THE UNIVERSITY OF MELBOURNE

Faculty of Medicine, Dentistry and Health Sciences

Melbourne Medical School
Department of Medicine – Western Precinct

Research Opportunities 2016-17

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A word from the Chair of Medicine

Prof. Gustavo Duque

Welcome to the Department of Medicine – Western Precinct

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

Our Precinct provides with the most appropriate resources, expertise and personnel to those students interested in pursuing Honours, Master's 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 have 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/out-patients 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 also testing effective interventions to prevent disability and frailty in our older population.

In summary, the possibilities of performing research at Western are infinite. I invite you to look though this brochure, look at the project(s) of interest to you, and contact our researchers and supporting personnel.

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

Professor Gustavo Duque, MD, PhD, FRACP, GSAF
Chair of Medicine, Western Precinct

My experience at Western

Ella Bocquet-Gaylard

UROP Student

Having just started my UROP placement at the Department of Medicine-Western and AIMSS, I'm very excited to get a taste for research and working in a professional laboratory. As an undergraduate, working with experienced researchers to solve a relevant problem is an amazing experience and a challenge that I'm very excited to take up!

Ahmed Al Saedi

Current PhD Candidate and Research Associate

Studying and working at the Department of Medicine – Western has been one of my best life experiences so far. This friendly environment incorporates state of the art laboratories, modern facilities, and collaborative partnerships between strong research entities such as Western Health and the Australian Institute for Musculoskeletal Science (AIMSS). I encourage others to join our Department and profit from this unique experience.

Catherine Shore-Lorenti

Former student and current Research Assistant

My journey with the Department of Medicine - Western Precinct began in 2011 when I started Honours at Footscray hospital. I've made some life-long friendships during my time with the Department and have been lucky enough to work casually as a Research Assistant while also completing my Masters degree here. My group is a driving force within the Australian Institute for Musculoskeletal Science (AIMSS), and focuses predominantly on preventing falls and fractures in older adults. Since 2011 we've relocated to Sunshine Hospital where we are able to enjoy state-of-the-art equipment to measure bone density and muscle quality, a friendly and collaborative open-plan environment with Western Health and Victoria University, as well as access to clinical rooms, seminar rooms, a research gym, PC2 laboratory and a library. Being co-located with Sunshine Hospital- one of Victoria's fastest growing hospitals, facilitates patient recruitment. There are fantastic opportunities here for anyone interested in clinical musculoskeletal research.

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 33 in the world (Times Higher Education World University Rankings 2015-2016).

Melbourne Medical School

The **Melbourne Medical School** is part of the Faculty of Medicine Dentistry and Health Sciences. 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.

Department of Medicine - Western

The **Department of Medicine – Western** 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 (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.

The **Australian Institute for Musculoskeletal Science (AIMSS)** is a collaborative institute for research into disorders of bone, muscle and joint; and the promotion of disease prevention and evidence-based interventions including exercise and nutrition. AIMSS is founded on research excellence in bone and muscle to address chronic disease such as osteoporosis, arthritis and sarcopenia. Our expertise spans basic and translational research, clinical trials and population health. We are committed to building our current strengths and providing opportunities to expand current projects into larger programs of research. AIMSS is a partnership between researchers and clinicians from Western Health, Victoria University and The University of Melbourne.

1. COMPUFALLS: Computer-based System to Early Detect Risk of Falling in Older People: An International Collaborative Study

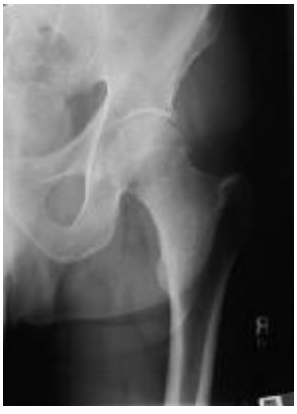
Supervisors: Professor Gustavo Duque and Team of Supervisors at AIMSS
Project Site: Multi-Centre (international) and Australian Institute for Musculoskeletal Science (AIMSS)
Contact: Aloka Carbone (aloka.carbone@unimelb.edu.au) and Rita Kinsella (rita.kinsella@wh.org.au)

Project description: COMPUFALLS aims to prolong healthy and independent living of the older population, enhancing functional autonomy by early detection of falls-risk. To do so, COMPUFALLS will develop a system for long term unobtrusive monitoring and intelligent analysis of behavioural patterns of older people, detecting slowly developing anomalies, such as difficulty undertaking activities of daily living and falls and will correlate these behavioural patterns with clinical and functional data. Thus, early diagnostic markers can be obtained as an alternative to obtrusive clinical methods. COMPUFALLS will provide flexible solutions tailored to assessing the risk of falling in older people who have never fallen and to model the risk of re-falling in those who already have a high falls-risk. COMPUFALLS proposes a Decision Support System (DSS) that detects the risk of falling, by combining clinical, functional, and behavioural data and comes up with personalised interventions through a NoFallAction module in order to reduce the risk. The COMPUFALLS DSS's brain is the risk stratification module that generates a predictive model of falling for the first time (FallRisk); and risk modelling of re-falling for older persons at high risk (ReFallRisk). COMPUFALLS will generate two predictive models combining the information coming from the behavioural monitoring and analysis through a NoFallMonitor accompanying the user. The NoFallMonitor mission is twofold: on the one hand it monitors the user behavioural patterns; and on the other hand it executes the personalised interventions that come from the NoFallAction module. Later, COMPUFALLS will analyse the correlation between behavioural patterns (from the NoFallMonitor) and the risk prediction models obtained from the clinical and functional data (from the FallRisk and ReFallRisk) to establish the link and propose refined models.

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: Australian Institute for Musculoskeletal Science (AIMSS)
Contact: Aloka Carbone (aloka.carbone@unimelb.edu.au) and Rita Kinsella (rita.kinsella@wh.org.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: Professor Gustavo Duque, Dr. Lakshman Singh, Steven Phu, Rita Kinsella and team of Supervisors at AIMSS
Project Site: Australian Institute for Musculoskeletal Science (AIMSS)
Contact: Aloka Carbone (aloka.carbone@unimelb.edu.au) and Rita Kinsella (rita.kinsella@wh.org.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 rage 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. Effect of Parathyroidectomy on Frail Older Persons: The Frail-Pathy Study

Supervisors: Professor Gustavo Duque, and team of Supervisors at AIMSS
Project Site: Australian Institute for Musculoskeletal Science (AIMSS)
Contact: Aloka Carbone (aloka.carbone@unimelb.edu.au) and Rita Kinsella (rita.kinsella@wh.org.au)

Project description: This case-control study aims to identify whether correcting serum parathyroid hormone (PTH) after parathyroidectomy would have an effect on the clinical criteria for frailty, which are highly prevalent in older persons suffering from primary hyperparathyroidism (pPTH). Women (65 and older) undergoing neck exploration for pHPT will be assessed for general functional parameters (gait, balance, and muscle power and strength) and clinical criteria for frailty (Fried's criteria) before and after surgery. Women of the same age undergoing neck exploration for benign nontoxic goitre will serve as controls. This study will provide a new understanding of the role of PTH in the pathophysiology of frailty. We will also identify novel potential interventions to prevent frailty, falls and fractures in high-risk older persons with alterations in their calciotropic hormones.

5. Gait, Cognition and Decline (The GOOD Project)

Supervisors: Professor Gustavo Duque and team of Supervisors at AIMSS
Project Site: Multi-Centre (international) and Australian Institute for Musculoskeletal Science (AIMSS)
Contact: Aloka Carbone (aloka.carbone@unimelb.edu.au) and Rita Kinsella (Rita.Kinsella@wh.org.au)

Project description: Declines in performance of gait and cognition are very common in older adults, with a prevalence of around 20% estimated among adults aged 65 years and over, often co-existing within a same individual. This coexistence is responsible for falls and related adverse health consequences.
Between 20-30% of older adults with cognitive decline, regardless of the nature of the underlying process, fall at least once in their lifetime, i.e. 2 to 3 times more than age-matched adults without any cognitive decline. Falling leads to injuries, hospitalisation, loss of independence and poor quality of life, as well as higher costs to public health and social services. To avoid these adverse health events, it is essential to better understand the association between gait and cognitive decline at the early stage of the physio- pathological process, as this first step is crucial for implementation of

effective prevention strategies. Until recently, gait and cognitive declines were studied and assessed as distinct declines. This may have led to a gap in our understanding of the cognitive-motor interactions that affects pathways to disability in older adults. The time has come to address gait and cognitive declines as interrelated outcomes associated with ageing, with the aim to implement efficient and cost-effective interventions that may delay the transition to dementia and falls. We hypothesized that, compared to CHI, people with mild cognitive impairment (MCI) and mild dementia could be characterized by specific phenotypes of spatio-temporal gait parameters measured with the GAITRite® system, and that these profiles could be explained by declines in domain specific cognitive performance. The objectives of the GOOD project are:
1) To determine which spatio-temporal gait parameters (e.g., mean value and/or coefficient of variation) and/or combination(s) of spatio-temporal gait parameters best differentiate between CHI, individuals with MCI and those with mild dementia (Alzheimer disease and non-Alzheimer).
2) To examine which cognitive domains are associated with gait changes in individuals with MCI and mild dementia. The design of the GOOD project is cross-sectional and will involve evaluation of the databases (i.e., spatiotemporal gait parameters measured with a GAITRite® system, neuropsychological assessment and clinical examination) of several geriatric and neurological centres around the world including: Europe (France and Switzerland), United States of America, Canada and Australia.

CARDIOVASCULAR DISEASES

6. Non-Invasive Cardiac Haemodynamic Evaluation in Acute and Ambulatory Heart Failure

Supervisors: A/Prof. Christopher Neil, Director of CCU and Cardiac Ambulatory Care, Western Health, Clinical Associate Professor, University of Melbourne, Lynnette Reid-Price, Manager, Medical Specialty Diagnostics. Dept. Respiratory & Sleep Disorders, Medicine and Dept. Neurology & Neurophysiology, Western Health
Project Site: Melbourne Medical School (Footscray & Sunshine campuses)
Contact: Associate Professor Christopher Neil (christopher.neil@unimelb.edu.au)

Project description: Acute decompensated heart failure (ADHF) is the single largest reason for acute hospital bed occupancy, and represents a large public health problem and is therefore a major focus of attention for health professionals and health funders alike. ADHF represents a diverse group, in which a broad based “one size fits all” therapeutic strategy may not be appropriate. Hence, failure to appreciate this heterogeneity in cardiovascular and haemodynamic status and to tailor therapeutic manoeuvres accordingly, has been suggested to lie at the root of the problem, and specifically the failure to develop evidence-based treatment. The implications of this thought are significant and it is argued that haemodynamically guided application of existing medical treatment may actually translate to better outcomes. Therapeutic guidance will be aided with the use of a non-invasive cardiac output monitoring system, PhysioFlow®. PhysioFlow®is a system based on the principles of signal morphology impedance cardiography (SM-ICG™), measuring changes in the voltage of an electrical signal applied across an area of the body. This project aims to assess the potential of the PhysioFlow® to guide tailored therapy in heart failure patients by accurately describing the patient’s unique circulatory state, especially their vascular resistance, which is otherwise difficult to assess by standard clinical measures (such as clinical examination or blood pressure measurement).
This proposal will consist of a prospective randomised protocol and will aim to determine the place of the NICaS in guiding clinicians to optimise cardiovascular status in the acute phase of deteriorated HF with use of specific heart failure therapies in inpatients. This project is suitable for honours students who wish to experience translational cardiovascular research in a hospital environment. Furthermore, this project is advantageous for those applicants who may wish in the future to pursue hospital-based employment in the long term, (e.g. as a hospital scientist, technician) or as a prelude to further study in biomedicine.
We have already obtained Human Research Ethics Committee approval. Furthermore, working on the project will guarantee a publication for the work involved.

7. Serial Evaluation of Cardiac and Vascular Function in Preeclampsia: Full Recovery or Persistent LV Contractile Impairment?

Supervisors: A/Prof. Joanne Said, Maternal Fetal Medicine Subspecialist, Head of Maternal Fetal Medicine, Western Health. A/Prof. Christopher Neil, Director of CCU and Cardiac Ambulatory Care. Professor Jason Allen, Institute of Sport, Exercise and Active Living (ISEAL), Victoria University.
Project Site: Melbourne Medical School, Sunshine Hospital, St Albans
Contact: Associate Professor Joanne Said (J.Said@unimelb.edu.au)

Project description: Preeclampsia is a common disorder, which is increasingly believed to result in long term cardiovascular risk. In this case-control study, we propose to evaluate cardiac and cardiovascular function serially in patients presenting with preclampsia (n = 25, standard research definition; 36-40 weeks) and control patients enrolled during pregnancy (n = 25; 36-40 weeks). The time points of testing will be weekly until pregnancy, repeated at two weeks and 3 months post-partum. The methods of evaluation will utilize equipment currently owned by the Neil/Allen group, including (i) echocardiography with 2D speckle tracking and LV global longitudinal strain (GLS), (ii) impedance cardiography (ICG, PhysioFlow®) with simultaneous non-invasive blood pressure will be performed in order to assess haemodynamic status including cardiac output and systemic vascular resistance and (iii) arterial stiffness will be evaluated using the SphygmoCor®. Relevant blood biomarkers will also be measured serially: these will not be standard of care tests, but will include high sensitivity troponin and B-type natriuretic peptide (a marker of LV strain), as well as markers of vascular function (e.g ADMA, homocysteine) and taurine (proposed relevant factor). The advantage of this study will be the ability to compare cardiac functional impairment (GLS) with simultaneous measures of arterial function/vasoconstriction and afterload, which will be important for determining whether LV impairment is secondary to adverse loading conditions, versus due to a primary cardiac condition. Cardiac biomarkers will be used to evaluate the relationship of acute injury with long term impairment. This case-control study will provide unprecedented insight into cardiac and haemodynamic/vascular function over time, which has relevance to emerging ideas about the long term cardiovascular risk in patients with preeclampsia. This project is suitable for a student who wishes to experience a combination of fetal medicine and cardiovascular research in a clinical 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.

CELL AND MOLECULAR BIOLOGY

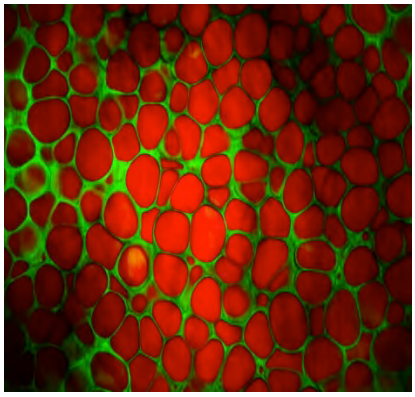
8. Genotype and Phenotype Characterisation Human Circulating Osteo-Progenitor (COP) Cells

Supervisors: Professor Gustavo Duque and team of Supervisors at AIMSS
Project Site: Australian Institute for Musculoskeletal Science (AIMSS)
Contact: Aloka Carbone (aloka.carbone@unimelb.edu.au) and Dr Lakshman Singh (lakshman.singh@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 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 an useful approach as a biomarker and/or treatment to musculoskeletal diseases and frailty.

9. The Effect of Antidepressants on Human Mesenchymal Stem Cell Osteogenesis and Adipogenesis

Supervisors: Professor Gustavo Duque and team of Supervisors at AIMSS
Project Site: Australian Institute for Musculoskeletal Science (AIMSS)
Contact: Aloka Carbone (aloka.carbone@unimelb.edu.au) and Dr Lakshman Singh (lakshman.singh@unimelb.edu.au)



Project description: Previous studies have shown a link between bone mass density and depression/antidepressant use. For example, analyses of clinical data have suggested an association between a low bone mass density and/or fractures, and symptoms of depression. In addition, low bone mass density and/or increased tendency to fracture appear to correlate with antidepressant use, particularly among specific antidepressant drug classes. There may be a molecular basis for these clinical data; however, the causative factor(s) have not yet been conclusively established. On the other hand, conflicting studies

have shown no association between symptoms of depression or antidepressant use and bone mass density.
Despite these clinical data, there has been limited biochemical data to substantiate these claims. One-way antidepressants may be affecting bone mass is through altering the ability of stem cells to differentiate into new, bone-building osteoblasts. Further, evidence of the role (if any) of antidepressants in the differentiation of stem cells into adipocytes is lacking in literature. Thus, we seek to discover whether antidepressants have any effect on the differentiation ability of human mesenchymal stem cells into osteoblasts and adipocytes within our *in vitro* cell systems.

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

Supervisors: Professor Gustavo Duque and Dr. Lakshman Singh
Project Site: Western Centre for Health Research and Education, Sunshine Hospital
Contact: Dr. Lakshman Singh (lakshman.singh@unimelb.edu.au)

Project description: Falls and fractures are highly prevalent in the elderly. Around 20,000 hip fractures cases are reported in Australia every year, and nearly 25% of patients who sustain a hip fracture die within an 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 aging 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.

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

Supervisors: A/Prof. John T. Price, Dr Chau H Nguyen
Project Site: AIMSS, Western Centre for Health Research and Education
Contact: A/Professor John T. Price (jprice@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.

12. Identification and Characterisation of Molecular Mediators of Cancer Metastasis

Supervisors: A/Prof. John T. Price, Dr Chau H Nguyen, Dr Craig Goodman
Project Site: AIMSS, Western Centre for Health Research and Education
Contact: Associate Professor John T. Price (jprice@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.

13. Elucidating the Inhibitory Effect of Fat on Bone Formation: The Relationship Between Osteocytes and Marrow Fat

Supervisors: Professor Gustavo Duque and team of Supervisors at AIMSS
Project Site: Australian Institute for Musculoskeletal Science (AIMSS)
Contact: Aloka Carbone (aloka.carbone@unimelb.edu.au) and Dr Lakshman Singh (lakshman.singh@unimelb.edu.au)

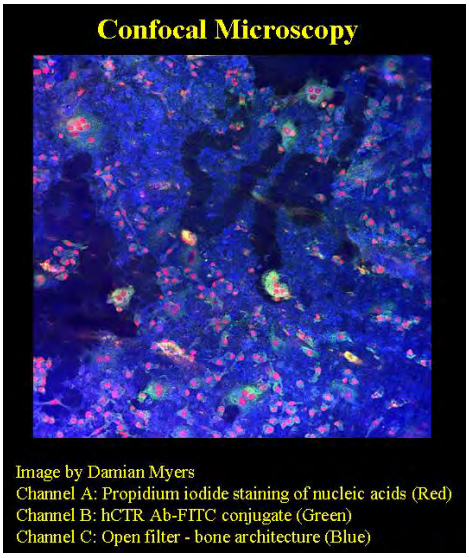
Project description: Osteoporosis affects the quality of life of older people. Although marrow fat infiltration is dramatically higher in human osteoporotic bone, the mechanism, consequences and potential therapeutic potential of this phenomenon remain unknown. Our team has characterised the mechanisms regulating the relationship between fat and bone. We have found that marrow fat secretes fatty acids (mostly palmitic acid [PA]) and adipokines, which are toxic to the osteoblasts (Ob). We demonstrated that inhibition of PA secretion by cerulenin (CER), an inhibitor of fatty acid synthase (FAS), rescued Ob from apoptosis while recovering their bone-forming potential. We also translated these findings by testing whether CER has a similar effect on bone of osteoporotic mice. OVX mice were rescued from osteoporosis by CER. In addition, we also found that PA affects osteocyte (Ocy) function and survival in vitro.
Hypothesis 1. PA has a lipotoxic effect on Ocy through the regulation of function and survival.
- Aim1. To determine the effect of PA on the most important bone-regulating Ocy-derived factors
- Aim 2. To identify the mechanism(s) of PA-induced apoptosis and autophagy in Ocy
Our proposed in vitro experiments will extend our previously successful and highly innovative studies in Ob. The first objective of this proposal is to fully investigate the lipotoxic effect of PA on Ocy. Our outcomes will lead to a solid understanding of the physiological and therapeutic role of marrow fat in bone metabolism. Our findings will provide strong impetus for a new line of therapeutic approaches to osteoporosis, which is highly needed.

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

Supervisors: Dr Craig A. Goodman, A/Prof. Alan Hayes
Project Site: Western Centre for Health Education and Research, Sunshine Hospital, St Albans, Victoria and AIMSS
Contact: Dr Craig A. Goodman (craig.goodman@vu.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 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.



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

Supervisors: A/Prof. Damian E. Myers, Natalie Sims, John T. Price, Prof Brett Paull
Project Site: AIMSS, Western Centre for Health Research and Education
Contact: Associate Professor Damian Myers (damian.myers@vu.edu.au or damianem@unimelb.edu.au), (03) 9919 2652

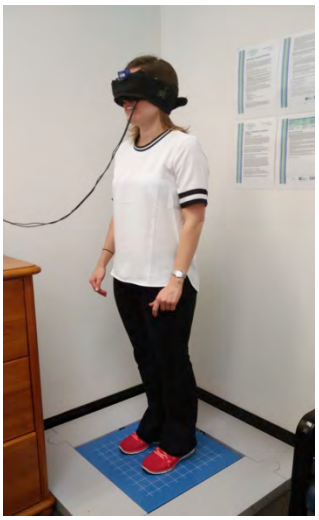
Project description: *Background*: Bone substrate can affect both bone cell formation and bone cell function. Dysregulation of bone cells and altered turnover of bone are central to pathophysiology of bone. Both physical properties and chemical components may play a role. This project has been designed 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 prepared 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.
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 immnunocytochemistry, quantitative techniques for gene expression (PCR techniques) and microscopy techniques including fluorescence and confocal microscopy.

CLINICAL TRIALS

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

Supervisors: Professor Gustavo Duque and team of supervisors at AIMSS
Project Site: Australian Institute for Musculoskeletal Science (AIMSS)
Contact: Aloka Carbone (aloka.carbone@unimelb.edu.au) and Rita Kinsella (Rita.Kinsella@wh.org.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 exercises 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 ear of falls and adherence rates will also be reported.



17. A Randomized, Double Blind, Placebo-controlled Trial to Determine the Effect of Vitamin D Supplementation on Balance Rehabilitation in Older Fallers (The ViDaBe Study).

Supervisors: Professor Gustavo Duque, Steven Phu, Rita Kinsella and team of Supervisors at AIMSS
Project Site: Australian Institute for Musculoskeletal Science (AIMSS)
Contact: Aloka Carbone (aloka.carbone@unimelb.edu.au) and Rita Kinsella (Rita.Kinsella@wh.org.au)

Project description: Recent studies have reported an effect of vitamin D supplementation on muscle performance (grip strength) and muscle mass that may explain the beneficial effect of vitamin D on falls. However, there is still a proportion of older fallers that benefit of vitamin D but do not show any changes in their muscle mass and function, suggesting that an additional mechanism may be involved. Amongst these mechanisms, vestibular and neurosensorial deficits have been associated with falls. Our team reported an association between vitamin D deficiency and poor vestibular parameters in the posturography in older fallers (Boersma et al, JNHA, 2013), which clearly established a link between balance performance and vitamin D. A meta-analysis by one of our international collaborations identified a similar association (Montero-Odasso et al., JAGS, 2013). However, the effect of vitamin D supplementation on balance performance in vitamin D deficient patients remains unknown. In this study, we hypothesize that, in older fallers with balance/neurosensorial deficits, the response to balance/vestibular rehabilitation is enhanced by vitamin D supplementation. Our expected outcomes include a new beneficial effect of vitamin D on falls prevention through the vestibular system, a change in management of older fallers with postural instability.

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

Supervisors: A/Prof. Keith Lim, Dr Albert Leung
Project Site: Western Hospital, AIMSS
Contact: Dr Albert Leung, +613 93181722

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.

19. 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: Melbourne Medical School, Sunshine Hospital, St Albans
Contact: Associate Professor Christopher Neil (Christopher.neil@unimelb.edu.au)

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 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 oxygen 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.

20. Novel Approaches in Therapeutic Endoscopy

Supervisor: A/Prof. Alan Moss
Project site: Footscray Hospital
Contact: Associate Professor Alan Moss (alan.moss@wh.org.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.

COMMUNITY

21. The Association between Social Adversity and Levels of Proinflammatory Cytokines Prior to The Achievement of Peak Bone Mass: A Systematic Review

Supervisor: Dr Sharon Brennan-Olsen
Project Site: Australian Institute for Musculoskeletal Science (AIMSS)
Contact: Dr Sharon Brennan-Olsen, (03) 8395 8108

Project description: There is substantial evidence for a social gradient to exist in osteoporosis, although the underlying mechanisms for this association are not known. It has been posited that greater social adversity across the life-course primes inflammatory pathways that in turn lead to enhanced states of inflammatory reactivity and oxidative stress; this places social disadvantaged individuals at an increased risk of osteoporosis. Given this, and in addition to the direct biological effects exerted on bone by factors like physical inactivity, lower vitamin D exposure, and inadequate calcium intake, the impact of chronic stress (due to adversity) and inflammation on bone remodelling may be disproportionately greater for disadvantaged individuals; this may potentially underpin the observed social gradient in osteoporosis. This project will undertake a systematic review to identify, collate, methodologically assess, and analyse available literature regarding the associations between levels of proinflammatory cytokines and parameters of social adversity from birth to young adulthood. This project has a particular focus on the second to third decade of life; the period where peak bone mass is achieved.
The candidate will conduct a systematic search of PubMed, OVID, and CINAHL databases to identify articles that investigate associations between levels of pro-inflammatory cytokines and parameters of social adversity. The project will involve a meta-analysis and the use of established statistical methods to identify and control for heterogeneity, where appropriate. However, should heterogeneity prevent a numerical syntheses, a 'best-evidence analysis' and comparative synthesis will be undertaken to determine the level of evidence for differences in pro-inflammatory cytokines between differing levels of social adversity, and to identify any potential confounders or mediators for differences in inflammation across social groups.
The findings of this systematic review will have implications for further research into the potential role of inflammatory processes as mediators between parameters of social adversity and osteoporosis.

22. 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: Dr Sharon Brennan-Olsen
Project Site: Australian Institute for Musculoskeletal Science (AIMSS)
Contact: Dr Sharon Brennan-Olsen, (03) 8395 8108

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.

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

Supervisors: Associate Professor H Karunajeewa (UoM/WH General Internal Medicine) & Professor P Clark, Health Economist School of Population Science UoM
Project Site: Sunshine Hospital
Contact: Professor 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 T (2016-2017).

HORMONES

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

Supervisor: A/Prof. Christine Rodda
Investigators: Associate Professor Christine Rodda, Mr Chris Harris 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: 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 possibility contribute to long term osteoporotic hip fracture in later life.

25. 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 Romane Blanchard, AssociateProfessor Peter Pivonka, Dr Michael Bullen, Mr Chris Harris 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.

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

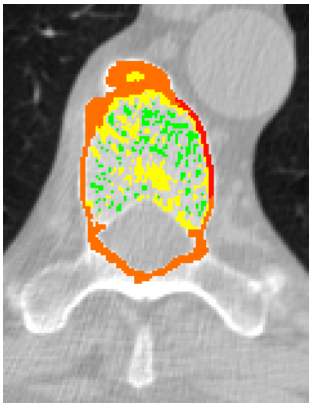
Supervisors: A/Prof. Itamar Levinger, A/Prof. Tara Brenan-Speranza, A/Prof. Shane Hamblin, Prof. Gustavo Duque
Project Site: AIMSS, Victoria University (ISEAL), Bosch Institute (University of Sydney) and Endocrinology Unit (Western Health).
Contact: A/Prof. Itamar Levinger (Itamar.Levinger@vu.edu.au)

Project description: Increased bone fragility and reduced skeletal muscle quality are under-recognised 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.

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

Supervisors: Professor Gustavo Duque, Steven Phu, Rita Kinsella, Dr. David Scott and team of Supervisors at AIMSS
Project Site: Australian Institute for Musculoskeletal Science (AIMSS)
Contact: Aloka Carbone (aloka.carbone@unimelb.edu.au) and Rita Kinsella (rita.kinsella@wh.org.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 right, 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 a more specific diagnostic method for the quantification of fat within bone and muscle, which would be not only 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.

28. Significance and Temporal Course of Advanced Echocardiographic Measurements of Left Ventricular Function in an Australian Cohort of Stage A Heart Failure, with High Baseline Cardiovascular Risk.

Supervisors: A/Prof. Christopher Neil, A/Prof. Chiew Wong, Head of Non-Invasive Cardiac Imaging, Western Health, Clinical Associate Professor, University of Melbourne.
Project Site: Melbourne Medical School (Footscray & Sunshine campuses)
Contact: A/Prof. Christopher Neil (Christopher.Neil@unimelb.edu.au)

Project description: Many individuals within our community are at risk of developing left ventricular dysfunction and heart failure (HF). The incidence of HF, therefore, continues to rise, in association with an increasing incidence of hypertension, diabetes and obesity. Whilst these latter conditions should be managed on their own merits, they are also known risk factors for the development of HF. In view of this, a conceptual category a preclinical stage in the continuum of HF risk, has been proposed and designated as Stage A HF (AHA, 2000). Patients in this category typically have hypertension, diabetes and/or obesity and it is believed that these conditions affect myocardial structure and function over time, whilst the patient remains asymptomatic. If LV structural or functional disease is detected, the patient is designated as Stage B HF, whereas who patients go on to develop symptomatology for HF are designated stage C, and those in advanced and refractory states of HF are designated stage D. Although this conceptual framework has existed for over 10 years, questions remain about the early stages, for example, the rate at which patients with Stage A progress to Stage B remains unknown.
In order to elucidate the progression of Stage A HF to Stages B and C, a prospective study of 600 patient was previous conducted (NIL-CHF study). High quality two dimensional echocardiograms were obtained at baseline and at intervals over 18months, in each subject. Various echo measurements have been proposed to predict the progression to HF (among these, LV global longitudinal strain and the myocardial performance index). The purpose of this project is to use this previously echocardiographic source data to measure novel echocardiographic parameters and thus to explore their significance in this large cohort, with reference to clinical events in patients, over time. This work will inform the cardiology community regarding the rate of change (or otherwise) of these novels parameters in patients with active cardiovascular risk and will provide new information regarding their predictive value in the important clinical context of preclinical HF. The student will work in an experienced cardiac imaging team and become proficient in the analysis of cardiac function, utilising state-of-the-art software. The results of this study will be highly relevant for publication and for discussion at national and international cardiology meetings.

29. Serum Parathyroid Hormone (PTH) as a Predictor of Poor Outcomes in Post-Hip Fracture Patients.

Supervisors: Professor Gustavo Duque, Steven Phu, Rita Kinsella, Dr. David Scott and team of Supervisors at AIMSS
Project Site: Australian Institute for Musculoskeletal Science (AIMSS)
Contact: Aloka Carbone (aloka.carbone@unimelb.edu.au) and Rita Kinsella (rita.kinsella@wh.org.au)

Project description: There is a lack of a reliable, objective and inexpensive test used as a screening tool to identify elderly hip fracture patients who are more susceptible to post-operative complications and poorer outcomes after a hip fracture. The hypothesis of this study is that serum concentrations of parathyroid hormone (PTH) can be used as a marker for predicting adverse outcomes for elderly patients with a hip fracture.
We propose a prospective analysis of older patients admitted in Western Health due to a hip fracture. Post-operative complications and survival one-year post hip fracture will be investigated.
This study aims to investigate the correlation between serum PTH in older hip fracture patients and post-operative complications, length of stay, in−patient mortality and survival one year post hip fracture.

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

Supervisors: Professor Gustavo Duque, Dr. Lakshman Singh, Mr. Steven Phu, Mrs. Rita Kinsella, Dr. David Scott and team of Supervisors at AIMSS
Project Site: Australian Institute for Musculoskeletal Science (AIMSS)
Contact: Aloka Carbone (aloka.carbone@unimelb.edu.au) and Rita Kinsella (Rita.Kinsella@wh.org.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).

31. Using wearable activity Trackers to Monitor Physical Activity in Older Adults Undergoing Exercise Interventions for Falls

Supervisors: Dr. David Scott, Prof. Gustavo Duque
Project Site: Australian Institute for Musculoskeletal Science (AIMSS)
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.

32. Quantitative Measure of Effusions

Supervisors: Dr Albert Leung, Dr Kim Le Marshall, A/Prof. Keith Lim
Project Site: Western Hospital and Sunshine AIMSS
Contact: Associate Professor 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.

33. Osteosarcopenia in Older Adults Attending a Fracture Liaison Service

Supervisors: Dr. David Scott, 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.

34. Improving Outcomes for People With Hip or Knee Osteoarthritis

Supervisors: Professor Kim Bennell (CHESM), Professor Rana Hinman (CHESM), Professor Gustavo Duque (AIMSS)
Project Site: AIMSS and Centre for Health, Exercise and Sports Medicine (University of Melbourne, Parkville)
Contact: Professor Kim Bennell (k.bennell@unimelb.edu.au) or (03) 8344 4135

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.

35. Effect of Whole Body Vibration (WBV) on Osteosarcopenia: A Randomised Placebo-Controlled study

Supervisors: Prof. Gustavo Duque, Rita Kinsella, Steven Phu
Project Site: AIMSS
Contact: Rita Kinsella (rita.kinsella@wh.org.au)

Project description: Whole body vibration training (WBVT) has been used as a supplement to conventional exercise training such as resistance exercise training to improve skeletal muscle strength and bone mass in older persons. In this population, the combination of osteopenia/osteoporosis and sarcopenia, known as osteosarcopenia, has been proposed as a subset of frailer individuals at higher risk of institutionalization, falls, and fractures. However, the effect of WBV on patients suffering from osteosarcopenia has not been assessed. Therefore, this study aims to identify the effect of WBV on osteosarcopenic older persons. Changes in bone and muscle mass will be assessed by DXA and pQCT. Muscle function and strength will be also assessed. Secondary outcomes will include falls and independence in ADLs and IADLs.

36. 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: Institute for Health & Ageing, AACU 215 Spring St, Melbourne
Contact: Prof Kerrie Sanders (ksanders@unimelb.edu.au)
******These projects are adaptable to be appropriate for Honours through to PhD.*
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.

NEUROLOGICAL DISEASES

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

Supervisors: Prof. Gustavo Duque and A/Prof. Tissa Wijeratne
Project Site: Sunshine Hospital and AIMSS
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.

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

Supervisors: A/ Prof. Tissa Wijeratne
Project Site: Sunshine Hospital
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.

39. High Dose Vitamin D and Post-Stroke Outcomes: A randomized Controlled Trial

Supervisors: Professor Gustavo Duque and Associate Professor Tissa Wijeratne
Project Site: Sunshine Hospital
Contact: Associate Professor 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 aimed 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.
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PHARMACOLOGY

40. Effect of Inhibition of Peroxisome Proliferator Activated Gamma 2 (PPARγ2) on Bone Formation

Supervisors: Prof. Gustavo Duque, Dr. Lakshman Singh and team of Supervisors at AIMSS
Project Site: Australian Institute for Musculoskeletal Science (AIMSS)
Contact: Aloka Carbone (aloka.carbone@unimelb.edu.au) and Dr Lakshman Singh (lakshman.singh@unimelb.edu.au)

Project description: Infiltration of bone marrow with fat is a prevalent feature in people with age-related bone loss and osteoporosis, which correlates inversely with bone formation and positively with high expression levels of peroxisome proliferator-activated receptor gamma (PPARγ). Inhibition of PPARγ thus represents a potential therapeutic approach for age-related bone loss. We have previously reported that BADGE (an inhibitor of PPARγ) induced higher levels of osteoblastogenesis and bone formation concomitant with decreased marrow adiposity and *ex vivo* adipogenesis in old male mice. However, BADGE is relatively toxic therefore new approaches (molecular and pharmacological) are still required. This project involves in vitro and in vivo experiments looking at alternative approaches to inhibit PPARγ in mesenchymal stem cells while inducing bone formation and decreasing adipogenesis with a subsequent beneficial effect on osteoporosis.

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

Supervisors: Dr Emma Rybalka and Associate Professor Alan Hayes
Project Site: Western Centre for Health, Research & Education, Sunshine Hospital
Contact: Dr Emma Rybalka (emma.rybalka@vu.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

42. 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; A/Prof. Shane Hamblin
Project Site: Melbourne Medical School, Sunshine Hospital, St Albans.
Contact: Associate Professor Craig Nelson (Craig.Nelson@wh.org.au), +61412412376

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.

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

Supervisors: Dr Sharon Brennan-Olsen
Project Site: Australian Institute for Musculoskeletal Science (AIMSS), Sunshine Hospital
Contact: Dr Sharon Brennan-Olsen, (03) 8395 8108

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. 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 disadvantage, or from culturally and/or linguistically diverse (CALD) 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 socially diverse and CALD backgrounds: 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.

RESPIRATORY MEDICINE

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

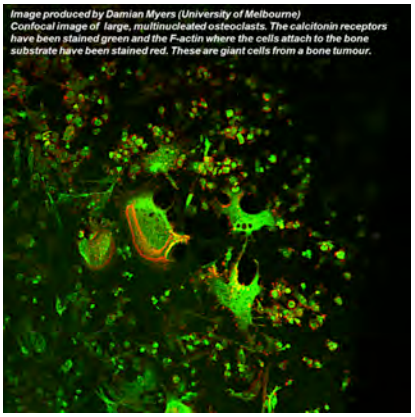
Supervisor: Associate Professor Lata Jayaram
Project Site: Western Health
Contact: Associate Professor Lata Jayaram (lata.jayaram@unimelb.edu.au)

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

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

Supervisors: A/Profs Damian E. Myers, John T. Price, Prof Gustavo Duque and Dr Kathy Traianedes.
Project Site: AIMSS, Western Centre for Health Research and Education
Contact: Associate Prof Damian Myers (damian.myers@vu.edu.au or damianem@unimelb.edu.au), (03) 9919 2652



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 been2 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.

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

Supervisors: Professor Gustavo Duque, Associate Professor Alan Hayes and team of Supervisors at AIMSS
Project Site: Australian Institute for Musculoskeletal Science (AIMSS)
Contact: Aloka Carbone (aloka.carbone@unimelb.edu.au) and Dr Lakshman Singh (lakshman.singh@unimelb.edu.au)

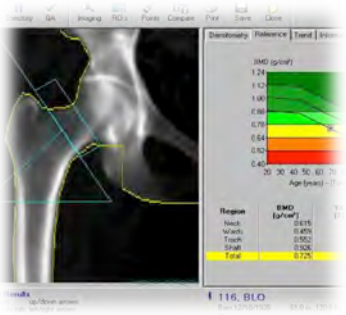
Project description: Sarcopenia – defined as low muscle mass and strength – is a major risk factor for falls and fractures in older persons. There is a subgroup of individuals with sarcopenia who also suffer from osteopenia/osteoporosis, a syndrome known as *osteosarcopenia*. Older persons suffering 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

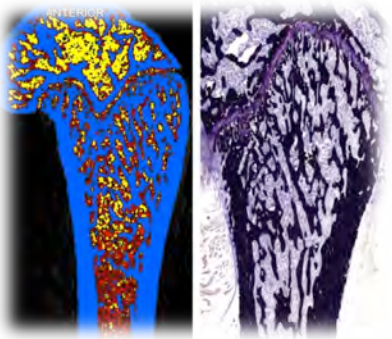
survival; a phenomenon known as *lipotoxicity*. Our team has characterised the mechanisms regulating lipotoxicity in bone. PA secreted by marrow adipocytes inhibits critical osteogenic pathways, induces osteoblast (Ob) apoptosis, and disrupts Ob metabolism affecting their capacity to eliminate PA from 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.

47. Investigating Possible Therapies for Sarcopenic Obesity

Supervisors: Assoc. Prof. Alan Hayes, Dr Craig A. Goodman, Dr Emma Rybalka
Project Site: Western Centre for Health Education and Research, Sunshine Hospital, St Albans, Victoria.
Contact: Assoc. Prof. Alan Hayes (alan.hayes@vu.edu.au)

Project description: Low muscle mass and poor function with ageing (sarcopenia) is associated with low quality of life, 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, and 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.





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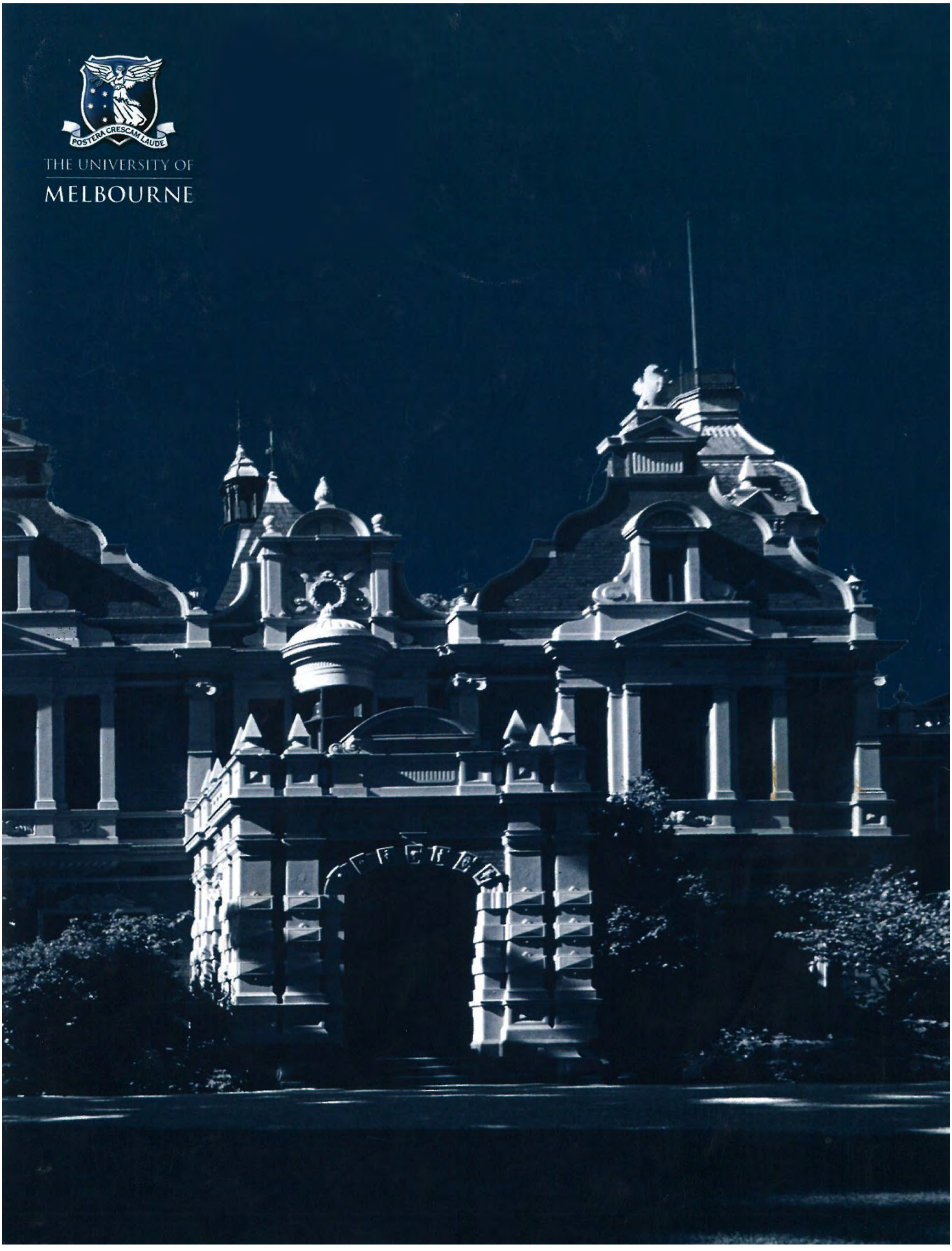
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