



## RESEARCH GRANTS LAY SUMMARIES

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**Name:** Michelle Rosan Abelson, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *IL-17-Mediated Regulation of C/EBPbeta: Signaling and Response in Arthritis*

**Institution:** University of Pittsburgh

**Supervisor:** Sarah L. Gaffen, PhD

**Award Period:** December 1, 2013 – November 30, 2015

**Study Section:** Molecular Biology and Gene Regulation

**Disease Focus:** Rheumatoid Arthritis

**Lay Language Summary:** Rheumatoid arthritis (RA) is a chronic, often debilitating autoimmune disease. RA primarily affects flexible joints but can target other organs and tissues. This disease is associated with progressive disability, early death and significant socioeconomic costs. Drugs that target “cytokines” such as tumor necrosis factor (TNF) have greatly improved treatment options in RA. Despite these advances, a significant number of patients do not respond to available anti-cytokine therapies. Interleukin-17 (IL-17) is another cytokine implicated in RA. Many of these patients have elevated levels of IL-17 in the serum and joints. Patients in early clinical trials testing IL-17 blocking antibodies have shown clinical improvements, suggesting that IL-17 may be another valuable drug target to treat RA and other autoimmune diseases. However, surprisingly little is known about IL-17 mechanisms of action and how this cytokine contributes to the pathogenesis of RA. We have shown that IL-17 activates its effects via the CCAAT enhancer binding protein beta (C/EBPbeta) transcription factor. IL-17 induces the expression of 3 protein forms of C/EBPbeta, named LAP, LAP\* and LIP. These C/EBPβ proteins differentially induce the expression of genes for normal cellular function. To date, the biological role of IL-17-mediated regulation of C/EBPβ has not been demonstrated in RA. This proposal investigates two aspects of the IL-17-C/EBPbeta signaling pathway. Aim 1 will assess molecular mechanisms by which IL-17 regulates expression of the different forms of C/EBPbeta. In Aim 2 we will determine the biological significance of certain C/EBPbeta isoforms in a collagen-induced arthritis (CIA), a mouse model of RA. Understanding the mechanism by which IL-17 mediates signaling, particularly in the context of arthritis, may aid in the development of drugs, vaccines or treatments in diseases affected by IL-17.

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**Name:** **Jailal Nicho Ablack, PhD**

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *MARCHing to a Halt: MARCH1 regulates Lymphocyte Proliferation Through CD98*

**Institution:** University of California, San Diego

**Supervisor:** Mark H. Ginsberg, MD

**Award Period:** July 1, 2013 – June 30, 2015

**Study Section:** Cellular Immunology

**Disease Focus:** Osteoarthritis

**Lay Language Summary:** Our adaptive immune system protects us infection and reactivates when exposed to the same infectious agent. Although our immune system is very effective a riding our bodies of foreign infectious agents, under the right circumstances our bodies can direct the immune response against a self tissue. Autoimmune diseases, such as Rheumatic disease, are the manifestation of an immune response directed at self tissues such as joints. Certain cell types, including white blood cells known as lymphocytes, are capable of very rapid growth known as clonal expansion which is critical for adaptive immunity. Clonal expansion allows lymphocytes to divide rapidly to fight infection but subsequently shut off and die when no longer needed. Thus, clonal expansion of lymphocytes is an ideal biological process to target in order to combat autoimmune diseases, including Rheumatic disease. My new mentor and colleagues have previously identified and characterized the role of a protein molecule called CD98 as essential for clonal expansion of lymphocytes using genetic deletion of CD98. Based on these studies, it may be possible to reproduce the effect of genetic deletion of CD98 by controlling CD98 regulation to provide a new avenue to combat autoimmunity. Very recently it was shown that a protein called MARCH1 that was known to remove and degrade other proteins from the cell surface also had a similar effect on CD98. However, the effect of MARCH1 on clonal expansion is still a mystery. I hypothesize that regulation of CD98 by MARCH1 is central to controlling clonal expansion and ultimately autoimmunity. I propose to examine the role of MARCH1 in control of CD98 during normal clonal expansion of lymphocytes as a model system. I will also investigate the consequences of uncoupling MARCH1 mediated regulation of CD98, using a mutant of CD98 that is resistant to MARCH1 degradation and lymphocytes from MARCH1 deficient mice. I will then apply these findings to a mouse model of induced arthritis to determine if manipulating MARCH1 can delay or prevent the onset of arthritis in joints. My experiments will define the role of MARCH1 in regulating clonal expansion of lymphocytes through CD98. Understanding this regulatory circuit for CD98 may provide a potential new strategy to combat autoimmune disease.

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**Name:** Sokratis Apostolidis, MD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *The Role of PP2Ac in the Th17/Treg Cell Balance in SLE*

**Institution:** Beth Israel Deaconess Medical Center

**Supervisor:** George C. Tsokos, MD

**Award Period:** July 1, 2013 – June 30, 2015

**Study Section:** Cellular Immunology

**Disease Focus:** Lupus

**Lay Language Summary:** Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown etiology. Research performed during the last decades has identified a large number of molecular abnormalities present in immune cells from patients with SLE. More recently, the results of genetic association studies have revealed the hereditary factors associated to lupus. As a result, a large number of genes have been identified that are abnormally regulated in SLE patients. However, for the majority of these cases we do not know the link between the genetic factors and the clinical characteristics of the disease. In our lab, we have identified an enzyme called PP2A that is abnormally regulated at the genetic level in patients with SLE. Using an animal mouse model which has higher activity of this enzyme and thus reflects what happens in lupus patients, we have shown that high levels of PP2A can lead to increased susceptibility to target organ damage through facilitating the tissue inflammatory response. My goal is to continue this work. More specifically, I will focus on the mechanisms by which increased activity of the PP2A enzyme promotes inflammation mediated by the immune cells. For this purpose, I will study the immune cell behavior and responses under various conditions and stimuli that resemble inflammatory responses. In the same animal model, I will also study the regulatory mechanisms of the immune system that normally promote homeostasis and prevent inflammation and autoimmunity, as our preliminary studies show that they are also affected in the presence of high PP2A levels. This work will reveal the molecular mechanisms by which PP2A contributes to the pathogenesis and clinical symptoms of lupus, as it will identify the pathways that connect high PP2A with inflammation, abnormal immune regulation and increased target organ damage. As a result, my work will be very important for the Arthritis Foundation mission, because it will answer questions that will provide a better understanding of SLE and other arthritis related diseases, with the goal to lead to the treatment, control and cure of these conditions.

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**Name:** Hildur Hronn Arnardottir, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Novel Resolvin D3 in the Resolution of Inflammation and Murine Arthritis*

**Institution:** Brigham and Women's Hospital

**Supervisor:** Charles N. Serhan, PhD

**Award Period:** July 1, 2013 – June 30, 2015

**Study Section:** Biochemistry

**Disease Focus:** Rheumatoid Arthritis

**Lay Language Summary:** Rheumatoid arthritis is a disabling, chronic inflammatory disease affecting millions of people, causing pain and joint destruction. Today's treatments aim to reduce inflammation, relieve pain and prevent joint damage, however many drugs have potentially serious side effects. Therefore safer, as well as, more cost efficient therapeutic options are needed to treat RA patients. Fish oil, rich in omega-3 polyunsaturated fatty acid, is thought to be beneficial in RA, but its molecular actions in RA remained unclear. My sponsor's laboratory discovered novel bioactive products of EPA and DHA (omega-3 fatty acids found in fish oil), called E and D series resolvins and are produced during resolution phase of inflammation. Resolvins potently reduce inflammation and inflammatory pain in arthritic mice, and are more potent than widely used anti-inflammatory and analgesic drugs used to treat RA. Therefore in this proposal we will identify new therapeutic targets for RA by applying our recent discovery of novel RvD3 in self-resolving inflammation to murine arthritis. Using mouse models of acute inflammation and lipid mediator metabololipidomics we are establishing the complete structure of a novel lipid mediator named RvD3. In work in progress we found that RvD3 has potent anti-inflammatory and proresolving actions. Interestingly RvD3 is produced late during resolving inflammation than other RvD, like RvD1 and RvD2, suggesting it might have a unique role and actions. We believe that dysregulation of RvD3 may explain diseases development in chronic inflammation. Determining the role and actions of RvD3 in arthritis will provide insights into the underlying mechanism of chronic inflammation and may ultimately provide a new therapeutic strategy in RA.

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**Name:** Byron Bento Au-Yeung, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *ZAP-70 inhibition as a therapeutic strategy for treating autoimmunity*

**Institution:** University of California, San Francisco

**Supervisor:** Arthur Weiss, MD, PhD

**Award Period:** July 1, 2011 – June 30, 2014

**Study Section:** Clinical Immunology

**Disease Focus:** Rheumatoid Arthritis

**Lay Language Summary:** A specialized subset of immune cells – T cells – play an important role in immune responses to infection. However, T cells can also initiate unwanted responses to one's own body, resulting in autoimmune disease. Rheumatoid arthritis (RA) is a T cell-dependent autoimmune disease that results from responses coordinated by T cells against joint tissues. Therefore, effective treatment of autoimmunity, including RA, must block or counteract the actions of self-reactive T cells. One strategy for blocking T cell function involves inhibiting the signals within T cells that promote T cell

activation. It is widely accepted that signals initiated by the T cell receptor (TCR) are critical for driving T cell activation. Our lab has extensively studied T cell signaling and in particular, ZAP-70, a protein important for transmitting activating signals from the TCR. We believe that ZAP-70 is an attractive target for autoimmune disease therapies. A major obstacle in testing whether ZAP-70 is a good drug target is the current lack of a specific ZAP-70 inhibitor. To bypass this problem, we have undertaken an unconventional strategy. As opposed to identifying a molecule that blocks the naturally occurring, or wild type (WT) ZAP-70, we introduced a mutation in the mouse ZAP-70, which allows it to fit, and be inhibited by, a known drug. This is a unique system in T cells, where the mutant, or “analog-sensitive” ZAP-70 is functional, but is selectively inhibited by a known inhibitor, called 3-MB-PP1. Additionally, 3-MB-PP1 is able to inhibit analog-sensitive ZAP-70 only, but not WT ZAP-70. We have characterized mouse T cells that bear the analog-sensitive ZAP-70 and found that conventional T cells nearly always require ZAP-70 to become activated. These results suggest that ZAP-70 inhibition could block the activation of self-reactive T cells in RA, and other autoimmune diseases. On the other hand, ZAP-70 activity was not required for the function of regulatory T (Treg) cells, whose specialized role is to suppress self-reactive T cells. These results imply that a ZAP-70 inhibitor could simultaneously dampen the activation of self-reactive conventional T cells, while leaving the function of Treg cells intact, two beneficial features for a potential autoimmune disease treatment. We will test whether ZAP-70 inhibition is effective as a therapy in a mouse model of RA, by treating mice bearing the analog-sensitive ZAP-70, with its inhibitor, 3-MB-PP1 (or similar compounds). Based on our work so far, we expect a ZAP-70 inhibitor will effectively dampen arthritis severity. Continuing these studies, we will analyze the patterns of genes expressed in T cells from mice undergoing ZAP-70 inhibitor treatment. We may find genes that correlate with successful or non-successful disease treatment. These gene patterns may be applied in the future to determine the best course of treatment for individual rheumatoid arthritis patients.

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**Name:** Arnold Hendrik Bakker, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Role of ERAAP polymorphisms in the onset of Ankylosing Spondylitis*

**Institution:** University of California, Berkeley

**Supervisor:** Nilabh Shastri, PhD

**Award Period:** July 1, 2012 – June 30, 2014

**Study Section:** Cellular Immunology

**Disease Focus:** Ankylosing Spondylitis

**Lay Language Summary:** Ankylosing Spondylitis (AS) is a chronic disease of the lower back. The disease causes joint inflammation of the spine and pelvis, ultimately leading to fusion of the spine. The risk of developing AS is mostly determined genetically and the disease affects people worldwide. For almost 40 years it has been known that the molecule HLA-B27 is strongly associated with AS: as many as 95% of patients are HLA-B27-positive. Unfortunately, this knowledge has not led to any major advancements in understanding the mechanism of this disease. The HLA-B27 molecule plays a key role in immunity by alerting the immune system when pathogens have infected a cell. It does this by presenting small pieces of the pathogen, called epitopes, on the surface of the infected cell. Other cells then recognize these epitopes and start an immune response. Recently, genetic studies have indicated another known player in this process, the enzyme called ERAAP, to have a large role in AS as well. ERAAP ensures that the pathogenic epitopes are processed in such a way that they fit properly on HLA-B27 and other related molecules. Several studies have now found point mutations in the gene for ERAAP that are present with

a higher frequency in AS-patients than healthy controls. This could indicate that in patients with AS the function of ERAAP is changed. This change in ERAAP function could then lead to differences in the epitopes for HLA-B27, which in turn could alert the immune system of a pathogen, while in reality there is no actual infection taking place. Ultimately, the immune system will be triggered continuously, leading to chronic inflammation. Since the link with ERAAP and AS has primarily been indicated through genetic studies, it is unclear if the previous explanation is indeed the reason for AS. The project that we propose here specifically aims to test this theory. Using a model cell system set up by our laboratory we will test how the point mutations in ERAAP change the function of this enzyme. We will also investigate how changes in ERAAP can lead to changes in a normal immune response. With these studies, we aim to better understand how HLA-B27 and ERAAP are involved in the chronic inflammatory disease Ankylosing Spondylitis. Additionally, our project will also give us new insights in how the immune system works in general.

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**Name:** Kenneth K.C. Bramwell, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Positional Cloning Implicates Gusb in the Pathogenesis of Lyme Arthritis*

**Institution:** University of Utah

**Supervisor:** Janis J. Weis, PhD

**Award Period:** July 1, 2013 – June 30, 2015

**Study Section:** Genetics

**Disease Focus:** Lyme Disease

**Lay Language Summary:** Lyme Disease is the most common illness that humans contract from insect bites in the United States. Up to six out of ten Lyme Disease patients may develop arthritis, while others may experience only brief flu-like symptoms. This strongly suggests that underlying genetic differences between patients influence susceptibility to the disease. Inbred strains of laboratory mice also exhibit a range of genetic susceptibility to Lyme arthritis. By interbreeding resistant and susceptible mouse strains, we seek to identify the underlying genes responsible for these differences. By identifying such regulatory genes and the inflammatory pathways they are involved in, we hope to discover ways to identify susceptible patients, and to find better treatments for Lyme arthritis and perhaps for other forms of arthritis that share similar pathways. Here, we describe our efforts to find a regulatory gene within a region of the DNA on Chromosome 5 that is most strongly associated with severe disease. We also describe some new strains of mice we have developed through a breeding strategy, which allow us to screen through smaller groups of genes, tens rather than hundreds. Finally, we explain our most recent progress with one gene we have selected for further study, discuss the outcome of several experiments we have already done and our interpretation of what they mean, and propose several new experiments that will help to conclusively determine what role this gene may play in the development and the severity of Lyme arthritis.

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**Name:** Laura Campisi, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *A regulatory population in the Th17 response and its role in autoimmunity*

**Institution:** Mount Sinai School of Medicine

**Supervisor:** Julie Magarian Blander, PhD

**Award Period:** August 1, 2011 – July 31, 2014

**Study Section:** Cellular Immunology

**Disease Focus:** Rheumatoid Arthritis

**Lay Language Summary:** Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that primarily affects multiple joints. A particular cellular subset of the immune system, called TH17 cells, seems to play a key role in the progression of the disease. Such TH17 cells are present in particularly increased numbers in the intestinal tract where the bacterial environment influences their emergence and maintenance. Notably, although the precise mechanisms remain elusive, TH17 cells generated in the gut could also modulate the onset of autoimmune disease like arthritis that are non directly related to this organ. Consistent with this, the gastrointestinal tract in humans has frequently been associated with inflammatory arthritis. Our laboratory has shown that entero-pathogenic bacteria causing cell death and tissue damage in the intestinal tract induce the generation of TH17 cells with both effector and regulatory properties. Here we set forth the hypothesis that within the TH17 cells expanding in the gut following infection, two different populations exist: one producing molecules involved in host defense and killing of pathogenic bacteria, the other producing molecules that modulate the ongoing effector response in order to prevent damage caused by excessive inflammation. We hypothesize that impaired or altered development of protective intestinal TH17 cells could reciprocally serve as a susceptibility factor in arthritis. We will look for these subsets in mice, and we will characterize their functions. We will particularly investigate whether protective populations of TH17 cells in the gut can modulate the incidence and severity of arthritis in a mouse model of arthritis.

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**Name:** Deva Chan, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Directing chondrogenic repair tissue in a novel murine microfracture model*

**Institution:** Rush University Medical Center

**Supervisor:** Anna Plaas, PhD

**Award Period:** July 1, 2013 – June 30, 2015

**Study Section:** Biochemistry

**Disease Focus:** Osteoarthritis

**Lay Language Summary:** Microfracture surgery is a common surgery that is used to help repair damaged articular cartilage. Unfortunately, the repair tissue is a combination of fibrous tissue, which is found in ligaments, and articular cartilage. Because the tissue is fibrocartilage, the repair is a poor substitute for healthy articular cartilage, and almost 25% of microfracture surgeries need further treatments after just two years. I propose that the quality of the repair tissue can be improved by helping to guide the repair towards articular cartilage. First, I will design and examine a microfracture surgery in mice. Next, I will determine when the gene signals that push the repair towards fibrous tissue are highest in normal mice

so that I know when this can be prevented. Then, I can apply certain treatments that act in favor of growing articular cartilage or against the development of fibrous cartilage. I predict that these treatments will help grow cartilage repair tissue that is a better substitute for healthy articular cartilage than a standard microfracture surgery. In the long term, this research will help researchers and doctors develop better ways to repair cartilage and prevent diseases like osteoarthritis.

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**Name:** Romy Christmann, MD, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *TSLP as a critical immune and fibrotic regulator in Systemic Sclerosis*

**Institution:** Boston University

**Supervisor:** Robert A. Lafyatis, MD

**Award Period:** July 1, 2012 – June 30, 2014

**Study Section:** Inflammation

**Disease Focus:** Scleroderma

**Lay Language Summary:** Systemic sclerosis (SSc) is an autoimmune disease, meaning that white blood cells, normally cells that help protect the body from infections, attack and damage organs in the body. In SSc the main organs attacked are the skin and lungs. The cause of the disease is still unknown, although several genes have been shown to be involved, and probably external factors such as virus or bacteria might be involved. Patients with SSc have an increased risk of dying, mainly because of scarring in the lungs. In addition, since the scarring spreads throughout the body, it can be a very debilitating disease. Therefore, finding a potential therapeutic target for this disease is essential. In this proposal we will study an important regulator of white blood cell response in the body, TSLP (Thymic Stromal Lymphopoietin). The body produces TSLP as one of the first responses to triggers, such as virus, bacteria or even traumatic injury. It has already been shown that mice with a lot of TSLP in the skin and the lungs (genetically modified) develop a disease with features similar to SSc and we have found that SSc skin shows a lot of TSLP in white blood cells. To understand how TSLP might lead to fibrosis and inflammation in SSc we will utilize a mouse model that resembles human SSc, by injecting a substance that induces inflammation and fibrosis, (PolyIC), in the skin of mice for 7 days. We will investigate the importance of TSLP in this model by studying mice treated with mice that lack the gene TSLP. As a second strategy to understand the role of TSLP in skin fibrosis, we will inject TSLP itself in mouse skin in order to observe its effects on inflammation and fibrosis, and to clarify whether other mediators are induced by TSLP to mediate or amplify inflammation and fibrosis. The potential of this work is extremely high as currently there is no curative treatment for Scleroderma. Thus, better understanding the role of TSLP, a key molecule in the white blood cells, promises to provide more information about the cause of fibrosis and maybe reveal a possible target for future therapies.

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**Name:** Erika Darrah, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Novel Regulators and Consequences of PAD4 Activation in RA*

**Institution:** Johns Hopkins University

**Supervisor:** Anthony Rosen, MD

**Award Period:** July 1, 2013 – June 30, 2015

**Study Section:** Cell Biology

**Disease Focus:** Rheumatoid Arthritis

**Lay Language Summary:** Under normal circumstances, the body makes antibodies to help prevent the spread of infection by binding to viral or bacterial proteins. In the case of autoimmune diseases, like Rheumatoid Arthritis (RA), the immune system attacks healthy tissue and makes antibodies that bind to proteins normally found in the body. Antibodies in the blood that bind to modified proteins, called citrullinated proteins, are a common laboratory finding in patients with RA and are useful markers for disease diagnosis. Citrullinated proteins are generated by enzymes called PADs. Citrullinated proteins and PAD enzymes are found in cells of the immune system and accumulate in the joints of patients with RA. Recent studies by our laboratory have shown that approximately 12-18% of RA patients have antibodies that bind specifically to one of the PAD enzymes. Interestingly, patients with these antibodies have the most severe RA and are more likely to get worse over the course of a year, compared to individuals without the antibodies. This group of PAD antibodies may be a useful marker to identify people with the highest risk of developing severe disease. Additionally, binding of these antibodies to the PAD enzyme turns the enzyme on and stimulates the generation of larger amounts of citrullinated protein. The antibody may therefore bind to PAD in the same way that other proteins in the cell normally do to turn on PAD activity. By studying what factors help turn the PAD enzyme on under normal circumstances we hope to understand how these processes could be altered in RA. Additionally, we hope to determine if increased amounts of citrullinated proteins are able to directly turn on cells of the immune system to invade and attack the joint. Understanding these processes could lead to the development of new drugs for the treatment of RA.

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**Name:** Grayson DuRaine, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Combinatorial stimuli in cartilage tissue engineering*

**Institution:** University of California, Davis

**Supervisor:** Kyriacos Athanasiou, PhD, PE

**Award Period:** September 1, 2011 – August 3, 2014

**Study Section:** Technologies/Biomechanics

**Disease Focus:** Osteoarthritis

**Lay Language Summary:** Failure of the cartilage in the joints results in pain and a reduction in quality of life. The goal of cartilage tissue engineering is to replace or regenerate these mechanically loaded tissues to restore function to the joint. The long-term goal of this research is to produce tissue engineered articular cartilage for the treatment of arthritis. To produce a replacement for damaged

cartilage, tissue engineering must generate neocartilage with properties similar to native cartilage tissue. Native tissue is tough enough to withstand direct compression, and it features a slippery, low-friction, lubricated surface to ensure slick, painless movement of the joints. Current technologies are focused on making tough cartilage, but methods still need to be developed to make the cartilage slippery. Superficial zone protein (SZP) has been identified as a lubricant present in articular cartilage and the joints. Not only does it make the tissue slippery, SZP also helps to maintain the health of the cartilage during movement. Lack of the SZP lubricant results in damage to the cartilage, and in osteoarthritis animal models decreased levels of SZP have been observed. SZP can be increased by “exercising” the native cartilage using sliding motion. Translating this finding to engineered cartilage, lubrication will be engineered into articular cartilage constructs by using the same specific form of sliding motion to increase the levels of the SZP lubricant. In addition, several chemical and biological factors have been shown to improve engineered cartilage, but, thus far, these have been used independently. This proposal seeks to use these chemical and biological factors in combination to further improve the slipperiness of engineered cartilage. This proposal will address the need for tissue engineered cartilage with clinically relevant mechanical and lubricating properties in three ways; 1) by determining the optimal application time and duration of sliding motion needed to enhance the lubricating properties of engineered cartilage; 2) by identifying the combination of chemical and biological factors that results in the most improved engineered cartilage and, 3) by combining both of these methods to produce engineered cartilage with mechanical properties and lubrication approaching that of the native cartilage in the joint. Aside from generating articular cartilage with clinically relevant mechanical and lubricating properties, the understanding that this proposal yields of how lubrication is regulated will also provide insights into how one might reduce friction in diseased joints.

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**Name:** Alice Huang, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *The Role of Activin in Tendon Development*

**Institution:** Shriners Hospitals for Children - Portland

**Supervisor:** Ronen Schweitzer, PhD

**Award Period:** July 1, 2013 – March 1, 2014

**Study Section:** Technologies/Biomechanics

**Disease Focus:** Osteoarthritis

**Lay Language Summary:** Tendons and ligaments are connective tissues that transmit forces and provide joint stability. Their poor healing results in permanent loss of function following damage from injury or diseases such as arthritis. In patients with rheumatoid arthritis for example, tendon inflammation and ruptures are common. While anti-inflammatory therapies slow disease progression, the damaged tissues do not regenerate and prognosis after surgery remains poor. Injury to tendons/ligaments, such as the anterior cruciate ligament, may also alter joint kinematics and lead to osteoarthritis. Therefore, successful treatment and prevention of arthritic diseases requires a multi-faceted approach that includes the repair of these tissues to restore function. While development of regenerative therapies requires an understanding of the factors that regulate tendon/ligament differentiation and maturation, almost all of these molecules are unknown. One key molecule strongly implicated in the formation and

biology of these tissues is TGF $\beta$ . TGF $\beta$  is essential for establishing the early events of tendon/ligament formation, as deletion of TGF $\beta$  signaling results in an early and complete loss of all tendons and ligaments. Surprisingly, while TGF $\beta$  is detected in tendons at later stages, our preliminary data suggests that TGF $\beta$  signaling alone is not essential for later tendon growth or matrix synthesis. We therefore looked for redundancy with other members of the same family that have been largely overlooked in musculoskeletal development. We found strong indication that Activin signaling may be important during these stages. In this proposal, we therefore test the hypothesis that activin signaling, alone or in tandem with TGF $\beta$  signaling, regulates later aspects of tendon/ligament growth and maturation, including cell recruitment, proliferation and matrix synthesis. In Aim1, we evaluate the role of activin signaling alone in tendon growth and maturation. In Aim2, we assess redundancy between activin and TGF $\beta$  signaling pathways by deleting both receptors. And finally, the purpose of Aim3 is to test the potential use of activin for tendon repair. Using cells derived from wild type and mutant embryos, we will determine the effects of activin on tendon differentiation and proliferation, evaluate TGF $\beta$  and activin signaling pathways, and assess compensation between activin and TGF $\beta$ . The proposed work will determine the full extent of the role played by this particular family of molecules in tendon development and the regulatory and functional interplay between the TGF $\beta$  and activin molecules, thereby opening new avenues for tendon/ligament regenerative therapies and treatment of arthritis.

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**Name:** Wendy Hurd, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Enhancing Outcomes After Shoulder Arthroplasty*

**Institution:** Mayo Clinic

**Supervisor:** Kenton R. Kaufman, PhD, P.E.

**Award Period:** August 1, 2011 – July 30, 2014

**Study Section:** Clinical/Therapeutics/Outcomes

**Disease Focus:** Osteoarthritis

**Lay Language Summary:** The overall goal of this work is identify strategies for enhancement of rehabilitation interventions and ultimately improve outcomes for patients who undergo shoulder arthroplasty. Consistent with this goal, this study will 1) evaluate patient outcomes during the early course of recovery after shoulder arthroplasty, 2) determine which clinical characteristics influence patient function early after shoulder arthroplasty, and 3) distinguish outcomes after shoulder arthroplasty for patients with a primary diagnosis of rheumatoid arthritis versus osteoarthritis. Patient impairment measures include shoulder motion, strength, and pain. Patient function and activity will also be assessed. These measures will be assessed at one, three, six, nine, and twelve months after surgery in a group of patients with a primary diagnosis of osteoarthritis (N=50) and rheumatoid (N=50) arthritis. A group of matched control subjects (N=100) will also be recruited and undergo the same testing procedures once.

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**Name:** Tanisha Jackson, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *The effect of Csk expression on BCR signaling and autoantibody production*

**Institution:** The Feinstein Institute for Medical Research

**Supervisor:** Betty Diamond

**Award Period:** July 1, 2012 – June 30, 2014

**Study Section:** Cellular Immunology

**Disease Focus:** Lupus

**Lay Language Summary:** Systemic lupus erythematosus is an autoimmune disorder that affects the skin, joints, kidneys, brain and other organs. This and other autoimmune disorders are characterized by an immune reaction against one's own tissue and include the presence of specific proteins called antibodies. In this disease, the body's immune system attacks healthy tissues in the body leading to chronic inflammation. The primary cause of lupus is unknown. Immune cells in the body called B cells are activated during a protective immune response; an example is in response to a foreign microbe. These cells play an important role in fighting disease. However, when B cell activity is unregulated, they can produce autoantibodies which attack and cause damage to normal tissues and organs. A cascade of signaling in B cells controls the production of antibodies. Csk (c-src kinase) is a molecule involved in regulating B cell receptor signaling events. Studies of the human genome have allowed scientists to identify lupus susceptibility genes. Variants in genes involved in immune cell signaling have been shown to be directly associated with lupus in both mice and humans. Early studies in our lab have shown an association between CSK gene expression, increased production of auto-antibodies, and altered B cell signaling and development in mice and humans. Our objective in this study is to examine the effect of differential CSK gene expression on B cell signaling. We will analyze the role that CSK may play in immune tolerance, check points in B cell development when autoreactive cells are removed. We have designed experiments to study how CSK contributes to lupus-like autoantibody production in mice during different stages of B cell development. Our goal is to understand how increased CSK expression leads to autoreactivity and apply this knowledge to target CSK expression in B cells as a therapeutic option for lupus.

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**Name:** Shinu John, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Cellular and molecular mechanisms by which TLR9 regulates lupus disease*

**Institution:** Yale University

**Supervisor:** Mark J. Shlomchik, MD, PhD

**Award Period:** July 1, 2011 – June 30, 2014

**Study Section:** Cellular Immunology

**Disease Focus:** Lupus

**Lay Language Summary:** Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE) are autoimmune diseases affecting over one million people in the United States. Normally, the immune system functions to protect against foreign pathogens but in autoimmune disease the immune system erroneously attacks self-tissues. There is increasing evidence that in SLE and RA, the immune

dysregulation occurs mainly in a class of cells known as B cells. The importance of B cells in driving disease pathology is revealed by clinical improvements in RA and SLE patients receiving B cell depletion therapies. Normal B cells function to produce antibodies against foreign pathogens, but in autoimmune diseases B cells are autoreactive, producing antibodies against self components such as RNA and DNA. This occurs due to recognition of RNA and DNA respectively by two similar receptors, TLR7 and TLR9 that are expressed on B cells. Intriguingly, deficiency of TLR7 protects against disease whereas TLR9 deficiency worsens disease in mouse models of lupus. This proposal investigates how and why TLR7 and TLR9 behave differently. Understanding the basic biology of how these receptors function is pivotal for the development of novel and effective therapeutics for autoimmune diseases such as SLE and RA.

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**Name:** [Cheilonda Johnson, MD](#)

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Determinants of Rheumatoid Arthritis Associated Interstitial Lung Disease*

**Institution:** Johns Hopkins University

**Supervisor:** Sonye K. Danoff, MD, PhD

**Award Period:** July 1, 2013 – June 30, 2015

**Study Section:** Clinical/Therapeutics/Outcomes

**Disease Focus:** Rheumatoid Arthritis

**Lay Language Summary:** The proposed project will address significant limitations in the treatment of rheumatoid arthritis associated interstitial lung disease (RA-ILD). Rheumatoid arthritis (RA) is a condition that causes pain, swelling and stiffness in the joints. RA can also affect other parts of the body including the lungs. Interstitial lung disease (ILD) causes inflammation and scarring of the lining of the lung air sacs and is a major cause of death in patients with RA. Unfortunately, doctors cannot predict which patients with RA will develop ILD or how severe their lung disease will be. Furthermore, there are currently no effective therapies for RA-ILD. The lack of reliable tests and treatment is due in part to little information on how RA-ILD progresses over time. Our research team has access to three years of detailed information from approximately 200 patients with RA. We plan to use that information to identify risk factors that doctors can use to predict which patients develop RA-ILD and whether their disease will worsen over time. We believe that this study will increase our understanding of this serious complication of RA and will be a first step in finding effective treatments for RA-ILD.

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**Name:** [Byung-Seok Kim, PhD](#)

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *The role of ROR $\gamma$ t in Treg cells in the regulation of autoimmune arthritis*

**Institution:** University of Texas M.D. Anderson Cancer Center

**Supervisor:** Chen Dong, PhD

**Award Period:** July 1, 2013 – June 30, 2015

**Study Section:** Cellular Immunology

**Disease Focus:** Rheumatoid Arthritis

**Lay Language Summary:** Rheumatoid arthritis (RA) is an autoimmune disease characterized by a chronic inflammation in the joint and the subsequent destruction of cartilage and bone. The importance of IL-

17-producing T cells (Th17 cells) in the development of RA has been proven in the collagen-induced arthritis (CIA), an animal model of RA, by demonstrating that antibody-mediated neutralization of IL-17 could ameliorate the severity of the disease. From this point of view, anti-IL-17 antibody, which can block the action of IL-17 in the joint of RA patient, is currently being tested for the treatment of RA in clinical trials. Foxp3-expressing regulatory T cells (Treg cells) are another important player in the pathogenesis of RA. Depletion of Treg cells before the induction of CIA led to the increased severity of the disease. On the other hand, transfer of Treg cells ameliorated the disease in CIA. These results suggest that Treg cells can be a promising target for the treatment of RA. Here, I will clarify whether ROR $\gamma$ t, a Th17 cell-specific transcription factor, expression in Treg cells is important for the regulation of Th17 cells and the subsequent development of the autoimmune arthritis in mouse CIA model. This study will provide new insights for the development of a safe, but effective Treg cell-targeted tolerogenic immunotherapy against autoimmune arthritis.

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**Name:** Jennifer King, MD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *A Protective Role of Tissue-Resident Dendritic Cells in Autoimmunity*

**Institution:** University of California, Los Angeles

**Supervisor:** Ram Raj Singh, MD, FACP, FACR, FASN

**Award Period:** August 1, 2011 – July 31, 2014

**Study Section:** Cellular Immunology

**Disease Focus:** Lupus

**Lay Language Summary:** Dendritic cells (DCs) have long been coined the “sentinels” of the immune system, and have the potent ability to initiate or silence an immune response. In the setting of bacteria or viruses, DCs activate the adaptive immune system (i.e. lymphocytes) to attack and destroy invaders. However, in autoimmune diseases, some DCs can also aberrantly activate the immune system to attack itself, thus initiating the cascade of autoimmunity. Recent research has shown that DCs are a heterogeneous group of immune cells. Some of these DCs circulate in blood and are considered to promote the development of diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). There is another population of DCs that normally resides in tissues (i.e. skin), although these have been less well studied than blood DCs in autoimmune states. Guided by a novel discovery from our laboratory, my Project explores and proposes a previously undemonstrated protective role for tissue-specific DCs in autoimmune diseases. Our lab recently discovered that DCs that originate in the skin tissue were markedly reduced in the skin-draining lymph nodes of lupus animals that develop inflammation in almost every organ including skin, kidneys, joints and others. (Eriksson AU, 2008). Using this model of SLE, our lab reported that the paucity of skin-derived DC in lymph nodes of lupus mice was due to a defect in their capacity to migrate properly. This finding is important because in non-autoimmune conditions, DCs are believed to migrate at a low, constant rate from tissues to tissue-draining lymph nodes and signal the body to prevent the immune system from attacking itself. Thus, paucity of skin-derived DCs in the lymph nodes of autoimmune-prone animals might interfere with this signaling process, thus potentially leading to disease. These observations led me to propose that tissue-resident DCs (in contrast to the blood DC subsets) may play a protective role in autoimmune states, and

hence, when impaired (i.e. migration) can no longer protect against prevention of autoimmune organ disease. Using skin DCs (Langerhans cells – LCs) as a representative of tissue DCs, I will use a genetically altered ('knock-in') mouse model that will allow me to deplete LCs at various time points and examine subsequent clinical and immune effects. Based on my observations, I hypothesize that: a) LCs play a protective role against the development of tissue-specific (i.e. skin) autoimmunity in lupus prone mice, and b) LCs modulate the balance of regulatory ("good") or immunogenic ("bad") cells that determine the balance between prevention or onset of autoimmune disease. My research aims to shed light on the basic mechanisms of tissue/organ autoimmunity, and to translate these animal findings to human relevance using human tissue samples. Our project's ultimate goal is to promote discovery of new therapeutic strategies for autoimmune diseases.

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**Name:** Lick Pui Lai, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Identifying gene regulatory networks of chondrocyte development program*

**Institution:** University of Southern California

**Supervisor:** Andrew P. McMahon, PhD

**Award Period:** July 1, 2011 – June 30, 2014

**Study Section:** Molecular Biology and Genetics

**Disease Focus:** Osteoarthritis

**Lay Language Summary:** One of the key questions that developmental biologists strive to answer is how a single cell can initially divide, and then differentiate into different cell types, which ultimately form distinct tissues and organs. The journey that a cell takes is influenced by multiple factors. These factors change the gene expression profile of a cell, and as a result change the cell identity. During bone development, two key biosynthetic cell types are responsible for the generation of skeletal elements: cartilage-secreting chondrocytes and bone-secreting osteoblasts. Both cell types arise from a common mesenchymal progenitor cell type. Sox9 is one of the key factors that are required for the chondrocyte development commitment as well as maintaining the chondrocyte identity. Sox9 is a transcription factor, which by directly binding to multiple gene regulatory elements on DNA, regulates the gene expression profile of the cell. The aim of this project is to perform a genome-wide mapping of the interactions between Sox9 and the gene regulatory elements on DNA, and as a result identify all the genes that are regulated by Sox9 in chondrocytes. By building the Sox9 regulatory network in chondrocytes, we will have a better understanding of 1) how Sox9 can commit a naïve progenitor cell to the chondrocyte program; 2) how Sox9 is required for chondrocytes to maintain their identity and 3) identify other factors that mediate the effects of Sox9. Understanding how Sox9 initiates the chondrocyte development program is of great importance to regenerative medicine of permanent cartilage. During the disease state of osteoarthritis, chondrocytes change their cell identity and subsequently causes degradation of the surrounding cartilage matrix. Understanding how the chondrocyte identity is being maintained by Sox9 also facilitates the logical development of treatment options for osteoarthritis. In addition, our findings provide a more complete understanding of critical regulatory processes during chondrocyte development, and this will no doubt facilitate the logical development of treatment options for skeletal-based or skeletal-related diseases.

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**Name:** Erica Freem Lawson, MD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Transition to Independence: Optimizing Outcomes in Childhood-onset Lupus*

**Institution:** University of California, San Francisco

**Supervisor:** Edward Yelin, PhD

**Award Period:** July 1, 2013 – June 30, 2015

**Study Section:** Clinical/Therapeutics/Outcomes

**Disease Focus:** Juvenile Arthritis

**Lay Language Summary:** In the past, few children diagnosed with systemic lupus erythematosus (“lupus”) survived into adulthood. However, over the past 50 years advances in diagnosis and treatment have greatly improved survival rates, and most children diagnosed with lupus will survive into adulthood. While some research has already been done to describe the health of adults with childhood-onset lupus, we have very little information about how successfully and independently these patients are able to function as adults. This research project is designed to help us better understand how well people who were diagnosed with lupus in childhood are able to function as independent adults. We plan to describe how often these adults are able to find and keep a job, whether they are able to complete the important physical tasks of daily life, and how well they function mentally and emotionally. We also seek to understand the influence of race, ethnicity, education, income, and lupus severity on employment, physical function, and emotional function. Describing the ability of patients with childhood-onset lupus to function independently in adulthood is an important first step towards minimizing problems that begin when patients transition from childhood to adulthood. For example, putting programs in place to help provide a smooth transition from pediatric to adult doctors during the late teens and early 20s may help patients to improve their health during their college years, allowing them to complete their education and prepare for their future career. If people with childhood-onset lupus have difficulty finding jobs, career support programs may help them to successfully transition into the working world. While work has been done to describe the health of adults with childhood-onset lupus, we still know very little about their ability to function in the working world, and how racial or economic disparities may affect their ability to work. This study will be an important first step towards helping children with lupus not only survive into adulthood, but thrive.

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**Name:** Sin-Ae, Lee, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *CD98 in experimental psoriasis*

**Institution:** University of California, San Diego

**Supervisor:** Mark H. Ginsberg, MD

**Award Period:** July 1, 2011 – June 30, 2014

**Study Section:** Cellular Immunology

**Disease Focus:** Psoriatic Arthritis

**Lay Language Summary:** Psoriasis is a common autoimmune disease of the skin characterized by itchy, thick, red, inflamed plaques with silvery scales, affecting 2-3% of world’s population. In addition, one of five patients develops psoriatic arthritis. Although psoriasis is not fatal, it affects patients’ health-related

quality of life and results in a significant financial burden. Although the aberrant function of T lymphocytes has been proposed as a potential cause of psoriasis based on several lines of evidence, the precise pathogenesis remains unclear. However, over the last decade, genetically manipulated mice have been generated with epidermal expression of molecules shown to be elevated in psoriatic lesions. Many of these models have exhibited various aspects of psoriasis including epidermal hyperplasia with immune cells infiltrates. These evidences support the possibility that epidermal alterations are sufficient to initiate both skin lesions in psoriasis. Here, I focus on CD98 heavy chain (CD98hc, also known as 4F2hc antigen), a T cell activation antigen that the mentor's lab has shown is an important player in adaptive immunity in B cells. CD98hc is highly expressed in activated T cells, B cells, and in other proliferating cells. In addition, my preliminary data shows that CD98hc expressing keratinocytes are abundant in human psoriatic skin lesions. However, CD98hc's function in epidermal keratinocyte in psoriasis has not been reported. During last 2 years fellowship program, I found that that the CD98hc in the epidermal keratinocytes triggers chemokine/cytokine expression, which recruits neutrophils and macrophages to the epidermis thereby contributing to the phenotypic changes observed in psoriasis. In the final year of my fellowship, I will elucidate the mechanism by which CD98hc blocks experimental psoriasis. There is interest in developing anti-CD98 agents for cancer therapy; hence, a better understanding of the role of CD98hc in the development of psoriasis will allow the development of CD98hc targeted therapeutics to combat this disease.

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**Name:** Yiu Tak Leung, MD, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *IRF influences on the Epigenetic Landscape in SLE*

**Institution:** University of Pennsylvania

**Supervisor:** Kathleen E. Sullivan, MD, PhD

**Award Period:** July 1, 2013 – June 30, 2015

**Study Section:** Molecular Biology and Gene Regulation

**Disease Focus:** Lupus

**Lay Language Summary:** The immune system is an intricate defense network that protects the body against foreign pathogens. A fundamental task of the immune system is the capability to distinguish between foreign invaders and self. When a dysfunctioning immune system loses this critical ability, the body's own tissues are attacked by its defense system: a friendly-fire process known as autoimmunity. Systemic lupus erythematosus (lupus) is a quintessential autoimmune disease where multiple organs in the body are damaged by antibodies that the body produces against itself. Lupus affects an estimated 1.5 million people in the US and 5 million people worldwide. Like other complex diseases, lupus arises from a combination of genetic predisposition and environmental factors, though the exact cause is unknown. Epigenetics is a study of the changes to gene activity without changing the genetic code and may provide this link between nature and nurture. Epigenetics literally means "on top of or in addition to genetics". Exploration of epigenetic mechanisms may explain why identical DNA sequences can be turned into different phenotypes on both cellular and organism levels – for example, why do most identical twins not develop the same disease? Epigenetic modifications alter the availability of the DNA code to be read, thereby repressing or enhancing the actions of genes. We believe that the disease process in lupus creates changes to the epigenetic mechanisms. We previously showed that a type of

epigenetic modification, histone H4 acetylation(H4ac) is increased in the lupus monocytes, a subpopulation of white blood cells. It was also found that most of the genes with increased H4ac had potential association with a protein called IRF (interferon regulatory factor) 1. We propose to investigate the interactions between IRFs and epigenetic modification in patients with lupus as a step towards developing new targeted therapies.

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**Name:** Vladimir M. Liarski, MD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Pathogenesis of Tubulointerstitial inflammation in Human Lupus Nephritis*

**Institution:** University of Chicago

**Supervisor:** Marcus R. Clark, MD

**Award Period:** July 1, 2011 – June 30, 2014

**Study Section:** Clinical Immunology

**Disease Focus:** Lupus

**Lay Language Summary:** Role of inflammation in Human Lupus Nephritis Systemic lupus erythematosus (SLE) is a chronic autoimmune disease, in which the immune response is misdirected at normal tissues and sites of the body. One of the most frequently and severely affected sites are the kidneys, in a process termed nephritis. Previous studies and current ways of classifying SLE are aimed at studying a portion of the kidney responsible for filtering the blood, termed the glomerulus. Our observations have indicated that the portion known as the kidney interstitium, comprised of tubules and connective tissue, is also involved in this process and is at least equally important in the damaging the kidneys. Our preliminary investigations have shown that multiple inflammatory cells are arranged within the kidney interstitium and appear similar to other sites of organ inflammation in related autoimmune disease. We aim to confirm these findings and explore the ways in which this inflammation begins and how it alters the course of disease in human patients. We are also interested in examining the factors that predict which patients are at risk of this process.

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**Name:** Robert Michael Lowe, MD, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Epigenetic Regulation of CD154 Gene expression in Lupus*

**Institution:** University of Alabama at Birmingham

**Supervisor:** Rand Cron, MD, Ph.D

**Award Period:** October 1, 2012 – September 30, 2014

**Study Section:** Molecular Immunology

**Disease Focus:** Lupus

**Lay Language Summary:** Systemic lupus erythematosus (SLE) is a devastating autoimmune disease affecting approximately 1 in 2,000 women worldwide. There are many genes that are suspected to play a role in the development of lupus. CD154 is a key protein on the surface of certain white blood cells. In many patients with lupus, there is an abnormal increased amount of this protein that we believe could play a role in the development of their disease. There are many studies that have been performed looking for genetic changes or mutations in certain genes involved in controlling the immune system.

However, it has become clear that there are changes in immune system genes as well as other genes that are not mutations or changes in the genetic code that can greatly affect how well these genes function, called epigenetic changes. Based on prior research studies, we feel that epigenetic changes in the CD154 gene in patients with lupus may play an important role in the development of disease. In order to develop new therapies for lupus, we will need to understand if these epigenetic changes are present in patients with lupus compared to healthy individuals. The focus of my research is to identify how epigenetic changes in a particularly important immune gene, CD154, may influence the development of lupus in patients. We plan to obtain blood samples from patients with lupus and healthy individuals and compare whether the epigenetic changes present in their white blood cells leads to an abnormally increased amount of CD154 protein to be made.

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**Name:** Brandon Markway, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Optimizing Bioresponsive Hydrogels for Stem Cell-based Cartilage Repair*

**Institution:** Oregon Health & Science University

**Supervisor:** Brian Johnstone, PhD

**Award Period:** July 1, 2011 – June 30, 2014

**Study Section:** Technologies/Biomechanics

**Disease Focus:** Osteoarthritis

**Lay Language Summary:** Articular cartilage, the tissue covering the ends of bones, functions primarily to provide a smooth surface resistant to the regular compressive forces present in joints. Damages to the articular cartilage surface often occur as a result of mechanical trauma and this tissue lacks the ability to repair itself once damaged. This has led many researchers to seek ways to produce cartilage implants by tissue engineering strategies – using a mixture of cells and synthetic materials to develop tissue appropriate for repair. There are many unresolved issues related to the development of tissue engineered implants for articular cartilage repair. Presenting an even greater challenge than isolated trauma for tissue engineers are the disease conditions of osteoarthritis and rheumatoid arthritis. A significant obstacle to the use of tissue engineered cartilage implants in these chronic joint diseases is the associated inflammatory environment that promotes destruction of the tissue. Developing cartilage implants that consider the difficulties inherent in repair of joints in these diseases will have the greatest potential for broad use in articular cartilage regeneration. An important issue to consider for all cartilage repair strategies is which cells to use. Chondrocytes, the cells that make up cartilage tissue, are a logical choice but the extra surgery required to retrieve the cells may cause damage at the donor site resulting in problems later in life. Laboratory studies of mesenchymal stem cells (MSCs) found in bone marrow give hope that these cells may one day be used to create high-quality replacement cartilage. Furthermore, due to their anti-inflammatory potential, MSCs are considered a promising source for cellular repair in arthritic diseases. We have proposed a method to use MSCs for generating cartilage implants using a synthetic material to support the cells as they transform into cartilage. This material has been designed to degrade as the cells take on properties of cartilage, allowing the cartilage tissue formed to replace the synthetic material. We have also proposed to develop the implants in a low oxygen environment, similar to oxygen levels present in native cartilage and bone marrow and much lower than normal laboratory cell culture conditions. There is evidence that this type of environment is beneficial for growing cartilage and we believe it will also help form stronger implants more resistant to breakdown caused by the inflammatory factors prevalent in arthritic diseases. These novel implants

have the potential to be developed into a clinical application for the regeneration of articular cartilage and we believe the outlined studies will provide valuable insight into some of the unresolved issues surrounding tissue engineering for arthritic diseases.

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**Name:** Wenzhao Meng, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Antibody heavy chain selection in systemic autoimmunity*

**Institution:** University of Pennsylvania

**Supervisor:** Eline T. Luning Prak, MD, PhD

**Award Period:** July 1, 2011 – June 30, 2014

**Study Section:** Molecular Immunology

**Disease Focus:** Lupus

**Lay Language Summary:** B cells play a central role in the pathogenesis of systemic lupus erythematosus (SLE), a disease in which patients are frequently afflicted with arthritis. Patients with SLE exhibit altered antibody heavy (H) chain variable region gene (VH) usage and selection, in which some autoantibodies express specific VH genes. To gain insight into the mechanism of autoantibody regulation in SLE, we have developed a PCR-based assay that evaluates the selection of individual VH genes by measuring the fraction of their rearrangements that are in-frame (IF) in B cell genomic DNA. We have observed that the IF fractions of different VH genes differ, ranging from less than 10% to approximately 90%. We propose that VH genes with low IF fractions are more likely to form autoreactive or multireactive antibodies and that abnormal selection of individual VH predisposes to the future development of autoimmunity. To test this hypothesis, we will characterize the specificity, timing of IF fraction establishment and individual VH selection in normal and autoimmune-prone mice. We will first determine if low IF VHs are more likely to encode autoantibodies by cloning and expressing germline VH genes from 3 low IF VHs compared to 3 high IF VHs in combination with either a non-editor light (L) chain (Vk4) or an editor L chain (Vk21D) followed by evaluation of the antibody binding specificity. Next, we will determine if BCR (B cell receptor) or pre-BCR selection contributes to differences in the IF fraction in normal mice. To evaluate VH selection at the pre-BCR stage, we will establish bone marrow stromal cell cultures to determine if B cells that undergo the most rounds of cell division most frequently harbor the highest IF fraction VHs, and if the VH usage shifts in the presence vs. absence of galectin 1, a candidate pre-BCR ligand. To evaluate VH selection in vivo at and beyond the pre-BCR selection stage, we will measure the VH IF fraction at different stages of B cell development and use VH-specific quantitative PCR assays to determine if the frequencies of low IF VHs are increased amongst lambda+ (highly receptor edited) compared to kappa+ B cells or are found at increased frequencies in compartments where autoreactive B cells are sometimes sequestered: B-1a, B-1b or marginal zone B cell subsets. Finally, we will test our hypothesis that low IF VH genes exhibit relaxed selection in autoimmune-prone mice and that the abnormalities in selection precede disease onset by evaluating the manner of VH selection in autoimmune-prone mice of B6.Sle123. We will also evaluate the IF fraction in different B cell subsets in the autoimmune mice to determine the ontogenic timing of the establishment of the IF and to determine if low IF VHs reside in a broader distribution of B cell subsets compared to wild type mice.

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**Name:** Rachel Elizabeth Miller, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *MCP-1/CCR2 Signaling in the Maintenance of OA Pathology and Associated Pain*

**Institution:** Rush University Medical Center

**Supervisor:** Anne-Marie Malfait, MD, Ph.D

**Award Period:** July 1, 2012 – June 30, 2014

**Study Section:** Biochemistry

**Disease Focus:** Osteoarthritis

**Lay Language Summary:** Osteoarthritis (OA) is the most common joint disorder, and pain is its major symptom. Available therapies can alleviate mild-to-moderate pain in OA, but relief from severe chronic OA pain remains an unmet medical need and a major reason for seeking surgical intervention. In spite of its major impact on quality of life and health care management, our understanding of the mechanisms of pain in OA remains very poor. We study joint pathology in a surgical mouse model of knee osteoarthritis and analyze associated pain behaviors. We now propose to examine cellular and molecular mechanisms in this model. Specifically, we will focus on the role of chemokine signaling. In addition, we will test small molecule inhibitors of this chemokine signaling to examine if it is possible to inhibit chronic pain in this model. We propose that our observations will have the potential to be translated into new therapeutic advances for treating the disease.

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**Name:** Oscar R. Miranda, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Inflammation Responsive Hydrogels for Treatment of Inflammatory Arthritis*

**Institution:** Brigham and Women's Hospital

**Supervisor:** Jeffrey Karp, Ph.D

**Award Period:** July 1, 2012 – June 30, 2014

**Study Section:** Inflammation

**Disease Focus:** Rheumatoid Arthritis

**Lay Language Summary:** One of the hallmarks of inflammatory arthritis, for example, is its variable disease activity consisting of exacerbations of inflammation punctuated by periods of remission. This presents significant challenges for matching localized drug delivery with disease activity. Drug encapsulated self-assembled nanofibrous hydrogels that could release drugs in response to arthritic inflammation (proteolytic enzymes) in an on-demand manner is new paradigm in treatment of proteolytic inflammatory diseases. We are developing a potentially new way to treat arthritis. In this novel approach, drug encapsulated hydrogels will be injected into the joints that can serve as drug depots. These gels do not degrade in healthy joints, however, when inflammation occurs that trigger the release of drug to reduce inflammation at early stage. Hence, this novel-on-demand drug delivery will enable us to reduce the number of injections that require for efficient treatment of arthritis.

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**Name:** Devyani Misra, MD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Understanding Mortality in Knee Osteoarthritis*

**Institution:** Boston University

**Supervisor:** David T. Felson, MD

**Award Period:** July 1, 2012 – June 30, 2014

**Study Section:** Clinical/Therapeutics/Outcomes

**Disease Focus:** Osteoarthritis

**Lay Language Summary:** Knee Osteoarthritis (OA), a common joint condition affecting older adults, results in significant problems due to pain, limitation in performing certain activities, and disability. As the population is aging, number of people with knee OA is rising and so are its consequences. Thus, it is important to study the overall impact of knee OA, beyond what is known so far. An area that has not been studied widely to date is the risk of death related to having knee OA. The few studies that have looked into risk of death in knee OA have limitations due to study design and statistical issues. In the face of rising numbers of people with knee OA, this knowledge gap needs to be addressed. How knee OA can increase risk for death? One mechanism might be due to a condition in elders known as frailty. Older adults with frailty have weakness, weight loss and are unable to perform certain activities (similar to knee OA) and are at risk for bad outcomes, including death. Although not known, it is possible that those with knee OA who are also frail are at greater risk for dying. Another possible mechanism might be through physical inactivity. People with knee OA often have pain and are unable to do certain activities, which might lead them to become physically inactive, which in itself increases risk for death. Additionally, those who are physically inactive may become overweight and that can lead to many medical problems including heart disease and even death. Even though problems associated with knee OA such as pain and limitation in function are well-recognized, because of lack of good treatment, knee replacement surgery remains the definitive treatment option for knee OA. Knee replacement is a relatively safe operation and is associated with improvement in pain and function in the majority of people. Whether such improvements can also make a person more active and thereby lose weight, thus lowering their risk for heart disease and even death is not known but possible. However, studies have not yet evaluated whether knee replacement lowers the risk of death. Thus, we propose to address these questions by studying: 1) The relation of knee OA to risk of death due to all causes, heart disease and death due to heart disease; 2) The relation of knee replacement with risk of death. We will study the association of knee OA with risk of death and heart disease in the Framingham Osteoarthritis Study, where information regarding knee OA, frailty, physical activity, heart disease and death are recorded. We will study the possible lower risk of death related to knee replacement in The Health Improvement Network (THIN), which is a dataset in which information is recorded by general practitioners in the United Kingdom as part of regular patient visits but have been anonymized for research purpose. This dataset has information regarding knee OA, knee replacement, death, and other important factors that need to be considered for our in our study.

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**Name:** Johannes Nowatzky, MD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Monoclonal Treg cell transfer-based Immunotherapy for Behcet's Disease*

**Institution:** New York University School of Medicine

**Supervisor:** Nina Bhardwaj, MD, PhD

**Award Period:** July 1, 2011 – June 30, 2014

**Study Section:** Cellular Immunology

**Disease Focus:** Lupus

**Lay Language Summary:** Lupus (Systemic Lupus Erythematosus = SLE) is a sometimes devastating disease affecting several hundreds of thousands of people in the US. Lupus is characterized as an “autoimmune disease”, indicating that the human body erroneously directs the potential of its own immune system – normally used to fight off infection and cancer – to itself, thus causing damage in various organs. The exact mechanisms underlying this disorder remain unclear and are the subject of ongoing, intense research. Within the group of “rheumatic” diseases, such as osteoarthritis, gout or rheumatoid arthritis, lupus is a disease that attracts the attention of many researchers – not only for its obvious and potentially debilitating effects, but also because understanding this “typical” autoimmune disease may form the basis for understanding and treating other rheumatic diseases, which could improve the lives of millions. Today, treating lupus remains a challenge, and a cure is not in sight. While drugs that suppress the immune system, such as steroids and Cyclophosphamide, have been life-saving for many patients with lupus, their use comes at the high price of sometimes severe side effects that can cause serious problems and even reduce the life expectancy of patients with lupus. Our laboratory at NYU is an international leader in the research and generation of modern forms of treatment that “teach” the immune system to “see the right thing”. By manipulating the behavior of certain immune cells, called “dendritic” cells, we have found strategies to program those to fight viruses, such as HIV, or cancer cells. We have successfully administered more than 200 such vaccines to patients with melanoma, a deadly form of skin cancer, here at NYU. Recently, we have started to program cells to “tolerate” certain molecules in the human body that would otherwise be attacked by immune cells in diseases such as lupus and cause symptoms and findings. Much remains to be learned before we can adopt our first findings to the treatment of humans, however. This study will help find strategies to influence the behavior of dendritic cells in ways that support other, “protective” immune cells, called T-regulatory cells, and limits the actions of a newly-discovered type of “aggressive” cells, called Th17 cells, which have recently been shown to contribute to the organ damage caused in lupus and other diseases. If effective, such a form of treatment could avoid many of the serious side effects of conventional treatment for lupus.

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**Name:** Simanta Pathak, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *A novel gene for receptor revision in mature B-cells*

**Institution:** University of Houston

**Supervisor:** Chandra Mohan, MD, Ph.D

**Award Period:** July 1, 2011 – June 30, 2014

**Study Section:** Cellular Immunology

**Disease Focus:** Lupus

**Lay Language Summary:** Systemic Lupus Erythematosus (SLE) is an autoimmune disease in which our body's immune system can't differentiate between foreign and the body's own components and end up attacking body's own components. B-cells are a group of immune cells specialized to produce antibodies. Therefore, B-cells play an important role in the development of lupus. B-cells possess receptors (called B cell receptor or BCR) on their cell surface which can specifically bind to various substances (called antigen). BCR on normal mature B-cells bind only to foreign antigens and not to body's own antigens. Therefore normal B cells can discriminate between self and non-self antigens and attack only the non-self antigens by producing antibody against them. In Lupus, the B-cells lose their capacity to discriminate between self and non-self antigens. This is largely because the BCR on some of the B-cells of the Lupus patients cannot discriminate between self and non-self and therefore binds body's own (or self) antigens. In a normal individual, the immune system has stringent measures through which B-cells with BCR that can bind body's own antigens are eliminated from the system. One such measure is called receptor editing by which the immature B-cells (in bone marrow) that possess a self-antigen try to repair their BCR. A similar mechanism exists in case of mature B-cells and is termed receptor revision by which mature B cells can change the specificity of their BCR for the antigen that they bind to. Sle2z is a segment of mouse chromosome that has been reported to be associated with lupus in mouse. This chromosomal segment (also called locus) is responsible for high level of antibodies in serum that are capable of binding to various antigens, many of which are body's own antigens (also termed as polyclonal and polyreactive antibodies). However, it is not known what gene(s) in the Sle2z locus is responsible for increased polyclonal and polyreactive antibody levels caused by the Sle2z locus. Answer to these unresolved questions may contribute to our knowledge about the mechanism of development of lupus in human, given that mice with Sle2z exhibit the same immunological phenomenon seen in patients with lupus.

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**Name:** Rahul Devdas Pawar, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *The role of Neutrophil Gelatinase Associated Lipocalin in Lupus Nephritis*

**Institution:** Albert Einstein College of Medicine of Yeshiva University

**Supervisor:** Chaim Putterman, MD

**Award Period:** July 1, 2011 – June 30, 2014

**Study Section:** Clinical Immunology

**Disease Focus:** Lupus

**Lay Language Summary:** Many lupus patients have kidney involvement in the form of inflammation, otherwise known as lupus nephritis. While we know that antibodies against DNA are important in lupus nephritis, how they induce kidney damage is not yet clear. Previously, we had found that anti-DNA antibodies can induce kidney cells to secrete a protein called NGAL. We propose to study if high levels of NGAL are instrumental in the kidney damage that is occurring. We will also investigate if serum or urine NGAL levels can be helpful as diagnostic markers for lupus nephritis.

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**Name:** Yu Qiao, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Epigenetic regulation of inflammatory gene expression in human macrophages*

**Institution:** Hospital for Special Surgery

**Supervisor:** Lionel Ivashkiv, MD

**Award Period:** October 1, 2012 – September 30, 2014

**Study Section:** Molecular Biology and Gene Regulation

**Disease Focus:** Rheumatoid Arthritis

**Lay Language Summary:** Macrophages are cells that play important roles in promoting inflammation in diseases such as rheumatoid arthritis (RA). Macrophages produce pathogenic cytokines such as TNF and IL-6, and treatments that block TNF and IL-6 have been very successful in treatment of RA patients. We are interested in understanding how the genes that encode pathogenic cytokines such as TNF and IL-6 are regulated. We propose to investigate new mechanisms that regulate the expression of these genes at the level of epigenetics, namely regulation of proteins that bind to and regulate DNA and responses of genes to environmental factors. Increased understanding of these epigenetic mechanisms can contribute to development of new treatments for RA that would be safer and more effective.

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**Name:** Maury Raycroft, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *A Novel Mechanism of Antigen Trafficking in Autoimmunity*

**Institution:** Yale University

**Supervisor:** Mark Mamula, Ph.D

**Award Period:** July 1, 2012 – June 30, 2014

**Study Section:** Cellular Immunology

**Disease Focus:** Rheumatoid Arthritis

**Lay Language Summary:** We have determined that B cell antigen presentation and trafficking to other cell types is mediated by scavenger receptor A (SR-A). We have mouse data that suggests that this mechanism can be an important initiator of autoimmunity in RA and SLE. Recently, we have identified several novel small molecule inhibitors of SR-A, and we would like to evaluate these drugs in RA and SLE systems. Evidence suggests that SR-A links together important aspects of innate and adaptive immunity, and we will identify new targets for human therapeutics in these studies.

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**Name:** MeganElise Ruitter, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Ethnic Differences in Osteoarthritis Pain and Sleep*

**Institution:** University of Alabama at Birmingham

**Supervisor:** Laurence Bradley

**Award Period:** July 1, 2013 – April 30, 2014

**Study Section:** Clinical/Therapeutics/Outcomes

**Disease Focus:** Osteoarthritis

**Lay Language Summary:** Knee osteoarthritis is highly prevalent amongst middle-aged to older adults and it contributes to poor physical functioning, significant pain and sleep problems. Multiple studies and our own preliminary data show that ethnic minorities, particularly African Americans, exhibit poorer outcomes in all these health domains than non-Hispanic whites. However, the biological, behavioral, and social influences that may contribute to the presence of these ethnic differences are largely unknown. Knowledge of these influences would allow for the development of treatments that may benefit African Americans. Previous studies suggest that ethnic differences in perceived discrimination, ethnic identity, overnight sleep recording values, sleep-related behaviors, and pain sensitivity all may help explain why there are ethnic disparities in clinical pain, physical functioning, and disability status among patients with knee osteoarthritis. Therefore we plan to measure all of these indicators to see if they can explain ethnic disparities in health outcomes amongst a sample of African American and non-Hispanic white adults aged 45 to 80 years old with knee osteoarthritis. We predict that African Americans will display worse osteoarthritis-related pain, physical functioning, disability status, and sleep disturbance outcomes than non-Hispanic whites at the time of recruitment and over a six month time interval. We also predict that these ethnic differences in health outcomes will be explained by the previously mentioned indicators.

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**Name:** [Johannah Sanchez-Adams, PhD](#)

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *The Role of Collagen Type VI in Chondrocyte Mechanotransduction*

**Institution:** Duke University

**Supervisor:** Farshid Guilak, Ph.D

**Award Period:** July 1, 2012 – June 30, 2014

**Study Section:** Technologies/Biomechanics

**Disease Focus:** Osteoarthritis

**Lay Language Summary:** Osteoarthritis (OA) is a degenerative disease characterized by cartilage breakdown in articulating joints such as the knee. Though it affects millions of people, treatments are limited because the causes of OA are not well understood. Current research is targeting the role of cartilage cells (chondrocytes) in maintaining normal cartilage to improve our understanding of the factors that regulate the incidence of OA. Among these factors, the chondrocyte microenvironment, or pericellular matrix (PCM), is considered an important transducer of mechanical and chemical signals that can stimulate cartilage cells to repair or remodel the tissue, which may be an essential part of normal functioning that is lost in the progression of OA. A main component of the PCM in articular cartilage is collagen type VI, a molecule that binds both to the cell membrane and the surrounding tissue matrix. Recent evidence suggests that collagen type VI plays an integral role in normal cartilage development, as mice lacking the gene for collagen type VI (Col6a1<sup>-/-</sup> mice) display increased incidence of OA. While the mechanism by which collagen type VI deficiency affects the progression of OA is unknown, it likely disrupts the transduction of mechanical signals to the cells as the tissue is loaded during activities such as walking or running. Therefore, the goal of this project is to study the role of collagen type VI in cartilage PCM, especially as it relates to transducing mechanical signals to the cells. To achieve this goal, this proposal will examine three specific aims. Aim 1 is to characterize the mechanical and biochemical properties of cartilage PCM from normal and Col6a1<sup>-/-</sup> mice during different stages of development. Aim 2 is to test the properties of the newly-forming matrix of stem cells from normal and Col6a1<sup>-/-</sup> mice that are differentiating into cartilage cells at different developmental stages. Finally, Aim 3 is to examine the effects of compressive loading on the matrix formed by normal and Col6a1<sup>-/-</sup> stem cells as they differentiate into cartilage cells. The stem cells used in this proposal will be induced pluripotent stem cells (iPSCs) which are derived from skin cells and transfected with certain genes to reprogram them to an embryonic state. iPSCs are an attractive cell source as they can be derived from both normal and Col6a1<sup>-/-</sup> mice and differentiated into chondrocytes, allowing for the direct comparison of normal and Col6a1<sup>-/-</sup> PCM development. Overall, it is hypothesized that collagen type VI deficiency will alter the microenvironment of both chondrocytes and of differentiating iPSCs, which will be characterized by altered biochemical and mechanical PCM properties and an inability of the cells to respond to mechanical stimulation. The results from this proposal will help illuminate the role of collagen type VI in normal cartilage, and determine how its absence may relate to cartilage disease and degeneration.

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**Name:** John C. Scatizzi, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Identification of the Lbw2 Lupus Susceptibility Genes for Hemolytic Anemia*

**Institution:** The Scripps Research Institute

**Supervisor:** Dwight Kono, MD

**Award Period:** July 1, 2011 – June 30, 2014

**Study Section:** Molecular Biology and Genetics

**Disease Focus:** Lupus

**Lay Language Summary:** Systemic lupus erythematosus (SLE or lupus) is an autoimmune disease highly dependent on genetic susceptibility. The identification of genetic variances that cause lupus will not only inform researchers about the causes of the disease, but also guide the development of new drugs and provide early disease indicators. Using mice that spontaneously develop a disease similar to lupus, we will investigate the genetic difference between mice that develop disease and those whose genetic background suggests they should develop disease, but don't. Theoretically, the differences between the two groups of mice would be a single gene, and identifying that gene will expand current knowledge about lupus disease. The high probability that the gene we identify also plays a role in human lupus creates the potential of new therapeutic approaches for human lupus.

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**Name:** Gabriela Schmajuk, MD, MS

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *A rational approach to drug toxicity monitoring for methotrexate users*

**Institution:** University of California, San Francisco

**Supervisor:** David Daikh, Ph.D

**Award Period:** July 1, 2012 – June 30, 2014

**Study Section:** Clinical/Therapeutics/Outcomes

**Disease Focus:** Rheumatoid Arthritis

**Lay Language Summary:** Various national patient safety organizations have recently brought attention to the monitoring of toxic drugs used for patients with rheumatic diseases. Specifically, they have mandated the more frequent monitoring of liver-related laboratory tests (LFTs) for patients taking methotrexate. Methotrexate is an oral drug used as the first-line treatment for rheumatoid arthritis. The intent of monitoring LFTs is to reduce severe liver damage for patients taking methotrexate. However, it is not known whether increasing the intensity of laboratory monitoring leads to improved patient outcomes. On the contrary, more frequent monitoring may have unintended consequences that are inappropriate, burdensome, and expensive. Patients may have flares of their disease if methotrexate is unnecessarily stopped, total health care costs will rise if patients are switched to costly injectable drugs, or patients could be harmed if they are switched to steroid medications, which have more long-term toxicities. Our study aims to address the questions of (1) what is the current state of affairs around methotrexate liver monitoring and (2) what are the downstream consequences of frequent testing

(patient harms? Increased costs?). My long-term goal is to improve the quality and value of rheumatologic care by designing, implementing, and evaluating quality measures, rules or recommendations, that are based on evidence (and not only expert opinions). Although I have some training in biostatistics (Master's Epidemiology) and experience with analyzing large datasets, this project will train me to use data from the Veterans Affairs (VA) health system, an integrated system of care with an excellent electronic health record, which will be invaluable to my future career. The knowledge gained here will inform the next generation of patient safety measures in this area, potentially reducing unnecessary testing while promoting testing that is effective and improving patient outcomes and satisfaction.

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**Name:** Anita Tseng Shaw, MD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Effects of IL-17 on osteoblast inhibition in rheumatoid arthritis*

**Institution:** University of Massachusetts Medical School

**Supervisor:** Ellen M. Gravallese, MD

**Award Period:** October 1, 2011 – September 30, 2014

**Study Section:** Cell Biology

**Disease Focus:** Rheumatoid Arthritis

**Lay Language Summary:** Rheumatoid arthritis (RA) is a debilitating, chronic disease that leads to inflammation and bone loss, causing joint deformity. In healthy individuals, there is a balance between osteoclasts that break down bone and osteoblasts that form bone. However, in patients with RA, this balance is lost at sites of bone erosion and favors osteoclast activity, leading to bone loss. Bone formation by osteoblasts is decreased in RA and positive signaling through the Wingless (Wnt) pathway is crucial for osteoblast maturation and function. A group of proteins called proinflammatory cytokines are involved in causing inflammation and increasing osteoclast maturation in RA. Recently, interleukin-17 (IL-17) has emerged as a proinflammatory cytokine that is involved in causing bone erosion and joint deformity in RA. IL-17 boosts the maturation and activity of osteoclasts by increasing the levels of other proinflammatory cytokines, eventually leading to bone loss. However, the role of IL-17 on osteoblasts is still unclear. As osteoblasts are key players in balancing bone loss with bone formation, identifying the impact of IL-17 on osteoblasts is critical. In this research proposal, we will test the hypothesis that IL-17 inhibits osteoblast maturation and function at sites of articular bone erosion in RA, thereby enhancing the destruction of bone. We will culture osteoblasts in vitro and treat them with IL-17 to determine the effect of IL-17 on osteoblast maturation and function, as well as on the expression of Wnt pathway inhibitors. We will also use two mouse models of RA to examine the effect of IL-17 on the ability of osteoblasts to form bone in vivo. These studies are designed to identify the impact of IL-17 on osteoblast maturation and function in RA and to determine whether blockade of IL-17 will allow for healing of erosions in this disease. Additionally, bone loss is also seen in the skeleton in RA (osteoporosis) and has a similar mechanism to that of articular bone erosion. Thus, our findings regarding IL-17 have the potential to aid in the treatment of osteoporosis in RA as well.

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**Name:** Anirudha Singh, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Cartilage lubrication with biomaterials*

**Institution:** Johns Hopkins University

**Supervisor:** Jennifer Elisseeff, PhD

**Award Period:** July 1, 2012 – June 30, 2014

**Study Section:** Technologies/Biomechanics

**Disease Focus:** Osteoarthritis

**Lay Language Summary:** Tissue lubrication is crucial for the normal function of articular joints, eyes, and lungs. Compromised lubrication is a hallmark of disease in these organ systems, warranting investigation into therapeutic strategies to restore function. Current clinical strategies using injections or eye drops to deliver lubricating biopolymers such as hyaluronic acid (HA) to the diseased tissue have been largely ineffective because the lubricating liquid is quickly cleared from the area of need. The main goal of this proposal is to engineer the articular cartilage surface for enhanced lubrication with an injectable biomaterial. I propose to modify articular cartilage surface with a synthetic peptide-polymer system which will non-covalently bind HA to the tissue surface and work synergistically with HA for joint lubrication. This biomaterial-mediated strategy that will locally concentrate HA and create a self-healing coating of biological lubricant on tissue surfaces provide multiple physical and biological benefits to prevent and treat tissue-lubricating dysfunction.

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**Name:** Myoungsun Son, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Differential function of IgM and IgG anti-C1q antibodies on dendritic cells*

**Institution:** Feinstein Institute for Medical Research

**Supervisor:** Betty Diamond, MD

**Award Period:** July 1, 2011 – June 30, 2014

**Study Section:** Cellular Immunology

**Disease Focus:** Lupus

**Lay Language Summary:** Systemic Lupus Erythematosus (SLE) is an autoimmune disease characterized by the loss of tolerance to self-antigens, in particular DNA. Immune complexes (ICs) of IgG anti-DNA antibody and DNA can cause systemic inflammation and tissue injury. On the other hand, the effect of ICs composed of IgM anti-DNA antibody in SLE is not well understood. The classical complement pathway proteins appear to have both a harmful role and a protective role in the pathogenesis of SLE. Clinically, deficiency in complement, especially C1q, is strongly associated with the development of SLE and must contribute to incomplete maintenance of peripheral tolerance. However, the mechanism(s) responsible for linking the complement deficiency to the development of SLE is unclear. Dendritic cells (DCs) avidly sense both complement and ICs, and both play a role in DC maturation. The maturation of DCs regulates both the consequent immune response and the induction of tolerance. Unabated or

chronic stimulation of DCs may lead to a breakdown in peripheral tolerance and the development of SLE. Importantly, however, different DC subsets control different effector pathways of the immune system. Therefore, the mechanism responsible for DC maturation is crucial to understanding the etiology of SLE. We would like to clarify what stimulates DCs to promote the development of SLE. The hypothesis of this proposal is that circulating ICs containing IgM or IgG anti-DNA antibody prevent or promote, respectively, SLE and that the inclusion of C1q in those complexes modulate this process. We will explore the ways in which IgG or IgM anti-DNA antibodies and complement C1q regulate SLE. The rationale for the proposed work is that it will provide an enhanced understanding of the fundamental regulation of self reactivity.

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**Name:** Joshua Stefanik, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Effect of massive weight loss on patellofemoral joint structure and pain*

**Institution:** Boston University

**Supervisor:** David T. Felson, MD

**Award Period:** August 1, 2011 – July 31, 2014

**Study Section:** Clinical/Therapeutics/Outcomes

**Disease Focus:** Osteoarthritis

**Lay Language Summary:** Knee osteoarthritis (OA) is a serious health problem and leading cause of disability in the United States. Cartilage damage is the hallmark sign of OA along with damage to underlying bone. As cartilage does not have the ability to sense pain, bone damage may be the source of pain in individuals with OA. The knee joint is a complex structure and comprised of two smaller joints. One joint is between the knee cap (patella) and upper leg bone (femur) and the other is between the femur and the lower leg bone (tibia). It is commonly thought that pain that occurs with squatting, kneeling, walking up and down stairs, and prolonged sitting is a result of pathology from the joint where the knee cap sits on the femur. However, there is little evidence that pain that occurs with these activities results from structural changes in this joint. Obesity is strongly associated with knee OA and weight loss is known to decrease the risk of OA and alter the forces in the knee joint. Massive weight loss such as typically occurs after bariatric surgery (gastric bypass surgery) dramatically lessens knee pain, but it is unknown whether and how such weight loss affects joint structures. It is likely that massive weight loss will delay the onset of structural damage or stabilize the progression of further joint damage. In the current study we will follow subjects who undergo bariatric surgery and a control group not undergoing surgery. We hypothesize that compared to morbidly obese subjects not undergoing bariatric surgery, subjects undergoing surgery will have less worsening of joint damage. We will obtain baseline Magnetic Resonance Images (MRI) of subjects' knees from both groups at baseline (before surgery) and at follow-up (6-12 months after surgery when they have experienced maximal weight loss). We will quantify both cartilage and bone damage from MRI and determine the differences in this damage over time between the two groups. In addition to assessing the cartilage and bone damage using common methods from past research, we propose using a novel MRI approach that assesses cartilage biochemistry that may be more sensitive to early changes in cartilage.

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**Name:** Pei-Suen Tsou, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Contribution of oxidative stress to aberrant angiogenesis in scleroderma*

**Institution:** University of Michigan

**Supervisor:** Alisa Koch, MD

**Award Period:** July 1, 2012 – June 30, 2014

**Study Section:** Cell Biology

**Disease Focus:** Scleroderma

**Lay Language Summary:** Scleroderma (SSc) is characterized by early inflammation, thickening of the skin, and decrease in blood vessel formation. However, paradoxically, the expression of provascular mediators, such as vascular endothelial growth factor (VEGF), seems to outweigh the presence of anti-blood vessel mediators. Although these findings have been accepted as known paradigms of the disease, few studies have attempted to explain how misregulated new blood vessel formation occurs in SSc dermal vascular cells. It has been shown that oxidized lipids increase when the available supply of the body's antioxidants is insufficient to handle and neutralize free radicals of different types, which is observed in SSc. We hypothesize that increased production of oxidized lipids activates their receptor, the molecule on the surface of the cell that receives the signal from the lipids, in SSc vascular cells and leads to inhibition of VEGF activity. In this proposal, we will first isolate vascular cells from skin biopsies. The effect of oxidized lipids and their receptors on VEGF-induced blood vessel growth will then be examined. These approaches will allow us to evaluate the vascular issues of SSc in ways previously not explored and will provide avenues for us, and other investigators, to move the field forward. Moreover, identifying the mechanisms of reduced blood vessel growth in SSc skin is critical to the development of therapies aimed at promoting vascular formation in the skin of these patients.

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**Name:** Veronica Ulici, PhD, MD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Chromatin Remodeling Changes in Posttraumatic-Osteoarthritis*

**Institution:** University of Pittsburgh

**Supervisor:** Rocky Tuan, Ph.D

**Award Period:** July 1, 2012 – June 30, 2014

**Study Section:** Molecular Biology and Gene Regulation

**Disease Focus:** Osteoarthritis

**Lay Language Summary:** Osteoarthritis (OA) is the most common cause of disability in older adults. Numerous factors are thought to contribute to OA development and progression. Mechanical stress and trauma, aging and genetic predisposition are among the primary causative factors. Aging-related changes in joint tissues likely act by increasing susceptibility to degeneration when other factors are present. In addition to genetic factors which predispose us to diseases such as OA, modifications in

chromatin structure were also shown to be present in OA. Chromatin is the complex of proteins (histones) and DNA that is tightly packed to fit into the nucleus; the degree to which DNA is packaged controls the activity of the genes in this part of DNA. A number of different proteins modify the chromatin structure; among these, histone deacetylases (HDACs) are responsible for modifications of histones which lead to increased interaction between them and DNA and interference with gene expression (activation). A number of HDACs were found increased in chondrocytes isolated from OA patients. Mechanical injury of cartilage is also known to lead to cartilage degradation. However, no studies have investigated the collaboration between mechanical stress and chromatin remodeling changes in OA. This research project aims to analyze the interaction between these two potential causative factors of OA and how aging cartilage responds to this interaction. We will analyze the changes in the levels of HDAC proteins between normal and OA cartilage samples in addition to the effect of mechanical stimulation. Understanding in more depth the role of chromatin changes in OA and the connection with mechanical stimulation will hopefully lead to molecular therapeutic targets in combination with specific physical activity regimens. Most likely OA will require a complex targeted therapy in which the manipulation of multiple factors will have to be considered.

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**Name:** Haopeng Wang, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *FAK Family Kinases: Role in Controlling T Cell Responses and Autoimmunity*

**Institution:** University of California, San Francisco

**Supervisor:** Arthur Weiss, MD, PhD

**Award Period:** July 1, 2011 – June 30, 2014

**Study Section:** Molecular Immunology

**Disease Focus:** Rheumatoid Arthritis

**Lay Language Summary:** How does our immune system prevent millions of T cells in our body from attacking ourselves? One of the major strategies our immune system using is to render those potential autoreactive T cells unresponsive to self-antigens expressed on our tissue cells. T cells require two signals to become fully activated: one through the T cell receptor (TCR), and a second through a co-stimulatory receptor such as CD28. Without signal from CD28 mediated costimulation, TCR stimulated T cells often become non-responsive. There are no co-stimulatory molecules, such as CD28 ligands, expressed on our tissue cells. Therefore T cells recognizing self-peptides on tissue cells lacking co-stimulatory activity are not activated. However, in most of autoimmunity conditions, such as rheumatoid arthritis, the immune system loses this protection for unknown reasons. Currently, targeting CD28-mediated costimulation is considered to be a very effective therapeutic strategy for human autoimmune diseases. For instance, Abatacept (CTLA4-Ig), an inhibitor of CD28-mediated costimulation, has been approved by FDA for treatment of rheumatoid arthritis since 2006. Although we have known about the importance of CD28-mediated costimulation for the T cell activation for more than 25 years, the mechanism by which costimulation regulates T cell activation is still poorly understood. My study is focusing on a genetic modified mouse in which gene PYK2 is deleted by gene-targeting approach. Surprisingly, T cells from these mice are able to bypass the requirement of CD28 costimulation. These

mice also developed exaggerated disease in a mouse model for multiple sclerosis. Therefore, studying of the role of PYK2 in T cell activation provides a unique opportunity to dissect the molecular mechanism of the CD28-mediated costimulation, which may allow us to identify new therapeutic targets for autoimmune disease.

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**Name:** Hui Wang, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Spatio-temporal dynamics of Rho family signaling in leukocyte TEM*

**Institution:** University of North Carolina at Chapel Hill

**Supervisor:** Klaus M. Hahn, PhD

**Award Period:** October 1, 2011 – September 30, 2014

**Study Section:** Cellular Immunology

**Disease Focus:** Ankylosing Spondylitis

**Lay Language Summary:** Rho family GTPases plays central role in regulating leukocyte transendothelial migration (TEM) via which leukocytes undergo TEM to reach the joints. The dysregulation of TEM can play major roles in spondyloarthritis, including rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA). However, TEM is a highly dynamic process which requires precise spatio-temporal coordination of signaling at a seconds and submicron level. In this research, I propose to use mRNA display, a powerful high-throughput selection method, to develop an approach to activate Rho family GTPases by light which will allow me to manipulate these GTPases with high spatio-temporal precision. I will use this approach to study the roles of the Rho family GTPases in TEM by activate a single GTPase or a pair of GTPases in different temporal manner. I will also study the regulation between different Rho GTPases by activating one while observing another.

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**Name:** Shaofeng Wang, MD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Functional study of SLE-associated risk variants in UBE2L3*

**Institution:** Oklahoma Medical Research Foundation

**Supervisor:** Patrick M. Gaffney, MD

**Award Period:** July 1, 2013 – June 30, 2015

**Study Section:** Genetics

**Disease Focus:** Lupus

**Lay Language Summary:** Systemic lupus erythematosus is an autoimmune disease that results from a complex interaction of genetic and environmental factors. Large genetic surveys in subjects with SLE have identified over 30 regions of the human genome that are likely to be important in SLE genetic susceptibility. UBE2L3 is a gene locates in one of these regions, encodes the ubiquitin-conjugating enzyme, UBCH7 that plays an important role in targeting other proteins for degradation and regulating immune signaling pathways. However, the exact mechanism by which UBE2L3 influences risk for SLE is

unclear. We plan to perform a series of experiments in order to better understand the precise location and functional impacts of the genetic variants that are likely to contribute most to the SLE causation.

We analyzed a dense set of genetic markers spanning UBE2L3 in case-control sample sets of diverse ethnic origins, identified a single risk haplotype present in all populations. Subjects who carry this risk haplotype produce higher levels of UBE2L3 mRNA and UBCH7 protein suggesting a potential mechanism by which genetic variants on the risk haplotype influence susceptibility to SLE. This project seeks to identify causal variants in the UBE2L3 region and characterize their functional effects in order to better understand the complex mechanisms that determine SLE risk. We believe that the investigation and mechanistic characterization of causal variants in each SLE risk loci is critically needed to formulate a cogent view of the SLE genetic landscape and provide new opportunities to improve the diagnosis and treatment of patients with SLE.

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**Name:** Vincent Payne Willard, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *In Vitro Models of Osteoarthritis for Personalized Medicine*

**Institution:** Duke University

**Supervisor:** Farshid Guilak, PhD

**Award Period:** July 1, 2013 – June 30, 2015

**Study Section:** Technologies/Biomechanics

**Disease Focus:** Osteoarthritis

**Lay Language Summary:** Osteoarthritis (OA) is a degenerative joint disease that afflicts millions of people in the United States and carries with it a large economic burden. While the true causes of OA are still under investigation, joint inflammation is known to cause rapid progression of the disease, leading to breakdown of the articular cartilage and other joint tissues. Continued cartilage degradation within the joint in OA ultimately causes many patients to seek a total joint replacement. Unfortunately, current therapeutics are only effective at treating the symptoms of the disease rather than halting its progression. Therefore, new approaches are needed to identify therapeutics that can stop the disease before it becomes debilitating. The development of new OA drugs is limited by the lack of cartilage for laboratory testing. Recently, stem cell research has shown great potential to enhance our understanding of OA, which could lead to effective therapies. Induced pluripotent stem cells (iPSCs) are a particularly attractive cell type for understanding cartilage development and OA as they are derived from adult cells, but behave like embryonic cells, being able to multiply indefinitely, and become any cell type in the body. Given these traits, iPSCs could provide a personalized and unlimited source of cartilage-producing cells for arthritis research in the laboratory. The goal of this project is to determine if stem cell-derived cartilage is a good substitute for native cartilage when trying to model arthritis outside the body. This proposal will address the need for new ways to screen OA therapeutics in three steps: 1) iPSCs will be created from patients while native cartilage is collected from the same patients, 2) the response of iPSC-derived cartilage to an inflammatory environment will be compared to that of native tissue, and 3) inflammatory signaling will be blocked in iPSC cartilage using a variety of inhibitors, as a model of therapeutic intervention. The successful completion of this proposal will result in a personalized

laboratory model of arthritis that may be used to screen prospective OA therapeutics in an efficient manner. Furthermore, the potential long term impact of this work is the identification of personalized medicines to stop or reverse the progression of OA, rather than just treating its symptoms.

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**Name:** Kai Yang, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Modulation of S1P/S1P1 signaling in autoimmune diseases*

**Institution:** St. Jude Children's Research Hospital

**Supervisor:** Hongbo Chi, PhD

**Award Period:** July 1, 2011 – June 30, 2014

**Study Section:** Cellular Immunology

**Disease Focus:** Rheumatoid Arthritis

**Lay Language Summary:** Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the loss of tolerance to self-antigens, which affects the skin, joints, kidneys, and other organs. Autoreactive effector T cells play an important role in the pathogenesis of lupus in humans and mice. Defects in the frequency and function of regulatory T cells (Treg), a subset of CD4+ T cells with a central role in immune tolerance and prevention of autoimmunity, have also been linked to the development of lupus. In humans, Treg cells are decreased in subjects with active SLE, but these cells increase with treatment and clinical improvement. Altered Treg numbers, functions or responses have also been observed in various murine lupus models. Although restoration of Treg defects has been proposed as a novel therapeutic strategy for lupus, this approach has not been materialized because of the limited information on the control mechanisms in Treg cells. Sphingosine 1-phosphate (S1P) is a bioactive lipid molecule found at high levels in the blood. S1P signaling through its G protein-coupled receptor S1P1 is critical for thymocyte egress into circulation. Abnormal S1P formation is related to angiogenesis, inflammation, cancer, and autoimmunity. Elevated expression of S1P and S1P1 has been observed in arthritis and other autoimmune conditions and postulated to contribute to the pathogenesis. Mice that constitutively express S1P1 in T cells (S1P1-Tg mice) developed a lupus-like autoimmune syndrome, which was characterized by aberrant Treg development and accumulation of spontaneously activated T cells and high titers of autoantibodies. Altogether, these results suggest that S1P/ S1P1 signaling pathway has an important role in the pathogenesis of lupus. Based on our discovery that S1P/S1P1 as a novel non-cytokine pathway is implicated in the regulation of immunity and tolerance, in this grant proposal, we will define the underlying mechanisms of S1P/S1P1 signaling in the regulation of T cell lineage specification and explore novel therapeutic strategies in lupus models by modulating S1P/S1P1 signaling pathway.

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**Name:** Nianlan Yang, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *Functional Fragment of GILZ as a New Anti-arthritis Therapy*

**Institution:** Georgia Health Sciences University

**Supervisor:** Xing-Ming Shi, Ph.D

**Award Period:** July 1, 2012 – June 30, 2014

**Study Section:** Molecular Biology and Gene Regulation

**Disease Focus:** Rheumatoid Arthritis

**Lay Language Summary:** The long term goal of this research is to develop a new molecule with the beneficial anti-arthritis effect of corticosteroids (such as Prednisone), but without the detrimental effects on the bone. Between 56% and 68% of patients with rheumatoid arthritis are treated more or less continuously with corticosteroids. However, long-term usage of corticosteroids causes a host of debilitating side effects. Corticosteroid induced osteoporosis or bone loss is considered one of the most severe side effects related to long-term usage of corticosteroids. This is a particular complication in rheumatoid arthritis, since the pre-existing inflammation induced bone loss may be even exaggerated by corticosteroid usage. Thus, if we could find a way to uncouple corticosteroid's desired anti-inflammatory effects from its side effects, the clinical benefits would be enormous. Recently, a protein named glucocorticoid induced leucine zipper (GILZ), was indicated to be an important mediator of corticosteroid's anti-inflammatory effect. Our previous research in mesenchymal stem cells (MSCs) has shown that: 1) GILZ protein mediates the anti-inflammatory effect of corticosteroids and blocks signals from inflammatory stimuli; 2) GILZ shifts the balance between bone and fat production and cause MSCs to differentiate into more bone-forming cells; 3) GILZ preserves bone formation upon treatment of TNF- $\alpha$ , which is a driving force of arthritis inflammation and bone destruction. Since MSCs can develop into bone and fat cells, they are considered important sources for bone formation and renewal. Research in rheumatoid arthritis patients and animal models have demonstrated that inflammatory stimuli inhibit MSCs from developing into bone-forming cells, which results in low bone formation and eventually bone loss. Thus, our results indicate that GILZ may be a potential medicine for rheumatoid arthritis since it can mimic corticosteroid's anti-inflammatory effect while preserves bone formation. In this proposed study, we are planning to identify a functional fragment of GILZ which is required for its anti-inflammatory effect, and then synthesize a small molecule based on its structure and sequence. We will test the anti-inflammatory effect of the peptide in cells and in arthritis mouse model. This research is designed based on our previous experiences, the materials and reagents are available, the techniques and procedures are well established in our lab. Also, we already performed some preliminary experiments and demonstrated that 1) A GILZ mutant protein, which is much smaller than the original GILZ, blocks inflammatory signals from TNF- $\alpha$  just as GILZ does; 2) GILZ protects mice from developing arthritis. Thus, by designing a small molecule which can mimic GILZ's anti-inflammatory effect, the results of the proposed research may provide valuable information in the design of new drugs to control rheumatoid arthritis.

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**Name:** Minjun Yu, PhD

**Award Type:** Postdoctoral Fellowship – PF

**Amount:** \$50,000.00

**Project Title:** *A novel mouse model for immune-mediated skin fibrosis*

**Institution:** Columbia University

**Supervisor:** Donna Farber, Ph.D

**Award Period:** July 1, 2013 – June 30, 2015

**Study Section:** Cellular Immunology

**Disease Focus:** Scleroderma

**Lay Language Summary:** Scleroderma is a chronic autoimmune disease of varying severity whose key feature is thickening and hardening of the skin, through a process called fibrosis. There is currently no cure for scleroderma and treatments that can help alleviate symptoms in other autoimmune diseases like arthritis are not effective in treating patients with scleroderma because the two diseases have different immune etiologies. In order to make advances in developing treatments and cures for this devastating illness, it is necessary to have an animal model, as mouse models for other autoimmune diseases have served as important pre-clinical tools to understand the disease process and test treatment strategies. Unfortunately, no such animal model exists that mimics the key features of scleroderma which are autoimmunity and skin fibrosis. We have developed a novel mouse model in which certain subsets of T lymphocytes are deficient in a molecules that controls survival and function. The resultant mice are born healthy, but spontaneously and progressively develop skin fibrosis and thickening which is similar to that observed in human scleroderma. In addition, these mice exhibit similar immune system dysregulation as observed in the human disease. In the proposed study, we propose to use this novel and potentially very useful animal model to understand mechanisms for the initiation of skin fibrosis and also to test treatment strategies. This animal model could enable large advances to be made in finding treatments and cure for scleroderma and improving the lives of those affected with this disease.

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