Melbourne Academic Centre for Health

University of Melbourne and the Melbourne Academic Centre for Health (MACH)

PhD studentship opportunity for research-minded doctors training in any hospital specialty or general practice

The MACH Track: A new pathway for integration of research career development with completion of medical vocational training, commencing February 2021.

Applications are encouraged from doctors in vocational training who are keen to pursue early steps towards a career in clinical academic medicine and a role as one of the future leaders of clinical innovation in Australia. The MACH-Track pathway is open to doctors training in any recognised specialty, including General Practice. Applicants should have won a place in a Melbourne-centred vocational training program approved by the relevant Royal/Specialist College; for specialties with two-stage programmes (eg physicians) trainees should have secured a place in an advanced training program. Applicants must be currently in post in one of ten MACH-affiliated health services in Central, West and North Melbourne (for details see below), or be on a training rotation that will bring the trainee to a MACH-affiliated health service by February 2022. General Practice trainees will require sponsorship by the University of Melbourne Department of General Practice (see below). Successful applicants will complete their current vocational training program with flexible extension by around three years to accommodate pre-PhD, PhD and post-PhD training in research associated with the University of Melbourne Faculty of Medicine, Dentistry and Health Sciences and eight affiliated Medical Research Institutes. During the pathway's three-year period of registration as a full-time PhD student with the University of Melbourne, trainees will receive an enhanced stipend supplemented by around 8 hours per week of guaranteed paid clinical employment, which may be recognised as fulfilling part of vocational training requirements on a case-by-case basis. This structured pathway will offer field-leading mentorship and support tailored to the needs of early career clinician researchers of exceptional promise.

The Melbourne Academic Centre for Health

The Melbourne Academic Centre for Health (MACH - pronounced "Mack") is a NHMRC-designated Advanced Health Research Translation Centre (https://www.machaustralia.org/). Comprised of 10 health services, 8 Medical Research Institutes and the University of Melbourne Faculty of Medicine, Dentistry and Health Sciences (which administers the MACH). This collaboration aims to translate research to improve health and healthcare, and to stimulate the economy. The Executive Director is Professor Sir John Savill FRCP FMedSci FRS, formerly Director of the Edinburgh Clinical Academic Track in the UK.

The health service members are-
Austin Health, Melbourne Health (incorporating the Royal Melbourne Hospital), Mercy Health, Northern Health, Peter MacCallum Cancer Centre, Royal Children's Hospital, Royal Victorian Eye and Ear Hospital, Royal Women's Hospital, St Vincent's Hospital, Western Health.

The Medical Research Institute Members are-
Bionics Institute, Centre for Eye Research Australia, Florey Institute, Murdoch Children's Research Institute, National Ageing Research Institute, Olivia Newton-John Cancer Research Institute, St Vincent's Institute, Walter and Eliza Hall Institute. The collaboration represents the largest concentration of health

and medical research in Australia, typically accounting for around 25% of the nation's expenditure in the field. There are also superb opportunities for interdisciplinary research involving other Faculties in the University of Melbourne.

The MACH-Track

The MACH-Track is a structured, mentored and fully-funded career development pathway for exceptional research-minded doctors training in hospital specialties or general practice (see diagram below). It seeks to develop the future leaders of clinical innovation by offering an opportunity to integrate pre-PhD, PhD and initial post-PhD research training with completion of clinical training of the highest standard. Integration will be achieved by delivery of the trainee's planned vocational training program on a flexible basis. The Track is supported by the leadership of all 19 MACH partners and by all Royal and Specialist Colleges so far approached. Once appointed each trainee will work with the MACH Office, clinical employers and the relevant training committees of their Royal/Specialist College to craft a bespoke program that will ensure completion of an excellent clinical training. Inevitably the pathway will add ~3 years to the duration of clinical training but the Track will reward this investment of trainee time by providing an exceptional pathway towards leadership and through enhanced income during the PhD phase when compared to conventional PhD stipends (typically ~$30k pa tax-free). The pathway comprises:-

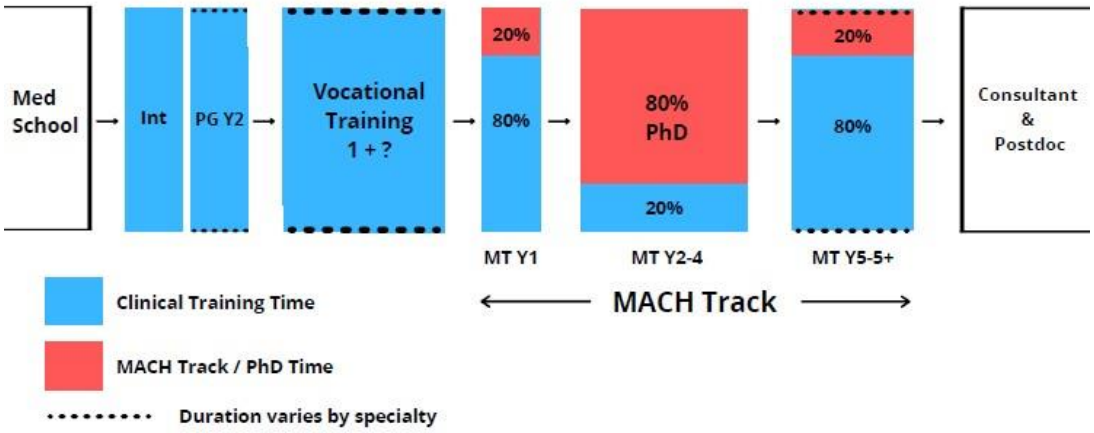
Year 1- 80% Clinical training / 20% PhD run-in training. Health services will employ the carefully selected trainees on a 100% contract for their previously planned training post, but allow an average of 20% of time for Track work over the year, starting in February 2021. Comparable arrangements will be made to support General Practice trainees. There will be an introductory one-week course and up to 3 "taster" mini-projects undertaken on a flexible one day per week basis and offering potential progression to a PhD. Towards the end of the first year trainees will select the PhD opportunity that suits their needs best and prepare a PhD proposal. This will be defended at an interview with a panel of Track leads (with time for amendment before commencing the project). Such preparation and planning ensures that the trainee "hits the ground running" for the next phase:-

Years 2, 3, 4 - 80% PhD / 20% clinical training. The carefully selected PhD program will then be pursued, ideally with two supervisors, who could be from different MACH members if appropriate; the first cohort will start in February 2022. The lead Research Institute or University Department will top up the three year full-time University Research Training Program PhD studentship stipend to the maximum allowed by regulations, $54,600 tax-free per year at 2020 rates (likely to increase by ~2% per year). Unrelated to the PhD course of study, the trainee will also be employed by their parent health service, with the opportunity to work clinically up to an average of 8 hours per week, which subject to clinical training requirements could include mutually attractive night and weekend work. Comparable arrangements will be made to support General Practice trainees.

Year 5- 80% Clinical training / 20% preparation for post-doc fellowship application. As the trainee works towards completion of clinical training and eligibility for (in hospital specialties) consultant-level appointments, an average of 8 hours per week will be remunerated by the parent health service during which the trainee can prepare and defend their thesis (essential for progression to year 6), publish papers and subject to external funding, continue research. Comparable arrangements will be made to support General Practice trainees as they complete the requirements for Fellowship of RACGP and

specialist registration with AHPRA. The aim of this academic activity is to position the carefully mentored trainee for a post-doctoral fellowship enabling transition to professional independence.

Years 6 and 6+ Where necessary, as for year 5 to completion of vocational training (the end point of the Track) and, ideally, a post-doctoral fellowship. Trainees will be assimilated into the Melbourne Medical School Clinician Scientist Pathway that offers support and mentorship at the stage of transition to academic independence and a substantive university appointment.



The MACH-Track offers the following benefits:-
Continuity- Engagement with both clinical and research training on an 80/20 or 20/80 basis throughout will ensure continued engagement with the translational mission of the MACH.
Cohort- Appointees will join a MACH-wide community of well-mentored MACH-Track colleagues and are also members of a cohort of developing leaders in their parent health service; Track leads and PhD supervisors also benefit from cross-fertilisation as they provide supervision and mentorship to Track trainees.
Choice- The trainee will select from a wide range of potential two-supervisor 3 year PhD projects towards the end of the initial year of 80/20 clinical training/ PhD run-in, which provides "taster" mini projects.

University of Melbourne and the Faculty of Medicine, Dentistry and Health Sciences

The University of Melbourne Faculty of Medicine, Dentistry and Health Sciences is Australia's pre-eminent medical, health sciences and biomedical faculty and is recognised for its research, teaching, training and policy leadership across all of these fields. The Faculty employs more than 1 900 members of staff, attracts more than 8 000 students each year and comprises six schools; 33 departments, centres and institutes; and offers 128 courses.

The Faculty is Australia's overall leader in clinical, pre-clinical and health sciences and was ranked 9th globally in 2018 by the Times Higher Education World University Rankings. In the field of clinical medicine and pharmacology, the Jiao Tong ranks the University of Melbourne as the first in Australia and number 29 in the world in 2019. The University educates more health professionals, graduates, research and higher degree students and attracts more national competitive funding than any other Australian university.

The Faculty employs over 1 300 academic research staff. Hospital departments employ 39 per cent of MDHS academic staff. The University has over 2 000 hospital-based honorary staff and more than 500 honorary staff in partner institutes. The Faculty's annual research income is more than A$225million: 50 per cent of the University of Melbourne total.

Faculty researchers publish more than 4,000 peer reviewed publications every year: 44 per cent of publications include an international co-author, hailing from more than 140 countries in the last five years. The top five countries represented are the United States, United Kingdom, Canada, Germany and the Netherlands.

Approximately 1 500 graduate research students conduct research supervised by over 1500 staff and honoraries across the Faculty's six schools and in affiliated health services and research institutes.

Specimen PhD projects available

To give applicants a flavour of the range of PhD opportunities available for appointees to consider during Year 1 of the Track, here is a selection from a large number of projects that will be on offer - there will be a "taster" Year 1 mini-project available for each substantive 3-year PhD project:

Centre for Eye Research Australia

Satellite imaging to transform detection of diabetic retinopathy and other retinal vascular diseases
Our group is amongst the first in the world to use hyperspectral imaging to detect biomarkers of the eye and brain diseases. The approach combines novel imaging technology, first developed by NASA for remote sensing of the Earth, with state-of-the-art artificial intelligence image analysis methods. We seek to validate this technology for the detection and prognostication of diabetic retinopathy. In excess of 430M people worldwide have diabetes and diabetic retinopathy remains a leading cause of blindness despite the fact that most vision loss is avoidable through timely detection and management. We have identified novel imaging biomarkers of diabetic retinopathy that we now seek to validate as predictors of retinopathy progression. This research seeks to inform personalised risk prediction and change the impact of this disease. The project involves a combination of applied clinical research with cutting edge imaging and artificial intelligence. Prior experience in programming or image analysis are desirable, but not mandatory.

Repair of the cornea to restore vision: Translation to a Surgical Repair Device
Trauma and disease damage to the corneal surface is currently treated by corneal transplants and lifelong anti-rejection drugs. Many countries do not have sufficient donors to meet the increasing demand for this procedure. The aim of this project is to discover a new source of corneal endothelium (CEC) as an alternative for endothelial transplant surgery, using human iPS cells and expand them on patented hydrogel films. In this ocular research the student will work with corneal surgeons, chemical engineers and veterinary scientists to develop engineered constructs for implantation to the damaged corneal endothelium, and preclinical transplantation studies will be carried out in sheep in the veterinary facility. For this project the student will work with close supervision to derive corneal endothelial cells from iPS cells and grow these on patented hydrogel films to replace damaged endothelium. This will provide a source of potential autologous cells for expansion studies and culture on tissue plastic as well as our patented hydrogel films. Alternatively, the reprogramming of appropriate

cells from patient donors direct to corneal endothelium will be explored. Mechanisms of cell adhesion and proliferation will also be examined, and preclinical transplantation studies will be carried out in sheep, as previously.

Neuronal responses to mtDNA haplogroups
There is growing evidence that differences in mitochondrial (mt) DNA may have an important influence on susceptibility to neurodegenerative diseases, including those which affect the eye. We have found that mouse fibroblasts respond to the presence of different mtDNA genotypes with very large changes in nuclear gene expression, with the innate immune response being one the key affected pathways. In this project we will create a new human cellular model to investigate nuclear response to human mtDNA haplogroups. We propose production of trans-mitochondrial cybrids using a single fibroblast nucleus but with haplogroups representing European, Asian and African populations. Fibroblasts will be transdifferentiated to neuronal cultures, and RNAseq used to define transcriptomes of each nucleus/mtDNA pair. We will also compare fibroblast cybrid and derived neuron transcriptomes. This project will uncover novel data on how mtDNA genotypes may alter nuclear responses in ways relevant to human neurodegenerative disease susceptibility.

Department of General Practice

Utilising technology to optimise the management of heart failure in primary care
Future Health Today, a partnership between the University of Melbourne and Western Health, is offering a PhD position for the development of a heart failure module.
Future Health Today (FHT) is a software program which integrates with the electronic medical records of participating general practice clinics to optimise implementation of evidence-based guidelines, providing opportunities for early intervention to reduce the development or progression of chronic disease. This is important for the 85% of Australians who visit general practice at least once a year. The candidate will have the opportunity to work as part of a multidisciplinary team including GPs, hospital clinicians, implementation scientists, health informaticians and computer scientists. They will also have opportunities to engage with the Centre for Research Excellence in Digital Technology to Transform Chronic Disease Outcomes. Using the Knowledge to Action Framework, the candidate will develop and implement an intervention that aims to optimise the medical management of heart failure. Depending on the candidate's interest, this might include:
- Qualitative study to understand key barriers and facilitators of medical management of heart failure
- Co-design of intervention with health professionals, people with heart failure, and stakeholder groups
- Implementation and evaluation of peer-based learning to increase knowledge about heart failure management
- Development of an application to facilitate self-management of heart failure that integrates with the general practice electronic medical record
- Implementation and evaluation of a point of care decision support tool to optimise prescription of beta blockers and ACE inhibitors in people with heart failure.
The Future Health Today program is funded by the Paul Ramsay Foundation and has received funding support from the Melbourne Academic Centre for Health.

The clinical utility of pharmacogenomic testing to inform antidepressant prescribing in primary care
Up to a half of patients with major depressive disorder do not respond to their first antidepressant and remission rates are as low as 37.5%. Genetic factors contribute up to 50% of this variance in drug response. International pharmacogenomic-based guidelines recommend using genotype-predicted

metaboliser phenotypes of the cytochrome P450 genes CYP2D6 and/or CYP2C19 to select type and dose of antidepressant. A meta-analysis of RCTs of pharmacogenetic-informed prescribing for antidepressants suggests potential clinical utility but there remain several gaps in the evidence. Previous trials were affected by multiple risks of bias, were not generalisable to primary care where the majority of depression is treated and lacked longer term follow-up or economic evaluation.
This PhD will be embedded within the PRESIDE trial, a double-blinded RCT in primary care which aims to evaluate the efficacy, safety, and cost-effectiveness of pharmacogenomically-informed antidepressant prescribing compared with Australian Therapeutic Guideline-based prescribing. This four-year trial has recently been funded by the MRFF and will commence patient recruitment in 2021. It would be suitable for a range of clinical disciplines including general practice, psychiatry or genetic medicine.

Florey Institute

Investigating the Role of Epigenetics in Multiple Sclerosis
Multiple Sclerosis (MS) is a central nervous system (CNS) disease whose onset is associated with both environmental and genetic factors. These factors likely act, at least in part, through epigenetic alteration, a modifiable mechanism of gene regulation. DNA methylation is a well-characterized epigenetic mechanism that can be evaluated at the genome-wide level with the aid of high throughput scanning technologies. Studies of MS patients at disease onset that include epigenetic factors in conjunction with genetic and environmental factors will provide new insights into disease etiology and thus guide better preventive and treatment strategies**.** The Ausimmune multi-site case control study, Australia, has identified a range of genetic and environmental factors which influence risk of a first clinical diagnosis of CNS demyelination (FCD), clinically definite (CD) MS and the early phases of MS disease course. The PhD candidate would work on assessing environmental factors associated with the FCD and MS DNA methylation profiles identified in other study arms.

Developing novel therapies to harness the progression of Multiple Sclerosis
Multiple Sclerosis (MS) is a complex inflammatory demyelinating disease of the central nervous system (CNS) and is the most common neurological disorder in young Caucasians. Peripheral immune cell infiltration into the CNS and subsequent demyelination are significant components of the disease progression in MS, ultimately leading to irreversible neurodegeneration. Thus, limiting inflammatory demyelination is a critical step to “stall” disease progression and neurodegeneration. However, current therapies for MS are limited both in their efficacy, only partially effective in reducing relapses but not progressive disabilities, and in their selectivity, associated with strong side effects. Thus, identifying more specific therapeutics that can be efficaciously modulated is highly desirable for clinical translation. Sphingosine 1-Phosphate lyase (S1PL) is an enzyme that enhances immune cell “invasion” into the central nervous system. We have recently performed a high throughput drug screen and discovered new S1PL inhibitors with high potency in vitro and in vivo. This project will investigate their therapeutic efficacy and mechanism of actions to combat inflammatory demyelination and promote remyelination using experimental models of MS together with genetic approaches. Results of this project will prompt future pre-clinical and clinical evaluation in MS with broader implications in other neurodegenerative diseases.

Murdoch Children’s Research Institute

Understanding disease mechanisms and outcomes in Australian children with acute stroke using sophisticated blood and neuroimaging biomarkers

Childhood stroke is a devastating condition affecting up to 13 per 100,000 children annually. Aetiology of childhood stroke differs from adult stroke, with nonatherosclerotic arteriopathies and cardiac disease being the most commonly identified causes. Between 50% and 90% of survivors experience life-long neurological impairments. The study will investigate the predictive utility of blood and neuroimaging markers to identify underlying aetiologies, functional outcomes, and recurrence, in a prospective national cohort of Australian children with acute ischaemic and haemorrhagic stroke. The project will provide the trainee with the opportunity to develop expertise with the application of innovative proteomic and advanced brain imaging techniques.

Taking placenta to scale: The population burden of disordered placentation and placental function
The placenta regulates a healthy pregnancy. The population burden of disordered placentation and function is unquantified but potentially immense. This highly novel PhD takes placental research to scale, developing innovative high-throughput placental imaging and sampling within the 'Generation Victoria' cohort, targeting all 160,000 Victorian births over two years and all 70 birthing hospitals. Initially focusing on the placental pathophysiology of the great obstetric syndromes, the resource once established can later quantify placental roles in maternal, fetal, childhood, adult and transgenerational health. The landmark GenV thus offers immense opportunities to establish a career and leadership in transformative pregnancy and newborn research.

Early life inflammation in non-communicable childhood disease
This project will use samples collected in early life from children with a range of non-communicable diseases (respiratory disease, autoimmunity, allergy) to understand the role of tissue-specific and systemic inflammation in development of disease and in predicting disease outcomes in later childhood. Training provided: This project will leverage valuable clinical samples and associated clinical data to provide lab-based immunology and molecular biology training, as well as training in analysis of big data.

National Ageing Research Institute

A tool for predicting prolonged grief in family carers of people living with dementia
The death of a loved one is a significant life event, bringing with it significant physical, social and psychological ramifications. For many individuals the intensity of grief related distress gradually declines over time without clinical intervention. However, some individuals experience a condition known as complicated grief or prolonged grief disorder whereby bereavement triggers an enduring grief reaction lasting for over 6 months and characterised with persistent yearning for the deceased or preoccupation with the deceased, accompanied by intense emotional pain. Studies have shown that individuals suffering from complex or prolonged grief are at higher risk of suicide, experience higher levels of anxiety and depression, as well as decreased quality of life.
In the general population complicated grief affects roughly 7% of bereaved individuals. However, for carers of people living with dementia (PLWD) the rates of complicated grief are closer to 20% at 12 months post-death. This increased risk of prolonged grief may in part be explained by the dynamic and unique characteristics of the dementia-related bereavement process. Unlike many other terminal illnesses, dementia often does not afford families the opportunity to reconcile past conflicts, or say a final goodbye due to their inability to engage in reciprocal communication.
This proposed project will focus on family carers of people living with dementia currently in aged care and aims to:
1. Explore the recent experience of carers after the death of a PLWD
2. Identify the risk factors associated with the development of complicated grief

Identifying elder abuse in medical settings
Elder abuse is a significant, global, public health and human rights issue, with harmful consequences for the health and wellbeing of older people, as well as enormous social costs. A recent systematic review and meta-analysis estimates the global prevalence of elder abuse in community settings at 15.7%, while within institutional settings, the global prevalence of elder abuse is estimated at 64.2%. With estimates from the United Nations suggesting that the number of people aged 60 years and above will increase to about 2 billion by 2050, the problem of elder abuse is a major concern. Despite the scale of this problem, there remain many gaps in knowledge in current research on the topic of elder abuse, including the role of screening tools. This project would examine how screening tools can be used to identify cases of elder abuse in hospitals and the relative success rates of "universal screening" versus other case-finding approaches.

Enhancing 3D (dementia, delirium, depression) care for older people in residential care via micro-learning
Increasingly older people in residential care have the greatest and most complex care needs. Staff are expected to deliver skilled care, yet opportunities for adequate and ongoing training are limited due to time, geographical and cost factors. This project will explore the use of micro-learning in delivering targeted evidence-based information on dementia, delirium and depression identification and management to front line aged care workers. The study will be a mixed-methods exploration with 3 sub-studies: 1) co-design of content and features that make learning more effective for this particular cohort (e.g. timing, dose, content, delivery), 2) creation of an integrated training program, 3) implementation and evaluation.

Olivia Newton-John Cancer Research Institute

Strategies to enhance the efficacy of targeted therapies in gastrointestinal cancers
Precision therapies which target specific molecular alterations (e.g. EGFR, ERBB2, FGFR, BCLXL overexpression, mutant BRAF, KRAS, IDH) have demonstrated efficacy in several gastrointestinal cancers. However, the duration of these responses is inevitably short lived due to the rapid onset of acquired resistance, or expansion of resistant clones. Our group has identified a number of mechanisms which drive resistance to targeted therapies in colorectal, gastric and biliary tract cancer cell lines, unveiling potential new avenues for overcoming resistance. We are searching for highly motivated PhD students with an interest in gastrointestinal cancers to pursue these findings. The project will involve pre-clinical investigating the efficacy of novel drug combinations in genomically characterized cell lines, interrogation of changes in cell signalling and gene transcription, and pre-clinical testing in animal models. These studies will be specifically designed to inform early phase testing of novel drug combinations, which are urgently needed to improve outcomes for these patients.

A) Improving tyrosine kinase inhibitors-based therapies for metastatic Her2+ breast cancer
B) Investigating the contribution of matrix/integrin signalling in breast cancer metastasis and therapy resistance
Research in the Matrix Microenvironment & Metastasis (MMM) laboratory focuses entirely on breast cancer metastasis. Projects available for PhD students build upon prior work from our group and revolve around two key themes. The first explores the role of extracellular matrix proteins and adhesion receptors in driving breast cancer metastasis and their potential as biomarkers and/or therapeutic targets. Secondly, we are particularly interested in developing better therapeutics for the management

of incurable brain metastases. Our approach is highly translational and relies heavily on the use of a wide range of mouse models developed in-house.

A) Deploying novel technologies to identify resistance mechanisms in patients with haematological malignancies receiving targeted therapies
B) Identifying new strategies for minimum residual disease monitoring to optimise response assessment in myeloid & lymphoid malignancies.
We have a large investigator-initiated multicentre trial program (>$10million funding, 8 studies across 4 disease subtypes), which incorporates biomarker and imaging sub-studies. In addition, we have an established tissue bank with >500 samples to date from leukaemia and lymphoma patients receiving standard therapy, access to National Registry data and an onsite molecular haematology service. Part of our work is exploring novel therapeutics which have the potential to revolutionise the treatment of leukaemias and lymphomas. Understanding mechanisms of resistance is a key project in our portfolio. Exploring how tumours evade selective pressure is a key step in fulfilling the promise of such therapies. We plan to explore this tumour evolution using the rich resource of our established biobank samples and corresponding clinical dataset to identify mechanisms of resistance to novel therapies. To achieve this, the student candidate will interrogate samples through genomic and transcriptomic approaches as well as using evolving approaches in examining plasma DNA. Our goal is to complete the loop of translational research and utilise clinical observations to drive ongoing basic scientific research.

Peter MacCallum Cancer Centre

Understanding the behaviour of cancer at single cell resolution
Whilst it is well recognised that all cancer cells are heterogeneous in terms of their genetic, epigenetic, metabolic and transcriptional states; tumour evolution is most commonly viewed through a genetic lens. The 'Darwinian' selection of mutant cells carrying a relevant mutation acquired by chance leads to a shift in clonal composition whereby certain mutant cells are passively selected by metabolic, nutritional, anti-cancer immune surveillance or therapeutic pressure over time. In contrast, Lamarckian evolution hypothesized that organisms were able to adapt to their environment during their lifetime in order to survive and pass these changes onto their offspring, similar to a scenario whereby cancer cells harness various non-mutational adaptative process to meet and overcome the challenges within the tumour microenvironment and pass on these learnings to their offspring. Clearly in cancer both Darwinian and Lamarckian principles are at play, however understanding their relative contributions to cancer initiation, maintenance and therapeutic resistance requires sophisticated model systems and analytical tools. This PhD project will focus on the key goals of studying the complex adaptive behaviours of cancer cells under environmental and therapeutic pressure in the tumour microenviroment. The project will involve developing and employing single cell technologies to understand genetic, transcriptional and metabolic changes within cancer cells to provide novel insights into (i) clonal competition in the context of environmental and therapeutic pressure and (ii) clonal escape in the context of anti-cancer immune surveillance. Ultimately, the ambition is to use these insights to design new therapies or therapeutic strategies to improve outcomes for patients with cancer.

Improving management of infections in cancer
Infection is a common complication of cancer treatment resulting in excess hospitalisation and death. With the rapid expansion of novel cancer and immune targeted therapies, new approaches are required to manage the risk for infectious complications. Emerging fungal and antimicrobial resistant infections are a threat to the long-term health care of cancer patients. The traditional approach of prolonged,

empirical broad spectrum antibiotic and antifungal therapy results in “collateral damage” of increasing antimicrobial resistance and host gut microbiome dysfunction; predisposing to further infectious complications and reduced efficacy of cancer therapies. In an era of increasing antimicrobial resistance, changing infection epidemiology and rapid emergence of new cancer treatments, we need to better understand which patients are at risk for these serious complications and where clinical, immunological and microbiome risk profiles can build a more personalised approach to infection risk. The broad suite of health Services research within the Peter MacCallum Cancer Centre has precinct, national and international collaborations. Depending on interests and skills of the candidate, there are several PhD opportunities might include (i) establishing a well characterised cohort of highly immunosuppressed patients with follow-up immune, microbiome and clinical data to look for predictors of infection and outcome (ii) evaluate the impact of rapid nucleic acid based testing for infection diagnosis (iii) participate in clinical trials of novel anti-infective agents, iv) design, implement and evaluate new pathways of care harnessing digital health. The vision is to translate these findings into new prevention or treatment strategies for infection.

Clinical investigation of the immune response to radiotherapy and immunotherapy
Solid organ malignancies account for the major proportion of cancer-related deaths worldwide. Prior to immunotherapy, conventional drug therapies have typically modest benefits that are rarely durable, and despite recent advances, relatively few patients have ‘actionable’ mutations that can be addressed with targeted drug therapies. In this context, checkpoint immunotherapy, which amplifies a patient’s immune response to their tumour, has recently shown efficacy in a wide range of tumour types. However, most patients do not at present benefit from this approach, likely due to weak pre-existing immunity. One approach to this problem involves using radiotherapy, a potent immune stimulus, to ‘kickstart’ the immune response in order to maximise the effects of immunotherapy. The MACH clinician PhD candidate would work with recently initiated early phase clinical trials that combines cutting edge radiotherapy with immunotherapies in a range of solid tumour subtypes. Collectively, these studies include sequencing studies investigating timing of radiotherapy and anti-PD-1/L1 combinations, investigating ‘Abscopal’ tumour regression after combination radiotherapy and immunotherapy, and addressing the effect of radiotherapy dose/fractionation on tumour immunogenicity, in the context of non-small cell lung, hormone-refractory prostate, renal cell, and breast cancers. The candidate would work closely with expert teams bridging laboratory and clinical research across Radiation Oncology, Medical Oncology and Surgery at the Peter MacCallum Cancer Centre.

Walter & Eliza Hall Institute

Translational research into haematological malignancies
All major advances in care for patients with haematological malignancies have arisen from investigations focused on understanding the biology of the disease, how it relates to and differs from normal blood cell development and function, and how it can be perturbed for therapeutic advantage by selective therapies (e.g. rituximab, imatinib, venetoclax, CAR-T). In this lab there are opportunities to explore (i) discovery projects such as the genetic basis of blood cancers or the mechanisms of susceptibility or resistance to targeted therapies; or translational projects such as the development of rational combination therapies for low-survival blood cancers or interventional research associated with clinical trials or registries. These can be tailored to a student’s major interest and/or to the research skill they wish to master. All projects typically have a strong link to clinical medicine, even if basic discovery research. By way of more detailed example of a potential project area, our program has pioneered the development and use of BH3 mimetics as transformative therapy for selected haematological cancers.

We have also led the field in determining the mechanisms of primary and secondary resistance in patients with leukaemia. Now we are defining the most common mechanisms in patients and designing rational combinatorial therapies to pre-empt the development of secondary resistance and overcome primary resistance. Laboratory research on patient samples will complement early phase clinical trials which are testing specific hypotheses.

Utilising pre-clinical models to discover novel therapies for tuberculosis
Intracellular pathogens manipulate host cell survival to facilitate their persistence and dissemination. Our lab investigates these interactions to identify genetic and/or pharmacological strategies of sensitising infected cells to die in vivo. Potential targets are tested in cutting-edge pre-clinical models to determine the effectiveness and feasibility of translation to patients. Students will utilise the Institute's PC3 high containment facility to work with higher-risk pathogens, namely Mycobacterium tuberculosis. This project employs a pre-clinical model of tuberculosis to make clinically relevant discoveries that are eminently translatable to patient care. We are one of only a few institutes in the world capable of performing this research, and as such, the project will be highly rewarding. Students will become adept in pre-clinical infection models, flow cytometry, histology, molecular biology and tissue culture.

Hyposplenism in coeliac disease
Reduced spleen function (hyposplenism) is associated with potentially life-threatening health complications as a major role of the spleen is to develop protective immunity to infectious agents. Coeliac disease (CD) is a common immune illness caused by dietary gluten and is an important cause of hyposplenism. Patients with coeliac disease and hyposplenism show impaired immunisation responses and higher rates of sepsis and death from encapsulated organisms such as Pneumococcus. Remarkably, there is sparse data on its prevalence in coeliac disease and the factors that modify its development and course and a complete absence of Australian data. This project will: • Determine the prevalence of hyposplenism in Australians with CD at diagnosis and after treatment with a strict gluten free diet; • Undertake detailed B cell immunophenotyping and innate immune assessment in CD patients with and without hyposplenism and healthy controls to link circulating IgM memory B cell pool and immune function with clinical outcomes; • Compare screening strategies for hyposplenism including Howell-Jolly Body screening, pitted red cell analysis and spleen ultrasound to "gold standard" immune assessment; • Assess Streptococcus pneumoniae immunisation responses to two different vaccines to identify an optimal vaccination strategy; • Correlate hyposplenism and B cell function with CD activity, HLA status, clinical phenotype and vaccine responses; • Identify an optimal hyposplenism screening and vaccination strategy to inform a Clinical Practice Guideline.

Application procedure

Pre-application enquiries may be sent to Meredith Bickley (meredith.bickley@unimelb.edu.au); potential candidates concerned about eligibility should provide brief details of scheduled appointments in their College-approved vocational training program. Trainees in General Practice should consult A/Prof Jo-Anne Manski-Nankervis (jomn@unimelb.edu.au) as sponsorship by the University of Melbourne Department of General Practice is a requirement.

Applications should be sent by **9am Monday 3rd August 2020** to meredith.bickley@unimelb.edu.au and must include:-
1) A letter of application no longer than 500 words explaining why the applicant wants to pursue PhD training through the MACH-Track; **NB** it is not necessary to express interest in any of the specimen PhD projects described above, but it would help if applicants could identify a general area of interest such as 'cancer research' , 'big data', 'clinical trials' or any other broad area of research interest;
2) Brief details of the candidate's vocational training program, with dates and location of each attachment; proposed end date; and details of the relevant College training committee including email contact for the lead College administrator;
3) Full CV, to include brief details of any research projects undertaken, with details as to how these were disseminated (report for supervisors, abstract presentation at meeting, publication etc).
4) A brief letter of support from an academic referee able to comment on the candidate's potential for completing a PhD;
5) A brief letter from the candidate's current clinical training supervisor confirming that the candidate is making satisfactory progress in vocational training and stating support for the candidate seeking flexibility in clinical training if appointed.
6) For General Practice trainees, a brief note from A/Prof Jo-Anne Manski-Nankervis confirming sponsorship by the University of Melbourne Department of General Practice.

Candidates short-listed for interview will be informed by **29th August 2020**. Short-listed trainees in hospital specialties will be required to provide by **27th September 2020** a brief letter of support signed by the CEO of the MACH-affiliated health service in which they would spend Year 1 of the Track confirming that they will be provided with an average of 8h per week research flexibility with no loss of earnings; a template will be provided.

Interviews will be held in the first two weeks of October 2020 ahead of a February 2021 start (the start date can be deferred to February 2022 to suit individual circumstances).