2015 ARTHRITIS AUSTRALIA NATIONAL RESEARCH PROGRAM RECIPIENTS LAY SUMMARIES

Fellowships

AFA-ARA Heald Fellowship - $50,000
(funded jointly by Australian Rheumatology Association and Vincent Fairfax Family Foundation)
Dr Sultana Hussain
Department of Epidemiology and Preventive Medicine, Monash University
Project: ***Towards a better understanding of low back pain***

The recent Global Burden of Disease study ranked low back pain second only to cancer as the leading cause of disability in Australasia. Moreover, musculoskeletal disease, of which low back pain is the most prevalent and costly, is the 7th National Health Priority Area in Australia. Low back pain causes true functional disability, not just pain and is poorly treated. There is increasing evidence that obesity, which is in epidemic proportions, is a risk factor for low back pain. However, it is unclear how obesity and low back pain are linked. While it is clear there is an urgent need for innovative and cost-effective treatments for low back pain, these are currently limited. There is widespread concern on the increasing use of narcotics to manage low back pain, since this is associated with significant side effects, including deaths. This fellowship program aimed to identify modifiable risk factors for low back pain and the prevalence of narcotic use among the low back pain patients. It was found that body weight, body size, weight gain, body composition, television viewing a marker of physical inactivity, inflammation predicted the risk of low back pain and those who suffer from low back pain use more narcotics. This project has the potential to improve the understanding of the pathogenesis of low back pain and identify novel targets for disease prevention. Furthermore, this will improve our understanding on the determinants of narcotic use among those suffering from low back pain.

The ARA Victorian Fellowship - $12,500
(funded by Australian Rheumatology Association – Victoria)
Dr Lucy Croyle
Centre for Inflammatory Diseases, Monash University
Project: ***Optimising treatment in systemic lupus erythematosus***

Treatment algorithms are glaringly absent in systemic lupus erythematosus (SLE), possibly due to the multisystem nature of the disease and imprecise treatment targets. There are, however, tools that can be applied to improve current treatment strategies. Three of the widely used medications in SLE, utilised for all manifestations of the disease, have quantifiable whole drug levels. Research over the past 15 years has provided good evidence that attaining certain levels of these drugs correlates with attaining and sustaining remission, flare prevention and avoidance of serious toxicity. Additionally, these measurable drug levels can give reliable indications of patient compliance, which is well evidenced to be poorly intimated by physicians as a whole. Further, these three medications show large interpatient variability, and current weight based dosing regimens do not appropriately incorporate this variability. Dosing algorithms based on measurable levels have potential to be a cost effective strategy through use of single time appropriate measurements to achieve therapeutic targets and decrease morbidity associated with ongoing disease activity. Current available evidence is scant in lupus and this project sought to add to this in order to employ a dosing algorithm based on metabolites or whole blood levels. During the course of this grant, we built on the prior retrospective review of the Monash lupus cohort from 2007-2012 that determined the characteristics of azathioprine use and cessation.

We found that AZA was frequently used, especially in SLE patients with more severe disease, and active lupus nephritis was evident in patients escalating to mycophenolate mofetil (MMF) from AZA. AZA was safely ceased due to low disease activity in 50% of cases and cessation for toxicity was uncommon in our cohort. This was presented as a poster at ARA in Hobart 2014, and published as an abstract in an IMJ 2014 supplement.

The ARA Victorian Fellowship - $25,000
(funded by Australian Rheumatology Association – Victoria)
Dr Claire Owen
Department of Rheumatology, Austin Hospital
Project: *Predictors of relapse in polymyalgia rheumatica patients treated with low-dose glucocorticoid therapy*

Despite polymyalgia rheumatica (PMR) being the most common inflammatory rheumatic disease of the elderly, it is poorly understood. With no diagnostic tests available, diagnosis is dependent upon a history of muscle pain and stiffness in the hip and shoulder regions, combined with raised inflammation levels in the blood. Treatment consists of Prednisolone (commonly referred to as 'cortisone') prescribed in a 'one size fits all' approach. However, the way in which PMR patients' symptoms respond is highly variable; some improve almost overnight, while other individuals require higher doses for much longer periods of time. Unfortunately, such long-term Prednisolone use can result in many complications including osteoporosis, weight gain, high blood pressure and diabetes. Similarly, uncontrolled PMR is associated with increased risk of heart attacks and stroke. Therefore, this project aimed to identify the characteristics of those PMR patients that fail to respond adequately to standard Prednisolone treatment. By identifying this population, it is hoped that Prednisolone-related complications can be prevented and further study of alternate therapy in this group investigated.

Patients with suspected PMR attending the Austin Hospital or referred by general practitioners and rheumatologists in the Hospital's catchment area (north-eastern suburbs of Melbourne, Victoria), were invited to partake in the study.

At present, recruitment for this study is ongoing with the aforementioned grant utilised to fund the second of three consecutive years of research. To date, 26 participants have been enrolled (recruitment target ~30 participants). Therefore, the discoveries made up to this point pertain to cross-sectional rather than longitudinal data because the latter is presently incomplete.

The average age of the participant cohort to date is 68.3 years, with a male predominance observed (59.1%). Shoulder pain is the most common symptom (100%), followed by hip pain (81.8%). A high frequency of peripheral joint involvement, particularly at the knees (81.8%) and hands (63.6%), is also reported. Most patients have experienced an extended duration of symptoms prior to a diagnosis of PMR being made (mean 233 days) and consequently encounter severe disability as measured by a dedicated questionnaire. Taken together, these results suggest that PMR is often overlooked by general practitioners and specialists alike, presumably due to uncertainty about this common condition and the lack of a diagnostic test.

The distribution of inflammation seen on whole body PET/CT scanning has revealed distinct findings in patients with PMR. In particular, abnormalities are clearly seen in the shoulders (84.62%), hips (92.31%) and back (76.92%). Whilst these findings have been documented in other studies, this project has also detected characteristic inflammation in the pelvis (95.4%) and knees (76.2%) too (Figure 1). Furthermore, a high proportion of patients have been found to have abnormalities in their wrists/hands (72.7%). These scans therefore imply that PMR is not purely a disease affecting the shoulders and hips, but that it can have more widespread joint involvement. The long-term implications for the patients' treatment response of these differences on whole body PET/CT scanning are now eagerly awaited.

With respect to the aforementioned pelvic and knee findings, further study utilising Magnetic Resonance Imaging (MRI) has now clarified the anatomical structures that are typically inflamed in PMR at these sites. In particular, inflammation of the hamstring tendons at their origin in the pelvis and insertion at the knee has been demonstrated. This likely explains the buttock and posterior thigh pain that is common to patients with a clinical presentation of PMR. Furthermore, it contributes to our growing understanding of the distinct manifestations of this disease and inherent differences between it and related conditions like rheumatoid arthritis (RA).

Arthritis Australia and State & Territory Affiliate Grant - $50,000
(funded by Arthritis South Australia)
Dr Benny Eathakkattu Antony
Menzies Research Institute Tasmania, University of Tasmania
Project: *Vitamin D effects on osteoarthritis: A randomised control trial*

This project will take advantage of a National Health and Medical Research Council (NHMRC) funded clinical trial - Vitamin D Effects in Osteoarthritis (VIDEO) - which has recently completed a 24 month follow-up of 410 participants. Vitamin D deficiency affects up to 80% of older adults and is associated with knee pain and knee cartilage loss. The aim of this study is to compare, over a two year period, the effects of vitamin D supplementation versus placebo on knee pain and knee structural change (assessed by Magnetic Resonance Imaging, MRI) in patients with symptomatic knee osteoarthritis. Identifying the significance of vitamin D is an important step towards disease prevention and it may be possible to slow disease worsening and delay or prevent subsequent joint replacement.

We found that vitamin D supplementation over two years did not significantly reduce WOMAC (a pain measuring scale) - measured knee pain and knee cartilage volume loss (measured using MRI) over 2 years. However, participants who took vitamin D had significantly reduced VAS (another pain measuring scale)- measured knee pain and improved physical function compared to placebo in patients with knee osteoarthritis and moderate vitamin D deficiency. There were more OMERACT-OARSI (Outcome Measures in Rheumatology Clinical trials- Osteoarthritis Research Society International) responders in the vitamin D group than the placebo group (35% vs. 25%) and vitamin D group did not increase the effusion (local swelling) compared to placebo. These results were reported as oral presentations at international conferences, and a paper has been published in the top-tier medical journal of the American Medical Association (JAMA).

Furthermore, there have been few long-term studies examining structural disease-related risk factors associated with joint replacement. This fellowship program allowed me to describe what knee structures predicted knee replacement surgery, cartilage volume loss and knee pain over 10.7 years in the Tasmanian Older Adult Cohort (TasOAC) study. We found that cartilage defects, bone marrow lesions, infrapatellar fat pad signal changes (all these measures are commonly detected using MRI), were found to predict knee replacement surgery, cartilage volume loss and knee pain over 10.7 years.

The Arthritis Queensland Fellowship - $50,000
(funded by Arthritis Queensland)
Dr Karsten Schrobback
Institute of Health and Biomedical Innovation, Queensland University of Technology
Project: *Biomarkers of mechanical stress and harmful loading on osteoarthritic knee cartilage*

Osteoarthritis (OA) is an age-associated disease affecting 1.6 million Australians but there is no cure, due in large part to our lack of understanding of the disease. Abnormal biomechanical loading of cartilage tissue in the joint plays a major role in the development of knee osteoarthritis and is linked to important osteoarthritis risk factors, such as obesity, joint injury and overuse.

Early diagnosis of osteoarthritis is challenging with symptoms, such as pain and limited joint function, only occurring after potentially irreversible damage to the joint. In addition, imaging techniques such as X-ray or magnetic resonance imaging that are widely relied upon in the diagnosis of osteoarthritis in clinical practise are not very effective in picking up early changes in joint tissues during disease development. Given that it takes years for degenerative changes and symptoms in the joint to develop, early identification of individuals under the risk of developing osteoarthritis remains difficult. Measuring levels of specific molecules in blood and urine, also known as biomarkers, can be a valuable tool for the diagnosis and prognosis of OA. However, current approaches in biomarker discovery have failed to yield molecules that sufficiently discriminate between various stages and types of knee OA. Main shortcomings have been identified as a lack of adequate research into validation and the tissue origins of the markers as well as insufficiently controlled sampling time points.

This project, therefore, was aimed at first identifying proteins that are released from cartilage in response to moderate or high, mechanical, compressive loads in a laboratory setting. The identity and quantity of secreted proteins was measured using highly sensitive mass spectrometry, which allows for simultaneous detection of a large amount of biomarkers. We then went on to look for these markers alongside other interesting molecules in blood and urine of people under risk of developing osteoarthritis in comparison to individuals with self-reportedly healthy joints.

Cartilage is a load-bearing tissue that is capable of withstanding high loads and even requires regular mechanical stimulation for normal tissue function and maintenance. However, excessive loading decreases the formation of new cartilage and increases levels of tissue-degrading enzymes. To analyse proteins secreted by cartilage in response to healthy and harmful loading in the laboratory, samples were collected from knee cartilage of mainly elderly people with osteoarthritis after total knee replacement surgeries.

The injurious impact load had the greatest effect on protein secretion from cartilage samples and also led to a high number of dead cells in these tissues. Only between 30 to 60 % of cells in the impacted samples survived the injurious load compared to 60-90 % in the control and cyclical loaded samples. We detected between 100-150 secreted proteins in each group after loading. However, 58 unique proteins were found to be secreted only after injurious load but not in any of the other groups. Moreover, of the cartilage proteins detected in all groups, we found highly important matrix molecules, such as aggrecan and cartilage oligomeric matrix protein, at 3 or 1.6 times higher quantities in the medium surrounding cartilage samples after injury compared to other groups. The proteins identified here were higher and/or exclusively expressed during harmful loading of cartilage and represent, therefore, potential biomarker candidates, for which we will specifically look in blood and urine samples collected during part two of this project.

In contrast to injurious load, we did not see considerable differences in secreted proteins between samples not loaded and those that received cyclical loads even at relatively high strain levels. This is quite surprising considering that the strain levels during high, cyclic stimulation were only a slightly lower (50 %) than in the impact group (60 %). However, the strain rate or the speed, at which the load was applied to the cartilage was three times higher in the impacted group than in the cyclic compression group. This could, therefore, mean that the speed of the compressive load is much more important to the health of cartilage and its cells than the strain levels at which it is stimulated. Our results also suggest that knee cartilage even from patients with osteoarthritis can tolerate relatively high levels of strain during moderate exercises. It may also mean that cells in aged, osteoarthritic cartilage should be considered as rather inactive and that physical stimulation of the cartilage of elderly people is insufficient to promote the secretion of proteins and the formation of new tissue.

We expect more exciting data from the second part of the project. Samples from all study participants have been collected and are in process of being analysed. This should be completed by the end of this year.

The Ken Muirden Overseas Training Fellowship - $100,000
(funded jointly by an educational research grant by Australian Rheumatology Association and Roche Products Pty Limited)
Dr Ju Ann Tan
Department of Experimental Medicine, University of British Columbia, Vancouver, Canada
Project: *Overall and cause-specific mortality in patients with systemic vasculitis*

Aims:
1. To determine overall mortality risks in patients with AAV (MPA, GPA and EGPA), PAN and GCA.
2. To determine cause-specific mortality risks (including cardiovascular disease, infections, malignancy and renal disease) in patients with AAV (MPA, GPA and EGPA), PAN and GCA.

ANCA-associated vasculitis is an inflammatory disease of the blood vessels which is associated with the autoantibody, ANCA. It affects approximately 68 000 to 140 000 persons per year globally and in Australia 1 in every 50 000 people is diagnosed annually. The disease causes narrowing of the blood vessels, or in some cases, formation of a blockage (thrombosis) and these can lead to a disruption of blood flow and delivery of oxygen to vital organs such as the skin, brain, heart, kidneys and lungs. Most cases involve only single organs but when it is widespread, it can be a devastating disease. In its severe form, it is known that without treatment 80% will die within a year.

Significant advances in the medical treatment and care of these patients have greatly improved their survival chances to more than 70% at five years. However, there are still limitations to this current body of knowledge. As it is a rare disease, the studies involved small patient numbers and were subjected to biases that might affect the accuracy of the findings. Therefore, my thesis research focused on the mortality in ANCA-associated vasculitis. The primary purpose of my research was to determine the risk of death and major causes of death in these patients. To estimate these as accurately as possible, a large body of data is necessary and to that purpose I conducted my research in Canada, where a framework is available to collect healthcare information on the population of British Columbia.

The preliminary findings of my research has already been presented at the 2015 American College of Rheumatology Annual Conference and it showed that these vasculitis patients still carry a 2.5 times greater risk of dying compared to the general population, ie those without the disease. On a positive note, this mortality risk is reducing over time which means that we are on the right track in terms of patient care. It would be of great interest to clinicians and sufferers of this disease to also know what the specific causes of death are and the associated risks. With this knowledge, we would be able to identify these risk factors and to develop strategies to mitigate these risks in the hope that we will further improve patient survival. I plan to continue research in this area and look forward to sharing the results of my findings with my peers and the public.

This population-based study shows that survival of GPA patients has improved over the past decade, suggesting the new treatments and improved management of the disease and its complications may be providing substantial benefits.

Leanne Stafford Award - $50,000
(funded by Australian Rheumatology Association)
Dr Richard John Holland
Department of Rheumatology,Royal National Hospital for Rheumatic Diseases, UK
Project: *Evaluation of the PsAID Questionnaire*

Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy affecting up to 40% of patients with skin or nail psoriasis. Disease activity and damage contribute to reduced physical and psychosocial health-related quality of life, with significant social and economic impact. Psoriasis is a complex disease, and has a multitude of clinical manifestations including dactylitis, enthesitis, peripheral joint disease, and axial

disease. This complexity has resulted in the development of a number of disease activity indices, all of which perform similarly and use a 'biomedical model' for determining disease activity[3].

Patient reported outcomes (PROs) have been found to be a reliable indicator of baseline status, change during treatment and are predictive of long-term outcome. There is a therefore a need to measure PROs as part of routine clinical practice and current treatment recommendations for psoriatic arthritis suggest measuring the patient global assessment (PGA) to assess overall disease burden, the health assessment questionnaire (HAQ) for physical function as well the short-form 36, SF-36) as a measure of health status.

A recent literature review indicated that pain, PGA and HAQ were frequently measured in clinical trials. However other measures of how the patient feels or functions, such as fatigue and sleep, were rarely reported. The SF-36, whilst a recognised measure of the economic impact of disease, is long and the interpretation of the score is complex. The HAQ has also been shown to change with disease duration, and with longer disease duration less reliably reflects active disease.

A EULAR taskforce developed a questionnaire to calculate a score reflecting the impact of psoriatic arthritis from the patients' perspective, termed the Psoriatic Arthritis Impact of Disease (PsAID) questionnaire. Development of this questionnaire involved 12 patient research parties and determined 12 domains important to health and well-being, including fatigue, functional capacity, sleep and coping. The PsAID questionnaire was validated with more than 470 patients, and had good face validity and good generalizability and also correlated strongly with patient global assessment. The authors noted that further validation of the PsAID score was needed, in particular regarding sensitivity to change in comparison with other outcome measures.

A similar score has been developed for rheumatoid arthritis, and has been shown to correlate strongly with other global measures of health (patient global score, Rheumatoid Arthritis Disease Activity Index), can be used to define an acceptable disease status, and is also sensitive to change. The PsAID could be similarly useful in clinical trials as well as in standard clinical practice to comprehensively measure the patient-reported burden of disease.

The RNHRD is ideally suited to undertake research in PsA as it has the largest individual database of patients with psoriatic arthritis in the UK. It has clinical, demographic and radiographic data from a cohort of over 700 patients with PsA. Statistical support will be available from the department of Pharmacoepidemiology at the University of Bath, which has extensive experience on the analysis of large epidemiological data sets, and a strong track record of high impact publications.

We collected data prospectively from a single centre cohort of patients with psoriatic arthritis. A total of 81 patients (43 female) had stable disease and contributed to the assessment of reliability and construct validity, and 76 patients had active disease requiring a change in treatment and were recruited to the arm of the study investigating sensitivity to change. Clinical measures and PROs, including the PsAID, were completed at baseline and the PsAID was repeated at 1 week in all patients. In those with active disease a further assessment was undertaken at 3 months, and clinical and patient reported outcomes were recorded.

The first objective was to assess the reliability of the PsAID questionnaire. In patients with stable disease, we determined an average PsAID12 score (out of 10) at baseline was 3.11 and 1 week later was 3.06. The scores for the PsAID9 were similar. Including those patients with active disease, the average score was slightly higher, with an average score of 3.49 at baseline and 3.38 at 1 week. Overall there was very little variability in the score from week to week, indicating that the questionnaire was extremely reliable; a single score would give an accurate indication of the impact of the disease on a patient at a specific time point. There was a weak floor effect, with substantially more scores at the lower end of the scale (<2) than at the upper end of the scale (>8).

Interestingly scores in females were significantly higher than in males. Analysing all patients, we found that the average score in females was 4.49 vs 2.75 in males. When individual components of the PsAID12 were analysed females scored significantly higher in 9 of the 12 items. In this cohort, we found that females scored higher in all the patient reported outcomes studied, except for the DLQI.

The PsAID correlated well with most of the clinical and patient reported outcomes measured. There was a strong correlation with the PsA Quality of Life questionnaire, joint and global VAS scores, EQ5D-5L Index and VAS scores, mCPDAI, HAQ, and FACIT fatigue scale, the strongest correlation seen with the EQ5D Index. There was moderate correlation between the PsAID and the tender and swollen joint counts. There was weak correlation with the DLQI and no correlation with the PASI, which may be due to the fact that this population had, on average, very mild skin disease. The correlation of the PsAID was not affected by disease severity. These results demonstrate that the PsAID has excellent construct validity, corresponding well to other measures of disease activity, impact or function.

Work is still underway to assess the sensitivity to change and minimal clinically important improvement of the PsAID questionnaire. Results to date indicate that it can detect change when patients improve, although only half of the patients have completed the three-month follow-up. It is expected that within the next four months all patients will have completed follow-up allowing for full analysis of the data.

The PsAID score therefore provides a reliable and precise assessment of the impact of PsA, helping healthcare providers and patients to make shared treatment decisions that target the areas that are of most concern to the patient. Analysing the individual components of the score can highlight areas that need greater emphasis, improving overall wellbeing for that particular patient.

UCB Australia Fellowship - $50,000
(funded by UCB Australia Pty Ltd)
Dr Helen Benham
Autoimmunity Division, Diamantina Institute,University of Queensland
Project: *Pre-clinical rheumatoid arthritis - prediction and prevention*

Rheumatoid arthritis (RA) is a common and incurable chronic inflammatory joint disease affecting 1- 2% of the population. It is a disease associated with significant disability and reduced life expectancy leading to enormous social and economic burden. In this project Dr Benham will investigate at-risk first-degree relatives (FDR) of patients with RA. She will establish a prospective cohort of FDR to identify genetic, environmental and immunological factors contributing to the development of RA in order to find predictive risk biomarkers prior to the onset of disease. These biomarkers will be used in future trials of preventative strategies including lifestyle interventions and novel immune therapies.
Dr Benham will also initiate in the FDR cohort a trial of a disease-modifying agent currently used in early RA patients, to attempt to delay or prevent the onset of RA.

We have established a cohort of 222 participants that currently includes 116 RA, 63 FDR and 43 HC. Our recruitment continues and we have also commenced annual review of many of the early participants. We have initially discovered differences in demographics and environmental factors amongst participants with RA compared to FDR and HC. To date these include increased numbers of females and smokers in the RA group and increased episodes of previous infections, particularly dental infections as well as possible differences in weight and alcohol intake. We have identified differences in the microbiome of RA participants by analyzing the microbial signatures in both the mouth and the gut. We have identified a distinct 'signature' within RA compared to FDR and HC and we are in the processing of analyzing particular organisms of interest. Currently we are undertaking experiments and analyzing preliminary results regarding the genes known to be associated to RA and immune status and function in RA, FDR and HC.

The initial funding from this UCB Arthritis Australia grant has allowed us to instigate this program of research through the establishment of the cohort. The recruitment of participants and the collection of extensive demographic, medical and environmental data in parallel with a biobank of samples for analysis is allowing us to investigate the intersection of genetics, environment, microbiome and immune function in RA. We hope to provide those people living with RA and their families' participation in research that will result in new knowledge generation regarding the pathogenesis, prediction and ultimately prevention of RA.

Scholarships

Marion A Simpson Grant - $25,000
(funded by The Estate of the Late Marion Alice Simpson)
Mr Raul Chavez Valencia
Department of Paediatrics, University of Melbourne
Project: *Investigating the epigenetic profiles of children with Juvenile Idiopathic Arthritis (JIA)*

Epigenetics is touted as the exciting link between nature and nurture, as it is a mechanism for regulating gene expression and is responsive to environmental stimuli. In complex diseases like juvenile idiopathic arthritis (JIA), where the interaction of genes and environment contributes to disease risk, epigenetic disturbances are highly likely to form part of the disease risk profile. Whilst the epigenome of adult rheumatoid arthritis has been repeatedly examined, the JIA epigenome is largely unexplored. Mr Chavez Valencia is undertaking this research project to unveil the epigenetic profile of JIA CD4+ T cells, an immune cell type highly relevant to the JIA disease process. Specifically, he is looking at a critical epigenetic mark, DNA methylation, one essential for immune cell development.

This project compared CD4+ T cell DNA methylation across the genome between children with active JIA, and healthy children. 60 pairs of children have been selected from the CLARITY JIA biobank, extracted CD4+ T cells from their blood, and measured T cell DNA methylation at over 480,000 sites across the genome. By studying the relevance of epigenetics to JIA, this project is highly likely to produce data of considerable impact. In doing so, they can begin to piece together the links between nature and nurture in JIA whilst providing significant potential for translation to improved clinical outcomes.

I compared DNA methylation patterns across the genome between 60 children with JIA, and 60 healthy children, matched by age and sex. I focussed on one particular immune cell type known to play an important role in JIA, CD4+ T cells. I measured methylation at over 450,000 sites in the genome. I found lots of differences, but because I performed 450,000 statistical tests, I applied a very stringent set of criteria to the data to make sure these differences were not due to chance. No statistically significant differences were found after applying these criteria. This suggests that there are no substantial differences in DNA methylation in CD4+ T cells between children with JIA, and healthy children. Smaller differences are still possible, and my data suggests this is likely as patterns in the data identify cases as a separate group to controls. But much larger numbers of children would need to be examined to find these with statistical certainty.

The data generated from the main study was used to further explore possible disease mechanisms, finding that DNA methylation did vary according to genetic differences, and that a larger study would be able to more accurately identify which genes are potential links between nature and nurture.
Further, I was able to investigate the issue of JIA subtype. This is pertinent since controversy surrounds the current criteria used for subtyping children with JIA (International League of Associations for Rheumatology criteria) and do not entirely align with clinical groupings. One debate surrounds the use of age of diagnosis as a subtype criterion, since clinical experience demonstrates grouping of children with similar disease patterns based on age. Yet little biological data is published to support this hypothesis. Using the DNA methylation data I generated in JIA, I was able to detect subgroupings of JIA cases based

on age. This may provide insights into different disease processes in children diagnosed younger vs older, who may require different clinical management.

DNA methylation data were also used to look for differences between children with JIA whose disease gets worse, and children whose disease stays more stable. Our analysis suggests that there may indeed be a methylation signature, present early in disease, which is associated with a worsening disease course. Future studies exploring this finding, if this holds true, will suggest that DNA methylation signatures might be able to be developed into a prognostic test to help clinicians identify and better treat those who are at risk of worse disease.

Altogether, this work has provided a platform from which further investigation of DNA methylation in JIA can be launched. A grant application aiming to do this has been submitted to NHMRC by the head of our group, A/Prof Justine Ellis.

SA LSS Support Group Grant & Arthritis Australia and State & Territory Affiliate Grant - $30,000
(funded by Arthritis South Australia)
Dr Premarani Sinnathurai
Rheumatology Department, Royal North Shore Hospital
Project: *Psoriatic arthritis in Australia*

Psoriatic arthritis (PsA) is an inflammatory arthritis which occurs in association with psoriasis. PsA can present in a variety of ways in patients, affecting different patterns of joints. It can also vary greatly in its severity, causing significant deformity and disability in some patients. The aim of this study was to investigate factors, which predict which patients may develop particular variants of psoriatic arthritis and the severity of the disease. This research involved analysis of data from the Australian Rheumatology Association Database. A cohort of patients with psoriatic arthritis were recruited and followed over time. Their disease was assessed clinically, in addition to the measurement of laboratory markers of inflammation in blood and also the measurement of other factors, which may be associated with disease presentation and severity.

We analysed information from the Australian Rheumatology Association Database (ARAD). This is a voluntary national registry in which people with inflammatory arthritis complete surveys including health information every six to twelve months. There were 490 participants with psoriatic arthritis and it was very common for them to have other medical conditions. Over half of these patients had at least two extra medical conditions on top of their arthritis. High blood pressure and depression were the most commonly reported conditions and diabetes and high cholesterol were also common. Whilst infections were common, there was no difference in the number of infections in patients taking a newer type of medication for their arthritis, known as biologic medicines, compared with the older medications.

We asked ARAD participants how they were managing their risk factors for heart disease. It was encouraging that most people with high blood pressure, high cholesterol and diabetes were taking medicines to treat these conditions. However, fewer people had been able to make lifestyle changes to decrease their risk of heart disease. About one third of participants who were obese had made a dietary change for their health in the last year, and about half of participants were meeting the recommended level of physical activity. Arthritis was by far the most common medical condition which limited their ability to be active. We also held focus groups as part of an international study exploring the areas of health which are important to people with psoriatic arthritis. The results were combined with those from focus groups around the world. In addition to symptoms like joint pain and joint swelling, patients told us that issues of emotional well-being, fatigue and the ability to maintain independence and take part in daily activities were important to them and should be measured when we are assessing how well they are doing.

Grant-in-aid

ARA Project Grant- $10,000
(funded by Australian Rheumatology Association)
Dr Elizabeth Hoon
School of Population Health, The University of Adelaide
Project: *Developing a patient reported outcome measure in polymyalgia rheumatica*

Polymyalgia rheumatica (PMR) is a common inflammatory disease effecting older people. While new treatment options have emerged for many inflammatory diseases, treatment for PMR continues to rely on corticosteroids. These steroids are known to cause adverse effects with long term use, and the dilemma for people with PMR is that they are commonly unable to cease steroids because their symptoms cannot be adequately controlled without them. Although common steroid side effects in inflammatory diseases are somewhat understood, less is known about how these effects impact on people with PMR, as well as the impact of other adverse events (e.g. mood and sleep disturbance, skin fragility and body image). It is also recognised that current tools used by researchers and clinicians to measure side effects may not be relevant or sensitive enough to capture PMR patient experiences. In order to progress new treatment options it is therefore important to gain greater understanding of patient experiences of PMR, the specific side effects of steroids and how people with PMR manage them. This project contributed to the first important stage in the development of more appropriate patient outcome measures. It focused on prioritising patient experiences using an explorative research approach.

Participants in this preliminary study described a wide range of experiences related to side effects of the commonly used steroid treatment prednisolone. Some participants reported no side effects while others reported many. Where people reported side effects, these tended to occur after they experienced a quick initial positive effect of the steroid treatment. People also reported that the dosage level of their steroid treatment influenced their experiences of side effects.

For those reporting side effects related to prednisolone, weight gain, changes in the shape of their face and neck, and insomnia with associated fatigue, were the most commonly reported effects. A build-up of many side effects was also identified as a problem by some participants, along with difficulties in distinguishing side effects from the symptoms of PMR (e.g. fatigue).

A recurrent theme identified in this preliminary study was a level of uncertainty related to both the recurrence of PMR symptoms, treatment and possible side effects experienced. Many people described how living with this uncertainty impacted on their overall quality of life. Some participants also reported that they had to manage some level of distrust expressed by some clinicians, family members and friends related to the possible side effects of prednisolone, while at the same time benefitting or managing their steroid treatment and PMR condition.

In June 2016 the preliminary findings of this study were presented to a special interest group meeting of OMERACT (Outcome Measures in Rheumatology). OMERACT is an independent initiative of international health professionals interested in outcome measures in rheumatology (www.omeract.org). An important aspect of OMERACT is the integration of patients and their perspectives into outcome measure development.

This special interest group received contributions from a number of similar international pilot studies and the collective findings will inform the development of specific and accurate measures of adverse events for the PMR population, which in turn, may inform evaluations of the effectiveness of changes to treatment for PMR.

By continuing to work with the OMERACT collaborators, there is the ability to validate findings from this study in other international PMR populations. At this year's OMERACT meeting there was agreement that a patient reported outcome instrument should be developed. The group established a research agenda includes the broadening of understandings of the impact of corticosteroids side effects across different conditions, age groups and doses.

ARA Project Grant- $10,000
(funded by Australian Rheumatology Association)
Dr Bernadette Fitzgibbon
Monash Alfred Psychiatry Research Centre, Monash University
Project: *Interventional repetitive transcranial magnetic stimulation treatment for fibromyalgia*

Fibromyalgia is a complex and debilitating pain disorder. Despite its high prevalence, there are limited effective treatment options. The purpose of this grant was therefore to investigate the use of repetitive Transcranial Magnetic Stimulation (rTMS) as a potential treatment for the symptoms of fibromyalgia. Previous experience has shown that people with fibromyalgia may have an imbalance in the excitability, or 'activity levels', of cells in the brain. rTMS appears to work by changing how excitable the cells of the brain are, which may help reduce or alleviate fibromyalgia symptoms. Several studies support the use of rTMS in the treatment of fibromyalgia, however, these effects are usually only brief. In this study, we used longer treatment course to explore whether the effects of rTMS can be extended.

We have completed data collection for a total of 16 participants who underwent a four week daily treatment of rTMS to the frontal cortex. Data was processed in preparation for analysis. However, in a pilot analysis of five patients with a formal diagnosis of fibromyalgia, we observed a significant decrease in pain intensity and unpleasantness ratings post treatment course compared to baseline. In addition, we also observed significant differences following treatment compared to baseline in a number of secondary measures assessing **symptom impact and interference, quality of life, and mood.** Together, the results of this pilot analysis demonstrate a four week rTMS treatment course applied to the DLPFC to significantly reduce symptoms in a small sample of patients with fibromyalgia. Thus, the results of the current study support the potential role of rTMS as a new pain management option for fibromyalgia.

Fibromyalgia is a debilitating disease with few sufferers receiving adequate treatment. At present, treatment options for fibromyalgia are largely and often unsuccessfully limited to strong pharmaceutical medications (e.g., opioids) which are associated with several notable side effects including sedation and addiction. There is therefore urgent need to identify new treatment options for sufferers. The pilot results of the study suggest rTMS may be an effective treatment option for symptoms of fibromyalgia. However, the provision of rTMS is time-consuming which may substantially impair the uptake of this treatment option in patients with fibromyalgia. A newer brain stimulation method, Theta Burst Stimulation (TBS), has been found to elicit similar effects as standard rTMS and is able to do so in a fraction of the time. Future research will therefore investigate these newer protocols of rTMS in fibromyalgia patients (more details below).

Our results from the work suggest rTMS applied to the frontal cortex for fibromyalgia has the efficacy, treatment tolerability and safety required for further investigation into this modality. However, given the time commitment required by patients for standard rTMS, our research will now move towards exciting newer rTMS protocols such as TBS. TBS is a patterned form of rTMS where magnetic pulses are applied in very short bursts (three pulses at a time) but at high frequency (usually ~50 Hz). These short bursts are repeated at an inter-burst interval of 200ms. This type of stimulation produces change in brain activity that is greater and longer than that brought about from standard rTMS, despite taking only a fraction of time (i.e. 3 vs 45mins). In addition to exploring the potential of TBS as a stand-alone treatment for fibromyalgia, we also plan to explore its impact when paired with current pain management methods, such as mindfulness or cognitive behavioural therapy. Our ultimate aim to carry out such investigations within large multisite, potentially international, trials.

ARA Project Grant- $15,000
(funded by Australian Rheumatology Association)
Mr Jason Rogers
Menzies Research Institute Tasmania, University of Tasmania
Project: *Clinical and metabolic factors and imaging abnormalities in chronic plantar heel pain*

Pain under the heel (plantar heel pain) is common and affects people from all walks of life, from older sedentary people to young fit athletes. The current evidence says we are not very good at treating it. Our study has set out to answer very basic questions about plantar heel pain - what structures are at fault, what findings help us identify important sub-groups that may behave differently, and what factors tell us whether a patient is likely to get better or worse over time?

It will offer detail on many firsts for this area of study, including the use of novel bone imaging, objective activity monitoring with movement sensors, and the assessment of new blood based markers of inflammation. Finding answers to these questions will enable our group and other researchers to target current treatments more effectively, and to potentially explore new treatment options.

Our initial project has expanded from a small study of 30 people with, and 30 people without, heel pain, to an internationally significant sized investigation with 220 cases and 100 matched control participants. We are now also reviewing the cases 12 months after their baseline testing to better understand what happens to people with heel pain over time, with or without treatment.

A consequence of this increased study size is that we are still collecting data, and have not yet moved into the analysis phase. We have just completed the baseline assessment of all cases, and are currently one third of the way into our follow-up assessments. We are also about to start recruitment of the heel-pain free comparison group.

Our very preliminary observations are that bone swelling (termed bone marrow lesions) in the heel is surprisingly common, and appears to be associated with the pain that heel pain sufferers experience when they first put weight on the foot. Bone swelling lesions have been identified elsewhere in the body, such as in the knee and hip, and have been linked with the pain of osteoarthritis. Importantly, they are also under investigation as a target for novel treatment in the management of osteoarthritis.
We don't know yet if bone swelling in the heel carries the same significance as it does in joints elsewhere, but the study is powered to look closely at this question. We will also be measuring how this bone swelling changes over the period of one year, which gives us a stronger indication of where it might sit in the pathway of cause and effect for pain. These findings represent a new area of focus in plantar heel pain, and might open up new avenues for treatment in a major heel pain sub-group that has not been previously identified.

Our significantly expanded study continues to operate in the data collection phase. We are not yet at the stage where we have results that formally translate to the wider heel pain population. However, the finding on preliminary review of the baseline MRI scans that swelling events in the heel bone are common, has already had research consequences for this study. We are now also measuring these events with MRI at the 12-month follow up period to see how changes in bone swelling correlate with changes in pain and function. We expect results from this study will help us identify sub-groups of people with heel pain that require different treatments. For example, individuals with heel fat pad problems might logically require a different treatment approach to someone with swelling in the heel bone or evidence of nerve compression. Surprisingly, current heel pain treatment regimens are not clearly targeted due to a lack of awareness of these possible sub-groups. Further research to test the effectiveness of targeted treatment will be necessary. Part of this could involve the testing of new or novel therapies, such as those to reduce bone swelling in the heel. For example, trials are currently underway investigating the capacity of drug therapies to shrink bone swelling events in the osteoarthritic knee. Finally, knowing the factors that predict a good or poor outcome will help clinicians decide when to intervene, but also when not to.

This research is ongoing and we have significantly expanded the scope of our initial project. From a small comparison of cases and non-cases we are now testing a much larger population, and following those with heel pain over the course of at least one year. We anticipate completing the 12-month follow-up assessments and all control participant assessments by June 2017. This will improve our basic understanding of plantar heel pain, and will help inform clinical practice with the goal of improving patient outcomes. From this, we expect to seed further research investigating the effectiveness of treatments that are targeted along specific lines of diagnosis. The new bone swelling findings look promising as one of those targeted treatment avenues, but it is too early to tell yet.

ARA Project Grant - $15,000
(funded by Australian Rheumatology Association)
Dr Linda Rehaume
Diamantina Institute, The University of Queensland
Project: *Immunogenetic background and microbiota interaction promotes ileitis in the SKG mouse model of spondyloarthropathy*

Spondyloarthropathy (SpA) describes a group of common rheumatic disorders that cause inflammation of the spine, joints, skin, eyes, intestine (ileum and colon) and site of tendon/ligament insertion into bone (enthesis). Depending on which clinical feature(s) dominates, patients are diagnosed with ankylosing spondylitis (spine inflammation and bone fusion), reactive arthritis (arthritis following infection), arthritis associated with inflammatory bowel disease (IBD) or psoriasis. These conditions share overlapping symptoms and gene mutations, but the genetic risk factors do not absolutely predict development of disease. Environmental factors may also contribute to disease but their identity and involvement are not well understood. In particular, there is evidence that commensal bacteria (microbiota) of our skin and gastrointestinal tract play a role. Current therapies target the inflammation associated with SpA but do not treat the underlying cause(s) of disease.

We have described the SKG mutant mouse as a novel model of SpA that recapitulates human disease, however the genetic mutation of the mice is not one identified as a risk factor for SpA in humans. This points to common mechanisms affected by genetic background, and we already had evidence indicating that microbiota composition is an important factor. In this project we hypothesized that genetic risk factors influence gut microbiota, and the relationship of the microbiota to inflammation in different organs. Our previous data show that the intestinal microbiota is different in SKG and wild type BALB/c mice, and that SKG mice lacking microbiota (germ-free) have reduced arthritis frequency and absent intestinal (ileum) inflammation. Expression of inflammatory markers within the ileum was dependent on the presence of the microbiota. When mutant SKG and WT BALB/c mice were housed together SKG mice had reduced ileum inflammation, which we propose is through transfer of protective microbiota. A key aspect of this research is determining which bacteria promote ileum inflammation, how these bacteria mediate disease, and how genetic mutation(s) affects the host-microbiota relationship. This project aimed to address these questions to determine the bacterial and host factors predictive of disease to design novel therapeutics targeting synergistic host-microbiota disease-promoting mechanisms.

During the course of the grant I optimised and refined a challenging laboratory technique called IgA-SEQ. This technique separates bacteria based on their interaction with the host immune system leading to the decoration of the bacteria with different levels of a mucosal-associated antibody called IgA, and identifies the bacteria by DNA sequencing. IgA protects mucosal surfaces from infection from pathogens, like for example Salmonella that causes food poisoning, and constrains bacteria that are a part of the normal, beneficial (commensal) bacteria, known as the microbiota. Bacteria that are decorated with a lot of IgA antibody are thought to induce a larger immune response (highly immunogenic) than those with lower levels (less immunogenic).

The microbiota are part of the normal intestinal ecosystem and are usually symbiotic with the host, however sometimes bacteria within the microbiota, so-called pathobionts, can promote disease development when specific genetic or environmental conditions are altered in the host. It is thought that alterations in bacterial community structure within the intestine and outgrowth of pathobionts is associated with disease development in people with SpA. We have previously demonstrated that the commensal bacteria are required for disease development in SKG mice and that the composition of the bacteria affects disease severity, therefore we wanted to use this particular technique to identify bacteria that may be pathobionts in the SKG model and drive disease (increased in abundance and highly immunogenic) and alternatively those bacteria that may be protective against disease (decreased in abundance and less immunogenic).

The original, published technique separated the bacteria into IgA-positive or IgA-negative fractions followed by DNA sequencing. I modified this technique to separate the bacteria into IgA-bright, IgA-dim and IgA-negative fractions, which allowed for much better discrimination of those bacteria that are presumed disease-associated compared to those that are protective. I have tested two methods of separation of the bacteria, different processing regimes and performed a cell number titration in order to further optimize the procedure as well as make it higher through-put.

Whilst the findings of this research have not directly benefited people with musculoskeletal disease, I anticipate that they will be directly translatable within the next five years. In addition to the development and optimization of the IgA-SEQ technique, this project has identified consortia of SKG fecal bacteria that are preferentially increased in abundance within the IgA-bright fraction including those within the *Prevotellaceae* family, which is exciting as *Prevotella copri* has recently been associated with new-onset rheumatoid arthritis. Conversely, and equally exciting, I have identified a consortia of bacteria that are preferentially decreased in abundance within the IgA-dim fractions, including those within the *Lactobacillaceae* family that are often used as probiotics (e.g. present in yoghurt). These data confirm that the method is working and can discriminate between pathobionts and symbionts, and also gives us other candidate bacteria for future studies. I can also use this method to screen samples from patients with SpA to determine their IgA bacterial profiles and then compare with those obtained from the SKG mouse studies. It is my goal that disease-associated bacteria will be developed as a biomarker and disease-protective bacteria be used as a probiotic for genetically susceptible individuals or those suffering from SpA.

The research from this study is building upon the optimization of this challenging technique in order to further characterize the bacteria present in different mutant mice or mice treated with clinically relevant therapeutics. This will strengthen our initial observations and allow us to identify consortia of bacteria that are disease-causing or disease-protective because. The mice develop a spectrum of disease with respect to arthritis or inflammatory bowel disease, which means we will be able to correlate these bacteria with disease severity. I also intend to profile samples obtained from patients with SpA, before and after treatment, and healthy controls to determine how the microbiota profile in SpA differs from that of healthy controls and whether the effect of current clinical therapeutics is due (in part) to modification of the microbiota.

Arthritis Australia and State & Territory Affiliate Grant - $13,000
(funded jointly by Arthritis South Australia)
Dr Kade Paterson
Department of Physiotherapy The University of Melbourne
Project: *A multi-faceted podiatry intervention for the management of foot osteoarthritis: a pilot randomised controlled trial*

Foot osteoarthritis is as common as knee osteoarthritis, and is highly debilitating, however it is vastly under researched compared to osteoarthritis in other joints. Our grant was to fund an initial 'proof of concept' pilot study to determine whether a multi-faceted podiatry intervention has superior benefits on

pain and function in people with symptomatic foot osteoarthritis, compared to the usual care of analgesia advice. However, before we could conduct our pilot clinical trial, we first needed to find out how the condition is currently managed. Thus we also conducted an international survey to determine how podiatrists, physiotherapists and general practitioners evaluate and treat people foot osteoarthritis.

So far we have surveyed over 200 podiatrists and physiotherapists from Australia, the UK and elsewhere to determine their current clinical care of people with foot osteoarthritis. From this initial group, we identified 58 international experts who provided us with advice on their methods of assessing and treating this condition. We found that the health practitioners used a range of treatment techniques including different exercises, foot orthotics/insoles, manual therapy techniques and advice on diet and medications, all administered over multiple visits and in home education plans. This feedback has been used to draft our foot osteoarthritis assessment and treatment protocol for the multi-faceted podiatry intervention arm of our pilot clinical trial.

We have also accessed data from 138 general practitioners to determine the most common management practices of foot osteoarthritis in general practice. This data showed us that GPs mostly provide medication prescription or advice. This will be used for the usual care intervention arm of our pilot clinical trial.

This information is valuable because before now it was unknown how allied health and general practitioners treat this condition in clinical practice. The next phase of our project is now to recruit people in the community with foot osteoarthritis to take part in our pilot trial. Participants will be randomly allocated to receive either the multi-faceted podiatry intervention or usual care of analgesia advice for eight weeks, and we will determine (1) the feasibility, safety and patient response of the podiatry intervention in people with foot OA, and (2) the effect of the multi-faceted podiatry intervention, compared to usual care, on pain and self-reported function in people with foot osteoarthritis. This will help us to develop the first evidence-based treatment for people with this common and debilitating condition.

We have not published the results of our survey yet, or disseminated the findings to clinicians, and so there have been no benefits to people with foot osteoarthritis yet. We anticipate that we will publish our results and present the findings at conferences relevant to podiatry, physiotherapy, general practice and osteoarthritis in the coming months and years.

We have used the findings of our international survey and general practice data to inform the podiatry and usual care treatment arms of our pilot clinical trial. We anticipate this trial will be completed by the end of this year, and we intend to use these results to apply for funds to undertake a large clinical trial comparing our multi-faceted podiatry intervention to usual care of analgesia advice in people with foot osteoarthritis.

Eventide Homes Grant and Arthritis Australia and State & Territory Affiliate Grant - $15,000
(funded jointly by Eventide Homes NSW and Arthritis Australia)
Mr Adam Culvenor
School of Allied Health, College of Science, Health and Engineering, La Trobe University
Project: *Identification of phenotypes in early post-traumatic knee osteoarthritis: an exploratory study*

Rupture of the largest knee ligament, the anterior cruciate ligament (ACL), increases a person's risk for early-onset knee osteoarthritis (OA) development, irrespective of conservative such as exercise therapy or surgical ACL reconstruction management. Since most ACL injuries occur in adolescents and young adults, these individuals are prone to develop OA before they reach 40 years of age. But not everybody progresses to OA after ACL injury.

There is limited knowledge of potential factors that drive the development and progression of early knee OA after ACL reconstruction. Cartilage deterioration (ie. thinning) is a marker of early OA that can be detected on magnetic resonance imaging (MRI) scans and can potentially be treated to prevent the progression to end-stage OA seen on X-ray. Whether modifiable factors such as body mass, activity Level/sports participation, physical performance, knee range of movement, strength and flexibility, knee symptoms, concomitant injury and/or surgery to meniscus increase the risk of cartilage deterioration is not known, but these factors may provide possibilities to modify the course of disease. This project set out to identify phenotypes (subgroups with certain factors/characteristics) that may be at particular risk of accelerated disease progression following ACL reconstruction.

Specifically, the grant enabled a group of 75 patients who demonstrated knee cartilage loss at one year post-ACL reconstruction in our previous study, to be followed up and re-evaluated at five years post-ACL reconstruction with identical MRI scans, physical testing and questionnaires.

The knowledge obtained from this study will create opportunities for improved, targeted application of therapeutic strategies to help reduce the morbidity associated with commonly performed ACL reconstruction.

Patient-reported symptoms and function were obtained in conjunction with the imaging (MRI and X-ray), and are equally important in characterizing knee OA. This grant enabled us to uncover important relationships between early cartilage damage, functional performance, activity levels, knee symptoms, and quality of life in young adults after ACL reconstruction.

It revealed that at five years following surgery, ACL reconstructed patients report a significantly lower quality of life when compared to a healthy population. We also showed that patients with more severe cartilage damage at one year post-ACL reconstruction report worse sports and recreation function at five years after surgery.

Patients with poor performance on physical testing at one year post-ACL reconstruction report worse knee pain function and quality of life at five years compared to those who have good physical performance. This is an important finding, which may suggest restoring full physical functioning after ACL reconstruction is important for optimizing outcomes in the future.

We were successful in re-recruitment of the 75 patients who demonstrated knee cartilage loss at one year post-ACL reconstruction. The MRI scans obtained at five years post-ACL reconstruction are currently being analyzed by an experienced radiologist who also analyzed the MRI scans at one year post-surgery. We hypothesize that a significant number of patients will show deterioration of their knee cartilage from one to five year post-ACL reconstruction. Once analysis of the completed MRI scans has been completed (end 2016), we will determine the rate of progression of early OA from one to five years post–ACL reconstruction, and be able to identify which modifiable factors increase the risk of early OA (cartilage) progression.

The patients who have undergone ACL reconstruction in the study have benefited greatly from the follow-up assessments. The physical testing gave patients an insight into the level of strength and function of their operated limb compared to their non-operated limb. Individual patient results have been sent their results in report format with the addition of comparison to group averages. This has often prompted them to continue working on their physical functioning to maximise levels of activity.
This is important, as there is good evidence for conservative management (strengthening and activity modification) for knee OA.

In addition, translation of important knowledge regarding good physical functioning and awareness of the risk of knee OA has benefited study participants. Previous research has shown that only 26% of patients following ACLR have the discussion regarding the elevated risk of OA with their treating physiotherapist,

and 65% incorrectly believe that ACL reconstruction reduces their risk of OA. Patient information sheets have been created, not only educating the study participants about OA but these will also be placed on our research centre website/blog.

Presentation of the research project and findings will be presented at various sports medicine, physiotherapy and rheumatology conferences, sports medicine clinics and disseminated via social media platforms. This will enable health researchers and practitioners to gain important insights regarding the risks of poor outcome following ACL reconstruction and potential modifiable factors to minimize such risk.

The discovery of key risk factors for poor outcomes following ACL reconstruction, have informed the focus of our next research project. If we know which patients and which factors following ACL reconstruction are likely to have deteriorating symptoms and quality of life, can we perform an intervention that can prevent or slow this progression?

This next project has commenced and is aimed at determining the effectiveness of targeted physiotherapy intervention in a group of patients one year post-ACL reconstruction, who are identified as being at particular risk of poor future outcomes. Most patients following ACL reconstruction cease physiotherapy prior to 12 months post-surgery, despite research showing that physical deficits continue to persist greater than one year. If outcomes can be improved by targeting these persistent deficits, this will provide impetus to improve the standard of function of patients at 1 year following surgery, at a time when many are wanting (and expecting) to return to demanding sports, recreational and work activities.

We have ethics approval to continue to follow-up this cohort and record functional, imaging and symptomatic/activity level data at 8 and 10 years post-ACL reconstruction. This will provide valuable insight into the medium to long term burden experienced by patients following ACL reconstruction. Previous research shows that at this time point (5-10 years post–ACL reconstruction) patients continue to have significantly lower quality of life compared to uninjured healthy populations, and this is related to worse symptoms, function and participation in sports.

Our future research of this unique cohort will provide a rare advantage - we are able to relate this medium-long term deterioration to risk factors during the very *early* stages (ie. 1, 3 and 5 years) post–ACL reconstruction. The advanced knowledge of factors predicting those who are at increased risk for poor outcomes will help health professionals in the future intervene at an earlier time point to slow or prevent worsening long-term outcomes. Physiotherapists will be able to target specific modifiable factors identified to increase the risk of poor long-term outcome during the rehabilitation process.

Eventide Homes Grant - $15,000
(funded jointly by Eventide Homes NSW)
Dr Brigitte Tampin
Physiotherapy Neurosurgery, Sir Charles Gairdner Hospital
Project: *Assessment of neuropathic pain and altered sensory nerve function in patients with lumbar radicular pain*

Low back pain affects 80 – 85% of people over their life time. Low back-related leg pain or sciatica is a common variation of low back pain – this is pain running down the leg and coming from the back. The pain can be sharp, stabbing and like electric shocks or a dull ongoing ache.

Sciatica is common affecting about 43% in the general population. For about 1 in 3, pain is ongoing for one year or longer. This is a problem because it affects daily life and attracts high health costs.

In this study, we were interested to find out in people with sciatic pain, how their nerves function. We test this using a number of different sensations that we commonly encounter every day (heat and cold, light

touch, pressure, pin-prick and vibration). In this way we can establish if the nerves are functioning normally and we can watch if this affects people's pain over time, at 3 and 12 months. Nerves can sometimes have a lesser sensitivity, other times an increased sensitivity. We were interested to test if people with increased sensitivity may be more prone to ongoing pain. We can test this using technical laboratory tests and comparing those with simple tests performed every day in the clinic. We then compare these findings with those of healthy people who do not have pain. This tells us if we can continue to use simple bedside tests, or if we need the more technical testing to give us a clearer answer.

We have not yet completed all data collection. However, to date all 26 people with sciatica have been recruited to the study and all have been tested with both laboratory and clinical tests. Our initial findings show a lot of differences in sensitivity across the group (some low sensitivity, some middle and some high).

We still need to test the healthy people to allow for comparison.

Our initial findings are novel:

- No other study so far has demonstrated this varying sensitivity in people with sciatica.
- The different sensitivities we have found mean it is important to assess each person with sciatica individually so we know what their nerve function is and how this might influence what the best treatments for them are.
- The findings from healthy people are important as this will help us to decide what is 'normal' nerve variation and what is not.

We are currently conducting a second study using a similar approach. This extra study will:

- test if sensitivity can predict who does better where surgery is required as a treatment for their sciatica
- We have recruited 53 patients for this study.
- They were assessed with the same methods as described above and they will be followed up at 3 and 12 months post-surgery.
- We are in the process of collecting the follow-up data.

We have also set up a research data base to collect findings from previous and current studies. We are also extending the current 'healthy' database for sensory testing. This is important because:

- We can build our research capacity further at Sir Charles Gairdner Hospital for testing larger clinical populations with nerve-related leg pain.
- Using the 'healthy' data can help us better understand who needs what medicines or possibly surgery. This is important so people with nerve-related pain can get the right treatment, at the right time and by the right team.

UCB Australia Grant in aid - $15,000
(funded jointly by UCB Australia Pty Ltd)
Assoc Prof Helen Keen
School of Medicine and Pharmacology, University of Western Australia
Project: *The prevalence of subclinical synovitis and urate deposition in a pyperuriceamic cohort of the Fremantle Diabetes Study*

Gout is a common form of arthritis, and Australians are affected second most commonly in the world. Gout is increasingly common in Australia, due to the obesity epidemic, and our ageing population. Gout causes not only pain, and problems form missed days off work. It also damages joints, and is associated with heart and kidney disease. High levels of serum uric acid in the blood cause gout, and seem to be the only risk factor that can predict the development of gout. However, 90% of people with high uric acid don't actually ever get gout. We have been able to show that in people with gout, who have no symptoms

of arthritis, we can see inflammation and uric acid deposition in the joints. We thought that if we examined people with high levels of uric acid in their blood, who don't yet have gout, we might be able to find inflammation or uric acid deposited in the joints, and that may in people who are not known to have gout, then this may have implications for predicting who will develop gout, or for instituting early therapy to prevent the development of gout and its consequences.

The Fremantle diabetes study has been following people with Diabetes for six years, and had collected uric acid levels of these people, so we were easily able to identify people with high levels of uric acid in their blood, who did not have a history of gout. We aimed to have 100 of those people to attend a single clinic visit, involving questionnaires, an examination, and ultrasound of their joints, and a blood test to measure their uric acid levels.

The most important finding from this study is that in this people at risk of developing gout because they have asymptomatic but high levels of serum uric acid, one third had evidence of joint inflammation, and about one quarter had ultrasound evidence of urate deposition in their joints.

This finding is of importance, as it identifies that uric acid deposition in the joints in people at risk of developing gout is common. These people may be at high risk of developing gout. Furthermore, the presence of inflammation in these people may mean that they already have subclinical gout. The consequences at present are unknown. We are planning to follow this cohort of 100 patients over time to see who develops the need for gout treatment (allopurinol), and how attends hospital, and whether they are given a diagnosis of gout during that hospital visit.

It is highly likely that the uric acid deposition predicts the development of gout, and that in the long term, the people with evidence of inflammation will have worse health, possibly due to heart disease. This important insight into what may be a preclinical phase of gout, and or predictor of worse health outcomes may allow early medical treatment to improve the outcomes for these people.

Zimmer Australia Grant - $15,000
(funded by Zimmer Australia)
Ms Carina Blaker
Kolling Institute of Medical Research, University of Sydney
Project: *Investigating osteoarthritis following different injury mechanisms*

The anterior cruciate ligament (ACL) is one of the major stabilising structures within the knee. It is commonly injured resulting in acute pain and disability and an approximately 5-fold increased risk of post-traumatic osteoarthritis (PTOA) within 10-20 years. The majority of ACL injuries occur in active adolescents and young adults resulting in patients as young as 30-40 years of age developing a chronic disease of the joints for a prolonged period of time. Joint instability following ACL injury is often perceived as the greatest contributor to this increased risk and thus reconstructive surgery is usually recommended to restore stability and function to the knee. Unfortunately for patients, surgery has not been shown to alter the incidence of PTOA post-ACL injury, suggesting that there are additional factors driving the onset and progression of disease. It is not yet clear what these additional factors may be or how they may be targeted but it has been proposed that the severity of the initial trauma and the ensuing inflammatory response may play important roles in addition to any residual instability. The aim of this grant was to investigate the role of trauma severity in PTOA using animal models with different mechanisms of ACL injury. A better understanding of the specific risk factors of ACL-induced PTOA has the potential to provide vital information for improving diagnostic and prognostic capabilities leading to better patient stratification and early treatment of at risk patients.

The data collected from this grant has provided evidence that the onset and rate of progression of OA is not solely determined by ACL induced knee instability. The results from this grant demonstrate a

complex relationship between the level of impact loading, the specific joint structures damaged, and altered joint stability in the development and severity of PTOA.

Using different animal models of ACL injury we were able to vary the severity of the initial trauma and closely track the subsequent response of the knee joint. In this grant we initiated ACL injury through either (1) surgically cutting the ACL causing acute instability without impact loading, (2) applying an external load to the knee to induce an ACL tear (instability and impact loading), or (3) combining the external load with an additional period of compression after ACL failure (instability, impact and additional loading). The initial joint instability was measured for each model followed by an assessment of OA development with time.

All three models of ACL injury were found to cause an immediate increase in knee laxity, similar to what is observed in humans. Importantly the increased laxity of the knee was not significantly different between the three models despite there being differences in the mechanism of injury (e.g. targeted instability through surgical cutting of the ACL versus impact induced ACL tears which also loads other supporting structures of the joint). Interestingly, the lack of separation in joint laxity did not correspond with OA development over time. The most traumatic ACL injury group involving an impact induced tear with additional loading showed a rapid and severe amount of cartilage loss, formation of bone spurs and inflammation compared to the two "milder" ACL injury models (surgical ACL injury and impact loading alone). These two milder injury groups showed evidence of osteoarthritic changes but the extent of joint damage was reduced. There was however some evidence of worsening over time which may indicate a more slowly progressive disease state in the milder injury models.

OA is a disease with no available structural disease-modifying therapies and as a result, an enormous and growing socio-economic burden. To aid in the reduction of the substantial patient and societal impact it is important to understand how the disease develops and progresses over time and how it differs between individuals. PTOA has a known initiating event such as an ACL injury however, not all patients with an ACL injury will go on to develop disease. We can more closely examine the reasons for this through animal models such as those used in this project. Targeting the same joint structure through three different injury mechanisms has provided evidence that not all ACL injuries result in the same outcome with respect to OA.

We have highlighted that the severity of the initial trauma is an important factor to consider when assessing risk of OA post-injury which may affect tracking of at risk patients over the long term and improve the success of early intervention strategies.

Secondary findings from this grant have also lead to the development of a research project investigating the risk of OA following mild joint injuries (e.g. sprains or severe bruising, distinct from overuse or repetitive loading injuries). These injuries are not routinely tracked in humans but results from our research may indicate their importance in the care and management of patients with acute injuries and chronic arthritis.

Ongoing studies are using these models of ACL injury to further investigate the development of post-traumatic osteoarthritis at longer time points post-injury with the aim of determining if joint changes following milder ACL injuries stabilise, revert or progress with time. Measures of knee laxity are being conducted at similar time points to better understand changes in joint function following injury and OA. These outcomes are being complemented with additional measures of pain and behaviour/activity in order to determine if these factors are indicative of OA severity and/or rate of onset and progression. Answering these questions may provide evidence to encourage improved tracking of more specific aspects of patient symptoms and function for better identification of at risk groups and early OA treatment.

Zimmer Australia Grant - $15,000
(funded by Zimmer Australia)
Ms Charlotte Ganderton
Physiotherapy Department, La Trobe University
Project: *Hormone replacement therapy and exercise in post-menopausal women with greater trochanteric pain syndrome*

This study is comparing the effectiveness of female sex hormone supplementation (FSHS) alone, and with the combination of exercise therapy, to treat pain and dysfunction associated with greater trochanteric pain syndrome (GTPS). This condition is associated with pathology of the gluteus medius and minimus tendons and trochanteric bursa and is most prevalent in post-menopausal women. It causes as much debilitating pain and dysfunction in women as those waiting for a hip replacement for severe osteoarthritis. Limited evidence in laboratory and clinical studies suggests hormone decrease after menopause may have a negative effect on tendon and that exercise may be beneficial. It is essential that this population is active. GTPS prevents or reduces activity, and interventions for this condition that reduce pain and increase function and activity will have important health benefits for these women. This study was pragmatically designed to ensure that the interventions in this study can be easily integrated into clinical practice if found to be effective in the treatment of GTPS in post-menopausal women. We have not yet reached a conclusion on the effects of exercise and hormone interventions in these women as the study is still recruiting.

We are continuing to recruit participants, at this stage we have 52 out of 120 women enrolled. We have not yet examined the results. During the research process, we have undertaken several smaller studies to support the methods used in this trial. We have investigated clinical tests used in the diagnosis of GTPS, and have incorporated the most accurate tests in our eligibility screening, to confirm a diagnosis of GTPS. We also investigated the exercises chosen for the trial using electromyography (a method used to determine the amount of muscle activation elicited during a task). The intervention exercises prescribed in this trial were found to elicit high levels of muscle activity in muscles that are known to be weak in GTPS (gluteus medius and minimus). We also identified that the VISA-G questionnaire, used as the main outcome measure of the study, is a valid score for measuring the severity of disability associated GTPS.

At this stage, findings from the study have not been concluded. However, any participant that was excluded for reasons that prevented use of the hormone therapy (e.g. hysterectomy, history of breast cancer), were able to participate in a single arm RCT (education and sham exercise vs education and intervention exercise), that we opened up to accommodate for this. This involved the participants being randomised into only the exercise component of the study. If participants were excluded, or reported not wanting to participate in either study, they were provided with an education sheet on the condition and referred to a physiotherapist for treatment in their local area.

We are continuing recruitment for the 2 x 2 factorial trial until we have sufficient participants to provide evidence on the effects of the combination of hormone therapy and exercise on GTPS in post-menopausal women. It is thought that this trial will be completed by the end of 2017. The single arm RCT is fully recruited and the 12 month follow up will be completed by December 2016.

Zimmer Australia Grant & Arthritis Australia & State and Territory Affiliate Grant - $10,000
(funded by Zimmer Australia & Arthritis South Australia)
Assoc Prof Leslie Nicholson
Biomedical Sciences, Physiotherapy, The University of Sydney
Project: *Clinical characteristics of children with generalized joint hypermobility – 3 year follow up*

Joint Hypermobility Syndrome (JHS) is a genetic disease that has attracted significant attention from researchers since the 1970's when the first tool to diagnose generalised joint hypermobility was first developed. Since then studies have confused localised and generalised hypermobility, acquired and inherited hypermobility, benign and profoundly symptomatic hypermobility - often recruiting patients

with a variety of these conditions and labelling them ambiguously. This has not been helpful for clinicians who treat the signs and symptoms of those affected. Our research has set out to identify the condition of our participants and to use reliable and valid measures to quantify the extent of their condition and the efficacy of our treatments.

Despite the large number of published studies, no study has followed a group of patients with a defined diagnosis to determine the prognosis of the disease. Many health professionals (medical and allied health) generally believe that hypermobility is "normal" in children, decreases with age and that it is not a clinical condition. Yet the Connective Tissue Dysplasia Clinics at the Children's Hospital at Westmead and the Westmead Hospital sees thousands of patients per year whose musculoskeletal and systemic symptoms related to their hypermobility disorder result in school absenteeism, days off work, inability to work and poor quality of life.

While the baseline study began prior to the follow-up supported by this grant, we aimed to understand how JHS affects sufferers over time. Do they really become less hypermobile? Does that mean that their symptoms also resolve? Do they seek treatment? What is the impact of their disease on their lives? Can we sub-classify or group them into similar presentations that might help to direct their treatment better?

At this point in time we have collected three sets of data in this longitudinal study of children with JHS (Baseline, 18 months and three years). We have discovered so much about these children that we are sharing with the world as this is the ONLY longitudinal study of people with this disease. We have discovered that the children vary in the extent that they exhibit the disease but that it is very much multi-systemic even at this very early stage of their lives. The systems most involved are firstly their joints. These may be painful, have excessive movement, sublux and may even dislocate during activities of daily living. Followed by:

- their cardiovascular system which can be involved as they get dizzy, have palpitations and pass out after exercise, getting up from lying or after a hot shower. Some have fragile blood vessels and varicose veins
- some have gastrointestinal involvement particularly diarrhoea and abdominal pain
- about 23% have urinary incontinence which even their parents did not know about
- some have skin involvement with overly stretchy skin that scars in a very distinctive manner, stretch marks and bruise easily.
- there is a relatively high prevalence of low force bone fractures and
- they suffer from severe fatigue and report their quality of life as worse than children with cancer.

Because we have followed these children over 3 years we have been able to observe if they get better, worse or stay the same and it appears that the boys fare better than the girls. The more multi-system complaints they have the more likely it is that they will worsen over time.

We have collected data on the children's pressure pain thresholds as well and now know that children with the chronic pain of EDS have lower pressure pain thresholds than healthy children and this suggests that generalised hyperalgesia explains, at least in part, the persistence of their pain.

We compared the children who undertake formal dance lessons and compared them to those that do not and found that they suffer less fatigue and better quality of life.

We have looked at the cost of health care for these children and found that families are spending on up to $10,000 per child per year on outpatient medical and allied health appointments.

We are getting interest in the research from medical practitioners and patients - informing them is key to improving the lives of those with JHS. We have demonstrated the benefits of multi-disciplinary care and while this is not yet available to adults with JHS or children in most Australian states other than NSW – hopefully our research will spawn this. We have presented our findings at numerous symposia, in-services

and conferences to disseminate information to relevant health professionals in order to improve assessment and treatment outcomes for patients. As a result of the publications that have resulted from the studies funded by Arthritis Australia, Dr Pacey and I have been asked to join iFlex, an international hypermobility research group. We believe that this international collaboration (The Netherlands, Belgium, Denmark and Australia) will be very beneficial to moving the research forward.

Three other studies have been written up as manuscripts and are almost ready for submission to international peer-reviewed journals. One chronicles the 3-year journey of children with JHS, looking at how they progress over time, identifying 3 groups of children by their presenting symptoms who may respond to different treatments. This will help us to prescribe the best treatments for these children. Another paper describes the way the children's nervous system has responded to chronic pain by becoming more sensitive. This will assist doctors and therapists to target treatments better.

The third paper documents the effect of dance training on children with JHS finding that those children who undertake regular formal training actually have less fatigue and report better quality of life. Again this suggests that regular exercise will benefit these children. A fourth paper, "Anxiety and depression in Australian children and adolescents with Ehlers-Danlos Syndrome-Hypermobility Type" is at manuscript preparation stge.

There are still more findings from the current study to be reported. In addition, we hope to undertake a five year follow up. This will see children becoming adolescents and adolescents becoming adults.

Zimmer Australia Grant - $15,000
(funded by Zimmer Australia)
Mr Tom Ranger
Department of Epidemiology and Preventive Medicine, Monash University
Project: *Does the structure of the spine matter in low back pain?*

The aim of our study was to assess the association between structural changes in the low back, observed on magnetic resonance imaging (MRI), and low back pain. Individuals from the Monash University Obesity Study were recruited in 2012/13 and were invited to have an MRI of their lower back and provide information about whether they had low back pain, and if so, the characteristics of their pain. Two years later they were invited to have a second MRI and provide information about any low back pain they had or were experiencing. Collection of data on individuals over a 2-year period allowed the changes that occur over time in people with and without low back pain to be observed. Investigating this relationship is important because it is currently not clear which structural changes, if any, are related to low back pain. A greater understanding of this relationship will allow us to inform the development of preventive and treatment strategies for people with low back pain.

1. Association between fascia and pain. In this study we found that the length of connective tissue (fascia) in the back was related to the severity of a person's low back pain. That is, people with shorter fascia were more likely to have high levels of low back pain. However, we found that the length of the fascia was not predictive of low back pain intensity. It is not clear why this is the case. However, we may have had insufficient statistical power to detect an association due to a modest number of participants examined.

2. Association between muscle and pain. During the application process for this grant we identified many studies investigating change in muscle associated with low back pain. However, these studies presented conflicting results and there was no comprehensive review available that provided an overall understanding of the role of muscle in low back pain. We therefore conducted a systematic review to identify all studies relevant to this topic and then examined the strength of evidence available based on the study results, design and quality. We are currently preparing this review for submission.

3. Association between disc degeneration and pain. In this study we found preliminary evidence for a relationship between worsening disc degeneration over 2 years and high pain intensity. We also found a trend for a relationship between gender and degeneration of the intervertebral discs in the spine, with males showing greater levels of degeneration than females.

These results improve our understanding of the natural changes that occur with ageing in the lower back and the changes that occur with low back pain. These are important as they allow us to understand the factors that contribute to low back pain and in turn provide information that informs the development of both prevention and management strategies for low back pain.
We are continuing to perform analyses and write publications associated with this cohort study. Two students have undertaken work on the dataset and are continuing to pursue their postgraduate studies in this field with the established database. We have also commenced international collaborative work in this field with the Spine Centre of Southern Denmark, Hospital Lillebaelt and University of Southern Denmark.

Project Grants

The Allan and Beryl Stephens Grant - $30,000
(funded by The Estate of the Late Beryl Stephens)
Dr Gethin Thomas
Diamantina Institute, University of Queensland
Project: *An oasis in the desert: A novel non-coding RNA underlies the genetic association with ankylosing spondylitis at the 21q22 gene desert locus*

Ankylosing spondylitis (AS) is a common inflammatory arthritis affecting over 22,000 Australians and costs up to AUD$500M annually. Current treatments only slow disease progress thus new therapeutic approaches are urgently needed. There is a strong genetic link to the risk of developing AS however it is not clear exactly which genes are responsible for driving the disease. Previously we have undertaken a number of large-scale genetic studies which have shown that particular sections of the genome, containing no known genes, contribute towards AS. Currently it is not well understood how these 'intergenic regions' or 'gene deserts' contribute to diseases. It is thought they do not directly produce any factors but likely contribute to disease by altering a genetic control mechanism called transcription. Transcription is the production of "working blueprints" called transcripts from the genome which act as the template for production of proteins which go on to cause disease.

Our preliminary studies have identified a novel transcript being produced from the 21q22 region of the genome, a region that has been shown to be linked to AS. The transcript is only produced from monocyte cells. Monocytes are a type of immune cell which are well known to play a role in many autoimmune or auto inflammatory disease including many forms of arthritis. We therefore hypothesized that monocytes may play a key role in the severe inflammation seen in AS. In this proposal we will investigate the product of the 21q22 region. If we can identify novel regulators of disease in AS we will increase our knowledge of disease biology and possibly identify new potential diagnostic and treatment options.

A key approach to working out how the 21q22 transcripts might cause or contribute to AS is to actually change the levels of 21q22 in cells thought to be important in AS. Having identified 21q22 as only being produced in monocytes which are important cells in inflammation we therefore focused on altering 21q22 activity in monocytes. To do this we developed a genetically modified virus (Lentivirus) that can infect monocytes and then produce high levels of the 21q22 in those cells. It is quite complicated to produce these genetically modified viruses and the original collaborator with whom we planned to undertake these studies was unable to produce the virus for us. Fortunately a new researcher, Dr Andrew Brooks, was recruited to the UQ Diamantina Institute and he was able to generate 21q22-producing Lentivirus. The

next challenge was to identify the best cells in which to test the virus. Two options are available to look at monocyte cell activity. One option is to use "monocyte cell lines" which are cell derived originally from monocytes but have been altered to make them easier to grow but do not show display all the biological attributes of normal monocytes. Alternatively you can use "primary monocytes". These are monocytes that are grown directly from human blood samples and are therefore normal monocytes. However these cells are difficult to grow and are very sensitive to manipulation such as viral infection. We initially tested our virus in the THP-1 monocyte cell-line and established our virus worked OK. We then moved to use primary monocytes as a better representation of what occurs in real AS patients. We then spent the remainder of the duration of this grant testing the best approach to infect monocytes with our virus. Unfortunately we did not reach the stage of testing the effect of increasing levels of 21q22 in the cells. However these studies are continuing on and a
full-time post-doc is now following up on these findings.

ARA Project Grant - $25,000
(funded by Australian Rheumatology Association)
Prof Matthew Brown
Human Genetics Group, Diamantina Institute, University of Queensland
Project: *VCAM1 as a therapeutic target in scleroderma*

Scleroderma treatments are limited, with no treatments available which change the natural history of the disease or induce remission. Treatments that are available are supportive or reduce symptoms, but have not been shown to increase life expectancy. We have identified genetic variants in the gene *VCAM1* which codes for a protein (called VCAM-1) which is found on the lining of blood vessels. When there is inflammation of those blood vessels, more VCAM-1 is produced. VCAM-1 catches passing white cells by interacting with a protein on those white cells called VLA-4. By catching the white cells and moving them into the inflamed tissue surrounding the blood vessel, VCAM-1 increases local inflammation. VCAM-1 is therefore a potential target for new therapies in scleroderma. Our studies aimed to test whether VCAM-1 function is increased in scleroderma, as our preliminary data suggests. If this is proven to be the case, then inhibiting the function of VCAM-1 would be likely to be of benefit to scleroderma patients.

We collaborated with the Australian Scleroderma Interest Group (ASIG) to gain access to clinical samples from scleroderma patients. We used these samples to investigate levels of VCAM-1 in the circulation of patients and compared that with levels measured in healthy controls. We found the VCAM-1 was elevated in scleroderma patients. There are two forms of scleroderma, termed 'limited' and 'diffuse'. Our data suggests that VCAM-1 levels are equally high in both forms of disease indicating that VCAM-1 is globally important in scleroderma. We also determined that VCAM-1 expression increases as disease progresses likely indicating that VCAM-1 plays an important role in driving disease-causing inflammation in scleroderma. Together, our data show, for the first time, that VCAM-1 is an important 'driver' of inflammation in scleroderma and suggest that therapies that try to target the effects of VCAM-1 may be of great clinical importance.

Our findings have not yet directly benefited Scleroderma patients but our data to date provides strong rationale for investigating new ways of targeting VCAM-1 that may provide much needed new drugs to treat Scleroderma. We are currently working towards proof-of-principle studies of our new therapeutic approach in a mouse model of scleroderma.

Since completion of our funded research, we have continued this project to look in more detail at binding of VCAM-1 to its partner protein, VLA-4 in order to better understand how VCAM-1 is influencing inflammation in Scleroderma. We have also established a mouse model of Scleroderma in our laboratory to investigate whether targeting of interaction between VCAM-1 and VLA-4 may be of therapeutic benefit. In addition, we have forged links with rheumatology colleagues in Wenzhou, China, who can provide us with large numbers of clinical samples to further our studies in patients.

H J & G J McKenzie Grant - $30,000
(funded by The Estate of the Late Heather Joy McKenzie)
Dr Nagaraja Haleagrahara
Physiology and Pharmacology, James Cook University
Project: *Molecular mechanisms and therapeutic potentials of anti-inflammatory bioflavonoids in collagen-induced arthritis*

Rheumatoid arthritis (RA) is a serious illness affecting the joints that causes swelling and pain. It affects around 3million people over 60 years in Australia. It is a chronic debilitating illness requiring treatment for the rest of the life in these patients. Standard medical therapy for RAs are expensive and would have unwanted side effects, which can be quite adverse. There is an urgent need to find new and safe drugs to treat RA. Modern nutritional science has shown that natural substances occurring normally in the diet exhibit a variety of beneficial effects on health. Quercetin is a chemical compound that belongs to the class of flavonoids. It is most abundant in onions, apples, green tea and berries. It is a powerful agent and is known to have the abilities to reduce the harmful effects of inflammatory chemicals in the body and reduce inflammation. In this study, we have conducted three sets of experiments to see whether quercetin could be used against RA in a laboratory model. RA was induced in mice and small amounts of quercetin was given to these animals for three weeks as a protective nutrient. The animals treated with quercetin showed improved joint health and reduction in arthritis compared to animals not treated with this compound. When compared to the mice treated with the standard anti-arthritis drug methotrexate, quercetin was equally effective in reducing joint swelling and inflammation. The inflammatory chemicals were significantly reduced with quercetin treatment and quercetin also dampened the progression of joint destruction. In the group of mice treated with both quercetin and methotrexate, there was a significant reduction in inflammatory chemicals and joint destructing enzymes. In another group, where quercetin was given for three weeks and then induced with arthritis, similar joint protective changes where seen with quercetin. Thus, in this study quercetin was discovered to regulate the function of the cells involved in attacking the joint cells. These results offer new insights into the mechanisms responsible for the protective effects of flavonoids in RA.

The aims of the current available therapy for RA are to prevent pain and reduce joint inflammation. However most of those treatments require higher doses of drugs, need several weeks to work, and are very expensive. Quercetin, which has been proved to be safe to consume might be a promising therapeutic agent for reducing joint damage, pain and joint deformity in RA.

Current research looked at only one dose of quercetin therapy against RA. Two of the models that were used were preventive models, where quercetin was used before animals had arthritis. However, human patients do not start anti-arthritic medication until they are diagnosed with RA. Following on from our exciting and new discovery, the next step is to explore the effects of different doses of quercetin and related anti-inflammatory flavonoid chemicals on joint health, pain and joint cartilage in arthritis. Since quercetin has minimum or no side effects, studies will be conducted on quercetin combined with other common anti arthritic medications to explore its ability to reduce joint damaging processes in RA.

Marion A Simpson Grant - $25,000
(funded by The Estate of the Late Marion Alice Simpson)
Dr Tania Crotti
Discipline of Anatomy and Pathology, School of Medical Sciences, The University of Adelaide
Project: *Abrogating inflammation and bone loss in a mouse model of inflammatory arthritis*

Local bone loss is a serious complication of chronic inflammatory diseases such as rheumatoid arthritis (RA) and there appears to be an intimate relationship between the inflammation and bone lysis. As RA is a systemic disorder, it is now appreciated that changes occur within organs outside of the joint including the gastrointestinal tract. This may result from the disease process but more commonly as a

side-effect of treatments. Since the implementation of methotrexate as a first line therapy the disease activity of RA has been dramatically reduced, however 50% of patients are non-responsive. Anti-TNF treatments have been revolutionary in reducing the inflammation and bone loss in patients non-responsive to methotrexate, however not all patients achieve remission, they require regular visits to their doctor for injections and there can also be various adverse side effects. In addition by the time patients are started on anti-TNF the erosion may have already occurred.

There are few effective therapies that specifically target both inflammation and bone loss. It is, therefore, not surprising that in RA most bone erosion occurs in the first 2 years after diagnosis. Targeting inflammation alone achieves limited benefits in regard to bone erosion. This means that inflammation is often only controlled in order to restore function and reduce pain but it is not eliminated thus allowing chronic bone erosion to progress. It also takes time it to establish the correct therapy and in this time there is continuing bone destruction. Caffeic Acid Phenethyl Ester (CAPE), an antioxidant derived from the propolis of honeybee hives, has been shown to have immunomodulatory and anti-inflammatory properties and inhibit cancer at high doses. At low dose we demonstrated the ability of CAPE to reduce bone loss in a mouse model of implant wear particle induced bone loss.

We sought to use a mouse model of inflammatory arthritis to test whether CAPE is able to inhibit the local bone loss, inflammation and systemic bone resorption. We also sought to assess the systemic effects of the inflammatory arthritis and CAPE treatment on the gastrointestinal tract.
Significance: This treatment could provide add on treatment to conventional disease modifying anti-rheumatic drugs (DMARDs).

During this time our microCT machine was moved and thus had to be re-calibrated. This brought about delays in starting the model and completing the bone analyses.

The induction of mild disease in the inflammatory mouse model was variable. We have since optimised the technique of delivering the antibody cocktail to induce disease. We have also since compared two doses of bacteria (endotoxin) to activate disease.

Greater paw scores (clinical grading indicating swelling) and percentage change in paw volume (amount of bone present) were observed in the inflammatory arthritis model with CAPE treatment compared to the control group. Bone volume overtime remained unchanged (this reflects no growth occurring in these mice) and the number of bone breakdown (TRAP-positive) cells was greatest in inflammatory arthritis model with CAPE treatment mice. Levels of systemic markers of inflammation (CRP) and bone loss (CTX-1) did not differ between groups. The mice with inflammatory arthritis with CAPE treatment exhibited lower colon toxicity scores and a reduced percentage of caveated goblet cells in the colon crypts compared with inflammatory arthritis mice. Microscopic changes in the gut were not detected.

Inflammatory arthritis did not reduce paw inflammation or bone loss in the inflammatory arthritic mice but did induce specific changes in the colon of the inflammatory arthritic mice.

In these controlled models we hope to unravel the systemic effects of the disease and treatment on the musculoskeletal system and the gastrointestinal tract.

We are currently utilising harvested tissue to investigate the effects of this disease model and treatment on pain and potentially running a more chronic model of longer disease duration.