2016

AWARD RECIPIENTS

ADVANCING TREATMENT AND FINDING CURES

LEADING INNOVATION

Patient treatment options have come a long way since the Rheumatology Research Foundation was established in 1985, but there is still so much to discover. The Foundation is pleased to continue to offer a wide variety of programs focused not only on innovative research to help advance these discoveries, but also on funding education, training, and career development for the next generation of rheumatology professionals.

The Foundation has committed nearly $10.5 million in the coming fiscal year (July 1, 2016 – June 30, 2017). About half of those awards will support the education and training of future rheumatology professionals. The rest will fund innovative research projects that will lead to breakthroughs in treating people with rheumatic diseases. Since it was established, the Foundation has committed more than $143 million to fund more than 3,000 awards, making it the largest private funding source of rheumatology research and training in the United States.

The Scientific Advisory Council oversees the process of determining which projects and programs ultimately receive funding from the Foundation. We take a great deal of pride in the peer review process to ensure every application is given a thorough and impartial assessment. Only the best of the best receive funding. I hope you will enjoy learning about these projects, and that they bring you as much anticipation and excitement about the future of rheumatology as they do for me.

TIMOTHY B. NIEWOLD, MD

CHAIR, SCIENTIFIC ADVISORY COUNCIL
RHEUMATOLOGY RESEARCH FOUNDATION

ASSOCIATE PROFESSOR OF MEDICINE
MAYO CLINIC

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INNOVATIVE RESEARCH GRANT RECIPIENTS

SUPPORTING INNOVATIVE RESEARCH IDEAS IS ESSENTIAL TO BETTER UNDERSTANDING RHEUMATIC DISEASES, THEIR CAUSES AND THE BEST WAYS TO TREAT THEM. THE INNOVATIVE RESEARCH GRANTS PROVIDE INDEPENDENT INVESTIGATORS WITH THE FUNDING THEY NEED TO PURSUE IDEAS THAT COULD LEAD TO IMPORTANT BREAKTHROUGHS IN DISCOVERING NEW TREATMENTS AND, ONE DAY, A CURE.

MICHAEL B. BRENNER, MD

BRIGHAM AND WOMEN'S HOSPITAL

IDENTIFICATION OF PATHOLOGICAL T HELPER SUBSET IN RHEUMATOID ARTHRITIS

T cell-B cell aggregates are a distinctive feature of rheumatoid synovium; however, the characteristics of the T cells that promote B cell responses within peripheral, non-lymphoid tissues remain unclear.

In lymph node follicles, "follicular helper" T (Tfh) cells, identified by CXCR5 and PD-1, are the major CD4+ T cell population that supports B cell activation and maturation. Our work to date identifies a population of PD-1hi CD4+ T cells uniquely abundant in the blood and synovial fluid of seropositive RA patients that lacks CXCR5, the canonical marker of Tfh cells, but efficiently promotes B cell differentiation into plasma cells. We find that circulating PD-1hi CXCR5neg cells and Tfh cells show remarkable similarities in phenotype, gene expression profiles, and B cell helper functions in vitro. However, PD-1hi CXCR5neg cells are distinguished by expression of cohort of receptors conferring migration to peripheral sites of inflammation. Importantly, PD-1hi CXCR5neg cells, but not Tfh cells, are significantly expanded in the circulation of seropositive RA patients.

We hypothesize that PD-1hi CXCR5neg cells are "peripheral helper" T cells optimized to support B cell responses in non-lymphoid tissues. Here, we explore the role of T peripheral helper (Tph) cells in driving pathologic B cell responses in RA patients.

In Aim I, we will evaluate the relationship between circulating Tph cell frequency and activated circulating B cells, autoantibodies, and disease activity in seropositive RA patients. In Aim II, we will map the localization of Tph and Tfh cells in RA synovium. In Aim III, we will compare the effector functions of circulating Tph and Tfh cells, and evaluate the transcriptional control of these functions by two candidate transcription factors, Maf and Blimp1.

By systematically comparing the frequency, localization, and function of "follicular helper" and "peripheral helper" T cells, we aim to define the key features of peripheral T cell-B cell interactions. Understanding these interactions is critical for identifying the pathological T cell population that drives autoantibody production in RA. Their identification may be important for developing biomarkers to identify patients most likely to respond to therapies that affect this axis and to identify new therapeutic targets that modulate this pathway.

GARY S. FIRESTEIN, MD

UNIVERSITY OF CALIFORNIA, SAN DIEGO

INTERPLAY OF GENOMICS AND EPIGENOMICS ON LBH REGULATION IN RHEUMATOID ARTHRITIS

Joint damage and synovial inflammation in rheumatoid arthritis (RA) are influenced by genetic and environmental factors. Epigenetics offers new ways to think about how environmental exposure and stress in inflamed tissues can alter gene expression and cellular function. One of the best-studied mechanisms is DNA methylation, which can profoundly alter cellular function by repressing gene expression. Methylation typically occurs on CpG loci and is mediated by DNA methyltransferases (DNMTs). Methylation status is modified by the environment or through preprogrammed events during embryonic development. DNMT expression can maintain methylation during cell division, thus preserving the cellular imprinting from the environment in daughter cells. We recently showed that RA fibroblast-like synoviocytes (FLS) exhibit a distinct DNA methylation pattern that can regulate expression of key genes. The pattern can persist for many months in vitro, suggesting that the cells are permanently imprinted. Subsequently, we integrated genetic, transcriptomic and methylation datasets for RA FLS that pointed to the Limb bud-Heart (LBH) gene as a candidate gene involved in the pathogenesis of RA. This gene, which plays a role in skeleton, cartilage and heart development,

was identified because an upstream putative enhancer contains a closely associated differentially methylated locus (DML) and an RA-associated single nucleotide polymorphism (SNP). We then showed that LBH plays a key role in synoviocyte proliferation, and low levels allow cells to progress past the G1 checkpoint in the cell cycle and begin proliferating. In this proposal, we will explore how the RA-associated DMLs and RA-associated SNPs in this regulatory region act in concert to enhance RA FLS aggressive behavior. We will accomplish this by: 1) evaluating the function of SNPs and DMLs in the LBH enhancer; and 2) determining how LBH affects cell phenotype by interacting with and regulating cell cycle genes. These data will help define the molecular mechanisms behind the destructive phenotype of RA synoviocytes, and will show how genetic and epigenetic changes influence disease severity.

VERONIQUE LEFEBVRE, PHD

CLEVELAND CLINIC

QUALITY-BY-DESIGN APPROACH TO CREATE SYNOVIAL CELLS FROM PLURIPOTENCY

Fibroblast-like synoviocytes (FLSs) and synovial stem cells (JSCs) line articular cavities and normally maintain the integrity of joints. In rheumatoid arthritis (RA), they become transformed, exhibit an aggressive cancer-like behavior, and produce proteinases, cytokines, and inflammatory mediators that contribute to the progressive destruction of joint tissues. Even when inflammation subsides in response to disease-modifying anti-rheumatic drugs (DMARDs), RA JSC/FLSs remain transformed and continue to induce joint deterioration. A main challenge in RA management is thus to find ways to directly target JSC/FLSs. This project will test the hypothesis that deep understanding of the identity of JSC/FLSs and the powerful assets of OH-Alive will allow the development of FDA-compliant protocols to generate healthy JSC/FLSs from patient-derived induced pluripotent stem cells (iPSCs). To test this hypothesis, the first aim of the project is to use cutting-edge high-throughput sequencing approaches to fully define the transcriptome and epigenome of JSC/FLSs. The second aim is to develop optimal protocols to generate healthy FLSs/JSCs from patient-derived iPSCs. OH-Alive is a novel Stem Cell Innovator Facility that combines a large-scale, automated cell-culture platform with sophisticated analysis software for Multivariate Data Analysis (MVDA) in order to implement the so-called Design-of-Experiment (DoE) approach. The founding principle of this approach is that computer-based experimental designs can provide the needed multidimensional interrogation that facilitates delineation of the exact composition of matter necessary to achieve rapid, unidirectional and complete differentiation of specific cell types. OH-Alive has already developed protocols for several nonskeletal cell types. It is anticipated that it will enable optimization of protocols that are fully defined chemically and thus FDA-compliant to generate pure populations of healthy JSC/FLSs. Once novel protocols are developed for iPSC lines from healthy donors, they will be tested and eventually adjusted with RA patient-derived iPSCs. The project will be run by a team of investigators with complementary clinical, scientific and technical expertise. New findings and protocols are expected to be instrumental in the near future to increase understanding of RA disease mechanisms and to develop fully efficacious treatments for RA patients.

ANDREW D. LUSTER, MD, PHD

MASSACHUSETTS GENERAL HOSPITAL

IN VIVO IMAGING OF ARTHRITIC JOINTS REVEALS NEW FUNCTIONS FOR OLD MEDIATORS

Joint destruction in inflammatory arthritis is caused by immune cells, which are recruited from the blood into the joint in a highly regulated process controlled by chemoattractants. The immune cell infiltrate in RA is composed of multiple cell types, including lymphocytes, macrophages and neutrophils. The neutrophil, surprisingly, makes up over 50 percent of the leukocytes found in RA synovial fluid, yet it is often overlooked as a critical cell in RA pathogenesis. Neutrophils are likely a critical cell in the initiation of joint inflammation as they are the first responders at sites of inflammation and infection. Activated neutrophils within the joint release many potent mediators, such as proteases, cytokines, chemokines and NETs that drive RA pathogenesis directly or indirectly by recruiting and activating other cells within the joint that are important in RA pathogenesis, including fibroblast-like synoviocytes (FLS). In fact, in a murine model of immune-complex induced arthritis, the neutrophil is the key cell required to initiate arthritis. Thus, the control of leukocyte entry into the joint represents a major point at which new therapeutics could be developed to attenuate inflammatory arthritis. We found that at least four different chemoattractant receptors (CKRs) contribute to neutrophil recruitment into the joint in this autoimmune immune-complex induced model of arthritis. We believe understanding the specific roles of individual chemoattractants in the process is not only of scientific interest, but it is also of practical and translational importance as it will allow the rationale combinatory targeting of receptors that may function in similar steps in the leukocyte recruitment cascade, and therefore may be required to target in combination to completely shut down ongoing arthritis. We have therefore developed techniques to apply multiphoton intravital imaging (MP-IVM) technology to visualize the process of leukocyte entry into the arthritic joint to understand specific functions for individual CKRs. Our new joint imaging technique has discovered new, unexpected biology concerning the specific functions of the chemoattractants that regulate neutrophil entry in joints in vivo. We have found that the complement C5a receptor (C5aR) plays a unique role in capturing neutrophils on the joint endothelium and was the critical initiator of neutrophil adhesion. The leukotriene B4 receptor (BLT1) was required for the initial entry of neutrophils into the joint. In contrast, CXCR2 was critical for the accumulation of neutrophils in the synovial fluid. However, many important questions still remain whose answers will inform new therapeutic approaches to block the entry of immune cells into the arthritic joint. The goal of this project therefore is to: (1) determine the mechanism by which C5a is generated and retained on the blood vessel in a biologically active form that is required to initiate neutrophil adhesion and joint inflammation, and if this process is generalizable to rheumatoid arthritis; (2) to determine how LTB4 produced from C5a-stimulated neutrophils promotes the entry of the first neutrophils into the joint in a BLT1-dependent process in vivo; and (3) to determine how chemokines are generated from neutrophils within the synovial tissue and joint space, and how they regulate neutrophil behavior once in the joint that contributes to the pathogenesis of arthritis. We believe our new method of joint MP-IVM will, for the first time, allow us to address these and many other important questions whose answers will inform novel approaches to develop new therapies for RA.

MANDY J. MCGEACHY, PHD

UNIVERSITY OF PITTSBURGH

TH17/TFH CELL FUNCTION AND REGULATION IN RA PATIENTS

Biologic drugs that specifically target the immune system have revolutionized outcomes in RA. However, ~40 percent of patients fail to respond to a given therapy. Therefore, there remains a great clinical need to understand the unique mechanisms of action of different biologics, and ultimately use this information to develop better methods to predict responses. T cell dysregulation is implicated in RA pathogenesis through genetic susceptibility studies, as well as cellular studies in patients and in mouse models. The phenotype of the pathogenic CD4+ T cell driving RA remains unclear. Th17 cells produce IL-17 and other cytokines known to activate joint-resident cells. On the other hand, T follicular helper cells (TfH) promote B cell activation and are thought to drive autoantibodies in rheumatic diseases. The proportion of TfH cells that co-express markers of Th17 cells (Th17/TfH) correlates with disease activity in juvenile dermatomyositis and Sjogren's syndrome. In new preliminary data, we show that Th17/TfH cells also correlated with disease severity in patients with active RA. Th17/TfH cells remained stable over time in RA subjects, and were not altered by TNF blockade. Th17/TfH cells pre-TNFi initiation also correlated with numbers of swollen joints after one year of therapy, suggesting a predictive value for therapy outcome. TNF inhibitors likely act downstream of T cell activation, and correspondingly TNF did not directly promote IL-17. In contrast, CTLA4Ig (abatacept) directly blocks the CD28:B7 interaction between T cells and innate cells. The effects of abatacept on Th17/TfH cells are unknown, but we did find an unexpected inhibition of human Th17 differentiation by CD28, and a corresponding enhancement of TfH development. This raises the possibility that abatacept may inadvertently alter Th17/TfH ratios in RA, contributing to therapy response. These preliminary data inform our central hypothesis that Th17/TfH cell activity in RA is one of the underlying immunopathologic factors that determines disease severity and responsiveness to different biologics. The goals of this proposal are to interrogate CD28 regulation of Th17/TfH ratios and functions, and to determine whether the different effects of TNF versus costimulation blockade on a baseline population of Th17/TfH cells contributes to outcome of biologic therapy in RA. This contribution will inform our understanding of how different therapies work in individual patients and, most importantly, why some patients respond to a particular therapy while others do not. This will ultimately lead to better decisions about how to best use these drugs in clinical practice. These data will also advance our understanding of the complex immune mechanisms that mediate RA, including the role of Th17/TfH cells which were only recently identified to contribute to autoimmune disease.

ALEXIS OGDIE-BEATTY, MD, MSCE

UNIVERSITY OF PENNSYLVANIA

OPTIMIZING CLINICAL TRIAL DESIGN IN PSORIATIC ARTHRITIS

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis associated with psoriasis, a common skin disease. PsA is a complex disease with disease manifestations including inflammatory arthritis, spondylitis, dactylitis ("sausage digits"), enthesitis (inflammation where a tendon or ligament inserts onto the bone), skin psoriasis, and nail disease. However, current PsA clinical trials focus on the peripheral arthritis. PsA trials often enroll a predominantly polyarticular phenotype and use a primary outcome derived for rheumatoid arthritis. Optimizing clinical trials to account for the complexity of PsA could result in more efficient development of safe and effective therapies and more comprehensive information for patients and physicians when selecting a therapy. The goal of this proposal is to enhance the design of clinical trials in PsA to determine the best instruments to measure disease activity in PsA and develop simulation models that can be used to guide the design of clinical trials specifically for PsA. We propose the following Aims: 1) examine the construct validity and sensitivity to change of disease activity measures used in clinical trials of PsA; and 2) simulate novel PsA clinical trials that account for the complexity of the outcomes in PsA. To address these Aims, we will utilize patient-level data from four recent clinical trials. Data from one of the trials will inform the base population for the simulation models. The simulation models will be used to project the results of clinical trials that: a) broaden the enrollment criteria to include patients representative of all patients with PsA (not just those with polyarticular disease); 2) enrich for individual disease manifestations (e.g., spondylitis); 3) use alternative outcome measures reflective of the complexity of PsA, such as composite measures; and 4) examine a head-to-head trial of two biologic agents among patients who have failed a TNF alpha inhibitor. The study team is composed of leaders in the fields of PsA clinical trials, PsA pharmacoepidemiology, PsA outcome measures and biostatistical methods for clinical trials. Access to the required datasets has been granted, allowing for successful completion of the projects within the study period. The proposed work is critical to designing clinical trials specific to PsA that maximize our knowledge about disease manifestations and improve the efficiency of PsA clinical trials.

VEENA K. RANGANATH, MD, MS

UNIVERSITY OF CALIFORNIA, LOS ANGELES

ULTRASOUND ASSESSMENT OF OBESE RA PATIENTS ON A WEIGHT-LOSS PROGRAM

Rheumatoid arthritis (RA) is a destructive autoimmune arthritic disease leading to premature patient morbidity and mortality, and the judicious use of immunosuppressive agents minimizes poor outcomes. Despite significant advances in RA therapeutic options over the last few decades, the obese RA patient, in particular, poses considerable management challenges. In the U.S., 60-70 percent of RA patients are overweight or obese. Several studies have shown that overweight/obese RA patients are less likely to achieve remission, and their therapeutic response is lower than for nonobese patients.

Due to the substantial economic and public health concerns (estimated costs of $147 billion/year), RA research groups advocate for weight loss in obese and overweight RA patients. Unfortunately, there are no currently validated interventions to control obesity in RA patients. There are limitations to the broad use of exercise regimens due to patients' and physicians' fears of aggravating disease activity; thus there is stronger appeal in diet programs to reduce weight in obese RA patients. However, there is a clear lack of evidence to substantiate dietary weight-loss programs' impact on RA disease activity, which is a major consideration for patients.

The Divisions of Nutrition and Rheumatology are uniquely poised to leverage their skills in successfully collaborating on a randomized controlled weight-loss study in obese RA patients, and to accurately assess RA clinical and imaging outcome measures (musculoskeletal ultrasound [MSUS]). We hypothesize that weight loss will not only improve validated disease activity measures in obese RA patients but also improve MSUS synovitis measures.

In a 12-week pilot randomized controlled trial of 60 obese RA patients on stable therapy (DAS28>3.2), we will investigate the efficacy of a weight-loss program in the following ways: 1) to examine whether weight loss by dietary modification will improve conventional disease activity measures (DAS28) and MSUS synovitis measures in obese RA patients; and 2) to determine if biomarkers and adipokines will correlate with DAS28 and MSUS synovitis measures.

Promising results would motivate and encourage obese RA patients to join weight-loss programs that would improve disease activity outcomes. We anticipate that the results of this pilot study will also support advocating for weight loss prior to change or escalation of RA therapy, and provide preliminary data for a larger validation study to also investigate the complexities of adiposity and RA disease severity.

TERESA K. TARRANT, MD

UNIVERSITY OF NORTH CAROLINA

LIGHT-MEDIATED DELIVERY OF THERAPEUTICS
FOR RHEUMATOID ARTHRITIS

A variety of potent anti-inflammatory/immunosuppressive agents are used to treat a number of autoimmune conditions, including rheumatoid arthritis. Unfortunately, there are a number of moderate to severe, undesirable systemic side effects associated with the long-term use of these drugs. One way to reduce or eliminate these side effects is to target drug application to sites of inflammation. Although biologics have been introduced in this regard, they are expensive, contribute to systemically delivered immune suppression with adverse outcomes, and require significant intervention by a health care provider.

We've designed a novel technology that, if further advanced, could facilitate the selective delivery of medications directly to the joint; specifically, red blood cells containing implanted molecular devices (Phototherapeutic RBCs). These species are capable of launching therapeutic agents in response to wavelength-embedded commands. Since these light-triggered molecular launching pads detect red, far-red, and near-infrared deep-tissue penetrating light, they can receive external photo instructions even when deeply embedded within tissue. The molecular basis of this strategy is derived from our recent discovery that drugs, covalently appended to vitamin B12 derivatives, can be rendered photo-releasable at wavelengths up to 800 nm. This wavelength range falls well within the optical window of tissue, and thus, in conjunction with existing light sources, potentially places therapeutic application at the site of inflammation in the hands of the patient and/or his or her physician provider.

The primary goal of this research program is to identify molecular photoresponsive constructs that, within the context of cell-mediated drug transport, facilitate the highly focused delivery of RA therapeutic agents selectively to sites of inflammation. Aim 1 seeks to assess the structure, function, and lifetime of Phototherapeutic RBCs, whereas Aim 2 will explore the ability of these cell-based therapeutics to furnish site-targeted anti-inflammatory control in a well-defined murine model of RA.

PAMELA F. WEISS, MD, MSCE

CHILDREN'S HOSPITAL OF PHILADELPHIA

SACROILIITIS IN CHILDREN WITH JUVENILE SPA:
IMPROVING DIAGNOSIS AND OUTCOMES

Improvement in the health management of children with juvenile spondyloarthritis (JSpA) is at a standstill for three reasons. First, we lack age and gender reference data for the appearance of the sacroiliac joints in the growing skeleton. This lack of reference data leads to large variations in the interpretation of imaging results for children and adolescents suspected of having spondyloarthritis. Second, radiographs remain the gold standard for diagnosis of ankylosing spondylitis because sites of bony fusion (ankylosis) are easily visualized. Given the short disease duration and rare occurrence of ankylosis in children, radiographs have less certain value and may cause unnecessary radiation exposure. Third, the effectiveness of biologics for axial disease is unclear in children.

Biologics help adults with spondyloarthritis symptomatically and may slow progression, but they do not halt it. In order to better understand the underlying pathophysiology and more effectively treat children with early axial disease, there is a critical need not only to accurately diagnose these children, but also to identify the impact of expensive biologics. Unless we address these gaps in knowledge, the development of effective and targeted intervention strategies to halt joint damage and prevent subsequent impaired function within this understudied population will remain difficult.

The long-term goal of this work is to effectively diagnose, treat, and prevent damage of the axial joints in children with JSpA. The overall objective in this application is to develop reference data for the normal appearance of the sacroiliac joints in children, ascertain the utility of radiographs in screening for sacroiliitis, and study the effects of biologics on inflammatory lesions and radiographic progression among children with sacroiliitis. The central hypothesis is that radiographs do not add incremental value to magnetic resonance imaging (MRI) in the evaluation of sacroiliitis, and that biologics are effective at minimizing both inflammatory lesions and radiographic progression in children. The proposed plan of research will address these issues by pursuing three specific aims: 1) describe the age-related MRI features of the sacroiliac joints in healthy children; 2) evaluate the accuracy of radiographs to diagnose sacroiliitis in children, as compared to MRI as the reference standard; and 3) study the effect of biologics on MRI inflammation and structural lesions in the sacroiliac joints in children.

This study is innovative because it will establish greatly needed reference data for the normal appearance of the sacroiliac joints in the growing skeleton; it will be the first study to systematically evaluate the utility of radiographs in children suspected of having JSpA; and it will be the first MRI study to evaluate the longitudinal changes of sacroiliitis in children. These contributions are highly significant because they will allow clinicians and scientists to accurately and reliably evaluate and diagnose children with axial JSpA, and predict their responses to biologics—essential steps in effectively treating and preventing irreversible damage of the axial joints in children with JSpA.

PILOT GRANT RECIPIENTS

THE PILOT GRANTS ENCOURAGE ESTABLISHED INVESTIGATORS TO BEGIN TESTS OF NOVEL RESEARCH IDEAS INTO ARTHRITIS AND RELATED INFLAMMATORY DISEASES BY PROVIDING SEED FUNDS TO GATHER PRELIMINARY DATA.

BRYCE BINSTADT, MD, PHD

UNIVERSITY OF MINNESOTA

TARGETING INFLAMMATORY JOINT PAIN WITH ULTRA-POTENT ANALGESICS

Patients with rheumatoid arthritis and other chronic inflammatory conditions typically also have chronic pain. The molecular mechanisms governing chronic inflammation and chronic pain intersect. This proposal focuses on how chemokine receptors, key mediators of inflammation, interact with opioid receptors, critical mediators of analgesia. Recent evidence suggests that neurons and leukocytes can express both chemokine and opioid receptors. Furthermore, these receptors can heterodimerize. How the heterodimers function to control pain and inflammation remains poorly understood. In this proposal, a rheumatologist and medicinal chemist have partnered to study a novel bivalent compound consisting of an opioid receptor agonist (analgesic) and chemokine receptor (CCR5) antagonist. This compound, termed MCC22, is designed specifically to treat inflammatory pain and has demonstrated exceptional potency in preliminary studies. Importantly, MCC22 does not appear to cause tolerance, a major problem limiting the use of traditional opioid analgesics for patients with chronic pain. We propose to study the analgesic and anti-inflammatory efficacy of MCC22 in a mouse model of inflammatory arthritis. Additional studies will define whether MCC22 exerts its effects by acting primarily on white blood cells or on neurons. These studies are expected to lay the groundwork for future studies using MCC22 or related compounds for the treatment of chronic pain in patients with rheumatoid arthritis and other chronic inflammatory diseases.

AILEEN Y. CHANG, MD, MSPH

GEORGE WASHINGTON UNIVERSITY

A PILOT STUDY OF THE PATHOGENESIS OF CHIKUNGUNYA ARTHRITIS IN THE AMERICAS

Chikungunya is rapidly spreading throughout the Americas and causing debilitating chronic arthritis in approximately one-fourth of patients. There is currently no standard treatment for chikungunya arthritis 3, and the mechanisms leading to this chronic arthritis are unclear. Further characterization of the disease pathophysiology is needed in order to guide evaluation of potential therapeutics and improve understanding of the mechanisms of viral arthritis in general. Our general hypothesis is that chronic chikungunya arthritis is due to persistence of active virus in the synovial fluid, where macrophages serve as a viral reservoir. The predominance of activated macrophages in persistently infected tissue, and the presence of viral genome within these macrophages in non-human primates, makes our hypothesis plausible. To test this hypothesis, we have designed a study with three specific aims. In Aim 1, we will describe how host demographics and HLA type affect susceptibility to severe or persistent arthritis. In Aim 2, we will determine if CHIKV persists in synovial fluid and synovial fluid monocytes/macrophages in humans as shown in non-human primates. In Aim 3, we will investigate how this process may be modulated by cytokines. To investigate these specific Aims, this pilot study will examine the blood and synovial fluid of 20 patients with chronic effusions after chikungunya infection. We will evaluate their serum and synovial fluid for persistent viral infection and cytokine elevations as potential therapeutic targets. To date, these pathophysiologic factors have not been well characterized in humans. Information gained from this study can directly lead to recommendations for the further evaluation of antiviral versus immune modulating therapeutics.

JARRED W. YOUNGER, PHD

UNIVERSITY OF ALABAMA AT BIRMINGHAM

BRAIN THERMOMETRY: A NONINVASIVE METHOD FOR DETECTING NEUROINFLAMMATION IN RA

Approximately half of individuals with rheumatoid arthritis (RA) complain of profound fatigue, widespread pain, and cognitive issues, even when their joint disease activity is significantly improved by mainstream medications. The reported symptoms are highly consistent with the known effects of neuroinflammation, suggesting that systemic inflammation in RA has migrated to the central nervous system. This important hypothesis is difficult to test because immune cells in the brain are not accessible to direct interrogation. Brain thermometry may provide a valid proxy for the direct measurement of neuroinflammation in humans. In our proposed approach, magnetic resonance spectroscopy (MRS) can be used to noninvasively acquire an absolute temperature across the entire brain.

The two specific Aims for this project are: (1) to determine if fatigue and other symptoms of neuroinflammation in RA are associated with higher brain temperatures; and (2) to explore region-specific brain temperatures for focal areas of neuroinflammation in RA. Fifteen individuals with RA and 15 age- and gender-matched healthy control participants will complete whole-brain (multi-voxel, multi-slice) MRSt on a 3T Siemens Magnetom Prisma scanner housed at the University of Alabama at Birmingham. The primary hypothesis is that the RA group will show significantly greater brain temperature than the control group, as well as significantly greater discrepancy between brain and body temperature. Those findings would suggest the presence of chronic brain inflammation that is not being managed by mainstream medications. A secondary hypothesis is that the abnormally elevated brain temperature will not be homogenous across the brain, but will be seen in specific brain regions associated with fatigue and malaise, such as the hypothalamus, amygdala, and rostral anterior cingulate cortex.

If successful, the MRSt method will provide the first completely noninvasive method for detecting neuroinflammation in RA. The tool could aid diagnostic accuracy, as well as treatment decisions, and can also be a useful biomarker for drug discovery and testing. The potential applications and clinical utility of non-invasive measurement of brain temperature are widespread and would be of great interest to many researchers. By calling attention to inflammation not only in the body, but also in the brain, RA patients may be more completely managed, allowing them to live a higher quality of life.

CAREER DEVELOPMENT BRIDGE FUNDING AWARDS:
R BRIDGE RECIPIENTS

THE R BRIDGE AWARD ENCOURAGES ESSENTIAL RHEUMATOLOGY RESEARCH BY SUPPORTING PROMISING INVESTIGATORS WHO ARE REVISING OUTSTANDING NIH R01 OR VA RCS/ORD AWARD APPLICATIONS.

ALISON CHANG, PT, DPT, MS

NORTHWESTERN UNIVERSITY

GAIT RETRAINING VIA VISUAL FEEDBACK TO REDUCE LOADING IN KNEE OSTEOARTHRITIS

Walking is the most common load-bearing activity and recommended as a safe, accessible, and effective form of physical activity, yet pain during walking is a frequent complaint in persons with knee OA. Gait modifications that reduce knee load and pain may serve to promote physical activity as well as delay OA progression. Given that there is no cure for OA, and it is typically progressive in nature, non-pharmacological managements that reduce load, improve symptoms, and facilitate self-management are urgently needed. This project aims to test a novel gait retraining intervention to attenuate lower-limb impact, and consequently reduce knee load and pain during walking via visual feedback, in persons with knee OA. If proven effective, this study will advance the field by providing a novel, practical, and individualized intervention strategy for persons with knee OA.

KATHERINE P. LIAO, MD, PHD

BRIGHAM AND WOMEN'S HOSPITAL

LIPIDS, INFLAMMATION AND CARDIOVASCULAR
RISK IN RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic inflammatory disease linked with 1.5-3-fold excess risk of cardiovascular disease (CVD) compared to the general population. Understanding the complex relationship between inflammation and lipids can inform strategies to reduce CV risk in RA. Treatments that reduce inflammation such as tumor necrosis factor inhibitors (TNFi) result in an increase in low-density lipoprotein cholesterol (LDL-C) levels, suggesting higher CV risk. However, large observational studies suggest the opposite, that TNFi treatment reduces CV risk. Thus, a gap in knowledge exists regarding the relationship between inflammation and lipids, and the overall impact of both on CV risk in RA. Our central hypothesis is that reducing inflammation will be associated with reduced CV risk, as reflected by advanced lipoprotein measures of composition and function, despite increases in LDL-C. In Aim 1, we will examine the relationship between changes in inflammation with changes in lipoprotein levels and function in n=200 subjects from a longitudinal RA cohort study. In Aims 2 and 3, we will recruit n=75 TNFi naive RA patients with moderate to high disease activity and use TNFi as an intervention to reduce inflammation. Inflammatory and lipid biomarkers, as well as coronary flow reserve (CFR), a validated surrogate marker of CV risk, will be measured before and after the intervention. In Aim 2, we will test the hypothesis that the inflammation is linked with subclinical myocardial injury by measuring high-sensitivity cardiac troponin (hs-cTn) levels, and that reducing inflammation would result in normalization of hs-cTn levels. In Aim 3, we will use CFR to determine the impact of reducing inflammation and changes in lipids on CV risk. The study is significant because it will elucidate the relationship between lipid measures and changes in inflammation, providing insight into better clinical management of CV risk among patients with RA.

CAREER DEVELOPMENT BRIDGE FUNDING AWARD: K BRIDGE RECIPIENT

THE K BRIDGE AWARD ENCOURAGES JUNIOR INVESTIGATORS TO CONTINUE CONDUCTING RESEARCH INTO NOVEL IDEAS WHILE REAPPLYING FOR AN NIH OR VA CAREER DEVELOPMENT AWARD.

DEEPAK KUMAR, PHD

MEDICAL UNIVERSITY OF SOUTH CAROLINA

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FEASIBILITY OF "MIND YOUR WALK" INTERVENTION FOR KNEE OA

The overarching goal is to develop an effective walking-based intervention that reduces disability and also maintains joint structure for people with knee osteoarthritis (OA). Walking disability leads to an increased risk of early death in people with knee OA. Furthermore, people with knee OA walk with movement patterns that overload the cartilage and may lead to rapid OA progression. Current gait interventions use expensive devices, target a single joint, or focus on only reducing the knee adduction moment. Furthermore, these interventions do not address adherence, dissemination, and scalability, and most do not utilize the ubiquity of mobile technology. This project proposes to demonstrate the feasibility of an innovative community-based intervention ("Mind Your Walk") that incorporates whole-body movement retraining based on biomechanical principles, along with mindful body-awareness skills. The results from this project will support the design of a larger randomized trial comparing this intervention with standard exercise programs. To achieve this goal, this project will focus on: 1) demonstrating feasibility of recruitment, adherence, and retention; 2) quantifying the variability of biomechanical and functional outcomes; and 3) development of a mobile health (mHealth) application using an iterative patient-centered approach for monitoring, gathering patient-reported outcomes, and maintaining engagement. Participants with mild-moderate radiographic and symptomatic knee OA (n=62) will participate in the feasibility study. Another group (n=20) will participate in the development of the mHealth platform. The intervention will be delivered using community-based group sessions over six months. After that the participants will practice on their own for another six months. The attention-matched control group will receive education on OA. In addition to feasibility data, knee loading during walking will be quantified using an EMG-driven knee model and gait analyses at baseline and six months. Daily activity using accelerometers and self-reported pain will be recorded at baseline and every three months for a period of one year.

CAREER DEVELOPMENT BRIDGE FUNDING AWARD: K SUPPLEMENT RECIPIENTS

THE K SUPPLEMENT AWARD ENCOURAGES JUNIOR INVESTIGATORS TO EXPAND PROMISING RESEARCH BY PROVIDING ADDITIONAL SUPPORT TO COVER RESEARCH COSTS AND HELP INVESTIGATORS BECOME INDEPENDENT.

SHAUN W. JACKSON, MD, PHD

SEATTLE CHILDREN'S HOSPITAL

CYTOKINE REGULATION OF AUTOREACTIVE B CELL ACTIVATION IN SLE

Although B cells are critical in the pathogenesis of systemic lupus erythematosus (SLE), the specific factors responsible for the initial activation of autoreactive B cells remain unclear, hampering efforts to develop targeted therapies for this disease. Recent evidence suggests that dysregulated B cell signaling can directly initiate lupus pathogenesis by promoting autoreactive T cell activation, spontaneous germinal center (GC) formation and the generation of autoantibody (autoAb)-producing plasma cells. In this context, we recently developed a novel murine SLE model that has provided important insights into the B cell-intrinsic signals required for generation of spontaneous, autoimmune GCs. Using this strategy, we uncovered a critical role for B cell-intrinsic IFN-γ signals in initiating spontaneous autoimmune GCs and systemic autoimmunity in murine SLE (Jackson SW, et al. J Exp Med, 2016). In the current proposal, we take advantage of this novel lupus model and propose a series of experiments aimed at further delineating critical B cell-intrinsic cytokine signals promoting humoral autoimmunity, focusing on: 1) the importance of B cell-derived IL-6 in promoting CD4+ T cell activation and T follicular helper cell formation; 2) the cell-intrinsic requirements for the pro-inflammatory TH1 cytokine IL-12 in driving autoimmune GC formation; and 3) dissecting the functional significance of a loss-of-function polymorphism in Tyrosine kinase 2 (TYK2P1104A), downstream of several cytokine receptors including type 1 IFN and IL-12, on B and T cell activation in SLE using a novel murine knock-in strain and primary human cells from TYK2P1104A carriers. Thus, our proposed studies promise to significantly advance our understanding of lupus pathogenesis by interrogating the immune mechanisms underlying initial breaks in B and T cell tolerance to self-antigens. Together, these studies hold the promise of informing the development of new therapies targeting specific cytokines and signaling pathways relevant to the pathogenesis of SLE.

JOANNE M. KAHLENBERG, MD, PHD

UNIVERSITY OF MICHIGAN

INTERFERON KAPPA AS A NOVEL TARGET IN CUTANEOUS LUPUS

Type I interferons (IFNs) are increased in cutaneous lupus erythematosus (CLE) lesions and contribute to disease pathogenesis, yet skin-intrinsic sources of type I IFN have not been explored. Keratinocytes are the primary source of IFN kappa (κ), a type I IFN that is a genetic risk factor for cutaneous lupus, significantly upregulated in CLE skin lesions, and is produced more robustly from systemic lupus erythematosus (SLE) vs. control keratinocytes. Importantly, neutralization of IFNκ signaling eliminates hyper-inflammatory responses to UVB in SLE keratinocytes. Thus, IFNκ primes the abundant cutaneous inflammatory response to UV light in SLE. It is consequently critical to understand the role of IFNκ in regulation of inflammatory cytokine production and recruitment of cellular infiltrates as IFNκ may prove to be a specific target for treatment or prevention of cutaneous lesions and its specific inhibition may consequently avoid side effects from systemic blockade of other type I IFNs. The overall objective for this project is to define the mechanisms and consequences of aberrant regulation of IFNκ in SLE skin. We hypothesize that dysregulation and hyper-production of IFNκ is sufficient to induce overproduction of inflammatory cytokines and chemokines in response to UVB stimulation and thus promote CLE lesion formation. The proposal will address this hypothesis by investigation of the following: Aim 1: Identify the mechanisms underlying increased production of IFNκ in lupus keratinocytes. Aim 2: Identify the mechanisms by which keratinocyte-produced IFNκ promotes inflammatory responses. Aim 3: Identify the in vivo role of IFNκ overexpression on UV-induced cutaneous inflammation and systemic autoimmunity. Completion of this work will support a paradigm shift in which keratinocyte-derived IFNκ is recognized as an important step for priming and persistence of a hyper-inflammatory response in SLE skin and is identified as a specific target for future treatment and prevention of SLE-associated skin lesions.

JASON S. KNIGHT, MD, PHD

UNIVERSITY OF MICHIGAN

LUPUS NEUTROPHILS AS INSTIGATORS OF THROMBOSIS AND AUTOIMMUNITY

Cardiovascular disease is a leading cause of morbidity in lupus patients. Among the factors driving these vascular events are so-called antiphospholipid antibodies (present in one-third of lupus patients, and the leading acquired cause of thrombosis in the United States). Our preliminary data reveal (i) that antiphospholipid antibodies trigger the release of thrombo-inflammatory structures known as neutrophil extracellular traps (NETs, tangles of chromatin expunged from dying neutrophils); (ii) that injection of patient antiphospholipid antibodies into mice accelerates NET release and thrombosis; (iii) that disrupting neutrophil-endothelium interactions can protect against antiphospholipid antibody-accelerated thrombosis; and (iv) that beta-2-glycoprotein I (β2GPI, the key autoantigen recognized by antiphospholipid antibodies) binds to NETs, creating a milieu that may influence β2GPI's antigenicity. Our hypothesis is that lupus neutrophils circulate in a primed state, reacting in exaggerated fashion to endothelial activation. At the same time, we hypothesize that NETs (released in response to either infection or antiphospholipid antibodies) propagate autoimmune responses in lupus by unmasking cryptic epitopes that reside within key autoantigens such as β2GPI. The Aims of this project are: (1) To use flow chambers lined with endothelial cells to characterize how patient neutrophils and endothelial cells interact to promote thrombosis and inflammation. (2) To leverage our novel mouse model of antiphospholipid-accelerated venous thrombosis, along with intravital microscopy, to test neutrophil-endothelium interactions as potential therapeutic targets. (3) To determine the extent to which NETs promote autoimmune responses to β2GPI, assessing autoantibody avidity in vitro and murine immune responses in vivo. Overall, these studies should yield new insight into how neutrophils and NETs mediate vascular damage and autoimmunity in lupus, with the goal of developing novel therapies that will positively impact people with rheumatic disease.

INVESTIGATOR AWARD RECIPIENTS

THE INVESTIGATOR AWARD ENCOURAGES JUNIOR INVESTIGATORS TO CONTINUE CONDUCTING INNOVATIVE RESEARCH THAT WILL BE COMPETITIVE FOR MORE SIGNIFICANT FUNDING WHILE THEY ESTABLISH THEMSELVES AS INDEPENDENT INVESTIGATORS.

SHARON BOUT-TABAKU, MD, MSCE

THE RESEARCH INSTITUTE AT NATIONWIDE CHILDREN'S HOSPITAL

CHILDHOOD OBESITY AND MUSCULOSKELETAL DISEASE

The childhood obesity epidemic promises to adversely affect current and future joint health and function of children and adolescents. In adolescents, obesity is associated with lower extremity pain, poor health-related quality of life, and poor physical function and fitness, all indicators of joint morbidity. Emerging research shows that knee alignment, stance, movement patterns and postural stability in obese children are aberrant compared to nonobese children, which suggests abnormal loading mechanisms. The developing adolescent joint may be especially vulnerable to abnormal loads, which confers a greater risk of premature osteoarthritis (pre-OA); alternatively, adolescence may be a window of opportunity to intervene and prevent long-term sequelae of abnormal loading.

The central hypothesis is that sustained weight loss is expected to improve joint risk indicators such as lower extremity pain and function. Additionally, I hypothesize that weight loss improves performance outcomes through the mechanisms of improved movement patterns and neuromuscular control. Aim 1 will be a retrospective analysis of the Teen Longitudinal Assessment of Bariatric Surgery database to test the effect of weight loss on lower extremity joint pain and function on obese teens that completed bariatric surgery at multiple time points over three years. Aim 2 will be a prospective study of obese teens undergoing weight loss to test the effect of weight loss on objective performance measures over six months and determine predictors of improved performance. A secondary aim will test associations between improved objective performance and self-reported outcomes of knee-related quality of life and function.

I anticipate that weight loss in obese teens improves joint pain, function, and performance through improved lower extremity biomechanics. The results will suggest mechanisms to target, in addition to weight loss, that improve performance, biomechanics, and modify pre-OA risk factors.

ALICE CHAN, MD, PHD

UNIVERSITY OF CALIFORNIA SAN FRANCISCO

CHARACTERIZING MOSAIC, A NOVEL GENE CAUSING AUTOIMMUNITY

Autoimmune diseases arise from a breach in immune tolerance to self-antigens leading to immune destruction of various organ systems. A novel candidate gene, Mosaic (Multi-Organ System Autoimmunity in Canines), was recently identified as the culprit causing an early and severe multi-organ autoimmunity in a purebred canine population. This unique breed of dogs develops early-onset Addison's disease, arthritis, autoimmune cytopenias, hepatitis and uveitis. Adrenal tissue from affected dogs revealed a T cell infiltrate suggesting a T cell mediated autoimmune process. This gene has little known function and is conserved across all known vertebrae species, including humans and mice. The affected dogs possess a single-point mutation, resulting in an amino acid change of a proline to leucine residue in a highly conserved region. We have generated a Mosaic reporter mouse, which revealed differences in expression levels at various stages of T cell development. Thus, we hypothesize that Mosaic disrupts T cell tolerance, which leads to multi-organ autoimmunity. In Aim 1, using the reporter mouse, we will evaluate the expression of Mosaic in cellular subsets involved in central and peripheral tolerance. In Aim 2, we will characterize a mouse model carrying the mutant Mosaic allele. These studies will shed light on the role of this novel gene in mediating early-onset and severe multi-organ autoimmunity, which may lead to new therapeutic targets in treating autoimmune diseases.

LAUREN A. HENDERSON, MD, MMSC

BOSTON CHILDREN'S HOSPITAL

EMERGENCE OF TH17 AND TREG DYSREGULATION IN SJIA

Systemic juvenile idiopathic arthritis (sJIA) is set apart from other subtypes of JIA by its dramatic presentation that is characterized by fevers, rashes, and inflammation. This initial systemic phase of the disease is driven by inflammatory cytokines, including IL-1β and IL-6. In half of affected patients, the disease follows a biphasic course with improvement of the systemic symptoms and subsequent establishment of chronic arthritis. The factors that promote development of chronic arthritis in a subset of sJIA patients are not currently understood. It's known that IL-1β and IL-6 stimulate TH17 differentiation in naïve CD4+ T cells, while polarizing regulatory T (Treg) cells toward a TH17 phenotype. We propose that IL-1β and IL-6 excess in early sJIA is responsible for shifting the T cell compartment away from tolerogenic Treg cells toward pro-inflammatory TH17 cells, thus promoting the development of chronicarthritis.

To test this hypothesis, we propose three research Aims that will utilize novel technology to delineate the T cell compartment in sJIA. Cytometry Time of Flight immunophenotyping will be used to characterize T cell activation and T-helper lineage-specific markers in single Treg and Teff cells from patients with acute and chronic sJIA. Next-generation sequencing techniques will be leveraged to study T cell receptor repertoire diversity and clonality over the course of the disease. Finally, Treg function will be assessed through suppressive and Treg induction assays.

We expect to document progressive T cell-driven autoimmunity in sJIA with skewing of T cells toward a TH17 phenotype with reduced Treg function. The results of this study will aid in our understanding of the role of T cells in the pathophysiology of sJIA. If correct, our hypothesis would have a strong implication for the treatment of sJIA, indicating the need for first-line anti-cytokine therapy in sJIA to prevent T cell dysfunction and chronic arthritis.

SCIENTIST DEVELOPMENT AWARD RECIPIENTS

THE SCIENTIST DEVELOPMENT AWARD ENCOURAGES RHEUMATOLOGISTS AND RHEUMATOLOGY HEALTH PROFESSIONALS TO PURSUE INNOVATIVE BIOMEDICAL OR CLINICAL RESEARCH IDEAS.

ERIC J. ALLENSPACH, MD, PHD

SEATTLE CHILDREN'S HOSPITAL

SH2B3 IN AUTOIMMUNITY

Multiple non-HLA regions contribute genetic risk for development of rheumatoid arthritis (RA). Given the lack of validation of many GWAS loci, we developed an integrated approach to test human autoimmune risk alleles falling in genes of interest. One of the most promising loci associated with RA is 12q24.12, containing a proposed causal variant rs3184504 in the gene SH2B3. SH2B3 (also termed LNK) is an adaptor protein regulating both receptor and non-receptor tyrosine kinase signaling in leukocytes. The amino acid change in SH2B3 represents a strong causal candidate to explain the genetic autoimmune risk at this locus for RA and other autoimmune diseases. To date, no mechanistic studies evaluating the protein variant have been performed. We propose to introduce human SH2B3 variants into primary cells and lines using lentiviral transduction to study functional responses and characterize protein interactions using mass spectrometry. We created a novel murine knock-in model that introduces the human genetic variant into the conserved homologous murine locus, allowing further manipulation and study of the immune system with or without the variant on a uniform genetic background. In parallel, we will validate findings from the murine studies using an extensively genotyped biorepository of human peripheral blood samples. Lastly, we have established the DR4-IE transgenic mouse model of RA induced by citrullinated fibrinogen immunization. The model mimics the loss of tolerance to post-translationally modified host proteins increasing affinity to the shared epitope in HLA-DR4. The founder SH2B3 knock-in mice have been crossed to these mice to explore the role of the SH2B3 variant in the development or severity of RA. The direct testing of the SH2B3 variant in altering immune responsiveness or homeostasis remains critical to understanding the genetic risk of complex traits like RA.

LINDSAY B. KELMENSON, MD

UNIVERSITY OF COLORADO DENVER

PERIODONTAL INFLAMMATION AND IMMUNITY IN PRECLINICAL RA

Autoantibody (Ab) positivity prior to the appearance of the clinically apparent inflammatory arthritis (IA) of classifiable rheumatoid arthritis (RA) suggests that these Abs are generated outside of the joints. Importantly, several lines of evidence point to the mucosa as the site of this generation, including findings from our lab where we utilized a unique cohort of subjects who are at high risk for future RA to demonstrate that RA-related Abs are generated in the lung.

Notably, these studies have provided us with highly informative subjects, as well as the laboratory and analytic tools for studying the generation of RA-related Abs at a mucosal surface. However, in some subjects who had serum elevations of RA-related Abs, there were no elevations of RA-related Abs in their sputum, suggesting that there may be other mucosal sites for the generation of these Abs. To that end, there is strong evidence suggesting that periodontal disease and certain bacterial organisms play a role in the generation of RA-related autoimmunity.

However, a major gap is that clinical evaluation of periodontal disease, as well as the oral generation of RA-related Abs, has not been well characterized in those at high risk for future development of RA. Therefore, for this project, we will perform periodontal examinations, testing for ACPAs in gingival crevicular fluid, and microbial analyses in our well-established cohort of subjects who are at risk for future RA. These experiments will test a central hypothesis that periodontal inflammation is associated with ACPA positivity in the absence of IA and a site of generation of RA-related autoimmunity in association with specific bacterial organisms.

MICHAEL D. GEORGE, MD

UNIVERSITY OF PENNSYLVANIA

PERIOPERATIVE USE OF BIOLOGICS AND THE RISK OF INFECTION

The overall goal of this project is to better understand the risks of biologic therapy in the perioperative period, specifically whether biologic agents should be stopped before surgery and, if so, the optimal timing of stopping therapy. With the mentorship of Joshua Baker and Peter Merkel at the University of Pennsylvania, and the expertise and guidance of Jeffrey Curtis and his team at the University of Alabama, we propose to use national Medicare claims data from 2006 to 2013 to study whether the timing of biologic therapy before surgery is associated with postoperative complications.

We will identify patients with rheumatoid arthritis, inflammatory bowel disease, psoriatic arthritis, psoriasis, or ankylosing spondylitis who have received a biologic infusion within six months of elective total knee or hip arthroplasty. Because biologic infusions are coded as procedures in Medicare claims data, precise timing of medication exposure is available. The large size of the database will provide adequate power and allow for the adjustment for multiple confounders. The primary outcomes of interest are serious infection within 30 days of surgery and prosthetic joint infection within one year. Additional postoperative outcomes will also be explored. The overarching hypothesis being tested is that holding biologic therapy for greater periods of time before surgery reduces the risk of postoperative infection.
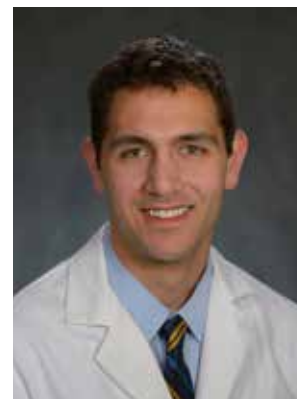
LIN SHEN, MD, PHD

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

LOSS OF ZAP-70 AUTOINHIBITION LEADS TO AUTOIMMUNITY

ZAP-70, a protein tyrosine kinase, is critical for T cell receptor (TCR) signaling and T cell development. Complete loss of function of ZAP-70 in humans causes severe immunodeficiency. Autoimmune disease due to mutant ZAP-70 alleles in human patients has not been reported. The Puck and Weiss labs recently discovered that compound heterozygous mutations R192W/R360P in ZAP-70 are responsible for a new familial autoimmune syndrome manifested as bullous pemphigoid, colitis, proteinuria, and autoantibody to factor VIII. Preliminary data from cell lines showed that the maternal allele R192W is a hypomorphic allele that leads to reduced binding of mutant ZAP-70 to the phosphorylated zeta-chain. In contrast, the paternal allele R360P in the catalytic domain causes weak constitutive activation of the TCR pathway that is suppressed by the wild type but not the R192W allele. K362E, a mutation adjacent to R360P, is an even stronger activator of the TCR signaling.

The proposed study will be directed toward obtaining a more detailed understanding of how the newly discovered hypermorphic mutant alleles in ZAP-70 affect TCR signaling, lymphocyte development and how mutations in ZAP-70, a gene primarily expressed in T and NK cells, lead to a primarily autoantibody-mediated autoimmunity.

My central hypothesis is that the R360P and K362E hypermorphicalleles of ZAP-70 result in enhancing TCR signaling through disruption of ZAP-70 autoinhibition, thereby leading to dysregulation of lymphocyte development, alteration of the balance between the immunogenic and tolerogenic processes, and the increase in antigen sensitivity leads to autoimmunity. I will test this hypothesis using ZAP-70 deficient Jurkat T cells or thymocytes reconstituted with mutant alleles of ZAP-70 and through generation of knock-in mice with R360P or K362E mutants of ZAP-70 using CRISPR. I anticipate the results of the study will provide us further insights into the role of TCR signaling in the development of autoimmunity.

ELENI TINIAKOU, MD

JOHNS HOPKINS UNIVERSITY

SPECIFIC CD4+ T CELLS IN ANTI-HMGCR AUTOIMMUNE MYOPATHY

Anti-HMGCR associated autoimmune myopathy is a type of myositis defined by the presence of autoantibodies against the C-terminus of HMGCR enzyme. This disease has a stunning association with statin exposure and the presence of HLA allele DR1*1101. Anti- HMGCR autoimmune myopathy provides a unique opportunity to understand the activation of CD4+ T cells, in the sense that it has a well-defined environmental trigger (statins), specific HLA framework (HLA DR1*1101) and is organ specific (skeletal muscle). One of the key questions in autoimmunity has been the nature of the trigger that activates the CD4+ T cells in a highly specific way. Therefore, unveiling the mechanism of CD4+ T cell activation in HMGCR myositis would be critical for establishing a meaningful model describing the relationship between statins as an environmental trigger and the development of autoimmunity. This will guide the study of other autoimmune diseases with related, but more complex, pathogenesis. Our hypothesis is that anti-HMGCR associated autoimmune myopathy is mediated by HMGCR-specific CD4+ T cells in an HLA DRB1*11:01-restricted fashion. HMGCR-specific T cells act on B cell activation and cause differentiation into plasma cells, resulting in autoantibody production. Our goal is to identify and characterize these specific CD4+ T cells using an in vitro T cell activation assay and also measure the effect of statins. We also want to determine the epitopes recognized by HMGCR-specific CD4+ T cells in DRB1*1101+ patients with anti-HMGCR associated autoimmune myopathy. This will be done through isolation and characterization of the peptides presented by dendritic cells incubated with HMGCR, with and without statins. We will use those peptides to identify the immunodominant epitopes, which have potential uses for monitoring and therapy.

ZACHARY S. WALLACE, MD

MASSACHUSETTS GENERAL HOSPITAL

PHENOTYPES AND BIOMARKERS OF IGG4-RELATED DISEASE

IgG4-related disease (IgG4-RD) is a systemic fibro-inflammatory condition responsible for organ damage, chronic morbidity, and death. It is considered an autoimmune disease given the identification of autoantibodies and suspected culprit autoantigens. The central goal of this grant is to fill critical phenotypic, etiologic, and management knowledge gaps in the field.

Knowledge of IgG4-RD as a systemic condition with diverse manifestations is limited because no study has included patients of all major ethnic backgrounds with diverse manifestations from multiple centers. We hypothesize that clinically meaningful phenotypic subtypes exist. In Aim 1, we will investigate this using an international multicenter, cross-sectional cohort assembled through an existing international collaboration of approximately 30 centers (N=1,000). We expect that organ involvement and other manifestations, but not ethnicities, will distinguish disease subtypes.

Similarities between allergic conditions and IgG4-RD, including elevations in IgG4, IgE, and absolute eosinophilia, in addition to frequent co-occurrence, have led to hypotheses that allergic conditions may be more common among IgG4-RD subjects. We will investigate this in Aim 2 through a case-control study using a single-center cohort (N=200) and matched controls. We expect IgG4-RD to be more often associated with a history of allergic conditions.

Effective treatments exist but flares are common, and longitudinal management is haphazard because of our inability to predict flares. We have identified circulating plasmablasts and SLAMF7+ CD4+ Te/m cells as likely pathogenically important cells that might serve as biomarkers in IgG4-RD. In Aim 3, we will retrospectively study these circulating cells as biomarkers of disease activity using a cohort of 100 patients. We expect plasmablasts to perform better than serum IgG4 and SLAMF7+ T cells as biomarkers.

The proposed project combines research in clinical epidemiology with sophisticated training and exceptional mentoring to position Dr. Wallace for a K23 application and a future career as an independent clinical.

The largest named endowment at the Rheumatology Research Foundation, established by a past president and member of the American College of Rheumatology, provides a permanent source of support in basic science research career development of early career investigators. Established in 2014 with a generous commitment from Mrs. Tobé and Dr. Stephen E. Malawista, who served his entire career at Yale University, this endowment ensures that physician scientists are able to continue their academic careers in vital rheumatic disease research. Annually, the Foundation's Scientific Advisory Council chooses an outstanding recipient of the Scientist Development or Investigator Awards to receive the Malawista designation.

DEEPAK A. RAO, MD, PHD

BRIGHAM AND WOMEN'S HOSPITAL

PD-1+ PERIPHERAL HELPER CD4+ T CELLS IN RA SYNOVIUM
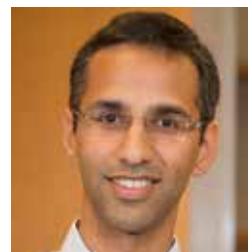
T cell-B cell aggregates are a distinctive feature of rheumatoid synovium. While T cell-B cell interactions within lymph nodes are increasingly well characterized, the T cell populations that promote B cell responses within peripheral, nonlymphoid tissues remain unclear. Our preliminary data reveal that a large fraction of CD4+ T cells in RA synovial fluid, identified by surface PD1, express a transcriptional program that strongly suggests B cell helper function. These cells lack CXCR5, which is commonly used to identify B cell-helping "follicular helper" T cells (Tfh). However, global expression profiling reveals a striking similarity between subpopulations of Tfh (PD1+ CXCR5+) and PD1+ CXCR5- cells. We find that both Tfh cells and PD1+ CXCR5- cells in circulation can promote plasmablast differentiation in vitro. We propose that PD1+ CXCR5- cells and Tfh cells share a common B cell helper capacity, but differ in their migratory patterns. Importantly, PD1+ CXCR5- cells, but not Tfh, are expanded in the circulation of active seropositive RA patients and decrease with response to DMARDs. Here, we explore the hypothesis that PD1+ CXCR5- cells are "peripheral helper" T cells (Tph) that promote B cell responses in synovium. In Aim 1, we will map the localization of Tph and Tfh in RA synovium. In Aim 2, we will compare the global transcriptomes of Tph and Tfh. In Aim 3, we will compare the functions of B cells stimulated by Tph and Tfh in vitro. By systematically comparing localization, gene expression, and function of "follicular helper" and "peripheral helper" T cells, we aim to define the key features of peripheral T cell-B cell interactions. Understanding these interactions is critical for identifying new therapeutic targets that modulate this pathway, and for developing biomarkers to identify patients most likely to respond to therapies that affect this axis.

CLINICIAN SCHOLAR EDUCATOR AWARD RECIPIENT

THE CLINICIAN SCHOLAR EDUCATOR AWARD SUPPORTS EDUCATORS DEDICATED TO DEVELOPING NEW AND IMPROVED PROGRAMS TO ENHANCE EDUCATION IN MUSCULOSKELETAL AND RHEUMATIC DISEASES FOR FUTURE DOCTORS AND RHEUMATOLOGY HEALTH PROFESSIONALS.

ARUNDATHI JAYATILLEKE, MD

DREXEL UNIVERSITY COLLEGE OF MEDICINE

GAME-BASED LEARNING IN RHEUMATOLOGY

Medical students are traditionally introduced to clinical skills via formal didactic lectures and hands-on workshops. Physical diagnosis rounds and standardized patient interviews often supplement this instruction. Although studies suggest that case-based and computer-based tools are effective methods of supplementing clinical skills curricula, clinical case instruction in a game-based environment has not yet been studied as an adjunct to the traditional curriculum.

I propose to develop an online digital game to teach elements of the musculoskeletal physical exam in the context of rheumatoid arthritis (and, ideally, other rheumatologic illnesses). My larger goal is to expand the learning tool to other areas of rheumatology instruction and other parts of the physical exam. The platform for this is an already-developed web-based application that simulates patient care in a virtual learning environment. The platform allows for interaction with a simulated patient, multimedia content that I will use to demonstrate musculoskeletal exam maneuvers, as well as links to outside resources and assessment questions during the case. These cases will be designed to augment the current curriculum for medical students learning clinical skills.

PEDIATRIC VISITING PROFESSORSHIP RECIPIENTS

The Pediatric Visiting Professorship provides support for a board-certified professor of pediatric rheumatology to visit an academic institution, ensuring that medical students and residents gain valuable exposure to pediatric rheumatology. Funding for this award is made possible through an endowment provided by Amgen, Inc.

B. ANNE EBERHARD, MBBS, MSC,
to visit University of Nevada
School of Medicine

SAMPATH PRAHALAD, MD, MSC
to visit University of Oklahoma at Tulsa

JENNIFER HUGGINS, MD
to visit Meharry Medical College

JAY MEHTA, MD, MS
to visit Marshall University School
of Medicine Program

ROBERT C. FUHLBRIDGE, MD, PHD
to visit Tulane University
School of Medicine

JIM JARVIS, MD
to visit Rush University Medical College

FELLOWSHIP TRAINING AWARD RECIPIENTS

The Fellowship Training Awards support the training of a rheumatology fellow to provide a more robust and highly trained workforce to care for people with rheumatic diseases.

TUFTS MEDICAL CENTER
Amgen Fellowship Training Award

UNIVERSITY OF PENNSYLVANIA
Amgen Fellowship Training Award

UNIVERSITY OF COLORADO DENVER
Amgen Fellowship Training Award

BAYLOR COLLEGE OF MEDICINE
Amgen Fellowship Training Award

JOHNS HOPKINS UNIVERSITY
Amgen Fellowship Training Award

DUKE UNIVERSITY
Amgen Fellowship Training Award

GEORGETOWN UNIVERSITY
Amgen Fellowship Training Award

NYU SCHOOL OF MEDICINE
Amgen Fellowship Training Award

THE CHILDREN'S HOSPITAL OF PHILADELPHIA
Paula de Merieux Fellowship Training Award
Funding for this award is made possible through an endowment from the estate of Paula de Merieux, MD

UNIVERSITY OF CALIFORNIA, SAN DIEGO
Amgen Fellowship Training Award

MASSACHUSETTS GENERAL HOSPITAL
Amgen Fellowship Training Award

UNIVERSITY OF CALIFORNIA, LOS ANGELES
Amgen Fellowship Training Award

HEALTH PROFESSIONAL ONLINE EDUCATION GRANT

The Health Professional Online Education Grant covers the cost of registration for either the Fundamentals of Rheumatology Course or the Advanced Rheumatology Course in order to increase the knowledge and skills of rheumatology professionals so they are better equipped to meet the needs of a growing rheumatology patient population.

ARLIZBETH ESTRADA ARIZANGA-LUNA, RN, BS
Pacific Arthritis Care Center

CHELSEA AUSTEN, MSPAS, PA-C
Columbus Arthritis Center

HANA CONLON, PNP, MSN, BSN
Columbia University Medical Center

MAIA ENTROPO, MS, ANP-C
Santa Cruz Rheumatology

MELISSA MICHELLE FELDER, FNP
Carolina's Medical Alliance- Rheumatology

ANDREA THERESA FRANTZ, MA, MSN, RN
Yale University

THERESA JENSEN, BSN, MSN
Michigan Rheumatology Group

BEVERLY J. METZE, MSN
Margaret Mary Health

LAURA REBECCA NEWEY, FNP-C
The Center for Rheumatology

LITING H. SUDANO, MSN, FNP-C
Catalina Pointe Rheumatology

ANNUAL MEETING AWARDS

ANNUAL MEETING AWARDS RECOGNIZE SCHOLARSHIP AMONG ASPIRING RHEUMATOLOGY PROFESSIONALS AND PROVIDE THEM THE OPPORTUNITY TO ATTEND THE PREMIERE SCIENTIFIC MEETING IN THE FIELD.

MEMORIAL LECTURESHIPS

Memorial lectureships honor rheumatology professionals who have made significant contributions to the field during his or her lifetime. The lectureships are presented each year at the ACR/ARHP Annual Meeting and feature outstanding investigators in various areas of rheumatology research.

Edmund L. Dubois, MD, Memorial Lectureship
KAREN H. COSTENBADER, MD, MPH

Paul Klemperer, MD, Memorial Lectureship
GARY S. FIRESTEIN, MD

Oscar S. Gluck, MD, Memorial Lectureship
KENNETH G. SAAG, MD, MSC

Memorial Lectureship *in Honor of Ephraim P. Engleman*, MD
ART WEISS, MD, PHD

MARSHALL J. SCHIFF, MD, MEMORIAL FELLOW RESEARCH AWARD RECIPIENTS

The Marshall J. Schiff, MD, Memorial Fellow Research Award encourages fellows to continue rheumatology research by providing an opportunity for them to present an abstract at the ACR/ARHP Annual Meeting. *Funding for this award is made possible through an endowment from Dr. and Mrs. Michael H. Schiff and friends.*

BRYANT ENGLAND, MD
University of Nebraska Medical Center

NICOLE YANG, MD
Brigham and Women's Hospital

PEDIATRIC RESEARCH AWARD RECIPIENTS

The Pediatric Research Award motivates residents and fellows to pursue subspecialty training in pediatric rheumatology by providing an opportunity to experience the field firsthand and present an abstract at the ACR/ARHP Annual Meeting.

LAURA RENE BALLENGER, MD
Nationwide Children's Hospital

DANIELLE BULLOCK, MD
University of Minnesota

MARGARET CHANG, MD, PHD
Boston Children's Hospital

SABRINA GMUCA, MD
The Children's Hospital of Philadelphia

CYNTHIA K. MANOS
The Children's Hospital of Philadelphia

MEDICAL AND PEDIATRIC RESIDENT RESEARCH AWARD RECIPIENTS

The Medical and Pediatric Resident Research Award motivates residents to pursue subspecialty training in rheumatology by providing an opportunity to experience the field firsthand and present an abstract at the ACR/ARHP Annual Meeting.

SARAH K. HASERODT, MD, BA

California Pacific Medical Center

MANJINDER KAUR, DO

University of Arizona

IRENE LAZARUS, MD

Texas Tech El Paso

ERNEST MANINGDING

Santa Clara Valley Medical Center

STUDENT ACHIEVEMENT AWARD RECIPIENTS

The Student Achievement Award encourages medical and graduate students to consider a career in rheumatology by recognizing promising work and providing an opportunity to present an abstract at the ACR/ARHP Annual Meeting

RASHID HASSAN AHMED, BS

Brown University

DESIREE AZIZODDIN, MA

Jesse Brown VA Medical Center

J. HEATHER BRUNNER, SPT

University of Illinois at Chicago

MATTHEW CHEUNG

Washington University School of Medicine

MARY LOUISE FOWLER

Boston University School of Medicine

SONIA JANE KHATTER, BS

University of Colorado School of Medicine

DAVID KREPS, BS

Brigham and Women's Hospital

LAURA A MCINTOSH, BA

Cincinnati Children's Hospital Medical Center

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Geisel School of Medicine at Dartmouth

MALKI S. PESKIN, BA

Albert Einstein College of Medicine

TAYLOR POSPISIL, BA, BS

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Baylor College of Medicine

DIANA M. TOLEDO, MS

Dartmouth College

STUDENT AND RESIDENT ACR/ARHP ANNUAL MEETING SCHOLARSHIP RECIPIENTS

The Student and Resident ACR/ARHP Annual Meeting Scholarship encourages students and residents in areas of the United States underserved by rheumatology professionals to consider a career in the field by providing them the opportunity to experience rheumatology firsthand at the ACR/ARHP Annual Meeting.

RASHID HASSAN AHMED, BS

Brown University

MUHSEN AL-ANI, MD

Maricopa Integrated Health System

ZUHAL ARZOMAND, MD

Roger Williams Medical Center

YASHARA AVERY BS, AS

Piedmont Technical College

ADAM BERLINBERG

University of Arizona

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Medical University of South Carolina

IDONA BREWER, MD, BA

University of Louisville School of Medicine

ELIZABETH BUI, MD

University of Mississippi Medical Center

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MEREDITH CHRISTIANSEN, PT, DPT

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Piedmont Technical College Newberry

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Maine Medical Center

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Tulane Medical Center

TIFFANY PHANHDONE, BS

Northwestern University

KELLY D. PIPPIN

University of Mississippi Medical Center

SARA PORTER

University of Mississippi Medical Center

CHRISTOPHER J. REDMOND, MD MSC

University of Kentucky

SONIA IQBAL SAVANI, MD

Medical University of South Carolina

JAVANEH TAMIJI, MD

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Banner University Medical Center

ANN VO

University of Vermont Medical Center

SASHA WALDSTEIN, MD

University of Vermont Medical Center

LINDA WANG, MPH

Tulane University

PRECEPTORSHIPS

PRECEPTORSHIPS ENCOURAGE STUDENTS AND RESIDENTS TO LEARN MORE ABOUT RHEUMATOLOGY AND PURSUE CAREERS IN THE FIELD BY SUPPORTING A ONE-ON-ONE, REAL-WORLD LEARNING EXPERIENCE.

RESIDENT RESEARCH PRECEPTORSHIP RECIPIENTS

The Resident Research Preceptorship encourages residents to consider a career in rheumatology research by supporting a full-time, in-depth research experience with an established rheumatology professional.

SARAH BAXTER, MD, PHD
Preceptor: Troy Torgerson, MD, PhD
University of Washington, Seattle
Children's Hospital

HEATHER BERENS-NORMAN, MD, PHD
Preceptor: M. Kristen Demoruelle, MD
University of Colorado Denver

SEBASTIAN BRUERA, MD
Preceptor: Sandeep K. Agarwal, MD, PhD
Baylor College of Medicine

PHILIP CHU, MD
Preceptor: Alfred Kim, MD, PhD
Washington University

RESIDENT RESEARCH PRECEPTORSHIP RECIPIENTS (CONTINUED)

ISAAC HARLEY, MD, PhD

Preceptor: Kevin Deane, MD, PhD
University of Colorado

TYLER STEPHENS REESE, MD

Preceptor: C. Michael Stein, MD
Vanderbilt University Medical Center

KIMBERLY SHOWALTER, MD

Preceptor: Monique Hinchcliff, MD, MS
Northwestern University

LAWREN H. DALTROY HEALTH PROFESSIONAL PRECEPTORSHIP

MEREDITH B. CHRISTIANSEN, BS, DPT

Preceptor: Daniel K. White, PT, ScD, MSc
University of Delaware

MEDICAL AND GRADUATE STUDENT PRECEPTORSHIP

The Medical and Graduate Student Preceptorship encourages medical and graduate students to consider a career in rheumatology by supporting a clinical or research mentorship with an established rheumatology professional.

BRITNI BEAGLEY

Preceptor: Robert W. Janson, MD
Denver VA Medical Center

KEVIN JAMES BYRNE

Preceptor: Robert H. Shmerling, MD
Beth Israel Deaconess Medical Center

JESSE C. CHRISTENSEN, DPT, PHD(C)

Preceptor: Jennifer Stevens-Lapsley, MPT, PhD
University of Colorado Denver

JOCELYN DURLACHER, BS

Preceptor: Cecilia P. Chung, MD, MPH
Vanderbilt University School of Medicine

KYLE FAHEY

Preceptor: Kaveh Ardalan, MD, MS
Northwestern University Feinberg School of Medicine

KATHARINE J. FOSTER, BS

Preceptor: Terry Moore, MD
Saint Louis University

DANIEL GEATING

Preceptor: Diane Kamen MD, MSCR
Medical University of South Carolina

DANIEL GRATCH, BA

Preceptor: Amit Saxena, MD, MS
New York University School of Medicine

MEDICAL AND GRAUDATE STUDENT PRECEPTORSHIP (CONTINUED)

JEANNE GOSSELIN
Preceptor: Edward Leib, MD
University of Vermont Medical Center

JOHNATHAN JIA, BS
Preceptor: John Reveille, MD
The University of Texas Health, McGovern Medical School

MEGHAN JOBSON
Preceptor: Mary Anne Dooley, MD
University of North Carolina at Chapel Hill

CHRISTINA L. KEARSE, BS
Preceptor: Diane L. Kamen, MD, MSCR
Medical University of South Carolina

JOSHUA KWON
Preceptor: Faye Hant, DO
Medical University of South Carolina

WENDY LI, BS
Preceptor: Daniel E. Furst, MD
University of California, Los Angeles

SAHAR LOTFI-EMRAN, BA
Preceptor: George Moxley, MD
Virginia Commonwealth University School of Medicine

POOJA MAHADESHWAR, BS
Preceptor: Anca Askanase, MPH, MD
Columbia University Medical Center

SHAWN A. MAHMUD, BA, PHD
Preceptor: Bryce A. Binstadt, MD, PhD
Regents of the University of Minnesota

DIVYA NARAYANAN, BA
Preceptor: Rebecca Cleveland, PhD
University of North Carolina, Chapel Hill

KUNWAL NASRULLAH
Preceptor: Robert H. Shmerling, MD
Beth Israel Deaconess Medical Center

TRAM NGUYEN
Preceptor: Kristen Demoruelle, MD
University of Colorado Denver

SUN JUNG OH
Preceptor: Laura Carbone, MD
Medical College of Georgia

CHARLES OSHINSKY
Preceptor: Svetlana Krasnokutsky Samuels, MD
NYU School of Medicine

DARSHAN RANDHAWA, BS
Preceptor: Ram Raj Singh, MD
UCLA Geffen School of Medicine

RACHELLE RIGAUD
Preceptor: Nancy J. Olsen, MD
Penn State Hershey Medical Center

JUDITH FAYE STAUB, BS
Preceptor: Carol Feghali Bostwick, PhD
Medical University of South Carolina

RACHEL TAN, BS
Preceptor: Grant Schulert, MD, PhD
Cincinnati Children's Hospital Medical Center

THOMAS WINANS, BS
Preceptor: Andras Perl, MD, PhD
SUNY Upstate Medical University

BRANDON WYMAN, BS
Preceptor: Andras Perl, MD, PhD
SUNY Upstate Medical University

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