WESTERN SYDNEY
UNIVERSITY

Medicine

SUITABLE FOR MASTER OF RESEARCH

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SUITABLE FOR MASTER OF RESEARCH OR PHD

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Using Human Stem Cell Technology to Discover Causes and Treatments of Human Age-related Diseases

Associate Professor Michael O'Connor: m.oconnor@westernsydney.edu.au

Research area: Stem cells, Regenerative medicine

The Regenerative Medicine Laboratory investigates debilitating diseases of ageing using human pluripotent stem cells. This includes studying the causes and potential new treatments for cataract, macular degeneration and gut motility disorders. Our research partners include surgeons, drug companies and patient advocacy groups.

We have pioneered world-leading approaches to create human cells and 3-dimensional organoid tissues from stem cells - such as light-focusing human micro-lenses - that we use for both academic and industry research. Our investigations are underpinned by expertise in a wide range of techniques including light and electron microscopy, genomics (e.g., RNA-seq, PCR, etc.), proteomics (e.g., 1D/2D electrophoresis, Western blotting, mass spectrometry) and bioinformatics.

A variety of projects are available that apply stem cells or primary human cells to study cataract, macular degeneration, gut motility disorders and bioinformatics. Project preferences can be determined in consultation with the supervisory panel, based on various factors including the alignment of the prospective student's research interest and skills with the available projects. Students within the Regenerative Medicine Laboratory typically work on their own project, with collaboration and support provided by other members of the team. In doing so, students become expert in a range of cutting-edge biotechnology skills suited to future careers in both academic- and industry-based positions.

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Gut Feeling of Class 3 Obesity and Weight Loss

Dr Milan Piya: m.piya@westernsydney.edu.au

Supported by: Associate Professor Anand Hardikar and Dr Mugdha V Joglekar

Research area: Obesity, Gut microbiota

Class 3 obesity is increasing in prevalence with 4% of the Australian population having a BMI >40 kg/m2. It is therefore important to understand the factors that contribute to this increasing weight, and more importantly, factors that are linked to helping with weight loss in this population.

Patients with class 3 obesity (BMI >40) are seen at the South Western Sydney Metabolic Rehabilitation and Bariatric Program in Camden. Plasma and serum samples are taken at baseline, 6- and 12- months, with the possibility to collect for and profile gut microbiome/metabolite changes using stool samples during these times. Data for anthropometry, clinical data, pathology data and questionnaires, as well as shearwave elastography (on a subset of individuals) will be available. This provides a unique opportunity to follow changes in a longitudinal (as well as cross-sectional) study and assess circulating biomarkers that are predictive of and responsive to intervention and/or lifestyle changes to treat obesity.

The student will work in A/Prof Hardikar's laboratory to measure molecular biomarkers including circulating cell-free (cf)DNA, microRNAs, telomeres and other metabolites using clinical as well as research (in vitro) samples. Techniques include routine molecular biology and analysis including real-time PCR, digital droplet PCR and transcriptome/chromatin analyses using chromatin IP.

The student will have the opportunity to work with samples taken from patients in an established weight management program to investigate clinical and/or molecular biomarkers associated with adiposity and predictive of treatment outcomes. The student will also have the opportunity to use machine learning approaches in analysing datasets for identifying newer signatures for obesity and intervention targets, identified through such analyses.

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Understanding a Bug's Life in the Fat Land

Associate Professor Anand Hardikar: a.hardikar@westernsydney.edu.au

Supported by: Dr Mugdha V Joglekar and Dr Wilson KM Wong

Research area: Obesity, Type 2 Diabetes

The prevalence of type 2 diabetes (T2D) and obesity is increasing and is a designated National Health Priority Area. This unique study aims to develop an understanding of

early life imprinting of obesity and metabolic disease and explores the value of gut microbiota analysis in predicting the progression to T2D.

Gut microbes are well-recognized to influence an individual's susceptibility to obesity and type-2 diabetes/T2D. Increased dietary fibre is associated with higher concentrations of short-chain fatty acids (SCFAs) in the gut (produced by fermentation of dietary fibre), which are known to stimulate the release of incretin hormones from enteroendocrine cells via activation of G-protein coupled free fatty acid receptor-2 (FFAR2).

Our preliminary data from a rat model of multi-generation under-nutrition and nutrient transition (Cell Metabolism 2015), confirm that i) the gut microbiota of lean and obese rats differs and ii) that obese rats benefit metabolically by transplantation of faeces from lean to obese rats through coprophagic feeding behaviour. Although similar human studies have confirmed that metabolic benefits could be proffered through faecal transplants, underlying mechanisms are not yet fully elucidated.

This study will use in vitro human colonic cell culture systems and clinical samples to understand the potential molecular mechanisms underlying obesity and excess weight loss with exposure to cutting-edge molecular and cellular tools involving analyses of genes and chromatin at single-cell resolution. Results will identify metabolic pathways that may direct future pre- and pro-biotic therapies in early life to prevent adult obesity and T2D, thereby reducing the personal and economic burden of these major metabolic illnesses.

Candidates undertaking this project will be trained in multiple cell and molecular biology techniques including cell imaging, chromatin IP, scRNA-sequencing/ATAC-seq, microRNA profiling and various machine-learning approaches using R/R-studio. Interaction with local, interstate and overseas collaborators and exchanges across academia and industry is anticipated.

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MALAT1 Long-non-coding(lnc) RNA in Prediction of Islet Transplantation Outcomes

Associate Professor Anand Hardikar: a.hardikar@westernsydney.edu.au

Supported by: Dr Wilson KM Wong and Dr Mugdha V Joglekar

Research area: Cell therapy, Type 1 Diabetes

Human islet isolation is a cost- and resource-intensive program generating islets for cell therapy in Type 1 diabetes. Human islet isolation costs are ~AU$56,000/per pancreas, due to good manufacturing practice (GMP)-grade reagents/workflows necessary for human islet transplantation. However, only around a third of the cadaveric pancreas that are selected for clinical islet transplantation end up being transplanted to patients due to low quality/number of isolated islets. Donor characteristics are important in selecting the cadaveric pancreas for islet isolation used for transplant. Whilst some

studies demonstrated BMI as a positive predictor of islet yield, viability, and insulin secretion, the Collaborative Islet Transplant Registry (CITR) data failed to validate this observation. Therefore, islet isolation centres still often face the difficult question if “GMP-grade” or (a much less costly) “research-grade” reagents should be used for a cadaveric pancreas. There is a need to identify biomarker(s) that predict the quality of islets, prior to initiating islet isolation.

Using machine learning algorithms, we recently demonstrated (Wong WKM et al 2019 JCI insight) that the levels of two gene variants of the long-non-coding (lnc)RNA MALAT1 can accurately identify transplantable cadaveric donor pancreas islets, and also enhance current algorithms in a combined prediction model, before initiating pancreatic islet isolation. Apart from the role of MALAT1 in islet cells, it is intriguing to note that MALAT1 is regulated by hypoxia. Indeed, hypoxia can be a major determinant of post-isolation islet quality and therefore the regulation of MALAT1 under hypoxic conditions can impact on islet survival.

In this project, we will test our hypothesis that MALAT1 lncRNA is essential for protecting against oxidative damage in islets. We will knock-down MALAT1 transcripts in islet derived cells using LNA technology which achieves up to 90% knockdown of lncRNAs in our hands. These cells will be exposed to different oxygen concentrations and then cell viability, function as well as oxidative gene expression will be assessed.

Overall, study outcomes will identify potential molecular mechanisms in MALAT1-regulated islet beta-cell survival and viability (islet quality) following hypoxia. This proposal is based on innovation and creative leads identifying the role of MALAT1 as pre-isolation predictor of post-isolation islet quality; and its regulatory capacity in islet Î²-cell survival. The present study will generate mechanistic understanding of MALAT1 upregulation under hypoxia in islet cells thereby offering new insights to reducing islet beta-cell death.

Techniques that candidates will be trained include: routine molecular biology techniques including real-time PCR, digital PCR, in vitro cell knock-down and overexpression analyses, RNA-pulldown assays, machine learning using R/R-studio, study design and biostatistical analyses, clinical and molecular biomarker profiling using high-density profiling workflows.

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Molecular Crosstalk in Immunomodulation by MicroRNAs

Dr Mugdha V Joglekar: m.joglekar@westernsydney.edu.au

Supported by: Associate Professor Anand Hardikar

Research area: Immunology, Diabetes

Type 1 diabetes (T1D) is characterized by autoimmune destruction of insulin-producing islet beta-cells and requires exogenous delivery of insulin for survival. The closest

clinically available therapy to T1D is cadaveric islet transplantation that is shown to offer insulin independence for up to five years with fewer episodes of potentially life-threatening hypoglycaemia. Use of immunosuppressive drugs is essential in islet transplant recipients to prevent graft rejection; however, these drugs have significant adverse side effects. It is therefore important to search for alternate immune-suppressive therapies to enable the long-term survival of islet grafts and a better quality of life for the recipient. Immunomodulation is a better alternative to immunosuppression.

We have previously described human islet-derived progenitor cells (hIPCs), a population of mesenchymal-like stem/progenitor cells obtained from human islets. We observe that when hIPCs are mixed with peripheral blood monocytes (PBMCs), they can significantly inhibit the proliferation of T-cells. T-cells play an important role in adaptive immune response and hence this inhibition of T-cell proliferation attracted a greater interest in our research on hIPCs. We observe that in a co-culture system, hIPCs can significantly inhibit in vitro proliferation of different immune cell subsets (CD4+ T, CD8+ T, CD19+ B) of (PHA)-stimulated PBMCs. We also observed that this inhibition is most effective when there is direct cell-cell contact, although significant inhibition is also retained in a transwell system.

In this proposal, we aim to identify mechanisms by which hIPCs retard immune cell function, mainly through signalling via extracellular/exosomal microRNAs. This project involves the use of multiple techniques including cell culture, flow cytometry, RNA isolation, real-time PCR, exosome isolation, fluorescence imaging, miRNA overexpression and knockdown experiments, as well as in silico analysis of miRNA-mRNA interactions. All methodologies are optimised and available through our group, based at the School of Medicine. This project will identify novel non-codingRNA molecules with a potential to translate into practice for the only approved cell replacement therapy for diabetes in Australia.

Techniques that candidates will be trained in include routine cellular and molecular biology techniques including real-time PCR, digital PCR, cell culture, flow cytometry, microRNA analysis, biostatistical analyses and validating biological pathways.

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Developing a Crystal Ball for Predicting Diabetes Progression (The PREDICT T1D Study Group: Plasma RNA Evaluation and Diagnosis in Children Progressing to Type 1 Diabetes)

Associate Professor Anand Hardikar: a.hardikar@westernsydney.edu.au

Supported by: Dr Mugdha V Joglekar and Dr Wilson KM Wong

Research area: Type 1 Diabetes, Prediction

Type 1 diabetes (T1D) is becoming a global concern with the number of affected individuals reaching nearly 300 million, and the incidence rate increasing at ~3% per

annum. Although daily insulin injections or insulin pump therapy can enable survival and control blood glucose concentrations; hypoglycemia, diabetic ketoacidosis and hyperglycemia, which promote long-term vascular and neurological complications of diabetes, still occur at unacceptably high rates. Islet cell death is a common feature of T1D, which commences many years prior to clinical diagnosis. Biochemical tests including fasting blood glucose, HbA1c, pro-insulin/C-peptide levels/ratios, tolerance tests and serum tests for islet auto-antibodies/immune molecules as well as genetic risk scores have not yet been able to efficiently predict T1D progressors from the general population.

Studies by our team indicate that a novel assay based on the quantitative estimation of a set of microRNAs (patent #: WO2019000015A1) can be used to measure (i) islet death in vitro, as well as, (ii) distinguish between individuals with or without diabetes in a cross-sectional study. MicroRNAs are a group of small (~22 nucleotides) single-stranded RNA molecules that do not code for any protein and can be both a marker and mediator of physiological and pathological processes.

In this project, we will test the hypothesis that signatures that are specific to human islet (beta) cells are detected in peripheral circulation and can be, collectively, used to derive a unique plasma signature of islet-cell death in diabetes. The specific aims are (i) validate our signature of miRNAs in existent clinical samples from different cross-sectional and longitudinal studies and, (ii) analyse data using machine learning workflows. This project will significantly advance the existing diagnostic/prognostic methods for T1D with potential for clinical risk stratification and T1D prediction using cross-technology platforms that we are developing/testing in parallel to this research.

Techniques that candidates will be trained in: routine molecular biology techniques including real-time PCR, digital PCR, epigenetic and RNA-based biomarker analysis, machine learning workflows using R/R-studio, study design and biostatistical analyses, clinical and molecular biomarker profiling using high-density profiling workflows.

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New Research Strategies for Preclinical Research into Amyotrophic-Lateral-Sclerosis

Professor Tim Karl: t.karl@westernsydney.edu.au

Research area: Amyotrophic-Lateral-Sclerosis, Amyotrophic-Lateral-Sclerosis-Frontotemporal Spectrum Disorder, Behavioural neuroscience, Preclinical research

Amyotrophic-Lateral-Sclerosis (ALS) is a neurodegenerative disorder and the most common form of motor neuron disease. ALS results in loss of motor neurons and causes progressively worsening movement-related symptoms, eventually leading to paralysis and early death. There is currently no cure for ALS and our understanding of the non-genetic risk factors for the vast majority of ALS cases is very limited. Furthermore, some of the genetic risk variants for ALS have recently been identified to play a role in the development of ALS-Frontotemporal Spectrum Disorder. Thus, our

team characterises established and new genetic mouse models for ALS more comprehensively, thereby also considering more complex behaviours including cognitive domains. These models are also utilised to evaluate novel treatment candidates for the disease.

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New Therapeutic Avenues for Dementia

Professor Tim Karl: t.karl@westernsydney.edu.au

Research area: Dementia, Neurodegenerative diseases, Behavioural neuroscience, Preclinical research

Dementia is neurodegenerative disorder and characterised by cognitive decline. The most common form of dementia, i.e. Alzheimer's disease, is described by extracellular amyloid deposition (building senile plaques) and tau hyper-phosphorylation (forming intracellular neurofibrillary tangles) and is accompanied by increased inflammation in the brain. Current treatment options are limited, are only effective in early disease stages, and do not stop or reverse its progression. Thus, new therapeutic candidates need to be identified and validated using established mouse models for the disease to inform future clinical trials. In this context it is interesting to note that the endocannabinoid system plays a role in brain immunity and neuroprotection and can affect cognitive domains. Indeed, recent animal research suggests that particular constituents of the cannabis plant might have beneficial effects on the pathophysiology of Alzheimer's disease and disease-related cognitive impairments. Thus, my team evaluates the neuro-behavioural effectiveness of cannabinoids (and other new treatment candidates) to reverse disease-relevant characteristics of genetic mouse models for dementia.

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New Treatments for Drug Addiction Behaviour

Dr Rose Chesworth: r.chesworth@westernsydney.edu.au

Supported by: Professor Tim Karl

Research area: Drug addiction, Substance abuse, Mental health, Behavioural neuroscience, Preclinical research

Drug addiction occurs approximately five times more frequently in patients with schizophrenia than in healthy populations. It is unclear what causes this elevated rate of abuse. There is some evidence for genetic predisposition increasing risk for both schizophrenia and drug addiction, and also for drug abuse being a precursor for schizophrenia. Our team seeks to untangle this complex interaction, using animal models of genetic predisposition to schizophrenia, and behavioural tests of drug-taking behaviour. We have a $1M state-of-the-art behavioural facility which allows high

throughput testing of all addiction behavioural tests, as well as other behavioural tests relevant to schizophrenia including cognition, sensorimotor gating, social behaviour. We analyse brain tissue following the completion of behavioural experiments, to examine drug-induced neural adaptations and alterations to drug- and schizophrenia-relevant brain regions. In addition, we are starting to examine new therapeutic options for comorbid drug addiction and schizophrenia, to better treat both disorders. Through this research, we hope to determine how and why drug addiction occurs so frequently in patients which schizophrenia, and how we can best treat these two disorders.

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Gene-environment Interactions in Schizophrenia

Professor Tim Karl: t.karl@westernsydney.edu.au

Supported by: Dr Rose Chesworth

Research area: Gene-environment interactions, Schizophrenia

Schizophrenia is a chronic and disabling mental disorder that affects 1% of the world's population. A complex interaction of environmental and genetic risk factors appears to be causal for the development of the disease. Preclinical research has been instrumental in advancing our limited understanding the impact of those risk factors, both in isolation or in combination, on behaviour and brain development. Our team models schizophrenia by developing and validating multi-factorial mouse models combining genetic and environmental disease risk factors. Genetically predisposed mouse mutants are exposed to disease-relevant environmental factors (e.g. chronic drug abuse, poor diet, stress) at critical stages of their development. Our team focuses on the neuro-behavioural characterisation of these models, applying a multitude of different neuro-behavioural phenotyping paradigms. This highly standardised research is necessary to determine disease-relevant interactions and to identify preventative and therapeutic measures for future clinical applications.

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SUITABLE FOR PHD

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Design and Delivery of an Integrated Community Care Model to Transition Adults with Class 3 Obesity from Tertiary Metabolic Services

Dr Milan Piya: m.piya@westernsydney.edu.au

Supported by: Dr Kate McBride

Research area: Healthcare delivery, Obesity

Two thirds of the Australian adult population have overweight/obesity. Class 3 obesity (BMI >40kg/m2) prevalence is ~4% and rapidly increasing. In response to the growing prevalence of clinically severe obesity, hospital-based multidisciplinary obesity services have been established to support individuals & their families to achieve better health outcomes. The South Western Sydney (SWS) Metabolic Rehabilitation and Bariatric Program in Camden offers support & allows individuals with class 3 obesity to work with teams of specialists (including endocrinologists, dietitians, clinical psychologists, specialist nurses, psychiatrists, gastroenterologists and physiotherapists) to improve their health outcomes. There is a very high demand for this service with increasingly limited consultation capacity and waiting lists of over a year. Therefore, there is an increasingly urgent need for them to be transitioned out of the clinic to create capacity for new patients. However, discharging from these specialist services is often associated with the risk of weight regain and improvements to quality of life, eating disorder risk and psychological distress may be lost. Transition is also likely beneficial given community-based care may be preferred due to issues around accessibility & acceptability of specialist obesity services.

The student will have the opportunity to work with the clinical and research team at the SWS Metabolic Rehabilitation and Bariatric Program and academics from the Diabetes, Obesity and Metabolic Translational Research Unit (DOMTRU) at Western Sydney University. The student will co-design a pragmatic, community-based intervention with patients (plus their families and carers), clinic staff, primary care (including GPs, community & allied health) & other key stakeholders, that aims to assist individuals with class 3 obesity to successfully transition to community-based care from tertiary services. As part of this project, the student may also assess the feasibility of linking community & clinical services with social support networks in a new integrated model, as well as the efficacy of the intervention on psychosocial & clinical outcome among individuals with obesity.

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Interventions to Reduce Psychological Distress and Eating Disorders in People with Class 3 Obesity

Dr Milan Piya: m.piya@westernsydney.edu.au

Supported by: Professor Phillipa Hay

Research area: Eating disorders, Weight disorders

Class 3 obesity is increasing in prevalence with two thirds of the adult population having overweight/obesity and ~4% of the Australian population having a BMI >40 kg/m2. At the South Western Sydney (SWS) Metabolic Rehabilitation and Bariatric Program, we have previously shown that eating disorders and psychological distress are very common in this clinic population, and it is therefore important to understand the associated factors, and more importantly, factors that may help reduce psychological distress and eating disorders, as well as help with weight loss in this population.

The student will have the opportunity to work with the clinical and research team at the SWS Metabolic Rehabilitation and Bariatric Program in Camden, NSW where the data for anthropometry, clinical data, pathology data and questionnaires for K10, SF36 (or SF12) and EDE-QS are routinely collected. The student will also have the opportunity to conduct qualitative interviews and/or focus groups with patients in the program to understand the existing services and barriers and co-design and test novel interventions that would reduce eating disorders and improve psychological distress. An additional area of study is elucidating the phenomenology of binge eating, food addiction and food craving and response to weight loss interventions. The student will also be supported by the award winning Western Sydney University interdisciplinary research groups - Diabetes Obesity and Metabolism Translational Research Unit (DOMTRU) and Eating Disorders and Body Image (EDBI).

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