new series of seminars, designed to provide opportunities for clinicians and scientists to expand their understanding of developments in clinical practice and clinical research.
The full schedule for 2010 is listed below.

SEMINARS IN ONCOLOGY 2010 SCHEDULE

Date	Presenters	Topic
1-Mar	Prof. David Ball, Dr Robin Cassumbhoy, Mr Gavin Wright	*Modern management of lung cancer (including new staging system)*
15-Mar	Assoc. Prof. Michael Henderson, Prof. Rod Hicks, Dr Damien Kee	*Multimodality management of stage IV melanoma (including new staging system)*
12-Apr	Assoc. Prof. David Speakman, Dr Kate Moodie, Prof. Stephen Fox	*Work up and management of breast lump*
24-May	Dr Gavriel Haime, Dr Sian Fairbank, Assoc. Prof. June Corry	*Surgical management of SCC of head and neck, including reconstructional options*
16-Jun	Mr John Spillane, Dr David Charlesworth, Assoc. Prof. Monica Slavin	*Management of neutropaenic patient*
30-Jun	Dr Trevor Leong, Mr Cuong Duong, Mr John Spillane	*Managing a patient with malignant dysphagia*
14-Jul	Dr Richard Sullivan, Dr Odette Spruyt	*Management of pain in a cancer patient and update on peri-operative care*
28-Jul	Dr Kate Moodie, Dr Nick Ferris, Assoc. Prof. Sam Ngan, Assoc. Prof. Alexander Heriot	*Update on management of locally advanced rectal cancer*
11-Aug	Prof. Rod Hicks, Dr Charuta Dagia, Dr Ben Thomson, Dr Say Ng	*Pancreatic cancer management in 2010*
25-Aug	Mr Simon Donahoe, Mr Felix Behan, Mr Miki Pohl, Mr Michael Findlay	*Reconstructional options for breast, abdominal and pelvic defects* *Versatility of local flap repair*
8-Sep	Assoc. Prof. Declan Murphy, Dr Farshad Foroudi, Dr Colin Styles	*Update on management of localised prostate cancer*
6-Oct	Dr Adam Cichowitz, Miss Belinda Hodgson, Dr Adrian Hall	*Impact of nutrition and patient's functional capacity on cancer outcomes*
3-Nov	Ms Meg Rogers, Ms Carolyn Atkin, Ms Lucy Pollerd	*Importance of supportive care in the management of GI cancer patients*
1-Dec	Mr Damien Tange, Dr Catherine Mendel, Dr Claire Phillips	*Management of cerebral met*

We thank Covidien Surgical Supply for its sponsorship of this seminar series in 2010.

For full information about Peter Mac's Cancer Research education and learning programs, visit: www.petermac.org/Research/EducationandCareers

5 Leadership and Governance

5

5 Leadership and Governance

With 18 years experience in laboratory accreditation, Jane King understands the importance of research governance and accountability. As Research Governance Officer at Peter Mac, Jane works to ensure that good and sensible governance practices are woven through all aspects of our research, and that the community's faith in Peter Mac's research continues to be well deserved.

'Governance really does matter—to patients and their families, to research funders and taxpayers, research colleagues and the community as a whole.'

5 Leadership and Governance

Peter Mac is committed to the development of a research culture that reflects the core values of excellence, innovation and compassion.

Peter Mac is one of the few hospitals in the world with the benefit of having its own integrated cancer research programs and laboratories, providing the opportunity to lead the way in translational research in cancer.

With a research program that continually drives improvements in all aspects of treatment and clinical care, our clinical and laboratory researchers are internationally renowned.

Our high quality, dedicated researchers are supported by specialised equipment, technology and expertise that ensures Peter Mac's research program is focused on delivering the best outcomes for each individual patient.

- Research leadership
- Cancer Research management
- Governance
- Ethical Conduct of Research
- Commercialisation.

Cancer Research Executive: Assoc. Prof. Ricky Johnstone (Deputy Director), Prof. Joseph Trapani (Executive Director), Ms Mary Harney (Chief Operation Officer), Assoc. Prof. Grant McArthur (Deputy Director).

5.1 Research leadership

We are always striving for a more dynamic, efficient environment that fosters innovation and collaboration among the hundreds of researchers who work at Peter Mac. At a time of rapid advances in the understanding of cancer biology and accelerated translation of research findings to the clinic, Peter Mac provides an exciting and supportive environment for cancer research.

Peter Mac's excellence in research is reflected in the strategic drive of our research leaders who help us keep our research at the forefront of discovery.

The committee structure now in place ensures that our laboratory and clinical translational research is fully supported by the strategic leadership of our senior researchers, as outlined below and in the committee organisational chart.

CANCER RESEARCH DIVISION EXECUTIVE AND MANAGEMENT

The Cancer Research management team meets regularly to advise the Executive Director of Cancer Research on key strategic matters, to flag new issues and assist Cancer Research in planning and implementing policy. The team receives reports from multidisciplinary groups as required, and reports to the Cancer Research Executive.

CANCER RESEARCH EXECUTIVE

Prof. Joseph Trapani
(Executive Director)

Assoc. Prof. Ricky Johnstone
(Deputy Director)

Assoc. Prof. Grant McArthur
(Deputy Director)

Ms Mary Harney
(Chief Operating Officer)

CANCER RESEARCH MANAGEMENT TEAM (RMT)

Prof. Joseph Trapani (Chair)

Assoc. Prof Ian Campbell

Assoc. Prof. Ross Hannan

Mary Harney

Assoc. Prof. Ricky Johnstone

Assoc. Prof. Grant McArthur

Assoc. Prof. Rick Pearson

Assoc. Prof. Rob Ramsay

Dr Helena Richardson

Dr Gian Sberna

Mark Shannon

Prof. Mark Smyth

Linda Stevens (Secretary)

RESEARCH ADVISORY BOARD (RAB)

The Peter Mac Research Advisory Board (RAB) provides advice on a range of issues, including oversight of research activities, to ensure that appropriate strategic planning processes are in place and implemented effectively.

The RAB is responsible for:

- Ensuring that research activities at Peter Mac are broadly consistent with Peter Mac's overall strategic directions and broader government cancer research priorities.
- Providing advice and guidance for all research activities conducted at Peter Mac.
- Monitoring compliance of research activities with policies and procedures and legislative requirements, in conjunction with other Peter Mac Board committees.
- Conducting regular reviews of research collaborations/partnerships, research commercialisation opportunities, metrics of research performance, and strategies to retain, as well as identify and attract, high-quality research staff.
- Receiving and reviewing regular reports on all research activities at Peter Mac from the divisional executive directors and other senior clinicians/researchers.

The Research Advisory Board reports to the Peter Mac Board of Directors.

RESEARCH ADVISORY BOARD MEMBERSHIP

Prof. John Mattick AO (Chair)

Prof. David Copolov OAM (Deputy Chair)

Peter Acton

Prof. Daine Alcorn

Prof. Ashley Dunn

Wayne McMaster

Prof. Christina Mitchell

Internal members:

Craig Bennett

Dr Shari Lofthouse

Prof. Joseph Trapani

Prof. John Zalcberg OAM

Les Manson (Secretariat)

DIVISIONAL RESEARCH EXECUTIVE

Prof. John Zalcberg OAM (Chair)

Prof. Sanchia Aranda

Jennifer Doubell

Prof. Gillian Duchesne

Mary Harney

Assoc. Prof. Alexander Heriot

Assoc. Prof. Ricky Johnstone

Assoc. Prof. Danny Rischin

Assoc. Prof. Penelope Schofield

Deborah Sullivan

Prof. Joe Trapani

Samantha Somers (Secretary)

5.1 Research leadership

CLINICAL RESEARCH GOVERNANCE COMMITTEE

As one of the core components of Peter Mac's business, clinical research must be conducted within a robust and dynamic governance framework to optimise outcomes and accord with local, national and international standards of research conduct.

The Clinical Research Governance Committee (CRGC) has been established to develop and oversee the framework within which clinical research is conducted at Peter Mac.

The functions of the CRGC are to:

- Develop and maintain a framework for clinical research governance at Peter Mac that ensures clinical research is properly conducted, including adherence to accepted ethical principles, local, national and international guidelines for clinical research practice, relevant laws and regulations and principles of risk management.
- Ensure that standards, guidelines and/or policies for clinical research and for continuously monitoring and improving the quality of clinical research at Peter Mac are in place and are followed.
- Evaluate the clinical research governance framework and oversee and facilitate compliance with the pertinent standards, in particular, the NHMRC documents National Statement on Ethical Conduct in Human Research (National Statement) and the Code for the Responsible Conduct of Research (The Code) and other relevant guidelines and/or policies.
- Make recommendations to the Executive, Human Research Ethics Committee or other appropriate body in relation to matters under the scope of this committee.

The CRGC receives reports from the Human Research Ethics Committee and the Study Coordinators Group, and reports to the Divisional Research Executive (DRE).

CLINICAL RESEARCH GOVERNANCE COMMITTEE MEMBERSHIP

Prof. John Zalcberg OAM (Chair)

Prof. Gillian Duchesne

Mr Cuong Duong

Mary Harney

Marianne Hundling

Dan Mellor

Dr Dina Neiger

Dr Jo Phipps-Nelson

Assoc. Prof. Danny Rischin

Assoc. Prof. John Seymour

Dr Dianne Snowden

Virginia Tuckwell

Shannon Uren

Jane King (Secretary)

5.2 Cancer Research management

The important work of Cancer Research is led by the Research Executive, and underpinned by the activities of the Research operations team, who provide support and resources for the essential processes and procedures required by Peter Mac's research efforts.

The activities of the operations team are driven by internal and external research management and reporting requirements. The scope of the operations team includes:

- Animal Ethics
- Commercialisation
- Communications
- Core Platform Technology Management
- Education
- Grant administration
- Human Resources
- Occupational Health and Safety
- Physical Environment and Infrastructure
- Research Education and Training
- Research Governance.

EXECUTIVE AND OPERATIONS PERSONNEL

RESEARCH EXECUTIVE

Director
Prof. Joseph A Trapani

Assistant Directors
Assoc. Prof. Ricky Johnstone
Assoc. Prof. Grant McArthur

Chief Operating Officer
Mary Harney

OPERATIONS & ADMINISTRATION

Chief Operating Officer
Mary Harney

Deputy Chief Operating Officer
Dr Gian Sberna

Human Resources Officer
Ms Sarah Dougas

IT Manager (Research)
Daniel Simpkins

Application Specialist
Zeus Villanueva

Education and Communications Officer
Dr Caroline Owen

Communications Assistant
Nick Sharp-Paul

Physical Infrastructure and Environment Manager
Mark Shannon

Physical Infrastructure and Environment Officer
Paul Dunne

OHS Specialist
Lisa Stevens

Intellectual Property and Development Manager
Mr Jerry de la Harpe (until June 2010)
Dr Shari Lofthouse

Governance Officer
Jane King (from July 2010)

AEEC Coordinator
Rosie Goldup (from July 2010)

Reception and AEEC Assistant
Kate McShane

Personal Assistants
Diana Motion (Director)
Linda Stevens (Assistant Director)
Jacinta Arnup (Operations)
Jade Tran (Cell Biology program and Commercialisation)
Marianne Ciavarella (Cancer Genomics program)
Belinda Kelly (Cancer Immunology program)

Research Grants team
Dr Gian Sberna
Marianne Ciavarella
Belinda Kelly
Katrina Wilson

5.3 Governance

In the words of Prof Joseph Trapani, Executive Director, Cancer Research, “it is of great importance that we get our research governance practices right.”

The Research Governance landscape is changing in Australia and internationally, with research funding increasingly being tied to tangible demonstration of research integrity and responsible conduct of research.

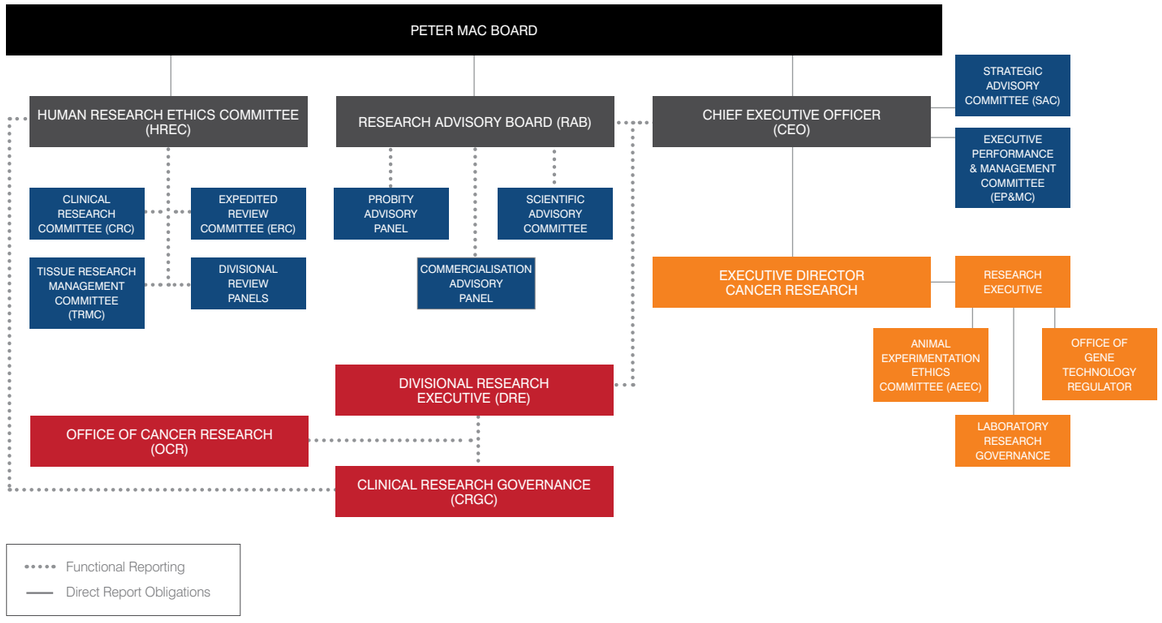
Consistent with this increased emphasis on governance and our desire to lead in all aspects of research, two major initiatives are being planned.

A Research Governance Program is in planning for delivery to all Cancer Research, from students, early career researchers through to long-standing researchers and operations staff. The program will define desired behaviour in the areas of conflict of interest, ethics, responsible publication practices and data management. This program aims to raise awareness of what constitutes research misconduct and to ensure that necessary subsequent procedures are in place.

Cancer Research has had a wide reaching set of operational procedures in place for many years and these are being reviewed and refreshed to coincide with the roll out of the Research Governance Program in early 2011.

During 2010, ties with Clinical Research Governance were further strengthened with the development of a research governance framework. The framework summarises research governance responsibilities and reflects the close ties between basic, translational and clinical researchers at Peter Mac. Peter Mac’s Clinical Research Governance Committee, chaired by Professor John Zalcberg OAM, has broad research representation, oversees the research governance framework and has a strong role in driving clinical research governance matters across the hospital.

Peter Mac Research Governance committee structure

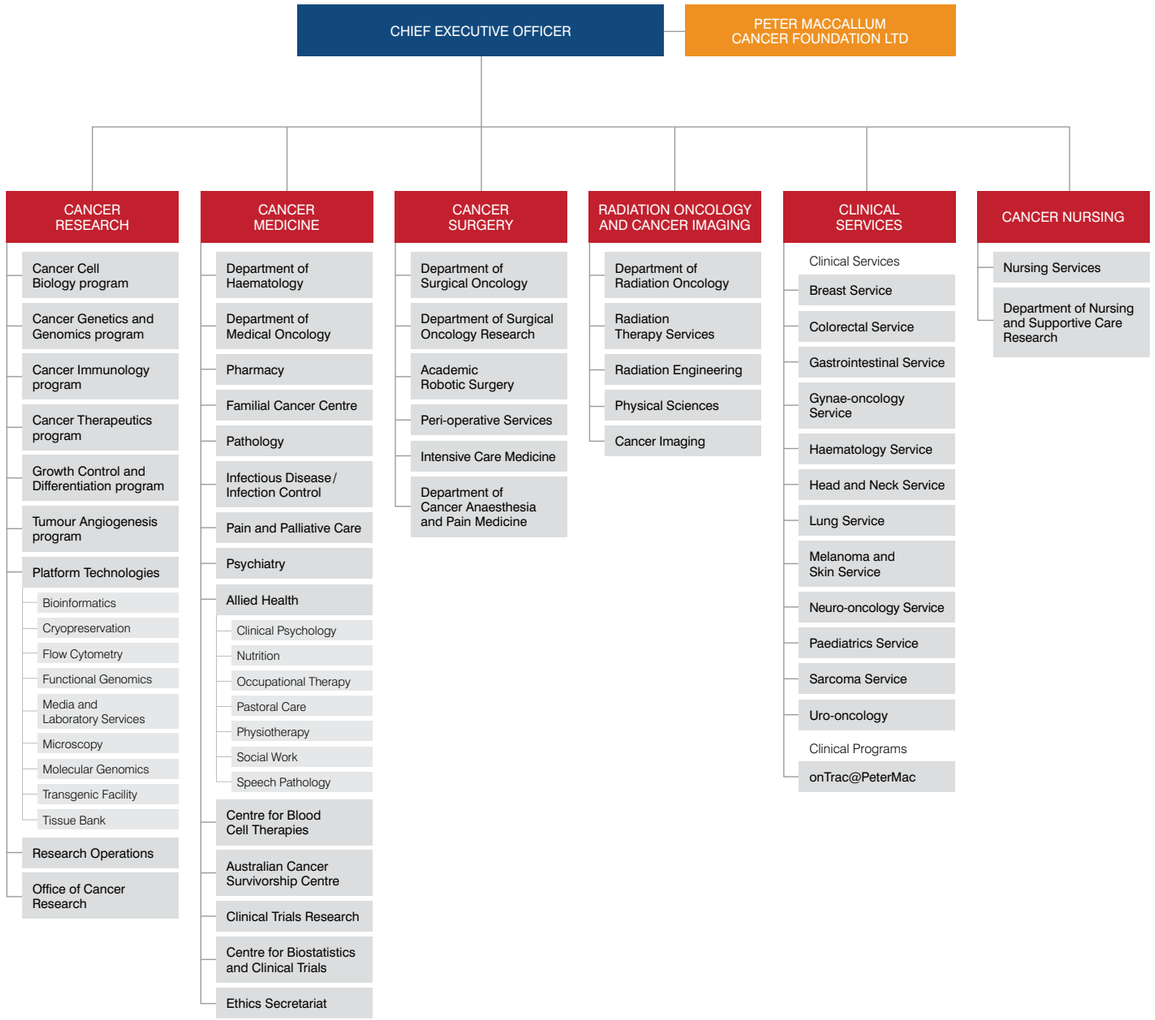


Research organisation

Over 400 researchers are based in 27 research laboratories within six key research programs: Cancer Cell Biology, Cancer Immunology, Cancer Genomics, Growth Control and Differentiation, Angiogenesis and Cancer Therapeutics. These are underpinned by an extensive infrastructure of core facilities and services: advanced microscopy, bioinformatics, flow cytometry and cell sorting, functional genomics and sequencing technology, microarray technology, molecular pathology, a tissue and tumour bank, and a transgenic and SPF facility.

Our outstanding clinicians, nurses and allied health professionals are involved in a broad and diverse portfolio of clinical studies to complement our activities in the basic and translational arenas. Their scope is wide-ranging, from early phase clinical studies which allow our patients access to novel anti-cancer drugs, through to international randomised controlled trials designed to answer key clinical questions in cancer care. With extensive cancer clinical trial activity, Peter Mac leads Australia in human and infrastructure resources.

Peter Mac research structure



5.4 Ethical Conduct of Research

Peter Mac Human Research Ethics Committee (HREC) and the Ethics Secretariat

The major role of the Human Research Ethics Committee (HREC) and the associated committees and review panels is the ethical review of human research. Human research is research conducted with or about people, or their data or tissue. In making decisions regarding the ethical conduct of human research the HREC relies on the guidance provided in the National Statement of the Ethical Conduct in Human Research which was developed by the NHMRC, Australian Research Council and Australian Vice-Chancellors' Committee.

The Ethical Conduct of Human Research requires that approval is obtained from the HREC for new human research projects, taking into account scientific advice from the Clinical Research Committee (projects involving human participants), or the Tissue Research Management Committee (projects involving human tissue). Review of projects involving analysis of retrospective clinical data is delegated to the Divisional Review Panels and review of low risk projects is delegated to the Expedited Review Committee (ERC). The HREC is also responsible for monitoring the ongoing conduct of all these projects.

Members of the HREC and associated committees are drawn from Peter Mac staff and external community members. All committee members kindly donate the time required to attend monthly meetings and to review new projects, amendments and other general matters.

The Ethics Secretariat coordinates the Committee system and provides administrative support for the review, approval and monitoring process. The Ethics Secretariat also provides general advice to researchers.

NEW IN 2010

In December 2009, as an initiative of the Victorian Government, the Single Ethical Review Process (SERP) for clinical trials undertaken in Victoria was introduced. This system is coordinated by the Consultative Council for Human Research Ethics and allows multi-site clinical trials within Victoria to undergo a single ethical review by an accredited HREC that is accepted by all participating sites. The aim of SERP is to provide a more efficient ethical review process for clinical trials to be conducted at multiple sites.

During the first 13 months of operation until the end of 2010 the Peter Mac Ethics Committee reviewed 11 projects on behalf of all participating sites and accepted the external ethical review of eight projects as a participating site.

COMING IN 2011

The Harmonisation of Multi-centre Ethical Review (HoMER) system is a NHMRC initiative that aims to reduce duplication of ethical and scientific review of health and medical multi-centre research. Under this system HRECs will conduct single ethical review of multi-centre research in accordance with agreed national criteria. Reviewing HRECs under the HoMER system must complete a rigorous certification process and maintain this certification for their ethical review processes. Institutions can also join the system as a site that accepts single ethical review by HRECs that have been certified under the HoMER system.

When fully implemented this system will be an extension of the existing SERP system and apply to multi-site trials throughout Australia. Currently Victoria, New South Wales and Queensland are working towards implementing this system.

During 2010 the following people served as members on the HREC or an associated committee or panel for all or part of the year:

The number of new projects and amendments to ongoing projects reviewed by the committees in 2010 is presented in the following table:

Clinical and laboratory projects reviewed by the Ethics Committee after scientific review by the Clinical Research Committee or Tissue Research Management Committee	**80**
Low risk projects reviewed by the Expedited Review Committee	**43**
Retrospective projects reviewed by a Divisional Review Panel	**44**
Major amendments reviewed by the Committee	**117**
Administrative amendments reviewed by the Ethics Secretariat	**37**

HUMAN RESEARCH ETHICS COMMITTEE (HREC)

Board Member

Prof. Peter Sheldrake (Chair)

Community Members

Mary Rydberg (Deputy Chair)
Anne Holmes
Dr Kate Jones
Catherine McKean
Dr Grant Moss
Tyson Wodak

Staff Members

Dr Lee-Anne Clavarino
Jill Davison
Tessa Jones
Jeremy Kenner
Helen McCallum
Assoc. Prof. Wayne Phillips
Assoc. Prof. David Ritchie
Sam Ruell
Shane Ryan
Dr Dianne Snowden
Dr Alison Trainer
Karen Wall
Assoc. Prof. Scott Williams
Assoc. Prof. Max Wolf

CLINICAL RESEARCH COMMITTEE (CRC)

Assoc. Prof. David Ritchie (Chair: Jan–July)
Assoc. Prof. Max Wolf (Chair: Aug–Dec)
Dr Sibilah Breen
Dr Jeremy Couper
Prof. Jim Cramb
Dr Carlene Cullinane
Jim Hagekyriakou
Marianne Hundling
Assoc. Prof. Mei Krishnasamy
Emma Link
Assoc. Prof. Michael MacManus
Dr Linda Mileshkin
Dr Donna Milne
Assoc. Prof. Dina Neiger
Dr Jo Phipps Nelson
Carol Rice
Caroline Sardjono
Dr Ben Solomon
Shannon Uren
David Willis

TISSUE RESEARCH MANAGEMENT COMMITTEE (TRMC)

Assoc. Prof. Wayne Phillips (Chair)
Dr Alex Boussioutas
Assoc. Prof. Ian Campbell
Samantha Cauberg
Marnie Collins
Assoc. Prof. Alex Dobrovic
Prof. Stephen Fox
Dr Simon Harrison
Dr Alan Herschtal
Colin House
Dr Andreas Moeller
Dr Normand Pouliot
Dr Rick Redvers
Dr Rik Thompson
Heather Thorne
Richard Young

EXPEDITED REVIEW COMMITTEE (ERC)

Dr Lee-Anne Clavarino (Chair: Jan–May)
Jeremy Kenner (Chair: June–Sep)
Dr Dianne Snowden (Chair: Oct–Dec)
Dr Sibilah Breen
Amrit Dhillon
Alison Hocking
Catherine Johnston
Lisa Macfarlane
Megan Rogers
Stewart Sandon
Lisa Sheeran
June Smith
Genevieve Story

DIVISIONAL REVIEW PANELS

Division of Surgical Oncology

Assoc. Prof. Michael Henderson (Chair)
Mr Cuong Duong
Emma Link
Mr John Spillane
Tina Thorpe

Division of Radiation Oncology & Cancer Imaging and Division of Cancer Medicine

Assoc. Prof. Michael Mac Manus (Chair)
Belinda Campbell
Vanessa Estall
Dr Sarah Everitt
Dr Farshad Foroudi
Dr Bronwyn King
Assoc. Prof. Trevor Leong
Richard Oates
Dr Rebecca Owen
Dr Gail Ryan
Dr Mark Shaw
Dr Ben Solomon (Cancer Medicine representative)
Assoc. Prof. Scott Williams
David Willis
Dr Andrew Wirth

ETHICS SECRETARIAT STAFF

Jeremy Kenner (Ethics Coordinator)
Dr Lee-Anne Clavarino (Assistant Ethics Coordinator Jan–May)
Dr Dianne Snowden (Assistant Ethics Coordinator June–Dec)
Sharon Reid
Namita Mazzitelli

5.4 Ethical Conduct of Research (cont.)

Ethical Conduct of Animal Research

The NHMRC has developed the Australian Code for the Responsible Conduct of Research, which is designed to ensure that research is conducted ethically and with integrity. In accordance with these guidelines, Peter Mac's Animal Experimentation Ethics Committee (AEEC) takes an important role in overseeing the ethical conduct of any work involving the use of animals for scientific purposes.

As described by the NHMRC, the primary role of the AEEC is to ensure that the use of animals in experimental research is justified, provides for the welfare of those animals, and incorporates the principles of 'replacement, reduction and refinement':

- Replacement of animals with other methods.
- Reduction in the number of animals used.
- Refinement of techniques used to reduce the adverse impact on animals.

The AEEC conforms to the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes. In conforming to the code, the AEEC works to ensure the ethical and humane care of any animals used for scientific purposes, and aims to promote the wellbeing of animals and minimise their experience of pain and/or distress.

The responsibilities of the AEEC include the development of policies and standard operating procedures, education of members and users, dispute resolution, reporting and auditing. While scientific expertise is derived primarily from the Peter Mac research community, welfare and lay membership comprises independent individuals who are not affiliated with Peter Mac, in order to ensure that committee decisions are impartial.

The Code requires that all proposals to use live animals are assessed by a quorum of AEEC members; that is, at least one committee member in each of the following categories must be present: (A) veterinarian, (B) scientific, (C) animal welfare and (D) lay.

For further information, visit: http://www.nhmrc.gov.au/guidelines/animal_guidelines.htm.

AEEC AND APPLICATION PROCESSING IN 2010

All researchers at Peter Mac who wish to conduct research involving animals are required to submit a written proposal to the AEEC relating to their intended use of animals. AEEC approval is required before the commencement of any project involving animals. Similarly, any amendments to existing projects involving animals must first be reviewed and approved by the AEEC. Researchers are required to submit annual reports to the AEEC outlining the work undertaken on their projects and the progress that has been made. In addition to this monitoring, the AEEC also conducts regular inspections of the facilities.

During 2010, the Peter Mac AEEC convened seven times and reviewed 27 new project proposals (up 17 per cent on the previous year), 221 minor amendment applications (up 307 per cent) and 54 annual and final reports (down 22 per cent). The rigour of this review process ensures a high standard of animal welfare is practiced and further to ensure that the animal facilities are maintained to the highest standard.

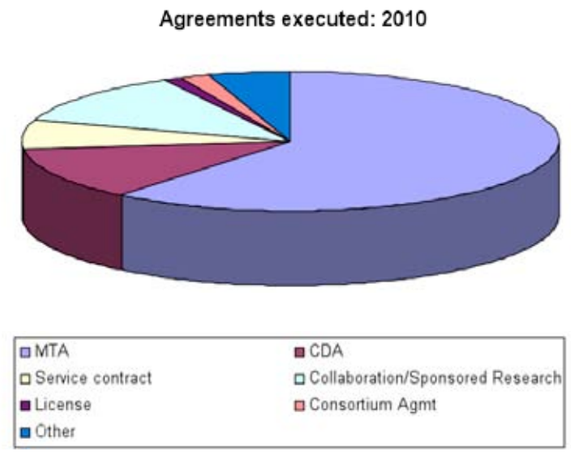
5.5. Commercialisation

Peter Mac is uniquely placed to facilitate rapid research translation through our governance structure and our many fostered relationships with industry.

Our engagement with industry provides benefits to our industry partners, to industry via access to our new technologies and intellectual property, and to our researchers through access to alternative sources of funding and a variety of research tools. The close interaction between our basic researchers and our industry partners enhances the understanding of the commercialisation process early on in research planning stages, and ultimately accelerates the flow of technologies into the clinic.

Peter Mac Commercialisation highlights in 2010:

- Continuation of the research and development agreement with Sirtex Medical Ltd for development of radioprotectors in collaboration with Prof. Roger Martin (Molecular Radiation Biology laboratory pg 54). This project supports a number of patent applications, with a new US provisional application being filed in 2010 for novel technologies arising from the project.
- Further development of the diagnostic assay for Cancers of Unknown Primaries (CUP). Through our licensee Circadian Technology, this project is developing the assay to a marketable form in conjunction with Healthscope Ltd. The assay draws on molecular data derived from a large library of tumour specimens and associated data to aid identification of the source of origin of CUP tumours, thereby enhancing treatment selection and patient outcomes.
- Although the initial contract for the Translational Oncology Research Collaborative Hub (TORCH) with Pfizer has now expired, Pfizer has provided an additional year of funding to continue certain studies arising from that collaboration. This program included studies directed towards molecular pathways in cancer and development of associated imaging techniques.
- Prof. Joseph Trapani was successful in obtaining an interim Wellcome Trust funding agreement in relation to the development of perforin inhibitors (Cancer Cell Death laboratory pg 26). Establishment of this agreement included execution of a series of intellectual property licenses and service contracts with our collaborative partners.
- The commercialisation office was involved in a number of consortia negotiations, including the National Breast Cancer Foundation Lifepool collaborative grant, the Australian Phenomics Network and the Victorian Cancer Biologics Consortium.
- In addition, ten new invention disclosures and continued developments in our existing projects resulted in a number of new patent application filings, as detailed in the table below.



Patent applications filed in 2010

Title	Type	Date Filed	Number
Cancer Diagnostic	Australian Provisional	6 Sep	2010903995
Stimulating Immune Response	Australian Provisional	21 Jun	2010902717
Methods of Treatment	Complete applications filed in Canada, Australia, US	26 Oct	2719442 2010236016 12/912,524
Method of Detecting Radiation Exposure and Adverse Toxicity Thereto	PCT	16 Jul	AU/2010/000913
Recombinant Perforin, Expression and Uses Thereof	Continuation	12 Feb	12/704715
New Perforin Compounds	PCT	22 Dec	PCT/AU2010/001731
Radioprotectors	US Provisional	6 Apr	61/321288

6 Publications

6

6 Publications

Anatomical Pathologist Dr Siddhartha (Sid) Deb is one of a growing number of clinicians undertaking postgraduate degrees to strengthen their clinical research focus. Sid's PhD research proposes to be the largest study to molecularly characterise male breast cancer, establishing a cohort for extensive clinicopathological investigation and allowing valuable assessment of genotypic-phenotypic patterns to contribute to the development of novel treatment strategies for breast cancers.

6 Publications

Refereed Research Papers

1. Ahmed, A.A., et al., Driver mutations in TP53 are ubiquitous in high grade serous carcinoma of the ovary. Journal of Pathology, 2010. 221(1): p. 49-56.
2. Ahmed, A.A., et al., SIK2 is a centrosome kinase required for bipolar mitotic spindle formation that provides a potential target for therapy in ovarian cancer. Cancer Cell, 2010. 18(2): p. 109-21.
3. Aide, N., et al., High throughput static and dynamic small animal imaging using clinical PET/CT: potential preclinical applications. European Journal of Nuclear Medicine and Molecular Imaging, 2010. 37(5): p. 991-1001.
4. Aide, N., et al., 18F-FLT PET as a surrogate marker of drug efficacy during mTOR inhibition by everolimus in a preclinical cisplatin-resistant ovarian tumor model. Journal of Nuclear Medicine, 2010. 51(10): p. 1559-64.
5. Akiyama, T., P.F. Choong, and C.R. Dass, RANK-Fc inhibits malignancy via inhibiting ERK activation and evoking caspase-3-mediated anoikis in human osteosarcoma cells. Clinical and Experimental Metastasis, 2010. 27(4): p. 207-15.
6. Akiyama, T., et al., The non-vascularised fibular graft: a simple and successful method of reconstruction of the pelvic ring after internal hemipelvectomy. Journal of Bone Joint Surgery (British), 2010. 92(7): p. 999-1005.
7. Akiyama, T., et al., PEDF regulates osteoclasts via osteoprotegerin and RANKL. Biochemical and Biophysical Research Communications, 2010. 391(1): p. 789-94.
8. Akiyama, T., et al., Systemic RANK-Fc protein therapy is efficacious against primary osteosarcoma growth in a murine model via activity against osteoclasts. Journal Pharmacy and Pharmacology, 2010. 62(4): p. 470-6.
9. Al-Badriyeh, D., et al., Pharmacoeconomic evaluation of voriconazole versus posaconazole for antifungal prophylaxis in acute myeloid leukaemia. Journal of Antimicrobial Chemotherapy, 2010. 65(5): p. 1052-61.
10. Andrews, D.M., et al., Innate immunity defines the capacity of antiviral T cells to limit persistent infection. Journal of Experimental Medicine, 2010. 207(6): p. 1333-43.
11. Andrews, D.M. and M.J. Smyth, A potential role for RAG-1 in NK cell development revealed by analysis of NK cells during ontogeny. Immunology and Cell Biology, 2010. 88(2): p. 107-116.
12. Anthony, D.A., et al., A role for granzyme M in TLR4-driven inflammation and endotoxicosis. Journal of Immunology, 2010. 185(3): p. 1794-1803.
13. Antill, Y.C., et al., Gene methylation in breast ductal fluid from BRCA1 and BRCA2 mutation carriers. Cancer Epidemiology, Biomarkers & Prevention, 2010. 19(1): p. 265-74.
14. Antoniou, A.C., et al., Common breast cancer susceptibility alleles and the risk of breast cancer for BRCA1 and BRCA2 mutation carriers: implications for risk prediction. Cancer Research, 2010. 70(23): p. 9742-54.
15. Arnold, J.M., et al., Frequent somatic mutations of GATA3 in non-BRCA1/BRCA2 familial breast tumors, but not in BRCA1-, BRCA2- or sporadic breast tumors. Breast Cancer Research and Treatment, 2010. 119(2): p. 491-6.
16. Augestad, K.M., et al., International preoperative rectal cancer management: staging, neoadjuvant treatment, and impact of multidisciplinary teams. World Journal of Surgery, 2010. 34(11): p. 2689-700.
17. Aymeric, L., et al., Tumor cell death and ATP release prime dendritic cells and efficient anticancer immunity. Cancer Research, 2010. 70(3): p. 855-58.
18. Azzato, E.M., et al., Association between a germline OCA2 polymorphism at chromosome 15q13.1 and estrogen receptor-negative breast cancer survival. Journal of the National Cancer Institute, 2010. 102(9): p. 650-62.
19. Bancroft, E.K., et al., The carrier clinic: an evaluation of a novel clinic dedicated to the follow-up of BRCA1 and BRCA2 carriers--implications for oncogenetics practice. Journal of Medical Genetics, 2010. 47(7): p. 486-91.
20. Bao, H., et al., Second harmonic generation imaging via nonlinear endomicroscopy. Optics Express, 2010. 18(2): p. 1255-60.
21. Barber, T.W., M.S. Hofman, and R.J. Hicks, Breast lymphatic drainage via the pulmonary lymphatic system. European Journal of Nuclear Medicine and Molecular Imaging, 2010. 37(11): p. 2203.
22. Barry, P., et al., Music therapy CD creation for initial pediatric radiation therapy: a mixed methods analysis. Journal of Music Therapy, 2010. 47(3): p. 233-263.
23. Bayne, M., et al., Reproducibility of "intelligent" contouring of gross tumor volume in non-small-cell lung cancer on PET/CT images using a standardized visual method. International Journal of Radiation Oncology, Biology, Physics, 2010. 77(4): p. 1151-7.
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25. Bollag, G., et al., Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma. Nature, 2010. 467(7315): p. 596-9.
26. Bolton, K.L., et al., Common variants at 19p13 are associated with susceptibility to ovarian cancer. Nature Genetics, 2010. 42(10): p. 880-4.
27. Bonelli, M.A., et al., Synergistic activity of letrozole and sorafenib on breast cancer cells. Breast Cancer Research and Treatment, 2010. 124(1): p. 79-88.
28. Boonzaier, A., et al., The practical challenges of recruitment and retention when providing psychotherapy to advanced breast cancer patients. Supportive Care in Cancer, 2010. 18(12): p. 1605-13.
29. Brady, J., et al., The Interactions of Multiple Cytokines Control NK Cell Maturation. Journal of Immunology, 2010. 185(11): p. 6679-88.
30. Brennan, S., et al., Prospective trial to evaluate staged neck dissection or elective neck radiotherapy in patients with CT-staged T1-2 N0 squamous cell carcinoma of the oral tongue. Head & Neck, 2010. 32(2): p. 191-8.
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32. Broadhead, M.L., et al., Thigh enlargement and the art of misdirection. ANZ Journal of Surgery, 2010. 80(11): p. 839-40.
33. Buchert, M., et al., Genetic dissection of differential signaling threshold requirements for the Wnt/beta-catenin pathway in vivo. PLoS Genetics, 2010. 6(1): p. e1000816.
34. Buckland, A.J., et al., Periprosthetic bone remodeling using a triple-taper polished cemented stem in total hip arthroplasty. Journal of Arthroplasty, 2010. 25(7): p. 1083-90.
35. Bushnell, D.L., Jr., et al., 90Y-edotreotide for metastatic carcinoid refractory to octreotide. Journal of Clinical Oncology, 2010. 28(10): p. 1652-9.
36. Butow, P.N., et al., From inside the bubble: migrants' perceptions of communication with the cancer team. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 2010. 19(2): p. 281-90.
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41. Caddy, J., et al., Epidermal wound repair is regulated by the planar cell polarity signaling pathway. Developmental Cell, 2010. 19(1): p. 138-47.
42. Campbell, B.A., et al., Long-term outcomes for patients with limited stage follicular lymphoma: involved regional radiotherapy versus involved node radiotherapy. Cancer, 2010. 116(16): p. 3797-806.
43. Cappellini, M.D., et al., Tailoring iron chelation by iron intake and serum ferritin: the prospective EPIC study of deferasirox in 1744 patients with transfusion-dependent anemias. Haematologica, 2010. 95(4): p. 557-566.
44. Carney, D.A. and J.F. Seymour, Therapy-related myelodysplasia and fludarabine combination therapy - do the benefits justify the risk? Leukemia & Lymphoma, 2010. 51(11): p. 1957-9.
45. Carney, D.A., et al., Therapy-related myelodysplastic syndrome and acute myeloid leukemia following fludarabine combination chemotherapy. Leukemia, 2010. 24(12): p. 2056-62.
46. Carrington, C., et al., The Clinical Oncological Society of Australia (COSA) guidelines for the safe prescribing, dispensing and administration of cancer chemotherapy. Asia-Pacific Journal of Clinical Oncology, 2010. 6(3): p. 220-37.
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49. Chandra, R., C.H. Pilgrim, and V. Usatoff, Staged liver resection for colorectal metastases: a valuable strategy or a waste of time? Hepatobiliary and Pancreatic Diseases International, 2010. 9(6): p. 600-4.
50. Chirgwin, J., et al., Does multidisciplinary care enhance the management of advanced breast cancer?: evaluation of advanced breast cancer multidisciplinary team meetings. Journal of Oncology Practice, 2010. 6(6): p. 294-300.
51. Clark, J.C., et al., New clinically relevant, orthotopic mouse models of human chondrosarcoma with spontaneous metastasis. Cancer Cell International, 2010. 10: p. 20.
52. Clarke, C.J., et al., Inducible activation of IFI 16 results in suppression of telomerase activity, growth suppression and induction of cellular senescence. Journal of Cellular Biochemistry, 2010. 109(1): p. 103-12.
55. Clemons, N.J., et al., Nitric oxide-mediated invasion in Barrett's high-grade dysplasia and adenocarcinoma. Carcinogenesis, 2010. 31(9): p. 1669-75.

6 Publications

56. Corcoran, N.M., et al., Open-label, phase I dose-escalation study of sodium selenate, a novel activator of PP2A, in patients with castration-resistant prostate cancer. British Journal of Cancer, 2010. 103(4): p. 462-8.
57. Couper, J.W., et al., Predictors of psychosocial distress 12 months after diagnosis with early and advanced prostate cancer. Medical Journal of Australia, 2010. 193(5): p. S58-S61.
58. Crosbie, J.C., et al., Tumor cell response to synchrotron microbeam radiation therapy differs markedly from cells in normal tissues. International Journal of Radiation Oncology, Biology, Physics, 2010. 77(3): p. 886-94.
59. Cullinane, C., et al., Preclinical evaluation of nilotinib efficacy in an imatinib-resistant KIT-driven tumor model. Molecular Cancer Therapeutics, 2010. 9(5): p. 1461-8.
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61. Da Silva, L., et al., HER3 and downstream pathways are involved in colonization of brain metastases from breast cancer. Breast Cancer Research, 2010. 12(4): p. R46.
62. D'Angelo, M.E., et al., Cathepsin H is an additional convertase of pro-granzyme B. Journal of Biological Chemistry, 2010. 285(27): p. 20514-9.
63. Dass, C.R. and P.F. Choong, Sequence-related off-target effect of Dz13 against human tumor cells and safety in adult and fetal mice following systemic administration. Oligonucleotides, 2010. 20(2): p. 51-60.
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