



RESEARCH GRANTS LAY SUMMARIES

Name: Sheila Leah Arvikar, MD

Award Type: Clinical to Research Transition Award – CRTA

Amount: \$60,000.00

Project Title: *P.gingivalis* and Rheumatoid Arthritis: Exploring the Mouth-Joint Connection

Institution: Massachusetts General Hospital

Mentor: Allen steere, MD

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

Study Section: Clinical Immunology

Disease Focus: Rheumatoid Arthritis

Lay Language Summary: Rheumatoid arthritis (RA) is a systemic autoimmune disease, characterized by chronic joint inflammation and destruction. The cause is unknown, but it is suspected that infectious agents may trigger autoimmunity in genetically susceptible individuals. Recently, there has been increasing evidence of a connection between periodontal disease and RA. Specific bacteria in dental plaque can cause periodontitis (inflammation of the tooth-supporting structures), leading to bone and tooth loss. Numerous studies have shown that the prevalence and severity of periodontal disease is increased in RA patients. Treatment of periodontal disease in some preliminary studies has improved RA disease activity. Moreover, periodontal disease and RA share similar risk factors such as genetic predisposition and smoking. One of the major bacterial pathogens that causes periodontal disease is *P. gingivalis*. This organism has also been linked to RA with immune responses to *P. gingivalis* found in RA patients. The studies examining the connection between RA, periodontal disease, and *P. gingivalis* have done so only in patients with longstanding RA whom were already taking immune modulating medications. In an effort to demonstrate a causal role for *P. gingivalis* and periodontal disease in RA, it may be more instructive to assess patients who have early disease and who have not been treated with medications which may alter the immune responses. Furthermore, if treatment of periodontal disease could improve the outcome of RA, it would be more likely to have an impact early in the course of RA. We have established a prospective cohort study of early RA patients at Massachusetts General Hospital. We have now enrolled >60 untreated RA patients with early disease. In our cohort, antibody responses to *P. gingivalis* were significantly increased in untreated early RA patients compared with those in healthy controls or in patients with established RA. The experiments proposed here are designed to better characterize the relationship of periodontal disease, *P. gingivalis*, and RA, using immunologic and

microbiologic methods. These studies will be performed in both newly diagnosed, untreated early RA patients, and in more established RA patients, already undergoing treatment. *P. gingivalis* is a promising candidate organism as a trigger of autoimmunity in RA. Our unique study involves a high degree of clinical characterization of patients by both rheumatologists and dentists. To our knowledge, this work will be the first to evaluate the frequency of *P. gingivalis* immunity in a cohort of patients with early, untreated RA, and may further support a causal role for *P. gingivalis* in this disease. Further, we envision that this work will lead to an interventional trial of periodontal disease treatment in RA, which in addition to RA medications, may have a significant impact on disease activity and outcome for a subgroup of RA patients.

Name: Jennifer Belasco, MD

Award Type: Clinical to Research Transition Award – CRTA

Amount: \$60,000.00

Project Title: *Characterization of Inflammatory Pathways in Psoriatic Arthritis*

Institution: Rockefeller University

Mentor: James Krueger, MD, PhD

Award Period: September 1, 2012 – August 31, 2014

Study Section: Clinical Immunology

Disease Focus: Psoriatic Arthritis

Lay Language Summary: Psoriatic arthritis is an inflammatory joint disease associated with psoriasis. The earliest joint inflammation is thought to involve an area near the joint where muscle tendons and ligaments insert into bone. It also involves both abnormal bone formation and bone destruction. It is difficult to obtain tissue from this area for research purposes. For this reason having a surrogate tissue that is easier to obtain, such as skin, would be useful to show what is occurring in this area. In addition, we do not understand the link between the skin rash and joint symptoms of psoriatic arthritis. We have already started a study where we looked at patients with only psoriasis (skin rash) and patients with both psoriasis and arthritis (skin and joint symptoms). We have found many differences in the skin of patients with only psoriasis vs. patients with both psoriasis and arthritis. We believe that some of the differences we have found may indicate which patients have abnormal bone formation and destruction. Unfortunately, the patients with only psoriasis were not as carefully selected as would like and we would now like to recruit more patients that we are certain only have psoriasis or have both psoriasis and arthritis. We will also compare joint tissue from these patients to joint tissue from patients with other forms of joint inflammation and abnormal bone formation and destruction. These patients will have osteoarthritis and rheumatoid arthritis. This would be the first study to show that the skin shows signs of what is going on in and near the joint in patients with psoriatic arthritis. This may help us to identify which patients with psoriasis will go on to have psoriatic arthritis. In addition, our findings could be used to create new medications to treat these diseases. Furthermore, patients with psoriasis and psoriatic arthritis tend to have other related conditions that affect their whole body such as heart disease and diabetes. Our findings may also help us to understand why this happens and help doctors choose better medications to treat these problems.

Name: Elana J. Bernstein, MD

Award Type: Clinical to Research Transition Award – CRTA

Amount: \$60,000.00

Project Title: *A Submaximal Stress Test to Identify Pulmonary Hypertension in Scleroderma*

Institution: Trustees of Columbia University

Mentor: Lisa A. Mandl, MD, MPH

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

Study Section: Clinical Research

Disease Focus: Scleroderma

Lay Language Summary: Systemic sclerosis (SSc), or scleroderma, is an autoimmune disease that affects many organ systems, including the heart and the lungs. Pulmonary hypertension (PH), an increase in pressure in the blood vessels that connect the heart to the lungs, is the leading cause of death in patients with SSc. Right heart catheterization (RHC), a procedure in which a thin tube is inserted into the right side of the heart to measure pressure, is the gold standard for diagnosing PH. However, this is an expensive, invasive test with significant risks. Currently, echocardiogram, a test in which a probe is placed on the chest and ultrasound pictures of the heart are taken, is the most common noninvasive way to screen for PH. However, echocardiogram is much less accurate than RHC and can sometimes give incorrect results. Given the risks of RHC, patients with SSc are often not referred for RHC until they have trouble breathing. Unfortunately, by this time, irreversible changes in the blood vessels that connect the heart to the lungs have often already occurred. Given the effective therapies now available to treat PH, it is crucial that PH be identified as early as possible, ideally before permanent changes in the blood vessels that connect the heart to the lungs have occurred. A new, noninvasive stress test called the submaximal heart and pulmonary evaluation (SHAPE) may be a better way to evaluate for PH in patients with SSc. The SHAPE test is a 5.5 inch high step that patients step up and down on for 3 minutes at their own pace while their heart rate, heart rhythm, and breathing are monitored. It has been used to identify PH in other populations, but has never been evaluated in patients with SSc. Therefore, the main purpose of this study is to determine whether the SHAPE test can accurately distinguish SSc patients with PH from SSc patients without PH. Sixty patients with SSc will be recruited for this study. Results from RHC within the prior 24 months will be used to divide these 60 patients into those with PH and those without. The primary outcome will be change in end tidal carbon dioxide after 3 minutes of step exercise. This is automatically calculated by the SHAPE test. In healthy patients, end tidal carbon dioxide increases with exercise and is an indicator of how well a patient's heart and lungs are working. It is therefore hypothesized that SSc patients with PH will have a significantly lower mean change in end tidal carbon dioxide than SSc patients without PH. Patients will also complete questionnaires that assess their physical function, health-related quality of life, and perception of breathlessness. Blood will be collected to help evaluate lung function, to test for SSc autoantibodies, and to study genetic biomarkers. If the SHAPE test can accurately distinguish between SSc patients with PH and SSc patients without PH, further studies could be undertaken to see if the SHAPE test might be useful for regular PH screening in the SSc population.

Name: Daria B Crittenden, MD

Award Type: Clinical to Research Transition Award – CRTA

Amount: \$60,000.00

Project Title: *Effects of Colchicine on Cardiovascular Disease in Patients with Gout*

Institution: New York University School of Medicine

Mentor: Anthony Carna

Award Period: August 1, 2012 – July 31, 2014

Study Section: Epidemiology

Disease Focus: Inflammation

Lay Language Summary: Gout is the most common inflammatory arthritis, affecting approximately 12 million Americans. Gout patients are at increased risk for atherosclerosis and cardiovascular (CV) disease, such as heart attacks and strokes. It is increasingly recognized that atherosclerosis is an inflammatory process, and that patients with chronic inflammatory diseases such as gout may have increased CV risk because of their systemic inflammation. On this basis, investigators have begun to ask whether agents that reduce inflammation may have a beneficial impact on cardiovascular disease. Colchicine, often used for gout treatment, is one such agent. Colchicine is generally well-tolerated, and has effects on a number of cell types that are known to play a role in the build-up of atherosclerosis and progression to heart attack. However, little is known about whether there might be a role for colchicine in treating CV disease. In a pilot study looking at gout patients at the New York Harbor Veterans Affairs (VA) Health Care System, we observed that patients taking colchicine experienced a 64% reduction in myocardial infarction (manuscript in revision, *J Rheumatology*). However, by its design that study had a number of limitations, leading me to now propose further investigation. I will approach the question of colchicine and MI risk taking two different, but complementary approaches. In the first approach, we will conduct a detailed chart review of more than 7,000 gout patients who were cared for between 2000 and 2010 in our local VA hospital system; the nature of the VA medical record will permit us to precisely ascertain which patients were on colchicine, and how many events they had while on the drug. We will then validate our findings using the Geisinger Health System database. Although this second study will need to use coded information, rather than careful parsing of charts, the size of the Geisinger database (more than 2 million patients), its less homogeneous patient population (compared to the VA patients), and the power of its electronic search capacities should offset any limitation. These two methodologies should therefore complement each other and let us get a solid idea of the ability of colchicine to modify MI risk. If the results support my hypothesis—that colchicine use lowers CV risk—they could lead to prospective trials of colchicine for CV risk lowering in gout patients, or possibly even in non-gout patients. Thus, my project could lay important groundwork for further investigation into the relationship between inflammation and cardiovascular complications, and may shed light on potential new approaches to therapy. Given the overall tolerability of colchicine, finding that its use lowers CV risk could make it a valuable addition to the treatment of CV disease in gout and/or non-gout patients.

Name: Trevor E. Davis, MD

Award Type: Clinical to Research Transition Award – CRTA

Amount: \$60,000.00

Project Title: *Immune Cell microRNA Expression in Pediatric SLE*

Institution: Beth Israel Deaconess Medical Center

Mentor: George Tsokos, MD

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

Study Section: Clinical Immunology

Disease Focus: Juvenile Arthritis

Lay Language Summary: Pediatric systemic lupus erythematosus (SLE) is a prototypic autoimmune disease in which the immune system causes damage to multiple organs including the skin, joints, and kidneys and less often the heart, lung, liver, and brain. Antibodies are involved in the disease, however other immune cells, T cells, also play an important role. T cells directly infiltrate targeted organs and help produce autoantibodies instead of inhibiting their production. MicroRNAs (miRNAs) are newly identified DNA like molecules that can effect immune cells responses by blocking expression of target genes. Altered miRNAs have been identified in adult autoimmune diseases such as Rheumatoid Arthritis and SLE. These abnormalities have not been studied in response to medications used to treat SLE, correlated to arthritis in SLE patients, or examined in pediatric SLE. We hypothesize the miRNA are altered in pediatric SLE similar to adult SLE. Altered miRNAs will correlate to disease activity and treatments, including presence of arthritis and treatment with steroids. Methods Immune cells from pediatric SLE and healthy control subjects will be isolated and cultured. Microarrays, testing greater than a thousand miRNA and genes at one time, will be used to initially identify candidates. These candidates will be validated using a second lower throughput technique. Molecular techniques will then be used to examine the consequences of these altered genes. Conclusion Although it is known adult SLE immune cells display multiple altered miRNAs these findings are not yet validated in children. The proposed work will accomplish this validation but also has the potential to find novel aberrant miRNAs. Identified miRNAs could reveal specific targets for treatment, biomarkers of disease activity or inherent defects of pediatric SLE. This will significantly advance knowledge of both the field of miRNAs and immunology of pediatric SLE. Moreover these findings may have special importance for prognosis and treatment of pediatric onset SLE and pediatric arthritis.

Name: Maureen Dubreuil, MD

Award Type: Clinical to Research Transition Award – CRTA

Amount: \$60,000.00

Project Title: *Cardiovascular Disease and Diabetes in Ankylosing Spondylitis*

Institution: Boston University

Mentor: Hyon Choi, MD, PhD

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

Study Section: Epidemiology

Disease Focus: Ankylosing Spondylitis

Lay Language Summary: Objective: Patients with Ankylosing Spondylitis (AS) die earlier due to heart disease. This may be because AS patients are more likely to smoke and to be obese. As patients may also have greater risk due to certain medications, called NSAIDs, which are used to treat pain from the

disease. Studies have not addressed this yet, but experts in the field have agreed it is important. Similarly, AS patients may have diabetes more often than people without AS, though studies are unclear on this, as well. Methods: We will use medical records from 8 million patients in the United Kingdom, which were recorded by the patients' general practitioners (GPs). In this database, we will identify patients with AS, and compare the rates of heart disease and diabetes in AS patients, with the rates in people who do not have AS. We will use statistical methods to determine if higher rates of heart disease and diabetes are due to risk factors such as smoking and obesity, in AS patients, or if the risk is due to AS itself (chronic inflammation). We will also use statistical methods to determine if certain NSAIDs cause greater heart disease in AS patients than in people without AS, as the combination of risk factors may be important.

Expected results: The results of this study will allow doctors of AS patients to know what risk factors are the most important in terms of AS patients developing heart disease or diabetes. Doctors can then counsel their patients and treat them better. Similarly, doctors will be able to prescribe the safest NSAID medications to AS patients.

Name: [Beatriz Hanaoka, MD](#)

Award Type: Clinical to Research Transition Award – CRTA

Amount: \$60,000.00

Project Title: *Muscle architecture in chronic DM and PM*

Institution: University of Kentucky Research Foundation

Mentor: Leslie Crofford, MD

Award Period: July 1, 2012 - June 30, 2014

Study Section: Clinical Immunology

Disease Focus: Polymyositis

Lay Language Summary: Dermatomyositis (DM) and polymyositis (PM) are diseases that cause muscle inflammation leading to muscle damage and weakness. While some patients return to normal after being treated with medications, the large majority of patients suffer from chronic muscle weakness and disability. A better understanding of why this happens despite treatment will allow more effective and targeted therapies to be developed in the future. Muscle inflammation and/or its treatment may lead to certain changes in muscle architecture that contribute to ongoing muscle weakness in DM/PM patients. We will enroll 20 participants with DM/ PM and 10 healthy participants will be enrolled in this study over an 18 month period. Study participants will be interviewed and examined. They will also undergo a series of tests that will allow us to study their muscle strength and structure. The results of this study will allow us to determine the contributors to long-term muscle weakness and develop treatment approaches to prevent disability in DM/PM patients.

Name: Jonathan David Jones, MD

Award Type: Clinical to Research Transition Award – CRTA

Amount: \$60,000.00

Project Title: *Rituximab modulates B cell function through shaving*

Institution: Dartmouth College

Mentor: Willam Rigby, MD

Award Period: July 1, 2012 - June 30, 2014

Study Section: Cellular Immunology

Disease Focus: Rheumatoid Arthritis

Lay Language Summary: Background: Rituximab (RTX) is a medication that is used in several autoimmune diseases, especially in rheumatoid arthritis. This medication is an antibody that targets a particular immune cell, the B lymphocyte. Interestingly, though we know that this antibody binds B lymphocytes and results in a suppressed immune system with subsequent disease remission, we don't know the exact mechanism behind this effect. Historically, the major focus on RTX effect was in its ability to promote the death of B lymphocytes. However, depletion of these B cells has not correlated with clinical efficacy. The presence of B cells is determined by measuring a surface protein, CD19. We have shown that blood cells combined with RTX rapidly lose CD19, but that this is not because of cell death, but is rather due to loss of the CD19 protein from the surface through a relatively unknown process termed shaving. We hypothesize that the efficacy of rituximab treatment lies not so much in its ability to deplete B cells, but in its ability to promote loss of surface proteins from the B cells, therefore changing the function and cellular interactions of the B cells. Methods: To investigate our hypothesis we will build on the experience we already have with rituximab shaving of B cells to evaluate other surface proteins besides CD19 that are also removed with the addition of RTX. We will focus on those proteins that have a functional importance to the B cells through playing key roles in cell growth and differentiation or cell-cell interactions. We will also explore different subsets of B cells that may be more or less susceptible to RTX induced shaving. Our second emphasis will be evaluating functional changes of B cells induced by RTX-shaving by determining changes in B cell proliferation and cytokine production after RTX treatment. Additionally, we will examine the effect of RTX treatment on the B cells' ability to interact with and inform T lymphocyte function and differentiation. Anticipated Results: We expect to find several additional functionally significant surface proteins that are lost from B cells in the shaving process. We anticipate identifying changes in B cell function due to treatment with RTX related to cytokine production and T cell interactions. These findings will lead to additional clinical studies evaluating the in vivo effect of RTX in patients being treated for rheumatoid arthritis, and has the potential to opening the doors to additional therapeutic options for several autoimmune diseases.

Name: Suzanne Kafaja, MD

Award Type: Clinical to Research Transition Award – CRTA

Amount: \$60,000.00

Project Title: *Effect of Tyrosine Kinase Inhibitors on Fibrosis in Systemic Sclerosis*

Institution: University of California, Los Angeles

Mentor: Ram Raj Singh, MD

Award Period: July 1, 2012 - June 30, 2014

Study Section: Clinical Immunology

Disease Focus: Scleroderma

Lay Language Summary: Scleroderma is a chronic inflammatory disease that affects a number of organs in the human body including the skin, intestines, lungs, and kidneys. The cause of scleroderma remains unknown. It is believed to be due to abnormalities of immune system, where different components (cells) of immune system do not coordinate properly, resulting in damage to blood vessels, and replacement of normal organ cells with fibers. This process is called fibrosis. There are different types of immune cells. One of them is called dendritic cells. This project proposes to investigate the role of a subset of dendritic cells, called plasmacytoid dendritic cells. These cells normally circulate in blood and go to various organs such as skin and lung during infection and inflammation. We have studied these cells in the blood, skin biopsy and lung lavage fluid from patients with scleroderma. We have found that these cells are reduced in the blood, but abundant in the skin and lung lavage fluid, from patients with scleroderma. Importantly, the presence of these cells in lung fluid correlates with the extent of lung fibrosis seen on imaging of the lungs (CT scan). These cells were also noted to decrease in patients treated with a medication called Imatinib. In the proposed project, I will move forward the above preliminary work and investigate the role of plasmacytoid dendritic cells in modifying immune system in a way that leads to the formation of excess fibers in organs such as skin and lungs leading to scleroderma. This may in the future help us find a treatment for hardening of the skin and lungs of patients with scleroderma.

Name: Kichul Ko, MD

Award Type: Clinical to Research Transition Award – CRTA

Amount: \$60,000.00

Project Title: *Differential Gene Expression Analysis in Systemic Lupus Erythematosus*

Institution: University of Chicago

Mentor: Timothy Niewold, MD

Award Period: July 1, 2012 - June 30, 2014

Study Section: Genetics

Disease Focus: Lupus

Lay Language Summary: Systemic lupus erythematosus (SLE) is a heterogeneous disease characterized by a strong genetic contribution and activation of a number of immune system pathways. It manifests differently by ancestry as African American (AA) patients tend to have higher disease activity, kidney involvement and more autoantibodies compared to European American (EA) patients. Moreover, autoantibodies directed against the body's own cells (anti-RBP) are associated with different SLE

characteristics and activity. Our overall hypothesis is that the underlying mechanisms of SLE differ between AA and EA SLE patients, and between those with anti-RBP antibodies and those who lack these antibodies. We will explore this hypothesis by examining how genes are expressed differently in those groups and identify the key molecules for the differences. In this study, we posit that different autoantibody profiles and ancestral backgrounds in SLE are associated with different gene expression patterns. The knowledge of the relationships amongst gene expression, autoantibody profile and ancestral differences in SLE will significantly aid our understanding of the heterogeneity of pathogenesis and lay the foundation for individualized therapy. Moreover, discovering new pathways in SLE pathogenesis may identify potential therapeutic targets.

Name: Dana Orange, MD

Award Type: Clinical to Research Transition Award – CRTA

Amount: \$60,000.00

Project Title: *Using Dendritic Cells to Evaluate T cell Specificity in ACPA+ RA*

Institution: Rockefeller University

Mentor: Gila Budescu, PhD

Award Period: September 1, 2012 - August 30, 2014

Study Section: Cellular Immunology

Disease Focus: Rheumatoid Arthritis

Lay Language Summary: Recent advances in rheumatoid arthritis (RA) have improved the quality of life for many patients living with the disease. We now have potent drugs, which block cytokines such as TNF and IL6 inhibitors or lead to the death certain types of cells such as B cells . Still, many patients receive inadequate relief or unwanted side effects from those drugs. One major problem with cytokine inhibitors is that they do not block only arthritis-associated inflammation but all inflammation and so can lead to increased susceptibility to infection and possibly tumors. The goal of this project is to look at arthritis specific T cell responses in patients with rheumatoid arthritis with the hope that one day we can turn off the immune responses that cause arthritis without increasing susceptibility to infection. There are some hints that T cells may play a pivotal role in the initiation of arthritis: T cells can be found in inflamed joints, the gene that confers the most increased risk for arthritis is involved in activating specific T cells, and the antibodies seen in RA patients are of the type that are usually thought to require a “helper” T cell for their generation. We now have more sensitive ways of diagnosing rheumatoid arthritis earlier but we still don’t know how it starts. The ultimate goal is to figure out what causes arthritis so we can cure arthritis.

Name: Michelle J. Ormseth, MD

Award Type: Clinical to Research Transition Award – CRTA

Amount: \$60,000.00

Project Title: *HDL Dysfunction in Rheumatoid Arthritis*

Institution: Vanderbilt University Medical Center

Mentor: C. Michael Stein MD

Award Period: July 1, 2013 - June 30, 2015

Study Section: Clinical Research

Disease Focus: Rheumatoid Arthritis

Lay Language Summary: Patients with rheumatoid arthritis (RA) develop hardening of the arteries, called atherosclerosis, much earlier in life than healthy people. This leads to RA patients having double the risk of heart attacks compared to the general population. However, it is much harder to predict atherosclerosis in patients with RA than in the general population. High density lipoprotein (HDL) is considered “good cholesterol”, protecting most people from atherosclerosis by removing cholesterol from the artery wall. However, in RA patients HDL doesn’t seem to always be protective. We believe this is because HDL is made dysfunctional by inflammation and oxidative stress. For example, oxidative stress can rapidly damage proteins like HDL. This changes the protein structure, stops it working properly, and makes the protein unrecognizable to the immune system, resulting in the body making antibodies against the damaged protein. These antibodies can be an easily detectable marker that these changes have occurred or can attach to the protein and affect its function. We will determine if HDL dysfunction in patients with RA is associated with atherosclerosis, inflammation, oxidative stress and antibodies that bind to a damaged protein in HDL. To do this we will use stored blood samples from 169 RA patients and 92 non-RA controls that have been in other studies where we measured markers of inflammation, oxidative stress and atherosclerosis. We will add patient blood that is enriched with HDL to cholesterol-filled cells and measure how much cholesterol each person’s HDL removes from cells. We will also measure levels of antibodies that bind to a damaged protein in HDL. For analyses we will compare HDL function between RA patients and non-RA controls and the relationship between HDL function and measures of atherosclerosis, oxidative stress, inflammation and antibodies to modified protein component of HDL. This study is important because heart disease due to atherosclerosis is the most common cause of death in RA patients. This study will give us tools to better predict which patients are at highest risk to develop atherosclerosis, and provide important information to devise new ways to reduce atherosclerosis risk in order to prolong the lives of patients with RA.

Name: Julie Jisun Paik, MD

Award Type: Clinical to Research Transition Award – CRTA

Amount: \$60,000.00

Project Title: *Neuropathy in Scleroderma*

Institution: Johns Hopkins University

Mentor: Laura K. Hummers MD

Award Period: July 1, 2013 - June 30, 2015

Study Section: Clinical Research

Disease Focus: Scleroderma

Lay Language Summary: Nerve pain can cause significant disability and pain in patients with scleroderma. Since nerve conduction studies and muscle biopsies can provide objective evidence of

nerve dysfunction, we decided to study scleroderma patients with muscle weakness. Twenty-seven muscle biopsies were reviewed from scleroderma patients who had muscle weakness. Esterase staining, which is a special stain that is prominent on muscle biopsy if there is nerve damage was found in over 50% of these biopsies. Furthermore, 63% of the same group of scleroderma patients also had evidence of nerve damage on the gold standard test – nerve conduction study. To make sure that this was not coincidental, we also compared this group of scleroderma patients with 26 patients with another autoimmune muscle disease- dermatomyositis. There were only 15% of dermatomyositis patients who had evidence of nerve damage on biopsy and only 8% had evidence of nerve damage on the gold standard test of nerve conduction. Thus, overall 78% of scleroderma patients with muscle weakness had evidence of nerve dysfunction on muscle biopsy and or/nerve conduction study. Based on this preliminary data, the purpose of this proposal is to first determine what the rate of nerve dysfunction is in scleroderma patients since it is completely unknown. And second, once we determine which patients have neuropathy, we will determine if there is any clinical correlation between diffuse or limited scleroderma, autoantibody profile, muscle weakness, and disability. We expect to find that nerve dysfunction will be more common in patients with muscle weakness as shown in our preliminary study. This will be important because it can identify a special group of scleroderma patients who may have a different prognosis in terms of their disability and pain from not only scleroderma in of itself but also from nerve pain and dysfunction. Once identified, they may require even more tailored therapy for their disease to prevent further disability.

Name: Sebastian Horacio Unizony, MD

Award Type: Clinical to Research Transition Award – CRTA

Amount: \$60,000.00

Project Title: *Mechanisms of action of anti IL-6 therapy in Giant Cell Arteritis (GCA)*

Institution: Massachusetts General Hospital

Mentor: John Stone, MD, MPH

Award Period: October 1, 2012 - September 30, 2014

Study Section: Clinical Immunology

Disease Focus: Other

Lay Language Summary: Giant cell arteritis (GCA) is a disease that causes inflammation within the arteries of the human body with predilection for the aorta and its main branches. GCA is the most common form of “vasculitis” in adults, and more than 200,000 persons are affected by this disease in the United States now. Patients with this condition experience severe headaches, jaw pain, visual abnormalities, and generalized body aches, but the most feared complication is blindness, which occurs in about 1 out of 7 cases. Cells of the immune system called lymphocytes “attack” the arteries in GCA. Two specific types of lymphocytes, namely Th1 and Th17 cells, orchestrate this process. Besides infiltrating (occupying) the arteries, the number of these cells is increased in the blood of GCA patients. The treatment of GCA is challenging. This condition responds to moderate doses of glucocorticoids (prednisone) but most of the patients suffer disease exacerbations (flares) when trying to come off this medication. The reason for this is unknown, but might be related to the fact that the glucocorticoids only reduce the number of Th17 cells but spare the Th1 lymphocytes, that remain elevated. Moreover, the glucocorticoids cause undesirable side effects in the majority of the patients that use them (e.g., diabetes, high blood pressure, infections, cataracts, bone fractures, stomach bleeding, and weight gain).

Other drugs have failed to ameliorate the disease and reduce the requirement of glucocorticoids. Therefore, there is an unmet need for new medications to control the inflammation, and reduce the use and side effects of glucocorticoids in individuals with GCA. Research showed that a molecule called interleukin (IL)-6 may have an important role in causing inflammation in GCA. Tocilizumab (TCZ), a drug that blocks the actions of IL-6, has been developed. Studies using TCZ in a small number of GCA patients showed promising results, therefore, a large controlled trial is on its way. Despite these encouraging results, we do not know how TCZ works in GCA, or whether this medication is good for all the patients. We speculate that TCZ decreases the number of inflammatory lymphocytes, but we do not know if both (Th1 and Th17) lymphocyte types are targeted. To answer these questions, we will study patients with GCA treated with TCZ, and we will analyze the impact that this medication has in the lymphocytes that cause the disease. We will measure the number of Th1 and Th17 cells (and several molecules related with them) in the blood of these patients over the period of one year. If both cell types are decreased, then TCZ will prove to represent an alternative option for patients with GCA. If only one lymphocyte type is affected and the other type is spared, then we will provide a note of caution regarding the value of this medication in GCA.

Name: Yajuan Zhang, MD

Award Type: Clinical to Research Transition Award – CRTA

Amount: \$60,000.00

Project Title: *The role of IL-1 in SJIA monocyte phenotypes*

Institution: Stanford University

Mentor: Elizabeth Mellins, MD

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

Study Section: Cellular Immunology

Disease Focus: Juvenile Rheumatoid Arthritis

Lay Language Summary: Systemic idiopathic juvenile arthritis (SJIA) is a chronic childhood disease that causes arthritis, fever, rash and other kinds of inflammation (e.g. around the heart and lungs). It is unknown what causes this disease, or what drives one of its main complications, called macrophage activation syndrome. Notably, some patients respond to medication that inhibits IL-1, an inflammatory mediator made by the body. In conjunction with a trial of the IL-1 inhibitor Rilancept, we propose to investigate how IL-1 affects a particular immune cell type, the monocyte, which appears to be a key cell in SJIA pathology. We also hope to identify changes in monocytes during disease that predict response to Rilancept.
