RESEARCH GRANTS LAY SUMMARIES

Name: **Salah-uddin Ahmed, PhD**
Award Type: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *Mechanism of Mcl-1 regulation by EGCG in rheumatoid arthritis*
Institution: Washington State University
Award Period: June 1, 2014 – May 31, 2016
Study Section: Inflammation
Disease Focus: Rheumatoid Arthritis

Lay Language Summary: Rheumatoid arthritis (RA) is a leading cause of work-related disabilities and a significant socio-economic health challenge due to expensive, yet incomplete, conventional therapies. In RA, an increased expression of anti-apoptotic proteins such as myeloid cell leukemia-1 (Mcl-1) is associated with disease progression, resistance to therapies, and poor clinical outcome. Using human RA synovial fibroblasts (RA-FLS), and rat adjuvant-induced arthritis (AIA) model of RA, we propose to test the mechanism of Mcl-1 regulation by epigallocatechin-3-gallate (EGCG), a potential anti-inflammatory molecule, to sensitize RA-FLS to apoptosis. The success of these studies will lead to two distinct findings of clinical relevance: 1) the molecular mechanisms through which Mcl-1 dictates RA-FLS resistance to apoptosis, and 2) the mechanism of Mcl-1 regulation by EGCG to induce RA-FLS apoptosis.

Name: **Thomas Andriacchi, MD**
Award Type: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *Osteoarthritis: New concepts for early detection, prevention, and treatment*
Institution: Stanford University
Award Period: May 1, 2014 – April 30, 2016
Study Section: Technologies/Biomechanics
Disease Focus: Osteoarthritis

Lay Language Summary: 1. The stimulus-response model represents a potential paradigm shift in the analysis of biomarkers for osteoarthritis (OA) disease status. This model uses a mechanical stimulus to provoke a biological response that would be otherwise undetectable. This method could lead to the development of a possible OA 'stress test'.
2. Specific kinematic features of gait that emerge with aging have been identified as potential functional markers that precede symptoms of OA. This prospective study can provide insight into new prevention and treatment strategies.
3. A new cartilage patterning method has been developed to enhance the sensitivity of detecting cartilage changes using MRI by quantifying changes in the pattern of cartilage thickness that include swelling and thinning, as both can reflect degradation.
A cohort tested 6 years earlier allows for testing the above on a prospective basis.

Name: Nidhi Bhutani, PhD
Award Type: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *Novel epigenetic targets for Osteoarthritis*
Institution: Stanford University
Award Period: May 1, 2014 – April 30, 2016
Study Section: Molecular Biology and Gene Regulation
Disease Focus: Osteoarthritis

Lay Language Summary: Investigating DNA hydroxymethylation and its regulators as OA therapeutic targets is extremely novel and is based on our original findings that 5hmC homeostasis is dysregulated in OA (MS in revision). The proposed research has the potential to unearth novel therapeutic regulators for Osteoarthritis that remains an unmet medical need and is extremely well aligned with one of the critical missions of Arthritis Foundation. In addition, the proposal seeks to bridge the knowledge gap in understanding the epigenetic mechanisms underlying the onset and trajectory of joint failure. The research aims to stepwise delineate the fundamental molecular processes in OA disease onset and progression thereby being extremely responsive to the RFA.

Name: Carl P. Blobel, MD, PhD
Award Type: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *The Role of iRhom2 and ADAM17 in osteoarthritis*
Institution: Hospital for Special Surgery
Award Period: May 1, 2014 – April 30, 2016
Study Section: Cell Biology
Disease Focus: Osteoarthritis

Lay Language Summary: Osteoarthritis (OA) is a debilitating disease with increasing prevalence in the US population. One of the major causes of OA is the destruction of articular cartilage. The intricately constructed cartilage matrix is vital for maintaining the functional properties of the joint surfaces, and its destruction sets in motion a vicious cycle that promotes further destruction and activation of cartilage-degrading molecular scissors called proteinases, ultimately resulting in severely damaged joints

that necessitate joint replacement surgery. The current proposal is focused on a specific set of molecular signaling scissors that are called ADAM17 (a disintegrin and metalloproteinase 17), and their recently discovered regulator iRhom2, in OA. ADAM17 releases other molecules such as growth factors from cells, which in turn promote destructive molecular programs in the cartilage. ADAM17 is tightly controlled by a molecule called iRhom2 (inactive Rhomboid 2), and we therefore predict that iRhom2 will also regulate the destruction of the joint surface in OA. Since very little is currently known about the role of ADAM17 and iRhom2 in the pathogenesis of OA, we propose to study their functions as regulators of growth factor signaling in bone development and OA. For this purpose, we will use a mouse model for OA that recapitulates many aspects of the human disease to understand how iRhom2 and ADAM17 contribute to joint destruction in OA. The specific aims are:
Aim 1) Evaluate the function of ADAM17 in cartilage cells in the mouse OA model. We have generated mice lacking ADAM17 only in cartilage cells and have found that these have subtle defects in development that strongly support the notion that ADAM17 regulates growth factor signaling and activation of destructive pathways. We hypothesize that ADAM17 therefore plays a detrimental role in OA and will therefore be a good target for treatment of OA. Studies in mouse models for human OA will be complemented by studies with cells isolated from cartilage to determine how ADAM17 affects the specialization of these cells and the activation of destructive pathways. Aim 2) Understand the role of the recently discovered regulator of ADAM17 termed iRhom2 in bone development and in OA. We have identified a novel essential regulator of ADAM17 termed iRhom2. We will use mice in which iRhom2 was inactivated to study the role of iRhom2 in bone development and OA. These experiments promise to provide exciting new information on the role of iRhom2 in regulating the ADAM17/growth factor pathway in cartilage, and have the potential of uncovering new possibilities for blocking the inappropriate activation of degradative pathways in OA.
We anticipate that the proposed studies will provide new insights into the mechanism underlying the development of OA, and that they will uncover new targets for treatment of this highly prevalent and debilitating disease.

Name: **Ru Bryan, PhD**
Award Type: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *AMPK as a Potential Therapeutic Target for Osteoarthritis*
Institution: Veterans Medical Research Foundation
Award Period: March 1, 2013 – February 28, 2015
Study Section: Cell Biology
Disease Focus: Osteoarthritis

Lay Language Summary: Osteoarthritis (OA) is the most common form of arthritis. Progressive degeneration of articular cartilage in OA leads to functional failure of the joint and permanent disability. However, we do not yet have effective disease-modifying OA drugs, and this is an urgent unmet medical need. Since chondrocytes, the only cells residing in the cartilage matrix, are responsible for maintaining the cartilage homeostatic balance between matrix anabolism and catabolism, one approach to rationally designed new OA therapies that target pathogenesis and disease progression is to improve chondrocyte function. AMP-activated protein kinase (AMPK) is a "super-regulator" of energy homeostasis and cellular metabolism. AMPK activity exerts anti-inflammatory effects. We recently discovered that AMPK activity, which is constitutively present in normal articular chondrocytes/cartilage, is decreased in human knee

OA chondrocytes/cartilages. In addition, inflammatory cytokines and biomechanical injury cause rapid loss of AMPK activity, correlated with increased catabolic responses in chondrocytes. Moreover, AMPK pharmacologic activators are able to inhibit excessive catabolic responses induced by inflammatory cytokines and biomechanical injury. These findings implicate that AMPK activity is important for cartilage matrix homeostasis, and chondrocyte bio-energetics could be served as a site for novel therapy intervention. In this study, we propose to test the novel translational hypothesis that "therapeutic/preventive" induction of AMPK activity by the selective AMPK pharmacologic activator inhibits cartilage injury and suppresses development and progression of OA. Completion of these translational studies will provide new insights into how chondrocyte bio-energy mechanisms sub-serve matrix homeostasis. Targeted activation of AMPK by pharmacological means may provide a novel approach to suppress the development and slow the progression of OA. Particularly, these preclinical studies are performed to provide a foundation for translation into humans.

Name: Motomi Enomoto-Iwamoto, PhD
Award Type: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *Protection of Articular Cartilage by Blocking Alpha 5 Integrin*
Institution: The Children's Hospital of Philadelphia
Award Period: May 1, 2014 – April 30, 2016
Study Section: Cell Biology
Disease Focus: Osteoarthritis

Lay Language Summary: Osteoarthritis (OA) is a multifactorial disease that involves progressive loss of chondrocyte function and matrix structure. Current therapeutic attempts often target a given parameter, but not the overall process. Our data reveal that inhibition of the alpha5 integrin signaling pathway prevents cell death and matrix loss in articular cartilage and reduces hypercellularity responses in synovium in a mouse model of OA. Thus, inhibition of this pathway may offer a comprehensive therapeutic tool that would aid and even restore function in both articular cartilage and synovium. This pathway is being extensively studied in cancer, and many clinically relevant tools to manipulate it are already available. Thus, our project is highly innovative and will lead to major steps ahead toward novel and encompassing therapeutics for osteoarthritis, a topic of this Innovative Research Grant Program.

Name: Gary S. Firestein, PhD
Award Type: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *Integrative analysis of epigenetics in rheumatoid arthritis*
Institution: Regents of the University of California, San Diego
Award Period: May 1, 2014 – April 30, 2016
Study Section: Inflammation
Disease Focus: Osteoarthritis

Lay Language Summary: Research on rheumatoid arthritis (RA) susceptibility has often focused on DNA sequences, especially through gene associations in genome-wide association studies. Our proposed studies will define a novel way of thinking about disease pathogenesis by exploring the DNA methylation

signature of RA and integrating it with genomics and transcriptomics data. The approach uses unbiased technology to analyze DNA methylation in cells isolated from the diseased tissue rather than a candidate gene approach and will use systems biology to determine which pathways are affected. This unbiased integrative method will reveal new targets and lead to novel biomarkers. Thus, the proposal meets the criteria for the Innovation Award by expanding our understanding of the fundamental mechanisms of disease in RA, developing new therapies, and identifying diagnostic biomarkers.

Name: Andres Jose Garcia, PhD
Award Type: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *IL-1Ra-Tethered Nanoparticles to Treat Joint Inflammation and OA*
Institution: Georgia Tech Research Corporation
Award Period: February 1, 2012 – January 31, 2014
Study Section: Technologies/Biomechanics
Disease Focus: Osteoarthritis

Lay Language Summary: Osteoarthritis (OA) is a highly prevalent and debilitating condition with staggering socioeconomic costs. OA affects cartilage and bone within articular joints. Inflammatory mediators play central roles in the progression of OA, and anti-inflammatory drugs are currently used for treating arthritis through intra-articular (into the joint) injections. However, these anti-inflammatory therapies have not been effective and are limited by currently available drug delivery materials. In particular, a major challenge is rapid clearance of the injected agent from the joint, which significantly decreases the therapeutic effect and reduces the benefits of local administration. The objective of this project is to engineer nanoparticles presenting the potent anti-inflammatory agent IL-1Ra to enhance intra-articular delivery and retention of this agent in order to reduce inflammation and OA progression. We hypothesize that controlled delivery and retention of this anti-inflammatory agent via these nanocarriers will result in sustained therapeutic doses that reduce inflammation and OA progression compared to soluble IL-1Ra and untreated controls. These nanoparticles represent an innovative and promising delivery vehicle for articular tissues with several advantages over existing biomaterials, including high flexibility in the synthesis and functionalization to control particle size and chemistry, drug dosing, and ability to incorporate additional agents such as pain killers and drugs that protect cartilage. We expect that delivery of nanoparticles presenting IL-1Ra will increase the retention in the joint by reducing clearance from the joint. In addition, presentation of multiple IL-1Ra molecules on the surface of the nanoparticles will result in a significant enhancement in the effective local concentration. We will first engineer nanoparticles presenting IL-1Ra and examine dosing and retention in an animal model of OA. We will then evaluate the effects of IL-1Ra-tethered nanoparticles on joint inflammation and degeneration in this animal model of OA. This innovative project will establish nanoparticles presenting IL-1Ra as a robust therapeutic delivery platform to ameliorate joint inflammation and OA progression. This research will provide critical data necessary for translating into larger and more representative models of OA.

Name: Andres M. Griffin, PhD
Award Type Timothy: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *Molecular Mechanisms of OA Pain Relief with Exercise*
Institution: Oklahoma Medical Research Foundation

Award Period: March 1, 2013 – February 28, 2015
Study Section: Technologies/Biomechanics
Disease Focus: Osteoarthritis

Lay Language Summary: There is a fundamental gap in our understanding of why exercise is one of the safest and most effective means of managing osteoarthritis (OA) pain. Identifying the molecular mechanisms underlying this clinical observation represents an important opportunity for developing improved drug treatments for OA pain that have fewer adverse side effects. The long-term goal is to better understand how different ways of loading joints, such as with changes in bodyweight or activity, can be protective rather than damaging for treating and preventing OA. This application focuses on the beneficial aspects of increased joint loading with exercise for reducing OA pain. The objective here is to identify how exercise changes the molecular composition of tissues within the knee joint to reduce pain using mouse models of knee OA. The central hypothesis is that exercise reduces the chronic activation of a particularly reactive sensory nerve channel called TRPA1 by improving the cellular mechanisms that regulate inflammation and oxidation within the knee fat pad. This hypothesis has been developed based on preliminary data generated in the applicant's laboratory. Guided by these data, the project will test the hypothesis using two parallel aims. The first aim will identify the oxidative and inflammatory processes associated with OA pain and TRPA1 activation that are most sensitive to exercise treatment. The second aim will identify the role of TRPA1 in mediating OA pain using genetically altered mice and chemicals that activate or inactivate TRPA1 function. A key innovation in these proposed experiments is the use of a new technology to assess clinically relevant pain behavior in mouse models of knee OA. The applicant's lab has developed a force-sensing running wheel that allows clinically relevant gait biomechanics data to be collected non-invasively while mice run on the wheel. This new technology is expected to improve the relevance of findings from pain studies in mice to humans. The proposed research is significant because it is expected to identify the mechanisms through which exercise reduces pain-sensitizing factors in the knee fat pad of OA joints. Ultimately, such knowledge is expected to lead to the development of improved drugs for reducing arthritis disability.

Name: **James N. Jarvis, MD**
Award Type: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *Epigenetic Regulation of JIA Neutrophils*
Institution: The R F for SUNY
Award Period: January 1, 2013 – December 31, 2014
Study Section: Molecular Biology and Gene Regulation
Disease Focus: Juvenile Arthritis

Lay Language Summary: Physicians and scientists have accepted for a long time the idea that juvenile idiopathic arthritis (JIA) is triggered by complex gene-environment interactions, but we have not been able to characterize how those interactions actually happen. The new field of epigenetics, the study of alterations in DNA that occur as the result of environmental cues but don't alter the actual genetic code, provides tremendous opportunity to understand these complex interactions. In this project, we will be examining epigenetic alterations in a specific type of white blood cell in JIA, called a neutrophil. Neutrophils are a cell of the innate immune system, the part of the immune system that does not require prior exposure to a germ or virus for maximum function. We have previously shown that these cells show specific alterations in juvenile arthritis, and this study is intended to understand those

alterations in function at the genome level. We will look across the genome at specific epigenetic changes in JIA neutrophils, and examine how those changes affect what genes and gene variants JIA neutrophils use, comparing the results to healthy control children. This project, then, will set the stage for deeper and more complex studies into how the genome functions in JIA and an understanding of both the disease and its response to therapy at the genome level.

Name: **Yukiko Kimura, MD**
Award Type: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *Implementing CARRA Standardized Treatment Plans for JIA*
Institution: Hackensack University Medical Center
Award Period: March 1, 2012 – February 28, 2014
Study Section: Clinical/Therapeutics/Outcomes
Disease Focus: Juvenile Arthritis

Although there are many treatment options now available to treat Juvenile Idiopathic Arthritis (JIA), we still do not know which treatments will achieve the best outcomes for individual patients. A formal research study such as a clinical trial that compares different treatments in JIA would be ideal, but such studies are often not feasible in JIA. A novel approach to evaluating the comparative effectiveness of these treatments is to collect data resulting from the use of standardized treatment plans in actual clinical practice rather than in a clinical trial. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) has made standardizing treatments for pediatric rheumatic diseases (such as JIA) a top priority, because by decreasing variability in the way patients are treated, we will be able to learn more about the effectiveness of the treatments and improve the quality of care that patients receive. In order for this approach to succeed, however, the treatment plans must be widely used by CARRA pediatric rheumatologists. Four standardized treatment plans were developed for new onset systemic JIA (sJIA) by consensus as part of a National Institutes of Health grant to CARRA. SJIA was chosen as the first JIA disease-type to study because it is a relatively uncommon, severe disease which often does not respond to traditional treatments, and this has currently led to a great deal of variability in sJIA treatment by pediatric rheumatologists. Therefore, learning which treatments are the best is critically important for patients with this disease. Developing a strategy that will allow widespread and easy use of the consensus treatment plans (CTP), including pilot testing of the plans and data collection process is necessary before they can be widely disseminated. This proposal seeks to pilot the use of the CTPs to treat 30 sJIA patients in 15 CARRA Registry sites. Attention will be focused on developing ways to encourage and facilitate using the plans, including support for entering the data, general instruction on the plans, tools to help with physician decision making and feedback about how each site is performing. Once successful tools and ways to use the plans are developed, they will be shared, so that similar CARRA projects in other rheumatic diseases of childhood can also succeed. Lastly, this proposal will provide the necessary information that will support a larger scale grant to implement the CTPs across all CARRA Registry sites, which will then allow comparison of the effectiveness of the sJIA CTPs.

Name: **Thorsten Kirsch, PhD**
Award Type Timothy: Innovative Research Grant – IRG

Amount: $100,000.00
Project Title: *Novel Imaging Biomarker and Treatment for Osteoarthritis*
Institution: New York University School of Medicine
Award Period: March 1, 2013 – February 28, 2015
Study Section: Cell Biology
Disease Focus: Osteoarthritis

Lay Language Summary: Osteoarthritis (OA) and post-traumatic osteoarthritis (PTOA) are painful and debilitating diseases that often dramatically limit the quality of life of affected patients. Worse, there is no cure for OA and PTOA. Currently, treatments are often limited to pain management, and the common end point is total joint reconstruction with a prosthetic device. PTOA often requires joint replacement surgery in relatively young patients. Joint replacement surgery, however, is problematic in young patients for two reasons: (a) the life span of a prosthetic device is limited and joint replacement revision surgery has much higher complication and failure rates than primary joint replacement surgery; and (b) the prosthetic devices only partly restore joint function and do not allow performing all activities. Therefore, the development of novel therapeutic strategies for the treatment of OA and PTOA, which would prevent joint replacement surgery at young age, is absolutely critical. However, the development of novel therapeutic strategies is hampered by the lack of appropriate targets for treatment and the lack of detection methods for early stages of OA/PTOA and responses to treatment. Over the last several years, our research team has developed new magnetic resonance imaging (MRI) methods for the early OA diagnosis, and has generated preliminary findings suggesting that novel bisphosphonates may have a great potential as OA/PTOA disease modifying drugs since they may inhibit cartilage destruction during OA via protecting articular chondrocyte function and phenotype and inhibiting initial subchondral bone losses. Based on these findings we are now proposing to develop (1) advanced cutting edge technology that will allow validation and rapid clinical translation of quantitative non-invasive MRI for early OA/PTOA detection and monitoring the efficacy of novel treatment strategies, and (2) a novel strategy for the treatment of OA/PTOA. With the successful completion of this proposal we expect to have established a MRI method that detects early stages of OA/PTOA and can be used to monitor the efficacy of new treatment strategies. In addition, we will correlate early cartilage extracellular matrix changes determined by our new MRI sequence with early subchondral bone changes determined by micro-CT to obtain novel information regarding the interplay between cartilage changes and subchondral bone changes in OA/PTOA. In addition, we expect to establish that new bisphosphonates provide a novel therapeutic strategy for the treatment of OA/PTOA.

Name: **Virginia Byers Kraus, MD, PhD**
Award Type Timothy: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *Post-translationally Modified Proteins as Biomarkers of OA*
Institution: Duke University
Award Period: March 1, 2012 – February 28, 2014
Study Section: Biochemistry
Disease Focus: Osteoarthritis

Lay Language Summary: Osteoarthritis (OA) affects 27 million Americans and is the most common type of arthritis and the leading cause of disability among persons aged 18 years and older. Blood and urine tests for OA offer the hope of diagnosing OA early, at a time when it might be possible to prevent

subsequent pain and disability. We have developed a method of monitoring the degeneration of a joint that relies on the identification of changes in proteins that occur naturally with age. We have developed a new test for OA based on measuring an age-related change in a specific cartilage protein known as Cartilage Oligomeric Matrix Protein (COMP). Our preliminary data indicate that this blood test is a specific indicator of hip OA. It has also provided amazing new insights into the ability of cartilage to repair itself and has suggested that knee OA cartilage is much more readily able to repair itself than hip OA cartilage. In this study we propose to use the new hip OA biomarker test to evaluate individuals with hip and knee OA and their rate of OA progession in a very large cohort of ~3,000 individuals whose blood and knee and hip X-rays have already been acquired and banked away for just such a purpose. From this we will hope to validate that this test is indeed specific for hip OA and determine if it can predict an individual's risk of OA progression and measure the rate of progression over time. In addition we will develop new biomarker tests based on the second most abundant protein in cartilage known as aggrecan. Aggrecan is responsible for the compressibility of cartilage and is lost very early in the OA disease process. We hope through development of new tests to measure aggrecan degradation that we will be able to identify OA very early at a time when it will more likely be able to be effectively halted or reversed through prescribing of early prevention and treatment strategies.

Name: **Christian Lattermann, MD**
Award Type: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *IL-1RA Treatment in Patients with Acute ACL Tear and Painful Effusions*
Institution: University of Kentucky Research Foundation
Award Period: March 1, 2012 – February 28, 2014
Study Section: Clinical/Therapeutics/Outcomes
Disease Focus: Osteoarthritis

Lay Language Summary: Injury to the knee during sports participation often involves partial of full detachment of the anterior cruciate ligament (abbreviated as ACL). ACL tears cause pain, swelling and inflammation. While the swelling and inflammation usually goes away in time, individuals with ACL injuries may experience pain and notice knee instability (knee slipping, etc.). Often surgery can repair or replace the ACL within the joint, allowing individuals the ability to walk or run again pain free or participate in sports. Unfortunately, osteoarthritis of the knee, which also causes pain and swelling, can occur in that same knee 10-20 years later for reasons which are not well understood. Because ACL injuries more typically happen to active, young adults during sports participation (while playing basketball, soccer, and skiing), chronic osteoarthritis strikes when these individuals are relatively young and healthy. Imagine the reduced quality of life a 38 year old father of very young children with painful, crippling osteoarthritis in the knee will experience due to an ACL injury he suffered in his late teens or early 20's. In this research study, we hope to prevent the development of osteoarthritis in individuals with ACL injuries by treating them within 1-2 days after their injury with a drug that blocks a protein known as Interleukin 1, which is one of many proteins in the knee that cause knee swelling and pain. We will treat approximately 34 clinical trial patients with this drug, injected on one or two different occasions into the knee joint. Thirty-four additional patients will receive harmless salt solution (called a placebo) into their knees either with or without an injection of the drug we are testing. During this trial, no one will know which patients receive the drug and which patients receive the placebo at any time point. All individuals in our clinical trial will be compensated for their participation and will be required to answer questions related to how well they feel, how well they can perform activities in their day-to-day lives, and their level of pain, if any, before and after treatment. Lastly, we will withdraw a small

amount of fluid within the knee joint with a small needle and measure the amount of Interleukin 1 and other proteins in the knee. We predict that at the conclusion of the trial, when we find out who received the drug and who received the salt solution that individuals receiving one or two injections of drug will have experienced less pain, felt better overall, and were able to return to normal activities sooner. This clinical trial is the first of its kind and will allow health care professionals and researchers to answer many questions about the reasons why ACL injury leads to knee pain and disability and osteoarthritis. We also hope that this study will be the beginning of new, more powerful and safer drugs to help patients with ACL injuries heal sooner and return to sports or daily activities pain free.

Name: **Lydia Li, PhD**
Award Type: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *Acupressure for Older Adults with Symptomatic Knee Osteoarthritis*
Institution: Regents of the University of Michigan
Award Period: February 1, 2013 – January 31, 2015
Study Section: Clinical/Therapeutics/Outcomes
Disease Focus: Osteoarthritis

Lay Language Summary: Knee osteoarthritis is a leading cause of disability in the elderly and this disability is commonly attributed to knee pain. Current treatments for knee pain are only modestly efficacious, and some common treatments like non-steroidal anti-inflammatory drugs (NSAIDS) have adverse long-term effects. Acupressure is an inexpensive and noninvasive treatment that has the potential to be a useful long-term self-management strategy for pain. Acupressure can be easily taught and is safe enough to self-apply without supervision. The primary objective of this project is to determine whether self-administered acupressure is an effective and feasible self-management strategy for older adults with symptomatic knee osteoarthritis. Participants will be randomized to three treatment groups: pain-relief acupressure, sham acupressure, and usual care. The intervention will last for 8 weeks during which participants in the pain-relief and sham acupressure groups will be taught the assigned treatment by a trained research assistant who is blinded to the treatment arm, and provided with a DVD to aid their practice at home. The research assistant will make weekly phone calls to support the participants' adherence to treatment. Participants in the usual care group will also receive weekly phone calls offering emotional support but no other intervention. Data will be collected at baseline, mid-point (4 weeks after baseline) and the end (8 weeks) of the intervention. These results will help us assess the efficacy of pain-relief acupressure on knee pain in older adults, and plan for a future study involving a larger and more diverse sample of older persons with symptomatic osteoarthritis. Since no studies have involved older adults in self-administered acupressure, information about feasibility of and adherence to using this method in older adults would be invaluable.

Name: **Suzanne C. Li, MD, PhD**
Award Type: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *Developing Tools for Localized Scleroderma Comparative Effectiveness Studies*
Institution: Hackensack University Medical Center
Award Period: March 1, 2012 – February 28, 2014
Study Section: Clinical/Therapeutics/Outcomes
Disease Focus: Scleroderma

Lay Language Summary: Our goal is to improve the long-term outcome of patients with juvenile localized scleroderma (jLS), a disease that often causes major musculoskeletal problems for children including arthritis, limited joint mobility, and defective growth of the affected limb. Because the disease often lasts throughout childhood, children are at risk for permanent disfigurement and disability. Identifying the best treatments for this disease has been difficult because there have been no agreed upon standards to use to evaluate patients or to say if they have had a good response to treatment. A group of pediatric rheumatologists and dermatologists, based in a North American pediatric rheumatology collaborative research group (CARRA), have spent the last two years developing these tools, and standard treatment plans. These treatment plans represent the treatment patterns of the majority of pediatric rheumatologists in North America. Our group proposes studying the developed tools and treatment plans in a prospective pilot treatment study of 50 jLS patients so that we can determine how well our tools work and if there are any issues with the developed treatment plans. The study data will be entered into an established Web based data collection system; this will help us monitor many patient features and be able to compare our study results with future studies. We will also collect blood samples from the study patients to be able to look for disease biomarkers in future studies. The information we learn from this study will help us design future multi-center prospective comparative treatment studies. We hope to establish a process for carrying out such studies so that we can identify optimal therapy for jLS and thereby reduce or eliminate the risk for severe morbidity and long-term problems for these patients.

Name: **Taras Lyubchenko,**
Award Type: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *Pathogenic role of autoreactive anergic B cells in Rheumatoid arthritis*
Institution: University of Colorado Denver
Award Period: July 1, 2014 – June 30, 2016
Study Section: Clinical Immunology
Disease Focus: Rheumatoid Arthritis

Lay Language Summary: Achieving the goals of this study will establish the loss of anergic immune tolerance in a subset of autoreactive B cells as one of the factors in the development of autoimmune inflammatory rheumatoid arthritis (RA) and facilitate the development of new treatments that specifically target B cell receptor signal transduction intermediaries involved in the loss of anergic immune tolerance and identify signaling-based functional biomarkers associated with it. The novelty of our study is in addressing the signaling pathway involved in the maintenance and pathological alteration of anergic immune tolerance through a comprehensive phospho-protein array. To our knowledge, the proposed study will be [among] the first to address the role of B cell receptor signaling mechanisms in the loss of anergic immune tolerance in RA. Autoreactive subset of anergic B cells was recently identified in humans.

Name: **Andrew Mellor, PhD**
Award Type: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *Engineering DNA Nanoparticles as Novel Treatments for Arthritis*
Institution: Georgia Health Sciences University Research Institute

Award Period: March 1, 2013 – February 28, 2015
Study Section: Cellular Immunology
Disease Focus: Rheumatoid Arthritis

Lay Language Summary: The immune system mediates progressive joint injury in patients with rheumatoid arthritis (RA). Immune modulators ameliorate clinical RA symptoms and severity but patient responses to immunotherapy are unpredictable, often transient, and have undesirable effects including suppressed immunity to pathogen infections. The goal of studies proposed is to use novel reagents – DNA nanoparticles (DNPs) as versatile tools to augment expression of the enzyme indoleamine 2,3 dioxygenase (IDO), which naturally regulates immunity at sites of chronic inflammation. IDO activity is elevated in inflamed joints of RA patients, and data from mice shows that natural IDO activity inhibits immune-mediated joint injury. We hypothesize that DNP treatment to enhance IDO activity impedes RA progression and alleviates pre-existing RA symptoms by suppressing autoimmunity that causes joint pathology and injury. In recent published studies we reported that DNP treatment alleviated immune-mediated joint injury in a mouse model of antigen-induced arthritis (AIA). In preliminary studies we have identified cells and pathways targeted by DNPs that promote immune regulation, and show that DNPs containing novel biodegradable polymers induced IDO to block T cell responses to vaccines in mice. In studies proposed, we will test the hypothesis above by elucidating cellular and molecular components of the immune regulatory pathway targeted by DNPs, and by testing the therapeutic efficacy of DNPs in well-accepted mouse models of RA, including collagen-induced arthritis (CIA), the classic model of human RA. Completing these studies will generate scientific and technical data needed to evaluate DNPs as potential new drugs to treat patients with RA.

Name: **Naoki Nakayama, PhD**
Award Type: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *Making the hES/iPS cell-derived chondroprogenitor a novel therapeutic tool*
Institution: The University of Texas Health Science Center at Houston
Award Period: March 1, 2012 – February 28, 2014
Study Section: Cell Biology
Disease Focus: Osteoarthritis

Lay Language Summary: Cell-based therapy offers the most feasible alternative strategy to the current clinical practice of joint replacement surgeries for the treatment of osteoarthritis. Mesenchymal stromal cells (MSCs), defined in culture by their potential to generate bone, cartilage and fat cells, are currently the prime candidate for such cell-based therapies. However, it is difficult to obtain enough MSCs for treatment without causing significant damage at the site of cell harvest. Expansion culture is thus necessary, but tends to cause loss of long-term viability and chondrogenic capacity of MSCs. Cartilage formation is most active during embryogenesis. Therefore, embryonic cartilage-forming (i.e. chondrogenic) cells may be better suited than adult MSCs to regenerate cartilage. Since embryonic cells have greater potential for growth, it might also be possible to expand the embryonic chondrogenic cells while retaining their chondrogenic potential. Pluripotent stem (PS) cells from embryos or somatic tissues are capable of differentiation into all the somatic cell lineages through processes that mimic embryogenesis. For humans, PS cells are the only practical source of embryonic chondrogenic cells. We propose to establish methods for the generation and expansion of chondrocyte precursor (i.e. chondroprogenitor) cells from the human (h)PS cells, to obtain enough cells for transplantation and drug

screening. The PIâ€™s group has developed methods that generate chondrogenic paraxial mesoderm (the precursor of back bone and disk) and neural crest (a precursor of head bone and cartilage) from PS cells and defined essential signaling events. His group has also established a method for the generation and long-term expansion of chondroprogenitors from the hPS cell-derived neural crest progeny. We will establish conditions for generating and expanding chondroprogenitor activities from hPS cell-derived mesoderm. We will refine conditions for expanding the chondrogenic paraxial mesoderm, then examine factors known to be involved in embryonic bone and cartilage formation to establish optimal conditions for generating and expanding chondroprogenitor activity from the hPS cell-derived lateral plate mesoderm (the precursor of limb bone and cartilage). Next, we will establish methods to maintain the cartilage developed from the chondroprogenitor cells. Clinically relevant chondroprogenitor cells should be able to form a large cartilage construct, which requires the use of a scaffold or matrix. We aim to establish conditions for the hPS cell-derived chondroprogenitor cells to form a hyaline cartilage (i.e. joint cartilage)-like construct in hydrogel, based on our earlier findings. Stable maintenance of the developed chondrocytes will be important in determining a successful outcome of cartilage cellular therapy. This study therefore will determine essential signaling factors that control the maturation state of cartilage construct in culture and also in mice.

Name: **Tuhina Neogi, MD, PhD**
Award Type: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *Bisphosphonate Effects in Knee Osteoarthritis*
Institution: Boston University
Award Period: May 1, 2014 – April 30, 2016
Study Section: Clinical/Therapeutics/Outcomes
Disease Focus: Osteoarthritis

Lay Language Summary: This proposal focuses upon osteoarthritis (OA), a targeted disease for this RFA. We will evaluate the effect of altering bone remodeling by bisphosphonates on pertinent OA outcomes, including trajectory of OA progression and joint failure (knee replacement surgery). As such, the proposal addresses the RFA by evaluating alterations in normal joint homeostasis on OA outcomes and their trajectory. The proposal is innovative in several regards. This is the first comprehensive assessment of the long-term effects of bisphosphonates on knee OA, which is controversial due to conflicting trial results and concerns about altering bone properties over the long-term. We will use novel image analysis techniques (3D bone shape, bone marrow lesion volume) and novel statistical analytic techniques (trajectory analysis), and leverage existing data, making this proposal cost-efficient.

Name: **Sampath Prahalad, MD**
Award Type: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *Risk stratification using genetic & microbial determinants in childhood RA*
Institution: Emory University
Award Period: March 1, 2013 – February 28, 2015
Study Section: Genetics
Disease Focus: Juvenile Arthritis

Lay Language Summary: Rheumatoid arthritis (RA) is the most common cause of inflammatory arthritis, with a peak onset age of ~50 years. Some children with juvenile idiopathic arthritis (JIA) test positive for blood markers seen in adults with RA. Children with JIA that is identical to adult RA can be described as having Childhood Onset Rheumatoid Arthritis (CORA). We believe that studying children with CORA will help identify genetic and environmental factors predisposing to RA.
To date, over 30 genetic variants that increase the risk of developing RA have been identified; however, most of these genes have not been studied in children. We aim to test whether these variants also predispose to CORA and seek to identify different subsets of patients with CORA in order to advance personalized medicine in RA. In order to accomplish this, we will develop a genetic risk score, which takes into account the combined effects of multiple genetic risk variants. We will determine if children with high and low scores have differences in clinical features such as gender, age at onset, joint counts, development of joint damage, and treatment response. A NIH-funded registry of children with arthritis and related conditions created by the Childhood Arthritis and Rheumatology Research Alliance (CARRA) provides us with a unique opportunity for such studies. We will recruit 200 children with CORA who are already enrolled in the CARRA Registry to complement samples over 300 samples we have collected previously. While smoking and gum disease have been implicated in the risk of developing RA in adults, these exposures are rare in childhood. This suggests that other triggers likely play a role in the development of CORA. Several recent studies have shown that changes in intestinal microbial populations, referred to as the "microbiome", can be associated with development of inflammatory arthritis in humans and animals. We propose to investigate the role of the microbiome in children with CORA. Specifically, we will determine if the microbiome in patients with CORA is different from that of age-matched healthy controls and healthy siblings. We will use state of the art genetic methods to sequence microbial DNA from stool specimens and then compare the absolute and relative quantity of bacterial families. Our proposal seeks to utilize the CARRA Registry to identify and enroll children with CORA. Grouping children into subsets of CORA based on genetic biomarkers has the prospect of aiding future development of personalized medicine in RA and CORA. In addition, we will investigate whether specific bacterial communities are associated with the natural history of CORA. We believe that our study will significantly improve our understanding of CORA and therefore allow for future innovation in the diagnosis and targeted treatment of the disease.

Name: **Jose U. Scher, MD**
Award Type: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *Pan-Microbiome in At-Risk Subjects and New-Onset Rheumatoid Arthritis*
Institution: New York University School of Medicine
Award Period: May 1, 2014 – April 30, 2016
Study Section: Clinical Immunology
Disease Focus: Rheumatoid Arthritis

Lay Language Summary: Microbial antigens have long been thought to trigger RA. However, culture conditions are unknown for the vast majority of bacterial organisms, whether commensal or pathogenic. Given the long-considered hypothesis that bacterial infection could represent an environmental trigger of RA, the application of modern technology (16S pyrosequencing methods) to assess this question could have significant impact on the field. We will therefore apply – for the first time – high-throughput bacterial sequencing to define the characteristic pan-microbiome of RA in various stages of disease, including the pre-clinical and new-onset. In line with the Arthritis Foundation's Innovative Grant RFA,

this project will serve as the basic platform for a broader collaborative investigation to determine whether human mucosal-residing microorganisms are responsible for initial development or progression of RA.

Name: Neil Segal, MD
Award Type: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *Early Targeting of Knee Osteoarthritis: Predictive Value of Contact Stress*
Institution: University of Iowa
Award Period: March 1, 2012 – February 28, 2014
Study Section: Technologies/Biomechanics
Disease Focus: Osteoarthritis

Lay Language Summary: The long-term goal of this study is to develop a person-specific means of predicting early knee osteoarthritis (OA) to guide preventive measures. Osteoarthritis affects over 25 million Americans, resulting in significant pain and mobility limitations. Despite its high prevalence, predicting who will develop knee OA has not been possible because, until recently, the lack of non-invasive assessment methods for the joint has been a critical barrier to progress. Recent advances in magnetic resonance imaging (MRI) have enabled visualization of certain signs of early OA in the knee, such as damage to cartilage and bone. Bone marrow lesions (BMLs), areas of high signal intensity on MRI in the bone beneath the joint surfaces, have been linked to risk factors for knee OA. The size of BMLs correlates with both anatomic and symptomatic course. Given that most BMLs are reversible, identification of how they occur and what causes them could help to guide therapies, advancing public health. The etiologies of cartilage loss and BMLs are not fully understood, but adverse loading almost certainly plays a role. Ideally, assessment of loading would be knee region-specific, accurate, and generalizable for widespread clinical use. Although contact stresses in the human knee cannot be measured, computational simulation, using new analysis methods presents an expeditious and practical method to estimate them, based on commonly used x-rays and MRI. This non-invasive method takes advantage of recent advances to predict not only in whom, but also where in the knee early OA will develop, with the potential to provide 3D guidance of preventive rehabilitation and surgical treatments. The proposed research will determine the extent to which stress in each part of the knee joint predicts early signs of knee joint damage: cartilage loss and BMLs (Aim 1) as well as whether higher stress predicts worsening of physical function (Aim 2). Rather than recruit a new subject cohort, the proposed study will leverage a wealth of information already collected, through adding person-specific knee joint stress analysis to an existing study that is already longitudinally assessing knee joint structure and physical function, the Multicenter Osteoarthritis (MOST) study. This study is following 3,026 community-dwelling men and women, age 50-79, who have higher risk for knee OA, based on a history of knee injury or surgery or being overweight or obese. These participants are representative of those who would be most likely to benefit from development of a clinical measure to guide prevention of knee OA, making this the ideal cohort in which to test our hypotheses. The expected products of this research, (1) a method for assessing subregion–specific contact stress on a large scale and (2) an advanced

understanding of risk for worsening will powerfully influence strategies to preserve knee joint structure and human function.

Name: **Michael E. Selsted, MD, PhD**
Award Type: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *Novel macrocyclic peptides for in vivo blockade of arthritogenic proteases*
Institution: University of Southern California
Award Period: March 1, 2013 – February 28, 2015
Study Section: Inflammation
Disease Focus: Rheumatoid Arththritis

Lay Language Summary: Rheumatoid arthritis (RA) is an autoimmune disease characterized by erosion of joint tissues. The erosive changes are mediated by inflammation, the proliferation and invasion of joint-lining cells, and dysregulation of enzymes that are normally involved in remodeling of healthy tissues. In RA, these remodeling enzymes are induced by inflammation and are thus over-produced and become destructive, degrading joint cartilage and bone. Indeed these elevated enzyme levels are major contributors to joint erosion in RA. The Principal Investigator of this project has discovered a family of naturally-occurring molecules that are highly effective in reversing the course of experimental arthritis in rats. Preliminary studies indicate that these molecules, which are normally expressed in white blood cells, block the digestive activities of joint degrading enzymes. The studies proposed will determine the mechanisms of enzyme blockade and will test these mechanisms in a rodent model of RA. The subject molecules are extremely well tolerated in animals indicating that they are excellent candidates for development of drugs for treating RA.

Name: **Shiva Shahrara, PhD**
Award Type: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *The novel role of CCL21 and CCR7 in RA pathogenesis*
Institution: University of Illinois at Chicago
Award Period: June 1, 2012 – May 31, 2014
Study Section: Inflammation
Disease Focus: Rheumatoid Arththritis

Lay Language Summary: In this proposal we have identified novel genes that are highly elevated in rheumatoid arthritis (RA) joints and our aim is to determine the mechanism by which these identified genes cause disease. We will also determine whether these genes can be utilized as markers for RA disease progression. Overall, this study will advance our understanding of the mechanism underlying pathophysiology of RA and may lead to identifying novel therapeutic targets.

Name: **Najia Shakoor, MD**
Award Type: Innovative Research Grant – IRG

Amount: $100,000.00
Project Title: *Biomechanical effects of flexible footwear in osteoarthritis of the knee*
Institution: Rush University Medical Center
Award Period: March 1, 2013 – February 28, 2015
Study Section: Clinical/Therapeutics/Outcomes
Disease Focus: Osteoarththritis

Lay Language Summary: Knee osteoarthritis (OA) is a significant source of disability and impaired quality of life worldwide. There is evidence to support that high loads on the knees during walking are a risk factor for this disease and for worsening of the arthritis over time. There is also evidence and that these knee loads may be affected by footwear. Dr. Shakoor evaluates the effects of footwear on knee loads and pain in people with knee OA. Her research has shown that flat flexible footwear may help lower knee loads. Her current research aims to evaluate why and how this flexible footwear leads to knee load reduction and whether it also delays progression of the arthritis. 30 persons with painful knee OA will be evaluated in this study. They will undergo testing with a specialized "gait analyses system" which evaluates how they walk, how their joints move, and how much load/force they put on their joints. They will be provided and asked to wear flexible study shoes for 6 hours daily at least 6 days a week. They will then return at 12 weeks and 6 months for repeat "gait analyses". They will also undergo a specialized x-ray evaluation of their knees at the first study visit and at 6 months which gives information about the bones at their knees joints. The collected information will be evaluated to see how the forces and movements at the knees and feet change from the beginning of the study to 12 weeks and 6 months from wearing the provided flexible study shoes. Similarly, the bone at the knees will be evaluated to see if changes in knee loading with the shoes lead to beneficial changes to the bone at the knees. The study will provide novel information about shoe properties and how they affect knee loads in OA. It could also provide useful information both for shoe manufacturers and patients with OA who are searching for the appropriate shoe for their arthritis.

Name: **Patrick J. Smits, PhD**
Award Type: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *Transcriptional control of articular cartilage specific gene expression*
Institution: Children's Hospital Boston
Award Period: March 1, 2012 – February 28, 2014
Study Section: Molecular Biology and Gene Regulation
Disease Focus: Osteoarththritis

Lay Language Summary: In osteoarthritis (OA), articular cartilage is worn away resulting in intense pain, stiffness and joint swelling. OA becomes more severe over time eventually leading to impaired movement. Age is the most important risk factor, but obesity, sports activity and joint trauma are also risks leading to OA. As no efficient treatment is available, OA is a major health care issue. As the elderly population in the USA is gradually increasing and obesity has taken on epidemic proportions, the health care burden of OA will increase substantially in the next decades. One obstacle in developing a cure for

OA is that we do not fully understand how articular cartilage forms during development from embryo to adulthood. Articular cartilage is characterized by the expression of specific genes that are not found in other cartilages. Identifying the regulatory proteins (transcription factors) responsible for the expression of these genes in articular but not other cartilages would be a major step forward. In order to function, transcription factors bind to specific stretches of DNA (enhancers) in the genome. One way to uncover which transcription factors are involved in articular cartilage specific gene expression is to determine which enhancers are needed for this expression. The Prg4 gene is specifically expressed in articular cartilage. Our goal is to identify the enhancers that control the articular cartilage specific expression of Prg4 and subsequently identify the interacting transcription factors.To identify enhancers it is often necessary to study long stretches of DNA. In the laboratory, we can put large stretches of DNA into Bacterial artificial chromosomes (BACs). Once contained within a BAC we can manipulate the DNA sequence by introducing marker-genes, such as the enzyme LacZ, which when exposed to its substrate results in a blue stain. By placing the LacZ marker within the gene of interest, its expression will be controlled by the enhancers of this gene. Injection of such a manipulated BAC into fertilized mouse egg cells will result in a mouse in which all cells that express the gene of interest will turn blue when exposed to the LacZ substrate. We have inserted a LacZ marker gene into a BAC containing the Prg4 gene. Injection of this BAC into fertilized mouse cells produced mice in which the articular cartilage of the knee turned blue. We will now determine where the articular cartilage specific enhancers are located by meticulously shortening the DNA sequence of the BAC until LacZ expression in the articular cartilage is lost. The transcription factors interacting with the identified enhancers will then be isolated. Identification of these transcription factors will have major implications for OA research. The pharmaceutical industry could use them for developing new drugs. They will also be useful in tissue engineering, as they could help the differentiation of stem cells into proper articular cartilage for use in surgical repair of OA.

Name: Jeremy Sokolove, MD
Award Type: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *Autoantibody Profiles to Predict Disease Outcome in Rheumatoid Arthritis*
Institution: Palo Alto Insitute for Research and Education
Award Period: March 1, 2013 – February 28, 2015
Study Section: Clinical Immunology
Disease Focus: Rheumatoid Arththritis

Lay Language Summary: Rheumatoid arthritis (RA) is a common disabling condition afflicting nearly 1% of the US population. It is now well established that early and aggressive treatment of RA improves disease outcomes, however, not all patients require the same level of treatment to prevent untoward outcomes. The prediction of RA disease severity is important clinically, and would influence the rheumatologists' selection of the treatment regimen. If a patient were predicted to develop severe disease outcomes, the rheumatologist could treat the patient aggressively from the outset. In contrast, patients predicted to have a mild course would be treated with a less-aggressive regimen of disease-modifying drugs, which would minimize the risk for drug-related toxicities and reduce health care costs.

Name: Michael Stein, MB, ChB
Award Type: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *Inflammation and the Heart*
Institution: Vanderbilt University Medical Center
Award Period: March 1, 2012 – February 28, 2014
Study Section: Clinical/Therapeutics/Outcomes
Disease Focus: Rheumatoid Arthritis

Lay Language Summary: Heart failure, a serious and often fatal illness, is twice as common in patients with rheumatoid arthritis (RA) as in the general population. The reason for the increased risk of heart failure in RA is not known, but there is evidence that the chronic inflammation that accompanies RA may damage the heart. There is also evidence in the general population that inflammation can damage the heart. Additionally, we have found that levels of two markers of heart muscle stress are increased in patients with RA. However, the idea that heart muscle dysfunction is present in patients with RA, and can be reversed by the drugs used to treat it, has not been tested. We believe that inflammation has deleterious effects on the heart and that these can be improved by control of inflammation. New MRI technology allows us to image the heart and obtain precise measurements of its structure and function and the amount of scar tissue present without exposing patients to radiation. We propose to test the idea that increased inflammation in patients with RA is associated with deleterious changes in the structure and function of the heart and that these will be improved by disease modifying anti-rheumatic drug (DMARD) therapy. We will perform cardiac MRI scans in patients before they start new DMARD therapy with anti-TNF drugs or methotrexate for active RA, and again after 6 months of treatment. We anticipate that control of inflammation will improve heart function. However, based on studies in animals, and the fact that anti-TNF drugs made heart failure worse in studies in the general population, it is possible that methotrexate and anti-TNF drugs may have different effects. Thus, we will compare the effects of the two therapies on the heart. The lack of information about the effects of common therapies for RA on the heart is a critical knowledge gap that we will address. If our idea is correct it will change the way physicians approach heart disease in RA. It will shift current practice from treating heart failure when it occurs, to identifying heart muscle stress early, before heart failure occurs, and intervening to reverse the process and prevent heart failure.

Name: Susan D. Thompson, PhD
Award Type: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *Exome sequencing studies in Juvenile Idiopathic Arthritis*
Institution: Cincinnati Children's Hospital Medical Center - Research Foundation
Award Period: March 1, 2013 – February 28, 2015
Study Section: Genetics
Disease Focus: Juvenile Arthritis

Lay Language Summary: Juvenile Idiopathic Arthritis (JIA) is the major autoimmune arthritis of childhood and there are about 50,000 children in the USA with JIA causes of this disease are not well understood, but include a genetic component. New technologies such "Next Generation" DNA sequencing may now make it possible to refine our understanding of JIA. JIA most often occurs as sporadic cases, with no history of disease in the family. While we know of many genes that each contribute a small amount to disease, there are still missing pieces. One possible contributor might be a new or "de novo" mutation, that occurs when the DNA replication machinery makes an error during the formation of the gametes in a parent. These errors, depending on their location in the gene, may alter the function of the protein encoded by that gene. This advanced sequencing approach, focusing on the expressed portion of the genome, termed the "exome", provides an unbiased way to discover new mutations that directly alter protein function. We will use DNA samples that have been collected from children with JIA and their parents. More than 500 of these trios are in the freezer. This large collection gives us the opportunity to select patients who had a very young age at disease onset and have severe disease to maximize our chances for success. The de novo sequence mutations will be found by comparing the DNA code of the JIA child to both parents. Advanced bioinformatic approaches will help us determine whether the predicted changes in the coded protein are important for JIA. We will also study the exome sequence for a small number of families where there are strong patterns of disease inheritance. This type of inheritance pattern is not seen often in JIA families, but we are fortunate to have nine such pedigrees, where there are 3 or more related people with JIA, represented in our DNA collections. Each of these families has the potential to provide new information about a gene or biological pathway important in disease. We expect to find very rare DNA sequence variants in one or both parents that explain the pattern of inheritance. In this case the important DNA sequences will be identified by determining what the affected family members share in their exome that is different from the unaffected members. Our DNA collection also includes five monozygotic (identical) twinsets, where only one twin has JIA. One possible explanation for this is a DNA mutation occurred after fertilization and the twinning. Thus, a mutation that accounts for disease could be present in one twin but not the other. There is precedent for this mechanism in other diseases. Together, the rapidly evolving exome sequencing methodologies and the unique and extensive JIA DNA collection on hand will most likely lead to the identification of new genes and pathways related to JIA susceptibility. This information could lead to earlier and more definitive diagnoses as well as suggest new drug targets.

Name: **Emily von Scheven, MD**
Award Type: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *Standardizing and Optimizing Childhood Lupus Nephritis Treatment with CARRA*
Institution: University of California, San Francisco
Award Period: March 1, 2013 – February 28, 2015
Study Section: Clinical/Therapeutics/Outcomes
Disease Focus: Juvenile Arththritis

Lay Language Summary: Children with SLE (cSLE) often develop more severe organ involvement than adults. And this frequently includes the development of renal disease, called lupus nephritis (LN).

Optimal control of lupus nephritis in children (cLN) is one of the most critical problems facing these children. This is because uncontrolled cLN can lead to end-stage renal disease, the need for dialysis, and increased death. Unfortunately the best treatment for these children is currently not known. Traditional research study designs used to determine optimal treatments in adult diseases, such as randomized controlled trials, are often not feasible in children due to fewer patient numbers and ethical concerns. And comparing the effects of treatments provided by various physicians in practice is often not reliable because physicians use so many different treatment approaches and track patients differently. Thus, historically, many medical providers have simply applied what is learned in adult research studies to the treatment of their children. However, that may not always be valid due to differences related to the underlying disease or to the way children respond to medications. Another approach for comparing the effects of different treatments is to standardize treatments that are used in routine practice so that they can be reliably compared. Thus, the pediatric rheumatology community, working through the Childhood Arthritis and Rheumatic Disease Alliance (CARRA), recently completed the development of Consensus Treatment Plans (CTPs) for cLN. These provide a standardized approach for the induction and maintenance treatment of proliferative cLN with the goal of comparing the effectiveness and safety of cyclophosphamide, mycophenolate mofetil, and Azathioprine, the most commonly used medications for cLN. The CTPs also provide standardized steroid regimens. At many centers patients with cSLE enroll on a registry (CARRAnet) which allows for data collection. With the use of these new CTPs we will be able to collect data to determine how these medications compare for the treatment of cLN. However, prior to conducting a large large-scale comparison, it is necessary to assess the usability of these CTPs in the community. Thus, this proposal aims to demonstrate that the standardization of treatment using CTPs for cSLE therapies among pediatric rheumatologists is feasible, and to obtain initial information about how these treatments compare.

Name: Donghai Wang, PhD
Award Type: Innovative Research Grant – IRG
Amount: $100,000.00
Project Title: *Regulation of Inflammation by the Mevalonate Pathway in a Mouse Model of RA*
Institution: University of Massachusetts Medical School
Award Period: May 1, 2014 – April 30, 2016
Study Section: Molecular Immunology
Disease Focus: Rheumatoid Arththritis

Lay Language Summary: We propose to use a novel mouse model of inflammatory arthritis to study how protein geranylgeranylation regulates inflammation and osteoclast differentiation and function, two important pathways in the pathogenesis of rheumatoid arthritis. Dysregulation of protein geranylgeranylation as a result of disturbances in the mevalonate pathway leads to enhanced innate immune signaling and abnormal osteoclastogenesis, and can result in erosive inflammatory arthritis. The proposed study represents a unique opportunity to elucidate the mechanisms by which aberrant innate immune signaling contributes to the pathogenesis of RA, and may provide important data for developing novel therapeutics for RA.

Name: Ae-Kyung Yi, PhD

Award Type: Innovative Research Grant – IRG

Amount: $100,000.00

Project Title: *PKD1 inhibitor as a target therapeutic for arthritis*

Institution: University of Tennessee-Health Science Center

Award Period: February 1, 2013 – January 31, 2015

Study Section: Clinical/Therapeutics/Outcomes

Disease Focus: Rheumatoid Arththritis

Lay Language Summary: Rheumatoid arthritis (RA) is an autoimmune disease manifested by swollen joints, development of auto-reactive T-lymphocytes, and destruction of cartilage and bone in joints. Cells involved in this inflammatory response have proteins called "Toll-like receptors (TLRs)." These TLRs detect components of bacteria, viruses and damaged cells, and send signals to our immune cells to produce many destructive proinflammatory mediators (i.e., proteins called cytokines, chemokines, and adhesion molecules). These proinflammatory mediators encourage infiltration and development of auto-reactive T- and B-lymphocytes, as well as inflammation. It is currently thought that RA may be started by signaling through TLRs that leads to chronic inflammation. Therefore, disruption of the signaling pathway used by TLRs may provide an opportunity to prevent the disease process before irreversible joint damage occurs. This would be a highly desirable treatment for RA. We recently found that an enzyme called protein kinase D1 (PKD1) is activated by TLRs and plays an indispensable role in production of proinflammatory mediators. In addition, we found that PKD1 is activated in synoviocytes isolated from RA patients, and that inhibition of PKD1 works well in several animal models of arthritis. Our findings imply that PKD1 may be an effective molecular target for arthritis therapy. Because PKD1, just like any other enzyme, can be involved in many different normal processes (some of which are known and others unknown), inhibiting all enzyme activity in the whole body might cause unexpected and unwanted side effects as well as the intended beneficial effects. Inhibition of PKD1 activation induced only by TLR without affecting its activation by other factors would be a safer therapy. In addition, suppression of PKD1 activity only in the inflamed joints rather than in the whole body might be a more ideal approach. Therefore, using knowledge we acquired from our recent studies we propose to develop a new way to inhibit PKD1 activation in a TLR pathway-specific manner and to deliver this therapy to the inflamed arthritis joints using an innovative target-specific drug delivery system. We believe that, if successful, our new therapeutic approach might effectively improve the outcome of RA with fewer and less toxic side effects.