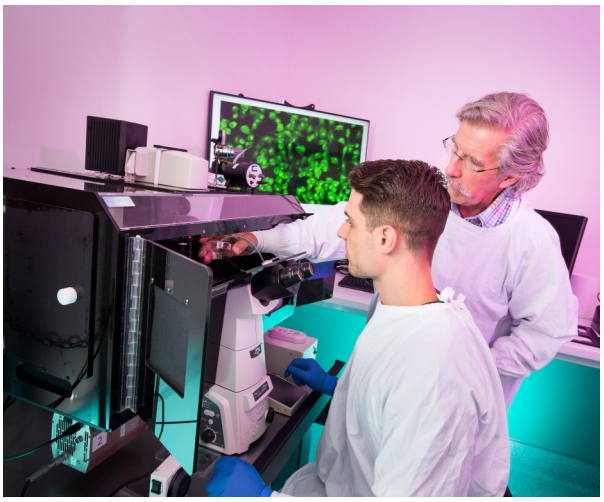
THE UNIVERSITY OF MELBOURNE

Faculty of Medicine, Dentistry and Health Sciences

Melbourne Medical School
Department of Medicine – Western Health



Research Opportunities 2019-20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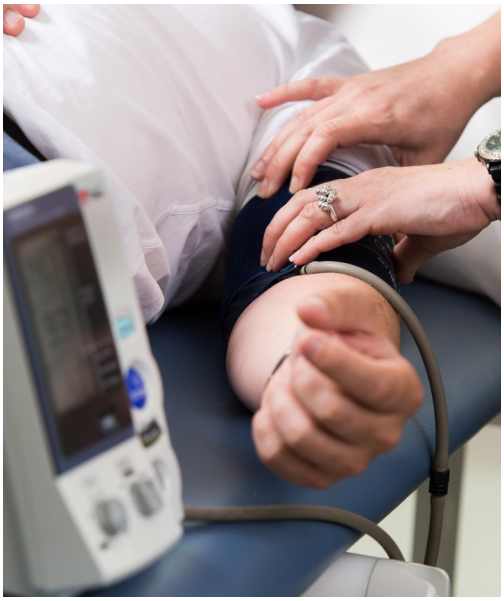
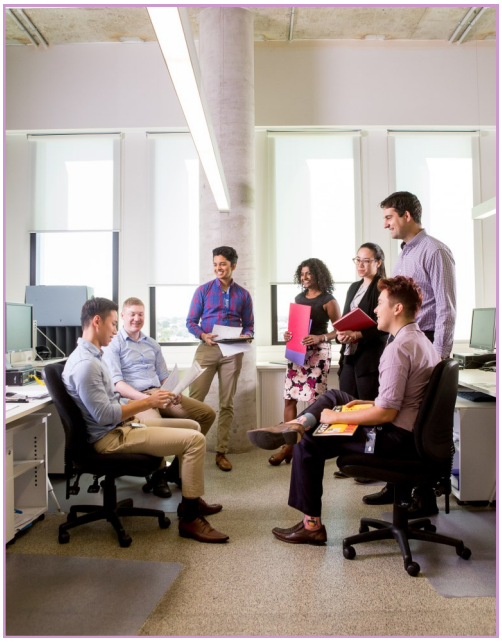




A Word from the Chair of Medicine

Professor Gustavo Duque

Welcome to the Department of Medicine – Western Health

If you are a potential student looking for great opportunities, **you are in the right place!**

Department of Medicine - Western Health provides state-of-the-art facilities, expertise and personnel to Graduate Research candidates who are interested in pursuing Honours, Masters or PhD degrees.

In terms of potential supervisors, we have a strong team composed of more than sixty academics specialising in all areas of Medicine. Together, we published more than 300 research papers last year.

Our *state-of-the-art facilities* at the **Western Centre for Health, Research and Education** include a clinical trials area, a well-equipped gym, wet lab facilities, imaging (DXA, pQCT, etc.), animal facilities and a translational research unit.

For those of you interested in clinical research, our Department of Medicine at Western has strong links with the three Hospitals managed by Western Health: Sunshine, Footscray and Williamstown. Our Department runs an average of 20 clinical trials per year with more than 1,000 participants being recruited from our in/outpatients services. In addition, our Department of Allied Health at Western is also research-oriented, thus promoting an atmosphere of multi and inter-disciplinary research.

As a translational research centre, our Department promotes those ideas with a strong potential to benefit our communities as a whole. Our *bench-to-bedside-and-back* philosophy looks at clinical applications of our discoveries, while also testing new proof of principles and applications to well-known medications and therapies.

Our Community and Population Research Program evaluates the impact of chronic diseases on our community whilst testing effective interventions to prevent disability and frailty in our older population.

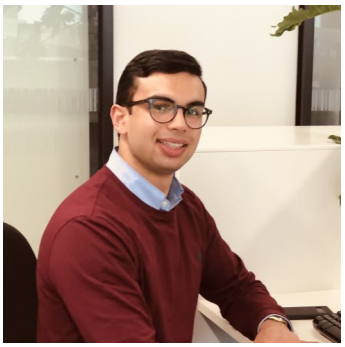
In summary, the possibilities of engaging in research at Western are infinite. I invite you to look though this brochure, and contact our researchers and supporting personnel to discuss projects that are of interest to you.

Your career as a researcher could start at Western Health, and we are always happy to help!

Professor Gustavo Duque, MD, PhD, FRACP.
Chair of Medicine – Department of Medicine - Western Health

My Experience at the Department of Medicine - Western Health

Isaac Buratto – MPHIL Candidate



Doing research through the University of Melbourne has allowed for ongoing academic interaction in seminars hosted by the hospital's esteemed researchers and medical professionals. My clinical experience has allowed me to interact and engage with patients from diverse cultural, socioeconomic and non-English speaking groups. Beginning as an Honours student, I have been nominated for student research awards and have featured in the Western Health magazine for contribution to research. Transitioning into my Masters has allowed for further engagement in presentations to my peers, supervisors and other academic staff. I work collaboratively with other researchers and medical professionals. The University of Melbourne program in conjunction with Western Health has developed my leadership skills to result in optimal patient care during my study.

Dr Julia Jones - PHD Candidate

I am a nephrologist doing clinical work at Western Health as well as working on my PhD with the University of Melbourne, based at Western Health. My PhD consists of research looking into the use of electronic technology based interventions to improve the detection and management of chronic kidney disease in primary care. It has been great being able to learn from and collaborate with people based at both Western Health and the University of Melbourne.

Ghazala Naureen - PHD Candidate

I am a final year Graduate Researcher at the Department of Medicine – Western Health with Associate Professor Sharon Brennan-Olsen as my primary supervisor. Firstly, I wholeheartedly thank my supervisor and all members of the department for making me feel incredibly welcome here. It is absolutely a great opportunity to meet, learn and share research with people working on diverse projects in musculoskeletal health. The team members are very determined, approachable, supportive and always willing to share and communicate knowledge and experience, and as a growing researcher in the field, I am very thankful for this. I am really gaining rewarding experience here. I am highly passionate to continue with the musculoskeletal health research team in the future after completion of my PhD.

Dr Jesse Zanker - PHD Candidate

PhD candidates at the Department of Medicine are surrounded by supportive, enthusiastic and approachable colleagues and mentors. Research opportunities and potential for collaboration, including international exchanges, are abundant. The leadership group in the department are highly aspirational and aim to facilitate candidates flourishing in their fields. Administrative staff are friendly and supportive…and work hard to keep the PhD candidate stress-free!

The University of Melbourne

Established in 1853, the University of Melbourne is a public-spirited institution that makes distinctive contributions to society in research, learning and teaching and engagement. It's consistently ranked among the leading universities in the world, with international rankings of world universities placing it as number 1 in Australia and number 32 in the world (Times Higher Education World University Rankings - 2019)

The Melbourne Medical School

The **Melbourne Medical School** is part of the Faculty of Medicine, Dentistry and Health Sciences of the University of Melbourne. It is the oldest medical school in Australia and internationally renowned for global leadership in teaching and training, health research, policy and practice. The School encompasses all major fields of medicine and rural health.

The Department of Medicine – Western Health

The **Department of Medicine – Western Health** conducts high quality research into acute and chronic diseases common in the western suburbs of Melbourne. We are a multidisciplinary group who has extensive experience in the design and conduct of large-scale, clinical randomised controlled trials, and public health and translational research.

Western Health

Western Health (WH) manages three acute public hospitals: Footscray, Sunshine and Williamstown. Western Health also manages a wide range of community-based services. Western Health provides a comprehensive, integrated range of services from its various sites; ranging from acute tertiary services in areas of emergency medicine, intensive care, and medical services, through to sub-acute care and specialist ambulatory clinics. Western Health provides a combination of hospital and community-based services to aged, and adult patients.

Australian Institute of Musculoskeletal Science (AIMSS)

The **Australian Institute for Musculoskeletal Science** (**AIMSS, www.aimss.org.au**) is a medical research institute based on a collaborative partnership between the University of Melbourne, Victoria University and Western Health. Its positioning at Western Health's Sunshine Hospital enables translational research and close links with clinicians. AIMSS has world class dedicated clinical research facilities supported by a research management infrastructure which aids grant administration and clinical trial management. Co-located with the clinical facilities are basic sciences laboratories with state of the art research equipment, enabling a true two-way bench to bedside approach.

Facilities

Clinical Research Facilities

The Department of Medicine - Western Health has world class dedicated clinical research facilities. Located on-site at Western Health - Sunshine Hospital, there is convenient access for clinical collaborators, easy client access to the facility and nearby access to an experienced clinical trials pharmacy and commercial pathology service. Co-location of clinical research facilities with our basic science research facility also helps to support translational research, and provides easy access for rapid processing and storage analysis of patient samples.

The facility houses 8 clinical trial rooms, with equipment to conduct clinical assessment, patient consultation and counselling, and also to perform procedures such as phlebotomy. In addition, there are several specialist spaces.

Gait and Balance Gym

The Gait and Balance Gym (Gabagym) is a 21 square metre space with free and machine weights, as well as exercise bikes and treadmill. Equipment available at the Gabagym includes the Balance Rehabilitation Unit (BRU), a 3D virtual reality system that can be used for posturography assessment and balance training, a GAITrite pressure sensitive walkway to measure temporal spatial parameters and identify gait anomalies, and whole body vibration platforms used to increase bone and muscle mass in older persons.

Falls and Fracture Clinic

A dedicated Falls and Fracture Clinic undertakes clinical assessments, exercise interventions and educational programs, combined with imaging-informed lifestyle modification.

Metabolic Testing and Imaging

The metabolic testing area houses a research grade treadmill and lode bike, as well as metabolic cart and a 12 lead ECG for cardiopulmonary testing and analysis. Modern imaging facilities also include: two Hologic Horizon DXA systems, allowing assessment of bone density and body composition, and a peripheral quantitative computed tomography machine (pQCT) to assess bone and muscle quality.

Basic Sciences and Animal Laboratories

The Physical Containment (PC2) and Office of the Gene Technology Regulator (OGTR) certified laboratories, which are housed on the same floor as the clinical spaces to provide better integration between basic science and clinical application, contain numerous state-of-the-art research equipment, which are made freely available to AIMSS members from the three partner organisations. These features include: animal housing facility, including a separate breeding room, animal behavioural testing, animal X-ray, as well as a brand new IVIS Lumina III capable of imaging both fluorescent and bioluminescent reporters. Additional experimental facilities include: two

technician-operated fluorescence-sorted cell sorters (FACS), providing great sensitivity and precision sorting; a 4-laser confocal microscope; histology facility for paraffin embedding and cutting, cryostat for frozen sectioning, and specialised microtome with plastic knife for bone analysis; image analysis platform; bioplex for multiple cytokine analysis; multi-wavelength absorbance and fluorescence plate reader; two tissue culture rooms; Seahorse metabolic testing system; whole muscle and single fibre ex vivo analysis systems; and extensive ultra-freezer and liquid nitrogen storage facilities.

Infrastructure Support

Post Graduate Research Candidates are supported by a research management infrastructure that aids grant and clinical trial management, research recruitment, basic science and project administration. Staffing includes a Clinical Research Manager, Clinical Trials Coordinators and Research Assistants, Exercise Physiologists, Medical Imaging Specialists, Technical and Research Support Officers, Animal and Laboratory Technicians, Laboratory Managers, a Registered Nurse and specialist clinicians (e.g., geriatricians, endocrinologists).

Joseph Polidano - PHD Candidate
Department of Medicine - Western Health
Post Graduate Student Representative

I began my PhD project at the Department of Medicine - Western Health in July 2017 under the supervision of Associate Professor John Price. My project is exploring new and effective anti-metastatic cancer therapies. Completing a PhD can be quite challenging, but it is also extremely rewarding. Having access to the excellent lab spaces we have here and being surrounded by passionate and enthusiastic researchers is extremely motivating, and I consider myself to be very fortunate to have been given this exciting opportunity.

1. Circulating Osteogenic Precurors: Building Bone from Blood

Supervisors: Prof Gustavo Duque and A/Prof Kulmira Nurgali
Project site: Western Health
Contact: Prof Gustavo Duque (gustavo.duque@unimelb.edu.au)

Project description: Circulating Osteogenic Precursor (COP) cells are a newly discovered type of stem cell located in the blood. It is hoped that these cells could be a readily accessible target for cellular therapies in a range of diseases in the aging musculoskeletal system, however before they can be utilised clinically their biological nature and relationships with both normal physiology and pathology must be investigated. Our research takes a translational approach to the investigation of COP cells, with basic science research informing clinical investigation, which further influences our laboratory studies. Our current basic science studies are currently exploring the potential for COP cells to multiply and expand in cell culture, their ability to differentiate into different tissue types (such as bone, fat and muscle), as well as their genetic makeup. Clinically we are identifying their relationships with vitamin D and bone density to inform their potential for future development as biomarkers or therapeutic approaches for musculoskeletal disease. COP cells are an exciting, novel field of research, of which our team is at the forefront - ensuring a wide array of potential discovery and innovation.

2. Assessment of the Falls and Fractures Prevention Clinic as the Most Effective Setting to Reduce Falls and Fractures in High-Risk Older Persons: A Care Program Assessment

Supervisors: Team of Supervisors at AIMSS
Project site: Western Health
Contact: Steven Phu (steven.phu@unimelb.edu.au)

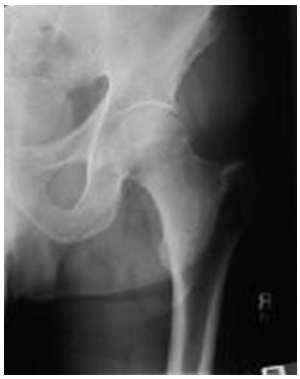
Project description: Western Health is one of the two centres in Australia that have implemented a new Falls and Fractures Prevention Clinic (FFPC). However, the effectiveness of this care model has not been assessed. We will assess the impact of the FFPC at reducing falls and fracture risk from initial assessment to six month follow up. Falls-risk factors assessed at the FFPC will include orthostatic hypotension, sarcopenia, depression, balance or vestibular abnormalities, dizziness, medication risks for falls, vasovagal symptoms and number of previous falls. Fracture risk factors screened at the clinic will include medications, nutrition, bone mineral density and secondary causes of osteoporosis. Patients will also be offered a DEXA scan if appropriate. The relationship between interventions and falls and fracture risk from that recommended at the initial assessment to the six month follow up will also be assessed. In addition, effectiveness of the following interventions – usually recommended at the clinic – will be assessed alone or in combination: osteoporotic medications; vitamin D and calcium supplementation; balance training; gentle balance exercise; protein supplementation; hip protectors; occupational therapy and physiotherapy.

3. Predicting Disability and Frailty in Older Persons: The Western Osteosarcopenia and Frailty (WOSF) Study

Supervisors: Prof Gustavo Duque and Steven Phu
Project site: Western Health
Contact: Diana Navarro-Perez (diana.navarroperez@unimelb.edu.au)

Project description: The anticipated rise in the number of older people this century will inevitably be accompanied by an increase in the number of people with disabilities. Frailty, which comprises changes associated with ageing and chronic disease, usually precedes disability. Several potential operational definitions of frailty have been proposed, but none

has become the gold standard for identifying frailty in the clinical or research setting. Therefore, the research agenda on frailty is focusing on the development of robust biomarkers and diagnostic tests for frailty.



Sarcopenia is a geriatric syndrome encompassing the loss of muscle mass and strength or physical performance with age. Sarcopenia is a major determinant of frailty. The term osteosarcopenia has been used to describe those frailer subjects suffering from both osteopenia/ osteoporosis and sarcopenia. Between 2009-15, we comprehensively assessed 960 older fallers from Western Sydney (mean age=82, 62% female). We found that 40% of this population fulfilled clinical criteria for osteosarcopenia. In addition, this sub-population was frailer and showed a higher prevalence of falls and fractures. We locally tested and validated quantification of the percentage of circulating osteoprogenitors (COP) cells (%COP) as a surrogate of mesenchymal stem cells (MSCs). Our results demonstrated an age-related decline in %COP, while also allowing us to identify a reference range of %COP in an age and gender-matched population, which was previously unknown. We also found that this method is non-invasive, reliable and easy to perform, with strong potential to translate into clinical practice in the near future. We hypothesise that %COP is highly likely to become a robust biomarker for frailty and a predictor of osteosarcopenia, frailty and disability in older persons. The Western Osteosarcopenia and Frailty (WOSF) Study will comprehensively assess and closely follow a larger sample of older persons (65 and older) in Western Melbourne once a year for a period of 3 years. Expected outcomes will include the validation of a new biomarker for the diagnosis of frailty, and the identification of its predictive value for osteosarcopenia, frailty and disability.

4. Mid-Thigh Bone and Muscle Mass Measurements as an Assessment Tool for Diagnosis of Osteoporosis/penia, Sarcopenia and Osteosarcopenia: A Longitudinal Validation Study

Supervisors: Prof Gustavo Duque and Dr Ebrahim Bani Hassan
Project site: Western Health
Contact: Dr Ebrahim Bani Hassan (ebrahim.bani@unimelb.edu.au)

Project description: As we get older we lose bone and muscle mass and quality, known as osteoporosis and sarcopenia, respectively. As we lose bone mass our bones become brittle and easier to break. With less muscle mass we become weaker and possibly frail, in addition to becoming prone to falls. Those who have both weak muscles and brittle bones are called osteosarcopenic. Such patients are very prone to frailty, falls and fractures.

DXA is a technique that takes x-ray images of the body and estimates the amount of bone, muscle and fat in our body. This technique is used to diagnose osteoporosis, sarcopenia and osteosarcopenia. Currently the DXA measurements (at femoral neck and spine for bone, and whole-body for muscle mass) for early detection, prevention and treatment of the abovementioned diseases are not optimum. In other words, their ability to predict the rate of bone and muscle wasting with age can be improved.

Our preliminary (pilot) study demonstrated that the middle of the thigh might be a better place to measure muscle and bone mass in DXA images as the bone and muscle mass size in this area is most strongly related to age. However, long-term studies are required to determine if mid-thigh bone and muscle mass declines over time predict outcomes, like falls and fractures better than the customary methods.

We will use a dataset of a study at the University of Western Australia to further validate our previous studies and we will include mid-calf and total thigh regions of interest in the new study as well. This study is called “Longitudinal Study of Aging in Women” (LSAW). The results of this study can increase our ability to detect bone and muscle loss at earlier stages and possibly pre-

dict the risk of falls and fractures with higher precision.

5. Investigating the Relationship between Fat, Bone and Muscle

Supervisors: Prof Gustavo Duque and Dr Ebrahim Bani Hassan
Project site: Multi-Centre (international)
Contact: Dr Ebrahim Bani Hassan (ebrahim.bani@unimelb.edu.au)

Project description: Osteoporosis, sarcopenia, frailty, falls and fractures in older Australians are a huge burden on the economy and health system. There is a great opportunity to address the issue by investigating how changes in the musculoskeletal system can lead to the weakening of our bones and muscles as we age; and how we can prevent falls and fractures by understanding such changes.
Using 3D CT scans of the musculoskeletal system, we will study and determine how the bone, muscle and fat interact and can influence the occurrence of falls and fractures. This research is computer-based and involves learning image analysis and elementary statistics.

6. New Methods for Investigating Bone Muscle and Fat Mass Using 2D DXA Images to Predict Performance, Risk of Falls and Fractures

Supervisors: Prof Gustavo Duque and Dr Ebrahim Bani Hassan
Project site: Multi-Centre (international)
Contact: Dr Ebrahim Bani Hassan (ebrahim.bani@unimelb.edu.au)

Project description: Dual X-ray absorptiometry (DXA) is the standard technique to study bone, muscle and fat mass and diagnose diseases such as osteoporosis, sarcopenia and obesity. However, the current techniques of scanning are time consuming and require multiple scans to assess various tissues.
We have a new region of interest for analysing whole body DXA scans that can determine muscle, bone and fat mass in one go and in a matter of seconds. If validated, we can develop a quick, affordable and efficient way of screening people for bone, muscle and fat mass in one go.

We are looking for an enthusiastic research student to undertake a project for 6-12 months and study our newly defined variables' ability in predicting muscle performance, falls and fractures. This research is computer-based and involves learning image analysis and elementary statistics.

7. Understanding the Role of Vitamin D in Muscle Adaptation

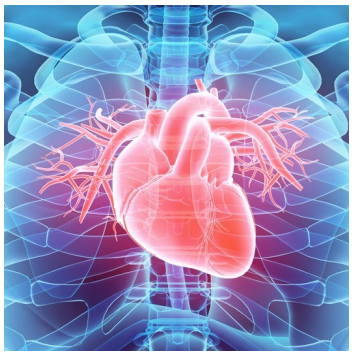
Supervisors: A/Prof Alan Hayes and Prof Gustavo Duque
Project site: Western Health
Contact: A/Prof Alan Hayes (hayes.a@unimelb.edu.au)

Project description: Vitamin D deficiency is common place and older individuals in particular suffer fatigue and muscle weakness as a result. The resultant low bone mineral density and increased falls risk makes fractures and subsequent disability a major consequence. While supplementation is able to reverse this, there is evidence that increasing levels too quickly increases the risks of falls and fractures, possibly due to direct effects of vitamin D on muscle. Indeed, we have recent data that supports a differential role for vitamin D in regulating muscle strength and recovery from fatigue. Interestingly, our most recent study suggests that vitamin D may sensitise skeletal muscles to the effects of exercise. As such it may be important to include activity and exercise with any vitamin D supplementation regime. We aim to further explore this effect with a multifaceted approach to complement our current human trials.

This study aims to understand the complex interplay of vitamin D with muscle function. We will feed animals diets containing different levels of vitamin D, with and without exercise, to deplete,

replete and increase vitamin D levels beyond usual physiological levels. At the same time, key enzymes implicated in the sensitizing effect and the vitamin D hormone-muscle molecular pathways will be knocked down or overexpressed to elucidate potential mechanisms of action. Analysis of muscle will be undertaken at the molecular, mitochondrial, single fibre and whole muscle level to provide a complete picture of the direct effects of vitamin D on skeletal muscle. This project will include the use of animal exercise models and dietary supplementation, animal surgery, recombinant DNA purification and protein purification, the transfection of muscles *in vivo*, isolation and analysis of single muscle fibres, *ex vivo* muscle testing, Western blotting, immunohistochemistry, microscopy and enzyme activity assays.

CARDIOVASCULAR DISEASES



8. Health Outcomes in Culturally and Linguistically Diverse Patients Hospitalised with Heart Failure: Exploring Health Disparities in an Australian Population

Supervisors: A/Prof Christopher Neil and A/Prof Sharon Lee Brennan
Project site: Western Health
Contact: A/Prof Christopher Neil (christopher.neil@unimelb.edu.au)

Project description: Heart failure (HF) is a large chronic disease group which continues to pose a significant challenge to the Australian Health System. We previously identified an apparent health disparity among patients presenting with this diagnosis to a particular Health Network in Metropolitan Melbourne (Western Health), in that culturally and linguistically diverse (CALD) patients suffered relatively worse outcomes (published 2019). The work proposed in this project will be an extension of the previous work to a cohort including all HF presentations in the state of Victoria over a defined period (>20,000 patients), utilizing a matched administrative data set derived from the Victorian Admitted Episodes Dataset. The primary purpose of this work will be to determine whether CALD patients are subject to differential rates of hospitalized and mortality. Secondary analyses will explore socioeconomic determinants of outcome in this chronic disease group.
The project is well defined, with ethics and governance currently in place. The supervisory team has extensive experience in data linkage methodology, epidemiological research in health disparity, as well as subject matter expertise in HF. Given the magnitude of the dataset and matching methodology to be employed, both computing skills (including proficiency in Stata or R programs) and statistics will be required and supported within the Department of Medicine - Western Health. The work arising from this project is of high strategic interest to Health Care in Australia and will suit a candidate wishing to become established in data linkage and epidemiological research.

CELL AND MOLECULAR BIOLOGY

9. Enteric Neuropathy as a Target to Alleviate Gastrointestinal Side-effects of Chemotherapy

Supervisors: A/Prof Kulmira Nurgali
Project site: Western Health
Contact: A/Prof Kulmira Nurgali (kulmira.nurgali@unimelb.edu.au)

Project description: Chemotherapy is given to most cancer patients before or after surgery. Diarrhoea, constipation, oral mucositis, nausea and vomiting are experienced by 80-90% of patients as gastrointestinal (GI) side-effects of chemotherapeutic medications. As a result, patients often develop malnutrition and dehydration. Early death rates of up to 5% associated with chemotherapy are primarily due to GI toxicity. The GI side-effects often limit the dose of chemotherapy

reducing the efficacy of anti-cancer treatment. Chronic post-treatment diarrhoea can persist for over 10 years in cancer survivors. Most drugs used clinically to alleviate GI side-effects of chemotherapy have adverse effects themselves and often have limited efficacy, thus a search for novel therapies is crucial.
The traditional view is that GI side-effects of anti-cancer drugs are due to mucosal damage. However, while mucosal damage is undoubtedly significant for the acute symptoms associated with chemotherapy, persistence of GI symptoms long after treatment suggests that there is long term damage to GI innervation. The enteric nervous system resides within the gut wall and controls GI functions. Despite mounting evidence for chemotherapy-induced enteric neuropathy, research in this area is scarce.
Our recent published and unpublished studies in both chemotherapy-treated patients and animals revealed damage and death of enteric neurons contributing to GI side-effects. Our studies provide strong evidence that oxidative stress, direct toxicity and inflammation induce enteric neuropathy associated with chemotherapy. Our data demonstrate that co-treatment with neuroprotective and anti-oxidant agents alleviates enteric neuropathy and GI dysfunction as well as potentiates the anti-tumour efficacy of chemotherapy.
Novel therapies targeting specific molecules both for prevention and reversal of enteric neuropathy and GI dysfunction hold promise for a breakthrough therapy that could significantly improve patients' quality of life after anti-cancer treatment. This novel neuroprotective strategy will lead to the development of therapies without adverse effects and provide avenues for safe chronic long-term anti-cancer therapy at the most effective tumour suppressing doses.

10. Mesenchymal Stem Cell-based Therapies for Inflammatory Bowel Disease and Colorectal Cancer

Supervisors: A/Prof Kulmira Nurgali
Project site: Western Health
Contact: A/Prof Kulmira Nurgali (kulmira.nurgali@unimelb.edu.au)

Project description: Inflammatory bowel disease (IBD), comprising 2 main pathologies, ulcerative colitis and Crohn's disease, affects >85,000 Australians. The severity of chronic inflammation leads to gut perforations, fistulae, cancer and death. Current therapeutics for IBD are very toxic, have severe adverse effects and become ineffective over time. Thus, 70-90 % of IBD patients undergo surgical removal of the damaged intestinal tissue during the course of the disease; about 40% of these patients require repeated surgery. Thus, the search for novel therapies for the treatment of IBD is crucial.

Gastrointestinal (GI) functions are mostly controlled by the enteric nervous system (ENS) embedded in the gut wall. We have demonstrated that structural and functional changes in the ENS can result in persistent alterations of intestinal functions long after the acute stage of inflammation. Damage to the ENS is prognostic of disease progression and recurrence. Therefore, the ENS is a viable target for effective therapies to attenuate GI dysfunction and decrease disease severity.
Mesenchymal stem cells (MSCs) have strong anti-inflammatory and neuroprotective properties. My group is the first in the world to provide strong evidence that treatment with MSCs alleviates enteric neuropathy and GI dysmotility associated with acute intestinal inflammation. We showed that MSCs have the ability to attenuate tissue damage and promote functional recovery by producing trophic factors that stimulate endogenous tissue repair mechanisms and induce survival of enteric neurons. To date, no studies have addressed the long-term side-effects of such therapies. Our team is in an excellent position to test the effects and mechanisms of MSC treatment using a mouse model of spontaneous chronic colitis with symptoms very similar to human IBD. Studies in this model will provide invaluable data on the efficacy of the MSC-based treatments at different stages of disease (early, advanced) and periods (remission, relapse) making the study clinically relevant.
The proposed project will investigate the role of neuroprotective factors released by MSCs in alleviation of colitis-associated enteric neuropathy. Understanding mechanisms of neuroprotective

effects of MSCs will lead to target identification for therapeutic intervention and provide avenues for the development of MSC-based therapies for IBD.

11. Role of the Nervous System in Cancer Development and Progression

Supervisors: A/Prof Kulmira Nurgali
Project site: Western Health
Contact: A/Prof Kulmira Nurgali (kulmira.nurgali@unimelb.edu.au)

Project description: The nervous system governs functional activities of many organs. Solid tumour like organs are also innervated by nerve fibers. The nervous system can modulate angiogenesis, the tumor microenvironment, immune functions and inflammatory pathways to influence metastases. Peripheral nerve invasion provides an alternative pathway for the spread of cancer cells when blood and lymphatic metastases are absent.

It is reasonable to hypothesize that different stages of cancer progression may be controlled by the changes in different types of nerve fibers, receptors and neurotransmitters influencing the immune response, tumour microenvironment and angiogenesis. Moreover, anti-cancer chemotherapy might modify these neutrally-induced processes, in some cases leading to chemotherapy-resistant tumourigenesis.
Aims of this study: In the colon tissues from animal models and patients with primary and metastatic colorectal cancer:
To determine the changes in innervation correlated to the different stages of cancer development and progression.
To investigate the interaction between innervation, immune cells, inflammatory mediators and tumour progression.
To understand the role of the nerve fiber proliferation in tumour angiogenesis.
To study the effects of anti-cancer chemotherapy on the colon innervation and the role of chemotherapy-induced oxidative stress in neurally-induced angiogenesis.
Significance of the project:
Despite the increasing interest to the role of the nervous system in cancer development and progression, the knowledge in this area is scarce. The blockers for α- and β-adrenergic receptors and neurotransmitter antagonists have exhibited promising anti-tumour activities in experimental studies. Further elucidation of the molecular mechanisms will provide better understanding of the relationship between innervation, immune system, and tumour progression. Revealing the interplay between the nervous and immune systems in cancer may open new avenues for understanding mechanisms of tumour development and progression, identification of new biomarkers for cancer diagnosis and prognosis, and defining novel targets for therapeutic interventions.

12. Inflammation-induced Cancer: Mechanisms and Novel Treatments

Supervisors: A/Prof Kulmira Nurgali
Project site: Western Health
Contact: A/Prof Kulmira Nurgali (kulmira.nurgali@unimelb.edu.au)

Project description: Colorectal cancer (CRC) is the second most commonly reported cancer in Australia. It accounts for over 1.4 million reports with over 700,000 deaths globally. Chronic inflammation has been considered a direct link to CRC susceptibility. Inflammatory Bowel Disease (IBD) is considered a risk factor for CRC. Our collaborator Dr R Eri from the University of Tasmania recently established a novel model of colitis-associated colorectal dysplasia. We have established pre-clinical models of IBD and colitis-associated colorectal cancer closely resembling symptoms and pathophysiology of human diseases. We hypothesise that progression of chronic intestinal inflammation into colorectal cancer results from alteration to gastrointestinal innervation and neuro-immune interactions.
Project Group Major Aims:

1. To investigate immunological pathways and checkpoint biomarkers involved in colitis-associated colorectal cancer in pre-clinical mouse models.
2. To determine the effects of CRC progression on gastrointestinal innervation in the models of IBD and colitis-associated colorectal dysplasia.
3. To determine the effects of anti-eosinophil drugs, neuroprotective drugs and checkpoint inhibitors on the ENS and GI dysfunction in the models of IBD and colitis-associated colorectal dysplasia.

This is the first study to investigate the development and progression of colorectal cancer in a mouse model of spontaneous chronic colitis. Bioactive factors and their molecular signalling pathways by which CRC develops in an inflamed environment will be determined.

This study is the first to test therapeutic potential of anti-eosinophil drugs, neuroprotective drugs and checkpoint inhibitors on the development and progression of inflammation-induced colorectal cancer.

13. Defining the Role of Transcriptional Stress Pathways in Cancer Cell Resistance Towards Anti-Cancer Therapeutics

Supervisors: A/Prof John T. Price
Project site: Western Health
Contact: A/Prof John T. Price (john.price@unimelb.edu.au)

Project description: *De novo* and acquired resistance of cancer cells towards chemotherapeutics, hormonal treatments, as well as recently developed targeted therapeutics such as those that inhibit the actions of EGF-R family members like HER2, has become a major clinical issue. Almost always co-associated with the emergence of an aggressive and often highly metastatic cancer phenotype, drug resistance is intimately linked with cancer recurrence and in most cases precedes poor patient health, the escalation of disease progression ultimately leading to the death of the patient. Although substantial insight has been gained in the molecular pathology of many cancer types such as breast, lung, prostate and melanoma, still our knowledge of resistance mechanisms or more importantly its translation to the clinical scenario to combat the emergence of drug resistance is greatly needed. Findings from our laboratory have identified that many anti-cancer drugs stimulate transcriptional pathways in cancer cells that mediate the cytosolic stress, ER stress and genomic stress responses that may enable cancer cells to counteract the actions of the anti-cancer drugs. This project will examine the role of stress transcription factors such as Heat Shock Factor 1 (HSF1) and a number of its downstream targets and their role in anti-cancer drug resistance in breast, lung and melanoma cancer cells towards traditional chemotherapeutics as well as recently clinically relevant targeted therapeutics. This project will utilise molecular, cellular, pharmacological and biochemical approaches to determine the role of these molecules in both de novo and acquired drug resistance. It is expected that this project will contribute to identifying the role of stress responses in drug resistance mechanisms, provide novel biomarkers for predicting drug responsivity in differing cancer types and contribute to the training of the candidate in molecular, cellular, pharmacological and biochemical approaches in cancer research.

14. Investigating Lipotoxic Impacts of Fatty Acid Synthesis on: (1) Osteoblasts, and (2) Osteoclast, *in Vitro and (*3) Skeletal Muscle

Supervisors: A/Prof Damian Myers and Dr Ahmed Al Seadi
Project site: Western Health
Contact: A/Prof Damian Myers (damianem@unimelb.edu.au)

Project description: Bone is a dynamic organ that remodels and changes in composition throughout the lifespan. As a vital organ, bone is required for weight-bearing and motion, for haematopoiesis and energy storage, among others (Suchacki et al. 2017). Dysregulation of remodelling of bone can lead to pathological bone states such as osteoporosis and fractures (Frost 2003). Early in life, a beneficial relationship exists between body weight and bone density as fat mass positively correlates with bone strength and decreased fracture incidence in at-risk popula-

tions (Cornish et al. 2002). However, with ageing, high fat mass can have negative impacts on bone. In the elderly, evidence suggests that fat tissue can undergo a toxic shift in which adipocytes secrete excessive lipids, predominantly fatty acids such as palmitic acid (PA) (Gasparrini et al. 2009, Tagliaferri et al. 2015). The transition for when the benefits of increased adipose tissue in bone results in pathological impacts is unclear (Ilich et al. 2014) and further research is needed into how lipotoxicity affects each of the cells that control bone turnover, the osteoblasts and the osteoclasts.
Hypothesis: Fatty acid synthase inhibition by CER has been identified as a possible candidate for future treatments of musculoskeletal diseases but the mechanisms of action is not known. We propose that CER may affect either osteoblasts or osteoclasts, individually; however, CER may also affect the coupling that occurs between osteoblasts and pre-osteoclasts during osteoclastogenesis.
In this study we will investigate the impacts of CER on each of the osteoblasts and osteoclasts in in vitro culture as well as the effects of CER on co-cultures of osteoblasts and monocyte/ macrophages, the pre-osteoclastic cells.
Outcomes: This project will define whether FAS inhibition affects osteoblasts and osteoclasts in in vitro culture and, also, whether CER may have an impact on bone turnover by affecting osteoclast coupling and osteoclast formation (osteoclastogenesis).

15. Genotype and Phenotype Characterisation Human Circulating Osteo-Progenitor (COP) Cells

Supervisors: Prof Gustavo Duque and Team of Supervisors at AIMSS
Project site: Western Health
Contact: Jack Feehan (jfeehan@student.unimelb.edu.au)

Project description: COP (circulating osteogenic progenitor cells) is a term referring to circulating bone marrow-derived progenitor stem cells, which are able to participate in bone formation such as bone marrow-derived mesenchymal stem cells (MSC) and endothelial progenitor cells (EPC). The origin and function of COP cells remain unknown. However, some studies have reported that COP cells are recruited from bone marrow and perivascular niche to fracture sites in order to enhance healing. COP cell levels have been reported to be associated with postmenopausal-osteoporotic state and heterotopic calcification or bone formation states. A low bone mineral density (BMD) in postmenopausal women seems to have an inverse relationship with COP cell levels. Low percentage of COP cells has been also associated with disability and frailty in older persons. However, the genetic and biological phenotype of COP cells has not been fully characterised. This project will use genetic and molecular techniques to fully characterise COP cells from young and older individuals. Results of this project will allow us to determine whether COP cells could be a useful approach as a biomarker and/or treatment to musculoskeletal diseases and frailty.

16. Bone Substrate Composition Affecting Bone Cell Formation, Function and Bone Turnover

Supervisors: A/Prof Damian E. Myers, Prof Natalie Sims, and Prof Brett Paull
Project site: Western Health
Contact: A/Prof Damian Myers (damianem@unimelb.edu.au)

Project description: *Background*: Bone substrate can affect both bone cell formation and bone cell function. Dysregulation of bone cells and altered turnover of bone are central to pathophysiology of bone. Both physical properties and chemical components may play a role. This project has been designed to assess whether carbonate substitutions and phosphorylation of bone substrate can affect the formation of bone and then the function of these cells.
Approach and techniques: 3D bone substrates with different chemical properties will be pre-

pared and then human bone cells, both osteoclasts and osteoblasts, will be incubated in the scaffold for a period of 3-4 weeks. Substrates will include special cell culture polystyrene and bone cement that will be prepared with collaborators at the University of Tasmania.
Measures of cell activity will be monitored including proliferation and differentiation and physical features, as well as changes in the 3D bone substrate. These changes will be monitored using conventional histocytochemistry, RT-PCR and advanced imaging techniques including X-ray CT and confocal microscopy.

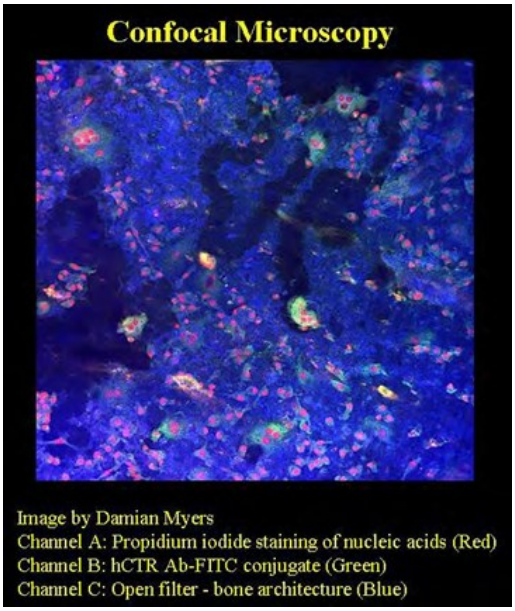


Image by Damian Myers
Channel A: Propidium iodide staining of nucleic acids (Red)
Channel B: hCTR Ab-FITC conjugate (Green)
Channel C: Open filter - bone architecture (Blue)

This project will involve interaction with the Australian Centre for Research on Separation Sciences (ACROSS) at the University of Tasmania (Prof Brett Paull).

Outcomes and skills: The candidate will learn tissue culture techniques as well as special techniques for the preparation and culture of different types of bone cells. This student will also become proficient at basic histology procedures including histochemistry and immunocytochemistry, quantitative techniques for gene expression (PCR techniques) and microscopy techniques including fluorescence and confocal microscopy.

17. Pre-clinical Analysis of Effects of Lamin A Overexpression on Mesenchymal Stem Cell Differentiation into Myocytes

Supervisors: Prof Gustavo Duque
Project site: Western Health
Contact: Dr Ahmed Al Saedi (ahmed.mohan@unimelb.edu.au)

Project description: Falls and fractures are highly prevalent in the elderly. Around 20,000 hip fracture cases are reported in Australia every year, and nearly 25% of patients who sustain a hip fracture die within a year. Since a large number of fractures occur due to a fall, decrease in muscle size and strength with age (sarcopenia) seems to relate directly with the incidence of fall-related fractures. Both muscle cells (myocytes) and bone forming cells (osteoblasts) arise from the same precursor (mesenchymal stem cell; MSC), which makes this link biologically significant. MSCs are known to have an altered protein expression profile with age. Lamin A is a nuclear lamina protein associated with translocation of key translational factors affecting the bone formation pathways in MSCs. Lamin A expression is known to decrease with age in MSCs. This leads to the possibility of its role in muscle ageing too. We hypothesize that overexpression of Lamin A in MSCs could reverse age-associated decrease in muscle cells.

We will use both *in vitro* and *in vivo* approaches in appropriate models to meet our goals. Students will be involved in *in vitro* studies involving MSC over-expression of Lamin A, differentiation of transformed MSCs into myocytes/osteoblasts/adipocytes, as well as *in vivo* tracking of injected MSCs in mice; bone histomorphometry and microCT analysis of mice/rat bones.

18. Identification and Characterisation of Molecular Mediators of Cancer Metastasis

Supervisors: A/Prof John T. Price
Project site: Western Health
Contact: A/Prof John T. Price (john.price@unimelb.edu.au)

Project description: Cancer accounts for 1/3 of all Australian deaths and is a major social

and economic burden. The prime feature of treatment failure as well as the cause of majority of death in cancer patients is due to the spread of the cancer to other sites within the body, a process termed metastasis. Major sites of metastasis include bone, brain, lungs, kidney and liver and although metastasis is a major clinical problem, still much is to be learned regarding the molecular drivers of metastasis and the translation of this knowledge to the generation of effective anti-metastatic cancer therapeutics. To address this, we have used a number of isogenic cancer cell lines with differing levels of metastatic potential and using gene expression analysis we have identified a number of putative molecular mediators of metastasis and therefore potential therapeutic targets of metastasis. This project will utilise a wide-array of molecular, cellular, and biochemical approaches as well as the use of *in vivo* metastatic models, to examine the role of these molecules in important cell biological features of the metastatic cancer cell such as seeding, survival, proliferation, migration, invasion and intracellular signalling pathways. Moreover, this project will also seek to identify and test inhibitory compounds towards these putative 'drivers of metastasis' to provide the basis for the development of novel anti-metastatic therapeutics. It is expected that this project will contribute to the identification of novel drivers of metastasis as well as leading to the isolation of new anti-metastatic therapeutics. It will also provide the successful candidate with intensive training in the areas of cancer cell biology, molecular biology, cell signalling, protein biochemistry and experimental *in vivo* metastatic cancer models.

19. Pre-Clinical Studies Identifying Novel Molecular Regulators of Skeletal Muscle Growth and Atrophy

Supervisors: A/Prof Alan Hayes
Project site: Western Health
Contact: A/Prof Alan Hayes (hayes.a@unimelb.edu.au)

Project description: Skeletal muscle play a fundamental role in the generation of movement and the regulation of whole body metabolism. Muscle mass is lost with prolonged periods of disuse due to injury or immobilization, with diseases such as diabetes, heart disease, cancer, and with ageing. Muscle mass decline can severely impair the ability to perform activities of daily living leading to a further reduction of physical activity and a vicious cycle of inactivity, muscle loss and inactivity-related disease. Thus, strategies aimed at preventing muscle loss and/or promoting muscle growth are essential to limiting disability and preventing disease. Consequently, a thorough understanding of the molecular mechanisms that regulate skeletal muscle mass is crucial to the development of effective exercise programs and potential pharmacological interventions aimed at preventing muscle atrophy/wasting and/or promoting skeletal

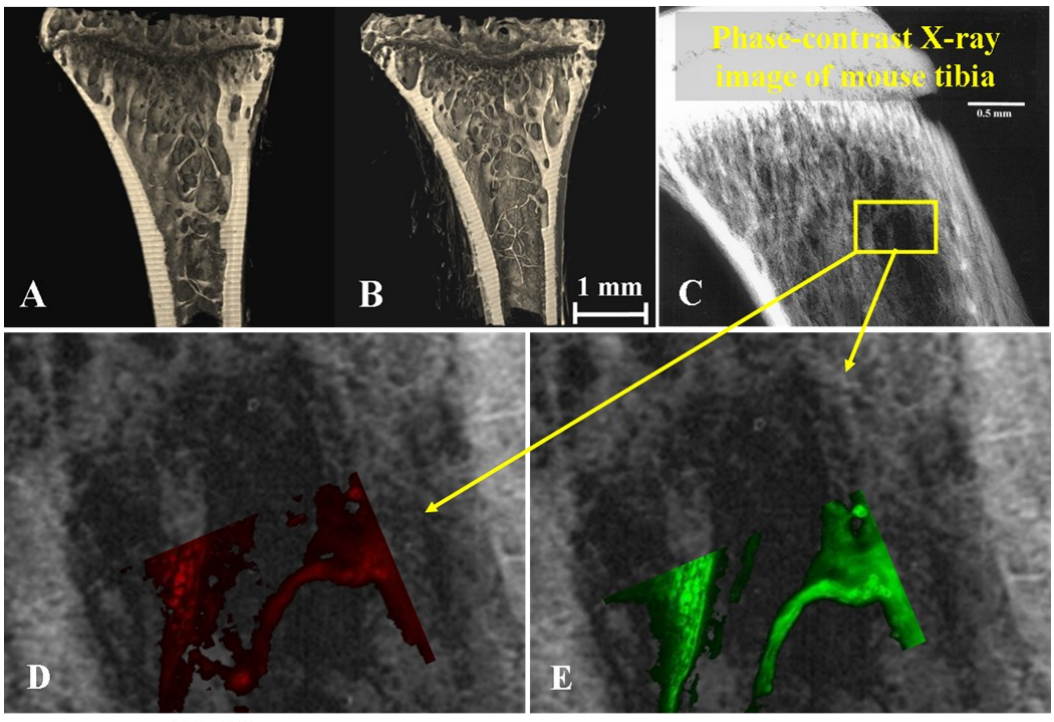


Figure 3: 2D and 3D PCI of whole mouse tibiae and immuno- and cyto-chemical staining to show osteoclast structure and function. Panel A shows a control tibia and Panel B is a tibia exhibiting effects of a drug causing bone loss. These are whole bones imaged using PCI tomography (not rendered) and analysed with XTRACT™ for electronic sectioning.

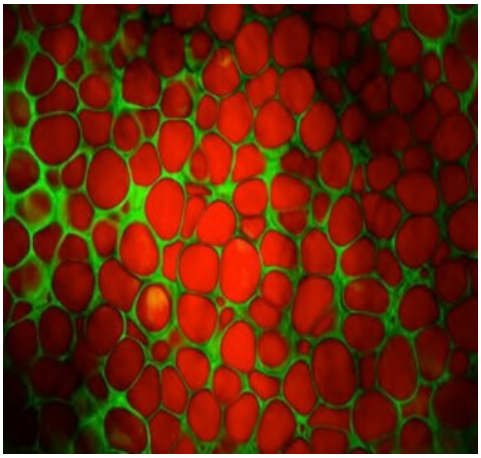
muscle growth.

The aim of this project is to use rodent- and cell-based models to examine the potential for specific growth factors, signalling molecules, metabolic enzymes and/or transcription factors to stimulate muscle growth or promote muscle atrophy. Genetic gain-of-function (overexpression) and loss-of-function (knockdown) studies will be used, as well as various models of altered physical activity (e.g. immobilization, denervation, mechanical overload) and altered nutrient intake (e.g. food deprivation, protein supplementation). Mechanistic insights into changes in muscle mass will be obtained using molecular analyses that include measures of changes in rates of protein synthesis and protein degradation, the phosphorylation of critical signalling proteins and transcription factors, and gene expression, and the use of DNA-based reporter constructs. Morphological and functional changes will also be examined. This project will include the use of animal surgery, recombinant DNA purification and protein purification, the transfection of muscles *in vivo* and in cultured cells, Western blotting, immunohistochemistry, microscopy and enzyme activity assays. We aim to report the findings of this project in high impact peer-reviewed scientific journals.

20. Pathology Begins in the Cells: Studying Lipotoxic Stress Generated from Adipocytes in Bone and Muscle Cell Cultures

Supervisors: A/Prof Damian Myers, Prof John Hamilton, A/Prof Andrew Cooke and Dr Ahmed Al Saedi
Project site: Western Health
Contact: A/Prof Damian Myers (damianem@unimelb.edu.au)

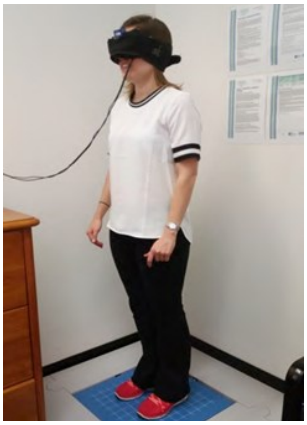
Project description: Osteopenia, osteoporosis and sarcopenia affect the lives of more than 2 million people in Australia and numbers are increasing exponentially due to increased life expectancy. Ageing is the strongest predictor of sarcopenia which is directly correlated with increased falls and bone fractures. The link between muscle health and the quality and strength of bone is underpinned by cell-cell interactions that regulate both cortical and trabecular bone turnover. The association between ageing and sarcopenia/osteopenia can be studied through temporal studies of appropriate animal models by recovery of bones for live-cell imaging of the cortical and trabecular bone. Also, gene modified animals with altered musculoskeletal outcomes can be used to study the onset of muscle and bone changes and for the study of factors that regulate progression of muscle-wasting and bone loss and interactions between muscle and bone. We need to understand how these processes in muscle and bone are linked so we can design and test appropriate interventions. This study focuses on mechanisms of disease that occur with ageing including osteoporosis, sarcopenia and osteopenia. Such pre-clinical models can be used for developing appropriate therapeutic interventions.
Hypothesis: There is a link between muscle loss and bone health and the metabolic dysregulation of lipids. Lipid accumulation in bone/muscle may lead to muscle wasting and bone loss. In this study, combined functional and structural imaging will be used in temporal studies to investigate onset and progression of lipotoxicity in muscle and bone.
Aim: To investigate cell-tissue interactions in pre-clinical models of bone and muscle disease. Biochemical and gene expression studies will be used in parallel with live-cell imaging to investigate cellular interactions in each of muscle and bone.



CLINICAL TRIALS

21. Implementing the Gait and Balance Gym and the Effect on Falls and Falls Risk Factors

Supervisors: Prof Gustavo Duque and Team of Supervisors at AIMSS
Project site: Western Health
Contact: Steven Phu (steven.phu@unimelb.edu.au)



Project Description: Located at the Australian Institute for Musculoskeletal Sciences (AIMSS), the Gait and Balance Gym (Gabagym) is a specialised clinic, which uses innovative and novel methods of training for falls prevention. By translating research into the clinical setting, older patients with a history of falls and fractures will undertake traditional exercise classes, virtual-reality balance training and whole body vibration.
Exercise has been extensively studied and shown to reduce the risk for falls, with the Otago protocol proving particularly effective. Virtual-reality balance training has recently gained prominence, particularly with the use of systems such as the Nintendo Wii. Our clinic makes use of the Balance Rehabilitation Unit (BRU) by Medicaa, a virtual-reality system which is valid and reliable in the assessment and training of static balance. Whole body vibration is another novel method of balance training, with our Powerplate platforms demonstrating positive effects on measures of strength, balance, mobility and bone mineral density in a time effective manner. This study aims to investigate the effect of three training modalities (exercise, virtual-reality and whole body vibration) on fall rates and identified measures of falls risk and function. Outcome measures will include the Short Physical Performance Battery (SPPB), handgrip strength, timed up and go, four square step test and posturography assessment (using the BRU). Subjective measures of fear of falls and adherence rates will also be reported.

22. The Correlation between Knee Effusions and Clinical Presentation in Patients with Knee Osteoarthritis

Supervisors: A/Prof Keith Lim and Dr Albert Leung
Project site: Western Health
Contact: A/Prof Keith Lim (kklim@unimelb.edu.au)

Project description: Knee osteoarthritis (OA) is one of the leading causes of disability worldwide and its prevalence is increasing. Locally, over 2.1 million Australians are affected and this figure is increasing secondary to our obesity epidemic. Previous studies indicate that there is discordance between radiographic severity and the clinical symptoms of knee OA patients. Our aim is to evaluate the correlation between the knee effusion size and the clinical presentation of knee OA patients. Utilising the patients enrolled from a dedicated hip and knee OA clinic, we will evaluate their baseline clinical parameters and the size of their knee effusions. We hope this would add to our understanding in managing knee OA patients.

23. Analysis of Synovial Fluid and Peripheral Blood Samples from Patients with Rheumatoid Arthritis and Using Patients with Osteoarthritis as Controls.

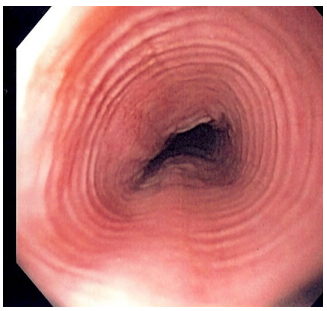
Supervisors: A/Prof Keith Lim and Prof John Hamilton
Project site: Western Health
Contact: A/Prof Keith Lim (kklim@unimelb.edu.au)

Project description: Better understanding of the pathophysiology of Rheumatoid arthritis (RA)

has led to the development of new therapeutic strategies. Despite this there is still an unmet need with an important number of patients not achieving low disease states or remission. Granulocyte macrophage-colony stimulating factor (GM-CSF) has been found to be a key mediator in inflammation and autoimmunity, and is seen as a novel target for treatment in RA. The downstream effects of GM-CSF blockade still need to be better delineated. We hypothesize that there is a pro-inflammatory autocrine/paracrine loop involving cytokines like GM-CSF and CCL17 which drives RA and possibly osteoarthritis (OA) pathogenesis. The primary aim of this study is to determine the ability of cytokines like GM-CSF to activate synovial fluid mononuclear cells or blood monocytes from RA and OA patients, and the ability of anti-cytokine antibodies to modulate such activation.

Methods: We are recruiting RA and OA patients with symptomatic swollen joints, who require joint aspiration for diagnostic and/or therapeutic purposes. Mononuclear cells and peripheral blood monocytes are isolated from collected samples and are either left stimulated or unstimulated with cytokines (GM-CSF) in the presence or absence of anti-cytokine antibodies. Inflammatory mediator mRNA expression is then measured using qPCR.

24. Novel Approaches in Therapeutic Endoscopy



Supervisor: A/Prof Alan Moss
Project site: Western Health
Contact: A/Prof Alan Moss (alan.moss@unimelb.edu.au)

Project description: The Western Health Department of Endoscopic Services provides a wide range of advanced gastrointestinal endoscopy services. The scope of minimally invasive therapeutic endoscopy is increasingly expanding in the modern era. Our research interests include advanced endoscopic resection techniques for large or complex colorectal polyps, novel approaches to an important and relatively newly described entity of flat colonic polyps known as sessile serrated adenoma (SSA) and endoscopic interventions in the setting of anti-platelet and anti-coagulant medications. Multi- centre randomised controlled trials are currently being initiated. This is the perfect time for a motivated post-graduate research student with an interest in clinical gastroenterology or endoscopy, to undertake a higher degree in a well- supported clinical research setting.

25. Effects of Dichloroacetic Acid (DCA) on Exercise Performance in Patients with Heart Failure with Preserved Ejection Fraction (HFpEF): a Randomized, Placebo-Controlled, Cross-Over Trial

Supervisors: A/Prof Christopher Neil
Project site: Western Health
Contact: A/Prof Christopher Neil (christopher.neil@unimelb.edu.au)
Suitable: PHD Only

Project description: Millions of people worldwide are living with chronic heart failure. 40-50% of these people have Heart Failure with a Preserved Ejection Fraction (HFpEF) contrasted with Heart Failure with a Reduced Ejection Fraction (HFrEF). Whilst there have been remarkable improvements in therapy and outcomes for people with HFrEF, no disease modifying therapy exists for those suffering from HFpEF, who are burdened by marked exertional intolerance. Due to this unmet need, HFpEF is a major research focus for the cardiology community globally. This study will elucidate the therapeutic potential of a metabolically active drug, Dichloroacetic Acid (DCA), in HFpEF Fatty acid (beta) oxidation is the primary pathway in which myocardial cells produce the high energy molecule adenosine triphosphate (ATP). ATP is then used to maintain the function and contractility of myocardial cells, on a beat to beat basis. Oxidation of fatty acids tends to produce ATP at a higher rate of ox-

ygen consumption, than oxidation of glucose, meaning that the latter is a more efficient metabolic fuel. DCA stimulates pyruvate dehydrogenase activity which enhances glucose metabolism. Due to this improved mechanoenergetic efficiency, it is expected that DCA administration may exercise myocardial function in patients with HFpEF. This project will be a randomized, placebo-controlled, cross-over trial involving 20 participants with HFpEF. Participants will receive 6 weight-adjusted oral doses of DCA in 12 hour intervals over 3 days, or a matching oral placebo. After the initial phase of dosing, participants will perform a maximal exercise test and, following one week of 'washout', subjects will then 'cross over' to the other treatment allocation and repeat exercise testing. This project is suitable for the honours student who wishes to experience translational cardiovascular research in a clinical and laboratory environment.

The project is furthermore advantageous for those applicants who may wish to pursue hospital-based employment in the long term or as a prelude to a further study in biomedicine.

COMMUNITY

26. Osteosarcopenia in Community-dwelling Older Adults Attending the Falls and Fracture Clinic

Supervisors: Prof Gustavo Duque and Steven Phu

Project site: Western Health

Contact: Prof Gustavo Duque (gustavo.duque@unimelb.edu.au)

Project description: The Falls and Fracture Clinic was developed to provide a comprehensive assessment for older adults with a risk or history of falls and fractures. As part of this clinic, older adults undertake assessments for their bone mineral density, body composition, function, nutrition and medical history to determine their risk of falls and fractures. With sarcopenia (the loss of muscle mass, strength and function) and osteoporosis being highly prevalent in this population, this project will aim to assess and increase knowledge of osteosarcopenia in older adults.

27. Balance Gym for Falls Prevention in Older Adults

Supervisors: Prof Gustavo Duque and Stephen Phu

Project site: Western Health

Contact: Prof Gustavo Duque (gustavo.duque@unimelb.edu.au)

Project description: The Gait and Balance Gym provides a community program for falls and fracture prevention in older adults through traditional and novel methods. This includes the use of exercise and virtual-reality balance training to improve balance and function. With regards to the virtual reality system available, the Balance Rehabilitation Unit (BRU) involves the use of a force platform and virtual reality goggles containing a head tracker to accurately assess and treat balance disorders. In this project the effect of the Gait and Balance Gym programs on falls will be investigated.

28. Low Health Literacy, Social Disadvantage and Low Treatment Adherence in Rheumatoid Arthritis: An Intervention to Improve RA-Specific Health Literacy in At-Risk Groups

Supervisors: A/Prof Sharon Brennan-Olsen

Project site: Western Health

Contact: A/Prof Sharon Brennan-Olsen (sbrennan@unimelb.edu.au)

Project description: Rheumatoid arthritis (RA) is a painful, debilitating autoimmune disease, in which the immune system may also attack the cardiovascular, respiratory, digestive and haemopoietic systems. Little is known about what influences the unpredictable clinical course of RA (characterized by exacerbations and remissions), why there is high variability in severity between patients, and why treatment adherence in RA is as low as 40% despite chronic, debilitating pain. The unpredictability of RA and treatment adherence has major implications for patient care and the burden on our healthcare system; effective management of RA offers much potential to reduce the high costs associated with this National Health Priority Area.

The social gradient of most chronic diseases is well documented; RA appears to be no exception. However, whether social disadvantage influences the severity of RA is unknown. Furthermore, low health literacy, strongly associated with social disadvantage, reduces patient adherence to treatment, thus increasing the likelihood of unmanaged disease activity; yet, the modifiable factor of health literacy has not been investigated to date.

This PhD or Masters project will identify the baseline magnitude of effect that low health literacy and social disadvantage have on RA severity. Using a clinical trial study design, and implementing 'teach-back' (a sustainable and affordable method to improve the quality of practitioner-to-patient health communications) to improve RA-specific health literacy, the candidate will intervene to improve RA-specific health literacy in the most socially disadvantaged patients, with the goal of increasing treatment adherence. The information from this study will be immediately transferable to clinical practice, and enable the target of clinical remission attainable for all patients.

The overall aims of this project are to (a) establish the baseline effect of low health literacy and social disadvantage on RA severity and treatment adherence; and (b) investigate whether improving RA-specific health literacy using 'teach-back' will increase treatment adherence.

29. Patient Reported Outcomes (PROMs) in Treatment of Community Acquired Pneumonia - a Sub Study of IMPROVe-GAP

Supervisors: A/Prof Harin Karunajeewa
Project site: Sunshine Hospital
Contact: Prof Edward Janus (edwarddj@unimelb.edu.au)

Project description: Using a $300,000 grant from HCF, patients treated for community acquired pneumonia (CAP) will be treated with a combination of four evidence based interventions never previously implemented in combination: specified antibiotic regimes with stopping rules, steroids unless contraindicated, early physiotherapy for mobilization and nutritional assessment and intervention. The study IMPROVe-GAP will be conducted following a step wedged design in 8 clinical teams over one year starting with usual care in all teams and ending with the full intervention in all teams and we expect to enrol 800 patients. In a pilot sub study in 100 patients the focus will be on patient reported outcomes, health economic data and testing for 29 potential bacterial and viral pathogens.

The research physiotherapist running the IMPROVe-GAP project will also undertake the sub study. The results from both will form the basis of a Masters degree. If the sub study shows a larger study is feasible and funds can be found the candidate will likely convert to a PhD.

Funding secured: HCF Project Grant A$300,000

Hospitalization for pneumonia in the elderly: Standardizing evidence-based interventions to shorten length of stay, reduce readmissions, reduce hospital costs and improve patient-reported outcomes. Janus E, Karunajeewa H, Skinner E, Ong ML, Karahalios A, Harrison R, Haines.

HORMONES

30. Effects of Vitamin D Status on DEXA Femoral Neck BMD in Children and Adolescents

Supervisor: A/Prof Christine Rodda
Project site: Western Health
Contact: A/Prof Christine Rodda (christine.rodda@unimelb.edu.au)

Project description: Vitamin D deficiency is a well-established risk factor for femoral neck fracture in the elderly. Furthermore, the antecedents to the development of osteoporosis in later life typically occur across the lifespan. Lifestyle factors leading to decreased direct sun exposure together with increased skin pigmentation, are major risk factors for vitamin D deficiency. At Sunshine Hospital we have previously shown that 82% of children and adolescents presenting with fracture, had clinical risk factors for vitamin D deficiency and half of these were shown to have a 25 hydroxy vitamin D less than 50nmol/l at the end of summer. Anecdotally we have also found that DEXA femoral neck BMD, in a small number of children and adolescents presenting with fracture and vitamin D deficiency, have demonstrated relative regional low BMD at the femoral neck. To date there is no robust data in this demographic to show increased fracture risk with mild to moderate vitamin D deficiency. Initially, a retrospective study will be conducted utilising the Western Health orthopaedic database to search for femoral neck fractures which have occurred in 6 – 18 year olds over the last 2 years. Results of femoral neck DEXA BMD performed on Sunshine Hospital Hologic machine will be retrieved for those who have had this performed, and will be assessed in those who have fractured but not had a DEXA BMD performed at the time of fracture.
A prospective study will then be conducted in the same age group, who present with fracture, and femoral neck DEXA BMD of those who are vitamin D sufficient (25 OH vitamin D greater than 75nmol/l) will be compared with those who are vitamin D deficient (25 OH vitamin D less than 50 nmol/l). Fracture sites and degree of trauma using modified Landin criteria and fracture healing rates will also be compared. It is expected that this study will demonstrate that mild to moderate vitamin D deficiency, without evidence of rickets, contributes to the development of low bone density in children and adolescence, and may possibily contribute to long term osteoporotic hip fracture in later life.

31. Effects of Vitamin D Status on Forearm Fracture Healing Rates in Children and Adolescents: A Pilot Study

Supervisor: A/Prof Christine Rodda
Investigators: A/Prof Christine Rodda, Dr Michael Bullen and Mr Phong Tran
Project site: Sunshine Hospital and Australian Institute for Musculoskeletal Science (AIMSS)
Contact: A/Prof Christine Rodda (christine.rodda@unimelb.edu.au)

Project description: The effect of Vitamin D deficiency on fracture healing rates in children and adolescents is currently unknown. This is a pilot study to investigate the use of pQCT in the evaluation of fracture healing rates, with or without vitamin D deficiency. We have validated the use of PQCT in the presence of casting applied to immobilise forearm fractures and will extend this work to evaluate fracture healing rates in this demographic. This study will be performed as a prospective observational pilot study in children and adolescents aged 8-18 years presenting to the Western Health Sunshine Hospital paediatric orthopaedic outpatients department with a forearm fracture. Eligible patients will be stratified into two groups based on their vitamin D status. Patients in both the vitamin D deficient group (less than 50 nmol/l) and the vitamin

D sufficient group (greater than 75 nmol/l) will be followed and compared over 6 weeks for characterisation of fracture healing and changes in bone structure using pQCT. Those in the vitamin D deficient group will also be allocated to a randomised, placebo control trial of vitamin D treatment versus placebo. The vitamin D treatment group will receive a bolus dose of vitamin D 170,000iu, immediately following fracture. The placebo group will be observed for the duration of the study (6 weeks) and after this will be provided with a bolus dose of vitamin D of 170,000iu. Muscle strength and cross sectional muscle area, of the unaffected arm will also be assessed at each follow up time point for all eligible patients. It is expected that the outcome of this study will provide the basis of a larger placebo controlled trial.

32. Elucidating the Effect of Hyperglycaemia (Short and Long Term) on Bone and Muscle Quality and Metabolism

Supervisors: A/Prof Itamar Levinger, A/Prof Shane Hamblin and Prof Gustavo Duque
Project site: Western Health
Contact: A/Prof Itamar Levinger (Itamar.levinger@unimelb.edu.au)

Project description: Increased bone fragility and reduced skeletal muscle quality are underrecognised complications of long-term hyperglycaemia in type 2 diabetes mellitus (T2DM). As a result, patients have an increased risk of falls, fractures, and a reduced quality of life. The effect of T2DM on bone structure and metabolism is not clear. Some reported that bone micro architectural parameters at the distal radius and tibia were not different between T2DM patients and BMI and age-matched controls while others have even reported improved trabecular microarchitecture. Most reports agree, however, that cortical porosity is increased and mineral strength is reduced in patients with T2DM. Patients with T2DM have reduced bone formation markers: procollagen type 1 N-terminal propeptide (P1NP), osteocalcin and alkaline phosphatase, and some evidence that resorption makers are reduced. In the case of muscle, high blood glucose is associated with fat infiltration and metabolic abnormalities that affect bone mass, strength and function. Whether these effects are due to the high glucose or insulin (hyperinsulinemia is common in T2DM, at least in early stages) is not clear. We hypothesise that bone metabolism and muscle mass and function are consequences of the suppressive effects of high blood glucose.

33. Oral Health and Attitudes in Young Adults Aged 15-25 Years with Diabetes Mellitus: A Case - Control Study

Supervisors: A/Prof Christine Rodda and Prof David Darby
Project site: Western Health
Contact: A/Prof Christine Rodda (christine.rodda@unimelb.edu.au)

Project Description: Adults with poorly controlled Diabetes Mellitus (DM) have more advanced gum disease and people with poorer gum health will have greater difficulty in controlling their DM. Most observational and intervention research has concentrated on the bidirectional association between DM and Periodontal disease in older adults and the oral health of children with Type 1 (T1) DM. As might be expected, the severity of the DM and its duration are also associated with oral health status of patients. It has also been found that people who have self-efficacy in their self-management of their T1DM similarly have better gum health, whereas people with poor or absent self-efficacy will have worse gum health. Self efficacy in both oral hygiene and T1DM management are related to lifestyle habits typically established during adolescence. However, to date there are few published data in this age group. The Young Adult Diabetes Service (YADS) clinic is attended by 15 to 25 year olds, with insulin dependent DM and the majority have T1DM. This age group also covers a period of cognitive and emotional maturation, typically character-

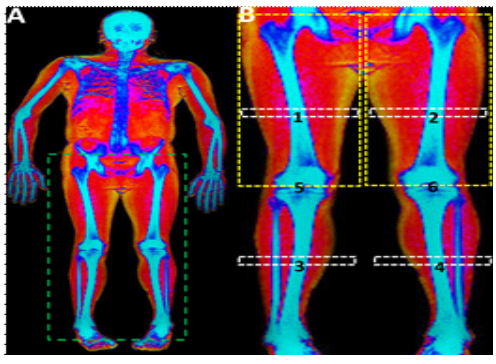
ised by emotional lability, and poor executive functioning. With ongoing separation from parental dependence, there is concurrent transition from dependency to independence of lifestyle routines, behaviours and dietary choices for all adolescents, including those with DM. There is a dearth of studies of this age group because changes are more obvious in later years for both types of DM. We will undertake a case control study with nested sample interviews to assess oral health knowledge, behaviours and attitudes, together with a dental history. The study will be undertaken within the monthly multidisciplinary Young Adults Diabetes Service (YADS) Clinic. Following obtaining signed informed consent, participants will be recruited. All participants, cases and controls, will receive a full dental examination. Dental examinations will be performed by Oral Health Therapists from Footscray Co-Health, under supervision of Dr Jamie Robertson. A short questionnaire for all participants on oral health behaviours and attitudes will be administered, and an interview will be conducted within a stratified sample of cases and controls.

IMAGING

34. Marrow Adipose Tissue Functions: Studying Lipotoxicity in Hip Replacement Candidates

Supervisors: Prof Gustavo Duque and Dr Ebrahim Bani Hassan
Project site: Western Health
Contact: Dr Ebrahim Bani Hassan (ebrahim.bani@unimelb.edu.au)

Project description: Seven million Australians (28%) have musculoskeletal conditions, resulting in the fourth largest overall contributor to direct health expenditure in Australia, accounting for 8.7% ($5.690 billion) of total health-care expenditure, above all types of cancers combined (AIHW 2014).[1] The majority of expenses are spent on two conditions: osteoporosis (OP) with associated fractures and osteoarthritis (OA). Yearly 144,000 older Australians sustain osteoporotic fractures at a significant cost of greater than $3.36 billion, excluding the burden, morbidity and mortality associated with osteoporotic fractures.[2] We already know that as we age fat moves from under skin (subcutaneous fat) into our abdomen and bone marrow (ectopic fat). This relocation and expansion of marrow adipose tissue (MAT) is accompanied by severe decline in human bone volume. To investigate whether expansion of MAT in the bone marrow can drive osteoporosis, we have shown in a mouse model that with ageing, MAT accumulates in bone marrow and causes a state called lipotoxicity. Lipotoxicity involves production of many inflammatory factors and fatty acids by fat cells (adipocytes) that have been shown to be toxic to other cells. Lipotoxicity can severely impair function and survival of osteoblasts (bone-forming cells). Consequently, osteoblasts may produce an anomalous bone organic matrix and mineralise it abnormally too; rendering fragile bone. Armed concrete analogy applies to bones where collagen fibres act like metal rods and hydroxyapatite functions like cement around the metal; and low quality or quantity of each can decrease concrete strength by many folds. However, the roles of lipotoxicity in initiation and progression of OP and risk of fractures has not been studied in humans; and if it is proven in a human study that marrow lipotoxicity drives osteoporosis, the treatment of osteoporosis and prevention of osteoporotic fractures can significantly improve.



We will study the molecular mechanisms of lipotoxicity in the samples collected from hip fracture patients and controls, and will investigate the bone and hematopoietic marrow (HPM) to study the effects of lipotoxicity using histology and also studying the molecular pathways. The results of this study will shed light on bone, fat and HPM biology, and more importantly might identify

mechanisms to prevent or treat OP and OA. The possible main outcomes of the study include: a. A MAT imaging tool to accurately predict bone loss and fracure risk; b. Identification of possible blood markers for MAT expansion and associated marrow lipotoxicity; c. Discovery of possible drug targets to prevent marrow lipotoxicity and associated bone and red marrow atrophy.

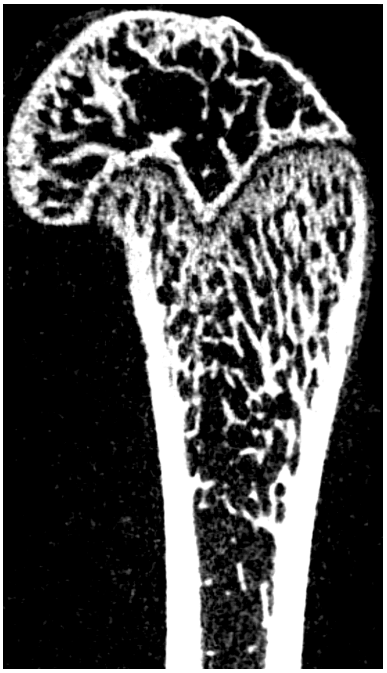
35. Using Marrow Adipose Tissue to Diagnose Osteoporosis and Predict Fragility Fractures

Supervisors: Prof Gustavo Duque and Dr Ebrahim Bani Hassan
Project site: Western Health
Contact: Dr Ebrahim Bani Hassan (ebrahim.bani@unimelb.edu.au)

Project description: Yearly 144,000 osteoporotic Australians fracture, that costs circa $4 billion. If fracture (Fx) risk is identified early, most Fx are preventable. Osteoporosis (OP) diagnosis and Fx risk estimation mostly relies on bone mineral density (BMD). However, up to 82% of people with Fx are not osteoporotic according to their BMD (T-scores> −2.5). Hence, they are not classified at risk of Fx and treated. Also, BMD improvement due to OP treatment does not explain >75% of reductions in Fx risk. Therefore, sensitive, specific and non-invasive methods for predicting Fx are mandatory.
In aged and osteoporotic bone, high levels of marrow adipose tissue (MAT) is a common observed feature. There is strong evidence that MAT expansion drives bone and red marrow atrophy by inducing a lipotoxic milieu that affects tissues in its vicinity; which is associated with altered matrix synthesis, abnormal mineralization, and reduced bone formation and mechanical resistance. MAT is inversely correlated with bone and unlike BMD can provide indirect information on other aspects of bone structure/strength, e.g. osteoblast health, collagen crosslinks and bone formation; and hence can act as a predictor of Fx.
Therefore, through two related studies we will: 1. Validate prediction of Fx risk using MAT and test its higher predictive value compared to BMD; 2. Identify the best imaging technologies that non-invasively, accurately and affordably quantify bone, red marrow and MAT volume.

36. Development of Marrow Fat Quantification as a Predictor of Poor Outcomes in Osteosarcopenia

Supervisors: Prof Gustavo Duque and Team of Supervisors at AIMSS
Project site: Australian Institute for Musculoskeletal Science (AIMSS)
Contact: Dr Ebrahim Bani Hassan (ebrahim.bani@unimelb.edu.au)



Project description: In older persons, the combination of osteopenia/osteoporosis and sarcopenia has been proposed as a subset of frailer individuals at higher risk of institutionalization, falls and fractures. The number of diagnostic methods for osteosarcopenia remains limited especially those with the reliability to predict poor outcomes in this population.
We have developed a new potential method for the diagnosis of osteosarcopenia which compares the volume of bone marrow and muscle fat infiltration vs. bone and muscle mass quantified in CT scan images. Our preliminary data has shown that this method is as sensitive as the histological one to quantify fat and bone volumes.

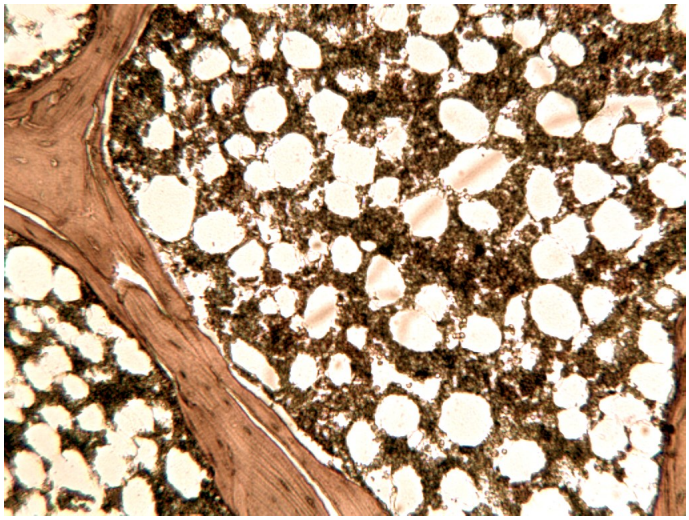
The aims of this project are to develop and validate a new potential diagnostic method for osteosarcopenia based on the fat volume within the bone marrow and muscles of humans (prospective study and retrospective analysis of images obtained in major human studies). If the hypothesis formulated in this

proposal is correct, this would be the initial step for the development of a new diagnostic method for osteosarcopenia. We feel that the use of image analysis of CT scans is just the initial step. Therefore, a long-term goal of this project is the development of a more specific diagnostic method for the quantification of fat within bone and muscle, which would be not only be affordable and non-invasive but also more specific for the prediction of fractures since it would look at one important aspect of bone and muscle quality that has not been previously assessed in large populations.

MUSCULOSKELETAL

37. Bone-muscle Interaction, Implications for Sarcopenia and Osteoporosis

Supervisors: A/Prof Itamar Levinger and Prof Gustavo Duque
Project site: Western Health
Contact: A/Prof Itamar Levinger (itamar.levinger@unimelb.edu.au)



Project description: Osteosarcopenia, low bone and muscle mass and strength, is associated with reduced physical function, increased risk of falls and fractures, and loss of independence and premature mortality. The skeleton (bone) and skeletal muscle are closely linked anatomically, chemically and metabolically, and function in an endocrine and paracrine nature. The exact mechanisms involved in bone-muscle cross-talk remain partially explored.
This project will explore different pathways by which bone and muscle communicate (directly and indirectly), and uncover whether targeting such pathways can be used to develop novel interventions to prevent or treat saracopenia and osteoporosis. The project will include basic and preclinical studies as well as, potentially, wide range of clinical interventions including pharmacological interventions and exercise and nutritional interventions) for older adults with sarcopenia and osteoporosis. The supervisory team has a vast experience in the research area with publications in the top journal in the field of research.

38. Effect of HMB and Vitamin D Supplementation on OsteosarcoPenia In OldeR PErsons (EMPIRE)

Supervisors: Prof Gustavo Duque and Dr Ben Kirk
Project site: Western Health
Contact: Dr Ben Kirk (ben.kirk@unimelb.edu.au)

Project description: Unfortunately, advancing age may comprise musculoskeletal health, with osteoporosis (low bone mass) and sarcopenia (low muscle mass and function) two chronic diseases, which together form a geriatric syndrome, coined osteosarcopenia. This syndrome predisposes an older person to increased risk of falls and fractures, compared to either disease alone, and induces alarming health care costs. As a result, suitable therapeutic strategies, which have dual affects on muscle and bone, are warranted. A protein metabolite, beta-hydroxy-beta-methylbutyrate (HMB), shows promising results in curbing sarcopenia, by upregulating muscle protein synthesis and downregulating protein breakdown rates. As many osteoporotic patients are also vitamin D deficient, supplementing with this nutrient may increase, or at least preserve, bone density too. Taken together, vitamin D and HMB may offer a suitable treatment strategy for osteosarcopenia. However, no study to date, has investigated the effects of Vitamin D + HMB in

osteosarcopenic patients, leaving a knowledge gap, which has the potential to not only improve the quality of life of older persons, but reduce socioeconomic costs in Australia, and worldwide.

Therefore, the purpose of this randomised, double-blind, placebo-controlled trial is to examine the effects HMB combined with vitamin D3 on appendicular lean mass, muscle strength and functional capacity, as well as bone turnover and microarchitecture in older adults (≥65 years) with osteosarcopenia.

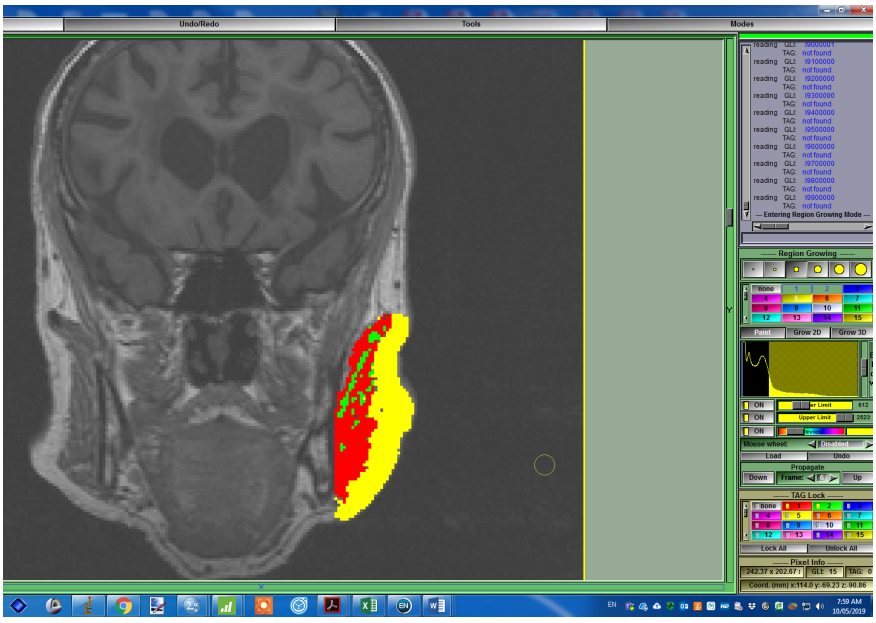
39. Adipocytes as Weapons of Bone Destruction: The Bone as a War Zone

Supervisors: Prof Gustavo Duque and Dr Ahmed Al Saedi
Project site: Western Health
Contact: Prof Gustavo Duque (gustavo.duque@unimelb.edu.au)

Project description: Osteoporosis in older persons is the consequence of predominant differentiation of mesenchymal stem cells (MSC) into fat at the expense of osteoblastogenesis and bone formation. We have obtained strong evidence that increasing marrow fat is toxic to bone cells and create an unfriendly bone marrow milieu. However, the mechanisms explaining this lipotoxic effect remain to be elucidated. In addition, the specific biological and metabolic characteristics of marrow fat remain unknown. These projects are aimed to characterise marrow adipocytes, determine their differences versus other types of fat, elucidate the mechanisms of lipotoxicity in bone, and develop new therapies to protect bone cells from lipotoxicity.

40. Osteosarcopenia as a Geriatric Syndrome

Supervisors: Prof Gustavo Duque and Dr Ben Kirk
Project site: Western Health
Contact: Prof Gustavo Duque (gustavo.duque@unimelb.edu.au)



Project description: Osteoporosis, the most common bone disease in humans, shares distinct pathophysiological mechanisms with sarcopenia. Sarcopenia, characterized by low muscle strength, mass and physical performance, is an important disease in older adults. Where osteoporosis and sarcopenia are both present, this is termed as 'osteosarcopenia.' A contemporary, comprehensive geriatric assessment should include assessment for osteosarcopenia and its associated risks, as this will enable effective management to reduce adverse outcomes. This group of projects are aimed to develop and support the concept of osteosarcopenia as a geriatric syndrome. The project includes biomedical and clinical studies looking at pathophysiology, clinical phenotype, diagnostic methods and new treatments for osteosarcopenia.

41. Inflammation-induced Osteosarcopenia: Mechanisms and Novel Treatments

Supervisors: A/Prof Kulmira Nurgali
Project site: Western Health
Contact: A/Prof Kulmira Nurgali (kulmira.nurgali@unimelb.edu.au)

Project description: Inflammatory bowel disease (IBD), comprising two main pathologies ulcerative colitis and Crohn's disease, affects >85,000 Australians. Almost 50% of patients with IBD

are affected by osteoporosis or osteopenia and with risk of bone fracture 40% higher than the general population. Many young Crohn's disease patients have osteoporosis and 60% of CD patients have sarcopenia when they should be at the peak bone and muscle strength. To date, no therapy proven to be efficacious in IBD-related osteoporosis/sarcopenia.
Gut-derived serotonin (GDS) regulates osteoblast proliferation and bone formation. *Serotonin increases a cytokine, osteoprotegerin, which inhibits osteoclasts and thereby reduces bone turnover.* Inhibition of tryptophan hydroxylase-1 (Tph-1), the initial enzyme in GDS biosynthesis stimulates bone formation in mouse model of ovariectomy-induced bone loss. However, the exact role of GDS on bone metabolism is not fully understood and needs further investigations. Other products of tryptophan metabolism are kynurenine (KYN) and its derivatives. This pathway metabolizes 95% of the dietary tryptophan, starting with the activation of indoleamine-2,3-dioxigenase-1 (IDO-1) converting tryptophan into KYN, which is then converted into picolinic acid. However, inflammation-induced changes in this pathway and its role in IBD-associated osteosarcopenia have not been elucidated. Studies on the mechanisms, prevention and treatment of IBD-related osteoporosis/sarcopenia are scarce mainly due to the lack of animal models. We have an excellent mouse model of spontaneous chronic colitis associated with high level of GDS, fragile bones, low muscle mass and, therefore, are an excellent model to study mechanisms of IBD-related osteosarcopenia.
The main aims of this study are:
1) To determine progression of changes in GDS and KYN pathways and their role in mechanisms underlying osteosarcopenia associated with chronic intestinal inflammation.
2) To evaluate therapeutic potential of MSC therapy and bone anabolic agent (picolinic acid) on the musculoskeletal phenotype.

42. Associations between Sarcopenia, Intramuscular Fat, Mental/Physical Function and Brain Atrophy: An Imaging and Machine Learning Approach

Supervisors: Prof Gustavo Duque and Dr Ebrahim Bani Hassan
Project site: Western Health
Contact: Dr Ebrahim Bani Hassan (ebrahim.bani@unimelb.edu.au)

Project description: Through a collaboration between AIMSS and our co-investigators in Norway we will quantify the volume of muscles of interest and the volume of intra/inter-muscular adipose tissue (IMAT) on MRI images of older adults. The research question is whether brain atrophy can lead muscle atrophy, or weakness, inactivity and loss of brain stimulation due to sarcopenia can cause cognition and brain volume decline. Muscle and IMAT volumes will be used as predictors of physical and nervous functions. Also, muscle and IMAT volumes will be correlated with the general and compartmental brain volumes to re-test the hypothesis that muscle decline and IMAT expansion is associated with brain atrophy and adverse events such as falls, cognitive decline and frailty.

43. Investigating the Anabolic Effect Drugs (Picolinic Acid) on Osteocytes in Vitro

Supervisors: Prof Gustavo Duque and Dr Ahmed Al Saedi
Project site: Western Health
Contact: Dr Ahmed Al Saedi (ahmed.mohan@unimelb.edu.au)

Project description: Wnt signalling proteins are small secreted proteins that are active in embryonic development, and tissue homeostasis. Wnt proteins bind to receptors on the cell surface, initiating a signalling cascade that leads to β-catenin activation of gene transcription. Our team has reported that Picolinic acid (PIC), an end product of the tryptophan degradation pathway, has an osteogenic effect on human mesenchymal stem cells (hMSCs). However, Osteocytes, >90% of the cells in bone, lie embedded within the mineralized matrix and coordinate osteoclast and osteoblast activity on bone surfaces. In addition, osteocytes as central target cells of the anabolic actions of canonical Wnt/β-catenin signalling in bone by mechanisms are still unclear. This project is aiming to explore the effect of PIC on human osteocytes in vitro.

44. Investigating the Rapamycin Effect on Induced-palmitic Osteocytes in Vitro

Supervisors: Prof Gustavo Duque and Dr Ahmed Al Saedi
Project site: Western Health
Contact: Dr Ahmed Al Saedi (ahmed.mohan@unimelb.edu.au)

Project description: The accumulation of fats in central regions of the body or peripherally can affect normal organ function, a condition referred to as lipotoxicity. This can also occur in bone and may affect bone health largely through the dysregulation of bone cell interactions and bone turnover. Within the bone marrow microenvironment, elevation in fatty acid levels may lead to an increase in osteoclast activity and a decrease in osteoblast number and function, thus contributing to age-related musculoskeletal diseases. In addition, Osteocytes is the orchestrator of bone remolding and decline in osteocyte autophagy is involved in senile osteoporosis. However, since rapamycin (RAP)-induced inhibition of target of rapamycin complex 1 (mTORC1) activates autophagy and prevents apoptosis, we hypothesized that RAP may preserve osteocytes viability and reduce PA-induced lipotoxicity.

45. Your Muscles Matter – The Sarcopenia Study

Supervisors: A/ Prof Alan Hayes and Dr David Scott
Project site: Western Health
Contact: A/Prof Alan Hayes (hayes.a@unimelb.edu.au)

Project description: Sarcopenia is associated with age-related loss of muscle mass and strength that can lead to reduced mobility, falls, fractures, loss of independence, and can become life threatening if undiagnosed and untreated. Sarcopenia is now formally recognised as a disease, which will increase awareness, diagnosis, and interest in treatments. Early diagnosis is important as increasing evidence demonstrates therapeutic interventions, particularly resistance training, can improve health and quality of life outcomes for those with or at risk of sarcopenia.

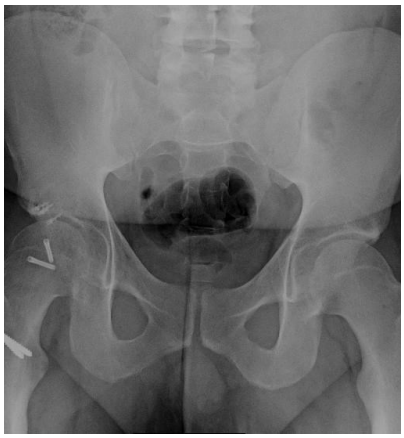
This project is in collaboration with Uniting AgeWell and will involve clients enrolled in exercise programs at their Allied Health and Therapy Centres at Forest Hill, Oakleigh, Noble Park, and Hawthorn. Research participants will include clients who live at home or in residential care. Body composition, physical function and quality of life assessments will occur at study commencement, and at six months and twelve months following an exercise intervention to assess muscle mass, strength and functional capability to assess sarcopenia prevalence and risk.

46. Musculoskeletal Health: Associations with Inflammation and Social Determinants in Young Adults

Supervisors: A/Prof Sharon Brennan-Olsen and Professor Gustavo Duque
Project site: Western Health
Contact: A/Prof Sharon Brennan-Olsen (sbrennan@unimelb.edu.au)
Suitable for: PhD

Project description: Although sarcopenia and osteoporosis are generally considered geriatric conditions, the attainment of peak bone mass and muscle mass/strength during young adulthood, and maintenance throughout mid-life, dictates the risk for frailty during later life. Our previous work has suggested that inflammation may influence differences in bone and muscle quality; differences that may be particularly observed in relation to our social circumstances, such as where we live, what our occupation is, the level of education we have. Little is currently known about this area of research, despite the importance of this information to health practitioners dealing with an increasingly aging Australian population, and efforts aimed at reducing the increasing healthcare costs associated with low bone and muscle quality. This study will: (i) estimate the extent that higher vs. lower skilled occupations are associated with differences in levels of lean mass, physical function, BMD, and/or cortical and trabecular bone, (ii) estimate the extent that higher or lower educational attainment is associated with differences in levels of these same musculoskeletal outcomes, (iii) estimate the extent that areas of lower or higher socioeconomic

position (SEP) are associated with differences in these musculoskeletal outcomes, (iv) quantify the involvement of biomarkers of inflammation in each of these models for musculoskeletal health. To answer these questions, we will recruit 400 adults aged 30-45 years, residing in the western suburbs of Melbourne. Comprehensive data regarding health status and medication use will be collected from each participant. Each participant will undergo whole body dual energy x-ray absorptiometry (DXA). Total lean/muscle mass will be determined from whole body scans. Other clinical measures include body weight and height, measured to the nearest 0.1 kg and 0.1 cm, respectively, which may be tested as confounders and/or effect modifiers in multivariable analyses. Each participant will undergo hand grip and quadriceps strength assessment, and the Short Physical Performance Battery. A morning, fasting blood sample will be collected from each participant; serum will be stored at –80C for batch analyses. From the serum, we will ascertain: (i) IL-6, (ii) high sensitivity CRP, and (iii) TNFα. Employment status, occupation type, and educational attainment will be collected, and categorized into binary variables for analyses. Residential address of each participant will be matched to the corresponding ABS Census data to identify area-level SEP. Linear regression models will be fitted to estimate the effects of SEP, occupation (professional/semi-professional vs other), education (completed some of secondary school vs completed all secondary school and above), and area-level SEP (lower vs higher SEP) on lean mass, function/strength, BMD, cortical and trabecular bone. The effect of confounders (age, smoking, physical in/activity, BMI, comorbidities, and medications) and inflammation factors will be estimated and quantified.



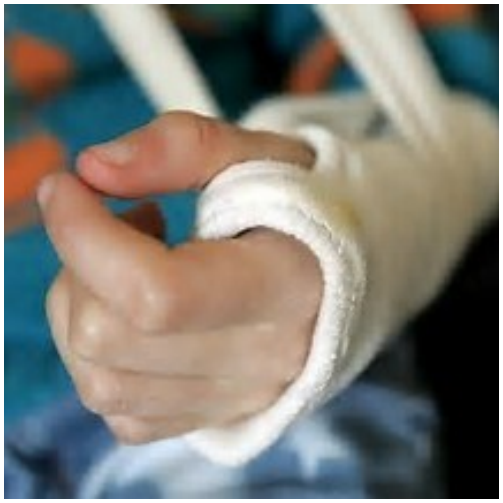
47. Quantitative Measure of Effusions

Supervisors: A/Prof Keith Lim
Project site: Western Health
Contact: A/Prof Keith Lim (kklim@unimelb.edu.au)

Project description: Knee effusions are common in mechanical and inflammatory arthropathies. Increasingly it has been recognized that removal/reduction of joint effusions play a key role in improving pain and dysfunction at the knee joint, enabling rehabilitation and recovery. It may be possible to use disease modifying agents to treat knee joints with OA in future. This project looks at different methods (clinical, imaging) used to measure the presence and size of joint effusions. The study aims to validate these methods, and compare them.

48. Characterization of Osteosarcopenia in Older Persons: A Bench to Bedside Approach

Supervisors: Prof Gustavo Duque and Team of Supervisors at AIMSS
Project site: Western Health
Contact: Steven Phu (steven.phu@unimelb.edu.au)



Project description: In older persons, the combination of osteopenia/osteoporosis and sarcopenia has been proposed as a subset of frailer individuals at higher risk of institutionalization, falls and fractures. However, the particular clinical, biochemical and functional characteristics of the osteosarcopenic (OS) patients remain unknown. In this study, we will use a bench-to-bedside approach to understand the molecular mechanisms of osteosarcopenia (muscle and bone interphase), biochemical and functional changes observed in osteosarcopenic individuals, potential biomarkers of osteosarcopenia, treatment

guidelines and innovative therapeutic approaches (pharmacological and non- pharmacological).

49. Using Wearable Activity Trackers to Monitor Physical Activity in Older Adults Undergoing Exercise Interventions for Falls

Supervisors: Dr David Scott and Prof Gustavo Duque
Project site: Western Health
Contact: Dr David Scott (d.scott@unimelb.edu)

Project description: Exercise targeting improvements in muscle strength and balance is beneficial for the prevention of falls in older adults. However, it is difficult to monitor physical activity levels in older adults who have been prescribed exercise training. Wearable activity trackers, such as Fitbit, may provide a useful tool for monitoring physical activity in this population. This study will examine three-month changes in physical activity, assessed by Fitbit devices, in older adults who have recently experienced a fall and who are completing either a personalised exercise program or usual care. We will determine whether fallers complete more physical activity when prescribed an exercise program compared to usual care, and whether higher levels of physical activity are associated with reduced risk factors for falls after three months. Students involved in this project will assist with recruitment of patients and data collection, including assessing changes in physical activity, physical performance and completing body composition scans.

50. Osteosarcopenia in Older Adults Attending a Fracture Liaison Service

Supervisors: Dr David Scott and Prof Gustavo Duque
Project site: Australian Institute for Musculoskeletal Science (AIMSS)
Contact: Dr David Scott (d.scott@unimelb.edu)

Project description: Osteosarcopenia describes the significant loss of bone and skeletal muscle mass that occurs during ageing. Although the condition is not well characterised, osteosarcopenia appears to be associated with increased risk for disability, institutionalisation, falls, fractures and mortality in older adults. This study will determine the prevalence of osteosarcopenia in older patients with a recent history of low-trauma fractures attending a Fracture Liaison Service. We will also assess how patients with osteosarcopenia recover from fractures, in comparison to those without the condition, over several months. Students involved in this project will assist with recruitment of patients and data collection, including assessing physical performance and completing body composition scans.

51. Improving Outcomes for People with Hip or Knee Osteoarthritis

Supervisors: Prof Kim Bennell, Prof Rana Hinman and Prof Gustavo Duque
Project site: AIMSS and Centre for Health, Exercise and Sports Medicine (University of Melbourne, Parkville)
Contact: Prof Kim Bennell (k.bennell@unimelb.edu.au)

Project description: We are seeking talented people to undertake a full time Masters or PhD program. Candidates from a range of clinical and non-clinical backgrounds will be considered.
The research would be undertaken as collaboration between AIMSS and the Centre for Health, Exercise and Sports Medicine (CHESM) in the Faculty of Medicine, Dentistry and

Health Sciences (located in Parkville). Our multi-disciplinary team at CHESM includes people with backgrounds in physiotherapy, podiatry, biomechanics, engineering and exercise science.

52. Pre-Clinical Studies Identifying Novel Molecular Regulators of Skeletal Muscle Growth and Atrophy

Supervisors: A/Prof Alan Hayes
Project site: Western Health
Contact: A/ Prof Alan Hayes (hayes.a@unimelb.edu.au)

Project description: Skeletal muscle plays fundamental roles in the generation of movement and the regulation of whole body metabolism. Muscle mass is lost with prolonged periods of disuse due to injury or immobilization, with diseases such as diabetes, heart disease and cancer, and with ageing. Muscle mass decline can severely impair the ability to perform activities of daily living leading to a further reduction of physical activity and a vicious cycle of inactivity, muscle loss and inactivity-related disease. Thus, strategies aimed at preventing muscle loss and/or promoting muscle growth are essential to limiting disability and preventing disease. Consequently, a thorough understanding of the molecular mechanisms that regulate skeletal muscle mass is crucial to the development of effective exercise programs and potential pharmacological interventions aimed at preventing muscle atrophy/wasting and/or promoting skeletal muscle growth.
The aim of this project is to use rodent- and cell-based models to examine the potential for specific growth factors, signalling molecules, metabolic enzymes and/or transcription factors to stimulate muscle growth or promote muscle atrophy. Genetic gain-of-function (overexpression) and loss-of-function (knockdown) studies will be used, as well as various models of altered physical activity (e.g. immobilization, denervation, mechanical overload) and altered nutrient intake (e.g. food deprivation, protein supplementation). Mechanistic insights into changes in muscle mass will be obtained using molecular analyses that include measures of changes in rates of protein synthesis and protein degradation, the phosphorylation of critical signaling proteins and transcription factors, and gene expression, and the use of DNA-based reporter constructs. Morphological and functional changes will also be examined. This project will include the use of animal surgery, recombinant DNA purification and protein purification, the transfection of muscles *in vivo* and in cultured cells, Western blotting, immunohistochemistry, microscopy and enzyme activity assays.

53. Re-Purposed Pharmacological Agents for Rapid Therapeutic Translation in Duchenne Muscular Dystrophy

Supervisors: A/Prof Alan Hayes
Project site: Western Health
Contact: A/Prof Alan Hayes (hayes.a@unimelb.edu.au)

Project description: Duchenne Muscular Dystrophy (DMD) is a devastating degenerative neuromuscular disease that is currently incurable, poorly treated and in all cases fatal. While the pathophysiology of DMD is complex, we and others have established that mitochondrial dysfunction and oxidative stress are key features of the disease. More specifically, dysfunctional mitochondria generate toxic levels of reactive oxygen species, and as such, there is considerable potential for mitochondrial and anti-oxidative medicines to be useful therapies for DMD. This hypothesis is strongly supported by the pending release of the first indication-specific pharmacological mitochondrial therapeutic for the treatment of DMD in Europe and the USA, idebenone (Raxone®, Catena®), by Santhera Pharmaceuticals.
Translating a novel drug from “benchtop to bedside” is arduous and expensive – on average it takes 15 years and US$2.6 billion to translate a new medicine to patients. However, drug repurposing (the investigation of already approved drugs to determine their safety and efficacy for treating a different condition) means they can be ready for clinical trials relatively quickly, expediting their review by regulatory bodies, and if approved, their integration into healthcare. In this project, we aim to determine whether two existing compounds have the potential to be re-purposed

for DMD. We have evidence that the purine nucleotide adenylosuccinic acid, which has similar functional properties to idebenone, improves histopathological features of DMD muscle. The aim of this project is to investigate known pharmacological modulators of mitochondrial function and oxidative stress that are already undergoing clinical testing in humans with the view to re-purposing them for DMD. The project will primarily use mouse models of DMD to pre-clinically evaluate skeletal muscle quality, function, histology, morphometry and mitochondrial metabolism. It will also involve culturing of human DMD muscle cells to explore mechanisms of action. Western blotting, immunohistochemistry, microscopy and enzyme activity assays will also be performed.

54. Optimising Recovery Following Fracture in Older Adults – What Does the Evidence Tell Us?

Supervisors: Prof Kerrie Sanders, Dr David Scott and Dr Lucy Busija
Project site: Western Health
Contact: Prof Kerrie Sanders (ksanders@unimelb.edu.au)

Project description: About 40% of women and 25% of men aged over 50 years will sustain an osteoporotic fracture (broken bone) in their lifetime. These fracture(s) are associated with a dramatic decline in health related quality of life and often lead to a loss of independence with suboptimal recovery of both physical functioning and quality of life. Management of these fractures imposes a substantial cost burden on the health system with individual fracture management costs ranging from a mean of $6,000 for wrist fracture to $32,000 for hip fracture. We propose that the cost and impact of fractures can be reduced by integrating a person-centred approach into fracture management plans. We aim to identify services associated with greatest recovery following fracture, specific to fracture site and socio-economic strata. The findings from two related projects will be used to characterise an efficient use of healthcare and community services. We will use our data to make recommendations for a fracture care pathway for each of the most common fracture sites (hip, vertebral, wrist, humeral and ankle). The recommendations will then be used in a pilot intervention study. We believe this novel approach will help maximise the proportion of older adults with fracture who return to their pre-fracture quality of life and optimal physical functioning within 12 months of the fracture. Our person-centered approach is unique in fracture care by integrating outcomes related to both physical functioning and quality of life. Findings will be used to develop evidence-based recommendations for fracture management pathways.
Project 1: Aim To examine existing evidence for health and community service use following fracture in older adults. The student will conduct a series of systematic reviews of health and community service use for recovery following fracture in older adults relating to functional outcomes and cost effectiveness. The evidence will be compiled from published randomised controlled trials, systemic reviews and meta-analyses that use a physical functioning or biological 'bone healing' outcome. The results will form the basis for evidence relating to fracture management pathways that optimize physical outcomes and be used in conjunction with findings from other projects focusing on quality of life outcomes. Future intervention studies will implement these fracture management pathways and compare outcomes with 'usual care' practice of fracture management. **Project 2:** Aim To identify the best 'mix' of health and community service use following fracture for optimal recovery of quality of life. We have access to several large data sets that can be used to identify determinants of recovery of quality of life following fracture in older adults. Using data collected from eleven countries the student will develop competence in biostatistics through undertaking supervised analyses to address the study aim. The results will form the basis for evidence relating to fracture management pathways that optimize quality of life outcomes and be used in conjunction with findings from project 1 that has a focus on physical function outcomes. Future intervention studies will implement these fracture management pathways and compare outcomes with 'usual care' practice of fracture management.

55. Lipotoxicity in Bone: Investigation of MSK Disease Processes Using Advanced Medical Imaging

Supervisors: A/Prof Damian Myers, Prof Gustavo Duque and Dr Chris Hall
Site: Western Health
Contact: A/Prof Damian Myers (damianem@unimelb.edu.au)

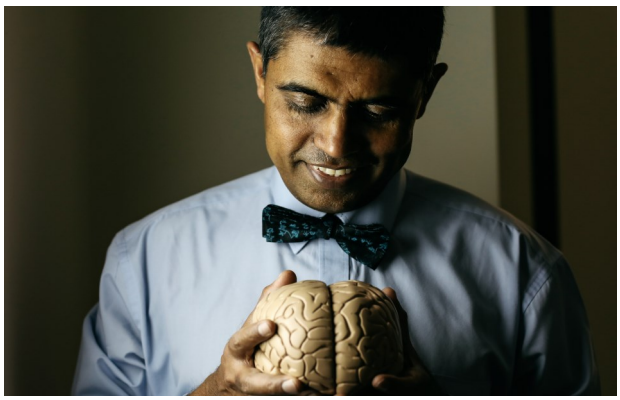
Background: Our knowledge and understanding of how bone and muscle health can be regulated by the different organs systems is still evolving and the key to novel therapies for bone and muscle pathogenesis will involve metabolic controls that link each of muscle, bone and fat tissue.
Biochemical, molecular and gene studies, linked with pre-clinical studies, have provided potential therapies for bone and muscle diseases, A fundamental requirement is the capability to define the disease state (osteoporosis/osteopenia) and then to monitor the disease progression and post-therapy outcomes. In preclinical models, several simple imaging modalities have been used but, recently, more sophisticated and informative imaging techniques have included live-cell imaging and co-registration of functional live-cell outcomes with cell and tissue and whole animal structural imaging. Also, using MRI/ PET and X-ray-based 3D tomography, we can now investigate MSK structure and function using 2D, 3D, 4D and 5D imaging. In particular, synchrotron science has greatly improved MSK imaging of bone and muscle in pre-clinical models. High-resolution and high-definition imaging enables simultaneous nano-, micro- and macro-imaging. Further, we can interpret outcomes beyond 3D with time-based studies (4D) and using multi-modal, combined and co-registered imaging.
Hypothesis: Muscle, fat and bone can be defined using advanced imaging to aid our studies into lipotoxicity in muscle and bone associated with sarcopenia, osteopenia and osteoporosis.
Aim: To perform temporal imaging studies in *ex vivo* tissue from clinical models to investigate lipotoxicity in muscle and bone. Outcomes from advanced imaging techniques including MRI, PET, X-ray tomography and advanced synchrotron science will provide crucial information about the onset and progression of bone and muscle disease including osteopenia, sarcopenia and osteoporosis.

NEUROLOGICAL DISEASES

56. Association between Serum Levels of Vitamin D and the Risk of Post-Stroke

Supervisors: Prof Gustavo Duque and A/Prof Tissa Wijeratne
Project site: Western Health
Contact: A/Prof Tissa Wijeratne (twi@unimelb.edu.au)

Project description: While low levels of serum vitamin D are common in patients with cognitive impairment and stroke, there has been little investigation on the associations between levels of vitamin D and post-stroke cognitive impairment. The aim of this study is to determine the relationship between vitamin D and post-stroke cognitive impairment. We hypothesize that low levels of vitamin D on admission would be significantly associated with lower cognitive functioning in post stroke subjects. A consecutive series of 100 first acute ischemic stroke patients (Mild stroke, NIHSS less than 5, no known cognitive impairment prior to the index stroke) will be recruited and followed up for one month. Serum levels of vitamin D will be measured within 24 hours of admission. All demographic characteristics (age, gender, marital status, economic status), level of stroke severity (National Institute of Stroke Severity



Scale), stroke outcomes (modified Rankin score and Barthel Index), and cognitive functioning (MOCA) will be collected. In addition, 100 healthy subjects will be recruited as controls, with measurement of serum vitamin D levels taken and non-stroke related assessments administered (i.e., MOCA) for comparison.

57. Stroke Biomarker Study; Role of Infections and Ischemic Stroke

Supervisors: A/Prof Tissa Wijeratne
Project site: Western Health
Contact: A/Prof Tissa Wijeratne (twi@unimelb.edu.au)

Project description: A blood biomarker of stroke can be any quantifiable entity that reflects the manifestation of a stroke related process. Most of the known biomarkers have very little practical value in stroke. The most useful application of stroke biomarkers is in areas where information from traditional clinical sources is limited.
The potential use of rapidly measurable blood biomarkers to determine the cause of stroke admission would help to identify patients who need specific preventative measures such as oral anticoagulation, and thus, facilitate better and precise secondary prevention with improved patient outcome.
Of particular interest, the role of infection in stroke is complex and remains incompletely understood. Therefore, this study is aimed at examining evidence of recent acute systemic infection of any type as a stroke trigger, focusing on the relationship between acute infection with timing of acute stroke in adult stroke patients admitted to Sunshine Hospital, prospectively.
100 patients with acute ischemic stroke will be recruited, whereby evidence of recent acute infections will be identified via collection of blood samples. Identification of the following organisms implicated in stroke pathogenesis will be of particular focus:
Bacterial infections including Treponema pallidum, Mycobacterium tuberculosis, Chlamydia pneumonia, Helicobacter pylori, Prophyromonas gingivalis and other periodontal pathogens, and viral infections including HIV, CMV, Varicella zoster, Herpes simplex types 1 and 2, Parvovirus B 19. Where consent is provided, spouse of patients will also be recruited into the study to identify any evidence of the same infections. We anticipate that this study will provide further understanding of the association between infections and stroke.

58. High Dose Vitamin D and Post-Stroke Outcomes: A Randomized Controlled Trial

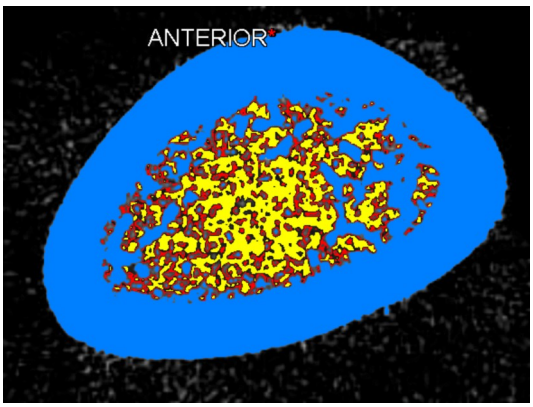
Supervisors: Prof Gustavo Duque and A/Prof Tissa Wijeratne
Project site: Western Health
Contact: A/Prof Tissa Wijeratne (twi@unimelb.edu.au)

Project description: Levels of serum 25-hydroxyvitamin D (25(OH)D) have been shown to serve as a predictor of cardiovascular disease risk, and an independent predictor of functional outcome post-acute ischemic stroke. While the prevalence of 25 (OH)D deficiency is high in patients with acute ischemic stroke, provision of vitamin D supplementation as a therapeutic agent has not clearly been established in this patient population. The current study aims to investigate the effects of vitamin D supplementation on functional outcomes. It is hypothesized that high dose vitamin D supplementation could improve post-stroke outcomes in acute ischemic stroke patients with low 25 (OH)D levels. 100 acute ischemic stroke patients with low 25 (OH)D levels will be recruited and be randomly assigned to one of two groups. One group will receive a loading dosing of 50000 units of vitamin D followed by 1000 units daily for three months. The other group will receive 1000 units of vitamin daily, without a loading dose. Stroke outcomes (death, disability using modified Rankin Score, NIHSS) will be compared across the two groups.

PHARMACOLOGY

59. The Kynurenine Pathway of Tryptophan Degradation as a Therapeutic Target

Supervisors: Prof Gustavo Duque and Dr Ahmed Al Saedi
Project site: Western Health
Contact: Prof Gustavo Duque (gustavo.duque@unimelb.edu.au)



Project description: Fractures due to osteoporosis have a serious impact on our older population. Reports of side effects with commonly prescribed osteoporosis drugs have led to the investigation of new and safer treatments with novel mechanisms of action. The kynurenine pathway of tryptophan degradation has shown promissory results as a new therapeutic approach to osteoporosis and possibly to sarcopenia. This project will focus on the identification of the mechanism of action of those end-products in bone and muscle and completion of preclinical validation of those compounds.

60. Methamphetamine-induced Depression: Mechanisms and Novel Treatments

Supervisors: A/Prof Kulmira Nurgali
Project site: Western Health
Contact: A/Prof Kulmira Nurgali (kulmira.nurgali@unimelb.edu.au)

Project description: Methamphetamine (METH) has become one of the most highly consumed narcotics, overtaking cocaine and heroin, with an estimated 35 million users globally. Long-term effects of METH use include anxiety, psychosis and depression leading to increased suicidal rates. Current anti-depressant treatments are ineffective in treating METH-induced depression and worsen symptoms following METH abstinence, therefore, a better understanding of the underlying mechanisms of METH-induced depression will lead to development of more effective treatments.

METH-mediated release of dopamine and norepinephrine can activate dopaminergic and adrenergic receptors on the enteric nervous system innervating GI tract and controlling its functions. Activation of these receptors results in a significant decrease in bowel contractility, decrease in intestinal smooth muscle tone and alteration of the migratory motor complex. The cocaine and amphetamine regulated transcript (CART) receptor has been discovered in the stomach, small and large intestines. However, mechanisms of METH actions on the enteric neurons and intestinal muscle have not been investigated.

Gut microbiota. Recent advances in research have described the importance of gut microbiota in many neuropsychiatric disorders. Current evidence suggests that multiple mechanisms, including immune, endocrine and neuronal pathways, may be involved in gut microbiota-to-brain signalling and that the brain can in turn alter microbial composition and behaviour via the enteric nervous system. Changes in the gut microbiota after METH use and the interplay between intestinal microbiota, immune response and neuropsychiatric manifestations associated with METH use have not been studied.

Sympathetic and parasympathetic nervous systems play important role in the regulation of the immune system. The effects of METH on the activity of sympathetic and vagus nerves and their modulation of the spleen and intestinal immune responses have not been studied.

This project aims to perform studies in animal models of METH use (acute/chronic/withdrawal) and human studies (blood samples from METH users and non-users) to investigate intestinal permeability, immune response, gut microbiota, changes in the nervous system.

61. Purine Nucleotide Therapy or the Treatment of Duchenne Muscular Dystrophy: A Preclinical Evaluation

Supervisors: A/Prof Alan Hayes
Project site: Western Health
Contact: A/Prof Alan Hayes (hayes.a@unimelb.edu.au)

Project description: Duchenne Muscular Dystrophy (DMD) is a rare and devastating degenerative neuromuscular disease that is currently incurable, poorly treated and in all cases fatal. Afflicted boys are wheelchair bound by their early teens and die of cardiorespiratory insufficiency thereafter. We have importantly established that mitochondrial dysfunction is a key feature of the myopathy, and that supporting cellular metabolism with energy-promoting supplements can ameliorate disease progression. With our collaborators, we have developed proof-of-concept and anecdotal clinical data demonstrating efficacy of purine nucleotide therapy for the treatment of DMD. This project aims to undertake the necessary preclinical research in a mouse model of DMD, to establish long-term clinically -relevant efficacy of purine nucleotide therapy sufficient to transition into phase II clinical trials in human DMD patients thereafter.
Due to the pre-clinical nature of this project, there are key outcomes associated with it. The first is to establish acute toxicity data for a specific target of the purine nucleotide cycle in a small animal model, to determine safety at upper dosage limits. The second is to investigate the long-term efficacy of this purine nucleotide in attenuating the natural history of DMD progression in a small animal model. The third is to identify the mechanisms of action by which this purine nucleotide affords its therapeutic efficacy. The project will primarily use mouse models of DMD to evaluate skeletal muscle quality, function, histology, morphometry and mitochondrial metabolism. It will also involve culturing of human DMD muscle cells to explore mechanisms of action. Western blotting, immunohistochemistry, microscopy and enzyme activity assays will also be performed.

PUBLIC HEALTH

62. Novel Ways of Detecting and Managing Chronic Diseases (Chronic Kidney Disease/ Diabetes/Cardiovascular Disease) in Primary Care

Supervisors: A/Prof Craig Nelson, Prof Edward Janus and A/Prof Shane Hamblin
Project site: Western Health
Contact: A/Prof Craig Nelson (nelsoncl@unimelb.edu.au)

Project description: Funding from the Victorian Department of Health Renal Health Clinical Network and Aboriginal Health has enabled Western Health to pilot a successful early detection program targeting patients at risk of developing kidney disease in the West of Melbourne. We now plan to extend this program to encompass Diabetes and Cardiovascular Disease with granted funds from the
Macedon Ranges and North Western Melbourne Medicare Local. It is estimated 80% of primary care practices in Australia have Electronic Healthcare Records (EHR) that are compatible with the eHealth tools to be developed. It is a powerful tool enabling monitoring of chronic disease risk, testing and management on large populations at the primary care level. Population Health data will be available on over 100,000 people for analysis and reporting. This would be an excellent experience in bridging the gap between primary care and hospitals and skills gained will include experience in population health and epidemiology.

63. Understanding Patient Capacity to Adhere to Prescribed Treatment Regime Post-Fracture

Supervisors: A/Prof Sharon Brennan-Olsen et al
Project site: Western Health
Contact: A/Prof Sharon Brennan-Olsen (sbrennan@unimelb.edu.au)

Project description: In 2012, 4.74 million Australians aged 50yrs or older (66% of those aged ≥50yrs) had poor bone health (22% osteoporosis, 78% osteopenia). Osteoporosis is characterised by low density and quality of bone, with a subsequent increased risk of fracture; currently one fracture occurs every 3.6 minutes. Data show that socially disadvantaged individuals have a disproportionately greater risk of osteoporosis and fracture compared to their less disadvantaged counterparts. Whilst current efforts are aimed at making 'the first fracture the last fracture', persistence with a prescribed treatment regime is imperative for effective prevention of secondary fracture. However, it is concerning that treatment adherence is only 43-53% for osteoporosis, a figure that is much lower compared to other diseases. Furthermore, persistence with a prescribed treatment appears strongly influenced by a patient's ability to seek, understand and utilize health information; aspects referred to as 'health literacy'. Estimates indicate that up to a quarter of the Australian population has suboptimal health literacy, and this is more commonly observed in individuals who are older, socially disadvantaged, or from culturally and/or linguistically diverse populations. To date, very little is known regarding the effect size of low health literacy on a patients' ability to persist with medication post-fracture. This project will recruit a new cohort of fracture patients from the Western suburbs of Melbourne: an area that is one of the most socially disadvantaged and culturally diverse within Victoria. Health literacy at the time of fracture will be determined, and the roles played by health literacy and social disadvantage in the ability to adhere with prescribed treatment regime over time will be investigated. By understanding situational and personal determinants of health literacy specific to osteoporotic fracture and treatment adherence, we will be better placed to improve healthcare provision and inform effective patient-practitioner alliances.

64. Associations between Health Literacy and Self-Efficacy in Older Adults with Sarcopenia

Supervisors: Dr. Alison Beauchamp and a team of supervisors at AIMSS
Project site: Multi-Centre across Melbourne
Contact: Dr. Alison Beauchamp (alison.beauchamp@unimelb.edu.au)

Project description: Sarcopenia (low muscle mass, strength and function) increases the risk of falls, disability, and mortality. Management of sarcopenia in the community is predominantly via exercise and dietary protein. However, older adults are shown to have limited adherence to similar recommendations for other musculoskeletal conditions. In order to feel confident to make a lifestyle-related change (self-efficacy), people must first understand what is required of them and have the health literacy skills and supports to make those changes. No published studies have examined the relationship between health literacy and self-efficacy among people with sarcopenia. This represents an important gap in our knowledge as it means that current efforts to optimise self-efficacy may not take health literacy into account. This project aims to describe the association between health literacy and self-efficacy among a sample of older people with or at increased risk of sarcopenia.

This will be a cross-sectional, prospective study using a mixed methods approach. Data will be collected from multiple sites, using validated instruments and semi-structured interviews. Cluster analysis and multivariate regression analysis will be used to show associations between health literacy and self-efficacy. Interview data will be thematically analysed to identify key themes relating to health literacy and self-management of sarcopenia. This project is suitable for an honours student.

65. A Co-design Approach to Implementing Teach-back in a Metropolitan Health Service

Supervisors: Dr. Alison Beauchamp and the Team of Supervisors at AIMSS
Project site: Western Health
Contact: Dr. Alison Beauchamp (alison.beauchamp@unimelb.edu.au)

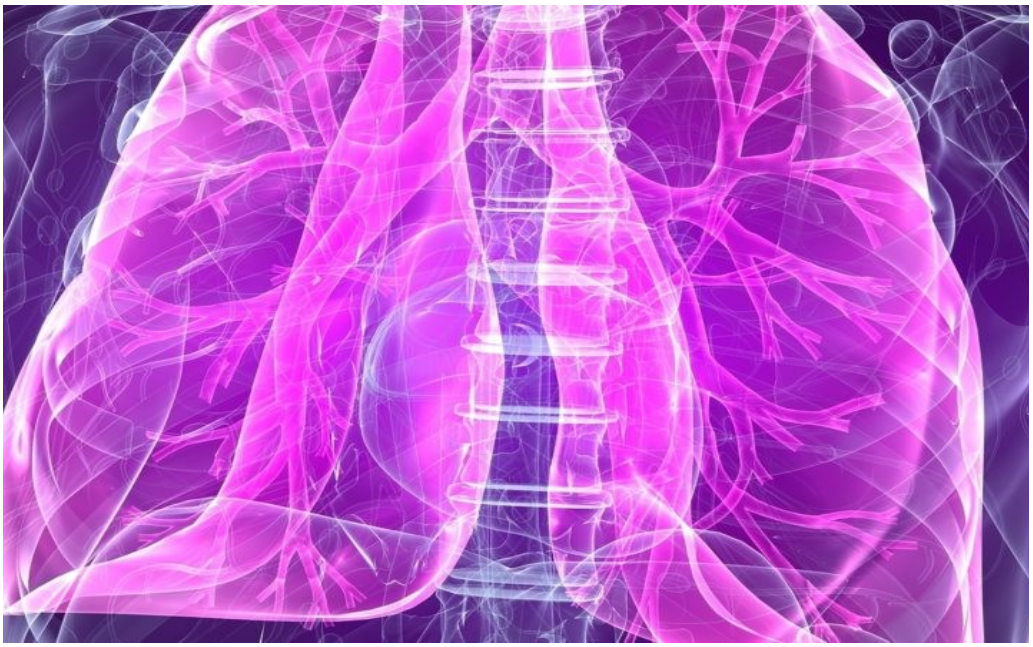
Project description: Health information is becoming increasingly complex, making it harder for people to understand the information that their health provider gives them. A structured communication approach called 'teach-back' is shown to be useful for helping providers quickly identify when a client has difficulty understanding health communications. In simple terms, teach-back involves a provider asking clients to explain in their own words what they have just been told. Evidence from other studies shows that teach-back can improve health outcomes. This mixed-methods implementation study aims to evaluate the use of teach-back within Western Health. The service will implement teach-back across two or more program areas as a quality improvement initiative within coronary care and orthopaedic units Staff working in those areas will work with researchers to co-design a strategy for ensuring that teach-back is used in a systematic way. A hybrid-type 3 design for implementation studies will be used to identify contextual factors that support uptake of the intervention, with clinical outcomes data also collected where feasible. This project is suitable for an honours student.

RESPIRATORY MEDICINE

66. Rationalising the Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease

Supervisor: A/Prof Lata Jayaram
Project site: Western Health
Contact: A/Prof Lata Jayaram (lata.jayaram@unimelb.edu.au)

Project description: Smoking related Chronic Obstructive Pulmonary Disease (COPD) is a disorder associated with significant morbidity and mortality. Patients with COPD are often misdiagnosed, and over treated or incorrectly treated for symptoms such as cough, wheeze and breathlessness on exertion. They are frequently started empirically on one or more of the many (and increasing) choice of inhalers available. This prospective cohort study aims to improve the accurate diagnosis and appropriate management of COPD in our patients by using a combination of clinically available tests.



TRANSLATIONAL

67. Long-Term Characterization and Assessment of 3D Stem Cell Cultures for The Study of Musculoskeletal Tissues and in Tissue Engineering

Supervisors: A/Prof Damian E. Myers, A/Prof John T. Price, Prof Gustavo Duque and Dr Kathy Traianedes
Project site: Western Health
Contact: A/Prof Damian Myers (damianem@unimelb.edu.au)

Project description: *Background:* Mesenchymal stem cells can form a range of tissue types dependent upon the provision of specific growth factors, cytokines and trophic factors. These pluripotent stem cells can form bone and adipose tissue, muscle, neuronal cells as well as cartilage and fibrous tissue. Projects have been designed to characterise and assess mesenchymal cell-derived cells/tissues in the *in vitro* setting for investigation of cell interactions in the musculoskeletal system as well as for bioengineered cell/tissue constructs.
A range of future projects: Projects will include: (1) Assessment of the impact of adipose cells on bone turnover; (2) Investigation of tumour cell metastasis such as in breast cancers; and, (3) Development of novel bioengineering strategies for long-term *in vitro* assessment as this is required prior to complex and expensive *in vivo* testing of bio-engineered tissues and devices. Experiments have been designed to optimise research outcomes prior to translation to animal models and through to clinical application.
Approach and techniques: Cultures of mesenchymal stem cells will be maintained in a live-cell perfusion chamber and various approaches will be employed to generate cells/tissues in bone, adipose and other cell lineages. Cells/tissues will be assessed using high resolution X-ray techniques such as micro-computed tomography (micro-CT), peripheral quantitative computed tomography (pQCT) and fluorescence and confocal microscopy. Standard assessment techniques to be used include histo- and immunocytochemistry, RT-PCR, qPCR and gene microarray analysis.
Outcomes and skills: Candidates will learn tissue culture techniques for cells of the musculoskeletal system. Students will become proficient at characterisation of assessment of musculoskeletal cells and tissues.

68. Targeting Fatty Acid Synthase as a New Therapeutic Approach to Osteosarcopenia

Supervisors: Prof Gustavo Duque, A/Prof Alan Hayes and Team of Supervisors at AIMSS
Project site: Western Health
Contact: Prof Gustavo Duque (gustavo.duque@unimelb.edu.au)

Project description: Sarcopenia – defined as low muscle mass and strength – is a major risk factor for falls and fractures in older persons. There is a subgroup of individuals with sarcopenia who also suffer from osteopenia/osteoporosis, a syndrome known as *osteosarcopenia*. Older persons suffering from osteosarcopenia are frailer and show a higher prevalence of falls and fractures. Fat infiltration is a frequent finding in osteoporosis, sarcopenia and osteosarcopenia. The role of fat infiltration in the pathophysiology of musculoskeletal diseases is intriguing. This fat, which is usually a repository of osteogenic factors in young bone and a source of energy in healthy muscle, suffers a toxic shift in which adipocytes secrete more fatty acids (predominantly palmitic acid [PA]), while oxidate less glucose thus affecting cell function and survival; a phenomenon known as *lipotoxicity*. Our team has characterised the mechanisms regulating lipotoxicity in bone. PA secreted by marrow adipocytes inhibits critical osteogenic pathways, induces osteoblast (Ob) apoptosis, and disrupts Ob metabolism affecting their capacity to eliminate PA from the cytosol via autophagy. Taken together, we hypothesise that *inhibition of PA synthesis by adipocytes will have a dual anabolic effect on muscle and bone*.

As a *proof of principle*, we added cerulenin (CER), an inhibitor of fatty acid synthase (FAS), to our *in vitro* model of Ob lipotoxicity. CER rescued Ob from apoptosis while recovering their bone-forming potential without affecting adipocyte differentiation or survival.
The main objective of this project is to test the effect of FAS inhibition *in vivo* as a new therapeutic approach to osteosarcopenia. In addition, based on our preliminary data on the effect of CER treatment on muscle mass and function, an additional objective is to investigate whether this effect is also observed in other muscles, and whether CER treatment increases muscle mass and function.

69. Investigating Possible Therapies for Sarcopenic Obesity

Supervisors: A/Prof Alan Hayes
Project site: Western Health
Contact: A/Prof Alan Hayes (hayes.a@unimelb.edu.au)

Project description: Low muscle mass and poor function with ageing (sarcopenia) is associated with a low quality of life, which promotes a lack of physical activity and accumulation of fat, and is a strong predictor of morbidity and mortality. Given that obesity is occurring in greater proportions than ever, the two conditions, “sarcopenic obesity”, are thought to complement each other to substantially increase the risk of morbidity and disability at earlier ages.
Ageing and obesity leads to infiltration of fat cells directly into skeletal muscles (known as inter and intra-muscular adipose tissue; (IMAT). Low muscle density (an indirect measure of IMAT) is associated with poor performance in older adults and IMAT explains two to three times more of the variance in mobility than lean mass in older adults. Furthermore, increased IMAT contributes to the reduced muscle strength and power, and poor fitness of obese older adults compared to normal weight controls. We are currently developing an animal model of sarcopenic obesity that will complement our current work in older humans.

The aim of this project is to develop a rodent-based model of sarcopenic obesity that mimics the loss of muscle mass and accumulation of IMAT observed in skeletal muscles. Once established, the model will be used to trial potential therapeutic compounds. Experience in sterile surgical techniques, removal and functional testing of the skeletal musculature and other organs will be obtained. Further histological and morphometric analyses will be undertaken, as well as mitochondrial function and mechanistic analyses, that include; measures of changes in rates of protein synthesis and protein degradation, analysis of critical signalling proteins and transcription factors known to stimulate muscle growth or promote muscle atrophy, via Western blotting, immunohistochemistry, and microscopy. Students will also get the opportunity to contribute to ongoing human trials and/or analysis of existing databases.

NOTES

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