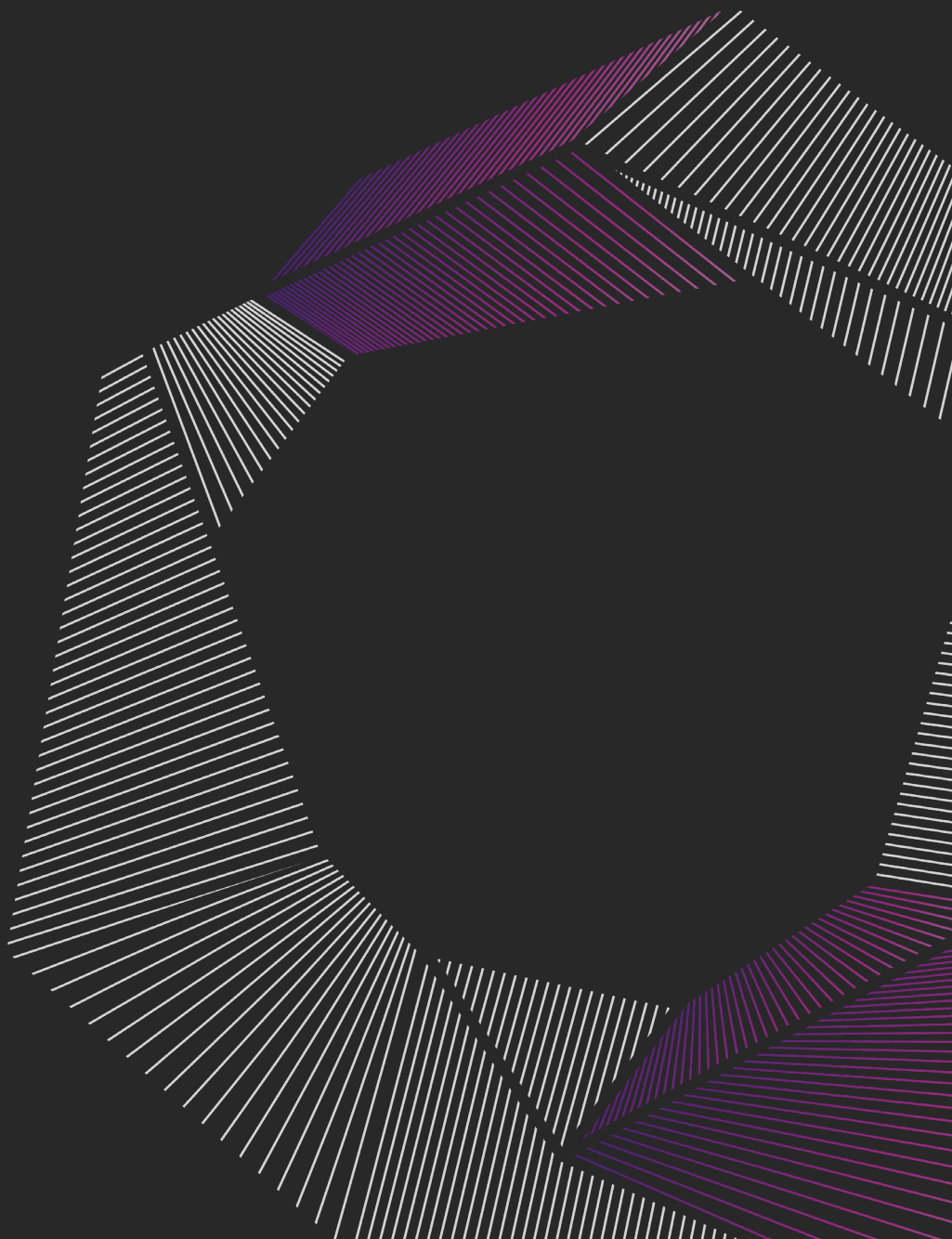
Peter Mac

Peter MacCallum Cancer Centre
Victoria Australia

# CANCER RESEARCH STUDENT PROJECTS 2026



# FROM OUR CANCER RESEARCH EXECUTIVE DIRECTOR

For over 70 years, Peter Mac has been providing high quality treatment and multidisciplinary care for cancer patients and their families. Importantly, we house Australia's largest and most progressive cancer research group, one of only a handful of sites outside the United States where scientists and clinicians work side-by-side.

Our research covers a diversity of topics that range from laboratory-based studies into the fundamental mechanisms of cell transformation, translational studies that provide a pipeline to the patient, clinical trials with novel treatments, and research aimed to improve supportive care.

The proximity and strong collaborative links of clinicians and scientists provides unique opportunities for medical advances to be moved from the 'bench to the bedside' and for clinically orientated questions to guide our research agenda. As such, our research programs are having a profound impact on the understanding of cancer biology and are leading to more effective and individualised patient care.

As Executive Director Cancer Research, it is my mission to strategically drive Peter Mac's standing as one of the leading cancer centres in the world by enhancing our research outputs, increasing our talent pool and enabling existing and new areas of research excellence.

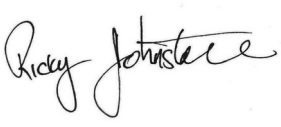
I firmly believe that our model of research-driven cancer care is the right one and Peter Mac is uniquely positioned to expand this paradigm both internally and with our external partners.

Peter Mac is committed to continue to support and build our broad research enterprise including fundamental research, and I am in no doubt that strong discovery-based research labs and programs are essential for us deliver the best care for our patients.

If you undertake your research at Peter Mac, you will be supported by a pre-eminent academic program, driven by internationally renowned laboratory and clinician researchers, with a strong focus on educating future generations of cancer clinicians and researchers.

You have the opportunity to work at the forefront of cancer care and make a contribution to our research advances.

Welcome to Peter Mac Cancer Research.



**Professor Ricky Johnstone**
Executive Director, Cancer Research

# CONTENTS

Peter Mac's comprehensive and internationally renowned cancer researchers seek fundamental biological and biomedical discoveries, and aim to facilitate the development and application of these discoveries to their full therapeutic potential.

Critical to this aim is our ability to recruit outstanding staff and students to drive our innovative basic and translational research.

This book provides an overview of project directions available for students across different disciplines, all with a focus on cancer and changing treatment outcomes for patients.

'Nothing but the best is good enough for the treatment of cancer'

Sir Peter MacCallum

# ABOUT OUR RESEARCH

Peter Mac is one of the world's leading cancer research, education and treatment centres globally and is Australia's only public hospital solely dedicated to caring for people affected by cancer. We have over 2,500 staff, including more than 700 laboratory and clinical researchers, all focused on providing better treatments, better care and potential cures for cancer.

Dedicated research is the key to better treatments, better care and cures for cancer. This is a place where normal days are extraordinary – as are the people we care for. Each day our team strives to provide the very best in cancer care, better treatments and potential cures for all people affected by cancer.

Globally, we are facing one of the most pivotal times in the pursuit of cancer cures, and Peter Mac stands at its forefront. Together, we aim to lead a new era of cancer prevention, care and discovery, supported by state-of-the-art facilities at our home within the Victorian Comprehensive Cancer Centre building.

Peter Mac is home to over 700 researchers, including more than 200 students (PhD, MPhil, Honours and others).

## LABORATORY RESEARCH

Peter Mac's comprehensive and internationally renowned cancer research laboratories seek fundamental biological and biomedical discoveries, and aim to facilitate the development and application of these discoveries to their full therapeutic potential.

Supported by core technology platforms, our research laboratories are organized into programs of laboratory-based and translational research:

- Organogenesis & Cancer Program
- Cancer Biology & Therapeutics Program
- Cancer Evolution & Metastasis Program
- Cancer Immunology Program
- Computational Biology Program

Peter Mac is home to many large, group [cohort] studies collecting biospecimens, blood samples and survey data from people with cancer to build large open-access resources for innovative research projects. Some studies also collect information from people who have never had cancer.

Cohort studies give our researchers, and researchers worldwide, access to a vast array of ethically collected clinical samples and associated clinical data. Our cohort studies include:

- Australian Ovarian Cancer Study (AOCS)
- BROCADE- BReast Origin CAncer tissue DonatEd after death
- CASCADE- Cancer Tissue Collection After Death
- Cancer 2015
- International Sarcoma Kindred Study
- kConFab
- Lifepool
- Melanoma Research Victoria (MRV)
- SUPER- Solving cancer of unknown primary
- ViP: Variants in Practice

## CLINICAL RESEARCH

Peter Mac is committed to linking patient care with cancer research. Our clinician researchers take their observations from the clinic and plan their research directions with patients in mind.

There are many specialised groups actively engaged in clinical research. Our aim is to improve treatment, and care and experience outcomes of cancer patients and their support networks.

Our clinician researchers work across all tumour types and services: the Bone and Soft Tissue, Breast, Cancer of Unknown Primary, Colorectal, Gynae-Oncology, Haematology, Head and Neck, Lung, Melanoma and Skin, Neuro-Oncology, Paediatric and Late Effects, Upper Gastrointestinal, and Uro-Oncology Services.

Clinical services research includes the following areas:

### Australian Cancer Survivorship Centre (ACSC)

The ACSC aims to better understand the issues that survivors experience and their needs, and develop and test interventions that improve survivors' well-being.

### Cancer Allied Health (CAH)

CAH research is focused on delivering high-quality evidence-based services to our patients, their families and carers.

### Familial Cancer Centre (FCC)

The Parkville FCC works with families to investigate hereditary cancer syndromes and how they can better manage their cancer risk.

### Imaging and Diagnostic Research

Imaging and diagnostic research is conducted in Peter Mac's Centre for Cancer Imaging. Our researchers image tumours to develop new therapies and improve imaging technologies for cancer patients.

### Infectious Diseases & Infection Control (IDIC)

Peter Mac's IDIC research group aims to improve cancer outcomes through enhanced infection services. This group is home to the NHMRC National Centre for Infections in Cancer - an integrated health care program for reducing infections in cancer.

### ONTrac

This multidisciplinary research group is committed to improving the understanding and knowledge of the health outcomes of young people living with cancer.

### Pain & Palliative Care (PPC) Research

PPC research focuses on symptom control, end-of-life care including advance care planning, and models of integration of palliative and acute care.

### Physical Sciences Research

Physical sciences research is focused on the delivery of cancer radiotherapy treatments that increase tumour exposure to effective therapy while reducing exposure to normal tissue.

### Radiation Oncology Research

Radiation oncology research aims to provide the most up-to-date and effective evidence-based treatment for patients with cancer who require radiotherapy as part of their treatment.

### Cancer Surgery & Anaesthesia Research

This clinical research group is working to improve the technical aspects and impact of cancer surgeries, and to improve the delivery and efficacy of anaesthesia and interventional pain medicine.

### Victorian Epigenetics Group (VEG)

The VEG supports clinical trials of "epigenetic drugs" for patients with blood cancers through preclinical evaluation, novel biomarker development and early phase clinical trials of new drugs.

### Biostatistics and Clinical Trials (BaCT)

Peter Mac is the leading biostatistical centre focusing on cancer clinical trials in Australia. The centre provides statistical expertise for national cancer trials groups including the Trans Tasman Radiation Oncology Group (TROG) and the Australasian Leukaemia and Lymphoma Study Group (ALLG).

### Radiation and Cancer Imaging

State-of-the-art radiation and imaging equipment underpins Peter Mac's efforts to enhance the delivery of radiation therapy, both as a single modality and, increasingly, as a combined modality therapy using novel chemotherapy and targeted therapy agents.

### Clinical Trials

Clinical trials are central to Peter Mac's commitment to finding more effective cancer treatments and improving care for people with cancer, their families and carers.

With more than 200 clinical trials active every year, Peter Mac has a comprehensive network of clinical trials support in place, bringing together laboratory researchers, medical, surgical and radiation oncologists, many of whom are clinician-researchers, pathologists, pharmacists, geneticists and clinical trials nurses.

The Parkville Clinical Trials Unit (PPCTU) incorporates the cancer clinical trials services of Peter Mac, the Royal Melbourne Hospital, and the Royal Women's Hospital.

## HEALTH SERVICES RESEARCH

The Department of Health Services Research supports the broader health services research and implementation science portfolio. The new department reinforces Peter Mac's investment in health services research and implementation science as a new major research theme in the 2020 - 2025 Research Strategic Plan.

The focus of the health services research and implementation science portfolio is to bring together Peter Mac researchers, clinicians and patients to deliver world class, equitable, and evidence-based patient-centred cancer treatments and care.

Health services research and implementation science, or HSRIS, complements Peter Mac's other major research themes to deliver a comprehensive 'bench to bedside and beyond' program of research.

Some of the department's strategic imperatives include:

- Leading data-driven priority setting for improving clinical care through assessment of needs, gaps and key outcomes.
- Identifying and harnessing existing research capacity, networks and relationships.
- Embedding a co-design model across all health services research, implementation science, and clinical trial activities.
- Facilitating high quality knowledge translation into policy and practice.

# PLATFORM TECHNOLOGIES

Our core facilities and platform technologies are the backbone of our research and ensure that the researchers are outfitted with the equipment and expertise needed to facilitate their research.

An important role of the core platform technologies is to also identify, import, and develop new technologies.

Peter Mac's core technologies and expertise are also made available to external researchers on a collaborative or cost recovery basis, thereby increasing research output in the wider bioscience community.

## Centre for Advanced Histology and Microscopy

The Centre for Advanced Histology and Microscopy (CAHM) underpins a multitude of cancer research projects with four core platforms:

- Histology – including tissue embedding and sectioning, slide staining, immunohistochemistry and multiplex immunohistochemistry
- Optical Microscopy- including widefield, slide scanning, confocal microscopy, super-resolution microscopy, multiphoton microscopy and spatial proteomics platforms
- Electron Microscopy- including sample preparation and acquisition for both transmission and scanning electron microscopy
- Image Analysis- including freeware and licensed software for the analysis of multiparameter microscopy data

Researchers utilising CAHM receive support, training and advice from expert technical scientists.

## Bioinformatics Consulting Core

The Bioinformatics Consulting Core provides services and know-how for the analyses of high-throughput genomics data. Our team of bioinformaticians and postdoctoral scientists work alongside laboratory and clinical researchers and contribute to their experimental design, grant applications and the analysis and publication of genomic and transcriptomic data. Data types analysed by the core include whole-exome sequencing, targeted re-sequencing, RNA-sequencing, ChIP-sequencing, NanoString and various types of microarray data.

## Flow Cytometry and Cell Sorting

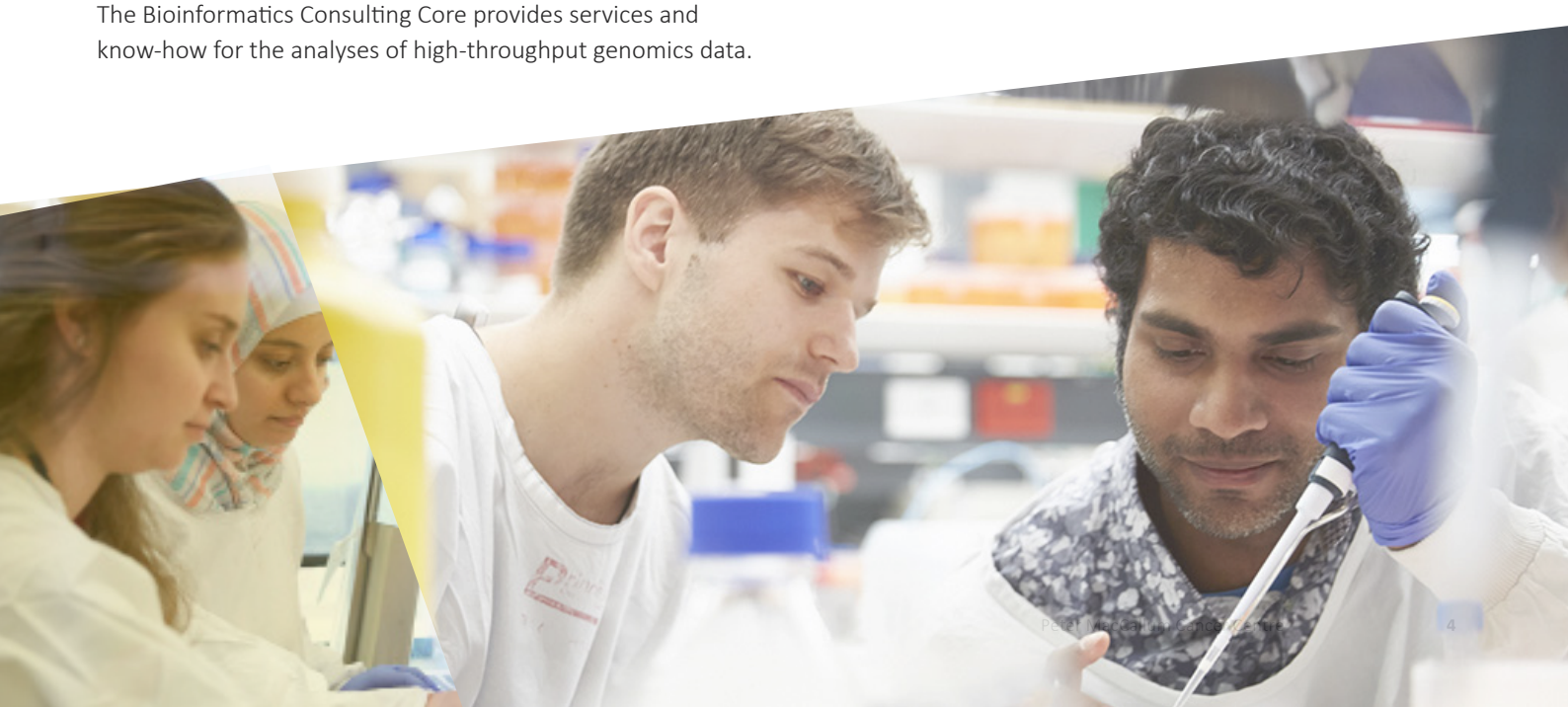
This facility provides researchers with access to state-of-the-art equipment and expertise that enables isolation, separation and analysis of cell populations based on their biological and therapeutic properties.

Flow cytometry is a powerful technique for the analysis of individual cells within complex populations. It is used in both research and clinical settings, and has an important role in the translation of knowledge from the research setting to the clinical area (translational research).

## Victorian Centre for Functional Genomics

Want to work with CRISPR? Want to knock down gene expression? Interested in growing your cells in 3D? Thinking about finding the next generation drug that targets your disease of interest? How about quantifying that cellular phenotype you are working on or the expression of a series of proteins? You can do all this and more in the Victorian Centre for Functional Genomics (VCFG) on Level 11 using the sophisticated liquid handling automation, high content microscopy, live cell imaging and specialised analysis pipelines.

The VCFG team are highly experienced technical experts in the areas of high throughput RNAi, CRISPR and compound screening coupled with many different types of functional readouts that best represent your cell biology and disease state. They revel in the challenge to take a regular bench



experiment and transpose it to a high throughput multiplexed approach.

The VCFG has developed an automated 3D cellular characterisation, imaging and screening pipeline that can be adapted to analyse cell lines and patient derived materials. This is the start of significant steps towards providing personalised medicine approaches. The VCFG operates a 'researcher-driven-staff assisted' model whereby someone from the team works with you through the process of your project, trains you to run some of the instrumentation and assists in analysis and interpretation. The opportunities are vast, it really just requires your imagination!

## Molecular Genomics

The Molecular Genomics Core is an exciting space with the most relevant state-of-the-art genomics technologies and highly skilled staff to support researchers conduct genomics experiments. At the MGC we process samples according to established methods and work with researchers to develop and implement the latest genomics tools and niche protocols. We also team up with other Core Facilities at PeterMac to integrate all aspects of sample processing and analysis, giving the researcher technical confidence to focus on the biology is trying to answer. Via the MGC the researcher has expert access to:

- **NGS, MiSeq, NextSeq and NovaSeq (Illumina):** whole genome sequencing, whole exome sequencing, targeted DNA sequencing, RNA-Seq, ChIP-Seq, ATAC-Seq, CRISPR-Seq, etc.
- **Single Cell Sequencing, Chromium (10x Genomics):** Single-cell gene expression, single-cell immune profiling, single-cell ATAC-Seq, etc.
- **Spatial Transcriptomics, GeoMX DSP (Nanostring) and Visium (10x Genomics):** gene expression with tissue information from FFPE or FF sections.
- **Others:** Nanostring for hybridization-based gene expression; DRUG-seq for high-throughput RNA-Seq; TapeStation for nucleic acid QC; liquid handlers for high throughput sample processing, etc.

## Research Computing Facility

The Research Computing Facility is responsible for administering Peter Mac's Computing Cluster and Linux environment, providing leadership in the area of data governance, managing the Research Data Repository/Archive and REDCap, administering cloud computing resources, and providing specialised software solutions and/or systems to support research. The facility also provides training for the software systems they administer as well as general bioinformatics and statistics.

## Tissue Bank

The Tissue bank is a member of the Victorian Cancer Biobank, providing researchers with ethically collected, high quality human tissue, blood and data samples for their investigative projects. It also supports clinical trials at Peter Mac by processing and storing blood and tissue specimens in accordance with trial-specific protocols.

## Research Laboratory Support Services

Research Laboratory Support Services (RLSS) provides a centralised, comprehensive range of services that support the researcher's needs in a timely and cost effective manner. This includes Media Kitchen, Labware Services and Research Store.

## Transgenic and SPF Facility

We currently breed and maintain approximately 20,000 mice, representing over 130 different strains of transgenic and gene-targeted mice.

Peter Mac's Animal Ethics Committee (AEC) has an important role in overseeing the ethical conduct of any work involving the use of animals for scientific purposes, conforming to the NHMRC Australian Code of Practice for the Care and Use of Animals for Scientific Purposes.

# CANCER RESEARCH PROGRAMS

## Organogenesis & Cancer Program

Research Labs:

- Andrew Cox
- Ben Hogan
- Kieran Harvey
- Louise Cheng
- Najoua Lalaoui

**The primary focus of the Organogenesis & Cancer Program is to investigate the process of organ development and how failure of organogenesis contributes to cancer.**

Despite being a fundamental part of life, we still lack a clear understanding of how individual organs know how to grow to the right size and maintain this size. The roles of stem and progenitor cells in the growth of different organs are also unclear, as is the impact of diet and nutrition on organ growth. To investigate these questions, our program leverages the unique strengths that are offered by different experimental systems, including Drosophila, zebrafish and organoid cultures. We also collaborate with clinicians from within the VCCC network to examine how deregulation of organogenesis signalling networks drive cancers such as melanoma, mesothelioma, glioblastoma and hepatocellular carcinoma.

We have specific interests in the following topics:

- How the Hippo pathway controls normal, neoplastic and regenerative tissue growth.
- The impact of diet and nutrition on organogenesis.
- The metabolism of cells in normal and neoplastic tissue.
- How deregulation of organogenesis signalling networks drive cancer.
- How the growth of different organs are coordinately regulated during development.
- How the proliferative potential of stem cells is controlled.

**Find Projects**

# CANCER RESEARCH PROGRAMS

## Cancer Biology and Therapeutics Program

Research Labs:

- David Bowtell
- Grant McArthur
- Kristin Brown
- Lev Kats
- Mark Dawson
- Melanie Eckersley-Maslin
- Ricky Johnstone
- Sarah-Jane Dawson
- Shom Goel

**The Cancer Biology & Therapeutics Program aims 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 for solid tumours.**

This integrated program allows insight into fundamental aspects of cancer biology through the identification of novel tumour-suppressor and tumour-initiating genes. We explore the functional relationships between altered cancer genetics and aberrations to the cancer epigenome, and a deeper understanding of the molecular events that drive oncogenic signalling networks. These findings serve as a basis for extensive translation-based studies to determine the potential therapeutic benefit of interfering with or augmenting the activity of key proteins involved in these signalling networks through pharmacological intervention.

**Find Projects**

## Cancer Evolution and Metastasis Program

Research Labs:

- Belinda Parker
- Elizabeth Christie
- Ian Campbell
- Kara Britt
- Kylie Gorringe
- Nicholas Clemons
- Stephen Fox
- Steven Stacker
- Wayne Phillips

**The Cancer Evolution & Metastasis Program focuses on understanding the mechanisms of cancer initiation, progression and metastatic spread.**

The program works across multiple tumour streams to ultimately uncover markers of risk and to develop precision therapeutics. The program encompasses three main themes:

- Risk and Prevention (Britt and Campbell labs)
- Therapy and Resistance (Christie, Clemons, Gorringe, Phillips and Ramsay labs)
- Progression and metastasis (Fox, Parker and Stacker labs)

The constituent laboratories explore these themes using a wide variety of approaches and technologies including whole-genome and single-cell genomics and transcriptomics; in vitro and in vivo tumour models, including patient-derived and animal models; high-content and spatial imaging; and high-throughput functional genomics, small molecule screening and biomarker discovery platforms.

**Find Projects**

# CANCER RESEARCH PROGRAMS

## Cancer Immunology Program

Research Labs

- Ajith Vasanthakumar
- Ian Parish
- Ilia Voskoboinik
- Jane Oliaro
- Joe Trapani
- Paul Beavis
- Paul Neeson
- Phillip Darcy
- Sherene Loi
- Sarah Russell
- Gail Risbridger
- Ben Solomon
- Riccardo Dolcetti
- Luc Furic
- Paul Ekert

**Harnessing the power of the immune system to fight cancer through research into cancer immune surveillance and chemo/immunotherapy, defining key cells and molecules that can elicit an effective response to tumours.**

We are interested in the very early stages of how immune cells can pick up and respond to the presence of cancer cells. We have demonstrated that specific toxins made by "killer T cells" can prevent the onset of certain cancers (immune surveillance), and are developing genetic technologies to modify and expand the activity of these cells to treat established malignancies. In addition, we are defining the molecular means by which new classes of anti-cancer drugs kill cancer cells, so that rational choices can be made on the most appropriate cancer chemotherapy for a patient.

**Find Projects**

## Computational Biology Program

Research Labs

- Alicia Oshlack
- Anna Trigos
- Gerry Tonkin-Hill

**The Computational Biology Program uses mathematics, statistics and computing to generate new discoveries in cancer. We develop new models, algorithms and software tools, and apply these to make sense of cancer data. This includes whole genome, exome, transcriptome and epigenome sequencing data.**

Our research interests encompass:

- bioinformatics algorithm and methods development
- computational cancer biology
- cancer evolution and genomics
- software tool development
- personalised medicine.

The program includes research laboratories, as well as the Bioinformatics Consulting Core and the Research Computing Facility. Scientists come from a range of disciplines including biology, computer science, mathematics and statistics, as well as software engineering.

**Find Projects**

# RESEARCH EDUCATION PROGRAM

## With strong links to local and international universities and research institutes, our research education program provides a training and support framework for the academic and professional development of our staff and students.

Peter Mac is home to over 200 research students undertaking postgraduate and honours research programs. Most students completing projects at Peter Mac are enrolled through The University of Melbourne. We also host students from Universities throughout Australia and overseas.

Our program provides students with the opportunity to expand their research knowledge and skills, while also developing important transferable skills that will make an important contribution to their future career directions.

We provide a structured yet flexible program to meet the varied needs of our students. This research environment supports all students during the development of the important research and professional skills that will allow our graduates to demonstrate their development as efficient researchers, and makes a significant contribution to improving the quality of research coming out of our Centre.

### Sir Peter MacCallum Department of Oncology, The University of Melbourne

The University of Melbourne's Sir Peter MacCallum Department of Oncology is located within the Peter MacCallum Cancer Centre.

The Sir Peter Mac Department brings to the university the strengths of world-class laboratory and clinical research conducted within a public cancer hospital, including:

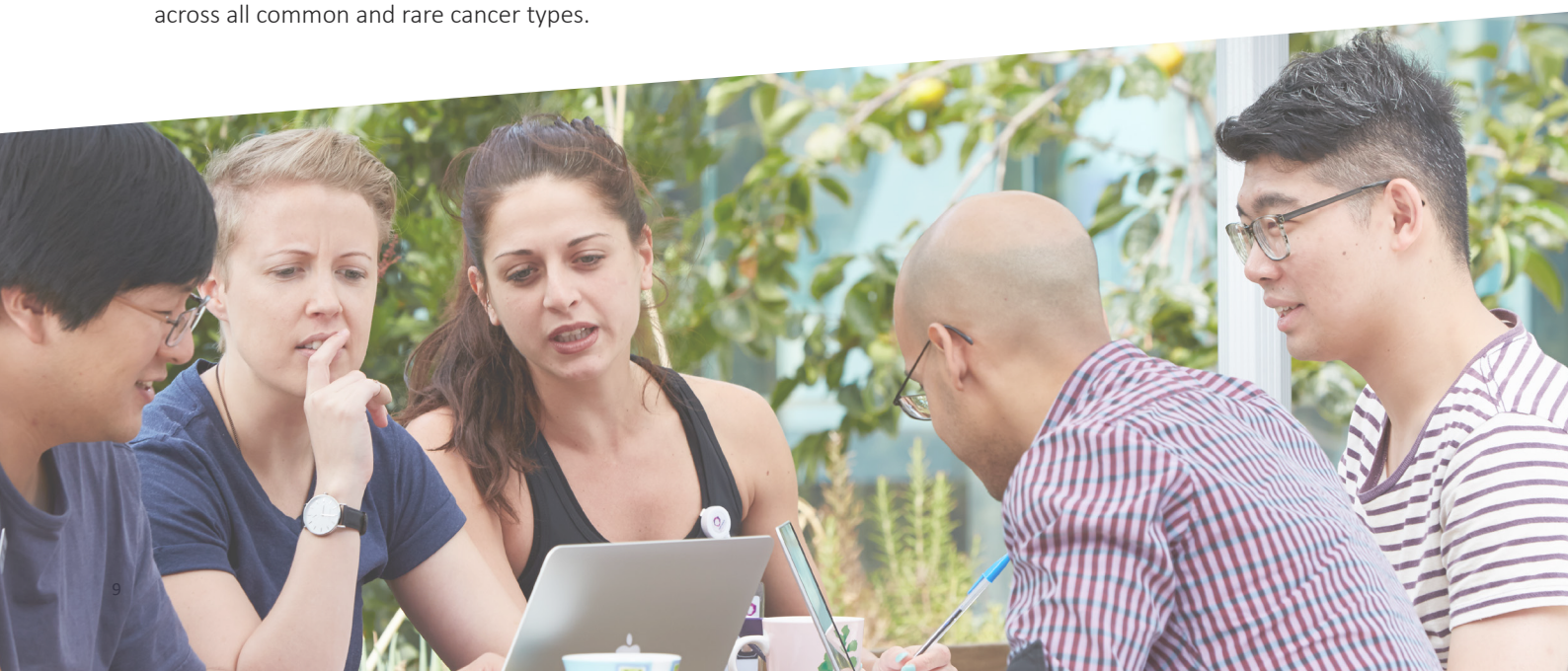
- The largest cancer research group in Australia, with laboratory-based researchers and clinicians working side-by-side;
- A strong academic program, driven by internationally renowned laboratory and clinical researchers, with a strong focus on educating future generations of cancer researchers;
- Highly sophisticated equipment and technology, enabling complex research projects through access to cutting-edge core research technology platforms
- A cancer stream-based and holistic model of care where multi- disciplinary experts come together to provide tailored treatment at all stages of a patient's disease, across all common and rare cancer types.

Peter Mac and the Sir Peter MacCallum Department of Oncology also provide research placements for medical research programs, for international postgraduate students, for undergraduate students associated with the Summer Vacation Research Program, undergraduate work experience and undergraduate research projects undertaken in the laboratories.

Postgraduate research students based in clinical settings are supported by the Cancer Research Education program in addition to the support offered by their clinical service teams.

The co-location of research and research training capability with a hospital dedicated to cancer treatment enables researchers and clinicians to work side-by-side to make significant contributions to basic research, translational research and clinical trials for cancer.

The Peter Mac Research Education program formed the basis of The University of Melbourne's Comprehensive Cancer PhD program, described in the following section.



# COMPREHENSIVE CANCER PhD PROGRAM

The Comprehensive Cancer PhD program (The University of Melbourne) supports the academic and professional development of students undertaking cancer-related research within the Victorian Comprehensive Cancer Centre (VCCC) Alliance.

This innovative and integrated program aims to produce graduates ready to conduct world-class cancer research and set them on a path to a broad range of career options.

The Comprehensive Cancer PhD (CCPhD) Program is designed to complement existing PhD activities by providing eligible students with opportunities to broaden the scope of their research knowledge, professional development and career training, and to develop research and professional skills that will help students to fulfil their career ambitions.

The Comprehensive Cancer PhD Program builds on established conventional training for cancer research students providing a coordinated program of skills, research and career training in addition to usual PhD activities.

Tapping into the depth and breadth of knowledge and experience of the VCCC alliance partners, the program provides a unique opportunity for multidisciplinary cancer-related PhD candidates to experience clinical and research activities across the alliance.

The program is managed by the Sir Peter MacCallum Department of Oncology (University of Melbourne), and is based on the gold-standard postgraduate program offered by Peter Mac.

All students engaged in postgraduate research studies at Peter Mac are enrolled in the CCPhD program, regardless of which university they are enrolled through.

The program includes:

1. Research skills development, including mastery of core technologies, cancer-specific seminars and presentations.
2. Professional and career development, including generic and transferable skills, mentoring, networking, leadership and career opportunities.
3. Communication skills development, including thesis and journal writing skills, and oral or poster presentations skills.

Examples of student activities in this program:

- Annual Student Symposium
- Annual Debate
- Thesis Bootcamp
- Annual Chat with a Nobel Laureate
- Topics in Cancer Seminar program, with recent topic themes including:
  - Cancer Immunotherapy
  - Oncogenes and Tumour Suppression
  - Pillars of Cancer Care
  - Cancer Genetics and Genomics
  - Hallmarks of Cancer
- Workshops including: presentation skills, communication skills, candidature management and CV preparation

For further information, email: ccphd@petermac.org

THE UNIVERSITY OF MELBOURNE

Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

VICTORIAN COMPREHENSIVE CANCER CENTRE

The Comprehensive Cancer PhD Program is supported by academic partner the University of Melbourne, Peter MacCallum Cancer Centre and the Victorian Comprehensive Cancer Centre Alliance

# BECOMING A STUDENT AT PETER MAC

We provide a world-class research education program at a leading Australian cancer research institution for students from The University of Melbourne and other national and international universities.

There are two general stages in preparing to become a student in our postgraduate and honours programs.

Students must:

1. Find a project and supervisor for their research program.
2. Meet the University degree eligibility and entry requirements.

## Postgraduate students

Applicants for postgraduate student positions at Peter Mac enrol through a university program that approves your project placement at Peter Mac. You must therefore satisfy the minimum entry requirements at the university through which you plan to enrol.

Entry to the Peter Mac postgraduate program is based on the availability of projects, student suitability and academic background.

To undertake a postgraduate project at Peter Mac, students need to:

- Demonstrate a genuine interest in biomedical research.
- Be happy to conduct your research candidature full time off-campus at Peter Mac.
- Look through the available project summaries and contact the project supervisor directly by email.
- Discuss your interest in the project with the supervisor.
- Meet with potential supervisors at Peter Mac to discuss the project, your interests, visit the lab and meet others in the research group. At this meeting, supervisors will also want to view your academic record. International students will 'meet' supervisors via zoom or similar.
- Meet university eligibility requirements for postgraduate degree candidature.
- Apply for candidature at The University of Melbourne or at an equivalent university when supervisor and project are confirmed. University of Melbourne students enrol with The Sir Peter MacCallum Department of Oncology, through the Faculty of Medicine, Dentistry and Health Sciences.
- Apply for a postgraduate scholarship. Note the different deadlines that apply to different scholarships, different universities, and for local versus international scholarships.

Peter Mac staff will work with students to facilitate these processes.

Applications for candidature/scholarships for all universities are online processes, requiring a letter of support from the proposed supervisor.

## Honours students

Each year we accept students from biomedical science and science programs to undertake one-year, full time Honours projects in cancer-related biomedical research.

Students undertake all of their scientific research work on site at Peter Mac, while undertaking their course work at the university department through which they are enrolled.

Our honours students come to us with a range of majors and backgrounds including biochemistry, chemistry, biomedical science, immunology, cell biology, medicine, pharmacology, molecular biology, pathology, physiology, anatomy and other similar subjects.

Most of our Honours students are enrolled at The University of Melbourne through departments of the Faculty of Medicine, Dentistry and Health Sciences, such as: Biochemistry & Molecular Biology, Clinical Pathology, Microbiology & Immunology, Anatomy & Cell Biology and Pharmacology.

Students who have completed their undergraduate degree at another university in Australia or overseas are also encouraged to contact us directly for further information on how to apply.

Students interested in undertaking an Honours project at Peter Mac need to:

- Demonstrate a genuine interest in biomedical research.
- Ensure their university/department approves them conducting their research project full time off-campus at Peter Mac.
- Look through the available project summaries and contact the project supervisor directly by email.
- Discuss your interest in the project with the supervisor.
- Meet with potential supervisors at Peter Mac to discuss the project, your interests, visit the lab and meet others in the research group. At this meeting, supervisors will also want to view your academic record.
- Apply for candidature at the University, meeting the university's application and eligibility requirements.

## Assistance in the application process

Further information about the postgraduate and honours projects, supervisor contact details and the application process is available online at:

www.petermac.org/education/research-education

For application assistance, contact:

Research.EducationAdmin@petermac.org

# WHERE DO OUR STUDENTS COME FROM TO STUDY AT PETER MAC?

We host students from countries and universities all over the world to undertake their research studies at Peter Mac. Our multidisciplinary and multicultural student cohort is at the heart of our research excellence.


# WHERE DO ARE OUR GRADUATES GO AFTER THEY COMPLETE THEIR DEGREES?

Our graduates have taken up research positions across the world at leading research institutes and universities as post-doctoral researchers and academic leaders, including:

USA: Memorial Sloan Kettering Cancer Center, Dana-Farber Cancer Center, MD Anderson Cancer Center, Stanford University, Harvard University, University of California (LA, Irvine, SF), St Jude's Children's Research Hospital, University of Pennsylvania, Mount Sinai Hospital, University of Pittsburgh, Medical College of Wisconsin Cancer Centre, University of Texas Health Science Center, Brigham and Women's Hospital, Boston; British Oregon Health and Science University, NYU School of Medicine, Colorado Cancer Centre, John Hopkins School of Medicine, Roswell Park Cancer Institute; Northwestern University; Columbia University.

CANADA: University of Toronto, British Columbia Cancer Agency, Vancouver.

UK: Cambridge University; Cancer Research UK; University College London; University of Dundee; The Beatson Institute for Cancer Research, Glasgow; Nottingham University Hospitals NHS Trust; St Andrews University Edinburgh; Sanger EBI; Medical Research Council; University of Birmingham.

EUROPE: Research Institute of Molecular Pathology, Austria; University of Zurich, Switzerland; NKI, Amsterdam; Max Planck Institute of Immunobiology and Epigenetics, Frieberg, Germany; Ludwig-Maximilians Universität München, Germany; Institute for Molecular Medicine, Finland; Karolinska Institute, Sweden; Stockholm University, Sweden; Gustav Roussy, France; University of Paris Sud XI, France; Antoni van Leeuwenhoek, Netherlands,

ASIA: Center for Genome Integrity, Institute for Basic Science, Korea; Nanyang University Hospital, Singapore.

Our graduates have taken up research positions across Australia and the world at leading companies including:

Amgen, Roche, Pionyr Immunotherapies, Comugen Ltd, GSK, Seres Therapeutics, Genesearch, Geneworks, Australian Department of Health (PBS), Davies Collison Cave Intellectual Property, Merck, QIAGEN.

# WORDS FROM OUR RESEARCH STUDENTS

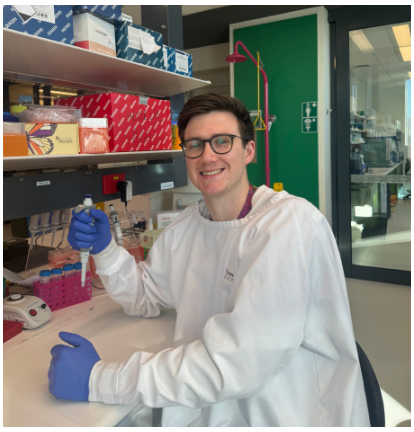
We are proud to offer a supportive and nurturing environment for our students throughout their degrees. Our researchers mentor and support our students throughout their research and towards their careers. Our student committee provides peer-to-peer mentoring opportunities through scientific and social events including an annual retreat and our annual student symposium.

*"Being a student Peter Mac over the past year has been so fulfilling, with the ability to work alongside a team of passionate researchers in a field so close to home. Every day brings a new opportunity to learn new skills and network with amazing researchers, allowing me to get the most out of my project. At Peter Mac, I have the chance to be at the forefront of exciting research that could one day save many lives"*

Ryan's first experience in the lab was as a summer student in 2018/19, followed by the completion of Honours in 2019 at The Institute for Molecular Biosciences. He moved to Melbourne in 2020 to begin his PhD investigating lymphatic recovery and regeneration in the zebrafish model.

**Ryan Brown:** PhD Student, Hogan Laboratory, Recipient of a Research Training Program (RTP)-Domestic Scholarship, Member, 2021 Postgraduate Student Committee.

*"There's no better place to research cancer in Australia than Peter Mac, and I have had an amazing time so far in my PhD. The combination of state-of-the-art technology and passionate researchers situated within a world-class cancer hospital makes this a fantastic place to learn and produce meaningful translational research. I'm grateful for the endless support and opportunities that are presented to me every day as a PhD student at Peter Mac, and I'm looking forward to continuing my research here for years to come"*



Tom completed his undergraduate degree at King's College London in 2020, before moving home to Melbourne and completing a Masters in Biomedical Science at UniMelb in 2022. Tom then moved across the road to Peter Mac to begin his PhD in 2023, focusing on identifying novel therapies to target bone metastasis in breast cancer.

**Tom Chadwick:** PhD Student, Parker Laboratory, Recipient of a Research Training Program (RTP)-Domestic Scholarship and the 2024 Tour de Cure PhD Support Scholarship. Member, 2024 Postgraduate Student Committee.

*"I have always wanted to work in a place doing cutting-edge research, and getting the opportunity to do my PhD at Peter Mac has truly been a dream come true. Despite being a relatively new student here, Peter Mac has already offered me numerous opportunities to grow as a person and as a researcher through the many seminars, retreats and symposiums they've held. The passion and drive everyone here hold towards research continues to amaze and encourage me every day, where I work with the hope that my findings too would one day be translational."*

The time Shenali spent working as a Research Assistant at the Institute of Biochemistry, Molecular Biology and Biotechnology (IBMBB), Sri Lanka was what made her fall in love with research in the first place. This then led her to complete her Honours degree in Immunology and integrative Molecular Biology at the University of Colombo and make the big move to Melbourne for her PhD at Peter Mac. She is now working on the molecular regulation and therapeutic vulnerabilities of RNA polymerase II transcription in cancer.

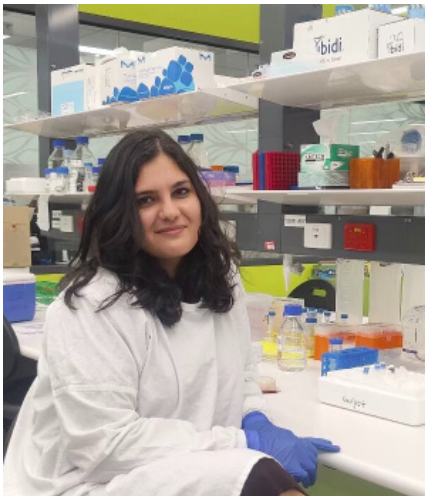
**Shenali Avishka Ranasinghe:** PhD student, Johnstone laboratory. Recipient of an International Melbourne Research Scholarship.

*"Peter Mac is one of the top research institutes in Australia. Through my time at Peter Mac I have been supported and encouraged which has helped to foster and advance my development as a research scientist. At PeterMac there is no shortage of equipment, services and help available to expand and innovate within your research. It is an incredibly rewarding feeling to be a part of the fight to cure cancer, with the hopes that all of us, through each bit of our research, can help to save the lives of many."*

After graduating from UoM, Madeline conducted Honours in Cancer Cachexia at Peter Mac in 2021. She worked as a research assistant for 1 year (2022) before commencing her PhD in 2023 within the Cox lab investigating cancer cachexia and liver cancer in the zebrafish.

**Madeline Webb:** PhD Student, Cox Laboratory. Recipient of 2023 Peter Mac Foundation Postgraduate Award and a Melbourne Research Scholarship.

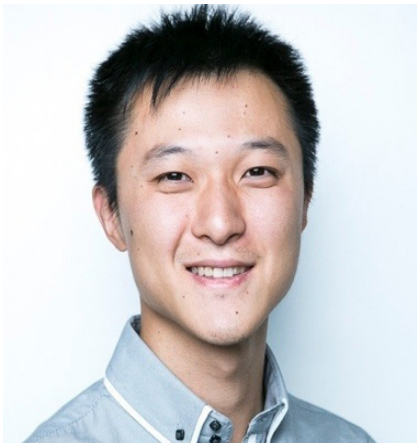
*"At Peter Mac, I am able to work with such passionate and driven research scientists as well as access world class facilities and equipment, especially the CAHM facility, which is where I carry out most of my work! The highly accessible, collaborative, and diverse community as well as being surrounded by such an encouraging and supportive environment is what I think sets Peter Mac apart. We're at the forefront of cancer research, from basic discovery to applied and translational research, and I can't wait to keep seeing more of the amazing work that's being done here!"*



Gurjeet completed her bachelor's in science in Biochemistry and Molecular Biology and took a year off to explore more options. She was an intern at the Brain Research Institute Monash Sunway (Malaysia) and this is where she first fell in love with research. She did her Masters and continued on as a PhD student in the Trapani lab where she is currently working on developing a new tool for RNA visualisation in live cells using CRISPR, to study RNA dynamics.

**Gurjeet Jagjeet Singh**: PhD Student, Trapani Laboratory. Recipient of an International Melbourne Research Scholarship.

*"Peter Mac is Australia's best location for conducting cancer research. I started working on my PhD in the Eckersley-Maslin Lab in January 2023. My research focuses on the link between developmental plasticity and cancer. The environment and culture of PeterMac is quite motivating. Everyday I get to interact with people who truly embody the true characteristics of a scientist."*



Tongtong completed a Bachelor of Science (Honours) at the University of Adelaide and has worked in 6 different laboratories, either as a research assistant or a student prior to his PhD.

**Tongtong Wang:** PhD Student, Eckersley-Maslin Laboratory. Recipient of a 2023 Peter Mac Foundation Postgraduate Award.

*"Peter MacCallum Cancer Centre prides itself in profound collaboration between world-class basic science researchers and clinicians and state-of-the-art facilities. The translational prowess of the research outcome attracted me to Peter Mac. I have benefited immensely from the supportive environment at Peter Mac research-wise and for personal development."*

Having worked as a clinician in Nigeria, Ibukun's daily encounter with patients with advanced cancer with no hope of survival informed his decision to pursue a career in cancer research. He then obtained an MSc in Biomedical Science (cancer biology) from The Hebrew University of Jerusalem, Israel. Ibukun commenced his Ph.D. in 2022 to uncover the cell of origin of Barrett's metaplasia and its progression.

**Ibukun Adesoji Adejumobi:** PhD student, Clemons laboratory. Recipient of an International Melbourne Research Scholarship.

# AVAILABLE PROJECTS BY RESEARCH PROGRAM

## Organogenesis and Cancer Program

### A/PROF LOUISE CHENG

**How do tumours grow at the expense of other tissues in cancer cachexia**

Supervior: A/Prof Louise Cheng

Cancer cells are known to drive altered metabolic circuits to meet the bioenergetic and biosynthetic demands of increased cell growth and proliferation. Under nutrient restriction, when growth of most organs shut down, cancer cells can bypass these brakes imposed on cellular growth, thus gaining a growth advantage under these conditions. Furthermore, during cachexia, which causes more than one third of cancer death, tumour derived factors can also induce the break down of fat and skeletal muscles, in order to generate metabolic intermediates necessary for the preferential tumour growth. The signalling between tumours and other tissues is highly complex, and the adaptations that allow cancer cells to preferentially activate growth are largely unknown. The student will work within a existing team to discover some of the mediators of cancer cachexia using Drosophila genetics, confocal microscopy, proteomics, metabolomics; the findings will be further validated in human samples.

Key Words: Cachexia, Interorgan Crosstalk

Target Students: Honours, Masters, PhD

For more information about this project please contact:

**A/Prof Louise Cheng:** louise.cheng@petermac.org

**Discovering mechanisms of dedifferentiation**

Supervior: A/Prof Louise Cheng

Dedifferentiation is a fundamental process, which allows post-mitotic (non-dividing, mature) cells to revert to a stem cell-like state. It is an important mechanism, which allows mature cells to re-enter the cell cycle to generate additional stem cells, and the regulation of this process has important implications for regenerative medicine, where it is not well understood how stem cells can be activated upon injury (in order to carry out repair). Deregulation of dedifferentiation also has important implications for tumour formation, as generation of ectopic stem cells can cause uncontrolled proliferation and cancer. We have so far identified a number of transcription factors important for dedifferentiation in the developing Drosophila CNS, in this project, we aim to explore how dedifferentiation is regulated, what types of cells are produced during dedifferentiation, how is the balance between dedifferentiation and tumour growth regulated. The student will use Drosophila genetics, genomics and imaging to answer some of these questions.

Key Words: Dedifferentiation, Neural Stem Cells

Target Students: PhD

For more information about this project please contact:

**A/Prof Louise Cheng:** louise.cheng@petermac.org

# AVAILABLE PROJECTS BY RESEARCH PROGRAM

**Non-autonomous regulation of tumour growth**

Supervisors: A/Prof Louise Cheng, Dr Joanna Dong

How tumours communicate with tissues to trigger their breakdown is a key unresolved question. We have generated novel genetic tools that allow independent spatial and temporal overexpression or knockdown of genes in multiple tissues simultaneously. Using these tools, this project aims to look at how brain tumours can interact with other tissues.

Key Words: Brain Tumour, Inter-Organ Communication

Target Students: Honours, PhD

For more information about this project please contact:

**A/Prof Louise Cheng:** louise.cheng@petermac.org

**Dr Joanna Dong:** qian.dong@petermac.org

## A/PROF ANDY COX

**Role of the Hippo-YAP pathway in tumour initiation**

Supervisor: A/Prof Andrew Cox

The Hippo-YAP pathway is an evolutionarily conserved cascade that plays a fundamental role in governing organ size control, stem cell homeostasis and cancer. The Hippo-YAP pathway is regulated by a range of environmental cues including nutrient status. Although many of the inputs into the Hippo pathway have been identified, less is known about how YAP drives tumourigenesis. Our previous studies revealed that the oncogenic Hippo-YAP pathway reprograms anabolic metabolism (nucleotide and lipid biosynthesis) to fuel liver cancer. Building on these studies, we currently have research projects that aim to:

1. Examine how YAP initiates liver tumour formation.
2. Elucidate the mechanisms by which YAP reprograms metabolism.
3. Examine role of YAP in regulating cancer-associated cachexia.

Students will gain experience in a variety of biochemistry/cell biology/molecular biology techniques including CRISPR/Cas9-mediated gene editing, Next generation sequencing (transcriptomics), Mass Spectrometry (metabolomics), tissue clearing and advanced microscopy.

Key Words: Cachexia, CRISPR, Liver Cancer, Metabolism YAP, Zebrafish

Target Students: Honours, Masters, MPhil, PhD

For more information about this project please contact:

**A/Prof Andrew Cox:** andrew.cox@petermac.org

**Investigating the interplay between oxidative stress and oncogenic KEAP1-NRF2 pathway in liver cancer**

Supervisor: A/Prof Andrew Cox

Many of the major risks factors for developing liver cancer such as alcohol, obesity, smoking and toxin exposure share in common a role for oxidative stress. NRF2 is a transcription factor that plays a pivotal role in the cell's adaptation to oxidative stress. The NRF2 pathway is frequently mutated in solid tumours, leading to NRF2 activation. Despite the high prevalence of NRF2 activation in cancers, we still lack a clear appreciation of how this major oncogene drives tumorigenesis. We have recently used transcriptomic and metabolic profiling in zebrafish models to examine the role NRF2 plays in remodeling metabolism during liver development, regeneration and cancer. Building on these preliminary studies, we currently have research project that aims to:

1. Develop new zebrafish models of liver cancers driven by oncogenic NRF2 activation.
2. Identify the metabolic dependencies of NRF2-driven liver cancer.
3. Reveal therapeutic vulnerabilities of NRF2-driven liver cancer.

Students will gain experience in a variety of biochemistry/cell biology/molecular biology techniques including CRISPR/Cas9-mediated gene editing, transcriptomics, tissue clearing and advanced microscopy.

Key Words: Cachexia, CRISPR, Liver Cancer, Metabolism YAP, Zebrafish

Target Students: Honours, Masters, MPhil, PhD

For more information about this project please contact:

**A/Prof Andrew Cox:** andrew.cox@petermac.org

# AVAILABLE PROJECTS BY RESEARCH PROGRAM

## PROF KIERAN HARVEY

**New treatments for mesothelioma**

Supervisors: Prof Kieran Harvey, Dr Aishwarya Kulkarni

Mesothelioma is a terrible disease that is most commonly caused by exposure to asbestos. There are limited treatment options for mesothelioma patients and survival rates are very low compared to most other cancers. Therefore, the need for new and effective mesothelioma treatments is urgent. Importantly, over the past 5 years, cancer genome sequencing studies have revealed that a particular signaling pathway – the Hippo pathway – is mutated in more than half of all mesotheliomas.

We are searching for ways by which we can modulate Hippo pathway activity to treat mesothelioma. Importantly, to ensure the potential of Hippo targeted therapies is met, we must gain a deeper understanding of exactly how they work. This project will investigate:

1. How targeting the Hippo pathway kills mesothelioma cells.
2. How mesothelioma cells become resistant to Hippo targeted therapies.
3. Potential combination therapies that work together with Hippo therapies to kill mesothelioma cells.

You will work as part of a collaborative team and receive excellent training in cell and molecular biology skills and advanced microscopy techniques. You will also receive training in problem solving, scientific writing, delivering oral presentations and how to critically appraise data.

Key Words: Cancer, Hippo Pathway, Mesothelioma

Target Students: Honours, MPhil, PhD

For more information about this project contact:

**Prof Kieran Harvey:** kieran.harvey@petermac.org

**Dr Aishwarya Kulkarni:** aishwarya.kulkarni@petermac.org

**Investigating how the TNF and Hippo pathways co-regulate genes to control neoplastic tissue growth**

Supervisors: Prof Kieran Harvey, Dr Katrina Mitchell

Organ size control, tissue damage and tumour growth are all tightly linked processes. Animals have evolved complex mechanisms to remove damaged or abnormal cells from a tissue in order to prevent tumour growth. We use Drosophila melanogaster to understand the mechanisms by which epithelial tissues can prevent tumours from growing. Neoplastic cells, which have mutations in conserved apical polarity genes (e.g. scribble), can form malignant tumours. Interestingly, if a tissue contains only a small number of these neoplastic cells, they are eliminated. We have identified that both the Tumour necrosis factor pathway (TNF pathway - also known as JNK pathway) and Hippo pathway play important roles in eliminating neoplastic cells. This project will involve investigating how these pathways can regulate the transcription of genes to control neoplastic tissue growth. You will use the following techniques: Drosophila organ growth assays, confocal microscopy analysis of gene and protein expression, molecular biology, genomics and bioinformatics.

You will work as part of a collaborative team and receive excellent training in the techniques listed above. You will also receive training in problem solving, scientific writing, delivering oral presentations and how to critically appraise data.

Key Words: Cancer, Hippo Pathway, Organ Size Control, TNF Pathway, Transcription

Target Students: Honours, Masters, MPhil

For more information about this project contact:

**Prof Kieran Harvey:** kieran.harvey@petermac.org

**Dr Katrina Mitchell:** katrina.mitchell@petermac.org

**Watching cancer gene transcription in vivo**

Supervisors: Prof Kieran Harvey, Dr Ben Kroeger

Cells make crucial decisions- whether to grow, divide, differentiate, or undergo apoptosis- based on external and internal signals. Signal transduction pathways, such as the Hippo signalling pathway, convey this information to transcription factors in the nucleus, which regulate the transcription of genes that drive a specific response. However, despite its importance, the dynamics of transcription, and how it is influenced by Hippo signalling, remains poorly understood. Live imaging is transforming our understanding of transcriptional regulation. Studies using live imaging have shown that transcription occurs in 'bursts', with different on and off durations that influence the extent of gene expression. We will use bacteriophage-derived RNA stem-loops, MS2 and PP7, and employ the Minos-mediated integration cassette (MiMIC) transposon system in Drosophila to insert MS2/PP7 cassettes into key Hippo pathway target genes. We will then use fluorescence microscopy to visualise transcription of these genes in growing tissues, and measure the transcriptional burst durations and off times under normal conditions, and when Hippo signalling is disrupted.

This project aims to:

1. Generate new reagents for live-cell imaging of transcription in vivo.
2. Characterise transcriptional dynamics of important Hippo pathway target genes.

# AVAILABLE PROJECTS BY RESEARCH PROGRAM

3. Assess how Hippo signalling influences transcription of its target genes.

You will work in a collaborative team and be trained in fruit fly genetics, cell and molecular biology, and advanced microscopy techniques. You will also receive training in problem solving, scientific writing, delivering oral presentations and how to critically appraise data.

Key Words: Organ Growth, Transcription, Microscopy

Target Students: Honours, Masters, MPhil, PhD

For more information about this project contact:

**Prof Kieran Harvey:** kieran.harvey@petermac.org

**Dr Ben Kroeger:** ben.kroeger@petermac.org

**Imaging cell signalling in living tissues**

Supervisors: Prof Kieran Harvey, Dr Sam Manning

Cells are building blocks of life and animals like humans are comprised of millions of cells, that all carry out special functions. To control their behaviour (e.g. whether to divide, grow, move or even die) cells send messages from their surface to the nucleus to change gene expression. One such signalling pathway that our lab studies is called the Hippo pathway, which operates in all animals on the planet to control organ growth and cell size. The Hippo pathway is also very important for human cancers; it is mutated in cancers and many Hippo targeted therapies are currently being trialled as new cancer therapies. Despite the Hippo pathway being discovered 20 years ago, the mechanisms by which it signals from the cell membranes to the nucleus are still mysterious. In this project, you will use advanced microscopy approaches to study individual Hippo pathway proteins at single molecule resolution in living tissues. You will use computational analyses to define when and where these proteins meet, and how they move within cells to execute their functions. In doing so, you will make new discoveries on how cancer signalling pathways control cell fate and organ growth. You will work in a collaborative team and be trained in cell and molecular biology, advanced microscopy and computational analyses, as well as problem solving, scientific writing, oral presentations and critically appraisal of data.

Key Words: Cancer Biology, Cell Signalling, Developmental Biology, Microscopy

Target Students: Honours, Masters, MPhil, PhD

For more information about this project contact:

**Prof Kieran Harvey:** kieran.harvey@petermac.org

**Dr Sam Manning:** sam.manning@petermac.org

## PROF BEN HOGAN

**Understanding the roles of novel membrane receptors in lymphangiogenesis and tumour vasculature**

Supervisors: Prof Ben Hogan and Dr Wei Chen

Lymphangiogenesis is the formation of new lymphatic vessels from pre-existing vessels. This process is crucial in both development and the metastatic spread of cancer. The transcription factor Prox1 has been shown to play important roles in the specification, transdifferentiation and maintenance of lymphatic endothelial cells (LECs) across species. A recent single cell transcriptomic atlas of lymphangiogenesis in zebrafish identified novel membrane receptor genes expressed specifically in lymphangiogenesis. CRISPR-Cas9 knockout of the candidate genes led to defects in lymphangiogenesis in development, but their mechanistic roles and contribution in disease have yet to be characterised. This project will use CRISPR-Cas9 generated stable knockout mutants of novel receptors important for lymphangiogenesis. Detailed characterisations of the mutants' lymphatic phenotypes will be conducted using state-of-the-art spinning disc confocal microscopy. Specific drugs for the target receptors will be applied to examine molecular pathways that are involved following receptor(s) activation. The results obtained will be validated using human lymphatic cell lines, genomics will be used to probe receptor roles in cancer and homology modelling is an optional approach to further shed light on receptor/ligand interactions. This project has translational potential and can enhance our understanding of lymphangiogenesis in both development and disease settings.

Key Words: CRISPR-Cas9, Development, Microscopy, Homology modelling, Lymphangiogenesis

Target Students: Honours, Masters, MPhil, PhD

For more information about this project contact:

**Prof Ben Hogan:** ben.hogan@petermac.org

**Dr Wei Chen:** wei.chen@petermac.org

# AVAILABLE PROJECTS BY RESEARCH PROGRAM

## DR NAJOUA LALAOUI

**Inflammatory cell death in cancer and inflammatory diseases**

Supervisor: Dr Najoua Lalaoui

Cell death programs are crucial processes in development, tissue homeostasis and immunity. 'Too much' cell death can lead to neurodegenerative and immune diseases and 'too little' cell death causes cancer. Consequently, re-activation of cell death within tumours is one of the major goals of cancer therapies. Until recently, it was thought that the unique purpose of programmed cell death was to kill cells. However, it has become clear that dying cells release a variety of signals that communicate with the microenvironment and the immune system. Thus, how the body responds to dying cells can influence cancer progression and cancer treatments. RIPK1 and RIPK3 are crucial kinases that regulate inflammatory cell death downstream of various innate immune ligands (e.g. TNF or TLR ligands). The student will work within an existing team to investigate the causes and consequences of cell death induced by RIPK1/3 using a range of cellular, and molecular techniques and in vivo models. This fundamental knowledge will be applied to design new therapeutic strategies for cancer and inflammatory diseases and to understand the impact of inflammatory cell death on cancer immunity and progression.

Key Words: Cancer, Cell Death, Inflammation, Innate Immunity, RIP Kinases

Target Students: Honours, Masters, PhD

For more information about this project contact:

**Dr Najoua Lalaoui:** najoua.lalaoui@petermac.org

## PROF SARAH RUSSELL

**How is fate determined during T cell development, leukemogenesis and responses**

Supervisor: Prof. Sarah Russell

Understanding how cell fate programming works will lead to improved diagnostic and therapeutic opportunities for leukemia, and to improved immunotherapies for cancer and infectious disease. We have developed new methods for imaging single cells and their progeny through many generations of T cell development and activation. These methods mean that we can now assemble pedigrees that describe both the relationships between different differentiation stages, and molecular and behavioral attributes of their ancestors and progeny. The next step is to use these pedigrees and the wealth of information associated with them to determine the relative contributions of genetic, epigenetic, extrinsic and stochastic influences on fate determination This PhD project will involve development of new computational approaches to determine how behaviours in the T cell progeny (differentiation, growth, death, division) are influenced by ancestory, intrinsic and extrinsic cues.

Key Words: Cell Signalling, Cellular Immunology, Differentiation, Haematology, Haematological Cancers, Immunotherapy, Tumour Immunology

Target Students: PhD

For more information about this project contact:

**Prof Sarah Russell:** sarah.russell@petermac.org

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# AVAILABLE PROJECTS BY RESEARCH PROGRAM

## Cancer Biology and Therapeutics Program

### A/PROF KRISTIN BROWN

**Targeting cell metabolism to overcome therapy resistance in cancer**

Supervisor: A/Prof Kristin Brown

Cancer cells exhibit dramatic alterations in their metabolism that serve to support cell growth, cell proliferation and cell survival. Our studies have revealed that metabolic reprogramming is also a component of the highly coordinated response to a variety of anticancer therapies that drives therapy resistance. Importantly, we have shown that the unique metabolic requirements of cancer cells induced by therapy exposure can be targeted for therapeutic gain. The aims of this project will be to:

1. Identify adaptive metabolic reprogramming events triggered by anticancer therapy exposure
2. Determine how these metabolic reprogramming events drive therapy resistance
3. Identify novel therapeutic approaches to exploit adaptive metabolic reprogramming events and sensitise cancer cells to therapy.

Students will gain experience in a variety of cell biology, biochemistry and molecular biology techniques including metabolomics, transcriptomics and CRISPR-Cas9 genetic screens.

Key Words: Cell Metabolism, Therapy Resistance

Target Students: Placements, Honours, Masters, MPhil, PhD

For more information about this project contact:

**A/Prof Kristin Brown:** kristin.brown@petermac.org

**Investigating altered nutrient availability as a microenvironmental factor that drives tumour progression**

Supervisor: A/Prof Kristin Brown

The metabolic state of a cancer cell is dictated by the interplay between cell-intrinsic factors such as genetic alterations, and cell-extrinsic factors including nutrient availability. Research in the field has been dominated by the idea that genetic alterations represent the major driving force underpinning metabolic reprogramming in cancer. However, cancer cells must also undergo extensive metabolic reprogramming to overcome adverse conditions in the tumour microenvironment (TME). There is a growing appreciation that nutrient scarcity is a feature of all solid tumours and that it represents a powerful stressor that cancer cells must overcome to survive in the TME.

Surprisingly, the mechanisms cancer cells employ to adapt to the deleterious effects of nutrient scarcity remain poorly understood. The aims of this project will be to:

1. Identify adaptive metabolic reprogramming events triggered by nutrient scarcity.

2. Determine how these metabolic reprogramming events drive cell survival and cell proliferation.

3. Identify novel therapeutic approaches to target cancer cells that have adapted to nutrient scarcity Students will gain experience in a variety of cell biology, biochemistry and molecular biology techniques including metabolomics, transcriptomics and CRISPR-Cas9 genetic screens.

Key Words: Cell Metabolism, Nutrients, Therapy

Target Students: Placements, Honours, Masters, MPhil, PhD

For more information about this project contact:

**A/Prof Kristin Brown:** kristin.brown@petermac.org

# AVAILABLE PROJECTS BY RESEARCH PROGRAM

## A/PROF MELANIE ECKERSLEY-MASLIN

**Investigating novel epigenetic regulators using embryonic stem and cancer models**

Supervisor: A/Prof Melanie Eckersley-Maslin

Epigenetics helps define current cell states, yet also shapes how cells respond to external cues such as differentiation or stress. The epigenetic plasticity of a cell describes how flexible this regulation is. Early embryonic cells are highly plastic in that they are able to generate all adult cell types. As development progresses, this plasticity is lost as normal healthy adult cells are locked in their identity. Crucially, aberrant reactivation may contribute to pathologies such as cancer. Our laboratory explores how epigenetic plasticity is controlled and regulated in development, applying these principles to understand how it is exploited by cancers. This project will investigate a class of poorly understood epigenetic regulators that are associated with severe developmental disorders and also implicated in cancers. The project will use high throughput CRISPR screens to systematically assess functional importance of these epigenetic regulators in embryonic stem cell and/or cancer cell models. Subsequent molecular experiments will uncover the mechanism and functional significance of these epigenetic regulators in shaping developmental and/or cancer processes. The prospective student will have the opportunity to use a range of cutting-edge technologies including chromatin assays, CRISPR-Cas genome engineering, epigenomic and transcriptomic analyses, cell culture and molecular biology techniques. The project is suitable for a student wishing to be solely lab based or those who also wish to do both experiments and bioinformatic analysis.

Key Words: Bioinformatics, Chromatin, Epigenetics, Plasticity, Next Generation Sequencing, Stem Cell Biology

Target Students: Honours, Masters, MPhil, PhD

For more information about this project contact:

**A/Prof Melanie Eckersley-Maslin:** melanie.eckersley-maslin@petermac.org

**Discovering regulators of lineage plasticity in non-small cell lung cancer**

Supervisors: A/Prof Melanie Eckersley-Maslin, Dr Janith Seneviratne

Lung cancer is the leading cause of cancer-related deaths world-wide. A significant factor in the high death rate of lung cancer is the acquisition of resistance to targeted therapies in patients. This is exemplified in a rare subtype of non-small cell lung cancer patients treated with targeted therapies who have good initial therapeutic responses but then experience disease recurrence due to "lineage plasticity". Lineage plasticity refers to the ability of cells to transition from one committed cellular behaviour to another. Lineage plasticity enables lung cancer cells to completely transform and escape therapy. Currently there are no therapies to combat lineage plasticity in lung cancer patients due to the absence of any clear actionable targets to develop drugs against. This project will aim to identify novel regulators of lineage plasticity in non-small cell lung cancer. The project will use an in vitro cell line model of non-small cell lung cancer that is both capable of, and reports upon, lineage plasticity. The prospective student will have the opportunity to use a range of cutting-edge technologies including; CRISPR-Cas9 genetic knockout screens, epigenomic and transcriptomic analyses, cell culture and molecular biology techniques. The project is suitable for a student wishing to be solely lab based or those who also wish to do both experiments and bioinformatic analysis.

Key Words: Bioinformatics, Chromatin, Epigenetics, Plasticity, Next Generation Sequencing, Non-Small Cell Lung Cancer, Screening

Target Students: Honours, Masters, MPhil

For more information about these projects contact:

**A/Prof Melanie Eckersley-Maslin:** melanie.eckersley-maslin@petermac.org

**Dr Janith Seneviratne:** janith.seneviratne@petermac.org

**Using machine learning to uncover how developmental transcriptional programs contribute to cancer**

Supervisor: A/Prof Melanie Eckersley-Maslin

The Eckersley-Maslin laboratory, based at Peter MacCallum Cancer Centre, uses both computational and experimental approaches to investigate the epigenetic and chromatin regulation of cell identity and adaptation using development and cancer models. Many principles of embryonic development are shared with cancers. In both contexts, cells readily acquire new identities, which are otherwise constrained in healthy adult cells. Embryonic cells and cancer cells have high proliferative potential and have the capacity to generate heterogeneous mixtures of cell types and states. Accordingly, cancers often undergo dedifferentiation and upregulate transcripts associated with stem cells and embryonic states. We have recently applied machine learning to systematically assess the extent and impact of upregulating transcriptional networks associated with the earliest stages of human embryonic development in cancers. In many contexts, upregulation of transcripts associated with early embryonic states is associated with altered outcomes for patients. In this project we will extend these models to include other important

developmental stages using the existing frameworks. This project will involve collating and integrating transcriptomic datasets to build developmental atlases, training and validating machine learning models, testing models on simulated datasets and ultimately running the models on large cancer datasets (e.g. TCGA, CCLE). Note that this is a dry lab-only project.

Key Words: Bioinformatics, Epigenetics, Plasticity

Target Students: Honours, Masters

For more information about these projects contact:

**A/Prof Melanie Eckersley-Maslin:** melanie.eckersley-maslin@petermac.org

**Regulation and function of bivalent chromatin in facilitating cellular plasticity**

Supervisor: A/Prof Melanie Eckersley-Maslin

A major challenge in eliminating cancer is its inherent plasticity. Research in our lab uses insights from development to give new perspectives into how cancer cells acquire heightened plasticity in the absence of additional genetic mutations. One example of epigenetic plasticity is bivalent chromatin, characterised by the co-occurrence of both activating and repressive histone modifications on the same chromatin fragment. It is typically found at gene promoters and thought to hold these sequences in a poised state for future expression or silencing. Crucially we do not understand the molecular regulation of bivalent chromatin hampering our ability to target this feature of plasticity. Bivalent chromatin is best understood in stem cells where it is most abundantly found, however cancer cells have also been described to have bivalent chromatin. Crucially, we do not know how bivalent chromatin is targeted to specific DNA regions and whether it promotes aspects of cellular plasticity.

The aim of this project is to characterise bivalent chromatin in both stem cell and cancer cell models to further understand the regulation and functional importance of this unique molecular structure. The study will involve both wet-lab and bioinformatic aspects and employ a range of techniques including cell culture, molecular cloning, flow cytometry, microscopy, CRISPR-technologies, epigenomics and bioinformatics. This discovery-project will reveal new insights into epigenetic plasticity required to develop future therapeutic strategies targeting cancer cell plasticity.

Key Words: Bioinformatics, Bivalent Chromatin, Chromatin, Epigenetics, Next Generation Sequencing, Plasticity, Stem Cell Biology

Target Students: PhD

For more information about this project contact:

**A/Prof Melanie Eckersley-Maslin:** melanie.eckersley-maslin@petermac.org

## PROF RICKY JOHNSTONE

**Molecular interrogation and therapeutic exploitation of dysregulated RNA Pol II transcription-cycles in cancer.**

Supervisors: Dr Jennifer Devlin, Prof Ricky Johnstone

Tightly controlled gene expression is essential for normal cellular development and homeostasis, and the dysregulation of gene expression is a universal feature of human disease and a hallmark of cancer. RNA polymerase II (Pol-II) dependent transcription of protein-coding genes is a highly coordinated, multi-stage process that is controlled by an expansive range of epigenetic and non-epigenetic regulators. Mutations impacting the expression and/or function of these regulators can lead to aberrant Pol-II transcriptional activity resulting in oncogenic gene expression and tumorigenesis. Pol-II progression through distinct transcriptional checkpoints (recruitment, initiation, pausing, elongation, termination) is controlled by a family of transcriptional-cyclin-dependent-kinases (tCDKs) including CDK7, CDK8, CDK9, CDK10, CDK11, CDK12, CDK13, CDK19 and CDK20. This project will use complementary genetic and pharmacological systems, and molecular biology and biochemistry experimental approaches, to investigate the mechanisms through which tCDKs regulate Pol-II transcription in normal and cancer cells. Key questions this project can address are:

1. How do independent tCDKs co-operate to modulate Pol-II transcription?

2. What are the molecular functions of understudied tCDKs (CDK10, CDK19, CDK20) for the control of gene expression in normal and cancer cells?

3. How can pharmacological inhibitors of tCDKs most effectively be used as therapeutic strategies for aggressive solid and blood cancers?

Key Words: Anti-Cancer Therapeutics, Biochemistry, Cancer Cell Biology, CRISPR-Cas9 Gene Editiing, Gene Regulation, Molecular Biology, Next-Generation Sequencing, Proteomics, Transcription

Target Students: MPhil, PhD

For more information about this project contact:

**Dr Jennifer Devlin:** jennifer.devlin@petermac.org

# AVAILABLE PROJECTS BY RESEARCH PROGRAM

**Investigating the molecular mechanism of mRNA stability in leukemia**

Supervisors: Dr Mary-Jane Tsang, Prof Ricky Johnstone

Messenger RNA (mRNA) is the fundamental link between the genetic information stored in DNA and the production of proteins necessary for cellular activities. Once produced, mRNA molecules persist for some time before being destroyed. This balance of synthesis and decay determines how much mRNA is present for each gene and that dictates cell identity and whether a cell is "normal" or cancerous. Aberrant levels of the oncogene c-MYC have been implicated in cancer formation and progression. Our lab developed a reporter system using a stabilized chimeric c-MYC mRNA transcript that decouples effects on c-MYC transcription from those on mRNA stability. Surprisingly, differences in mRNA stability are observed between global transcription inhibition and inhibition of selective targets using epigenetic drugs. This project will use molecular biology, genetics, biochemistry, and cell biology to identify novel or alternative mRNA decay pathways that either specifically target c-MYC or target a broad range of substrates.

Key questions that will be addressed are:

- How do cells respond differently to global transcriptional inhibition and selective inhibition by epigenetic drugs by focusing on c-MYC transcription and mRNA stability?
- What are novel cellular factors mediating mRNA decay upon transcriptional inhibition and how do they regulate mRNA stability in leukemia?

Key Words: CRISPR-Cas9 Gene Editing, Epigenetics, Gene Regulation, Molecular Biology, mRNA Stability, RNA Decay. Transcription

Target Students: Honours

For more information about this project contact:

**Dr Mary-Jane Tsang:** maryjane.tsang@petermac.org

**Manipulating T cell differentiation for more effective anti-cancer immunotherapies**

Supervisors: Dr Dane Newman, Prof. Ricky Johnstone

The clonal expansion of CD8+ T cells upon antigen activation is a remarkable process, with a single naïve T cell capable of producing thousands of activated progeny. Naïve T cells have stem-like properties and following antigen-induced expansion, they impute a complex array of environmental and cell-intrinsic stimuli and differentiate into a functionally diverse mix of T cell phenotypes. Notably, from a clinical perspective, the different T cell subsets also display different levels of anti-cancer activity, with those exhibiting stem-like or memory attributes being therapeutically superior to their more terminally differentiated counterparts. Understanding the environmental signals and epigenetic processes that influence T cell differentiation trajectories and 'fate-decisions' is therefore critical in the design and development of potent anti-cancer immunotherapies. Our team has recently developed a unique cytokine-conditioning approach that promotes the differentiation of a distinct form of stem-like CD8+ T cell with potent anti-tumour activity. We now aim to interrogate the environmental cues and underlying molecular signals that are necessary for the formation and propagation of these stem-like T cells, with the ultimate aim of increasing their abundance in cancer patients and transforming clinical outcomes. In this honours project, the student will employ sophisticated molecular biology techniques, high-throughput screening methods, multiplexed flow cytometry, T cell activation and cytotoxicity assays, and mouse tumour models to better understand the formation of stem-like CD8+ T cells in vitro and in vivo and discover new strategies to harness their therapeutic potential.

Key Words: CD8+ T Cells, Cell Signalling, Cytokines, Epigenetics, Immunotherapies, T cell differentiation

Target Students: Honours

For more information about this project contact:

**Dr Dane Newman:** dane.newman@petermac.org

**Characterisation of the complex interplay between transcriptional and chromatin modifying enzymes to regulate gene expression**

Supervisors: Prof Ricky Johnstone, Prof Jake Shortt, Prof Saverio Minucci

RNA polymerase II (Pol II) transcription is regulated across multiple distinct yet interconnected layers, including: a) the 3D organisation of the genome, b) global and localised modification of histone proteins and DNA (epigenetic regulation), and c) the coordinated activities of the multi-subunit Pol II complex, general and specific transcription factors, RNA processing modules (including splicing, cleavage, and polyadenylation factors) at individual genes. At each gene Pol II must complete a 'transcription cycle' progressing through distinct phases to produce mRNA transcripts. Progression through transcription cycle stages is controlled by a family of transcriptional cyclin-dependent-kinase/cyclin complexes (tCDKs), with roles described for CDK8 (recruitment), CDK7 (initiation), CDK9 (pausing/release, termination), and CDK12/CDK13 (elongation). Moreover, we have identified the PP2A-integrator complex as a phosphatase-containing complex that opposes the activity of

# AVAILABLE PROJECTS BY RESEARCH PROGRAM

CDK9 and potentially other CDKs to fine tune transcription in a highly dynamic manner. Interestingly, environmental conditions (such as nutrient availability) have a profound impact on these events and regulate the activity of PP2A, though the mechanistical implications remain largely unknown. We are interested to understand how transcriptional CDKs, PP2A and other transcription/chromatin regulatory proteins are dynamically recruited to or evicted from chromatin in response to different endogenous or exogenous stimuli.

This is a collaborative research project between The Faculty of Medicine, Nursing and Health Sciences at Monash University, the Peter MacCallum Cancer Centre and the Italian Institute for Genomic Medicine. The collaboration will allow students to spend up to 12 months of their PhD abroad in Italy.

Key Words: Biochemistry, Gene Expression, Molecular Biology, RNA Polymerase II

Target Students: PhD

For more information about this project contact:

**Prof Ricky Johnstone:** ricky.johnstone@petermac.org

## A/PROF LEV KATS

**Understanding and targeting heme metabolism in acute myeloid leukaemia**

Supervisors: Dr Alexander Lewis and A/Prof Lev Kats

Acute myeloid leukaemia (AML) is an aggressive and deadly blood cancer and is the most common acute leukaemia in adults. Identification of metabolic pathways that are dysregulated in AML offers significant promise for the development of new therapeutic strategies. Heme is an essential metabolite with broad biological activity that is required and produced by all cells. In addition to its catalytic role as a cofactor in hemoproteins, heme also directly regulates signalling and gene expression. We and others have shown that heme biosynthesis is transcriptionally suppressed to varying degrees by AML driver mutations, but whether or not this results in reduced heme levels in leukaemic cells has not been systematically analysed. Moreover, the implications for metabolomic and transcriptional pathways that are controlled by heme remain unexplored. In this project we aim to:

1. Characterise heme metabolism in AML using metabolomics and functional genomics.
2. Investigate the function of heme in regulating self-renewal and leukaemic stem cells (LSCs).
3. Develop new treatment paradigms for selective targeting of low heme AML cells.

Key Words: Cancer Metabolism, Haematological cancers, Leukaemic Stem Cells, Targeted Therapies

Target Students: Honours, PhD

For more information about this project contact:

**A/Prof Lev Kats**: lev.kats@petermac.org

**A Swiss Army knife approach for targeting therapy resistant multiple myeloma**

Supervisors: Dr Emily Gruber and A/Prof Lev Kats

Multiple Myeloma (MM) is a common, incurable plasma cell malignancy with an urgent unmet need for new therapies. MM cells are peculiar in their susceptibility to drugs disrupting protein homeostasis, such as proteasome inhibitors and immunomodulatory thalidomide analogues (IMiDs; e.g. lenalidomide). IMiDs modulate cereblon (CRBN), a substrate recognition subunit of the CRL4 E3 ubiquitin ligase complex that regulates proteasomal degradation of various client proteins. IMiDs engage CRBN and redirect the CRL4-CRBN complex to ubiquitinate neosubstrates, most notably the essential MM transcription factors IKZF1 and-3. The finding that IMiDs can induce targeted proteolysis represented a paradigm shift not only for MM, but for drug design more generally, and led to the development of a novel class of small molecules termed PROTACs. PROTACs are hetero-bifunctional compounds that link E3 ligase complexes with protein targets promoting their ubiquitination and degradation via the ubiquitin proteasome system. Although still in their infancy, PROTACs hold significant promise for drugging non-enzymatic proteins that may be difficult to modulate using more traditional drug design.

We reasoned that the identification of further E3 ligase substrate receptors that are essential in MM cells would enable a ‘Swiss Army knife’ approach to the development of novel anti-myeloma agents that would significantly increase the efficiency of our medicinal chemistry efforts. Not only could molecules that effectively bind to such proteins directly kill MM cells, but they could also be leveraged to design PROTACs with CRBN-independent anti-MM activity. We have identified VPRBP as a pan-essential gene in MM. VPRBP is a highly unusual substrate receptor that can direct ubiquitination of target proteins via two distinct E3 ubiquitin ligase complexes, the RING-type CRL4 complex and the HECT-type DYRK2/UBR5 complex. As VPRBP is a multi-domain, multi-functional molecule it can potentially be targeted by a range of medicinal chemistry strategies. Notably however, lack of fundamental knowledge of VPRBP biology in MM is a significant obstacle to these endeavours. In this project, we posit that VPRBP represents a distinct ‘druggable’ vulnerability

in MM that may be orthogonally targeted in a domain-specific manner by distinct small molecules, and seek to define key mechanistic determinants by which loss of VPRBP function induces MM cell death.

Key Words: Cancer Cell Biology, Functional Genomics, Haematological Cancers, Proteomics

Target Students: Honours, PhD

For more information about this project contact:

**A/Prof Lev Kats:** lev.kats@petermac.org

## PROF GRANT MCARTHUR

**Combining Novel Targeted Therapies With Immunotherapies in Melanoma**

Supervisors: A/Prof Karen Sheppard, Dr Reem Saleh

The development of both targeted and immune therapies has revolutionized the treatment of advanced-stage melanoma and improved the outcomes of patients. Unfortunately, the current BRAF/MEK targeted and immune therapies have limitations. Typically, targeted therapies are associated with very high initial response rates, followed by drug tolerance and then tumour progression. In contrast, immunotherapies provide more durable responses but have lower response rates. Current BRAF/MEK targeted therapies can alter the melanoma immune microenvironment, likely making it more amenable to immunotherapy. Thus, combining targeted therapy with immunotherapies might overcome the clinical limitation of the individual classes of therapy and potentially lead to more durable responses and even cure. Furthermore, novel targeted therapies are being developed that may overcome the development of resistance. This study aims to understand therapy-induced time-dependent changes in tumour cells and their microenvironment with both current and novel targeted agents. Understanding these changes will assist in the development of optimal scheduling strategies for combining targeted and immune therapies.

Key Words: Animal Models, Cancer Cell Biology, Melanoma

Target Students: Honours, PhD

For more information about this project contact:

**A/Prof Karen Sheppard:** karen.sheppard@petermac.org

**Novel approaches to evaluate tumour metabolism in melanoma**

Supervisor: Dr Aparna Rao, Prof Grant McArthur

Targeted therapies and immunotherapy have dramatically improved outcomes for patients with melanoma. However, many patients still succumb to metastatic disease highlighting the need for novel insights into the biology of this disease that can lead to innovative approaches to prevent metastasis and overcome therapeutic resistance. One aspect of melanoma biology that has recently garnered interest, in terms of both biomarker and therapeutics research, is cancer metabolism. Importantly, with recent ground-breaking technological developments in the field of cancer metabolism we now can directly evaluate tumour metabolism in patients, presenting an opportunity to harness these approaches to understand how metabolic phenotypes link with therapeutic response and resistance. We have established a translational research protocol in which patients with melanoma are administered peri-operative infusions of 13C-glucose to understand tumour fuel utilisation, using the technique of stable isotope tracing. Our preliminary analysis has highlighted the importance of glucose oxidation in melanoma. In this project, we aim to fully characterise oxidative metabolism in pre-clinical models of melanoma, using a novel PET tracer (18FBnTP), that measures changes in mitochondrial membrane potential, with the translational aim of developing a less invasive method to assess oxidative metabolism in melanoma. Specifically, this project will use a combination of syngeneic mouse models of melanoma and patient-derived xenografts, complementing our 13C-glucose infusion studies with standard-of-care FDG-PET and 18FBnTP-PET to ultimately investigate whether this dual imaging approach may identify highly oxidative melanomas, which may have prognostic implications. In addition, this combined approach will be used in the context of therapies (namely BRAF/MEK inhibition and immune checkpoint inhibition) to evaluate changes in metabolic phenotypes in the setting of both response and resistance to therapy.

Key Words: Cancer Cell Biology, Cell Signalling, Gene Regulation, New Cancer Treatments, RNA

Target Students: PhD

For more information about this project contact:

**Dr Aparna Rao:** aparna.rao@petermac.org

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# AVAILABLE PROJECTS BY RESEARCH PROGRAM

## Cancer Evolution and Metastasis Program

### A/PROF KARA BRITT

**The role of the macrophages in early breast lesions**

Supervisors: A/Prof Kara Britt, Prof Phil Darcy

Breast cancer is not considered immunogenic, as its incidence is not increased in immune suppressed patients (transplant patients and HIV patients). However, irrefutable data now show that the immune cell infiltrate of a breast cancer affects its growth and metastasis. Only limited data exist on the role of immune cells in the early stages of BCa. We have preliminary data showing that macrophages are important during the development of breast cancer. This project is focussed on testing macrophage targeting therapies in preclinical models to determine if we can block/delay cancer initiation. In addition to understanding the immune control of early cancer development, our goal is to delay tumour onset by orchestrating an anti-tumour immune microenvironment.

Key Words: Breast Cancer, Immune cells

Target Students: PhD

For more information about this project contact:

**A/Prof Kara Britt:** kara.britt@petermac.org

**Deciphering the mechanism between the APOBEC deletion polymorphism and breast cancer risk and mutagenesis.**

Supervisors: A/Prof Kara Britt, Dr Conor McGuinness and A/Prof Laura Forrest

APOBEC enzymes are known to cause somatic mutagenesis in breast cancer. A polymorphism that affects the APOBEC3B gene is associated with heightened breast cancer risk and a greater number of APOBEC mutations in breast tumours. This polymorphism is found at a relatively high frequency in non-European populations, including Indigenous Australians. APOBEC mutagenesis has been associated with poor response to standard of care treatments such as hormone therapy, but potentially enhanced response to immune checkpoint blockade. Therefore, we hypothesise that carriers of the polymorphism could benefit from targeted immunotherapy responses. Using cutting edge genomic techniques such as deep mutation profiling, scRNAseq, and multiplex immunofluorescence, we will decipher exactly how the polymorphism breast epithelial and immune cells. Additionally, there is an opportunity for engagement with Indigenous communities to inform governance of tissue and genomic data associated with this project. This process will follow guidelines for the establishment of partnerships between researchers and donors and use a qualitative approach to determine tissue and data governance for this research program. Students with Aboriginal/Torres Strait Islander background are strongly encouraged to apply.

Key Words: Indigenous health, breast cancer, immunotherapy

Target Students: Honours, PhD

For more information about this project contact:

**A/Prof Kara Britt:** kara.britt@petermac.org

**Determine how obesity impacts the breast to drive an increase in cancer risk**

Supervisors: A/Prof. Kara Britt, Prof Phil Darcy, A/Prof Kristin Brown

Obesity doubles the risk of developing hormonally driven breast cancer (75% of all breast cancers) yet we still do not know how it increases risk. This project will use our expertise in breast cell isolation, single cell sequencing and functional assays to determine how the breast epithelial and immune cells change in obese compared to lean women. The project involved collecting fresh human breast tissue and processing with numerous protocols to obtain cell number, activity and transcriptional changes. We will also work with international clinical collaborators to further our research using clinical samples from obese and lean women and those treated with anti-obesity drugs and surgery.

Key Words: Breast Cancer, Cancer Prevention, Human Samples, scRNAseq

Target Students: PhD

For more information about this project contact:

**A/Prof Kara Britt:** kara.britt@petermac.org

# AVAILABLE PROJECTS BY RESEARCH PROGRAM

## PROF IAN CAMPBELL

**Exploration of alternative mechanisms of hereditary breast cancer**

Supervisors: Prof. Ian Campbell, Prof Paul James

Pathogenic variants in BRCA1, BRCA2 and PALB2 are major contributors to hereditary breast and ovarian cancer (HBOC) but collectively explain less than a quarter of the families tested in clinical practice, leaving the majority with no identifiable genetic defect to inform cancer prevention strategies. Other HBOC genes explain only a small fraction (<5%) of families. In contrast to the intensive international efforts aimed at discovering new predisposition genes, little attention has been given to the potential for alternative pathogenic mechanisms in the already established HBOC genes. In this project bioinformatics approaches will be used to mine the large-scale genetic/epigenetic data available in the BEACCON study of 12,000 hereditary breast cancer (BC) cases and controls to explore the contribution of non-coding variants and inherited promoter hypermethylation silencing in BC predisposition. The proposed study is also underpinned by the unrivalled clinical and biospecimen resources of the Variants in Practice (ViP) study where data from thousands of hereditary BC family members are accessible for analysis. This study will advance the knowledge in the under-studied field of alternative mechanisms of HBOC predisposition.

Key Words: Bioinformatics, Familial Breast Cancer, Genetics

Target Students: PhD

For more information about this project contact:

**Prof Ian Campbell:** ian.campbell@petermac.org

**Novel cellular models to investigate the mechanism of polygenic risk of breast cancer**

Supervisors: Prof Ian Campbell and Prof Paul James

A large number of common genomic variants have been identified that are associated with differences in the risk of breast cancer (BC) in the general population. In combination these variants explain a large proportion of the heritable component of BC. Combined PRS influences major functional pathways involved in carcinogenesis and also modifies the established functional effects of known BC predisposition genes. Progress toward a functional understanding of these variants has been slow and focused on dissecting variants one locus at a time, despite the fact that it is only through their combined effect- as measured in a Polygenic Risk Score (PRS)- that they have significant impact. This project will take an entirely novel approach by studying induced pluripotent stem cell (iPSC) lines from women who have exceptional BC PRS results that put them into either the lowest or highest 0.1%. The molecular features of these model lines will be characterised, through gene expression studies and mutational signature analysis to measure the effect of polygenic risk on the hallmark pathways of cancer. Finally, mutations in BRCA1 and CHEK2 will be introduced by to examine the modifying effect of the PRS on these established BC genes.

Key Words: Cancer Genetics, Familial Breast Cancer, Polygenic Risk

Target Students: PhD

For more information about this project contact:

**Prof Ian Campbell:** ian.campbell@petermac.org

**Poor outcome breast cancer: Identifying genetic risk factors and new treatments**

Supervisors: Prof Ian Campbell, Prof Paul James

Outcomes for women diagnosed with a breast cancer (BC) <45 years are very poor compared with later onset BC (7% of cases but 15% of deaths). These young women, many of whom are mothers of young children and/or are pregnant at time of BC diagnosis, bear a disproportionality high impact compared to women diagnosed with later onset BC. Discovery of the germline and somatic genetic causes of many BC sub-groups has opened new avenues for effective screening and treatment, but such information is lacking for early onset breast cancers (EOBC). We hypothesise that EOBC differ biologically from other BCs and will be driven by unique predisposing genetic factors and will have therapeutic vulnerabilities that can be exploited to improve prevention and BC treatment. This information will be especially relevant for women at risk of developing a BC during pregnancy (Pregnancy Associated BC; PABC) where women often delay treatment to preserve the health of the baby but at the risk of their own health. We will use our unique cohort of cancer biospecimens to characterise the hereditary and somatic events that underlie the poor prognosis of EOBC and PABC as a means of linking this to modern molecular therapeutics.

Key Words: Bone Metastasis, Breast Cancer, Immune Therapy, Radiotherapy

Target Students: PhD

For more information about this project contact:

**Prof Ian Campbell:** ian.campbell@petermac.org

# AVAILABLE PROJECTS BY RESEARCH PROGRAM

## DR ELIZABETH CHRISTIE

**Analysis of treatment resistance in women's cancers**

Supervisors: Dr Elizabeth Christie

Acquired treatment resistance, whereby patients respond well to primary treatment but eventually develop drug resistance, is common across a range of cancer types. Through analysis of DNA and RNA sequencing data from primary, recurrent and end-stage patient samples this study aims to:

1. Identify acquired resistance mechanisms.
2. Understand their heterogeneity within and between patients.
3. Examine how tumour cells interact and evolve over time in response to chemotherapy.

Specifically, the bioinformatics analysis will identify mutations and expression changes that lead to resistance, and may also involve cell culture or other molecular biology techniques to validate findings. Students will receive training in genomics, bioinformatics and cancer cell biology, working with a team of wet-lab and computational biologists and clinicians.

Key Words: Endometrial Cancer, Genomics, Ovarian Cancer

Target Students: Honours, Masters, PhD

For more information about this project contact:

**Dr Liz Christie:** liz.christie@petermac.org

**Characterising the landscape of HGSC with WGD**

Supervisors: Dr Elizabeth Christie, Dr Nikki Burdett

Whole genome duplication (WGD) affects approximately 60% of high grade serous ovarian cancer (HGSC). Across cancers, WGD causes treatment resistance, increased genomic diversity and worsened survival outcomes. Several studies have suggested differences in the methylation and immune landscape of WGD, but this has not been extensively explored. In addition, we do not understand why one patient develops WGD in their cancer and another does not. This study aims to explore these factors: 1. Assess differences in methylation patterns and immune composition between HGSC with and without WGD 2. Assess whether TP53 mutation characteristics are associated with increased frequency of WGD This project will utilise existing whole genome sequencing, methylation array and RNA sequencing data from the International Cancer Genome Consortium, and TCGA data to validate findings. Methods will include bioinformatic analysis using programs like R. Prior coding (R, python) experience would be beneficial but is not necessary. Validation may include wet lab methods such as immunohistochemistry.

Key Words: Bioinformatics, Genomics, Ovarian Cancer, Whole Genome Duplication

Target Students: Honours

For more information about this project contact:

**Dr Liz Christie:** liz.christie@petermac.org

**Characterising acquired resistance in HR deficient HGSC**

Supervisors: Dr Elizabeth Christie

Acquired treatment resistance, whereby patients respond well to primary treatment but eventually develop drug resistance, is common in high-grade serous ovarian cancer (HGSC). In our previous work, we observed that many of the acquired resistance mechanisms in homologous recombination (HR) deficient HGSC were subclonal. Therefore, the aims of this project are to:

1. Identify additional non-genetic mechanisms of resistance
2. Investigate interactions between cancer cell populations that may contribute to treatment resistance.

The project will utilise transcriptomic and proteomic profiling in addition to multiplex immunofluorescence applied to HGSC patient samples to identify resistance mechanisms. To investigate the interactions occurring between different subclones, genetic barcoding will be applied to cell line and organoid models, which will be exposed to various treatments and single cell sequencing performed.

Key Words: Ovarian Cancer, Treatment Resistance

Target Students: PhD

For more information about this project contact:

**Dr Liz Christie:** liz.christie@petermac.org

**Investigating cell surface proteins as drug targets in ovarian cancer**

Supervisors: Dr Elizabeth Christie, Dr Kathleen Pishas

Resistance to chemotherapy and targeted therapy is a substantial challenge in the clinical management of patients with ovarian cancer. More effective treatments are needed to improve outcomes for ovarian cancer patients. Cell surface proteins, which differ among cell types and disease states, are attractive as biomarkers and drug targets due to their accessibility on the cell surface. We have performed cell surface proteomics on cell lines developed from ovarian cancer patients who developed treatment resistance, and identified proteins that represent potential drug targets. In this project you will Test whether drugs targeting the identified cell surface proteins are capable of killing cancer cells. Examine expression of these targets in patient samples and associations with patient outcomes and response to treatment.

# AVAILABLE PROJECTS BY RESEARCH PROGRAM

Key Words: Drug Targets, Ovarian Cancer

Target Students: Honours

For more information about this project contact:

**Dr Liz Christie:** liz.christie@petermac.org

## A/PROF NICHOLAS CLEMONS

**Characterisation of immune responses specific for preneoplastic lesions predisposing to oesophageal adenocarcinoma**

Supervisors: Prof. Riccardo Dolcetti and A/Prof. Nicholas Clemons

Esophageal adenocarcinoma (EAC) arises from Barrett's esophagus (BE), a precancerous replacement of squamous by columnar epithelium in response to chronic inflammation due to gastro-oesophageal reflux. Once diagnosed, patients with BE are kept on surveillance to detect progression so that timely intervention can occur with endoscopic therapy. Although several demographic and clinical risk factors are known to increase progression toward EAC, a reliable identification of patients at risk of malignant progression is still unavailable. Considering the inflammatory microenvironment that characterises BE, these patients may mount an abnormal immune response against proteins that are aberrantly overexpressed in these lesions. We will therefore identify immunogenic epitopes provided by proteins aberrantly overexpressed in BE and belonging to signaling pathways involved in the pathogenesis of BE, such as the Hedgehog pathway. Immunogenicity of these epitopes will be functionally validated using a reliable pipeline established in the lab. The presence of T cell responses specific for these epitopes will be investigated and characterised in blood samples prospectively collected from patients with BE or overt EAC representative of different stages of these diseases. A cohort of healthy donors will be also investigated as a negative control. The results obtained will allow us to assess whether these abnormal immune responses may serve as biomarkers predictive of the evolution of BE towards overt EAC. The immunogenic epitopes identified may be also exploited to develop vaccines potentially able to prevent this malignant evolution in patients at high risk.

Key Words: Adaptive Immunity, Anti-Tumour Immunity, Barret's oesophagus, Cancer Vaccines, Immunogenicity, Immunomonitoring, Immunotherapy, Oesophageal denocarcinoma, Tumour Antigens

Target Students: MRes, PhD

For more information about this research project contact:

**Prof Riccardo Dolcetti:** riccardo.dolcetti@petermac.org

**A/Prof Nicholas Clemons:** nicholas.clemons@petermac.org

## PROF KYLIE GORRINGE

**New therapies for mucinous ovarian cancer**

Supervisor: Prof Kylie Gorringe

The Gorringe lab has an ongoing program of research investigating a rare ovarian cancer subtype, mucinous ovarian carcinoma. This disease has no effective chemotherapies and women with advanced disease have dire clinical outcomes. We have a cohort of ~200 mucinous tumours, remarkable for such a rare disease, including with clinical, immunohistochemical, gene expression and genomics data (sequencing and copy number). We have an active tumour organoid program and are developing PDX models from primary patient material with which to test therapies. We will test existing therapies and combinations in these new patient models and discover new ones using our unique data set. This program would best suit a student looking for hands-on laboratory experience in cell culture, cancer drug discovery and 3D screening. In addition, we have an NHMRC-funded project to explore the cancer cell of origin for MOC. This would suit a student interested in spatial transcriptomics, genomics and bioinformatics.

Key Words: Bioinformatics, Cancer, Ovarian Therapy

Target Students: Masters, MPhil, PhD

For more information about this project contact:

**Prof Kylie Gorringe:** kylie.gorringe@petermac.org

## PROF BELINDA PARKER

**Enhancing immune targeting of metastatic cancers**

Supervisors: Prof Belinda Parker, Dr Nicole Haynes

Despite high 5-year survival rates, breast and prostate cancer remain the second leading cause of cancer-related deaths in Australia due to metastatic recurrence. Upon diagnosis of metastatic disease, the 5-year survival rate drops to less than 30%, emphasising the critical need for strategies to target metastases. A common feature of metastatic cancers is reduced cancer cell immunogenicity, rendering aggressive cancers invisible to the immune system and resistant to immunotherapy. Our laboratory has uncovered the key pathways in cancer cells that control cancer cell visibility and we now want to harness these discoveries to develop novel metastasis-specific therapies for breast and prostate cancer patients. This project utilizes preclinical metastasis models along with patient-derived tissues to dissect mechanisms of reduced immunogenicity and new therapeutic strategies to restore immune signaling and response to radiotherapy and immune checkpoint inhibitors. Key techniques include cell culture, organoid culture, mouse models of metastasis, histopathology, Opal multiplex immunostaining, T cell derivation and anti-tumour function assays, therapeutic

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screening, preclinical radiotherapy delivery, in vivo imaging, flow cytometry.

Key Words: Cytokines, Breast Cancer, Immune Therapies, Metastasis, Organoids, Prostate Cancer

Target Students: Honours, PhD

For more information about this project contact:

**Prof Belinda Parker**: belinda.parker@petermac.org

**Targeting bone metastases with radiation therapy**

Supervisors: Prof Belinda Parker and Dr Nicole Haynes

Bone is the most common site of metastasis in breast and prostate cancer patients. Once established, bone metastases significantly increase patient morbidity, with limited curative options. Radiation therapy (RT) remains a cornerstone of skeletal metastasis management, with 60-70% of patients receiving RT to alleviate pain and preserve bone integrity. However, its full therapeutic potential is constrained by loss of key immune responses in bone metastases. This project will test ways to enhance local and distant (abscopal) bone metastasis responses to radiotherapy using novel models of cancer and state-of-the-art RT and imaging equipment. Key techniques include: modelling metastasis, bioluminescence imaging, small animal radiotherapy, immunohistochemistry, flow cytometry and CRISPR-Cas9 technology.

Key Words: Bone Metastatis, Breast Cancer, Immune Therapy, Prostate Cancer

Target Students: Honours, PhD

For more information about this project contact:

**Prof Belinda Parker:** belinda.parker@petermac.org

# AVAILABLE PROJECTS BY RESEARCH PROGRAM

## PROF STEVEN STACKER

**Understanding tissue-specific vasculature in cancer metastasis**

Supervisors: Dr Aadya Nagpal Malhotra, Dr Rae Farnsworth and Prof Steven Stacker

Metastatic spread of cancer cells to distant sites is the most lethal aspect of cancer. It has long been observed that certain tumour types metastasise preferentially to particular distant organs. More recently, evidence has emerged that tumours can pre-emptively remodel these distant tissue environments to promote the future arrival and survival of metastatic cells, generating supportive "pre-metastatic niches"(1,2). Blood and lymphatic vessels throughout the body are frequently hijacked by tumours to promote tumour growth and metastasis. However little is understood about the underlying mechanisms, and how tissue-specific heterogeneity of these vessels affects tumour behaviour at different stages of progression. We have recently conducted single-cell RNA-sequencing to elucidate the unique molecular profiles of organ-specific lymphatic and blood endothelial cells in mouse models of cancer during early stages of metastasis, focussing on lymph node, lung and brain as important metastatic sites. In this project, students will functionally investigate one or more candidate genes arising from these studies using flow cytometry, multiplex immunohistochemistry, organotypic co-culture assays, integrated bioinformatics and molecular and cell biological techniques. Analysis of human tumour samples and preclinical models will further support understanding of the role and therapeutic or prognostic tractability of these candidates.

Key Words: Cancer Microenvironment, Metastasis, Solid Tumours, Transcriptomics, Vascular Biology

Target Students: Honours, Masters, PhD

For more information about these projects contact:

**Dr Aadya Nagpal Malhotra** aadya.nagpal@petermac.org

**Dr Rae Farnsworth** rae.farnsworth@petermac.org

**Prof Steven Stacker** steven.stacker@petermac.org

**Role of the RYK receptor in cancer therapy resistance and epithelial-to-mesenchymal transition**

Supervisors: Dr Aadya Nagpal Malhotra and Prof Steven Stacker

Acquired resistance to cytotoxic therapies becomes a major cause of therapy failure in patients with advanced metastatic cancer. Accordingly, the identification and targeting of novel signalling pathways involved in mediating drug resistance is essential to improving patient responses. Our lab has previously demonstrated a role of the WNT receptor and pseudokinase "RYK" in cancer growth and progression. Importantly, our findings identified a link between the RYK receptor and TGFb-mediated epithelial to mesenchymal transition (EMT), a process that is crucial to cancer metastasis and therapy resistance. This project will utilise advanced cellular and molecular biology techniques to identify the direct role of the RYK receptor in mediating therapy response and EMT. Students will use functional cell biological assays, molecular biology techniques, advanced microscopy, multiplex immunohistochemistry, analysis of cancer patient samples, and preclinical models to dissect the function and therapeutic benefit of targeting the RYK receptor.

Key Words: Therapy resistance; Epithelial to mesenchymal transition (EMT); Cancer cell signalling; Cancer therapeutics; Growth factor receptors

Target Students: Honours, Masters, PhD

For more information about these projects contact:

**Dr Aadya Nagpal Malhotra:** aadya.nagpal@petermac.org

**Prof Steven Stacker:** steven.stacker@petermac.org

**Developing a CAR T cell targeted to the Wnt receptor RYK**

Supervisors: Dr Rae Farnsworth and Prof Steven Stacker

RYK is a member of the Wnt-binding family of growth factor receptors involved in development and cancer. Using a human monoclonal antibody, we have demonstrated a role for tumour-expressed RYK in TGFβ-mediated epithelial to mesenchymal transition, migration and metastasis. Furthermore, RYK is highly expressed in a broad range of human cancer cell types, and is upregulated in cancer relative to normal tissues, making it a promising therapeutic target. We have now developed a novel chimeric antigen receptor (CAR) T cell targeting the RYK receptor. This project will involve engineering and testing the RYK CAR T cells for optimal efficacy against tumour cells in vitro and in mouse tumour models. Students will utilise molecular biology techniques, viral vector systems, flow cytometry and advanced real-time microscopic imaging techniques to generate and test CAR T cells in vitro. The anti-tumour efficacy of these RYK CAR T cells may also be assessed in mouse models of solid tumours or leukemias, using in vivo imaging, multiplex flow cytometry and multiplex immunohistochemistry to assess their effects and their therapeutic potential.

Key Words: Cancer Therapeutics, CAR-T Cells, Growth Factor Receptors, Immunotherapy

Target Students: Honours, Masters, PhD

For more information about these projects contact:

**Dr Rae Farnsworth:** rae.farnsworth@petermac.org

**Prof Steven Stacker:** steven.stacker@petermac.org

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# AVAILABLE PROJECTS BY RESEARCH PROGRAM

## Cancer Immunology Program

### PROF PHIL DARCY

**Targeting the epigenome to 'armour' CAR-T cells against solid tumours**

Supervisors: Dr Kevin Sek and Prof Phil Darcy

Chimeric antigen receptor (CAR) T cell therapy involves genetic engineering of a patients' own immune cells to express a synthetic receptor that recognises tumour antigens and drives potent tumour killing. CAR T cell therapy is highly efficacious against certain leukemias. However, it has shown only moderate effects in solid cancers. Our lab has established state-of-the-art technologies to enhance CAR-T cell function, including Single-cell resolution sequencing, CRISPR/Cas9 gene-editing and Viral or non-viral Lipid Nanoparticle gene-delivery platforms. In this project, the student will (i) explore the transcriptome and epigenome (multi-ome) of CAR-T cells at the single-cell level, (ii) utilize the aforementioned tools to armour' CAR-T cells, and (iii) demonstrate their enhanced ability to treat cancer in both mouse models and with patient-derived products. The outcomes of this project could lead to the development of a novel next-generation CAR-T cell product with potential for rapid clinical translation.

Key Words: CAR-T cells, CRISPR-Cas9, Multi-omics, Epigenetics

Target Students: Honours , PhD

For more information about these projects contact:

**Dr Kevin Sek:** kevin.sek@petermac.org

**Prof Phil Darcy:** phil.darcy@petermac.org

**Flexible Adaptors Empower CD19-CAR T Cells to Overcome Solid Tumour Barriers**

Supervisors: Dr Clare Slaney, Prof Phil Darcy and Prof Michael Dickinson

Chimeric Antigen Receptor (CAR) T cell therapy has transformed treatment for CD19$^{+}$ blood cancers but remains largely ineffective in solid tumours. Our previous work revealed that CD19-CAR T cells outperform solid tumour-targeting CARs in binding strength, intracellular signalling and in vivo efficacy. To extend this advantage, we have engineered bispecific adaptor proteins that link CD19-CAR T cells to solid tumour antigens such as HER2 and mesothelin. In this project, the student will design, produce, and test a novel adaptor molecule-contributing a key component to a broader therapeutic platform. They will evaluate the adaptor's ability to redirect CD19-CAR T cells to kill antigen-expressing tumour cells in vitro. If successful, they will test the strategy in preclinical solid tumour models. This work offers hands-on training in molecular design, cancer immunotherapy, and in vivo experimentation, and gives the student the opportunity to develop a therapeutic tool that could become a lasting part of our adaptor-CAR pipeline.

Key Words: Bispecific, Cancer Immunotherapy, CAR-T, Solid Tumours

Target Students: Honours, Masters, PhD

For more information about these projects contact:

**Dr Clare Slaney:** clare.slaney@petermac.org

**Prof Phil Darcy:** phil.darcy@petermac.org

**Prof Michael Dickinson:** michael.dickinson@petermac.org

# AVAILABLE PROJECTS BY RESEARCH PROGRAM

## PROF RICCARDO DOLCETTI

**Development of improved cancer vaccines to enhance the efficacy of immunotherapy combination strategies**

Supervisors: Prof Riccardo Dolcetti, Dr Roberta Mazzieri, Dr Bijun Zeng

Despite the ability of cancer vaccines to generate brand new and strong anti-tumour immune responses, their therapeutic efficacy is still unsatisfactory. This is due to the limited potency and antigen-specificity of available cancer vaccines, which need to be combined with other treatments to overcome the local immune suppression of tumour microenvironment. This project aims at developing new classes of clinically applicable cancer vaccines targeting tumours with limited inherent immunogenicity by exploiting our recently developed nanoparticle-based vaccination platform targeting cross-presenting dendritic cells in vivo. Novel and more immunogenic antigen formulations will be identified and therapeutically validated in different preclinical cancer models.

To overcome immunotherapy resistance and local immunosuppression typically associated with tumour progression, the project will explore mechanism-based combination therapies, also including cell- and gene-based strategies for the tumour targeted delivery of biomolecules. Proof of feasibility, efficacy, and safety, as well as insights into therapy induced immune modulation will be provided using both murine and humanised models of primary and metastatic tumours, including melanoma, breast, liver and brain cancers.

Key Words: Adaptive Immunity, Anti-Tumour Immunity, Brain Metastasis, Brain Tumour, Breast Cancer, Cancer Vaccines, Humanised Mouse Models, Immunogenicity, Immunotherapy, Melanoma, Neo-Antigens, Tumour Antigens

Target Students: PhD

For more information about these projects contact:

**Dr Roberta Mazzieri:** roberta.mazzieri@petermac.org

**Identification and characterisation of novel classes of therapeutically relevant tumour neo-antigens.**

Supervisors: Prof Riccardo Dolcetti, Dr Pouya Faridi, Dr Roberta Mazzieri

Knowledge about the peptide repertoire presented by human leukocyte antigens (HLA) holds the key to unlock target-specific cancer immunotherapies as vaccines and adoptive cell therapies. The recent advances in mass spectrometry approaches have greatly improved our ability to comprehensively characterise the HLA immunopeptidome of tumour cells. However, only a fraction of tumour peptides identified by immunopeptidomics strategies are real immunogenic epitopes able to elicit therapeutically relevant immune responses. Through the combination of mmunopeptidomics and an advanced immunogenicity screening pipeline, this project aims at identifying and characterising novel classes of tumour neo-antigens suitable for therapeutic purposes. The immunogenicity of the tumour neo-antigens identified will be also validated by detecting specific T-cell responses in the blood of cancer patients, thus paving the way for the development of new immunoassays for improved monitoring of tumour antigen-specific immune responses in patients treated with immunotherapies. The project will also exploit our nanoparticle-based vaccination platform targeting cross-presenting dendritic cells in vivo to investigate the feasibility and efficacy of vaccination approaches targeting the new antigens identified in suitable humanised mouse models.

Key Words: Anti-Tumour Immunity, Adaptive Immunity, Cancer Vaccines, Humanised Mouse Models, Immunogenicity, Immunomonitoring, Immunopeptidone, Immunotherapy, Neo-Antigens, Tumour Antigens

Target Students: PhD

For more information about these projects contact:

**Dr. Roberta Mazzieri** Roberta.Mazzieri@petermac.org

**Characterisation of immune responses specific for preneoplastic lesions predisposing to oesophageal adenocarcinoma**

Supervisors: Prof Riccardo Dolcetti and A/Prof Nicholas Clemons

Esophageal adenocarcinoma (EAC) arises from Barrett's esophagus (BE), a precancerous replacement of squamous by columnar epithelium in response to chronic inflammation due to gastro-oesophageal reflux. Once diagnosed, patients with BE are kept on surveillance to detect progression so that timely intervention can occur with endoscopic therapy. Although several demographic and clinical risk factors are known to increase progression toward EAC, a reliable identification of patients at risk of malignant progression is still unavailable. Considering the inflammatory microenvironment that characterises BE, these patients may mount an abnormal immune response against proteins that are aberrantly overexpressed in these lesions. We will therefore identify immunogenic epitopes provided by proteins aberrantly overexpressed in BE and belonging to signaling pathways involved in the pathogenesis of BE, such as the Hedgehog pathway. Immunogenicity of these epitopes will be functionally validated using a reliable pipeline established in the lab. The presence of T cell responses specific for these epitopes will be investigated and characterised in blood samples prospectively collected from patients with BE or overt EAC representative of

different stages of these diseases. A cohort of healthy donors will be also investigated as a negative control. The results obtained will allow us to assess whether these abnormal immune responses may serve as biomarkers predictive of the evolution of BE towards overt EAC. The immunogenic epitopes identified may be also exploited to develop vaccines potentially able to prevent this malignant evolution in patients at high risk.

Key Words: Adaptive Immunity, Anti-Tumour Immunity, Barret's oesophagus, Cancer Vaccines, Immunogenicity, Immunomonitoring, Immunotherapy, Oesophageal denocarcinoma, Tumour Antigens

Target Students: MRes, PhD

For more information about this research project contact:

**Prof Riccardo Dolcetti** riccardo.dolcetti@petermac.org

**A/Prof Nicholas Clemons** nicholas.clemons@petermac.org

### Next generation humanised mouse platform to study tumour immunology

Supervisors: Prof Riccardo Dolcetti and Dr Roberta Mazzieri

Immunotherapies are emerging as promising strategies to treat both primary and metastatic tumours. The development and deployment of novel therapies requires rigorous research in preclinical animal models before moving into clinical trials and gaining regulatory approval. Despite the unparalleled importance of animal models such as murine models in drug discovery, critical differences in the genetics and immune systems of mice and those of humans provide an important barrier to study the complex and dynamic interactions between a human tumour and the human immune system. Models involving humanised mice (Hu-mice) have evolved as a powerful tool to close this gap and are emerging as fundamental preclinical platforms for drug testing and therapeutic screening as recently stated by the FDA (Rouse, Ther Innov Regul Sci 52, 244-255, 2018). Hu-mice are created by introducing human immune cells, tissues, or genes into immunodeficient mice, enabling the preclinical study of human immune responses, tumour-host interactions, and evaluation of novel immunotherapies. Key limitations still restrict the use of Hu-mice in studying tumour immunology and preclinical testing of novel therapies including the limited development of innate immune cell populations, or the lack of renewable source of HSCs to humanise the mice. In this project the student will explore novel approaches to develop more advanced humanised models for the preclinical testing of emerging cancer immunotherapies, including cancer vaccines, or gene- and cell-based therapies.

Key Words: Immunotherapies, Preclinical Models, Tumour Immunology

Target Students: PhD

For more information about this research project contact:

**Prof Riccardo Dolcetti:** riccardo.dolcetti@petermac.org

## A/PROF LUC FURIC

### Pre-clinical testing of novel combination therapies in mouse models of prostate cancer

Supervisor: A/Prof Luc Furic

The prostate requires androgens for normal growth and functioning and the vast majority of prostate cancer (PC) are dependent on the androgen receptor (AR) for growth and proliferation. Androgen-deprivation therapy (ADT) remains the mainstay of therapy for advanced PC, but the disease invariably progress to a stage known as castration-resistant PC (CRPC). The last decade has seen the development of many new therapeutic agents targeting AR activity directly by inhibiting its transcriptional activity or indirectly by inhibiting the enzymes responsible for androgens synthesis. These agents have successfully increased survival in CRPC, but resistance emerges in a matter of months. It is therefore urgent to develop and validate new therapeutic targets in PC which are independent of AR activity.

This project will use genetically modified mouse models (GEMM) of PC to test novel small molecule inhibitors targeting key vulnerabilities of PC cells.

Key Words: Cancer Cell Biology, Cancer Therapy, Cell Growth, Cell Signalling, Molecular Targets, Prostate Cancer, Solid Tumours, Therapeutics

Target Students: Honours, MPhil, PhD

For more information about this project contact:

**A/Prof Luc Furic** luc.furic@petermac.org

### Targeting tRNA modification enzymes in prostate cancer

Supervisor: A/Prof Luc Furic

mRNA translation, also known as protein synthesis, is a key step in gene expression and is often dysregulated in cancer. During translation, mRNA codons are recognised by their corresponding tRNA anticodons. Chemical modification of tRNA bases is an important factor affecting codon recognition and mRNA translation efficiency. In addition to the standard Watson-Crick base pairing, the pairing between the 3rd nucleotide of the codon and the first nucleotide of the anticodon (N34) allows for non-standard “wobble” base pairing. A uridine at position 34 (U34) is often modified to stabilise wobble position base pairing, which subsequently

affects decoding and translation rates. One of the best characterised tRNA modification pathway is the three-step modification of U34: firstly, the Elongator complex made up of six proteins (ELP1-6) adds a cm5 moiety; next, the methyltransferase ALKBH8 transfers a methyl group to generate mcm5U34; and lastly, the thiouridylases CTU1/2 catalyses the formation of the mcm5s2U34. Recent studies from our group and others have demonstrated that tRNA modifications can readily be altered in response to various stimuli by modulating the activity of the U34-modifying enzymes. The aim of this project is to investigate whether the activity of U34-modifying enzymes can be targeted to suppress translation and inhibit prostate cancer growth. This project will apply techniques including but not limited to CRISPR gene editing, mammalian cell culture and mass spectrometry to characterise the role(s) of U34-modifying enzymes in prostate cancer aetiology.

Key Words: Cancer Cell Biology, Cancer Therapy, Cell Growth, Cell Signalling, Molecular Targets, Prostate Cancer, Solid Tumours, Therapeutics

Target Students: Honours, MPhil, PhD

For more information about this project contact:

**A/Prof Luc Furic** luc.furic@petermac.org

## PROF JOSEPH TRAPANI

**A New Era of Precision Medicine: CRISPR Therapeutics against Oncogenes and Pathogenic Viruses**

Supervisors: Dr Mohamed Fareh and Prof Joseph Trapani

Recent breakthrough discoveries have revealed that CRISPR effectors can function as programmable molecular scissors, allowing precise editing of the human transcriptome and genome. These revolutionary CRISPR technologies have opened up possibilities for targeting specific disease-causing genes. Our group is fully dedicated to the development of next-generation CRISPR therapeutics that specifically target pathogenic oncogenes and infectious viruses. We successfully reprogrammed a novel CRISPR protein called Cas13 to silence oncogenic RNA drivers (Hu et al, under review) and SARS-CoV-2 viral strains (Fareh et al, Nature Comms, 2021). We believe that these CRISPR therapeutics have the potential to revolutionize personalized medicine. Our current projects encompass several key areas:

1. We aim to comprehensively understand the underlying mechanisms of target recognition and editing exhibited by newly discovered and poorly characterized CRISPR effectors.
2. We aim to reengineer CRISPR-Cas effectors to achieve single-base accuracy in silencing tumor drivers, enabling highly precise and specific therapeutic interventions.
3. By leveraging "Big data" and high-throughput screening techniques, we aim to design multiplexed CRISPR tools capable of targeting entire families of pandemic viruses, such as Betacoronaviruses.
4. We are actively working on the engineering of mRNA and lipid-nanoparticles as delivery vehicles, paving the way for the next generation of CRISPR therapeutics.

A prospective student will have the opportunity to use cutting-edge interdisciplinary approaches including computational data mining, molecular cloning, CRISPR-Cas editing, CRISPR screens, super-resolution microscopy, RNA-seq, Mass Spec proteomics, FACS, RT-PCR, mRNA synthesis, and lipid nanoparticle-based deliveries.

Key words: CRISPR, Gene editing, Personalized therapy, RNA Therapeutics, AI, SARS-CoV-2, Molecular biology, Genetic screens

Target Students: Honours, Masters, MPhil, PhD

For more information about this project contact:

**Dr Mohamed Fareh:** mohamed.fareh@petermac.org

## PROF ILIA VOSKOBOINIK

**Understanding cytotoxic lymphocyte biology in health and disease**

Supervisors: Prof Ilia Voskoboinik, Prof Joseph Trapani

Cytotoxic lymphocytes – cytotoxic T lymphocytes and natural killer cells- are essential for our immune defence against disease, as they recognise and kill virus-infected or cancer target cells. The health consequences of cytotoxic lymphocyte dysfunction are catastrophic, and range from uncontrolled hyperinflammation to cancer.

Using a wide range of immunological, biochemical, molecular, biophysical and cellular approaches, and in collaboration with clinicians, we investigate:

1. The mechanisms that regulate the transition from a quiescent naïve lymphocyte to a potent killer cell.
2. Novel therapeutic strategies aimed at improving immunotherapy.
3. Mechanisms of primary immunodeficiencies and other disorders that can affect cytotoxic lymphocyte function in humans.

# AVAILABLE PROJECTS BY RESEARCH PROGRAM

Key Words: Cytotoxic Lymphocytes, Immunodeficiency, Immunotherapy

Target Students: Honours, Masters, MPhil, PhD

For more information about this project contact:

**Prof Ilia Voskoboinik:** ilia.voskoboinik@petermac.org

## DR AJITH VASANTHAKUMAR

**Understanding the role of regulatory T cells in gut microbiome-immunotherapy axis**

Supervisors: Dr Ajith Vasanthakumar and Dr Tobias Poch

The gut microbiome plays a critical role in educating various cell types of the mammalian immune system. A specialized subset of T cells known as regulatory T cells (Treg cells) are responsible for establishing tolerance against commensal microbiota in the gastrointestinal tract. While the microbiome and its products are known to shape the differentiation and function of multiple immune cell types, the role of immune cells in maintaining microbial niches remains unclear. We hypothesize that Treg cells are crucial for protecting microbial niches in the gut and contributing to immunotherapy responses to cancer. To test this hypothesis, we will use transgenic mouse models to selectively ablate Treg cells and analyze the gut microbiome of these mice at various time points. Our goal is to identify bacterial species that rely entirely on Treg cells for their maintenance. This study will reveal microbial niches that are irreversibly lost when Tregs are acutely ablated and have implications in cancer and immune checkpoint blockade therapy. We aim to gain a deeper understanding of the protective effects of Treg cells on the gut microbiome by using transgenic mouse models, full-length 16S rRNA/shotgun metagenomic sequencing, preclinical tumour models, bioinformatic analysis pipelines, and spectral flow cytometry.

Key Words: Gut Microbiome Cancer, Immunity, Immunotherapy, Tregs

Target Students: Honours

For more information about this project contact:

**Dr Ajith Vasanthakumar:** ajith.vasanthakumar@petermac.org

**Dr Tobias Poch:** tobias.poch@petermac.org

**How do oncometabolites shape the tumour immune landscape?**

Supervisors: Dr Ajith Vasanthakumar

Oncometabolites are metabolic intermediates produced by tumor cells that have a profound influence on the tumor microenvironment and immunotherapy outcomes. Although these metabolites are normal components of cellular metabolism, tumors produce them in abnormally high amounts. For example, in brain cancer, mutations in the Idh1 gene lead to the synthesis of the oncometabolite 2-hydroxyglutarate (2-HG), which is associated with therapy resistance. Conversely, mutations in the Sdha gene in gastrointestinal tumors result in the accumulation of succinate, an oncometabolite that has been linked to improved immunotherapy effectiveness. We hypothesize that oncometabolites shape the tumor immune landscape by promoting either cancer-killing immune cells or immunosuppressive populations, thereby influencing cancer progression and responses to immunotherapy. To test this hypothesis, we will introduce Idh1 or Sdha mutations in tumors to induce production of these oncometabolites and investigate their roles in modulating the tumour immune microenvironment. Additionally, we will examine how these metabolites affect the efficacy of immune checkpoint blockade therapy. This project will utilize preclinical tumor models combined with flow cytometry, single-cell RNA sequencing, metabolomics, and CRISPR technology to dissect the functions of 2-HG and succinate in shaping the tumor immune landscape and therapy responses.

Key Words: Anti-Tumour Immunity, CD8 T Cells, Immunotherapy, Oncometabolites, Tregs

Target Students: Honours, PhD

For more information about this project contact:

**Dr Ajith Vasanthakumar:** ajith.vasanthakumar@petermac.org

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# AVAILABLE PROJECTS BY RESEARCH PROGRAM

## DR IAN PARISH

**Discovering new approaches to reinvigorate CD8+ T cell anti-tumour immunity**

Supervisors: Dr Ian Parish, Dr Emily Lelliott, Dr Iván Pérez-Núñez

CD8+ T cells play important roles in preventing and restraining tumour growth, and reinvigorating function within T cells forms the basis of most clinically approved immunotherapies. Tumours can evade immunity by hijacking two regulatory processes: tolerance and exhaustion. The molecular basis of these processes is still poorly understood, limiting our capacity to disrupt them for cancer therapy. This project seeks to understand the molecular similarities and differences between tolerance and exhaustion using cutting-edge molecular technologies, such CRISPR screening, and state-of-the-art experimental models. These findings will then be applied to improve T cell immunotherapies for cancer. This project will address the following questions:

1. Which factors promote and restrain exhaustion? Can these pathways be leveraged to improve therapies such as CAR T cell therapy?
2. Which factors promote and restrain tolerance? Do these factors overlap with those factors control trigger exhaustion, and can they be therapeutically targeted to induce T cell immunity against immunotherapy resistant cancers?

Answering these questions may ultimately lead to new approaches for inducing more effective and durable T cell immunotherapies against a broad range of tumours.

Key Words: Cancer Immunotherapy, CRISPR Cas9, T Cells

Target Students: PhD

For more information about this project contact:

**Dr Ian Parish:** ian.parish@petermac.org

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# AVAILABLE PROJECTS BY RESEARCH PROGRAM

## Computational Biology Program

### DR GERRY TONKIN-HILL

**Investigating microbial evolution and host interactions in response to drug treatment using longitudinal metagenomics**

Supervisors: Dr Gerry Tonkin-Hill, Dr Sudaraka Mallawa Arachchi

Understanding bacterial evolution in humans is crucial for understanding critical health issues, including the rise of antibiotic resistance and the interactions between the microbiome and cancer immunotherapies. By analysing large metagenomic datasets (sequencing all bacterial genomes within a sample), it is possible to track the movement and evolution of bacteria within the host. This project will develop and apply novel computational methods for analysing longitudinal samples taken from patients undergoing treatment for cancer and other conditions to examine the effects of drug administration on bacterial evolution and host response. This is an excellent opportunity for students interested in contributing to research at the intersection of microbiology, genomics, statistics and machine learning.

Key Words: Bioinformatics, Machine Learning, Metagenomics, Microbiome, Statistics

Target Students: Masters, MPhil, PhD

For more information about this project contact:

**Dr Gerry Tonkin-Hill:** gerry.tonkin-hill@petermac.org

**The oral-gut microbiome in patients with advanced biliary tract cancer undergoing first-line systemic therapy**

Supervisors: Dr Gerry Tonkin-Hill

Biliary tract cancers (comprising gallbladder carcinoma and cholangiocarcinoma) are a rare and diverse group of cancers, most often diagnosed at an advanced stage and carrying a dismal prognosis. Recently, the addition of anti-PD-(L)1 targeted immune checkpoint blockade (ICB) was shown to improve outcomes when combined with platinum-doublet chemotherapy; however, we lack predictive biomarkers to guide optimal first-line therapy. Additionally, it is unclear how the gut and oral microbiome change under systemic (immuno)-chemotherapy, and whether their dynamic shifts may relate to patient outcomes. To address this, in collaboration with The Christie Hospital (Manchester, UK) and the Wellcome Sanger Institute (Hinxton, UK) we are sequencing longitudinal stool and saliva samples from two original BTC patient cohorts: 1) EMBRACER (total 130 samples sequenced from n=50 patients) and 2) ABC-12 (up to 270 samples from n=70 patients). The key questions this project will address are:

1. Can the gut and/or oral microbiome, in combination with clinical covariates, predict the outcome of patients with BTCs treated with standard 1st line therapy?
2. Are there generalisable shifts in oral and stool microbial compositions or the degree of strain-sharing between these communities under (immuno)-chemotherapy pressure?
3. Is immuno-chemotherapy associated with the emergence of antimicrobial resistance or other specific microbial functions in the gut or oral niche?

Key Words: Biliary Tract Cancer, Cholangiocarcinoma, Enterotypes, Gallbladder Carcinoma, Gut Microbiome, Metagenomics, Next-Gen Sequencing, Oral Microbiome, Salivatypes

Target Students: PhD

For more information about this project contact:

**Dr Gerry Tonkin-Hill:** gerry.tonkin-hill@petermac.org

# AVAILABLE PROJECTS BY RESEARCH PROGRAM

## DR ANNA TRIGOS

**Cancer evolution using multi-omics**

Supervisor: Dr Anna Trigos

Cancer evolution and heterogeneity limit the success of personalised medicine. These processes have traditionally been studied under the lens of genetic Darwinian evolution. However, recent technological developments have brought to light that beyond the presence of multiple clones, genetically identical cells often have different epigenomes. This project aims to elucidate how tumour cell states result from plasticity and clonal evolution and communication with the environment, and how these co-evolve during disease progression and the development of resistance. There is a wealth of opportunities for projects in this space, from understanding how tumour cells alter their own phenotype in response to genetic alterations, how they adapt to the microenvironment, how cell-cell communication between tumour cells and with the microenvironment is fundamental for the emergence of specialised tumour cell populations, and how the composition of tumour populations changes with treatment. For this, we use single-cell multi-omics, spatial transcriptomics, spatial proteomics, liquid biopsies and DNA sequencing data together with a combination of a diversity of data analyses techniques, such as bioinformatics, simulations, modelling and machine learning.

Key Words: Bioinformatics, Cancer, Data Analysis, Multi-omics, Machine Learning

Target Students: Honours, Masters, MPhil, PhD

For more information about this project contact:

**Dr Anna Trigos:** anna.trigos@petermac.org

**Development of methods to analyse the spatial distribution of tumour and microenvironment cells in tissues**

Supervisor: Dr Anna Trigos

Cancers are composed of a myriad of cell types, such as tumour cells and immune cells. However, rather than a homogeneous mixture of cells, cells are organised in biologically meaningful ways. For example, immune cells that are close to tumour cells might be recognising and killing tumour cells, whereas the absence or the random location of immune cells in the tissue might mean that such recognition is not taking place. Our group develops and applies computational approaches that allow us to quantify, compare and simulate such patterns from spatial proteomics and transcriptomics data. Techniques to be used include algorithm development, machine learning, data analysis and software development.

Key Words: Method Development, Spatial Analysis

Target Students: Honours, Masters, MPhil, PhD

For more information about this project contact:

**Dr Anna Trigos:** anna.trigos@petermac.org

**Deep learning to analyse patient imaging**

Supervisor: Dr. Anna Trigos

During treatment, cancer patients often receive a wealth of imaging, including PET scans, CT scans and MRIs. To date, these have been largely used to understand the extent of disease and tumour location and size. However, there is a clear potential of further information contained in these imaging modalities that can help understand disease evolution, development of resistance, and predict patient treatment response and survival. In this project we will extract imaging features from a diversity of imaging modalities of large patient imaging datasets, and associate with mutation, epigenetic and transcriptional information derived from tissue and liquid biopsies, and rich clinical data. The project will primarily involve the use of deep learning methods and would suit a student with a strong computer science background.

Key Words: Deep Learning, Patient Imaging

Target Students: Honours, Masters, MPhil, PhD

For more information about this project contact:

**Dr Anna Trigos:** anna.trigos@petermac.org

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# AVAILABLE PROJECTS BY CLINICAL RESEARCH PROGRAM

## RADIATION ONCOLOGY RESEARCH

**Immune-PET: Characterising the Immunophenotype with Novel PET Tracers**

Supervisors: Dr Fiona Hegi-Johnson, Prof Michael MacManus

Immune-PET is a multidisciplinary collaboration led by Dr Fiona Hegi-Johnson and Professor Michael MacManus. We are a group of radiation oncology and medical oncology clinicians at Peter Mac that in partnership with the research group of Professor Andrew Scott at the Olivia Newton John Cancer Research Institute (ONJCRI) and the Donnelly Laboratory at the University of Melbourne develop novel PET tracers to characterise the immune system.

We work closely with our laboratory colleagues, including Dr Magnus Dillon at the ICR in London and Dr Harriet Gee at the University of Sydney, to understand the mechanisms that underpin radiotherapy- induced immunotherapy responses, and our clinical trials couple novel imaging approaches with interrogations in tumour and host immunity through our collaboration with Professor Stephen Fox and Paul Neeson.

Key words: Lung Cancer, Immunotherapy, Nuclear Medicine

Target students: Honours, Masters, PhD

For more information please contact

**A/Prof Fiona Hegi-Johnson:** fiona.hegi-johnson@petermac.org

**Imaging of cancer immunotherapy targets with Positron Emission Tomography: Characterising PD-L1 with 89Zr-Durvalumab**

Supervisors: A/Prof Fiona Hegi-Johnson and Prof Michael MacManus

This PhD project is based on a clinical trial aimed at establishing the feasibility of 89Zr- Durvalumab as a novel imaging biomarker of PD-L1 activity during treatment for lung cancer, and embraces both clinical and translational research in novel-tracer PET/CT and molecular biology.

The project consists of a 20 patient Phase I study in which patients undergo sequential PD-L1 imaging before and during radical chemoradiation for Stage III NSCLC. This project runs in tandem with a translational analysis analysing serial liquid biopsies for circulating tumour cells (CTC), circulating tumour DNA (ctDNA) and changes in host immunity, as well as analysis of serial tissue biopsies of irradiated tumour that will characterise the T-cell repertoire and PD-L1 dynamics during treatment.

Key words: Lung Cancer, Immunotherapy, Nuclear Medicine

Target students: MPhil, PhD

For more information please contact

**A/Prof Fiona Hegi-Johnson:** fiona.hegi-johnson@petermac.org

**Defining the Immunophenotype of PD-L1 resistance with durvalumab and CD8 PET/CT: pathways to the development of novel treatment strategies**

Supervisors: A/Prof Fiona Hegi-Johnson and Prof Michael MacManus

This PhD project is based on a series of small clinical trials that will characterise the biology of PD-L1 resistance in the following patient cohorts.

1. Patients with oligoprogressive disease during PD-L1 therapy.
2. Patients with PD-L1 positive incurable NSCLC who are planned to receive palliative radiotherapy.

Novel tracer PET imaging of CD8, and other immune pathways will be used in conjunction with molecular analyses of liquid and tissue biopsy to characterise the biology of patients with disease progression during PD-L1 therapy, and to investigate whether radiotherapy can be used to modulate host and tumour immune responses.

The core skills that will be acquired by research candidates are:

1. Advanced skills in image analysis of PET/CT and the ability to interrogate the impact of radiotherapy treatment on dynamic changes on both FDG and 89Zr- based monoclonal antibody PET and other novel tracers.
2. An understanding of clinical trial design for novel-PET tracer multicentre studies.
3. Molecular biology: analysis of data acquired from the molecular translational work, including RNA-sequencing and ctDNA.
4. Bioinformatic analysis of the relationships between imaging and molecular data.

Key Words: Lung Cancer, Immunotherapy, Nuclear Medicine

Target Students: MPhil, PhD

For more information about this project contact:

**A/Prof Fiona Hegi-Johnson:** fiona.hegi-Johnson@petermac.org

# AVAILABLE PROJECTS BY CLINICAL RESEARCH PROGRAM

## RADIOPHARMACEUTICAL SCIENCES

**Design, chemical synthesis, characterisation and biological assessment of unnatural amino acids incorporated into novel peptides for use in theranostics**

Supervisors: A/Prof Mohammad Haskali, Dr Joseph Hilton-Proctor, Dr Wenxiao (Kay) Yue, Dr Jo-Anne Pinson

A cancer diagnosis impacts all Australians, with half the population expected to be diagnosed by age 85. Despite medical advancements, better treatments and diagnostics are still needed. Theranostics is a cutting-edge approach that uses a molecule targeting cancer cells combined with radioactivity to either image (e.g., Ga-68) or treat the tumour (e.g., Lu-177) enabling the capacity to "see what you treat". Peptides, which are tiny proteins, are very useful for theranostics and can be readily radiolabelled. However, peptide theranostics development is challenged by issues such as quick degradation and poor binding of these agents. A new and creative way to address these limitations is by stabilising peptide structures (constraining their flexibility) using chemically modified amino acids. These will be designed and synthesised in our lab. This is an exciting undertaking as this work has potential for very promising applications across nuclear medicine and theranostic development. As part of this project, students will develop hands-on experience in the design, synthesis, purification and characterisation of non-canonical (unnatural) amino acids incorporated into novel peptides for biological evaluation against a range of new cancer targets. This comprehensive project aligns with students interested in refining both their chemistry and biology skills.

Key words: Cancer, Nuclear Chemistry, Organic Chemistry, Peptide Chemistry, Radiochemistry, Theranostics

Target students: Masters, PhD

For more information please contact

**A/Prof Mo Haskali:** mo.haskali@petermac.org

## CANCER SURGERY (ANAESTHETICS)

**Mapping Clinical Outcome Data onto Health Utilities for Economic Evaluations**

Supervisors: Professor Gang Chen, Karen Trapani  Sponsor: Professor Bernhard Riedel

Health-related quality-of-life (HRQoL) tools such as the EQ-5D translate patients' self-reported health into utility index (anchored on a 0-1 death-full health quality-adjusted life year (QALY) scale). Real-world datasets rarely contain such measures, making economic evaluation harder. This project will test whether the routinely collected Post-operative Quality of Recovery Scale (PostopQRS) can be mapped to EQ-5D utilities. PostopQRS captures multi-domain recovery after surgery from patient and clinician perspectives, yet its composite scores cannot directly produce QALYs. A reliable mapping would let analysts value outcomes whenever only PostopQRS is available.  Work will proceed in two phases: Phase 1: protocol development for mapping analysis will be drafted, detailing candidate statistical models, covariates/ predictors, goodness-of-fit criteria, and validation analyses to assist the selection of optimal mapping functions.  Phase 2: develop mapping functions from PostopQRS onto EQ-5D using existing datasets. In this phase, both direct and indirect mapping approaches will be considered. The indirect mapping approach involves first predict the responses to each of the EQ-5D dimension before applying a country-specific value set to estimate the overall health utilities. The direct mapping approach focuses on predicting health utilities directly. The preliminary analyses will inform the feasibility to conduct direct and/or indirect mapping in this study sample.

Key words: Data Analysis, Health Economics, Statistical Programming

Target students: Placements, Honours, MPhil

For more information please contact

**Prof Bernhard Riedel:** bernhard.riedel@petermac.org

## TRANSLATIONAL RESEARCH

**Vaping-Associated Nasal and Intraoral Somatic Heterogeneity**

Supervisors: Prof Tom John, Prof Charlie Swanton, Dr Stephen Wong

Electronic cigarettes (vapes) are increasingly used by adolescents and young adults, often marketed as a safer alternative to smoking. However, the long-term health risks of vaping remain largely unknown. Recent advances in ultra-sensitive sequencing have revealed that somatic mutations and clonal expansions in normal tissues may act as early indicators of future cancer risk. This study aims to investigate whether vaping, smoking, alcohol use, or their combination are associated with increased oncogenic mutation burden or clonal expansions in the nasal and buccal epithelium-tissues directly exposed to inhaled and ingested substances. Understanding whether lifestyle behaviours in young adults leave detectable mutational footprints could help identify early biomarkers of cancer risk and inform future regulatory and prevention strategies.

# AVAILABLE PROJECTS BY CLINICAL RESEARCH PROGRAM

Key words: Carcinogenesis, Cigarettes, Genomics, Vaping

Target students: MPhil

For more information please contact

**Prof Tom John:** tom.john@petermac.org

**Dr Stephen Wong:** stephen.wong@petremac.org

## MEDICAL ONCOLOGY RESEARCH

**Maximising response to radionuclide therapy in metastatic prostate cancer**

Supervisors: Prof Shahneen Sandhu, Dr Richard Rebello

Precision radiotherapy is an effective treatment modality for prostate cancer, and targeted-systemic radionuclide therapies (RNT) are now widely adopted to treat the most lethal form of the disease, mCRPC (~3,900 cancer-related deaths p/a in Australia). This has sparked excitement for future RNT applications in many cancers, though mechanisms of efficacy are not yet fully elucidated. Lu-PSMA directs a β-radiation payload to multiple prostate specific membrane antigen (PSMA) positive cancer sites concurrently. Tumour clearance is thought to be facilitated by the release of both cell-free DNA (cfDNA) and neoantigen from dying cells, stimulating immune cell recognition of surviving cancer for destruction. Despite overall efficacy, a third of patients are unresponsive to Lu-PSMA, while a small subset achieves complete response. Therefore, understanding the molecular and cellular mechanisms behind efficacy of RNT, across a heterogenous spectrum of disease, is needed to maximise response and ensure that all patients benefit from RNT. In this project we will:

1. Define biological features within cancer tissue sampled from men who were treated with Lu-PSMA.
2. Define immune cell populations within the tumour microenvironment and circulating peripheral blood.

This project will involve generation and interrogation of genomic and transcriptomic datasets, FACS profiling, and clinical datasets. Students will gain experience in molecular and cellular biology techniques, as well as computational analyses.

Key words: Genomics, Immunotherapy, Prostate Cancer, Radiation Therapy

Target students: Honours, Masters, MPhil, PhD

For more information please contact

**Prof Shahneen Sandhu:** shahneen.sandhu@petermac.org

**Dr Richard Rebello:** richard.rebello@petermac.org

**Peter MacCallum Cancer Centre**

305 Grattan Street
Melbourne Victoria
3000 Australia

Locked Bag 1 A'Beckett Street
Victoria 8006 Australia

**www.petermac.org**

Follow us on **X @PeterMacCC**

For more information, please contact:

Research.EducationAdmin@petermac.org

Peter Mac

Peter MacCallum Cancer Centre
Victoria Australia