Rheumatology Research Foundation

2021
AWARD RECIPIENTS

Advancing Treatments, Finding Cures

35TH

ANNIVERSARY

LEGACY OF LEADERSHIP

This year marks the 35th anniversary of the Rheumatology Research Foundation. Since 1985, the Foundation has committed more than $192 million to fund more than 3,945 awards, making it the largest private funding source of rheumatology research and training in the United States. By advancing research and training, the Foundation is working to provide patients with better treatment and increased access to the rheumatology professionals specially trained to care for them.

While the growth and impact of the Foundation have been substantial, I have been inspired by the legacy of leadership that built this organization in a way that not only allowed, but encouraged, an emergency response to something that could not have been predicted. In October of 2020, the Foundation committed $1.65 million to fund five research studies exploring the relationships between rheumatic diseases and SARS-CoV-2, the virus that causes COVID-19, as well as the pandemic's effect on healthcare delivery. This COVID funding initiative adds to the existing extensive portfolio of other research funded through the Foundation's Awards and Grants program. These projects are included in the list of 2021 award recipients.

In fiscal year 2022 (July 1, 2021 – June 30, 2022), the Foundation is committing $12,836,250 to fund approximately 250 awards. Roughly a quarter of these awards will support efforts to recruit and train the next generation of rheumatology professionals, which will reduce patient wait times and increase access to rheumatology care. The remaining funds will be awarded to advance research projects that will lead to breakthroughs in treating people with rheumatic diseases.

Congratulations to the Foundation's latest award recipients. Their work is vital to creating a brighter future for the field of rheumatology and for people impacted by rheumatic disease. All of this is made possible with the generous support of our incredible donors, and to them we are forever grateful.

TED MIKULS, MD, MSPH

CHAIR, SCIENTIFIC ADVISORY COUNCIL
UNIVERSITY OF NEBRASKA MEDICAL CENTER

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35 YEARS OF ADVANCING PATIENT CARE

The Foundation is the largest private funding source of rheumatology research and training in the United States.

Established by the American College of Rheumatology in 1985 to support the needs of the rheumatology community.

Since 1985, the Foundation has committed

$192M

directly to

RESEARCH + TRAINING

COMMITTED TO FUND $12,836,250 IN FY2022:
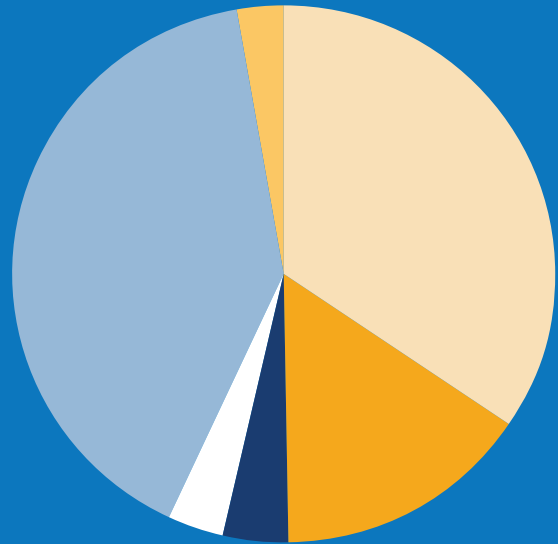
- Innovative Research $4,455,750
- Education & Training $1,950,000
- Recruitment $510,500
- Education Career Development $420,000
- Research Career Development $5,150,000
- Fellows Education Fund $350,000

THE FOUNDATION'S SUPPORT HAS LED TO RESEARCH INVESTIGATING MANY RHEUMATIC DISEASES, INCLUDING:

+ Ankylosing Spondylitis

+ Arthritis

+ Gout

+ Juvenile Dermatomyositis

+ Juvenile Idiopathic Arthritis

+ Osteoarthritis

+ Systemic Lupus Erythematosus

+ Rheumatoid Arthritis

+ Scleroderma

+ Sjögren's Syndrome

+ Spondylarthropathies

+ Systemic Sclerosis

+ Uveitis

+ Vasculitis

Demand for adult rheumatologic care will exceed supply by 138% in 2030; pediatric by 62%

IN THE LAST 5 YEARS, INVESTIGATORS WHO HAVE RECEIVED FOUNDATION FUNDING HAVE:

published **378** papers

received **$92.4M** in additional NIH funding

given **188** presentations worldwide

Approximately

31% (8.3 M)

working age adults with **doctor-diagnosed arthritis report being limited in work activities due to the disease.**

3,945 INDIVIDUAL AWARDS

The Foundation currently has

$37.5M IN ITS ENDOWMENT

APPROXIMATELY 300,000

CHILDREN IN THE U.S. HAVE BEEN DIAGNOSED WITH A RHEUMATIC DISEASE

REPRESENTING 1 IN EVERY 250

3.7 pediatric rheumatologists for every 1 million children

● = 10,000   ● = 1

Fellowship Training Awards were created in 2002 to ensure a robust supply of rheumatology providers. Fellowship graduates have increased by 53%.

INNOVATIVE RESEARCH

AWARDS

The Innovative Research Award encourages independent investigators to conduct novel studies that generate new insights into the cause, progression, treatment, and outcomes of rheumatic diseases.

BRYCE A. BINSTADT, MD, PHD

UNIVERSITY OF MINNESOTA

A Novel TNFR1-Selective Small Molecule Inhibitor to Treat Rheumatoid Arthritis and Related Inflammatory Diseases

TNF inhibitors (TNFi) have revolutionized the care of patients with rheumatoid arthritis and other inflammatory diseases. The existing TNF inhibitors are non-selective and can paradoxically provoke new autoimmune complications; they are also expensive and are delivered by injection or intravenous infusion. Our research project seeks to optimize a novel, selective TNF inhibitor that has several advantages over existing TNF inhibitors.

TNF exerts its biological effects by binding to the receptors TNFR1 and TNFR2. Binding to TNFR1 is responsible for most of the pro-inflammatory effects of TNF. In contrast, TNFR2 exerts both pro- and anti-inflammatory effects, including stimulation of regulatory T cells. The existing TNFi are non-selective, interfering with the interaction of TNF with both TNFR1 and TNFR2. Some patients treated with existing TNFi develop new autoimmune conditions, such as demyelination, which are attributed to blockade of TNFR2. Our team has developed a novel, TNFR1-selective small molecule inhibitor. Unlike existing TNF inhibitors that prevent the interaction of TNF with TNFR1 and TNFR2, this new inhibitor compound works by stabilizing the inactive conformation of TNFR1 and effectively inhibits TNF-mediated activation of NF-kB. The goals of this proposal are 1) to fully define the lead compound's TNFR1 specificity and its effects on TNFR1 and TNFR2 signaling pathways in vitro, 2) to test a panel of related novel TNF inhibitor compounds in two independent animal models of inflammatory arthritis, and 3) to use an iterative medicinal chemistry approach to optimize the potency and bioavailability of the compounds.

The long-term goal of this project is to develop a new drug to treat rheumatoid arthritis and related conditions. The new drug will potently inhibit the pro-inflammatory effects of TNF, similar to existing TNF inhibitors. However, the new drug will offer several advantages over existing TNF inhibitors including reduced autoimmune side effects, oral administration, and lower cost – all beneficial for patients.

MEGAN CLOWSE, MD, MPH

DUKE UNIVERSITY

Moving the ACR's Reproductive Health Guidelines into Practice

Despite advances in the management of lupus during pregnancy, many of the over 6,000 women with lupus who conceive each year in the US and their offspring continue to suffer the severe, life-long consequences of inadequate pregnancy planning and management. Studies indicate that pregnancies that are not planned account for a large majority of the catastrophic outcomes and that up to 15% of all pregnancies in women with rheumatic disease are conceived on a teratogen. To increase the likelihood that lupus pregnancies are clinically well-timed, rheumatologists must be proactive in ascertaining pregnancy intention and collaborating on a plan to prevent or prepare for pregnancy.

The recent publication of the ACR's first Reproductive Health Guidelines (ACR RHG) can advance this goal; however, guidelines alone are not sufficient. Working with the ACR's Rheumatology Informatics System for Effectiveness (RISE) Registry, community providers and staff, and women living with lupus, the initial phase of this project will develop quality measures. These measures will be incorporated into a provider-friendly dashboard within the RISE Registry for continuous performance feedback. While the RISE Registry automatically extracts electronic medical record (EMR) data from over 1/3 of practicing rheumatologists' offices daily, it cannot collect data that do not exist. Therefore, a second phase of the project aimed at addressing the data gaps using rapid cycle quality improvement methods with our community partners will identify best practices for capturing these critical metrics in EMR documentation. Finally, to better equip community rheumatologists to provide ACR RHG-aligned reproductive health care to women with lupus, this project will also create, pilot, evaluate, and refine an expert-led, case-based, tele-mentoring curriculum using the Project ECHO© Model. This curriculum will expand on the content and handouts included on LupusPregnancy.org to address the gaps in knowledge and skills among rheumatologists. Once complete, the dashboard and ECHO program will be ready for wide-spread testing and implementation across the US. Beyond meeting the specific goal of improving lupus pregnancy management, the dashboard metrics and tele-mentoring curriculum are easily applicable to other rheumatic diseases.

MARIA I. DANILA, MD, MSC

UNIVERSITY OF ALABAMA AT BIRMINGHAM

Effectiveness of Tele-Rheumatology for Delivering High Quality Rheumatology Care During the COVID-19 Crisis

EMERGENCY COVID FUNDING

The coronavirus disease crisis (COVID-19) has impacted nearly every facet of the U.S. healthcare system and dramatically altered healthcare delivery in the U.S. Since March 2020, remotely delivered care (e.g., tele-rheumatology) has seen exponential growth as providers and healthcare systems have worked to deliver care, especially in non-procedural specialties like rheumatology, which manages rheumatic and musculoskeletal diseases (RMDs). RMDs are one of the most common reasons to seek outpatient care, and patients living with RMD are distinctly at risk for COVID-19 due to multimorbidity burden. The standard of care for many RMDs (e.g., rheumatoid arthritis, lupus) is to use immunosuppressive drugs, which increase the risk for infections and require close monitoring for side effects. Little is known about whether higher risk and socially vulnerable groups of people with RMD have a greater burden of inadequate healthcare during the COVID-19 era. While tele-rheumatology may have an important role to play for delivering healthcare in this population, there exists a clear knowledge gap about the comparative effectiveness of tele-rheumatology versus in-person visits (i.e., usual care) especially in patients on immunosuppressive drugs and socially vulnerable persons. Thus, it is critical to rapidly and rigorously assess patients' acceptance, barriers, and satisfaction with tele-rheumatology. Given the protracted nature of the pandemic, this proposal advances the mission of the Rheumatology Research Foundation by improving our knowledge and understanding of urgent clinical and policy needs to provide safe, efficacious, and equitable care to diverse patients with RMDs during and beyond the COVID-19 pandemic.

DAVID R. FERNANDEZ, MD, PHD

HOSPITAL FOR SPECIAL SURGERY

CD8+ T Cell Mechanisms and Tailored Therapies in Inclusion Body Myositis

Inclusion body myositis (IBM) is an inflammatory muscle disease characterized by CD8+ T cell infiltration that injures muscle and results in disability. Unlike other forms of inflammatory muscle diseases and most autoimmune diseases, IBM does not respond to immunosuppressant medications, leaving no effective therapy for this disease. Interestingly, one recent study determined that over half of IBM patients had an expansion of CD8+CD57+ T cell clones in the blood, with many individuals meeting criteria for diagnosis of T-cell large granular lymphocyte (T-LGL) leukemia as a result.

The goal of our proposed study is to understand the mechanisms driving the replication and survival of these potentially damaging CD8+CD57+ T cell populations in IBM patients, as well as to find new therapeutics to treat this devastating condition. We will do this by isolating CD8+CD57+ T cells from IBM patients' blood and muscle to: (1) determine if the clones present in the blood and muscle are of the same origin; (2) analyze the transcriptomic expression profile of these damaging T cells in the muscles; (3) perform genetic testing to look for evidence of leukemia mutations; and (4) test available medications used in other diseases and cancers that share these damaged pathways.

All the above will be analyzed using single cell technologies that survey the cells' transcripts and gene products, as well as surveying genetic mutations with targeted DNA sequencing that can determine how these CD8+CD57+ T cells are transforming to cause muscle damage. These findings will lay the foundation to potentially understanding how these T cell clones are destroying the muscle, whether they have features of leukemic cells, and which pathways can be targeted using currently available drugs.

INSOO KANG, MD

YALE UNIVERSITY SCHOOL OF MEDICINE

Investigating the Role of Innate Immunity in CNS Lupus Using Human Brain Organoids

2021 AWARD RECIPIENTS

The pathologic hallmarks of systemic lupus erythematosus (SLE or lupus) are altered immune responses to autoantigens with autoantibody production and subsequent tissue injury. Although T and B cells are critical in the development of lupus, recent studies expanded this paradigm to a pathogenic role for innate immunity. With improved longevity in lupus patients, the late sequelae of this disease receive increasing levels of attentions. Lupus patients can develop manifestations of neuropsychiatric SLE (NPSLE) including depression, cognitive dysfunction, seizure, psychosis, and strokes. The mechanisms for NPSLE such as cognitive dysfunction and mood disorder remain mostly unknown. Some studies suggested the possible implications of autoantibodies, autoimmune complex, and cytokines in NPSLE. While the brain was previously considered as an immune privileged site protected by the blood–brain barrier (BBB), it is now recognized that the immune and nervous systems communicate in a highly organized manner. Cytokines released outside the brain can reach the brain through the circumventricular organs, areas devoid of BBB, or compromised BBB in the setting of brain trauma, exposure to environmental toxicants, and inflammation. Human monocytes (MO) can produce a set of inflammatory molecules in response to the lupus immune complex of dsDNA/anti-dsDNA and U1-snRNP/anti-U1-snRNP antibodies (hereafter referred to as lupus IC). However, it is largely unknown whether and how the molecules produced from such activated MO in lupus can affect neuronal cell function in the brain. Plus, it is conceivable that the same lupus IC can activate microglial cells (MG), the brain-resident macrophages, which share cellular characteristics with MO. Finally, there is no dependable model system for NPSLE where human cells are studied. The goal of this proposal is to tackle these issues using human cortical (brain) organoids derived from induced pluripotent stem cells (IPSC), leading to the development of a model system for studies on human NPSLE and to the elucidation of the effects of lupus IC-driven inflammation on neuronal cells. The proposed study would advance our understanding of the pathogenic mechanisms in NPSLE through establishing a model system comprised of lupus IC, human cortical organoids, MO, and IPS-derived MG-like cells, resulting in the development of therapeutic approaches targeting such mechanisms.

JASON S. KNIGHT, MD, PHD

UNIVERSITY OF MICHIGAN

Antiphospholipid Antibodies in COVID-19

EMERGENCY COVID FUNDING
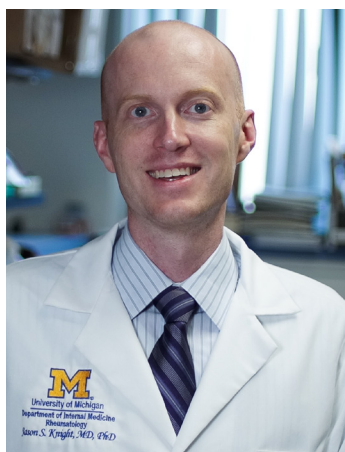
Individuals with severe coronavirus disease 2019 (COVID-19) are at high risk for thrombosis in macro- and microvascular beds. Antiphospholipid syndrome (APS) is an acquired autoimmune thrombophilia in which patients form autoantibodies to phospholipids and phospholipid-binding proteins such as prothrombin and beta-2-glycoprotein I (β2GPI). These antiphospholipid antibodies (aPL) then engage clotting factors and cell surfaces, where they activate coagulation cascades, endothelial cells, platelets, and neutrophils—thereby tipping the balance toward thrombosis. A defining feature of APS is its ability to promote thrombosis in vascular beds of all sizes, including both arterial and venous circuits. The catastrophic variant of APS (CAPS) is often fatal and bears many similarities to the coagulopathy seen in patients with COVID-19. Reports of aPL in COVID-19 and their possible relationship to thrombosis have begun to emerge in small case reports and series. While viral infections are known triggers of transient aPL, the extent to which these antibodies may be pathogenic has not been well defined. Our preliminary data testing patients hospitalized with COVID-19 reveal that half of patients have positive testing for at least one type of aPL. The presence of aPL correlates with neutrophil activation and disease severity. Our hypothesis is that aPL are targetable amplifiers of COVID-19 severity. If correct, the hypothesis has significant implications for treating patients with acute disease (anticoagulation, plasmapheresis), as well as disease that has resolved (antibody persistence, convalescent plasma). Aim 1 will expand aPL testing to hundreds of individuals hospitalized with COVID-19 in order to understand clinical correlations and determine long-term outcomes. The hypothesis is that aPL will associate with higher rates of macrovascular thrombosis (stroke, venous thromboembolism) and microvascular thrombosis (respiratory failure, kidney injury) in COVID-19. Aim 2 will characterize COVID-19-derived IgG/IgM fractions and affinity-purified aPL in vitro. The hypothesis is that COVID-19-derived aPL will have in vitro activities similar to aPL isolated from patients with established APS. Aim 3 will determine the extent to which COVID-19-derived aPL are pathogenic in animal models. The hypothesis is that transfer of COVID-19 antibody fractions into mice will potentiate thrombosis, thereby confirming the pathogenic potential of these antibodies in vivo.

ANNE-MARIE MALFAIT, MD, PHD

RUSH UNIVERSITY MEDICAL CENTER

Transcriptomal Analysis of Mouse and Human Dorsal Root Ganglia for the Identification of Novel Targets for Treating Osteoarthritis Pain

Osteoarthritis (OA) and low back pain are the major causes of musculoskeletal pain worldwide. Despite the availability of a variety of analgesics, OA pain is often inadequately controlled. The current proposal aims to devise innovative strategies to discover effective new drugs for pain control, using an approach in which we identify the "receptome" specific to dorsal root ganglia (DRG) neuronal subpopulations and interacting non-neuronal cells that are involved in OA pain, to develop targeted therapeutic interventions. We will do this using a stepwise approach. In Aim 1, we will perform single cell RNAseq of knee innervating DRG of naïve mice and mice with OA induced by destabilization of the medial meniscus (DMM). Data sets will be mined to identify (1) genes in naïve DRG that are selectively expressed by specific nociceptor subpopulations, for example, Mrgprd+ C fibers and C-low threshold echanoreceptors (C-LTMR), two subsets of nociceptors that we have shown to be involved in OA pain in mice; (2) genes in neuronal and non-neuronal cells (glia, immune cells) whose expression is altered 12 weeks after DMM surgery, a stage at which mice show chronic pain behaviors. We will focus on "druggable" genes such as G-protein coupled receptors (GPCRs), kinases, and ion channels. Results will be validated by in situ hybridization using RNAscope. In Aim 2, we will ensure translational potential of the genes identified by performing RNAscope on a unique cohort of L4-DRGs of human donors. Human validation is critical in view of emerging evidence that the overlap in receptome distribution between mouse and human sensory neurons is not perfect. Finally, in Aim 3, we will generate proof-of-concept data demonstrating that targeting selected gene products produces analgesic effects in the murine DMM model, using small-molecule pharmacological approaches as well as gene knockdown enabled by Crispr/Cas9 editing. For this, we will use well-established, standardized methods developed in our laboratory. Successful completion of these aims will generate a shortlist of druggable targets for OA pain, which will enable future design of novel agents that act upon these targets (drug development).

SUSAN L. MURPHY, SCD, OTR/L

UNIVERSITY OF MICHIGAN

Resilience-Based Energy Management to Enhance Wellbeing in Scleroderma (RENEW): Testing of a Peer-Mentored Web-Based Intervention

People with systemic sclerosis (SSc; scleroderma) report high fatigue and psychological issues that typically do not get attention in regular clinical management. Despite the need for fatigue management and resilience-based interventions to teach critical self-management skills, there are no existing programs to address these issues in SSc. Self-management interventions have strong evidence in helping people with various chronic conditions manage their disease, reduce symptoms, and increase function and are particularly important for SSc with no cure or highly effective treatments. For these programs to be most effective and relevant, they need to be grounded in behavior change theory and tailored to specific aspects of disease groups. Based on our team's extensive work with people who have SSc and in developing self-management programs, we have taken the next step to better address fatigue management in SSc. Our objective is to validate and refine our recently developed, theoretically grounded intervention addressing fatigue and known correlates called the Resilience-based Energy Management to Enhance Wellbeing (RENEW) intervention. Our long-term goal is to provide a relevant, evidence-based, widely accessible peer-mentored program for people with SSc to reduce fatigue and enhance well-being. The specific aims for this project are: 1) to engage patients and other stakeholders to assess whether the RENEW program has the face and content validity that people with SSc perceive they need to effectively manage their fatigue and 2) to examine effects of a remotely delivered, peer mentored, RENEW intervention compared to a waitlist control condition. For Aim 1, we will conduct focus groups with 40 patients with SSc and stakeholders and refine program content as needed. For Aim 2, a parallel stage II randomized controlled trial will be conducted. This project directly addresses the Rheumatology Research Foundation's Strategic Plan by seeking to provide patient-centered value-based care for people with SSc, a rare group with high unmet needs for fatigue management and holistic health interventions. Training peer mentors—people who also have SSc and share lived experience with the condition—as health coaches provides an innovative way to engage people with SSc in meaningful work that could provide benefits to mentors as well as program participants.

IRIS NAVARRO-MILLÁN, MD, MSPH

WEILL CORNELL MEDICINE

The Moving Well Intervention: A Peer Coaching Program for Patients with Osteoarthritis Planning Total Knee Arthroplasty

Patients with advanced osteoarthritis (OA) have obtained significant improvement in clinical outcomes with total knee arthroplasty (TKA), but up to 30% of patients may experience persistent knee pain after surgery. Currently, there are no pre-operative programs that address poor prognostic indicators such as obesity, pre-operative deconditioning, anxiety, and depression. There lacks sufficient evidence regarding adherence and effect of in-person pre-operative programs for TKA and total hip arthroplasty. In our qualitative research, participants who have undergone TKA demonstrated interest in a program that would help patients prepare mentally and physically for their TKA.

We propose in this Innovative Research Award to test the effectiveness of the Moving Well intervention. Moving Well consists of peer coaches assisting patients with OA to prepare mentally and physically for TKA, their recovery from TKA, and adherence with physical therapy sessions and exercises at home before and after TKA. Peer coaches are patients who have already undergone a TKA, trained to deliver this intervention, and offer support from their own personal experiences. A core component of the program will be cognitive behavioral training (CBTr), which has been used in other peer coaching interventions and has been shown to improve function, reduce depressive symptoms, and reduce pain. The peer coach will guide the participant through their weekly activity workbook, which includes mood and pain monitoring, exercises designed for pre-TKA, and educational materials about OA, TKA, and opioids. Through this intervention, we hope to improve TKA outcomes through modifiable psychosocial factors and encourage the responsible use of opioids post-operation.

The goal of this Innovative Research Award proposal is therefore to pilot test the Moving Well intervention in anticipation of a larger, multicenter, implementation trial. We aim to:

Aim 1: Engage 93 patients with OA scheduled for elective TKA and conduct a pilot RCT of the Moving Well intervention compared with usual care.

Aim 2: Determine the feasibility and acceptability of the Moving Well intervention among patients with OA who are scheduled for TKA.

DEEPAK A. RAO, MD, PHD

BRIGHAM AND WOMEN'S HOSPITAL

CD8 T Cell Functions in Checkpoint Inhibitor-Associated Arthritis

Immune checkpoint inhibitor therapies such as anti-PD-1 therapy have revolutionized the care of patients with cancer; however, these immune stimulating therapies frequently induce pathologic autoimmune conditions that resemble rheumatic diseases. Finding strategies to prevent or inhibit damaging autoimmune consequences, while not disrupting the anti-tumor immune response, is a key challenge in the use of checkpoint inhibitor therapies. Anti-PD-1 therapy induces a range of rheumatic adverse events, including an inflammatory arthritis that can resemble rheumatoid arthritis or spondyloarthritis. The development of inflammatory arthritis following anti-PD-1 therapy raises several interesting questions: does PD-1 blockade induce an autoimmune T cell response similar to that seen in rheumatoid arthritis or spondyloarthritis? Are the T cells in joints of patients with anti-PD-1 therapy like those that infiltrate the tumor? Are there pathways or cell types that drive the pathologic inflammatory response that are not critical for tumor killing?

Little is known about the phenotypes or functions of T cells that mediate adverse inflammatory effects of anti-PD-1 therapy. We have observed that T cells from synovial fluid of patients with checkpoint inhibitor-associated arthritis (CI arthritis) display a striking, distinct set of features compared to those from patients with rheumatoid arthritis and spondyloarthritis. Specifically, CI arthritis samples contain a markedly expanded CD8+ T cell subset characterized by high expression of CD38. We hypothesize that this large population of CD38hi CD8 T cells drives pathologic inflammation in CI arthritis through mechanisms distinct from those that dominate in rheumatoid arthritis or spondyloarthritis. This project involves 3 aims to study 1) the inflammatory and cytotoxic functions of CD38hi CD8 T cells, 2) the single cell transcriptomic trajectories and TCR repertoire of CD38hi CD8 T cells, and 3) the ability of signals in the local environment to induce a CD38hi T cell phenotype. Together, this work will establish the functions and identity of a unique T cell population expanded by anti-PD-1 therapy and may reveal new strategies to specifically target adverse rheumatic manifestations of checkpoint inhibitor therapies.

DANIEL H. SOLOMON, MD, MPH

BRIGHAM AND WOMEN'S HOSPITAL

Improving Virtual Care of Rheumatoid Arthritis: Integrating a Smartphone App into the EHR for Improved Timeliness of Visits

The American College of Rheumatology (ACR) predicts the rheumatology workforce will only be half as large as required by 2030. Can technology ameliorate the impending shortage by making more efficient use of the existing workforce, while maintaining, or even improving, quality of care? Over the last five years, we have developed a series of solutions to improve patient care in rheumatoid arthritis (RA). We have developed technologic solutions and propose to further enhance and evaluate our smartphone application ("app") for RA so that it facilitates access to care when patients need it, while reducing the volume of routine visits.

We hypothesize that the electronic health record (EHR) integrated app will improve the efficiency of care in RA and thereby lessen workforce shortages, by facilitating more timely visits and improving access to rheumatic disease clinicians. We propose the following aims to test this hypothesis. In Aim 1, we will employ user-centered design methods to upgrade the app, integrating the voice-enabled RA app into the EPIC EHR. In preliminary work, we used user-centered design methods to develop a voice-enabled app for RA and created a simple set of questions and answers (Q&A) about RA for patient education. The app has been well received in focus groups and is now being formally tested. Aim 1 is required before the proposed randomized controlled clinical trial (RCT) in Aim 2.

In Aim 2, we will conduct a small-scale RCT of the EHR-integrated ePRO voice-enabled app to assess whether it improves the timeliness of RA care. After integrating the app into the EHR, we will conduct an RCT to determine whether it improves visit timeliness, defined as an improved percentage of visits with recent flares or medication changes. We hypothesize that the intervention app will improve visit timeliness, while maintaining patient-reported clinical outcomes.

The work being proposed will help solve a pressing need in rheumatology by enhancing visit timeliness for RA. If successful, the app can be generalized to other rheumatic diseases. Our proposal builds on five years of work and employs user-centered design methods to develop and test an innovative cutting-edge technology in rheumatology care.

KEVIN WEI, MD, PHD

BRIGHAM AND WOMEN'S HOSPITAL

Targeting Angiocrine Morphogens in Rheumatoid Arthritis

Many rheumatoid arthritis patients do not achieve sustained remission, and there is no cure. Synovial fibroblasts have long been considered an attractive target in rheumatoid arthritis, yet no therapy directly targeting fibroblasts has been approved. This proposal details a two-year research plan with a scientific focus on defining the role of endothelial-derived morphogen signals in controlling synovial fibroblast pathology in patients with rheumatoid arthritis. The central hypothesis being tested here is that endothelium-derived morphogens represent therapeutic opportunities to halt arthritis pathology and promote normal joint function. The long-term objective of the proposed study is to develop a therapeutic strategy that abrogates fibroblast pathology and promotes normal fibroblast function through modulating endothelial-derived morphogens.

The specific aims proposed here utilize two complementary approaches to define the spatial pattern and function of endothelial-derived morphogens. In aim 1, we will define the anatomical location of morphogen gradients in rheumatoid arthritis synovia using confocal microscopy and spatial transcriptomics. In aim 2, we will interrogate the effect of morphogen signaling on the fate and functions of fibroblasts directly in patient-derived synovial tissue organoids. If proven correct, these studies will not only provide insight into rheumatoid arthritis pathogenesis but also facilitate therapy development targeting endothelial-derived morphogens.

DANIEL KENTA WHITE, PT, SCD, MSC

UNIVERSITY OF DELAWARE

Physical Therapy Exercise and Physical Activity for Knee Osteoarthritis (PEAK)

The objective of this proposal is to examine the efficacy of an innovative telehealth physical therapy (PT) program for adults with knee osteoarthritis (OA) to increase physical activity over three months in adults with knee OA compared to a control group receiving web-based resources about knee OA. This study meets the acute need to address inactivity in OA and 'myth-bust' common patient misconceptions that exercise cannot help and may be harmful for adults with knee OA. Our central hypothesis is that PEAK will effectively increase physical activity and improve the health belief that exercise is helpful and not harmful for adults with knee OA.

PEAK is poised to directly improve the health of people with rheumatic disease as a well-designed, low cost, and easily scalable telehealth PT intervention to increase physical activity among adults with knee OA. PEAK uniquely combines key, evidence-based practices for the management of symptomatic knee OA: physical-therapist delivered exercise, physical activity goal setting, and patient education about the benefits of exercise, in a readily accessible, remotely delivered format.

This award will impact patients by 1) providing a means to deliver much needed education and exercise recommendations from a qualified health professional to adults with knee OA, 2) equipping physical therapists to deliver care to patients with knee OA in a standardized and systematic fashion using existing training resources for PEAK, and 3) studying to what extent patient education can address misconceptions about the benefits of exercise for OA and support successful management of knee OA.

NORMAN B. GAYLIS, MD CLINICAL RESEARCH AWARD

Established with a generous commitment to the Foundation from Dr. Gaylis, the Norman B. Gaylis, MD Clinical Research Award provides funding for research that will impact community practice. Studies may include, but are not limited to, international collaborations, health services research, outcome studies, practice supply and demand, and/or clinician–patient communication.

SWAMY VENUTURUPALLI, MD, BS

ATTUNE HEALTH

Telehealth-Delivered Healthcare to Improve Care (THRIVE) in Community-Practice Rheumatology

In 2020, the advent of the COVID-19 pandemic resulted in a massive increase in the use of home-based telehealth to provide clinical care in community rheumatology, yet there are scant research studies that a) describe how to best implement telehealth; b) evaluate rheumatology patient satisfaction with telehealth; and c) enumerate the most relevant processes and outcomes and the associated factors that may mediate high quality telehealth care. This project will convene a set of stakeholders including community-practice clinicians, clinical researchers, telehealth experts, patients, and patient advocates to re-design community-based rheumatology telehealth care. Informed by a systematic literature review, we will codify the best practices in telehealth rheumatology, adapt those to the practice of rheumatology, and then implement those best practices to condition-specific care pathways in use by a large, 250+ provider community rheumatology network. We will measure rheumatology patient satisfaction with telehealth to inform these best practices with quantitative data, especially identifying the patient-, provider-, and practice-level factors associated with patients being satisfied (or not) with telehealth services. We will also create video-guided patient education to standardize elements of patient self-examination with a focus on RA and develop companion provider-facing training on how to conduct a standardized, structured exam over a telehealth video interface. This work will be supported by the rigor of a validation study that compares telehealth exam findings to in-person exam findings.

We will incorporate and disseminate these tools not only to the large rheumatology community provider network participating in this project but also to community rheumatologists everywhere through a variety of distribution channels. Our work encompasses several innovative research methods including community participatory research, patient involvement in research development, and use of both qualitative and quantitative methods to achieve our goals. Ultimately, these aims will solidify high quality telehealth as an integral part of rheumatology care and preserve access to telehealth services for patients and providers in the future.

This project is a collaboration with University of Alabama at Birmingham, Global Healthy Living Foundation, and Bendcare, LLC.

CAREER DEVELOPMENT

RESEARCH AWARDS

Increasing concerns over the decline in federal funding for rheumatology research have forced many investigators to reconsider their careers, resulting in fewer researchers making the important discoveries necessary to advance treatments and find cures. The Career Development Research Awards are designed to encourage early and midcareer investigators to continue vital research into the cause, prevention, and treatment of rheumatic diseases.

CAREER DEVELOPMENT BRIDGE FUNDING AWARD: R BRIDGE

The R Bridge Award encourages essential rheumatology research by supporting promising investigators who are revising outstanding NIH R01 or VA RCS/ORD award applications.

MELISSA A. CUNNINGHAM, MD, PHD

MEDICAL UNIVERSITY OF SOUTH CAROLINA

The Role of Estrogen Receptor Alpha Variant Size and Localization in Modulating TLR7-Induced Inflammation

Systemic lupus erythematosus (SLE) is one of many autoimmune diseases that disproportionately affects females. Although many risk factors for lupus are identified: >170 genes, myriad environmental exposures, and aberrant X chromosome inactivation, none of these sufficiently explain the steep rise in incidence of ADs at the time of puberty in a female-specific manner. Epidemiology suggests a major role for sex hormones and their receptors in autoimmune diseases. We previously showed that female lupus-prone mice, expressing only a short form of estrogen receptor alpha (ERα short), have significantly reduced renal disease and increased survival. Determining the mechanism of this protective effect, which is estrogen dependent, is the primary goal of this proposal. Of note, ERα-/- (null) lupus prone mice were not similarly protected. Combined, our data suggest that the presence of the short form of ERα confers protection, not the absence of full-length ERα. Our group and others demonstrated a critical role for ERα in dendritic cell (DC) development and Toll-like receptor 7 (TLR7) responsiveness. Interestingly, the ERα expressed in ERα short mice is similar in structure to an endogenous ERα variant (ERα46) that lacks the same AF-1 domain and differentially regulates gene transcription compared to full length ERα. In the proposed study, we will further investigate the role of ERα short in modulating TLR7-induced inflammation and determine whether genomic and/or non-genomic mechanisms of ERα46 action are protective. Our overall hypothesis is that the ratio of ERα46 to ERα66 is decreased in lupus patients versus healthy controls and that increasing expression of ERα short or ERα46 in immune cells will be anti-inflammatory. We also hypothesize that targeting immune cells with novel anti-inflammatory selective estrogen receptor modulators (SERMs) will uncouple estrogen-mediated anti-inflammatory responses from those impacting reproductive tissues. This therapeutic strategy, if successful, will provide novel approaches to immune modulation in lupus and other immune-mediated diseases, especially those with a significant sex bias.

CANDACE FELDMAN, MD, MPH, SCD

BRIGHAM AND WOMEN'S HOSPITAL

Leveraging Community-Academic Partnerships and Social Networks to Disseminate Vaccine-Related Information and Increase Vaccine Uptake among Black Individuals with Rheumatic Diseases

Racial/ethnic disparities in adverse, often avoidable outcomes occur in nearly all rheumatic diseases particularly among Black individuals. Despite the efficacy and safety of vaccinations in patients with rheumatic diseases, and the high burden of serious infections, rates are consistently poor. In the U.S. vaccine uptake is lower and vaccine hesitancy higher among Black patients compared with White patients, and this holds true in rheumatic diseases. With the profound disparities uncovered by the COVID-19 pandemic aggravated by proven disparities in rheumatic disease outcomes and heightened vulnerability to infections, there is an urgent need to address low vaccine uptake and hesitancy among Black individuals with these conditions.

There is also the need to improve vaccine uptake among the social networks of individuals with rheumatic conditions given the possibility of reduced immune response to the COVID-19 vaccine. Our team has forged longstanding community-academic partnerships to understand needs of Black individuals with lupus and the role structural racism plays. We aim to conduct a randomized controlled trial to implement a Popular Opinion Leader (POL) model. Community leaders (POLs) will be trained to disseminate information regarding COVID-19 vaccinations through their social networks in predominately Black communities to increase COVID-19 vaccine uptake and reduce hesitancy. We will test the efficacy of framing the POL training with a racial justice public health lens plus information about COVID-19 vaccine safety and efficacy compared with a training with information about vaccine safety and efficacy alone. We will conduct mixed methods social network analyses to understand how the training differences influence structural and compositional characteristics of the POL's outreach social networks. We hypothesize that POLs trained with a racial justice lens will reach larger social networks with a higher ratio of Black individuals. This project will provide important preliminary data to inform POL curriculum design and allow for the development and pilot testing of data collection tools and study materials among our community and academic partners and patient advocates.

CAREER DEVELOPMENT BRIDGE FUNDING AWARD: K SUPPLEMENT

The K Supplement Award encourages junior investigators to expand promising research by providing additional support to cover research costs and help investigators become independent.

JUDITH ASHOURI, MD

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Decoding the Signaling and Repertoire Threshold Required for Arthritis Development
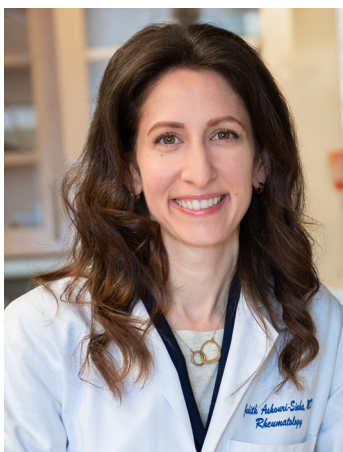
Activation of pathogenic CD4 T cells through their T cell antigen receptors (TCRs) is required for RA development. Paradoxically, signaling by the TCR in RA patients is diminished, yet their autoreactive T cells are hyper-responsive to self-antigens. How abnormal TCR signaling triggers T cells to initiate and propagate disease is unknown. The SKG mouse shares many features with human RA and its autoreactive T cell response is driven by a hypomorphic allele of the Zap70 kinase, a molecule critical for TCR signaling.

Recent studies by Dr. Ashouri introduced the GFP transcriptional reporter driven by the Nr4a1 gene that encodes the Nur77 orphan nuclear hormone into SKG mice. The reporter is rapidly and selectively upregulated in response to antigen or TCR stimulation, but not by inflammatory cytokines. Using these mice, we identified a subpopulation of CD4 T cells expressing high levels of GFP, indicative of strong TCR signaling, in the naïve T cell population from SKG but not WT mice that was enriched for its arthritogenic potential. Single cell RNA sequencing analyses identified TCR-regulated genes that were up- or down-regulated and also identified TCRs with restricted usage enriched in this subset of pathogenic T cells prior to the development of arthritis.

Our studies suggest that recognition of endogenous Super-antigens (SuperAgs) is critically important in the arthritogenic potential of these cells. We posit that an altered transcriptional landscape, in part due to abnormal TCR signaling and pathogenic TCR specificities, establish the arthritogenic potential of Ag-specific T cells. To test this hypothesis, we will: 1) Characterize the transcriptome, proteome, and repertoire of arthritogenic T cells; and 2) Determine whether endogenous viral SuperAg(s) drive arthritis in SGK mice. By understanding the genes or TCRs that define this threshold for arthritis development, we hope to identify critical features that might be therapeutic targets.

LAURA CAPPELLI, MD, PHD

JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE

## Evaluating Treatment in Immune Checkpoint Inhibitor-Induced Inflammatory Arthritis

Inflammatory arthritis (IA) due to immune checkpoint inhibitor (ICI) therapy for cancer is a problem seen increasingly by rheumatologists. ICI-induced IA can be severe, leading to erosive disease and disability, and can persist after treatment for cancer is stopped. The severity and persistence of IA in some patients has raised the question of whether patients should be treated more aggressively during an early window of opportunity with high dose steroids. Patients treated with ICIs for cancer, however, have the additional concern of impairing anti-cancer immune activity with immunosuppressive medications used in IA treatment. No prospective data currently exists to guide corticosteroid dosing. The proposed observational study will determine current initial corticosteroid dosing patterns and their association with IA outcomes in a multicenter prospective cohort of ICI-induced IA. The first aim of the proposal is to test the hypothesis that initial higher corticosteroid dosing will lead to better IA outcomes and lower cumulative corticosteroid exposure while not affecting tumor outcomes. Secondly, the study will evaluate baseline predictors for severity of ICI-induced IA, specifically for requirement of steroids, conventional synthetic DMARDs, or biologics and/or erosive joint disease on imaging. This aim will test the hypothesis that increased disease activity at presentation, combination immunotherapy, and increased ICI duration will predict severity of IA. Defining the patients most at risk for severe outcomes and regimens of corticosteroid dosing that should be tested for comparative effectiveness and toxicity will facilitate a clinical trial in ICI-induced IA. At the end of this award, Dr. Cappelli will have the necessary data to apply for a R01 clinical trial grant from NIAMS focusing on corticosteroid dosing in ICI-induced IA.

PUI Y. LEE, MD, PHD

BOSTON CHILDREN'S HOSPITAL

Defining the Immunometabolic Basis of Systemic Juvenile Idiopathic Arthritis and Macrophage Activation Syndrome
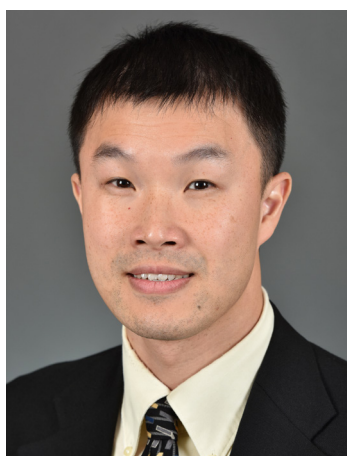
Systemic juvenile idiopathic arthritis (sJIA) is a severe inflammatory syndrome in children first recognized more than a century ago. In addition to prolonged fever, systemic inflammation, skin rash and arthritis, patients with sJIA may develop macrophage activation syndrome (MAS), a potentially fatal complication characterized by cytokine storm and hemophagocytosis. However, the pathogenesis of sJIA and the mechanistic connection to MAS are not well defined.

As an extension of the K08 studies, we recently discovered a new role of immunometabolism in sJIA. Using IL-1 receptor antagonist deficient mice (IL1rn-/-) to model the dysregulated production of IL-1 in sJIA, we show that IL-1 drives excess monocyte production and promotes arthritis through mTORC1 (mechanistic target of rapamycin complex 1) activation. Analysis of transcriptomic studies of sJIA patients consistently demonstrated an mTORC1 gene signature. Connecting the pathophysiology of SD and MAS, we generated mice with inducible deletion of the endogenous mTORC1 inhibitor Tsc2 (tuberous sclerosis complex 2) and demonstrated that uninhibited activation of mTORC1 is sufficient to induce an MAS-like disease with hallmark findings including hemophagocytosis. These findings have rapid therapeutic implications as mTOR inhibitors are available clinically.

The project will further define mTORC1 as a driver of systemic inflammation that connects the pathophysiology of sJIA and MAS. Aim 1 will establish an mTORC1 gene signature that can be applied readily to capture sJIA disease activity and treatment response in patients. Aim 2 will develop additional mouse models to address whether the degree of mTORC1 activation regulates the threshold for systemic inflammation. Data from these studies will strengthen the PI's first R01 application to study the role of immunometabolism in sJIA and MAS through transcriptomic, proteomic and metabolomic approaches.

ZSUZSANNA MCMAHAN, MD, MHS

JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE

Mesodermal-derived Enteric Neurons as a Target of the Autoimmune Response in Scleroderma

Gastroparesis is a complication that impacts 30-50% of SSc patients, and may culminate in nausea, weight loss, and parenteral nutrition. However, the risk factors and disease mechanisms for gastroparesis are unknown and existing therapies are associated with significant adverse effects. Furthermore, symptom control does not clearly prevent GI progression. An improved understanding of the key drivers of SSc gastroparesis, and the mechanisms that contribute to persistent disease activity and progression are therefore necessary to identify high-risk patients and learn how to modify disease course.

Interestingly, we have determined that sera from SSc patients with gastroparesis are significantly more likely to bind antigens in a distinct subset of enteric neurons (mesodermal-derived enteric neurons; MENS) that play a critical role in GI transit. In contrast, patients whose sera have autoantibodies targeting other types of enteric cells, such as glia, were unlikely to have gastroparesis.

Our goal will be to gain further insight into MENS as a novel target of the autoimmune response in SSc patients with gastroparesis, thereby extending my K23 award to focus on a specific cellular lineage within the GI tract. We plan to identify the autoantigen(s) in this subset of enteric neurons which are targeted by autoantibodies in SSc patients with gastroparesis, and define the prevalence and clinical features associated with this specificity. We have already identified a series of SSc patients with gastroparesis whose sera bind to these cells by immunofluorescence in the same punctate cytoplasmic pattern, suggesting these sera may recognize the same specificity. We will obtain GI lysate from our collaborators (Pasricha lab), which will be used for autoantigen identification by IP. Immune complexes will be immunoprecipitated and sent for mass spec analysis, and autoantigen(s) will be identified and validated. Convenient screening assays for any newly defined autoantibodies will be set up and used to test our existing SSc all-comers cohort. Finally, we will utilize the data in the Johns Hopkins Scleroderma Registry to identify associations with clinical phenotype. This project will allow me to broaden my K23 focus, and study antibodies targeting MENS, that may also have implications for patient risk stratification, classification and management.

RENUKA NAYAK, MD, PHD

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Regulation of Methotrexate Metabolism by Human Gut Microbiota

Dr. Nayak's project will lay the foundation to develop microbiome-targeted therapies to increase the response to methotrexate and advance precision medicine for patients with rheumatic disease. In recent years, we have learned that the microbes in our gut can have powerful influences on our health. They bring a large arsenal of enzymes that help metabolize the foods that we eat. These enzymes may also accidentally metabolize drugs used to treat disease, and in doing so, affect the way patients respond to medications. Our lab has found that methotrexate, a drug prescribed to millions of patients with autoimmune disease, is metabolized by human gut microbiota; this may explain why some patients fail to respond to methotrexate. Here, we will learn how methotrexate metabolism is regulated and whether metabolism can be reduced so that more patients can benefit from methotrexate, a drug that has been shown to reduce mortality and increase the efficacy of other drugs in rheumatoid arthritis.

JEREMY TILSTRA, MD, PHD

UNIVERSITY OF PITTSBURGH

Evaluating the Regulation and Modification of Kidney-infiltrating T Cells by the Kidney Parenchyma in Lupus Nephritis

Rheumatologic diseases, and specifically lupus, are characterized by immune activation, autoantibody production, and end-organ damage. The goal of this award is to further our understanding of how immune infiltrates change after invading target organs, such as the kidney in lupus, while at the same time evaluating how the organ tissue itself changes and impacts these in filtrating cells.

We have begun to generate significant data defining the transcriptional and functional changes that occur with immune cells enter the kidney in lupus mouse models. Furthermore, we have begun to explore if similar changes and alterations in the function of infiltrating immune cells occur in all organs affected by autoimmunity. By understanding, how these cells change and function in the target organ, we may be able to specifically target these pathogenic organ infiltrating cells, without targeting all immune cells, thus limiting systemic immunosuppression.

The second goal of the work supported by this award is to improve our understanding of how target organs change in the face of inflammation. Similar to tumors, varying organs may have the capacity to suppress or interact with infiltrating immune cells. In support of this theory, we have preliminary data which suggests that IFN signaling exerts pro-inflammatory, disease accelerating, effects through the hematopoietic compartment, but anti-inflammatory feedback through its actions on the target-organs. Therefore, rather than only targeting the immune system with therapies we may be able to target the tissue being invaded again allowing for side effects compared to therapies that deplete the immune system.

In all this work will allow us to more deeply explore the interactions between immune infiltrates and the organs they are invading to understand the nuance of how damage occurs in autoimmunity and in so doing develop therapies to stop chronic damage observed in many of these diseases.

ZACHARY WALLACE, MD, MSC

MASSACHUSETTS GENERAL HOSPITAL

Expansion of an ANCA-Associated Vasculitis Simulation Model to Personalize Care Using Novel Treatment Approaches

As part of my NIAMS/NIH K23 award, I am validating a simulation model of ANCA-Associated Vasculitis that uses a state-transition framework where disease progression is characterized as a sequence of transitions from one "health state" (e.g., remission, active disease) to another. Simulation modeling is a useful methodology which, unlike a single trial or cohort study, can assess the total collective impact of treatments, disease/patient characteristics, and events (e.g., severe infection) on clinically-oriented and patient-relevant outcomes. The original intent of this model was to project the quality and duration of life with different treatments. In my R01 proposal, I will expand this model so that it can then be used to personalize care by assessing the clinical impact and value of novel steroid-sparing approaches and varying maintenance treatment duration. This K Supplement will provide the additional resources needed to complete the following Aims and collect preliminary data for an R01 proposal. In Aim 1, I will develop an expanded microsimulation model of people with AAV by incorporating additional health states to reflect key glucocorticoid toxicities. In Aim 2, I will measure healthcare resource utilization and costs associated with key AAV health states.

CAREER DEVELOPMENT BRIDGE FUNDING AWARD: K BRIDGE

The K Bridge Award encourages junior investigators to continue conducting research into novel ideas while reapplying for an NIH or VA career development award.

DEANNA BAKER FROST, MD, PHD

MEDICAL UNIVERSITY OF SOUTH CAROLINA

The Role of Hormonal Dysregulation in Systemic Sclerosis

It is established that estradiol, a form of estrogen, is pro-fibrotic, increased systemically in patients with systemic sclerosis and associated with worse survival. Our long-term goal is to understand how estradiol influences fibrosis in systemic sclerosis. Estradiol utilizes estrogen receptors (both classical and non-classical) to perpetuate its cellular signal, leading to transcriptional and translational modifications. To date, few studies have examined the role of estrogen receptors in fibrosis. Therefore, we seek to close this knowledge gap through identifying which estrogen receptors are important in estradiol-induced fibrosis. The overall objective of this proposal is to identify the specific estrogen receptors that lead to downstream translational alterations in estradiol-induced fibrosis in the skin. We will use 3 different models to inhibit estrogen receptor signaling: mouse dermal fibroblasts which are genetically deficient in the classical estrogen receptor, a chemical antagonist to a non-classical estrogen receptor and siRNA technology to target the classical and non-classical estrogen receptors. In these experiments, we will define the role of the classical and non-classical estrogen receptors in fibronectin and TGFß1 translation, and demonstrate the feasibility of inhibiting non-classical estrogen receptors in human skin tissue using siRNA. Using these 3 models, we will establish the specificity of estrogen receptor signaling in the translation of extracellular matrix components and their contribution to dermal fibrosis. This research project will provide rationale for using medications that inhibit estradiol production and signaling (aromatase inhibitors and fulvestrant, respectively) for systemic sclerosis treatment.

INVESTIGATOR

AWARD

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.

KAVEH ARDALAN, MD, MS

DUKE UNIVERSITY

Psychological Stress and Cardiovascular Health in Juvenile Lupus and Dermatomyositis

Patients with juvenile systemic lupus erythematosus (JSLE) and dermatomyositis (JDM) are at high risk of premature cardiovascular disease (CVD). By young adulthood, JSLE/JDM patients are at 8 times greater risk of CVD than the general population. CVD risk in JSLE/JDM starts in childhood, when carotid intimal medial thickness progression is nearly 50% faster than in familial dyslipidemia. Premature loss of ideal cardiovascular health (CVH), defined as the sum of factors protecting against CVD, is evident in JSLE/JDM patients who have high rates of hypertension, dyslipidemia, and obesity. Chronic inflammation in JSLE/JDM patients further contributes to rapidly worsening CVH trajectories. Given that JSLE and JDM are independent CVD risk factors, affected patients urgently require interventions to bolster and maintain protective CVH trajectories.

In addition to biologic factors, psychological stress negatively impacts long-term CVH trajectories. Up to half of JSLE/JDM patients experience sufficient psychological stress to warrant professional mental health referral. Chronic stress triggers systemic inflammation that mediates subsequent declines in CVH.
We hypothesize that: 1) high stress and inflammation in JSLE/JDM create a "perfect storm" that depletes CVH, compounding CVD risk, and 2) stress is a modifiable risk factor amenable to intervention. In order to test these hypotheses, we will conduct a prospective longitudinal observational study with the following aims: 1) assess the association of psychological stress and CVH indicators in JSLE/JDM; 2) quantify
the mediating effect of inflammation on psychological stress and CVH in JSLE/JDM;
and 3) identify optimal stress-reduction intervention targets that moderate the impact of psychological stress on CVH in JSLE/JDM.

Successful completion of this study will produce the following expected outcomes: 1) quantitative support for a novel, generalizable framework relating stress, inflammation, and CVH in pediatric-onset rheumatic diseases and 2) preliminary data that will inform development and pilot testing of stress-reduction interventions to improve CVH in JSLE/JDM.

LIN SHEN, MD, PHD

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

The Impact of TCR Signaling Strength on Peripheral Tolerance and Autoimmunity

Autoimmune rheumatic diseases, which constitute a broad range of chronic illnesses, cause significant morbidity and mortality in the US and worldwide. The strong allelic association of major histocompatibility complex genes with rheumatoid arthritis and lupus in genome-wide association studies is compelling evidence that TCR recognition and signaling play a critical role in pathogenetic processes leading to autoimmune diseases. However, how altered TCR signaling strength affects peripheral tolerance and promotes autoimmunity remains incompletely understood. Here we seek to understand how abnormal TCR signaling resulting from mutations in ZAP70, including one from human patients with complex autoimmune syndrome, may alter T cell antigen sensitivity, affect T helper cell fate, and impair peripheral tolerance. We will test the central hypothesis that tuning TCR signaling strength can subvert mechanisms of peripheral tolerance to produce autoimmunity. The advance in understanding the mechanisms for peripheral tolerance, including regulation of T cell responsiveness and T helper cell fate, may have implications in preventing cancer immunotherapy related adverse events and identification of new therapeutic targets for autoimmune diseases.

EMILY A. SMITHERMAN, MD, MS

UNIVERSITY OF ALABAMA AT BIRMINGHAM

Evaluating Quality Measures in Childhood-Onset Systemic Lupus Erythematosus

2021 AWARD RECIPIENTS

Poorly controlled childhood-onset systemic lupus erythematosus (cSLE) associated with nephritis has high morbidity and mortality due to the risk of progression to end-stage kidney disease, complicated by racial and social disparities. There is a critical need to better understand how variation in health care quality impacts patient outcomes for cSLE nephritis to identify modifiable health system targets. Building on preliminary data, this project will further evaluate quality process measures for cSLE nephritis. Quality process measures represent minimum standards of care, and in other health conditions, completion of quality measures has been associated with improved health outcomes. Therefore, the objective of the current project is to understand the relationship between quality measure completion and patient-centered outcomes in cSLE nephritis. Aim 1 will assess variation in cSLE nephritis quality measure completion using existing data from a multi-center, North American pediatric rheumatology registry. Aim 2 will evaluate the association of cSLE nephritis quality measure completion with renal outcomes using a national administrative claims database. These aims will test the hypothesis that reliable completion of the cSLE nephritis quality measures will be associated with improved patient-centered outcomes. The proposed research will produce formative knowledge for a future pragmatic cSLE nephritis quality measure implementation trial.

SCIENTIST DEVELOPMENT

AWARD

The Scientist Development Award encourages rheumatologists and rheumatology health professionals to pursue innovative research ideas.

PATRICK CORRIGAN, DPT, PHD

NORTHEASTERN UNIVERSITY

## Asymmetric Walking as Risk Factors for Bilateral Knee Osteoarthritis

Knee osteoarthritis (KOA) is common and a leading cause of disability. Typically, KOA begins as a unilateral disease, with pain in only one knee. Yet, up to 88% of individuals with unilateral KOA develop bilateral disease within 10 years. To develop treatments that reduce the incidence of bilateral KOA, modifiable risk factors need to be elucidated. Asymmetric loading may play a critical role in the development of bilateral disease since individuals with unilateral KOA load their non-arthritic knee more than the arthritic knee. However, asymmetric loading has not been comprehensively evaluated as a risk factor for bilateral KOA. Furthermore, it is unclear how knee pain influences mechanics of other joints. Therefore, the objectives of this proposal are to evaluate asymmetric loading as a risk factor for bilateral pain and KOA and to gain a better understanding of how persons with knee OA modify their gait strategy to compensate for pain. Data from a NIH-funded cohort study of >3000 persons with or at risk for KOA and a NIH-funded clinical trial that is collecting biomechanical data and pain measures during a 30-minute walk will be leveraged. Aim 1 will determine if asymmetric loads are associated with incident knee pain and structural worsening of the non-arthritic knee for those with unilateral symptomatic KOA. Aim 2 will determine how individuals with KOA modify their gait strategy to compensate for pain during an extended walk. Findings may lead to knowledge about biomechanical risk factors in OA and provide the impetus for developing novel treatment strategies. The proposed research and training will enhance the applicant's skills in clinical biomechanics and add new skills in epidemiological methods, collectively increasing his likelihood of success in pursuing independent research that aims to improve outcomes for those with rheumatic diseases and musculoskeletal pathologies.

JIA (SIJIA) CHEN, MD, PHD

BRIGHAM & WOMEN'S HOSPITAL

Elucidating the Role of DNA-Sensing Pathways in Spondyloarthritis Bone Pathology

2021 AWARD RECIPIENTS
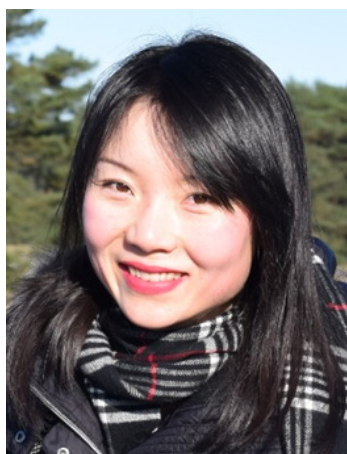
Pathologic entheseal bone formation causes morbidity and disability in spondyloarthritis (SpA) patients, and its prevention remains an important unmet clinical need. Contributing factors to entheseal bone formation include mechanical stress and entheseal inflammation; however, the mechanisms by which these factors result in bone formation are not understood. Both mechanical stress and inflammation accelerate cell death through apoptosis. We observed apoptotic cells in enthesis that precede entheseal bone formation. Our preliminary data indicate that the recognition of DNA, by cell death-associated molecular-pattern (CDAMP) molecules in macrophages, induces factors that promote entheseal bone formation through the cGAS-STING pathway.

This proposal entails multiple approaches to test the fundamental hypothesis that DNA recognition by macrophages affects pathologic entheseal bone formation in SpA. We aim to characterize a novel mechanism for both the initiation and perpetuation of SpA entheseal bone formation and to define the contribution of macrophages during this process with high-resolution technologies. Together, these studies could unravel the mechanisms that link entheseal bone formation to the contributing factors of inflammation and local mechanical stress. Our proposal may uncover novel therapeutic targets for preventing pathologic bone formation in the entheseal sites of SpA patients.

KRISTIN M. D'SILVA, MD

MASSACHUSETTS GENERAL HOSPITAL

EMERGENCY
COVID
FUNDING

Respiratory Complications of Coronavirus Disease 2019 (COVID-19) in Rheumatic Diseases

The coronavirus disease 2019 (COVID-19) pandemic is an unprecedented global health crisis. Globally, millions of people are living with systemic autoimmune rheumatic diseases (SARDs), defined as rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, systemic sclerosis, idiopathic inflammatory myositis, mixed connective tissue disease, and systemic vasculitis. Due to underlying interstitial lung disease and/or immunosuppressive use, patients with SARDs may be vulnerable to short- and long-term severe consequences of COVID-19 infections including respiratory failure, death, pulmonary fibrosis, and decreased health-related quality of life (QoL). Our central hypothesis is that patients with SARDs may have poor short- and long-term COVID-19 respiratory outcomes and health-related QoL after COVID-19 infection. In Aim 1, we will investigate short-term respiratory outcomes of COVID-19 infection retrospectively in patients with SARDs compared to age-, sex-, and date of COVID-19 diagnosis-matched patients without SARDs. The primary outcome of interest is mechanical ventilation, and all-cause mortality is a secondary outcome. In the cohort of COVID-19 infected patients with SARDs, we will assess key predictors of mechanical ventilation, such as pre-existing pulmonary disease and baseline glucocorticoid use. In Aim 2, we will prospectively determine long-term respiratory and general health-related quality of life twelve months after COVID-19 infection using validated survey instruments, including the St. George's Respiratory Questionnaire and Short Form 36-Item Health Survey. We will assess these outcomes in patients with SARDs infected with COVID-19 and patients with SARDs never infected with COVID-19 (matched on age, sex, type of SARD, and baseline oxygen use). The findings from this proposal will determine the short- and long-term impact of COVID-19 infection on patients with SARDs, a critical question for patients and rheumatologists during the ongoing COVID-19 pandemic.

REBECCA H. HABERMAN, MD, MSCI

NYU GROSSMAN SCHOOL OF MEDICINE

EMERGENCY COVID FUNDING

COVID-19 in Patients with Inflammatory Arthritis: A Prospective Study on the Effects of Immunomodulatory Therapy on Susceptibility and Clinical Outcomes

2021 AWARD RECIPIENTS

Patients with inflammatory arthritis (IA), including rheumatoid arthritis (RA), psoriatic arthritis (PsA), and spondyloarthritis (SpA), have an inherently heightened susceptibility to infection and are thus considered high risk for developing coronavirus disease 2019 (COVID-19). Furthermore, small molecules and biologics that aim to treat these diseases theoretically render these patients even more immunocompromised. Paradoxically, however, the use of immune pathway-specific cytokine inhibitors has been shown to improve outcomes of patients with COVID-19 through various mechanisms, including inhibition of the virus-triggered cytokine storm and amelioration of the damage resulting from systemic hyperinflammation. Given the novelty of both severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the pathogenesis of COVID-19, there is currently limited information that can guide clinicians on the appropriate monitoring and management of IA patients during the current global pandemic. To address this gap, we have established a prospective cohort of immune mediated inflammatory disease (IMID) patients to better understand the incidence and outcomes of COVID-19, namely web-based assessment of autoimmune, immune-mediated, and rheumatic patients during the COVID-19 pandemic (WARCOV). The overarching aim of this study is to determine whether having an IA and/or being on certain drugs with immune pathway-specific inhibition significantly impacts susceptibility to SARS-CoV-2 and, for those who become infected, COVID-19 symptomatology and disease course. Further, it aims to identify other risk factors for COVID-19 within this population, which, in turn, can lead to clinical stratification and closer monitoring and aid in therapeutic decision-making. We hypothesize that patients with IA on anti-cytokine therapy, and specifically tumor necrosis factor inhibitors (TNFis), will have improved COVID-19 outcomes (i.e., lower incidence, lower rates of hospitalization and death).

SICONG HUANG, MD

BRIGHAM AND WOMEN'S HOSPITAL

Inflammation and Association with Heart Failure in Rheumatoid Arthritis

Heart failure (HF) is a significant cause of cardiac morbidity and mortality in RA. However, studies of HF in RA have not kept pace with advances in HF management in the general population. Improved understanding of HF has identified two distinct subtypes: HF with preserved ejection fraction (HFpEF) and HF with reduced EF (HFrEF). HFrEF is characterized as a result of myocyte loss after an ischemic event leading to reduced EF. In contrast, ischemia is thought to play a lesser role in HFpEF, and inflammation is hypothesized to be a major driver. While HF is a major comorbidity in RA, there is a paucity of data regarding HF subtypes in RA. This is a result of several factors including the lack of large RA cohorts with EF data. Studying the impact of inflammation on HF in RA may provide guidance to improve management of risk factors leading to HF in both RA patients and potentially the general population.

Our studies propose to examine the association between inflammation and HF, including HF subtypes, using RA as a human model of inflammation. We will employ methods that enable accurate phenotyping of HF subtypes in a large RA cohort. Specifically, we will apply published approaches using natural language processing (NLP) for extracting detailed clinical variables such as EF and machine learning to phenotype patients. We will examine these associations in a database that includes information on many known general population risk factors for HF. The findings have strong potential to inform HF risk factor management in RA patients and the general population.

We hypothesize that inflammation is associated with an increased risk of HF in RA patients and that this association will be demonstrated through association between RA-specific epidemiologic risk factors and HF outcomes. Further, these associations may be stronger for the HFpEF subtype.

TIM WILSON, MD

UNIVERSITY OF COLORADO

Neutrophil Extracellular Traps and Microbiota in the Lung in Rheumatoid Arthritis-Associated Interstitial Lung Disease

Lung involvement is well recognized in the pathogenesis of rheumatoid arthritis (RA), with the most feared manifestation being interstitial lung disease (ILD). Clinically significant ILD affects up to 10% of RA patients and is associated with increased morbidity and mortality. Despite the identification of various clinical risk factors, the pathogenesis of RA-ILD remains poorly understood, and reliable biomarkers are critically needed to provide further insight into its pathogenesis.

Prior studies in idiopathic pulmonary fibrosis (IPF), a form of ILD that shares distinct clinical overlap with RA-ILD, can be used as a model to enhance our understanding of RA-ILD. In IPF, levels of neutrophils and the neutrophil chemoattractant IL-8 are increased in the lung and associated with mortality. Published data in murine models have also shown that neutrophil extracellular trap (NET) formation is elevated in tissue fibrosis. Our preliminary data using induced sputum found that IL-8 and NET remnant levels were elevated in the lung of subjects with RA-ILD. Another biomarker of interest in RA-ILD is the lung microbiome. Perturbations within the lung microbiome have been shown to correlate with altered host immune defense mechanisms in IPF, leading to dysregulated inflammatory responses and fibrosis. Our preliminary data demonstrate that distinct bacteria in sputum, including bacteria coated with IgA, are increased in association with RA-related immune dysregulation in the lung.

With this background, our overall hypothesis is that increased neutrophil-associated inflammation and distinct microbiota in the lung contribute to the pathogenesis of RA-ILD. In Aim 1, we will characterize the association between sputum-derived NET remnants and cytokine levels with the presence and severity of RA-ILD. In Aim 2, we will identify lung microbiota associated with the presence and severity of RA-ILD. Lung disease severity with be defined by pulmonary function tests and quantitative fibrosis on high resolution CT completed within 3 months of sputum collection. The proposed project will provide new insight into the pathophysiologic mechanisms involved in RA-ILD by using lung-derived biomarkers that have the potential to identify novel targets for intervention.

ROSEANNE (FANG) ZHAO, MD, PHD

WASHINGTON UNIVERSITY IN ST. LOUIS

Role of T Cells in a Mouse Model of STING-Associated Vasculopathy with Onset in Infancy

STING-associated vasculopathy with onset in infancy (SAVI) is a pediatric autoinflammatory disease that results in severe life-threatening disease including vascular inflammation, auto-amputation of digits, and lung disease. It is caused by autosomal dominant, gain-of-function mutations in the cyclic dinucleotide sensor, stimulator of interferon genes (STING). While SAVI is generally considered a type I interferonopathy, a causal role for type I interferon signaling in SAVI has not been demonstrated, and treatment with JAK inhibitors has not been effective for all patients. Heterozygous STING N153S mice with a human disease-associated gain-of-function mutation recapitulate key features of SAVI. Although STING N153S mice develop T cell cytopenia and T cell-dependent lung disease, the impact of STING signaling on T cell repertoire and function is less well understood. In preliminary experiments, we found increased proportions of innate/memory-like T cells in the thymus and spleen of STING N153S mice. These cells express high levels of the T box transcription factor eomesodermin and exhibit properties of innate lymphocyte lineages including the rapid production of IFN-gamma. Our data suggest a potential pathologic role for overactive, innate-like T cells, which have not previously been targeted in autoimmune or autoinflammatory disease. Our studies will define how constitutively active STING signaling affects T cell fate and repertoire, provide insight into perturbed signaling networks in dysregulated T cells associated with STING gain-of-function, and determine the specific T cell subsets that modulate inflammatory lung disease in STING N153S mice. These studies aim to identify the underlying causes of disease using a mouse model of SAVI, with the goal of better understanding the mechanisms of disease pathogenesis and identifying potential new targets for therapy.

TOBÉ AND STEPHEN E. MALAWISTA, MD ENDOWMENT IN ACADEMIC RHEUMATOLOGY

Established with a generous commitment from Mrs. Tobé and Dr. Stephen Malawista, this endowment ensures that physician scientists can continue their academic careers in vital rheumatic disease research. The Tobé and Stephen E. Malawista, MD Endowment in Academic Rheumatology provides a permanent source of support in basic science research career development for early career investigators.

ALISA A. MUELLER, MD, PHD

BRIGHAM AND WOMEN'S HOSPITAL

Wnt Signaling as a Driver of Rheumatoid Arthritis Via Fibroblast Expansion

Fibroblasts function as key aggressors in rheumatoid arthritis (RA), where they mediate cartilage and bone destruction, yet there are currently no therapies that directly target synovial fibroblasts. Recent studies from our group and others have shown that the expansion of an inflammatory subset of fibroblasts is critical to perpetuating chronic inflammation in RA, but mechanisms responsible for their excessive proliferation are not clearly delineated.

Our lab, in collaboration with the Accelerating Medicines Partnership (AMP), a consortium of scientists across the National Institutes of Health, academic centers, and industry, has led efforts to utilize high-dimensional profiling platforms to characterize synovial fibroblast subsets in RA. In our preliminary investigation, we found compelling evidence that suggests that synovial fibroblasts are uniquely poised to signal through the Wnt pathway and that Wnt activation promotes fibroblast activation. We hypothesize that Wnt signaling is critical for mediating inflammatory fibroblast pathogenicity and that Wnt inhibition can ameliorate joint damage in RA. This hypothesis is explored in three independent aims.

Aim 1: We define the role of Wnt signaling on pathogenic synovial fibroblast behavior using cell culture and synovial organoid systems.

Aim 2: We examine Wnt pathway activity in synovial fibroblasts of RA patients who fail to respond to conventional therapies by developing a fibroblast-specific Wnt transcriptional signature. We utilize this signature to evaluate Wnt activity in RA synovial fibroblasts from a clinically curated set of single-cell sequencing analyses generated by the AMP.

Aim 3: We evaluate the clinical utility of targeting stromal Wnt signaling therapeutically in mouse models of inflammatory arthritis by inhibiting Wnt signaling specifically in fibroblasts.

We anticipate that the significance of these studies will be to elucidate a molecular mechanism regulating fibroblast pathogenicity in RA and to address the unmet need for fibroblast-specific therapeutics. Ultimately, we hope to provide treatment alternatives that not only serve the broader RA patient population, but that may also provide particular benefit to patients who fail to respond to traditional therapies.

EDUCATION & TRAINING
AWARDS

Building the rheumatology workforce in order to satisfy the growing demand for rheumatologists and rheumatology professionals requires robust education and training opportunities. The Education and Training Awards help to cultivate future generations of rheumatology professionals and ensure people with rheumatic diseases have access to the care they need.

CLINICIAN SCHOLAR EDUCATOR AWARD

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.

JASON R. KOLFENBACH, MD

UNIVERSITY OF COLORADO

A Tele-Health & Outreach Curriculum to Improve Access to Rheumatology Providers

The 2015 Workforce and Training Study carried out by the ACR projected a loss in the number of rheumatologists nationally over the coming decade, as well as regional disparities in patient access in rural and micropolitan areas. Several strategies will be necessary to effectively manage this growth in demand and ensure optimal allocation of resources and quality of patient care. Telehealth technology provides several avenues to more effectively and equitably distribute the knowledge and skills of rheumatologists to patients and healthcare providers across the United States. Utilizing these technologies on a broader scale will be critical to the field of rheumatology, as it is recognized that the large demand in services cannot be met by an increase in rheumatology providers alone.

This project will develop curriculum and evaluation tools in these new modalities of healthcare delivery. The COVID-19 pandemic has shown us that utilization of telehealth services can be both rapid and widespread, but it has also occurred without clear data on the quality of such visits, nor with recommendations regarding faculty supervision and evaluation of trainees. This CSE award will help develop a formal educational program encompassing the areas of virtual/video clinical visits, e-consults, and tele-education. The educational program is intended to improve trainee knowledge and skills in these areas (including proper utilization of these modalities to maintain high-quality care), instruct educators in the assessment of these skills, and better prepare our specialty for healthcare delivery in the coming decade.

LISA ZICKUHR, MD

WASHINGTON UNIVERSITY IN ST. LOUIS

Designing and Evaluating a Telerheumatology Curriculum:
A Scholarly Approach
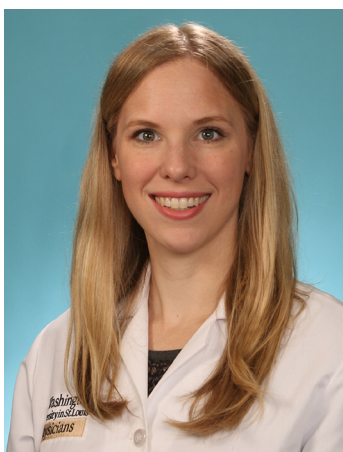
Telehealth and its subspecialty telerheumatology require unique communication and physical exam skills compared to face-to-face encounters; however, the virtual medicine community has not yet delineated the specific techniques needed to practice telerheumatology successfully. As a result, an evidence-based curriculum that teaches providers the best practices for telerheumatology with rigorous assessment methods does not exist. This project will use qualitative methods to identify the content and methods most important for the practice of telerheumatology and will design, implement, and evaluate a curriculum that teaches providers how to practice it.

FELLOWSHIP TRAINING AWARD FOR WORKFORCE EXPANSION

The Fellowship Training Award for Workforce Expansion supports the training of a rheumatology fellow at an institution wanting to create a new slot, or has previously been unable to fill ACGME-approved slots due to funding constraints. We provide this award to ensure an adequate supply of rheumatology providers in all areas of the country.

Rush University Medical Center

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FELLOWSHIP TRAINING AWARD

These 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 disease.

Baylor College of Medicine
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Children's Hospital of Los Angeles
Fellowship Training Award

Cincinnati Children's Hospital Medical Center
Fellowship Training Award

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Amgen Fellowship Training Award

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Fellowship Training Award

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Amgen Fellowship Training Award

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Fellowship Training Award

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Fellowship Training Award

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Fellowship Training Award

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Fellowship Training Award

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Fellowship Training Award

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Amgen Fellowship Training Award

University of California, San Francisco (Pediatric)
Amgen Fellowship Training Award

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Fellowship Training Award

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Fellowship Training Award

University of Pennsylvania
Amgen Fellowship Training Award

PAULA DE MERIEUX FELLOWSHIP TRAINING AWARD

The Paula De Merieux Fellowship Training Award provides support for the training of a promising rheumatology fellow who is an under-represented minority or a woman.

Children's Hospital of Philadelphia

AUDREY M. NELSON, MD PEDIATRIC RHEUMATOLOGY FELLOWSHIP ENDOWMENT

Dr. Nelson's exceptional support of the Foundation enabled the establishment of the Audrey M. Nelson, MD Pediatric Rheumatology Fellowship Endowment in Training. The endowment supports awards aimed at providing robust education and training opportunities for pediatric rheumatologists and addresses the growing demand for pediatric rheumatologists to ensure that children with rheumatic diseases have access to the care they need.

University of Washington/Seattle Children's Hospital

Fellowship Training Award for Workforce Expansion

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 to increase the knowledge and skills of rheumatology health professionals to ensure that they are better equipped to meet the needs of a growing rheumatology patient population.

Jacob Barney, MSN, FNP-C

Firth Medical Center PLLC

Emily Campbell, MPAS

Gundersen Health System

Carla Hill, DPT

UNC Health

Louise Thoma, PhD, DPT

The University of North Carolina at Chapel Hill, Chapel Hill, NC

MENTORED NURSE PRACTITIONER/PHYSICIAN ASSISTANT AWARD FOR WORKFORCE EXPANSION

The Mentored Nurse Practitioner/Physician Assistant Award for Workforce Expansion provides tailored training for nurse practitioners or physician assistants who are new to the field of rheumatology and who are in geographically underserved areas.

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Tracy Ting, MD, MSc, RhMSUS

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Virginia Mason Medical Center

Amish Dave, MD, MPH

Jennifer Wishinski, ARNP, FNP

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.

RHEUMATOLOGY FUTURE PHYSICIAN SCIENTIST AWARD

This award supports MD/PhD students who demonstrate outstanding potential and significant commitment to a career in rheumatology research, in order to support the nation's top emerging physician scientists in the field of rheumatology.

JUAN COLAZO, BSC

VANDERBILT UNIVERSITY
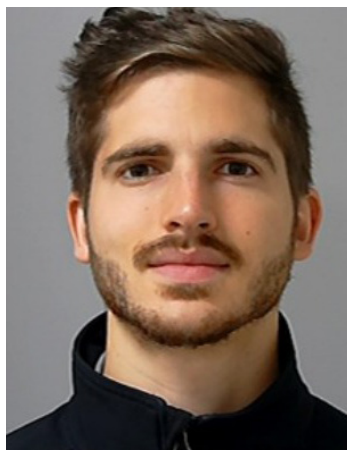
Osteoarthritis (OA) is a chronic, degenerative joint disease that can be associated with aging or caused by injury in the case of post-traumatic osteoarthritis (PTOA). Non-steroidal anti-inflammatory drugs are typically the first line of treatment to deal with pain but can cause gastric complications and do not slow cartilage deterioration. The Osteoarthritis Research Society International (OARSI) recommends intra-articular injection of corticosteroids for symptomatic knee OA, but steroids do not target the underlying cause of disease and may even worsen cartilage thinning and/or increase the chance of requiring joint replacement in the future. Furthermore, multiple joint osteoarthritis (MJOA) was found in a comprehensive review of 98 clinical studies to occur in over 50% of OA/PTOA cases, motivating development of systemic therapies that can reach multiple joints.

These shortcomings leave an unmet need for disease-modifying OA/PTOA drugs (DMOADs) that block or reduce disease progression. In PTOA, synoviocytes and chondrocytes produce inflammatory cytokines and matrix metalloproteinases (MMPs) that drive the joint degenerative process. In humans, MMPs 1 and 13 are promising DMOAD targets because they degrade the key structural protein collagen II, which is an irreversible step in cartilage destruction. Systemic delivery of small molecule MMP inhibitors has been tested clinically for cancer but was dose limited by toxicities (MSS, musculoskeletal syndrome) caused by the lack of MMP selectivity.

Use of RNA interference (RNAi) is a promising strategy to specifically inhibit therapeutic targets that are difficult to selectively modulate with small molecule drugs. Excitingly, the first siRNA drug patisiran (a lipid nanoparticle RNAi formulation) was approved in 2018, followed by givosiran (a "naked" siRNA conjugate) in 2019. However, targets outside of the liver remain under-developed because (1) nano-formulations preferentially accumulate in the liver over other tissues and (2) unmodified siRNAs have poor pharmacokinetics (PK) due to rapid renal clearance and poor bioavailability. To overcome these delivery barriers, we propose to synthesize siRNA molecules end-modified with a diacyl lipid (siRNA-L2) to spontaneously form a selective molecular complex with endogenous albumin (alb/siRNA-L2) in vivo. We hypothesize that this albumin "hitchhiking" siRNA-L2 will enhance siRNA pharmacokinetics, be safe, and increase the level and homogeneity of delivery, particularly to tissues characterized by inflammation and vascular leakiness. The overall goal of this proposal is to implement siRNA-L2 to block and treat PTOA/MJOA. The central hypothesis is that potent and safe dual inhibition of MMP1 and MMP13 by utilizing systemic siRNA-L2 will reduce disease progression.

CLAUDIA LOVELL, BA

UNIVERSITY OF PENNSYLVANIA PERELMAN SCHOOL OF MEDICINE

Approximately 80% of individuals diagnosed with autoimmune disease are female, but the underlying mechanisms that govern sex bias in immunologic pathology are not well understood. Susceptibility to systemic lupus erythematous (SLE) and Sjögren's syndrome increases with the number of X chromosomes carried by an individual. This suggests that carrying more than one X chromosome, which contains numerous immune-regulatory genes, may contribute to female-biased risk in developing autoimmune disease. The dosage of X-linked gene expression in mammals with more than one X chromosome is balanced by X-chromosome inactivation (XCI). When XCI occurs in early development, cells undergo random inactivation of all but one X chromosome. This process is initiated by expression of the long non-coding RNA Xist from the inactive X chromosome (Xi), followed by Xist RNA coating the Xi and recruiting heterochromatic repressive marks. Repression of the Xi is maintained in somatic cells through each cell division and into adulthood.

Our lab discovered that mouse and human naïve B cells contain no visualizable Xist RNA or have dispersed Xist RNA signal in the nucleus, a pattern that had not been previously observed in somatic cells. Upon B cell stimulation, Xist RNA and heterochromatic modifications re-localize to the Xi. This dynamic XCI maintenance is disrupted in B cells from SLE patients and mouse models of autoimmune disease, with incomplete re-localization of silencing marks to the Xi upon stimulation. Furthermore, B cells from SLE patients exhibit increased expression of X-linked genes, including some immune-related genes, likely due to incomplete XCI maintenance. I will study how impairments to XCI maintenance impact B cell homeostasis. I will focus on a special population of B cells, known as "age-associated B cells" (ABCs), which are broadly implicated in autoimmune disease and are more prevalent in females than males. Investigating the epigenetic mechanisms of XCI maintenance in ABCs will reveal how genetic contributions from the X chromosome are critical for B cell function and will unveil an X-chromosome based mechanism that contributes to female-biased autoimmunity.

BRENDA SEYMOUR, BS

UNIVERSITY OF COLORADO, DENVER

While evidence of microbial dysbiosis in patients with rheumatoid arthritis (RA) suggests that changes in the microbiome may contribute to the development of disease, the mechanisms by which this occurs have yet to be determined. The objective of this project is to determine how a specific microbial species isolated from a patient at-risk for RA alters intestinal dendritic cell (DC) function in a novel murine model of inflammatory arthritis. DCs are key mediators of intestinal homeostasis because they provide signals to T cells that dictate whether a response to a gut microbe is tolerogenic or pro-inflammatory. Ongoing studies in our lab have shown that a novel bacterial species within the family Ruminococcaceae (referred to here as Isolate 7), isolated from a patient at-risk for RA, is sufficient to cause inflammatory arthritis in mono-colonized germ-free (GF) DBA1/J mice. Another strain isolated from the same patient (Isolate 1) does not cause inflammatory arthritis in mono-colonized mice. Although the strains share 99.4% genetic sequence homology, Isolate 7 produces higher levels of indole metabolites compared to Isolate 1. Based on these observations, I hypothesize that indoles and/or antigens produced by Isolate 7 alter dendritic cell maturation, leading to changes in Signals 1, 2, and 3 for T cell activation and skewing naïve T cells towards an autoreactive (Th17) phenotype.

To test this hypothesis, my aims for this project are (1) to determine how Isolate 7 alters DC antigen uptake and presentation and (2) to determine how Isolate 7 alters DC cytokine production. These aims will be tested both in vitro (using bone marrow derived dendritic cells stimulated with indole +/- Isolate 1 or Isolate 7) and in vivo (using GF mice mono-colonized with either Isolate 1 or Isolate 7). Successful completion of these aims will demonstrate the first step of a mechanism by which a bacterial species isolated from a patient at-risk for RA induces inflammatory arthritis in mono-colonized mice. These findings could lead to a better understanding of how microbial dysbiosis may lead to the development of inflammatory arthritis in mice and/or rheumatoid arthritis in humans.

RESIDENT RESEARCH PRECEPTORSHIP

The Resident Research Preceptorship introduces residents to the specialty of rheumatology and attracts promising physician scientists to the field by supporting a full-time research experience.

Devin Driscoll, MD
Tuhina Neogi, MD, PhD (Preceptor)
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University of Nebraska Medical Center

Zandra Walton, MD, PhD
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Massachusetts General Hospital

Austin Wheeler, MD
Ted Mikuls, MD, MSPH (Preceptor)
University of Nebraska Medical Center

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.

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Boston Children's Hospital

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 Convergence and feature outstanding investigators in various areas of rheumatology research.

RHEUMATOLOGY RESEARCH FOUNDATION MEMORIAL LECTURESHIP TO HONOR WILLIAM P. AREND, MD
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www.RheumResearch.org/Donate

35TH ANNIVERSARY

Rheumatology Research Foundation