# ADVANCING TREATMENTS
# FINDING CURES

# 2022
# AWARD
# RECIPIENTS

**Rheumatology Research Foundation**

Advancing Treatment | Finding Cures

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# INNOVATIVE RESEARCH AWARD

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.

# Michael Brenner, MD
## Brigham and Women's Hospital

## *CD8 T cell-Derived Granzyme K Activates Complement That Drives Synovial Fibroblast Inflammation*

The role of T cells in RA is established, but nearly all research has focused on CD4 T cells. We show that CD8 T cells are highly expanded in inflamed RA synovium. These CD8 T cells are not the typical granzyme (Gzm) B+ CTL. Instead, they express high levels of GzmK. Remarkably, we find that GzmK activates complement. We show that GzmK can cleave C4 to C4b and C2 to C2a with formation of an active C3 convertase (C4b+C2a), which can cleave C3 to C3a and C3b. We show that fibroblasts express the highest amounts of complement components in the synovium. Just-published research (Immunity 54, 1-20, 2021) shows that complement activation drives synovial fibroblast priming with mTOR activation including downstream metabolic changes and inflammation.

We propose to determine if CD8 T cell-derived GzmK can induce synovial fibroblast activation and metabolic changes by mediating local cellular complement activation either extracellularly or intracellularly, via the recently identified complosome. In Aim 1, we ask if the complement components produced by synovial fibroblasts are targets for GzmK-mediated complement activation. We define how the expression, localization, and secretion of complement change after stimulation of synovial fibroblasts with IFN or TNF. Then, we will determine where GzmK elicits formation of an active C3 convertase—whether in the extracellular space, in intracellular compartments, or both. In Aim 2, we define the ability of GzmK to induce inflammatory priming of synovial fibroblasts via complement activation by determining the effects of recombinant or CD8 T cell-derived GzmK stimulation on the inflammatory and metabolic state of synovial fibroblasts and if these effects are mediated by complement.

Together, these studies will define a new CD8 T cell—GzmK—complement activation pathway that can drive inflammatory activation of fibroblasts and other cells that are highly relevant to understanding the tissue pathology in RA and point to GzmK as a new therapeutic target.

# Tanya Freedman, PhD
## University of Minnesota

### *LynB Kinase, TLR Signaling, Dendritic Cells, and Lupus*

Systemic lupus erythematosus (SLE) is driven by adaptive-immune cells via autoantibody production and innate-immune myeloid cells via impaired autophagy and chronic inflammation induced by Toll-like-receptor (TLR) and ITAM signaling. Myeloid dendritic cells (DCs) drive SLE in humans and in mouse models. In patients, kidney and other organ damage can be slowed via immunosuppression, which increases susceptibility to infection. Defining mechanisms by which DCs integrate proinflammatory and suppressive signaling inputs to support healthy immunity or to drive immune dysregulation remains an obstacle to developing better-targeted therapies for SLE. Functional loss of the Src-family kinase Lyn is a risk factor for human SLE and a driver of DC dysregulation. Lyn is expressed as two splice variants (LynA and LynB), which have been treated almost uniformly in the literature as a single entity. We recently generated isoform-specific LynA knockout (KO) and LynBKO mice and found that loss of LynB is the dominant trigger of lupus and increased TLR4 signaling in DCs and blood leukocytes.

We hypothesize that LynB protects against lupus-like disease by interacting with negative-regulatory signaling machinery in DCs, suppressing TLR signaling, promoting autophagy, and dampening inflammatory cytokine production. With the long-term goal of identifying new, safer therapies to block the progression of SLE, we propose to study LynB in cells and in vivo by (1) Defining the roles of LynA and LynB in DC TLR and autophagy pathways; (2) Defining the interactomes and substrates of LynA and LynB in DCs; and (3) Assessing contributions of DCs and B cells to LynBKO-driven lupus. Our novel LynAKO and LynBKO mice open the door to elucidating mechanisms directing activating vs. inhibitory functions of Lyn.

Ultimately, our insights into lupus pathogenesis and immune regulation will inspire the development of precision therapies and lead to safer, more effective treatment options for SLE patients.

# Ellen Gravallase, MD
## Brigham and Women's Hospital

## *Novel Mechanisms of Enthesial Bone Formation in Spondyloarthritis*

The spondyloarthritis (SpA) spectrum diseases share the feature of pathologic enthesial bone formation. This results in significant pain, inhibited mobility, and disability for patients. Although the BMP and Wnt signaling bone anabolic pathways have been implicated in the pathogenesis of enthesial bone formation, and mechanical stress contributes, the exact mechanisms by which bone is formed remain unclear.

Our preliminary data indicate that recognition of DNA, a Cell Death-Associated Molecular Pattern (CDAMP), by enthesial macrophages, and subsequent activation of the cGAS/STING pathway, may play a critical role. We show that in a mouse in which the enzyme DNase II is deleted leading to accrual of DNA in macrophages, there is evidence of significant new bone formation that is dependent upon an intact STING pathway. We will test the hypothesis that DNA from apoptotic or dying cells is engulfed by macrophages, leading in a cGAS/STING-dependent manner to the local production of anabolic factors that promote enthesial bone formation. Studies in this grant will determine the role of mechanical stress in the process of enthesial bone formation, using two relevant animal models. We will use AAV vectors to deliver DNase locally and quantify changes in enthesial bone formation by microCT. We will also study mice deficient in cGAS or STING to determine the contribution of this pathway to the bone formation process. Finally, we will utilize fate mapping systems available in our laboratory to determine the contribution of defined macrophage populations to enthesial bone formation and determine the transcriptional signatures regulating pro-osteogenic factors.

These studies will probe the mechanisms linking entheseal bone to inflammation and local mechanical stress and could identify a novel set of targets for the prevention or treatment of SpA-induced enthesial bone.
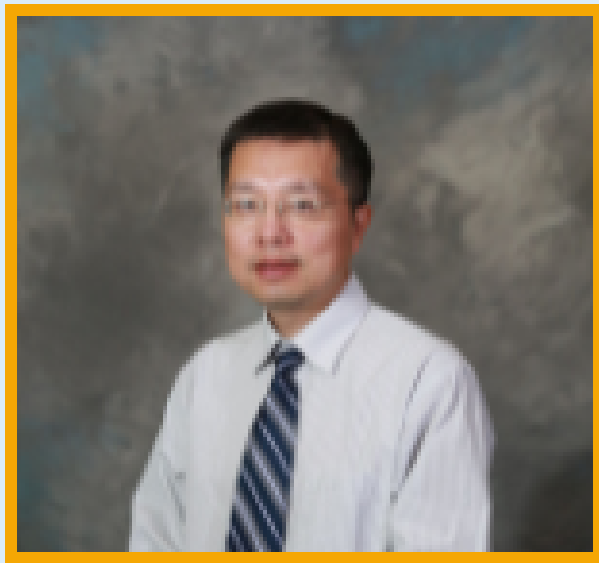
# Bin Guo, PhD
## University of Houston

## *A Novel Interleukin-15 Receptor Antagonist for the Treatment of Rheumatoid Arthritis*

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease. The efficacy of current medications is limited. Interleukin-15 (IL-15) is a cytokine that is detected in serum and synovial fluid of RA patients. Administration of IL-15 leads to the development of severe inflammatory arthritis in mice. Thus, IL-15 signaling is a potential target for treatment of RA.

We have discovered a new peptoid compound (IFRA3, Interleukin-15 receptor antagonist 3) that directly binds to and inhibits the IL-15 receptor. As a result of IL-15 inhibition, IFRA3Q1 (a tetramer of IFRA3) suppressed CTLL-2 cell proliferation (which depends on IL-15 activity) and exhibited strong in vivo anti-inflammatory activity in carrageenan-induced inflammation in mice. Furthermore, IFRA3Q1 inhibited collagen-induced arthritis in mice. The long-term goal of this study is to develop a new and effective RA therapy. The Specific Aims are to (1) Determine the therapeutic efficacy of IFRA3Q1 in murine models of human RA; and (2) Optimize the anti-inflammatory efficacy of IFRA3Q1 for arthritic therapy using medicinal chemistry. The efficacy of these compounds in arthritis suppression will be evaluated in vitro as well as in vivo in mice. IFRA3 has superior pharmaceutical qualities such as stability, cell/tissue permeability, and non-immunogenicity. We plan to understand the molecular action of IFRA3 and to further validate this new therapeutic paradigm. We expect to observe significant anti-arthritic activity with IFRA3Q1 and its optimized derivatives. The specificity and downstream mechanism of IFRA3Q1's action will be defined. Optimized IFRA3Q1 derivatives are likely to show improved activity in suppressing inflammation and arthritis.

These preclinical studies will lay the groundwork for future translational studies in RA.

# Betty Hsiao, MD
## Yale University

### *Overcoming Barriers to Treat-to-Target in Rheumatoid Arthritis Using Tailored Patient Videos*

Despite proven benefits and widespread endorsement of a treat-to-target (TTT) strategy in RA, implementation in the U.S. is low, as patient reluctance to initiate or escalate care remains a significant barrier to TTT adherence. Improving clinical outcomes requires developing interventions designed specifically to improve patient decision-making and buy-in to TTT strategies. To effectively communicate the benefits associated with TTT, interventions must reflect in-depth understanding of the complex influences on patient decision-making, such as culture, family, peers, media, and social group, as well as cognitive and emotional factors.

In a prior study, we used the Mental Models Approach to Risk Communication to identify critical discrepancies between the rheumatologist and patient mental models for RA treatment. Many patients who have struggled to initiate or escalate DMARDs emphasized the importance of learning from their peers, in addition to receiving information from their rheumatologists, prior to making a treatment decision. To address this need, we developed tailored patient narratives in the form of videos in which patients with RA described their experiences making difficult treatment decisions, designed to support patients who are hesitant to initiate or escalate DMARDs. We aim to determine how best to incorporate patient narratives into clinical practice by conducting semi-structured interviews with key stakeholders (patients, clinicians, nurses, and office staff), as well as performing usability testing. We will then conduct a pretest-posttest study to evaluate feasibility and clinical outcomes six months prior to and six months after, introducing the tailored videos.

The data generated from this study regarding enrollment, implementation of the intervention, and the potential effect of the videos on decisional conflict, choice predisposition, shared decision-making, and TTT rates will determine whether proceeding with a more rigorous trial is justified.

# Patricia Katz, PhD
## University of California, San Francisco

### *Development and Preliminary Validation of a Patient-reported Measure of Systemic Lupus Erythematosus (SLE) Disease Activity*

Much of the evidence demonstrating the impact of SLE on patients' lives, functioning, and quality of life has been generated from observational research, e.g., epidemiologic or cohort studies. For this type of research, in-person clinical assessments are often not feasible. Two primary aspects of disease status are relevant in SLE: disease activity and accumulated disease damage.

A validated patient-reported proxy of physician-assessed disease damage has been developed by our group. However, the only existing patient-reported measure of SLE disease activity has no correlation with the physician-assessed disease activity. The proposed project will address the need for a validated, patient-reported measure of SLE disease activity that can serve as a proxy for physician assessment. Project Aims are to (1) Develop the patient-reported SLE Disease Activity Questionnaire (SLEDAQ); and (2) Conduct cross-sectional and longitudinal validation studies of the SLEDAQ in two leading SLE clinical settings. An exploratory Aim will conduct a preliminary examination of the feasibility and usefulness of SLEDAQ in telehealth encounters. The study team for this project is uniquely qualified to perform the work, having successfully developed, tested, and validated the patient-reported proxy of SLE disease damage mentioned above.

Successful completion of this project will provide researchers with a questionnaire that can feasibly be integrated into observational research, and thereby increase the validity and scientific rigor of research into important issues surrounding the impact of SLE, quality of care, disparities in health care access and quality, and patient outcomes. The measure may also have clinical usefulness in tracking disease activity, as most clinical practices cannot or do not conduct formal assessments of activity, and in telehealth settings.

# Yvonne Lee, MD
## Northwestern University

*Transcriptional Profiles of Circulating Monocytes and their Association with Pain Centralization and DMARD response in Rheumatoid Arthritis*

Among patients with rheumatoid arthritis (RA), pain may persist even when inflammation is controlled. This pain may be due to pain centralization, a process that changes the way the brain and spinal cord regulate pain.

The goal of this proposal is to develop insights into the processes underlying pain centralization by studying the relationship between gene expression in monocytes (a type of white blood cell) and pain centralization. The rationale for studying monocytes is based on rodent models showing that monocytes are involved in maintaining chronic pain. The hypothesis is that uniquely characteristic patterns of gene expression are associated with pain centralization. The Specific Aims are to (1) Identify gene expression signatures in monocytes associated with pain centralization; and (2) Establish if the gene expression profiles predict pain after treatment with disease-modifying antirheumatic drugs (DMARDs). Fifty subjects with RA will be assessed before and 12 weeks after starting a DMARD. Subjects will complete surveys to characterize their pain experience and undergo quantitative sensory testing (QST) to assess patterns of pain sensitivity associated with specific pain pathways. Blood will be drawn to collect monocytes for RNA-sequencing. Machine-learning techniques will be used to model if gene expression is (a) Associated with QST patterns of pain centralization; and (b) Predictive of pain response after DMARD therapy. This research is innovative because it uses (1) Cutting-edge functional genomic approaches to identify pathways associated with chronic pain in RA; and (2) QST, in addition to self-reported measures of pain, to assess pain centralization.

This research is impactful because it would enable the development of non-opioid analgesics for chronic pain in patients with RA. This proposal is in-line with the Foundation's goal to support research that studies biological parameters associated with clinical manifestations and responses to therapy.

# Timothy McAlindon, MD, MPH
## Tufts Medical Center

## *Radiofrequency Ablation for Chronic Knee Pain After Total Knee Arthroplasty (RACK TKA)*

Each year over 600,000 adults undergo TKA in the United States. While TKA successfully improves function and pain in most patients who undergo the procedure, up to 40% subsequently report chronic pain, despite a well-functioning prosthesis. Chronic pain after TKA reduces quality of life and function, and increases risk of depression, anxiety, and long-term opioid use. However, patients with chronic pain after TKA are in a double bind because of a paucity of specific treatment options and lack of knowledge among health care providers about post-TKA knee pain. Orthopedists may view the TKA as a technical "success," while non-surgical practitioners may have trepidation intervening on a prosthetic knee following TKA. Genicular nerve radiofrequency ablation, which effectively reduces chronic pain and improves physical function among people with knee osteoarthritis, is a potential treatment for chronic pain after TKA. It uses a high-frequency electrical current to selectively denervate nociceptive input from the periphery to the central nervous system without damaging motor fibers. Preliminary evidence from observational case reports and a small clinical trial describe the initial efficacy of radiofrequency ablation in reducing chronic pain after TKA. Even though it is being used clinically, clinical trials with robust methodologies comparing an active and sham treatment are needed to estimate the acceptability, safety, and efficacy of radiofrequency ablation in people with chronic pain after TKA in the U.S.

The overall objective of this six-month study is to evaluate radiofrequency ablation as a clinically useful treatment. We will accomplish this with a double-blinded sham-controlled randomized clinical trial evaluating acceptability, safety, and potential for efficacy of genicular nerve radiofrequency ablation among 30 people=one year post-TKA who report an unacceptable symptom state and chronic pain.

Our long-term goal is to evaluate radiofrequency ablation as a readily available, non-surgical, non-opioid treatment to reduce chronic pain in people after TKA performed for knee osteoarthritis.
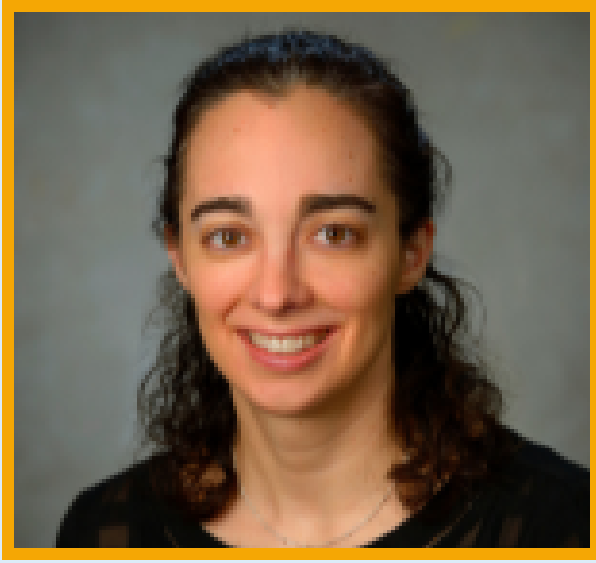
# Alexis Ogdie Beatty, MD, MSCE*
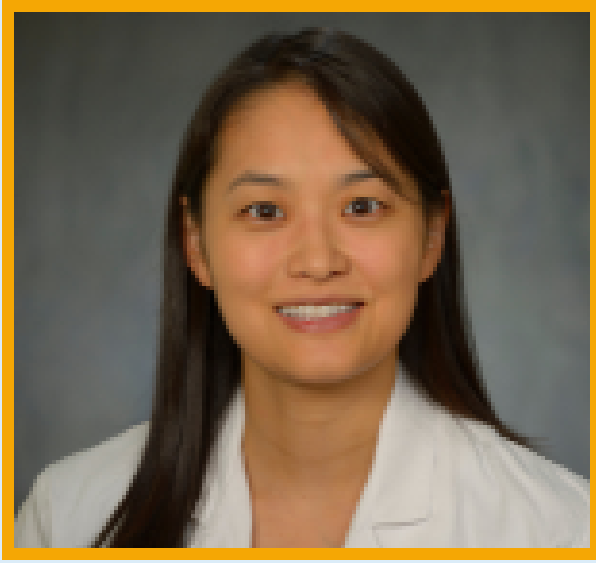## University of Pennsylvania

## Use of Telemedicine to Address "Off-target" Symptoms in Psoriatic Arthritis

The majority of patients with psoriatic arthritis (PsA) continue to have active symptoms on therapy.

We hypothesize that addressing "off-target" symptoms, comorbidities, and lifestyle factors through a holistic management approach will improve disease impact and increase the probability of achieving minimal disease activity (MDA). The Aim of this study is to test the acceptability, feasibility, and effectiveness of structured telemedicine visits to encourage lifestyle changes that will improve quality of life, disease impact, and disease activity in patients with PsA. We will conduct a single-arm trial that employs a telemedicine-based intervention conducted by nurses and nurse practitioners. Visits will be structured based on the previously validated PsoWell model, a motivational interviewing technique, and will employ a set of PDF and/or digital tools to assist patients in setting goals and achieving lifestyle changes (i.e., sleep hygiene to improve fatigue and sleep). In the proposed study, patients with PsA who are stable on therapy but have active symptoms as measured by the PsA Impact of Disease (PsAID) questionnaire will be enrolled. Two telemedicine visits will be conducted between standard office visits. Patients will select a target symptom and/or comorbidity, set goals, and follow up with the provider. Outcomes of the study include feasibility, acceptability to patients and providers, and effectiveness (achievement of PSAID score<4, the patient acceptable symptom state, and MDA).

At completion of the proposed study, we will have data to support use of the PsoWell model via telemedicine in clinical practice and the information needed to plan and conduct a pragmatic trial to address a holistic management strategy compared to standard of care in patients with PsA.

# Rennie Rhee, MD
## University of Pennsylvania

## *Molecular Interactions Between Nasal Bacteria and Epithelial Cells in Patients with Granulomatosis with Polyangiitis*

The goal of this project is to investigate interbacterial and host-bacterial molecular interactions associated with relapse in granulomatosis with polyangiitis (GPA). GPA is a systemic vasculitis associated with destructive sinonasal inflammation and frequent relapses. It is unknown what incites disease activity in GPA. Mechanistic and epidemiologic studies suggest microbes, in particular nasal microbiota, may be an important contributor to relapse in GPA. While previous studies in GPA focused on a single pathogenic microbe in isolation, studies in other populations demonstrate that interspecies interactions, either synergistic or antagonistic, influence pathogenicity. In GPA, little is known about polymicrobial interactions in the nasal cavity and their effects on immune responses.

Work from our group has uncovered novel relationships between nasal bacteria in GPA. Using unbiased molecular sequencing of nasal swabs obtained from a longitudinal cohort of patients with GPA, we identified dynamic changes months prior to the onset of clinical relapse in nasal Staphylococcus and Corynebacterium. Our findings are consistent with prior studies which demonstrated direct interactions between Staphylococcus aureus and Corynebacterium species in vitro. Building from our sequencing-based epidemiological studies, we will perform culture-based investigations to define the molecular mechanisms that govern these correlations. We plan to investigate how bacteria interact with each other and how bacteria interact with the host. Leveraging a well-characterized biorepository of over 500 nasal swabs from 106 GPA patients to harvest bacterial strains and epithelial cells, we will: (1) Determine the bacteria-bacteria molecular interactions and strain heterogeneity of nasal bacteria in GPA; and (2) Investigate host-bacteria interactions in vitro using cultured human nasal epithelial cells from patients with GPA.

The outcome of this study is a better understanding of the mechanisms by which communities of nasal bacterial incite relapse in GPA. This is the first step towards developing antimicrobial strategies that target disease-causing pathways while preserving the overall "healthy" diversity of the microbiome. Ultimately, we will broadly expand our knowledge of the role of the respiratory tract microbiome in autoimmunity.

# Shiva Shahrara, PhD
## University of Illinois at Chicago

## *Investigating the Metabolic Malfunction in RA*

Rheumatoid arthritis (RA) affects approximately 1% of our population, or 2.5 million Americans. RA is a chronic, disabling autoimmune disease in which the body attacks its tissues. If patients with RA do not receive treatment, this aggressive disease will severely destroy the joints to the point where they can no longer function. RA is also associated with depression, cardiovascular disease, and psychosocial stress. As RA progresses, performing simple daily activities becomes more challenging for patients suffering from the disease. There is no cure for RA and up to 50% of RA patients do not respond to the current therapies; therefore, novel therapeutic strategies are urgently needed.

The goal of this project is to develop a safe therapeutic agent for patients who do not respond to current therapies. As such, we have identified a novel pathway that can markedly alleviate inflammation and bone erosion in RA cells by rebalancing the pro-repair over the pro-inflammatory networks. This mechanism of action is not limited to a specific inflammatory factor and its function will impact multiple immune cell types that are in crosstalk. We are proposing a unique way of combating RA joint inflammation and bone erosion which has not been tested previously. Our short-term goal is to evaluate the effectiveness of blocking the identified network to rebalance pro-repair over pro-inflammatory factors. Our long-term goal is to engineer a specific inhibitor that can target metabolic malfunction by switching the inflammatory phenotype to a pro-repair immune response in the RA joints.

We hope that our work will lead to a novel type of treatment that can be a suitable option for suffering RA patients who are nonresponsive to traditional therapies.

# INNOVATIVE RESEARCH AWARD FOR COMMUNITY PRACTITIONERS

The Foundation recognizes the unique potential for research performed by rheumatologists and rheumatology professionals in community-based environments to advance our understanding of rheumatic diseases, their treatment and how to improve patient outcomes.

This award is targeted to community practitioners, who, in addition to being engaged in patient care or conduct, are interested in conducting research.

# Jenna Thomason, MD, MPH
## University of Washington

## *Development and Validation of Applying Thermal Imaging as an Adjunct Tool to Augment Physician's Assessment in the Telehealth Setting*

Use of telemedicine has exponentially increased in adult and pediatric rheumatology during the COVID-19 pandemic. Although for patients with inflammatory arthritis a comprehensive hands-on joint exam is crucial for an accurate assessment of disease activity and medical decision-making, such an exam is not assessed during telemedicine visits. We are acutely aware that methods of examination via telemedicine need improvement, validation, and standardization.

A recent survey amongst pediatric rheumatologists indicated that the use of the pediatric Gait, Arms and Legs (pGALS), a simplified musculoskeletal examination that assesses joint range of motion, was the most widely used visual exam during telemedicine visits at the height of the pandemic. It has since been proposed that this variation of the pGALS, known as the video-pGALS (v-pGALS), is one systematic exam approach that can be used in conjunction with patient history and patient-reported exam during telemedicine visits. However, there are no studies that compare its performance to the in-person joint examination. Additionally, infrared thermal imaging has been evaluated as a screening or supplementary tool for detecting or following up active arthritis in animal models, osteoarthritis, rheumatoid arthritis, and juvenile idiopathic arthritis (JIA). Infrared thermal imaging is a quick and noninvasive tool that has been proven sensitive in identifying active arthritis in knees. Thus, we believe that infrared technology has the potential to improve remote assessment of joint inflammation.

This study aims to assess the clinical performance of a joint count questionnaire with and without video-exam inspection during telemedicine compared to an in-person physician conducted joint exam in adults and children with chronic inflammatory arthritis. We also plan to further develop and validate the within-limb calibrated temperature measurement of joints using previously-established algorithms with a smartphone-attached thermal camera. Lastly, we will determine the added value of thermal imaging for physicians to assess joint disease status in a telemedicine setting and the utility of thermal imaging during long-term care.

# 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.

# Benjamin Korman, MD
## University of Rochester

### *Role of the CD47 Pathway in Rheumatoid Arthritis Pathogenesis and Treatment*

CD47 is a ubiquitously expressed surface protein which both regulates phagocytosis by interacting with SIRP-a to initiate "don't eat me" signaling, and modulates fibroblast matrix turnover and bone homeostasis via its interaction with thrombospodin-1, is elevated in RA, and may play multiple roles in disease.

The application's central hypothesis is that CD47 is critical to RA pathogenesis and reduction of CD47 signaling will ameliorate or reverse inflammatory arthritis via effects in both immune and mesenchymal cells. Furthermore, we hypothesize that over-expression of CD47 in RA prevents clearance of pathogenic immune cells from the synovium, promotes fibroblast activation, and accelerates bone loss. We will first test this hypothesis by characterizing CD47 and its binding partners in RA synovium histologically, functionally in relevant cells, and by single-cell RNA sequencing. Next, we will explore the role of CD47 in vivo by assessing clinical, histologic, radiographic, and genomic alterations induced by CD47 deficiency in mouse models of RA. Finally, we will test anti-CD47 based therapeutic strategies in synovial organoid cultures and in vivo arthritis models.

This application will support Dr. Korman's effort to generate preliminary data to improve and resubmit an R01 application investigating the role of CD47 in rheumatoid arthritis (RA) and career development.
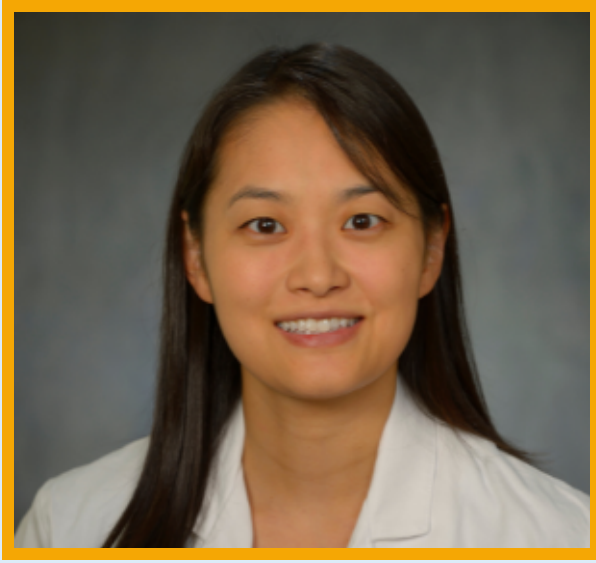
# Rennie Rhee, MD
## University of Pennsylvania

### *Advanced Vessel Wall MR Imaging of Scalp and Orbital Arteries in Patients with Giant Cell Arteritis*

GCA is a relapsing systemic vasculitis which frequently involves the scalp and orbital arteries. About 20% of patients present with visual impairment which can rapidly progress to blindness ("ocular GCA"). There is a critical need for a noninvasive imaging test that can accurately diagnose GCA, identify the subgroup with ocular GCA, and longitudinally monitor treatment response and relapse. cVW-MRI has the potential to address this need by visualizing vascular inflammation of multiple scalp and orbital arteries.

The goal of the project is to determine the utility of cranial vessel wall magnetic resonance imaging (cVW-MRI) in the diagnosis and disease surveillance of patients with giant cell arteritis (GCA, formerly "temporal arteritis"). This prospective observational study will enroll patients with suspected GCA, enriching for ocular involvement. Aim 1 will determine the utility of cVW-MRI as a noninvasive diagnostic tool in GCA by comparing scalp and orbital vessel wall enhancement in patients with suspected GCA, including ocular GCA. Aim 2 will define the longitudinal changes in cVW-MRI associated with disease activity and outcomes, including irrecoverable vision loss.

The outcome of this work is an imaging test that detects vascular inflammation of both the scalp and orbital arteries in GCA. The direct impact on patient care is the implementation of a single, 35-minute imaging exam that enhances current approaches to diagnosis and monitoring of disease activity in GCA. The RRF R Bridge Award will provide the critical support needed to transform clinical practice paradigms in GCA.

# 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.

# Theresa Wampler Muskardin, MD
## Hospital for Special Surgery

## *Type I Interferon Impacts Treatment Response in Rheumatoid Arthritis*

Rheumatoid arthritis (RA) is common, affecting approximately 1% of the world population. Delay in effective treatment results in increased morbidity and mortality, and a heavy economic burden. Current treatment strategies are empiric because we have no markers to suggest which therapy is best for an individual. Tumor necrosis factor inhibitors (TNFi) are the most common initial biologic treatment employed. Responses are variable, with approximately 30% not responding and another 30% having only partial response.

We have shown in test and validation cohorts that pre-treatment circulating type I IFN (T1IFN) activity predicts non-response to TNFi. Pre-treatment IFN-ß to IFN-a activity ratio>1.3 was strongly predictive of non-response to TNFi. No patient with a ratio>1.3 achieved remission or low disease activity. In RA, monocytes (Mo) from the blood invade synovium, and local stimuli drive expansion of macrophage (Mf) populations. We used single-cell analysis to study blood Mo gene expression in RA patients with high vs. low IFN-ß-to-a activity ratio and found major differences between the groups, supporting downstream effects upon a critical effector cell population. Dr. Wampler Muskardin hypothesizes that RA TNFi non-responders have increased IFN-ß relative to IFN-a, which results in increased diapedesis of Mo and associates with altered composition and pathway activation in the synovium. She will explore this overarching hypothesis by (1) Detecting differences in T1IFN, pathway activation, and histopathology in synovium of RA patients who have a EULAR good response or no response to TNFi; and (2) Determining the impact of IFN-a and IFN-ß on RA Mo, Mo-derived Mf, and fibroblast-like synoviocytes. Select coursework will complement her research and fortify her skills. Results will provide fertile ground for future directions.

Dr. Wampler Muskardin will gain new skills in biased and unbiased analyses, data architecture/artificial intelligence, and in use of a bioengineered microphysiological system to interrogate human RA biology, which is needed to successfully launch and establish herself as an independent investigator advancing precision medicine in RA.
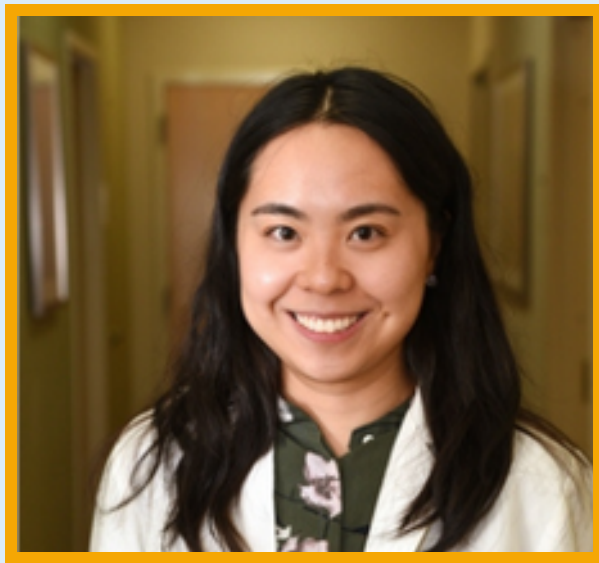
# Shudan Wang, MD
## Albert Einstein College of Medicine

*Membrane Attack Complex (MAC) and Other Complement Components as Markers of Kidney Injury and Treatment Response in Patients with Lupus Nephritis*

Lupus nephritis (LN) has significant morbidity and mortality given nonspecific treatment approaches. Only 24 to 50% of patients respond to current B and/or T cell targeting treatments and 10 to 30% of LN patients progress to end-stage renal disease (ESRD) within 10 years. The complement pathway is a promising target for LN treatment because it plays a central role in pathogenesis. LN patients who respond poorly to current therapies likely have complement-mediated inflammation as the main cause of kidney damage. There is an urgent need for complement biomarkers to identify these non-responders and guide targeted therapies.

The membrane attack complex (MAC) is a viable marker of renal outcome because it causes cell membrane lysis, drives inflammation and is involved in tubulointerstitial injury. The overall goal of this proposal is to evaluate MAC and other complement components as a marker of kidney injury and treatment response. We hypothesize that LN patients with MAC and other complement components in kidney tissues and urine will have severe complement-mediated kidney injury and worse outcomes. Our hypothesis will be tested using three different approaches: immunohistochemistry, urine proteomics and single-cell RNA sequencing (scRNA-seq).

This K-Bridge award will enable me to generate preliminary data, publications and broaden the scope of this study in response to reviewers' comments. Studies will be conducted using urine proteomics and scRNA-seq data to strengthen the premise of this research and optimize methods for a first K23 resubmission, with the following aims: 1) to associate MAC deposition in paraffin embedded kidney biopsies with renal outcomes; 2) to determine urinary complement profiles among LN patients using mass spectrometry; and 3) to identify complement gene expression in kidney cells using existing scRNA-seq data from the Accelerating Medicine Partnership (AMP) Lupus Network. We expect to find MAC in kidney tissue and urine among LN patients with worse renal outcomes and discover new complement biomarkers using omics analyses.

This study is significant because complement biomarkers can identify candidates for complement targeting therapies. The K-Bridge support will lead to a stronger K23 resubmission and prepare me for a career in omics research and biomarker discovery in lupus.

# 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.

# Kerry Costello, PhD
## Boston University

## *Deep Learning Analysis of Physical Activity Patterns in Knee Osteoarthritis*

While physical activity is widely recommended as a core management strategy for persons with knee osteoarthritis, little guidance exists regarding the appropriate dose of physical activity and whether this should differ based on individual patient characteristics. Importantly, individuals with knee osteoarthritis exhibit altered gait patterns that cause repetitive, abnormal forces on the knee joint and contribute to disease progression. Thus, physical activity prescription may need to be tailored to individual gait patterns. Existing research has been limited by the use of simplified metrics and models to describe the rich data source provided by these three-dimensional, time-varying physical activity and gait pattern data, and by failing to account for both contributors to loading.

This project will characterize the role of physical activity in knee osteoarthritis progression using agnostic machine learning approaches while accounting for individual patterns of loading during walking. Deep learning will be utilized to analyze accelerometer data (as traditional summary measures or raw patterns of physical activity) along with raw patterns of ground reaction force data to examine two-year change in structural and symptomatic osteoarthritis outcomes in the Multicenter Osteoarthritis Study. We expect models including ground reaction force inputs to outperform those without ground reaction force inputs, and expect models using raw physical activity patterns as inputs to outperform those using summary physical activity measures as inputs. We will utilize saliency maps to examine whether specific patterns of physical activity are associated with worse outcomes and in an exploratory analysis, whether patient characteristics such as age, sex, and obesity are associated with these patterns.

This research will provide valuable training in deep learning and big data management for the principal investigator and will contribute to understanding appropriate patient-specific physical activity dose for knee osteoarthritis.

# Alicia Hinze, MD
**Mayo Clinic**

## *Development of Radiomic Biomarkers to Determine Risk of Interstitial Lung Disease Progression in Systemic Sclerosis*

Systemic sclerosis (SSc) is a multisystem autoimmune disease characterized by widespread tissue fibrosis and vasculopathy. Interstitial lung disease (ILD) occurs in 50-80% of patients with SSc, and is a leading cause of morbidity and mortality. The clinical course of SSc-ILD is highly variable in expression and progression, with some patients experiencing progressive fibrosis despite receiving therapy while others remain stable without treatment. This heterogeneity results in a major unmet need for clinical tools that (1) Identify patients with SSc at highest risk for progression at baseline who would benefit from early initiation of treatment; and (2) Identify patients who may not be responding to their current ILD treatment and in whom alternative treatments should be considered.

In this proposal, we will leverage extensive imaging data (>4,500 high resolution computed tomography scans (HRCT)) and longitudinal outcomes from a large cohort of patients with SSc (n>1,300) seen at Mayo Clinic to develop radiomic biomarkers that associate with ILD progression. These radiomic biomarkers will be developed utilizing quantitative CT (QCT) technology combined with advanced statistical analytic approaches. We aim to (1) Identify radiomic biomarkers that associate with ILD progression in SSc patients on baseline HRCT; and (2) Establish the short-term rate of change in parenchymal features on QCT that associate with long-term ILD progression.

These studies will lay the foundation for future work aimed at validating these ILD radiomic biomarkers for widespread clinical and investigative trial use.
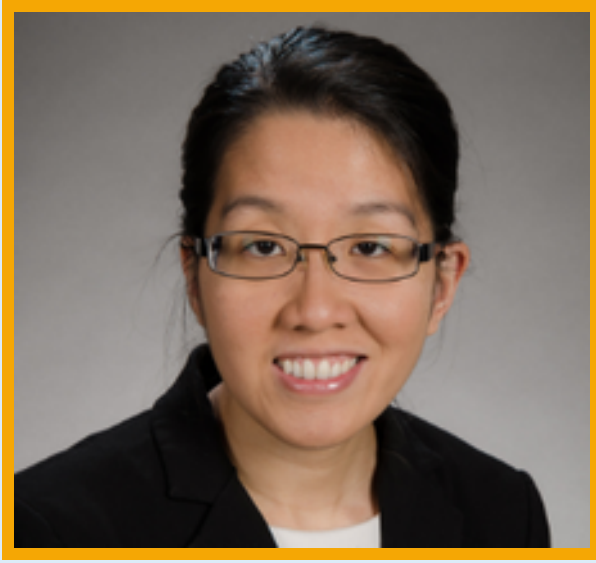
# Jean Liew, MD
## Boston University

## *The Impact of Axial Spondyloarthritis Treatment on Chronic Opioid Use*

Inflammatory back pain is the predominant feature of axial spondyloarthritis (axSpA), which affects over 1% of U.S. adults. Despite the rise in biologic use in axial spondyloarthritis (axSpA), many still do not experience a meaningful improvement in back pain symptoms. Up to one quarter of individuals with axSpA have been prescribed chronic opioids.

This proposal will evaluate how the timing and sequence of currently recommended therapies (tumor necrosis factor inhibitors and physical activity) impact chronic opioid use. Using advanced epidemiologic methods, we will leverage multiple complementary data sources, specifically aiming to (1) Describe time trends in opioid prescriptions in relation to the approval of TNFi for axSpa using three separate cohorts of individuals with ankylosing spondylitis (AS) from three real-world data sources. We will calculate the annual percent change of opioid prescription pre- and post- TNFi approval for AS. We hypothesize that opioid prescriptions decreased after TNFi approval; and (2) Assess the relation of early TNFi initiation to risk of chronic opioid use in a cohort of ~4000 individuals with AS starting TNFi therapy from the VA national administrative database between 2003 and 2019. We will examine the association of early TNFi initiation (within six months of diagnosis) with incident chronic opioid use. We hypothesize that early TNFi initiation results in a lower odds of chronic opioid use compared to delayed initiation; and (3) Assess the relation of physical activity to risk of chronic opioid use in a prospective cohort of ~1000 AS patients with data on medication use, physical activity, and disease activity measures. We hypothesize that greater physical activity is associated with later reduction in chronic opioid use in AS.

The findings from this proposal are expected to inform future guidelines on therapy in axSpA and impact clinical prescriptions of opioids and other axSpA therapies.

# Rebecca Sadun, MD, PhD
## Duke University

## *Immunogenicity and Risk of Autoimmune Cross-Reactivity of COVID-19 mRNA Vaccines in SLE*

Systemic lupus erythematosus (SLE) affects ~250,000 Americans. Vaccine-preventable infections are a leading cause of death for patients with SLE, underscoring the importance of vaccines in the care of SLE patients. SLE patients are highly vulnerable to critical illness from COVID-19, and the ACR recommends that SLE patients be vaccinated against COVID-19. It remains unclear whether the mRNA COVID-19 vaccines are immunogenic in SLE patients, many of whom are immunosuppressed. Similarly, it remains unclear whether mRNA COVID-19 vaccines will increase autoantibody production in SLE, a condition characterized by antibodies to nuclear antigens and in which RNA is known to stimulate unregulated inflammation.

To answer these questions, we analyze biobanked sera from SLE patients who received a COVID-19 mRNA vaccine to (1) Determine the humoral immunogenicity of the vaccine in SLE patients who are on various immunosuppressant medications; (2) Determine whether COVID-19 vaccination is associated with increased dsDNA, increased ESR, increased antiphospholipid antibodies, or lupus flare; and (3) Determine whether COVID-19 mRNA vaccination leads to the development of anti-spike antibodies with cross-reactivity to nuclear or cardiomyocte autoantigens.

Collectively, these analyses will help establish the safety and efficacy of COVID-19 mRNA vaccines in SLE, which is of vital importance in an era that is likely to be characterized by expanding mRNA vaccine technology.

# Brian Skaug, MD, PhD
## The University of Texas Health Science Center at Houston

## *Pathogenic Effects of the DNASE1L3 R206C Variant in Systemic Sclerosis*

Systemic sclerosis (SSc) is a debilitating and potentially fatal autoimmune disease whose pathogenesis is incompletely understood. Recent research has revealed certain genetic loci that are robustly linked to SSc susceptibility.

The focus of our research is to elucidate how a validated SSc genetic risk locus, encoding Arginine to Cysteine substitution of amino acid 206 in deoxyribonuclease 1-like 3 (DNASE1L3 R206C), contributes to disease pathogenesis. Previously published work by other investigators and our own preliminary data suggest that DNASE1L3 has a key role in digesting genomic DNA within the circulation, a process that is impaired in individuals with the DNASE1L3 R206C variant. Improperly processed DNA can induce excessive activation of the immune system, but the specific DNA populations most affected in those with the DNASE1L3 R206C variant, and their downstream effects in patients with SSc, are unknown. We hypothesize that certain populations of circulating DNA are incompletely digested in SSc patients with the DNASE1L3 R206C variant, and that this DNA contributes to the observed immune perturbations in SSc. Aim 1 of our research is designed to further define the circulating DNA profile of SSc patients with the DNASE1L3 R206C variant, examining specific populations of circulating DNA in SSc patient blood samples. Aims 2 and 3 are designed to determine downstream effects of incompletely digested DNASE1L3-substrate DNA on immune cell function, through molecular characterization of immune cells from a murine model and from SSc patients.

Together, these studies will shed light on the downstream biochemical and immunologic consequences of DNASE1L3 dysfunction, strengthening the foundation for development of targeted therapies to treat SSc.

# SCIENTIST DEVELOPMENT AWARD

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

# Sokratis Apostolidis, MD
## University of Pennsylvania

## *Understanding the Role of T cells in Rheumatologic irAEs with the Use of Deep Immune Profiling and Analytical Vaccination*

The proposed research explores the mechanisms through which PD-1 checkpoint inhibition leads to rheumatologic immune-related adverse events (irAEs). In this proposal, we hypothesize that PD-1 inhibition disturbs naïve T cell quiescence in patients with rheumatologic irAEs and generates heightened effector CD4 responses that can be probed with analytical vaccination.

To explore this hypothesis, we utilize two distinct cohorts: a prospective cohort of patients with cancer that initiate PD-1 immunotherapy and are monitored for irAEs (prospective irAE cohort), and a cohort of patients with melanoma on PD-1 immunotherapy that receive annual influenza vaccination as a model analytical vaccination (melanoma/influenza vaccine cohort). Using the prospective irAE cohort, we have previously demonstrated that the naïve CD4 T cell compartment is preferentially expanded in patients with irAEs. In this proposal, we will further analyze the heterogeneity and composition of the naïve CD4 T cells to identify any subpopulations enriched in patients with irAEs. We will also interrogate the effector/memory cells generated immediately after PD-1 inhibition to understand their transcriptional profile in patients with rheumatologic irAEs. Using the melanoma/influenza vaccine cohort, we will evaluate the single-cell transcriptional profile of activated circulating T follicular helper (Tfh) and T peripheral helper (Tph) cells responding to influenza vaccination in patients with rheumatologic irAEs compared to patients without irAEs and healthy controls.

These studies will advance our understanding of the contribution of T cells in the development of rheumatologic irAEs and can be used to design targeted future therapies for these patients. They will also provide insight into the function of PD-1+ expressing cells, specifically CXCR5+ cTfh and CXCR5- Tph cells, shown to be central in the pathogenesis of primary rheumatic diseases, including RA and SLE.
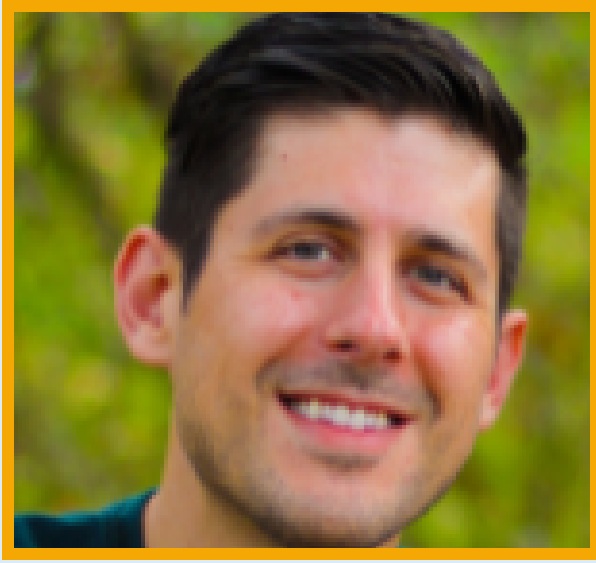
# Tarin Bigley, MD, PhD
## Washington University in St. Louis

## *Evaluating the Role of Neonatal Infections in Systemic Lupus Erythematosus*

Systemic lupus erythematosus (SLE) is a heterogenous, multi-organ system autoimmune disease. Dysregulation of T and B cells is characteristic of SLE. Studies suggest that autoantibodies and immune dysregulation start years before diagnosis. The etiology of SLE is unknown but likely includes genetic as well as environmental factors, such as viral infections. Increased activity of the toll-like receptor 7 (TLR7) has been suggested to play a role in the pathogenesis of SLE and dysregulation of T and B cells. Viruses are often studied in the context of active infection in patients already diagnosed with SLE and can stimulate the TLR7 pathway. Little is known about how past viral infections could predispose individuals to SLE. Murine roseolovirus (MRV) is a beta-herpesvirus that is genetically highly related to human roseoloviruses.

We have demonstrated that neonatal MRV infection induces autoimmune disease with development of autoantibodies in adult, wild-type mice. This occurs after acute viral infection has resolved, suggesting that neonatal MRV infection causes long-lasting loss of tolerance. Moreover, MRV disrupts key components of central tolerance. Adult C57BL/6 mice neonatally infected with MRV develop a lupus like-phenotype after TLR7 stimulation. Our findings suggest that roseolovirus infection results in disruption of immunologic tolerance. We propose to evaluate how MRV predisposes to development of lupus-like disease by elucidating the immunophenotype and transcriptome of T and B cells, and identifying the cells are necessary to develop disease. Furthermore, using MRV as an example, we will perform similar studies using other thymotropic viruses to investigate if disruption of central tolerance leading to autoimmunity is unique to MRV or shared amongst thymotropic viruses.

The studies performed in this proposal will provide key insight into how a virus can result in a predisposition to altered TLR7 response and SLE.

# Tiffany Hsu, MD, PhD
## Boston Children's Hospital

## *Phosphorylation of MDA5 to Restrict Aberrant Innate Immune Signaling*

MDA5 is a conserved innate immune receptor that detects viral double-stranded RNA (dsRNA) during infection and activates the antiviral immune response. However, aberrant activation of MDA5 in the absence of infection leads to "sterile" inflammation, which is associated with increased risk of systemic lupus erythematosus (SLE) and drives lupus-like autoinflammatory diseases.

We and others have discovered that MDA5 assembles into filaments upon binding to dsRNA, which signals the production of type I interferons. However, the regulation of MDA5 filament formation is poorly understood, and the role of post-translational modifications as a regulatory mechanism remains unclear. Our preliminary data reveal that inactive MDA5 is phosphorylated at a novel site in the helicase domain, which mediates dsRNA binding. Phospho-mimetic mutation in MDA5 impairs filament formation and downstream signaling while a phosphorylation-deficient mutant enhances filamentation and constitutively activates MDA5 signaling. Here, we explore the hypothesis that phosphorylation of the MDA5 helicase domain inhibits MDA5 filament formation in the absence of viral infection, which suppresses aberrant innate immune activation in inflammatory diseases like SLE. In Aim 1, we will examine the impact of MDA5 phosphorylation on filament assembly and disassembly and determine whether phosphorylation leads to conformational changes affecting MDA5 binding to dsRNA. In Aim 2, we will assess the use of unphosphorylated MDA5 as a biomarker of MDA5 activation in peripheral blood samples from patients with SLE and develop a novel assay that detects endogenous MDA5 filament formation.

Through our precision medicine-based approach to tackling SLE, we will identify the subset of lupus patients with aberrant MDA5 activation and delineate the regulatory steps of MDA5 filament formation that can be therapeutically targeted in these patients.

# Tate Johnson, MD
## University of Nebraska Medical Center

## *Immune and Inflammatory Mediators of Heart Failure Incidence and Severity in Rheumatoid Arthritis*

Heart failure (HF) is among the most burdensome chronic diseases and a leading cause of hospitalization in the United States. Compared to the general population, patients with rheumatoid arthritis (RA) are nearly twice as likely to develop HF and are at a higher risk of HF-related mortality. Prevention of HF development and improvement of HF-related outcomes would yield substantial benefits to the longevity and quality of life in patients with RA. However, critical knowledge gaps exist in the pathophysiology and natural history of HF in RA that limit the development of effective management strategies.

The overall objective of this study is to evaluate contributions of immune, inflammatory, and fibrotic mediators of HF incidence and progression in RA beyond traditional RA disease activity measures. In Specific Aim 1, we will evaluate the contribution of RA-related immune, inflammatory, and fibrotic mediators to the development of HF, independent of traditional and established RA-related risk factors, in a prospective cohort of patients with RA. In Specific Aim 2, we will leverage a large, national cohort of RA and matched non-RA patients to determine the excess burden of HF in RA manifest through recurrent HF exacerbations, a critical feature of severe or uncontrolled HF in RA that has not been previously studied. We will additionally use national echocardiogram data to evaluate the differential burden and outcomes of HF with reduced (HFrEF) and preserved (HFpEF) ejection fraction and identify risk factors that predict more rapid ejection fraction decline in RA patients with HFrEF.

These findings will begin to elucidate the mediators of cardiac dysfunction and comprehensively characterize the burden and trajectory of HF in RA. The PI will complete an accompanying rigorous research training program that will prepare him to lead future clinical and translational studies of cardiac dysfunction in RA.

# Paras Karmacharya, MD
## Vanderbilt University Medical Center

### Defining PsA Phenotypes and Probability of Response to Therapy

Psoriatic arthritis (PsA) is a chronic, progressive inflammatory disease of the skin and musculoskeletal system, affecting over 500,000 Americans. Despite improvement in therapies, only about half of the patients respond to therapy. In part, this is because PsA is studied and managed as if it is a single disease (polyarticular disease similar to rheumatoid arthritis). PsA, however, has high heterogeneity in its clinical presentation and impact. PsA affects a wide range of musculoskeletal (MSK) tissues, including peripheral joints, enthesis (insertion site of a tendon, ligament, or joint capsule onto bone), and is associated with dactylitis (swelling of an entire digit). Comorbidities and extra-MSK manifestations also have important implications for management. Combinations of disease features may indicate a "phenotype" that could inform their disease course. To improve treatment strategies and long-term outcomes, there is a critical need to understand the association between subgroups of PsA with therapy response.

In this proposal, we aim to use a multicenter longitudinal cohort to (1) Identify PsA phenotypes and the probability of change in phenotype over time; and (2) Identify PsA patients with a high probability of responding to therapy and those with a low probability of responding to therapy. These aims are the first key steps towards personalized medicine in PsA through characterization of PsA phenotypes and using disease characteristics to predict therapy response.

Through the outlined career development plan and the proposed research, Dr. Karmacharya will gain the required skills to achieve independence and to address his long-term objectives. He will leverage the existing R01 funded study led by his mentor to address the research aims. With Vanderbilt's commitment to young investigators, expertise in machine learning and personalized medicine, and outstanding mentorship, he will successfully leverage his innovative proposal for NIH K-award funding.
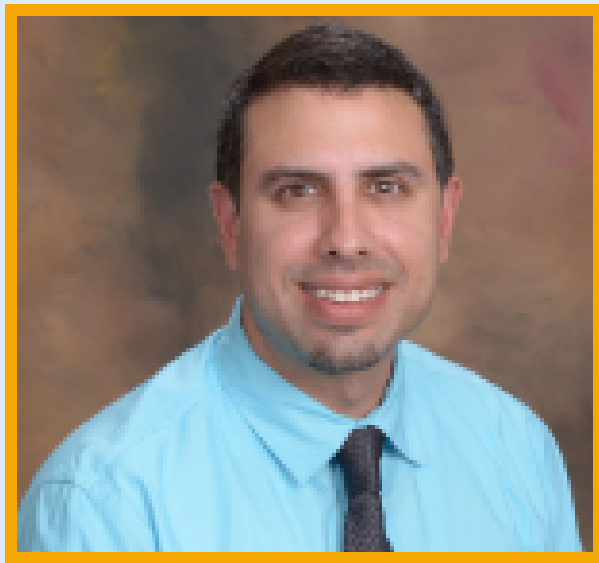
# Shawn Mahmud, MD, PhD
## University of Minnesota

### *Tracking Self-Reactive CD4+ T Cells Relevant to Mixed Connective Tissue Disease*

Mixed connective tissue disease (MCTD) features the formation of IgG autoantibodies (autoAb) specific for parts of the U1-snRNP spliceosomal complex. A strong link to the MHC II molecule, HLA-DRB1*0401 (DR4), and the presence of IgG autoAb, suggest the importance of CD4+ T cells in MCTD. Defining the specific, self-reactive CD4+ T cell populations that underlie this disease could help in developing specific therapies.

U1-snRNP is composed of U1-RNA bound by U1-70k, U1-A, and U1-C proteins. We used prediction algorithms to identify U1-70k peptides that strongly bind DR4, hypothesizing that these could serve as epitopes for self-reactive CD4+ T cells. These peptides were exchanged into DR4 tetramers and facilitated the detection of naïve, self-reactive CD4+ T cells in DR4 transgenic (DR4-Tg) mice. U1-70k:DR4-specific CD4+ T cells expanded 5-10-fold and became activated in DR4-Tg mice immunized with U1-70k peptides. A mouse model of MCTD has been previously described in which ~60% of DR4-Tg mice immunized with U1-70k protein and U1-RNA develop anti-U1-70k IgG, and ~50% develop interstitial lung disease (ILD) that histologically resembles the ILD seen in some MCTD patients. These novel tetramers and the established DR4-Tg mouse model provide new opportunities to study the role of self-reactive CD4+ T cells in the pathogenesis of MCTD. In Aim 1 of this proposal, we will comprehensively evaluate U1-70k, U1-A, and U1-C to find additional DR4-binding self-peptides that serve as self-epitopes in the established MCTD mouse model. We will develop additional DR4 tetramer reagents to determine the precursor frequencies of the corresponding naïve CD4+ T cells recognizing these epitopes. We will also determine if ablating Aire or Bim results in increased precursor frequencies of these self-reactive CD4+ T cells and increases disease penetrance in the MCTD mouse model. In Aim 2, we will test the hypothesis that U1-snRNP peptide:DR4-specific CD4+ T cells may be biased towards T follicular helper and T helper-1 or -17 phenotypes in animals that succumb to disease in the MCTD mouse model.

Notably, because they have been engineered with DR4, the tetramers developed in this study will be directly usable in studies of human patients with MCTD.

# Hailyn Nielsen, MD, PhD
## University of California, San Francisco

## *Control of T Cell Tolerance by the NR4A Family of Transcription Factors*

Self-reactive T cells are thought to contribute to the development of many autoimmune diseases, including rheumatoid arthritis and systemic lupus erythematous. Unfortunately, many current therapies impair both protective immune cells and disease-causing self-reactive T cells, leading to adverse side-effects such as infection. Selective manipulation of disease-causing self-reactive T cells could transform our treatment approach to autoimmune diseases. The NR4A family of nuclear receptors is a promising candidate drug target to address this unmet need because it is specifically expressed in and restrains self-reactive lymphocytes. Although NR4A family members are thought to function as ligand-independent, constitutively active transcription factors (TFs), small molecule agonist and antagonist ligands have been described, rendering them druggable. However, full therapeutic exploitation of the NR4A family is currently limited by major gaps in knowledge regarding its biology in thymocytes and mature CD4 T cells. Using innovative mouse models, this proposal seeks to fill these knowledge gaps about NR4A TFs. Study of the NR4A family in developing thymocytes and CD4 T cells has been hampered by significant functional redundancy among its members and its critical role in the generation of regulatory T cells (Treg). Namely, deletion of multiple—but not individual—NR4A TFs in the germline or CD4 T cell lineage leads to systemic autoimmunity due to a lack of Treg. Thus, it has been impossible to unmask redundant functions of NR4A TFs in central and peripheral T cell tolerance.

We developed a mixed radiation bone marrow chimera approach that restores Treg homeostasis in mice to overcome this obstacle. Our preliminary data support cell-intrinsic roles for the NR4A family in both clonal deletion of self-reactive thymocytes (central tolerance) and in CD4 T cell anergy (peripheral tolerance). In this proposal, we employ this chimera approach to extend these observations and explore the mechanism by which the NR4A family enforce both central and peripheral T cell tolerance.

Thus, this proposal lays the foundation to develop drugs that target and amplify the regulatory behavior of the NR4A family as future treatments for autoimmune diseases.

# Naomi Patel, MD
## Massachusetts General Hospital

### *The Association of the Glucocorticoid Toxicity Index (GTI) with Measures of Quality of Life and Health Care Resource Utilization*

Glucocorticoids are the cornerstone of therapy for many rheumatic diseases but are associated with numerous toxicities that are concerning to both patients and providers. Previously, there was no standardized way to quantify these toxicities. The Glucocorticoid Toxicity Index (GTI) is a recently- developed tool used to assess and quantify change in glucocorticoid toxicity in longitudinal studies. Quantifying glucocorticoid toxicities is critical for the evaluation of new rheumatic disease treatments that offer the potential for greater efficacy, as well as reduced glucocorticoid exposure. The GTI is increasingly being used as an outcome measure in clinical trials evaluating novel steroid-sparing agents. Health-related quality of life (QoL) and health care resource utilization are two key measures that contribute to our understanding of the comprehensive value of novel medications. The associations between GTI scores, QoL, and health care resource utilization will help to better understand the significance of differences in GTI scores across different patients and across different treatment groups in clinical trials.

This proposal will leverage data from the ADVOCATE trial of avacopan in ANCA-associated vasculitis as well as a novel, real-world prospective cohort of rheumatic disease patients receiving glucocorticoid treatment that will be developed and followed longitudinally. Using data from both cohorts, we will evaluate the relationships between GTI scores and health-related QoL. Additionally, in the real-world, prospective cohort, we will evaluate the relationship of GTI scores with health care resource utilization. Our data will be the first to lead to provide validation of the GTI in a real-world cohort of patients, thus allowing for essential close monitoring and quantification of glucocorticoid toxicity in real-world practice, and anticipated findings will inform how GTI scores should be interpreted in both prospective clinical trials and real-world practice.

Successful completion of this project will lead to further studies evaluating use of the GTI in a variety of settings to better understand the impact of different steroid-sparing treatment regimens.

# Elizabeth Sloan, MD
## University of Texas Southwestern Medical Center

*The Impact of Antiphospholipid Antibodies on Hypercoagulability in Children with Systemic Lupus Erythematosus*

Children with systemic lupus erythematosus (SLE) have a high prevalence of antiphospholipid antibodies (aPL), yet research on thrombotic risks associated with aPL positivity is limited in the pediatric population. Many children with SLE and positive aPL are managed with prophylactic aspirin without a clear understanding of how aPL impact hypercoagulability. Thrombin generation can be a useful tool to assess the influence of aPL and monitor the impact of antiplatelet therapy on the balance of coagulation.

In this proposal, we will use thrombin generation to provide new insights into aPL-induced hypercoagulability in children with SLE. Additionally, we will investigate how aspirin modulates this phenotype and impacts global coagulopathy in children with SLE and aPL positivity.

In the future, these tools may provide information for risk stratification for children with SLE at risk of thrombosis and inform daily practice when considering thromboprophylaxis. Further research studying pediatric aPL positivity and risk factors for the development of thrombosis are necessary to help guide clinicians in managing these challenging patients.
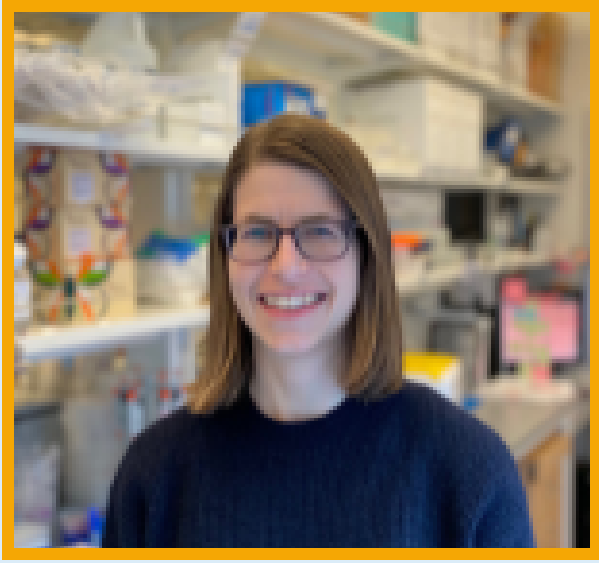
# Melanie Smith, MD, PhD
## Hospital for Special Surgery

### *Understanding the Role of HLA-DR+ Synovial Fibroblasts in Rheumatoid Arthritis*

Fibroblast-like synoviocytes (FLS) that are expanded in the rheumatoid arthritis (RA) synovium and associated with active disease are defined by high expression of MHC class II (HLA-DR+). These FLS were recently shown via single-cell RNA-sequencing (scRNA-seq) studies of RA synovial tissue to express pro-inflammatory cytokines and chemokines, which suggest interactions with tissue-infiltrating leukocytes.

In this project, we will investigate the etiology and functions of key populations of these FLS. Based on their specific locations within the synovial tissue, we hypothesize that these HLA-DR+ FLS have two divergent functions: those in the synovial sublining layer express specific cytokines and chemokines due to their interactions with interferon gamma (IFNg) and tumor necrosis factor-alpha (TNF)-expressing T cells, and HLA-DR+ FLS in the synovial lining layer express tissue-damaging matrix metalloproteinases (MMPs) and exhibit increased invasiveness due to their interactions with proinflammatory macrophages expressing Interleukin 1-beta (IL-1b) and TNF. To investigate this hypothesis, we will use multiparameter immunofluorescence of human RA synovial tissue to elucidate spatial positioning of HLA-DR+ FLS responding to TNF, IFNg, or IL-1b within the synovium in relation to T cells and macrophages. Using an in vitro co-culture system combined with bulk RNA-seq analyses, we will determine if the presence of activated T cells +/- inflammatory macrophages imparts upon FLS distinct transcriptional features of sublining versus lining HLA-DR+ FLS subtypes. Finally, we will use a fibroblast invasion assay to determine if the observed differences in FLS transcriptional profiles between co-culture conditions correlate with functional differences.

By understanding the drivers of these disease-associated FLS subtypes and how they affect cellular functions, we will uncover key receptors and ligands, pinpoint active pathways, and inform fibroblast-directed therapeutics.

# Ajay Tambralli, MD
## University of Michigan

## *Immunometabolism of Neutrophils in Lupus and APS*

Antiphospholipid syndrome (APS) is an autoimmune disease propelled by circulating antiphospholipid antibodies that is best known for causing thrombosis and pregnancy loss. Approximately one-third of APS cases are diagnosed in the context of systemic lupus erythematosus (SLE). The immunopathogenesis of APS and SLE are complex, with derangements present in both lymphoid- and myeloid-lineage cells. The latter compartment has received increased scrutiny in recent years, an example of which is the recognition of neutrophil extracellular trap (NET) release (also called NETosis) as an important player in both conditions. NETs are prothrombotic webs of decondensed extracellular chromatin and granule-derived proteins that are released by neutrophils in response to infectious and sterile stimuli. NETs play an important role in corralling infectious organisms; however, when dysregulated or released in the wrong space, NETs may promote thrombosis, endothelial damage, type I IFN production, and autoantibody formation. Previous studies have demonstrated how metabolism can guide immune cell fates. For example, in macrophages, switching from glycolysis to oxidative phosphorylation promotes a shift from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 phenotype. While accumulating evidence suggests that metabolic plasticity also guides some essential neutrophil functions, very few studies have examined the metabolic determinants of NETosis.

The underlying hypothesis shepherding this proposal is that dysregulated neutrophil metabolism contributes to the pathophysiology of APS and SLE, a deeper understanding of which is likely to illuminate new and more precise targets for therapy. Aim 1 will characterize the metabolic determinants of NETosis, especially as they relate to APS and SLE. Aim 2 will define the metabolic profile of neutrophils in APS and SLE patients and track them with measures of disease activity. Aim 3 will determine the effects of metabolic modulation on in vivo disease models, with particular focus on thrombotic and inflammatory phenotypes.

The information gathered in this project will lay the groundwork from which a therapeutic paradigm centered around modulating neutrophil metabolic pathways can be developed.

# 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.
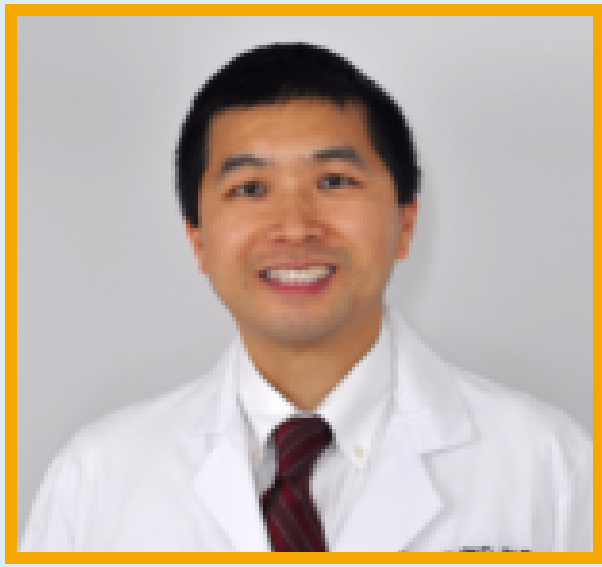
# Wilson Kuswanto, MD, PhD
## Stanford University

## *Deciphering the Mast Cell-Fibroblast Axis in Osteoarthritis*

Osteoarthritis (OA) affects over 300 million people worldwide and is a significant cause of disability and health-related costs. There are currently no disease modifying treatments for OA and treatments remain palliative. OA is the result of chronic, low-grade inflammation characterized by activation of the innate immune system. Mast cells are one of the only immune cell populations that are enriched in OA synovium and are associated with increased inflammation and damage. Functional studies show that mast cells promote inflammation and joint destruction in OA, yet it is unclear how mast cells modulate disease in OA. Preliminary data utilizing multiparameter imaging that enables visualization of 50+ cellular markers show that mast cells primarily co-localized with CD34+ and CD90+ fibroblasts in human OA synovium. Little is known regarding the roles of fibroblasts subsets in OA; however, it has been shown that CD90+ fibroblasts primarily drive inflammation whereas CD90- fibroblasts mediate joint damage in rheumatoid arthritis.

We hypothesize that mast cells induce pro-inflammatory CD90+ and CD34+ fibroblasts which drive inflammation and damage in OA. To address this, we will combine gene expression analysis with multiparameter imaging to reconcile the functional anatomic roles of mast cells and distinct fibroblast subsets in OA. Additionally, we will perform mechanistic in vivo studies to determine the direct effect of mast cells on fibroblast subsets.

Completion of these Aims will reveal how mast cells and fibroblasts contribute to joint destruction and may potentially identify novel disease modifying targets in osteoarthritis.

# EDUCATION AND 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.

# FELLOWSHIP TRAINING AWARDS 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.

## Children's Hospital of Los Angeles

## Hackensack University Medical Center

## Stanford University

## Vanderbilt University Medical Center

*Funding for these awards was provided in part by the Andrejeski Fund for Fellowship Training.

# FELLOWSHIP TRAINING AWARDS

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.

**Beth Israel Deaconess Medical Center**

**Children's Hospital of Philadelphia**

**Cincinnati Children's Hospital Medical Center**

**Duke University**

**Georgetown University**

**Indiana University**

**John Hopkins University**

**Massachusetts General Hospital**

**Montefiore Medical Center**

**New York University**

**Oregon Health & Science University**

**Tufts Medical Center**

**Stanford University**

**University of California, Los Angeles**

**University of California, San Diego**

**University of California, San Francisco**

**University of Chicago**

**University of Colorado, Denver**

**University of Michigan**

**University of Minnesota (Pediatric)**

**University of Nebraska Medical Center**

**University of Pennsylvania**

*Funding for these awards was provided in part by Amgen, Inc.

# 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.

## University of Alabama at Birmingham

# RISE PILOT PROJECT AWARD

The RISE Pilot Project Award provides resources to support the training and career development of early-career researchers and clinicians interested in pursuing research using real world electronic health data in the field of rheumatology. The purpose is to support trainees interested in pursuing rheumatology research utilizing the RISE research database and increase the supply of rheumatology professionals with knowledge of analytics using real-world data.

## John Bridges, MD
### University of Alabama at Birmingham

*Contraception Prescribing Patterns for Adult Females with Juvenile Idiopathic Arthritis on Teratogenic Medications in the Rheumatology Informatics System for Effectiveness (RISE) Registry*

## Sebastian Sattui, MD
### University of Pittsburgh

*Characteristics of Patients and Treatments for Polymyalgia Rheumatica under Rheumatology Care: Analysis from the Rheumatology Informatics System for Effectiveness (RISE)*

# PEDIATRIC VISITING PROFESSORSHIP

The Pediatric Visiting Professorship supports a board-certified professor of pediatric rheumatology to visit an academic institution that lacks expertise in the field to provide medical students and residents valuable exposure to pediatric rheumatology.

**Jay Mehta, MD, MSEd to visit Virginia Tech Carilion School of Medicine**

**David Sherry, MD to visit Allegheny Health Network Medical Education Consortium**

**Randy Cron, MD, PhD to visit Louisiana State University**

**Sampath Prahalad, MD, MSc to visit Ochsner Clinic Foundation**

**Mary Moore, MD to visit Ascension St. John Hospital**

**Tracey Wright, MD to visit University of California (Irvine)**

**Susan Shenoi, MBBS, MS, RhMSUS to visit Cedars-Sinai Medical Center**

**Kelly Rouster-Stevens, MD, MS to visit Medical College of Georgia at Augusta University**

# PEDIATRIC VISITING PROFESSORSHIP

**Robert Fuhlbrigge, MD, PhD to visit University of Tennessee**

**Jim Jarvis, MD to visit Temple University**

**B. Anne Eberhard, MD, MSc to visit Icahn School of Medicine at Mount Sinai**

**Megan Curran, MD to visit NYU Long Island School of Medicine**

**Jennifer Huggins, MD to visit Detroit Medical Center - Wayne State University**

**Brandi Stevens, MD, MSCR to visit Rush University Children's Hospital**

# MENTORED NURSE PRACTITIONER / PHYSICIAN ASSISTANT AWARDS 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.

**Idaho Arthritis & Osteoperosis Center PC**
Mikael Lagwinski, MD
Christopher Nicholas, MSN/FNP-C

**Idaho Arthritis & Osteoperosis Center PC**
Svetlana Meier, MD
Camille Buchmiller, PA-C

**Massachusetts General Hospital**
Sara R. Schoenfeld, MD
Elizabeth Patrick O'Connor, APRN

**Overlake Arthritis and Osteoporosis Center**
Arinola Dada, MD
Cayla Alexander, ARNP

**Regents of the University of Minnesota**
Erik Peterson, MD, BA
Megan Schoeberl, PA & Corinna Werner, NP

**SSK Physician Associates, PA**
Swati Kumar, MD
Shalicia Riggins, MSN, FNP-C, FNP-BC

**SIMEDHealth, LLC**
Donald Scott, MD
Vera Brecken-Marquis, DNP, APRN, FNP-BC

**University of Kentucky Research Foundation**
Kristine Lohr, MD, MS, BA
January Hamby, APRN, AG-NP

**University of Texas MD Anderson Cancer Center**
Lu Huifang, MD, PhD
Linda Bobby, BSN, MSN

# 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.

# Nozima Aripova, BS
## University of Nebraska Medical Center

### *Citrullinated and Malondialdehyde-acetaldehyde Modified Proteins Promote Cellular and Immune Responses Associated with Rheumatoid Arthritis*

The central objective of this project is to elucidate the combined contributions of citrullinated and malondialdehyde-acetaldehyde modified proteins in regulating cellular and immune responses in the context of rheumatoid arthritis (RA) pathogenesis.

We will examine the central objective through two Specific Aims that (1) Determine the role of citrullination and MAA-modification of proteins in activating different cell types (macrophages and fibroblasts); and (2) Evaluate immune responses in mice immunized with citrulline and/or MAA-modified proteins.

These studies will facilitate an understanding of how citrullination and MAA-modifications of different proteins contribute to immune responses that characterize RA and act as drivers of disease progression.

# Mitra Maz, BA
## University of Michigan

## *Understanding Innate Immune Cell-mediated Inflammation in UV-induced Skin Injury in Lupus-prone Mice*

For many of the estimated 5 million people worldwide living with systemic lupus erythematosus (SLE), avoiding the sun is critical to management of their disease. SLE is a heterogeneous and debilitating autoimmune disorder which is characterized by overproduction of type I interferons (IFNs). Up to 70% of SLE patients experience skin manifestations, called cutaneous lupus erythematosus (CLE), that can be triggered by exposure to ultraviolet (UV) light. Although UV radiation is one of few well-described triggers in lupus, precise mechanisms and cell populations that drive UV-mediated inflammation are incompletely understood, identifying a critical need for better understanding of CLE to develop novel, targeted therapies.

In non-disease states, UV exposure leads to antigen-specific immunosuppression in the skin. However, in SLE skin, the immunosuppressive effects of UV light are lost likely secondary to chronic IFN production. Through single-cell analysis of cutaneous lupus lesions, our lab has identified an increase in an activated, IFN-educated, monocyte-derived CD16+ dendritic cell population in both lesional and non-lesional skin of lupus patients compared with healthy controls. The goal of this proposal is to define the mechanisms of recruitment of these cells and their ultimate contribution to lesional inflammation. To that end, we have turned to the lupus-prone NZM2328 (NZM), iNZM (lupus-prone mice lacking the type I IFN receptor), and wild-type Balb/c mouse models. In these models, we have preliminarily identified a type I IFN-dependent increase in monocyte recruitment, monocyte-derived DC (moDC) differentiation, and moDC activation in UV-exposed NZM skin compared with iNZM and wild-type. We will further determine the mechanism and consequence of monocyte recruitment following UV exposure, as well as the effect of type I IFN on moDC on antigen uptake, CD4+ T cell skewing, and cross-presentation following UV exposure.

On completion of this project, we will have clarified UV- and IFN-induced mechanisms of moDC dysfunction in lupus skin and identified moDC dysfunction as an important IFN-dependent driver of photosensitive SLE skin disease, providing evidence for a novel target for future therapies.

# 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.

**Bahtiyar Toz, MD**
**Betty Diamond, MD (Preceptor)**
The Feinstein Institutes for Medical Research

**Krishnasai A. Madathanapalli, MBBS**
**Monique Hinchcliff, MD, MS (Preceptor)**
Yale University School of Medicine

**Daniele Marcy, MD**
**Kristen Demoruelle, MD, PhD (Preceptor)**
University of Colorado School of Medicine

**Philip Carlucci, MD**
**Jilll Buyon, MD (Preceptor)**
New York University School of Medicine

# Ephraim P. Engleman Endowed Resident Research Preceptorship

**Jennifer Hanberg, MD**
**Zachary Wallace, Md, MSc (Preceptor)**
Massachusetts General Hospital

# Lawren H. Daltroy Health Professional Preceptorship

**Megan Creasman, MD**
**Iris Navarro-Millán, MD, MSPH (Preceptor)**
New York – Presbyterian / Weill Cornell Medical College

# 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.

**Colleen Noonan**
**Daniel White, PT, ScD, MSc (Preceptor)**
University of Delaware

**Megan Armellini, DPT**
**Daniel White, PT, ScD, MSc (Preceptor)**
University of Delaware

**Priya Brito**
**Sampath Prahalad, MD, MSc (Preceptor)**
Emory University

**Niti Pawar**
**Patricia Katz, PhD (Preceptor)**
University of California (San Francisco)

**Henry Chen**
**Heidi Jacobe, MD, MSCS (Preceptor)**
University of Texas Southwestern Medical Center

**Clinton Kimzey**
**Melissa Griffith, MD (Preceptor)**
University of Colorado School of Medicine

**Sanjana Murthy**
**Shanthini Kasturi MD, MS (Preceptor)**
Tufts Medical Center

**Jessica Browder\*\*\***
**Diane L. Kamen, MD, MSCR (Preceptor)**
Medical University of South Carolina

**Katherine Ketcham**
**Jennifer Stichman, MD (Preceptor)**
University of Colorado School of Medicine

**Caitlyn Hott**
**JoAnn Zell, MD (Preceptor)**
University of Colorado School of Medicine

# Medical and Graduate Student Preceptorship

**Rick Saha**
**Rachel Elizabeth Elam, MD (Preceptor)**
Augusta University Research Institute

**Amanda Walker***
**Benjamin F. Chong, MD, MSCS (Preceptor)**
University of Texas Southwestern Medical Center

**Shannon Teaw, MS**
**Monique Hinchcliff, MD, MS (Preceptor)**
Yale University School of Medicine

**Aliza Spielman****
**Nancy Baker, ScD, MPH, OTR/L (Preceptor)**
Tufts University

**Donavon Sandoval-Heglund**
**Jinoos Yazdany, MD, MPH (Preceptor)**
University of California (San Francisco)

**Shivani Rangaswamy*****
**Julie Paik, MD (Preceptor)**
Johns Hopkins University School of Medicine

**Seong Hee (Joy) Park***
**Andras Perl, MD (Preceptor)**
SUNY Upstate Medical University

**Omkar Mayur*****
**Laura Carbone, MD (Preceptor)**
Augusta University Research Institute

**Catherine Lavallee**
**Melissa Lerman, MD, PhD (Preceptor)**
The Children's Hospital of Philadelphia

**Danielle Falkenstein*****
**Jim Jarvis, MD (Preceptor)**
State University of New York at Buffalo

**Brian Honick, DPT****
**Karin Gravare Silbernagel, PT, ATC, PhD (Preceptor)**
University of Delaware

# Medical and Graduate Student Preceptorship

**Raphael Kirou**
**Ellen Ginzler, MD, MPH (Preceptor)**
State University of New York Downstate Medical Center

**Janya Sims**
**Wambui Machua, MD (Preceptor)**
Piedmont Healthcare Foundation

**Sydney Liles**
**Daniel K. White, PT, ScD, MSc (Preceptor)**
University of Delaware

**James Sullivan**
**M. Elaine Husni, MD, MPH (Preceptor)**
Cleveland Clinic Foundation

**Ilan Schwell**
**Arundathi Jayatilleke, MD (Preceptor)**
Temple University

**Yuxuan Jiang**
**Daniel Solomon, MD, MPH (Preceptor)**
Brigham and Woman's Hospital

**Taylor Martinez, MS**
**M. Kristen Demoruelle, MD, PhD (Preceptor)**
University of Colorado School of Medicine

**Ashley Fellers**
**Alvin Lee Day, MD (Preceptor)**
University of South Carolina

**Kristina Deonaraine, MS***
**Jill Buyon, MD (Preceptor)**
The Research Foundation for the SUNY on behalf of University at Buffalo

The Rheumatology Research Foundation is able to fund cutting-edge research and the training of the next generation of rheumatology professionals because of the generous support of our donors, thank you.

If you would like to learn more about how you can make an impact at the Rheumatology Research Foundation, please contact Foundation@Rheumatology.org.

RheumResearch.org

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