

Rheumatology Research Foundation Advancing Treatment | Finding Cures

Advancing Treatment and Finding Cures

2015 AWARD RECIPIENTS





Investing in the Future

The Rheumatology Research Foundation is dedicated to serving the more than 52 million Americans affected by arthritis or other forms of rheumatic disease. By advancing research and training, the Foundation is working to provide patients with better treatments and increased access to the rheumatology professionals specially trained to care for them.

The Foundation has committed nearly \$13.2 million in the coming fiscal year (July 1, 2015 – June 30, 2016) to fund approximately 265 awards. About half of those awards will support the education and training of future rheumatology professionals. The rest will fund innovative research projects that will lead to breakthroughs in treating people with rheumatic diseases. In all, the Foundation has committed more than \$131 million to fund more than 2,600 awards since 1985, making it the largest private funding source of rheumatology research and training in the United States.

I would like to share my congratulations with the Foundation's latest award recipients. I believe their work is integral to creating a promising future for our field and our patients.



Timothy B. Niewold, MD Chair, Scientific Advisory Council Rheumatology Research Foundation

Associate Professor of Medicine Mayo Clinic



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Targeted Research Grants

Targeted Research Grants provide essential support for innovative studies focused on generating new insights into the cause, progression and treatment of rheumatoid arthritis and related autoinflammatory diseases.



INNOVATIVE RESEARCH GRANT RECIPIENTS

Innovative Research Grant encourages investigators to expand promising research into rheumatoid arthritis and related autoinflammatory diseases by providing support to established researchers.



Joan M. Bathon, MD Columbia University

Predictors of Progression of Atherosclerosis in RA

Cardiovascular disease (CVD) is the leading cause of premature mortality in RA. It is not clear whether exaggerated systemic or intravascular inflammation or both contribute to progression of atherosclerosis. In a currently enrolling cross-sectional NIH-NIAMS funded R01 study (J. Bathon, PI), 150 RA patients without history of clinical CV disease undergo cardiac FDG PET/CT to evaluate subclinical myocardial disease. However, we have also been able to incidentally quantify FDG uptake in the ascending aortas of the participants. Coronary artery calcification [CAC], a surrogate measure of atherosclerosis, was also obtained. In this study, we will invite participants to return 3-5 years post-baseline for a repeat CAC measurement to evaluate whether those with higher baseline levels of vascular inflammation are at higher risk for progression of CAC. We will also examine the ability of PBMC subsets to predict progression of CAC. Finally, identification of a proteomic biomarker that identifies

RA patients at highest risk for progression of atherosclerosis could obviate the need for vascular imaging. We will measure and analyze a ~320-analyte panel that encompasses numerous cardiovascular and inflammatory pathways in the baseline samples in order to identify a biomarker that predicts progression of CAC. Our aims are:

1) To determine prospectively in a cohort of RA patients whether the presence and/or extent of baseline vascular inflammation measured by FDG PET/CT is predictive of incidence or progression of atherosclerosis.

2) To determine prospectively in a cohort of RA patients whether higher levels of circulating CD4 and CD8 T cell subsets denoting activation, differentiation to memory effector and NK receptor expression, and/or higher levels of intermediate CD14hiCD16+monocytes, will be more likely to develop incident or progressive CAC than those with lower levels of these subsets.

3) To identify a proteomic multimarker that, when added to the Framingham or Reynold's score for CV risk, identifies RA patients at highest risk for incident or progressive atherosclerosis.

These studies have the potential to significantly advance understanding of the pathogenesis of accelerated atherosclerosis in patients with RA, which is essential to the development of targeted interventions aimed at reducing CV morbidity and mortality in RA.





Liana Fraenkel, MD, MPH Yale University

Preference Phenotypes to Support Dyadic Decision Making in Rheumatoid Arthritis

Despite the widespread endorsement of the shared decision making (SDM) model and the development of numerous decision aids ranging from simple education pamphlets to interactive web-based tools, patients are rarely effectively engaged in the decision making process. In order to address this gap, we propose to develop and test a novel, theory driven approach, to elicit and incorporate rheumatoid arthritis (RA) patient preferences at the point-of-care. Specifically, we will elicit preferences for competing treatment options using rigorous stated preference methods, perform latent class analysis to identify groups of patients whose values and preferences are similar to each other but distinct from other groups, and develop intuitive figures that illustrate each preference phenotype. We anticipate that 1) physicians will be willing to use these results with their patients in during clinical encounters; 2) patients will be able to choose the phenotype that best represents their preferences, and 3) this process will increase the proportion of visits in which the treatment plan is based on patients' preferences. The data from this pilot study will support a definitive study to determine whether providing patient-physician dyads with preference phenotypes is a practical and effective approach to realizing SDM in clinical practice.

The specific aims of this project are: 1) To develop representative patient preference phenotypes to illustrate the variability in treatment preferences for preferencesensitive treatment decisions commonly faced by patients with RA. We will ascertain preferences using discrete choice experiments. Preference phenotypes will then be identified using latent class analysis of the conjoint data. Each phenotype will describe the percent of patients preferring each specific option and their reasons why. Lastly, we will work with physicians and patients to determine how best to depict the preference phenotypes for use during clinical encounters; 2) To determine the feasibility of examining the efficacy and effectiveness of preference phenotypes in larger scale studies at the point of care we will conduct a pilot study using a pre-post-test design in which we will audiotape outpatient visits for 6 months prior to introducing the preference phenotypes and then for 6 months after introducing the preference phenotypes.



Lionel B. Ivashkiv, MD Hospital for Special Surgery

Epigenetic Regulation of RA Fibroblast-like Synoviocytes In rheumatoid arthritis (RA) inflammatory cytokines produced by synovial (joint) cells drive disease pathogenesis by activating cells in inflamed joints and inducing recruitment of inflammatory cells. Key pathogenic roles for the cytokines tumor necrosis factor (TNF) and interleukin-6 (IL-6) in human RA have been demonstrated by the efficacy of therapies that specifically target these cytokines using blocking antibodies or soluble receptors. The goals of this project are to understand how cytokines activate synovial cells to drive disease pathogenesis and cause morbidity, and to elucidate mechanisms that regulate production of pathogenic cytokines in the context of RA synovitis.

This project has focused on a key synovial cell type important in RA pathogenesis, fibroblast-like synoviocytes (FLS). We found that TNF induces a sustained inflamma-



Jon T. Giles, MD, MPH Columbia University

Adipose Inflammation and HLA-Obesity Interactions in Psoriatic Arthritis

Higher body mass index, a surrogate for adiposity, has been strongly linked to psoriatic arthritis risk and disease manifestations. In addition, treatment responses are blunted in psoriatic arthritis patients who are overweight or obese. Together, these findings suggest a mechanistic role for adipose tissue in the pathobiology of psoriatic arthritis. Activated macrophages and T cells, and their associated cytokines, contribute to the disease manifestations of psoriatic arthritis. Similarly, cellular infiltration of adipose tissue macrophages accompanies fat gain, with T-cells and other immune cells present and contributing to inflammatory function. Despite these compelling links, no studies have explored direct measures of adiposity in psoriatic arthritis, and none have yet evaluated adipose tissue inflammatory features in psoriatic arthritis in relation to disease manifestations and treatment responses. Additionally, inheritance of certain HLA-B and C alleles is associated with specific phenotypic manifestations of psoriatic arthritis, the penetrance of which may be

conditioned on an individual's level of adiposity. However, these gene-obesity interactions have received little prior investigation.

For this project, we will:

1) Compare measures of adipose inflammation, from tissue obtained from periumbilical subcutaneous adipose aspiration, between patients with psoriatic arthritis, rheumatoid arthritis, and controls without rheumatic diseases and evaluate the associations of adipose inflammatory tissue characteristics and metabolism with psoriatic arthritis phenotypic characteristics.

2) Quantify the effects of adipose partitioning and adipose tissue inflammation on treatment response in psoriatic arthritis.

3) Examine the interactions of adiposity and candidate HLA-B and C alleles and haplotypes on phenotypic characteristics of psoriatic arthritis using two well characterized Northern European psoriatic arthritis cohorts comprising over 500 psoriatic arthritis patients.

Psoriatic arthritis is one of the most common forms of inflammatory arthritis. Its manifestations can be severe and disabling, and affected individuals often have a reduced lifespan and a lower quality of life. Understanding how adipose tissue contributes to these manifestations of psoriatic arthritis may identify novel targets for intervention to allow psoriatic arthritis patients live longer, happier, and more productive lives.

tory response in FLS, including prolonged activation of NF-KB and transcription of genes that encode IL-6, IL-8 and MMPs. We propose that lack of effective deactivation of inflammatory responses in FLS, which contrasts with homeostatic feed-back inhibition ('tolerization') that deactivates hematopoietic cells, contributes to unremitting inflammation in chronic RA. Two complementary mechanisms underlying prolonged TNF-induced activation and inflammatory gene expression in FLS are ineffective termination of TNF and NF-KB signaling, and ineffective silencing of inflammatory gene loci by epigenetic chromatin-mediated mechanisms. Thus, ineffective engagement of homeostatic signaling and epigenetic mechanisms that terminate inflammatory responses in other cell types (such as macrophages) leads to sustained inflammatory responses in FLS.

Based on our overarching hypothesis that augmenting homeostatic mechanisms represents an effective therapeutic approach to suppress inflammation, we further investigated mechanisms underlying prolonged TNFinduced signaling and inflammatory gene expression. A mechanism underlying prolonged inflammatory gene expression is sustained opening of chromatin and hyperacetylation of histones, which results in sensitivity to inhibition by I-BET, a small molecule that blocks interactions of transcriptional co-activators with acetylated histones. A functional consequence of prolonged FLS activation by TNF is production of high amounts of cytokines, chemokines, MMPs and inflammatory mediators. In this project, we will investigate epigenetic mechanisms that regulate inflammatory activation of FLS. We anticipate that our studies will provide knowledge that can be used to develop RA therapies that target epigenetic regulators.



Vicki Kelley, PhD Brigham & Women's Hospital

IL-34: A Therapeutic for Inflammatory Arthritis

Rheumatoid arthritis (RA) is common chronic inflammatory, destructive joint disease of uncertain etiology that creates a prodigious financial burden for patients and society. While current biologic agents revolutionized the treatment of RA, far too many patients are poorly or non-responsive to these agents. Moreover, current therapeutic approaches often cause off-target adverse effects. Thus, there is a pressing need to pinpoint the pathogenic mechanisms central to RA and identify predictive biomarkers to guide individualized treatment of RA.

Myeloid cells, most notably macrophages (Mø) and neutrophils mediate tissue injury and repair, and are prominent in the synovium of patients with RA. Colony Stimulating Factor 1 (CSF-1) and the newly discovered, IL-34, are ligands for the CSF-1 receptor (CSF-1R) expressed on Mø, myeloid precursors and some other cell types including osteoclasts, but not neutrophils. IL-34 and CSF-1 express overlapping and distinct functions. As evidence for the divergent functions of these CSF-1R ligands in humans, our preliminary data indicates that IL-34, but not CSF-1, is robustly increased in the serum of patients with inflammatory arthritis (RA and lupus arthritis) compared to osteoarthritis and healthy controls. Paralleling our human data, IL-34 is upregulated in the synovium of serum-induced inflammatory arthritis, a model driven by passive serum transfer of autoantibodies in mice. Unexpectedly, we find that serum-transfer inflammatory arthritis is more severe and myeloid cells are more abundant in IL-34 null than wild-type mice. As inflammation sets the stage for healing, this suggests that the rise in IL-34 is countering intra-synovial myeloidmediated inflammatory arthritis. We propose to test the hypothesis that IL-34 is paradoxically both a therapeutic and biomarker for myeloid-mediated SLE inflammatory arthritis. We propose to establish whether:

1) IL-34 dependent mechanisms in synovial tissue counter myeloid-mediated inflammatory arthritis;

2) Administering IL-34 suppresses inflammatory arthritis; and

3) Monitoring serum IL-34 is a predictive biomarker for RA. As clinical trials in RA, including blocking the CSF-1R, are in progress, detailing the pathogenesis of IL-34 in inflammatory arthritis and identifying a predictive biomarker to guide individualized management of patients with RA are timely and critical.





Deborah J. Lenschow, MD, PhD Washington University School of Medicine

Immune Activation in Rheumatoid Arthritis vs. Chikungunya Viral Arthritis

Rheumatoid arthritis is an autoimmune disease whose etiology is unknown. A common hypothesis for many autoimmune diseases is that in patients with the correct genetic predisposition, an environment trigger, such as a viral infection, contributes to the onset of disease. Chikungunya virus (CHIKV) is an emerging mosquito borne alphavirus that frequently causes chronic debilitating, inflammatory arthritis, which clinically mimics seronegative rheumatoid arthritis (RA). This virus recently spread to the Caribbean in 2013 and to the United States in 2014. We have identified a cohort of travelers who were

nearly simultaneously infected with CHIKV and developed persistent, chronic arthritis. This cohort provides us with a unique opportunity to compare the clinical and immunological characteristics of patients with chronic CHIKV arthritis to patients with untreated RA. By using patient derived samples from these two groups we propose to use new technologies, including RNA seq of PBMCs to characterize RNA expression profiles, Luminex analysis of serum for cytokines/chemokines, and single cell mass cytometry (CyTOF) to delineate the interactions between distinct leukocyte subsets, all of which will identify immune pathways that are up or downregulated in both diseases. We will also utilize data obtain from this analysis to identify immune pathways that could be therapeutic targets for chronic CHIKV arthritis and test the utility of blocking these pathways in a murine model of CHIKV arthritis. Through these studies we hope to 1) identify immune pathways that contribute to disease pathogenesis of both RA and chronic CHIKV arthritis; 2) identify potential biomarkers that distinguish between these two diseases; and 3) identify potential therapies that could be utilized to treat chronic CHIKV arthritis.



David Markovitz, MD University of Michigan

DEK in the Pathogenesis and Treatment of JIA

Juvenile Idiopathic Arthritis (JIA) is a common cause of childhood disability, affecting one in every 1000 children less than 16 years of age with a significant risk of joint deformity and functional loss that may result in lifelong discomfort and disability. While JIA pathogenesis is unknown, disease management has improved in recent years with the advent of anti-cytokine therapy. Nevertheless, none of the drugs currently in use for the control of childhood arthritis are curative, their long term safety is unknown, they have many side-effects, and are very expensive. The biochemically distinct DEK protein has been implicated in the pathogenesis of JIA. The goal of this study is to understand the role of DEK protein in inflammation and to develop a new therapeutic modality to treat childhood

arthritis. DEK, normally a nuclear chromatin factor, is released by macrophages, T cells, and neutrophils, and when released from the latter is crucial to the formation of neutrophil extracellular traps (NETs), structures that are thought to be vital to innate immunity and to autoimmunity. Secreted DEK can also act as a chemoattractant for neutrophils and T lymphocytes, and genetic studies in a mouse model reveal that DEK is crucial to inflammation. A new approach to targeting DEK in inflammation has led to the development of single-stranded DNA aptamers that bind tightly to DEK and inactivate its functions, essentially blocking all NET formation, among other effects, and markedly reducing zymosan-induced arthritis in the mouse. The proposed experiments aim to understand the molecular mechanisms by which targeting DEK, especially with aptamers, blocks inflammation and how aptamers can be used to treat arthritis. We will use neutrophils from normal subjects, from the synovial fluid of patients with JIA, and from mice that do and do not express DEK to study how anti-DEK aptamers interfere with NET formation and other pro-inflammatory effects. We will also use two distinct mouse models to further study the potential to use aptamers to treat inflammatory arthritis, whatever the initiating event. The proposed studies could lead to a new paradigm in the treatment of inflammatory arthritis in general and JIA in particular.



Adam Mor, MD, PhD New York University

Targeting PD-1 in inflammatory arthritis

T cells mediate adaptive immunity and therefore must be tightly controlled. Dysregulation of T cells can lead to autoimmunity such as that underlying rheumatoid arthritis (RA). Among the ways T cells are controlled is through co-receptors that are engaged along with the T cell antigen receptor (TCR). Co-receptors can be negative or positive regulators of T cell activation. Among the most important inhibitory co-receptors is Programmed Death-1 (PD-1). Attention has focused on PD-1 in recent years because of the efficacy of interfering with the PD-1 pathway in cancer immunotherapy (in order to stimulate self-immunity). This suggests that a converse approach, stimulating PD-1 signaling, could prove efficacious in treating autoimmunity. A role for PD-1 in protecting against RA is suggested by the observation that PD-1 levels on T cells from RA patients correlate inversely with disease activity. Thus, stimulation of PD-1 could be a novel way of treating RA. Little is known about the signaling pathways downstream of PD-1. We discovered that by inhibiting activation of the small GTPase Rap1, PD-1 signaling inhibits integrin-mediated lymphocyte adhesion. We now propose to further elucidate the signaling pathways downstream of PD-1 in T cells and test the hypothesis that diminished PD-1 signaling plays a role in the pathogenesis of inflammatory arthritis with three aims:

Aim 1) To elucidate in vitro the mechanisms through which PD-1 signaling regulates T cell functions. Despite the potential clinical benefit of intervention at the PD-1 level, little is known about the signaling pathways downstream of this receptor. We propose to perform a structure-function analysis of PD-1. Specifically, we will generate multiple T cell clones in which the PD-1 cytoplasmic tail will be genetically modified. We will use these clones and advanced mass spectrometry to identify new PD-1-interacting molecules, and uncover the contribution of these molecules to T cell functions. This aim should uncover previously unrecognized molecules downstream of PD-1 that could potentially be targeted by small molecules to treat autoimmunity.

Aim 2) To reveal whether ligation of PD-1 in vivo amliorates disease activity in murine arthritis models. The finding that PD-1 regulates T cell proliferation, survival, cytokine secretion and adhesion suggests that intervention at the level of PD-1 might serve as a therapeutic approach. To explore this possibility, we will test whether ligation of PD-1 in vivo, using the PD-1 agonist PDL2-Fc, ameliorates disease activity in collagen-induced and KBxN arthritis models. This aim should examine the feasibility of therapeutic in vivo agonist administration.

Aim 3) To test the hypothesis that PD-1 regulates T cell functions in cells from rheumatoid arthritis patients. We will sample T cells from subjects with RA and characterize them for evidence of signaling differences in the PD-1 signaling pathways. We will sample the same RA cohort longitudinally and explore whether early signaling events in PD-1-expressing T cells are reversibly altered. Cellular functions such as proliferation, adhesion and cytokine secretion will be considered following ex vivo treatment with PD-1 agonists.





Daniel L. Mueller, MD University of Minnesota Medical School

Live Cell Autoreactive B cell Capture for Advanced Analytics in RA

Discovery in human autoimmune diseases such as rheumatoid arthritis (RA) has been greatly hampered by (a) the rarity of disease-provoking B cells that travel through the blood, (b) their lack of distinguishing features to easily discriminate autoreactive B cells from the remaining protective (or irrelevant) B cells, (c) their diverse immunoglobulin antigen specificities and binding affinities, and (d) their heterogeneous differentiation states and effector functions. Our laboratories have successfully developed reliable "citrullinated-peptide antigen tetramer" probe sets, multiparameter flow cytometry techniques, and single-cell C1/RNA-seq technologies that have the power to positively identify, capture, and probe individual live citrullinated-protein antigen-specific blood polyclonal B cells from patients with RA. We propose here a series of translational immunology experiments to move these



Mary C. Nakamura, MD University of California, San Francisco

Immune Mechanisms of Cardiac Remodeling in Inflammatory Arthritis

Cardiovascular disease is a major cause of morbidity and mortality in patients with rheumatoid arthritis (RA). RA patients have an increased incidence of both myocardial infarction (MI or heart attack) and congestive heart failure. Myocardial infarction continues to be the leading cause of congestive heart failure, and interestingly recent studies have demonstrated that inflammation and immune cells play a significant role in development of heart failure post-MI in animal models due to the role of inflammation during cardiac repair. Chronic inflammation due to RA has single-cell technologies and advanced analytics firmly into the arena of human RA clinical investigation. Specifically, in Aim 1 we will validate our citrullinated-peptide antigen tetramer-capture infrastructure at the University of Minnesota for the analysis of fresh RA blood samples collected at distant sites (in this case, RA subjects in the University of Pittsburgh RACER cohort). In addition, experiments will test a combination of PE/AF647 and V450/AF488 tetramer sets to enable simultaneous detection of rare citrullinated-filaggrin and -alpha enolase specific polyclonal B cells in RA subjects. In Aim 2, we will take advantage of multiparameter flow cytometry and Fluidigm C1 singlecell RNA-seq transcriptome analysis (together with our Mayo Clinic collaborators) to investigate the relationship between immunoglobulin gene rearrangement, somatic hypermutation, and the activation/differentiation state of live citrullinated-protein antigen-specific RA B cells. In the final Aim 3 of the grant, we propose a pilot clinical trial to evaluate citrullinated-peptide antigen tetramer-binding B cell frequencies prospectively in RA patients undergoing a DMARD or biological agent therapy change in response to a disease flare. Our primary goal in this trial is to test the power of citrullinated-protein specific B cell detection to predict response to therapy. With success in this effort, we will have established the paradigm for advanced live-cell analytic techniques that can facilitate the rational design of personalized strategies for the modulation of autoreactive B cells in the treatment of RA.

been postulated to be the major driver of cardiovascular disease in RA patients, however, the cellular mechanisms of inflammation that are responsible for the cardiovascular changes are incompletely understood. Our study builds on the recent finding that cardiac macrophage subtypes can influence the development of cardiac failure post-MI in mouse models by examining the effect of inflammatory arthritis on cardiac macrophage subtypes and cardiac outcomes in a mouse model for rheumatoid arthritis. Our studies will examine for specific changes in the cardiac macrophages induced by ongoing inflammatory arthritis in mice with myocardial infarction. We will then test the effects of an immune modulatory therapy that initiates a beneficial cardioprotective immune response in wild-type mice post coronary artery ligation tion and compare the effects of anti-TNF treatment on cardiac macrophage subtypes and cardiac remodeling post infarction in mice with inflammatory arthritis. Our studies seek to identify immune mechanisms in inflammatory arthritis that promote abnormal cardiac repair to enable us to target immune modulation to lead to better cardiovascular outcomes in rheumatoid arthritis patients.



Peter A. Nigrovic, MD Brigham and Women's Hospital

Experimental Identification of Functional Genetic Polymorphisms in Arthritis

Genome wide association studies (GWAS) have defined over 100 DNA loci that correlate with risk of rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA). Several of these loci correspond to effective treatment options, raising the possibility that rest represent a "library" of new drug targets. However, interpretation of genetic data is limited by the fundamental ambiguity of GWAS hits. Each locus contains a large number of variants, most commonly single nucleotide polymorphisms (SNPs), and it has proven quite difficult to determine which SNP drives a specific association. This limitation remains a major stumbling block in realizing the promise that GWAS data hold for unlocking the biology of RA and JIA.

In this project, we introduce two new techniques that help to bridge this gap. The first employs restriction enzymes in an innovative screen to identify SNPs that alter the binding of DNA regulatory proteins such as transcription factors. The second employs these SNP sequences as effective tools for identifying associated regulatory proteins. We will use these tools to accomplish two goals. First, we will complete a genetic dissection of the CD40 locus, implicated in B cell co-stimulation. Second, we will develop our methods into a novel high-throughput screen for functional SNPs in RA and JIA. Together, these studies seek to develop a new approach to the mechanistic dissection of adult and pediatric arthritis via human genetics in order to identify novel pathways that can be targeted therapeutically.



Anthony K. Shum, MD University of California, San Francisco

The Role of ER Stress in the Lung Epithelium as a Trigger for RA

The goal of this grant is to understand the role of the lung in the pathogenesis of Rheumatoid Arthritis (RA). Increasing evidence points to a central role of the lung in a subset of patients with RA. Studies show that cigarette smokers that express the HLA-DRB1 shared epitope (SE) alleles have an elevated risk for developing RA. The mechanism for this gene-environment association remains unknown. We uncovered a potential mechanism for the lung in RA by performing whole exome sequencing (WES) in a family with a rare autosomal dominant form of RA characterized by penetrant interstitial lung disease (ILD). We found a single, rare, non-synonymous variant on chromosome 10 in the Surfactant Protein A2 (SFTPA2) gene present only in diseased subjects. SFTPA2 is expressed in a tissue-restricted pattern that is limited to the lung. Mutations in the SFTPA2 gene are associated with familial pulmonary fibrosis and believed to cause disease through the induction of endoplasmic reticulum (ER) stress in the lung. However, none of the reported descriptions of families with SFTPA2 mutations include RA or autoimmunity as a clinical manifestation. In the family in this project, RA is the dominant phenotype in patients harboring an SFTPA2 mutation and in some patients the only manifestation of their disease. We hypothesize that the SFTPA2 mutation triggers ER stress in the lung epithelium and lung citrullination that in patients with HLA-DRB1 SE alleles drives citrulline-specific T and B cell responses to cause RA. We propose to study the role of SFTPA2 mutations in the development of RA through a variety of different approaches. These include in vitro studies of the mutant surfactant protein to determine its role in protein citrullination; animal studies to examine the role of lung ER stress in the development of lung citrullination and inflammatory arthritis; and finally, immunological phenotyping of patients with SFTPA2 mutations in order to establish a link between lung ER stress and clinical RA. Through these aims we seek to demonstrate that the SFTPA2 mutation provides a molecular link that establishes the importance of the lung in the development of RA and provide a new understanding of how lung citrullination may lead to inflammatory arthritis.



Geoffrey M. Thiele, PhD

University of Nebraska Medical Center

MAA and Anti-MAA Immune Responses in Rheumatoid Arthritis

Anti-citrullinated protein antibody (ACPA) is highly specific to rheumatoid arthritis (RA) with recent studies suggesting that ACPA are pathogenic with seropositivity portending a poor prognosis including more rapid joint destruction. However, the mechanism(s) by which citrullinated proteins/peptides are recognized and processed and presented in the context of co-stimulatory molecules is still not well understood. Studies have shown that a unique post-translational modification of proteins that occurs under oxidative stress by malondialdehyde (MDA) and acetaldehyde (AA), termed MAA, up-regulates MHC Class II, increases co-stimulatory molecules and generates cytotoxic and pro-inflammatory responses in the absence of exogenous adjuvant. For the first time, our group has shown that MAA modified proteins are detected in synovial tissues of RA patients and co-localize with citrullinated antigen. Additionally, anti-MAA antibody isotypes are

independently associated with ACPA concentration (p < 0.0001) in patients with established RA. Therefore, our overarching hypothesis is that these two post-translational modifications (MAA modification and citrullination) act in concert to drive tolerance loss resulting in the anti-citrulline autoimmune responses characteristic of RA. These studies have been devised to first evaluate antibody responses in individuals with preclinical RA to MAA-modified proteins, in order to evaluate the relationship between anti-MAA immune responses with the development of early RA. We will demonstrate that anti-MAA antibody is predictive of future RA. In Aim 2, the experiments have been devised in order to use antibodies to citrullinated and MAA epitopes to isolate and determine which modified macromolecules are detected in synovial tissues from the Nebraska Synovial and Tissue Bank (Neb-STB). In Aim 3, the specific receptor(s) that mediate the different biological effects (co-stimulation, cytokine production, adhesion molecule expression, etc.) following binding of MAAadducts and citrullinated proteins to antigen presenting cells will be identified. In these studies we will use citrullinated antigens that have been previously identified by our group and others. Finally, the presence of MAA-modified and citrullinated proteins in tissue, or the identification of high concentrations of antibody to these proteins strongly suggests they are both involved in the pathogenesis of RA. Therefore, using patient-derived materials, these studies will evaluate and validate MAA-modification as a potential biomarker and pathophysiological initiating factor in RA.



PILOT GRANT RECIPIENTS

The Pilot Grant encourages established investigators to begin tests of novel research ideas into rheumatoid arthritis and related autoinflammatory diseases by providing seed funds to gather preliminary data.



Antonios O. Aliprantis, MD, PhD Brigham and Women's Hospital

Bone Erosion: A NOGO for Rheumatoid Arthritis Patients

The destruction of periarticular bone by osteoclasts (OCs) in inflammatory arthritis (IA) patients leads to deformities and a poor prognosis. While small molecules and biologic agent can control disease activity, some patients with smoldering inflammation continue to accrue joint damage. Thus, a better understanding of OC-mediated bone erosion is needed. OCs differentiate from myeloid precursors in response to Receptor Activator of NF-kB ligand (RANKL), which is produced by immune cells and activated synovial fibroblasts. RANKL however is not sufficient to drive OC differentiation and co-stimulatory signals are needed. We have recently found a new costimulatory pathway that is necessary for OC differentiation and which may be amenable to therapeutic manipula-

tion in IA: the NOGO pathway. This pathway consists of a membrane bound ligand (NOGO) and the cell surface NOGO receptor 1 (NGR1), and was originally described in the central nervous system where it inhibits axon growth. Three pieces of preliminary data on the role of NOGO in OCs have been generated. First, NOGO promotes terminal OC differentiation in vitro and NOGO-deficient mice display elevated bone mass. Second, an NGR1 inhibitor blocks OC formation in cell culture. Third, the pro-inflammatory cytokine Interkeukin-1 stimulates chondrocytes and synovial fibroblasts to express a secreted NGR1 inhibitor called Cartilage acidic protein 1 (CRTAC1). These data suggest that the NOGO pathway is a key regulatory step in OC-mediated inflammatory bone erosion. Our two aims will investigate this hypothesis by testing mice deficient in NOGO, NGR1 or CRTAC1 in the KBxN serum transfer arthritis model. We predict that mice lacking NOGO or NGR1 will manifest reduced inflammatory bone erosion with fewer OCs. In contrast, CRTAC1 deficient mice should display the opposite phenotype with increased numbers of OCs and more bone erosion. Taken together, this pilot project explores the effector phase of OC-mediated bone erosion secondary to synovial inflammation. If the NOGO-NGR1 pathway is a critical co-stimulatory signal for OC formation in IA, therapeutic targeting may reduce bone erosion and morbidity in patients.





Partha S. Biswas, DVM, PhD University of Pittsburgh

Type I Interferon and the mechanism of TNF antagonists in RA

Studies have indicated that IFN-I inhibit Th17 development through the induction of IL-27 from macrophages. However, we have recently demonstrated that under inflammatory condition, IFN-I-induced IL-27 production is blocked by complement 5a (C5a) via activation of the C5a-receptor (C5aR). Our preliminary data indicate that TNF signaling in macrophages circumvents the IFN-IL-27 pathway through increased expression of C5aR, thus permitting the generation of pathogenic Th17 cells. Thus, we hypothesize that TNF antagonists will down regulate C5aR expression on macrophages resulting in increased expression of the IFN-I induced immunosuppressive cytokine IL-27. To address this hypothesis, we will analyze blood samples from RA patients with high baseline IFN-I levels and who have had a good or moderate EULAR response to treatment with a TNF antagonist using samples from the University of Pittsburgh Rheumatoid Arthritis Comparative Effectiveness Research (RACER) registry. This project will not only aid future development of clinically useful predictive biomarkers that will inform appropriate therapy decisions, but will also uncover novel mechanisms of pathogenicity and therapeutic efficacy in RA. We anticipate that this project will for the first time determine the mechanisms of efficacy of anti-TNF therapy in subset of RA patients with high baseline IFN-I levels and who have had a good or moderate EULAR response to treatment with a TNF antagonist.



Cong-Qiu Chu, MD, PhD Oregon Health & Science University

Molecular Probing TNF in vivo and Therapy of Arthritis with Aptamer

Tumor necrosis factor (TNF) is the first cytokine to be fully validated as therapeutic target for rheumatoid arthritis (RA). Blocking TNF activity has revolutionized the management of RA and other inflammatory diseases. The benefit of TNF inhibitors (TNFi) to RA patients has been well demonstrated in clinical practice. However, up to 40% of RA patients fail to achieve adequate response to TNFi. A TNFi response prediction guided personalized medicine is required, but still remains a challenge. Alternative approaches to identify patients who are likely to respond to TNFi and replacement of current expensive biological TNFi are unmet need. We hypothesize that the level of TNF expression in the joint of RA patients is positively correlated with the degree of response to TNFi therapy. We propose to probe TNF expression in vivo using aptamers in arthritic joints to guide therapy and to test therapeutic efficacy of aptamers to substitute for expensive biological TNFi. Aptamers are synthesized short and single-stranded nucleotides which can bind to protein ligands in high affinity and specificity and have been referred as "chemical antibodies". Production of aptamers is substantially cheaper. First, we will employ near infrared fluorescent dyes labeled TNF aptamers to probe TNF expression in the joint in live animals of human TNF transgenic mice. Second we will examine the therapeutic effect of aptamers in comparison with that of infliximab in human TNF transgenic mouse arthritis model and collagen-induced arthritis. Results from this project will provide invaluable information for future translational studies in RA using the same technology for personalized TNF targeted therapy to reduce the cost but maintain high efficacy.





Lindsey A. Criswell, MD, MPH, DSc University of California, San Francisco

A Pilot Study of DNA Methylation and Response to Treatment in RA

Epigenetic modifications, such as methylation of the 5' carbon of cytosine which occurs in the context of CpG dinucleotides, do not affect the genetic sequence; however, these modifications play a critical role in transcriptional regulation of a gene and subsequent gene expression. Increasing evidence implicates epigenetic factors, and in particular patterns of DNA methylation, in autoimmune diseases, including rheumatoid arthritis (RA). The maintenance of DNA methylation homeostasis appears to be critical for the development and function of immune cells, and changes in DNA methylation by exogenous agents can initiate autoreactivity in T cells, and induce autoimmune-like disease in mice. Results from several lines of evidence, including both human and animal studies, demonstrate that environmental exposures can modify DNA methylation profiles, including diet and tobacco smoke, and that these changes can occur later

in life. Thus, DNA methylation may provide a molecular link between environmental risk factors and autoimmune disease risk. Medications can also affect patterns of DNA methylation, and these epigenomic modifications may represent one mechanism by which these medications exert their effects. Further, patterns of DNA methylation have been shown in some cases to serve as predictors of treatment response. The current pilot study is based on the hypothesis that patterns of DNA methylation will serve as biomarkers of response to treatment of RA. In Aim 1, we will identify changes in DNA methylation patterns associated with treatment with methotrexate (MTX) and/or anti-TNF agents. In Aim 2, we will identify patterns of DNA methylation that predict response to treatment. Data for this project will derive from 30 patients initiating treatment with MTX and/or anti-TNF agents. Blood samples will be collected at baseline and at followup (on treatment) to identify changes in DNA methylation patterns associated with MTX and/or anti-TNF treatment. All samples will undergo FACS to isolate CD4+ naïve T cells and genome-wide methylation profiling will be performed using the Illumina Infinium HumanMethylation 450k BeadChip on both the CD4+ naïve T cell samples and the unsorted (PBMC) samples. Data collected and generated for Aims 1 and 2 will allow us to identify changes in DNA methylation patterns associated with treatment with MTX and/or anti-TNF agents, as well as DNA methylation profiles associated with treatment response.

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Career Development Research Awards

Career Development Research Awards are designed to encourage early and mid-career investigators to continue vital research into the cause, prevention and treatment of rheumatic diseases.

CAREER DEVELOPMENT BRIDGE FUNDING AWARD: R BRIDGE RECIPIENTS The R Bridge Award encourages essential rheumatology research by supporting promising investigators who are at risk of running out of research funding and are revising outstanding NIH R01 or VA RCS/ORD award applications.



Shervin Assassi, MD, MS University of Texas Health Science

Prediction of Treatment Effect in Systemic Sclerosis

Systemic sclerosis (SSc) has one of the highest standardized mortality ratios among rheumatic diseases. Interstitial lung disease (ILD) is the primary cause of diseaserelated death. Response to immunosuppression is highly variable and the clinical factors are not sufficient to predict this treatment response. The utilized medications are also associated with potentially serious adverse events, further underscoring the need for the development of reliable predictive biomarkers.

SSc patients have distinct gene expression signatures in skin and the peripheral blood. The type-I interferon signature is the most prominent transcript profile in the circulation while a prominent inflammatory profile has been also observed in the SSc skin. Furthermore, these



Megan A. Cooper, MD, PhD Washington University

Metabolic Regulation of Natural Killer Cell Activation

Natural killer (NK) cells are innate immune lymphocytes that serve as a critical first line defense against infection. We hypothesize that metabolic changes in the NK cell microenvironment and alterations of intrinsic cellular metabolism impact NK cell function in vivo. The longterm goal of this project is to improve our understanding of basic mechanisms of NK cell activation in health and disease. The importance of NK cells in human disease is exemplified by patients with selective defects in NK cells who suffer from recurrent and fatal herpesviral infections. Defects in NK cell cytotoxic function have also been associpatients have a distinct serum cytokine profile. There is emerging evidence that these inflammatory profiles can be used for monitoring/predicting treatment response in SSc patients.

The clinical data and biospecimens collected in SSc-ILD clinical trials represent an unparalleled opportunity for identification/validation of molecular predictors of response to treatment. Global gene expression profiling and multiplex proteomic assays can be utilized to reliably characterize patients' inflammatory state. Our objective is to determine the predictive significance of the interferon signature in the circulation or the skin inflammatory profile for response to immunosuppression by capitalizing on the resources of these clinical trials. This can ultimately lead to development and validation of prediction models for SSc-ILD that combine clinical data with multilevel molecular predictors. These models can also aid in the design of future trials by decreasing the numbers needed to enroll through more informed patient enrichment strategies.

Given that ILD is the most common cause of diseaserelated death in SSc, a clinically useful prediction tool for identifying highly responsive patients represents a major progress beyond the current "one-size fits all" approach and can lead to more effective and focused management of patients with SSc-ILD.

ated with inflammatory conditions including hemophagocytic lymphohistiocytosis (HLH) and systemic juvenile idiopathic arthritis (IIA). Metabolic regulation plays a key role in many aspects of immunity, including the activation and generation of memory T cells. The fuels that drive cellular metabolism (e.g., glucose, fatty acids) are altered in many disease states, and metabolic pathways are promising targets for drug candidates. The metabolic fuels needed for NK cell functional responses, the ability of NK cells to utilize those fuels, and the concept of metabolic regulation of NK cells have not been investigated. Our preliminary studies identified significant differences in the ability to activate NK cells depending upon the metabolic fuels available. The Specific Aims are: 1) Determine the metabolic fuels required for NK cell effector functions and the mechanism(s) whereby metabolism alters NK cell receptor-mediated IFN-gamma production and 2) Determine the in vivo metabolic phenotype of NK cells and the effect of metabolic modulation during a viral infection. We hypothesize that activation of NK cells via an activating receptor in vivo requires a metabolically-derived second signal and that these studies will lead to the identification of that signal.

CAREER DEVELOPMENT BRIDGE FUNDING AWARD: K BRIDGE RECIPIENTS

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



Anna Broder, MD, MSc Albert Einstein College of Medicine

The impact of hydroxychloroquine use on thrombosis and mortality in lupus-related end stage renal disease

Systemic lupus erythematosus (SLE) is an autoimmune disease that results in extensive inflammation and tissue damage. Approximately 60% of SLE patients develop kidney involvement (lupus nephritis), and up to 30% of these progress to end-stage renal disease (ESRD). The mortality rate in patients with SLE-related ESRD is 4-fold higher than of lupus nephritis alone, and twice as high as in non-SLE patients on hemodialysis. Although the development of end stage renal disease is one of the most common complications of SLE, there are no studies to date on how to improve outcomes in SLE ESRD.

The objective of this project is to study whether hydroxychloroquine use is associated with lower mortality in SLE ESRD. Although current guidelines for rheumatologists recommend hydroxychloroquine use in SLE ESRD, it is prescribed to less than 30% of these patients. To date, there are no studies specifically evaluating the clinical benefits of hydroxychloroquine in SLE ESRD patients. Such clinical knowledge would prevent under or overtreating these patients. Based on our retrospective studies, our guiding hypothesis is that hydroxychloroquine use will decrease morbidity and mortality in SLE ESRD patients undergoing the two most common renal replacement modalities, hemodialysis and kidney transplant. To investigate this, we will analyze data from the US Renal Database Systems (USRDS), the NIH-sponsored US - wide registry of ESRD patients, and collect longitudinal SLE-specific data that will be linked subsequently to the USRDS.

These studies encompass research in several fields, including rheumatology, nephrology, epidemiology and biostatistics, and build on work that Dr. Broder pursued during the completion of her Master's degree in Clinical Research. The clinical investigation will be carried out under the mentorship of three senior investigators in SLE. Dr. Broder's research focus represents a new direction to improve clinical decision making and individualize therapies in SLE ESRD.





Melissa A. Cunningham, MD, PhD Medical University of South Carolina

Mechanisms of ERa Modulation of SLE Dendritic Cells

Ninety percent of those diagnosed with systemic lupus erythematosus (SLE) are women, with peak incidence between the ages of 15 and 45, when women are most hormonally active. Despite significant research effort, the mechanisms underlying this sex bias remain unclear. Our laboratory previously backcrossed estrogen receptor alpha knockout (ERαKO) mice onto the NZM2410 lupus prone background. We demonstrated that female NZM/ ERαKO mice had significantly less renal disease and significantly prolonged survival compared to WT littermates despite similar serum autoantibodies and glomerular

immune complex deposition. ERaKO mice are not ERa null, but rather express an N-terminally truncated ERa. They have physiologic deficiencies including infertility due to disruption of a critical activation domain (AF-1). We showed that dendritic cells (DCs) from NZM/ERaKO mice have a blunted inflammatory response to Toll-like receptor (TLR) ligands. When these mice were ovariectomized, the protective phenotype was lost. Upon estradiol-repletion, protection was restored. True ERa null mice were not protected, suggesting that estrogen in the presence of the AF-1 mutant confers protection, rather than the absence of the full-length ERa66. Interestingly, the truncated ERa expressed in the ERaKO animal is structurally similar to ERa46, an endogenous ERa splice variant that lacks the AF-1 domain, and is a negative regulator of gene transcription. ER α 46 has an identical DNA binding domain to ER α 66 and is a powerful inhibitor of ERa66. We hypothesize that ERa46 expression has a protective effect in lupus. The goal of this project is to determine the role of ERa46 in SLE, and to improve our understanding of ERa-mediated transcription in DCs in the setting of TLR-induced inflammation.



Jan Hughes-Austin, PhD, MPT University of California, San Diego

ACPA, CVD, and Bone Disease in a Multi-Ethnic Population

Cardiovascular disease and osteoporosis affect more than one-third of older adults, are responsible for significant morbidity and mortality, and are linked processes. Antibodies to citrullinated protein antigens (ACPA), which are self-directed antibodies that induce a pathologic immune response, have been linked to bone loss and coronary heart disease in rheumatoid arthritis patients; and emerging evidence suggests that ACPA are detectable in the general population and may be associated with CVD and bone disease in non-rheumatoid arthritis settings. Above and beyond providing training for Dr. Hughes-Austin to transition to independence, this mentored research scientist development award will establish whether ACPA are indeed independently linked with CVD and bone disease, and will provide important information on whether or not ACPA levels are modifiable by statins. If the hypotheses prove true, this study will lead directly to Dr. Hughes-Austin's design and implementation of an intervention study to determine whether modifying ACPA may benefit CVD and bone disease in the general population.

CAREER DEVELOPMENT BRIDGE FUNDING AWARD: K SUPPLEMENT RECIPIENTS

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



Shelia T. Angeles-Han, MD, MSc Emory University School of Medicine

Risk Factors for Juvenile Idiopathic Arthritisassociated Uveitis

Pediatric uveitis leads to sight-threatening complications and vision loss. In North America, it is most commonly associated with juvenile idiopathic arthritis (JIA), affecting 10-20% of children with inflammatory arthritis. Children are asymptomatic at onset. Our work confirms recommendations for regular ophthalmology screening based on a child's risk factors such as JIA subtype, ANA status, age at onset, and disease duration. The ACR K supplement will enable us to generate preliminary data on potential genetic markers and biomarkers for the development of uveitis. This will provide insight into the mechanisms of the interrelationships between arthritis and uveitis in childhood, which would be examined in an anticipated R01. We will determine the combination of clinical factors, HLA alleles, and biomarkers that predict disease development and severe outcomes. Early identification of children at risk for severe uveitis will enable timely treatment prior to the onset of sight-threatening complications. Aim 1 is to explore HLA associations in African American children with uveitis. There are no genetic studies in this population. Our hypothesis is that there is a biologic etiology for the poor visual outcomes of AA children. This work will elucidate whether the impact of race is biologic in nature or secondary to health care access. Aim 2 is to conduct a prospective pilot study of differences in the tear proteomic profile of children with long-standing JIA alone (>4 years), JIA-associated uveitis, and chronic anterior uveitis. Our hypothesis is there is an overexpression of proteins in children with both arthritis and uveitis, due to increased inflammatory involvement, compared to children with JIA alone or uveitis alone. My career goal is to prevent vision loss and blindness through the early identification of children at highest risk for severe uveitis by identifying risk factors and initiating early, aggressive therapy to improve outcomes.





Cecilia P. Chung, MD, MPH Vanderbilt University

Pharmacogenetics of Immunosuppressants in BioVU

Immunosuppressive drugs have advanced the treatment of patients with autoimmune and inflammatory diseases. However, because of their narrow therapeutic indices, the frequency of clinically important side effects associated with these drugs can be as high as 50%. Therefore, there is an increasing need to provide individualized treatment and predict clinical outcomes, including side effects. Currently, assays evaluating genetic variants of function of thiopurine methyltransferase (TPMT) are the only tests available to guide the use of immunosuppressants in routine clinical practice and there are no other tests to guide personalized clinical decisions when other immunosuppressive agents are used. Thus, the overarching goal of this proposal is to define the genetic variants that influence severe toxicity associated with the use of three immunosuppressant drugs frequently used in rheumatology: azathioprine, cyclophosphamide, and mycophenolate.

We will use BioVU, a bank of de-identified DNA samples available at Vanderbilt University. BioVU is currently the largest clinical practice-based biobank in the U.S. Each DNA sample is linked to a de-identified version of the patient's electronic medical record. Clinical data available include all outpatient and inpatient notes, laboratory results, and medication lists, allowing us longitudinal follow-up and definition of clinical phenotypes.



M. Kristen Demoruelle, MD University of Colorado

Generation of ACPA at the Female Genital Tract Mucosa

Denver

The overall hypothesis of this project is that autoimmunity in RA is generated at the female genital tract (FGT) mucosa, and the generation of ACPAs in the FGT is associated with specific microbiota and/or neutrophil extracellular trap (NET)-associated citrullinated proteins. This hypothesis emerged from my original K23 project that hypothesized the lung mucosa is a site of generation of autoimmunity in RA. In Year 1 of the K23 using induced sputum testing, we identified a portion of individuals with and atrisk for RA who exhibited ACPA generation in the lung that was associated with specific lung microbiota. However, we also found that many women with systemic ACPAs did not have ACPAs present in their sputum suggesting another site of generation. Using our labs expertise with sputum, we developed protocols for self-collection and ACPA testing of cervicovaginal fluid (CVF), and our preliminary findings demonstrate that women with RA have significantly higher ACPA levels in the FGT compared to controls. In this K Supplement, we will build upon these early findings and use simultaneously collected CVF and serum in subjects with RA, subjects at-risk for future RA, and controls. In cross-section, we will determine the generation of ACPAs in the FGT with the hypothesis that ACPAs are generated in the FGT of a portion of women with and at-risk for RA. Next, we will characterize vaginal microbiota associated with ACPAs with the hypothesis that microbiota are involved in the local generation of ACPA in the FGT. Finally, we will quantify NET-associated citrullinated proteins in the FGT associated with ACPAs with the hypothesis that NETosis is a mechanism by which citrullinated proteins can become extracellular in the FGT and trigger ACPAs. In aggregate, these studies will provide key preliminary data to strengthen tentative Aims and increase competitiveness for a planned R01 grant submission.

INVESTIGATOR AWARD RECIPIENTS

The Investigator Award encourages junior investigators to continue conducting innovative research that will be competitive for more significant funding while they establish themselves as independent investigators.



Candace H. Feldman, MD, MPH Brigham and Women's Hospital

Medication Non-adherence in Lupus

Medication nonadherence, the failure to take medications as prescribed, is a widespread problem accounting for over \$100 billion in preventable healthcare costs in the U.S. annually. Prior studies suggest that nonadherence in systemic lupus erythematosus (SLE) may be a particularly serious problem. Characteristics unique to SLE may heighten nonadherence including frequent disease activity fluctuations, the complexity and toxicity of medication regimens, a high disease burden among lower socioeconomic status groups, and cognitive and psychological manifestations.



This project aims to understand predictors of nonadherence in SLE and the burden of associated, potentially avoidable adverse outcomes in order to design interventions targeting those at highest risk. We will use a novel method, group-based trajectory modeling, to define predictors of long-term nonadherence patterns among SLE patients and to understand the impact of nonadherence on serious outcomes. We will leverage nationwide Medicaid administrative data on >60,000 SLE patients from 2000-2010 with detailed medication refill data, as well as a registry of >1,000 validated SLE patients with complete medical records.

Our central hypotheses are that sociodemographic, psychosocial and disease-related predictors will vary across dynamic patterns of nonadherence and persistent nonadherence will result in the highest burden of adverse outcomes.

Specifically, our aims will determine: 1) predictors of dynamic nonadherence patterns in SLE patients, 2) the impact of nonadherence on hospitalizations and mortality, and 3) the role of psychosocial factors on nonadherence. The long-term goal of this project is to develop patient-centered interventions targeting the highest risk SLE patients to improve medication adherence and reduce racial, ethnic and socioeconomic disparities in outcomes.



Svetlana Krasnokutsky, MD, MSci NYU Langone Medical Center

Colchicine for the Treatment of Osteoarthritis

Osteoarthritis (OA) is the most common arthritis, and is accompanied by pain, debilitation, and disability. Current therapies treat pain only, often inadequately. To date, no disease-modifying osteoarthritis drug (DMOAD) has been identified. However, advances in OA pathobiology, and recognition of potential biomarkers hold promise for intervening in OA biology to alleviate pain, improve function and prevent future structural damage. Synovial fluid (SF) and peripheral blood biomarkers indicate increased inflammation in the OA joint, including evidence that IL-1 β plays an important role. Peripheral blood leukocytes (PBL) show evidence of activation, consistent with imaging confirming previously-underappreciated synovitis. Moreover, some studies suggest a possible role for calcium or urate crystals, and we have shown that the presence of

gout and/or hyperuricemia is predictive of higher rates of knee OA. Thus, the possibility that an anti-inflammatory strategy may reduce OA pain, function and/or structural progression deserves assessment. We propose to study colchicine in a placebo-controlled trial. Colchicine is a long-used, well-tolerated, once-daily oral agent; it inhibits IL-1ß production and cells implicated in OA pathogenesis, it inhibits crystal-mediated and other inflammation without major immune suppression, and pilot studies suggest benefit for OA pain. We will leverage an ongoing NIH-funded symptomatic knee OA (SKOA) natural history study, which follows patients for 5 years and provides us with baseline imaging, functional data and biomarkers. 120 completers with established SKOA (KL scores 2-3) will receive colchicine 0.6 mg daily or placebo for 1 year. Patients will be assessed for: 1) pain and function (VAS and KOOS pain, WOMAC scores); 2) plasma, SF and PBL markers of inflammation; 3) structural progression, using standardized knee films and knee ultrasound to assess cartilage/bone changes, as well as synovitis and presence/ absence of crystals at the articular cartilage. A beneficial result of colchicine in any predefined outcome would hold promise for the development of DMOAD therapy. Additionally, the study will shed light on OA progression, including impact of biomarkers, with or without colchicine therapy.



Maria A. Lopez-Olivo, MD, PhD The University of Texas, MD Anderson Cancer Center

Improving Decision Making after TNFi Failure in RA The objective of this application is to use knowledge synthesis methods to combine existing evidence from clinical trials and observational studies to evaluate the benefits, harms and cost-effectiveness of the currently approved targeted agents as monotherapy or in combination with traditional disease-modifying antirheumatic drugs (DMARDs) in patients with rheumatoid arthritis (RA) who have suboptimal or no response to at least one Tumor Necrosis Factor- α inhibitor (TNFi). The products arising from this research will inform healthcare providers and patients about the best available options after failing at least one TNFi agent, which ultimately can result in the optimal allocation of economic resources and the potential reduction of morbidity.

SCIENTIST DEVELOPMENT AWARD RECIPIENTS

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



Sheila L. Arvikar, MD Harvard Medical School/Massachusetts General Hospital

Immune Responses to P. gingivalis in Early RA

There is increasing evidence that periodontitis may be an environmental trigger of rheumatoid arthritis (RA), but specific mechanisms connecting periodontitis and RA are unclear. In my previous work, I have demonstrated that prior to immunosuppressive therapy, a subset of newonset RA patients has antibodies to the major periodontal pathogen P. gingivalis (Pg). We found that elevated levels of antibodies to Pg are associated with anti-citrullinated protein antibodies (ACPA), greater inflammation, and higher disease activity, even after a year of treatment. Moreover, in our cohort, these Pg antibodies correlated strongly with periodontitis on dental examination. We hypothesize that Pg may contribute to autoimmunity and disease severity in RA. A subset of RA patients may benefit from treatment of periodontitis in addition to treatment of joint disease. Pg antibodies may serve as biomarkers to help to identify such patients, however Pg antibody measurement has not been optimized. Moreover, T cell responses to Pg in RA have not yet been studied but may reveal important pathogenic mechanisms. This project will further explore humoral and cellular immunity to Pg in early RA.

For the studies proposed here, I will identify immunogenic Pg proteins and evaluate the utility of candidate antigens. These studies will identify targets of Pg antibody responses in RA patients and aid in the development of more reliable test strategies. I will also examine CD4+T cell subsets in peripheral blood and synovial fluid of early RA patients. Specific immune responses such as a greater Th17 response in Pg-antibody-positive patients would support a novel mechanistic link between Pg and RA, in addition to citrullination. Overall this project will define immune responses to Pg and may offer novel insights into RA pathogenesis. This work will refine Pg antibodies as biomarkers in RA and may further support the evaluation and treatment of periodontitis in RA patients.





Medha Barbhaiya, MD Brigham and Women's Hospital

Environmental SLE Risk Factors in Prospective Cohorts

The etiology of systemic lupus erythematosus (SLE) remains unclear, but it is thought to develop when genetically predisposed individuals are exposed to one or more environmental triggers. Various environmental exposures associated with increased SLE risk include oral contraceptive and postmenopausal hormone use, early menarche, crystalline silica, and potentially Epstein Barr virus. However, other environmental factors likely to be associated with SLE risk, but not yet established, include alcohol consumption, cigarette smoking, and ultraviolet-B radiation exposure.

Prior epidemiologic studies demonstrate conflicting results for alcohol and SLE. Several case-control studies have reported an inverse association between moderate alcohol consumption (< 10 grams of alcohol/day) and risk of SLE. The possible protective effect may be through anti-inflammatory and hormonal pathways. However, case-control studies are prone to recall bias and reverse causation bias. Only one prior prospective cohort study did not demonstrate an association between alcohol consumption and incident SLE, but was limited by small sample size. Conversely, several case-control studies have demonstrated increased risk of SLE among current smokers. While this was not demonstrated in two prospective cohort studies, both were substantially limited by sample size. Additionally, while the link between ultraviolet-B (UV-B) radiation exposure and SLE exacerbation is established, it is not clear whether chronic UV-B radiation exposure increases the risk for SLE. Several case control studies suggest elevated SLE risk with UV-B radiation exposure, but this may be due to reverse causation as photosensitivity from SLE itself could occur several years before diagnosis.

Thus, no prior large prospective cohort studies have investigated associations between smoking, alcohol consumption, or ultraviolet-B radiation with incident SLE risk. This project will examine the associations between these important lifestyle factors and SLE risk within the ongoing Nurses' Health Study cohorts, including over 330,000 women followed prospectively for incident disease for up to 40 years, and in the Black Women's Health Study cohort, comprised of 59,000 women followed prospectively for 20 years. Given the severe consequences of SLE, the identification of modifiable risk factors for its development could lead to new and important knowledge about disease pathogenesis, as well as to potential strategies for disease prevention.



Jennifer Belasco, MD The Rockefeller University

Molecular Signatures of Skin & Joint Tissue in PsA & PsV

It is unknown why 42% of patients with psoriasis vulgaris develop arthritis. We hypothesize that cytokines arising in the skin of psoriasis vulgaris patients will affect circulating immune cells and play a role in initiating joint disease. An extensive molecular and cellular profiling of the primary tissues involved in psoriatic arthritis (skin, the connective

tissue between tendon or ligament and bone known as the enthesis, synovium and bone) along with blood will be performed to investigate this hypothesis. Our preliminary data show that while the skin disease of psoriatic arthritis is histologically similar to the skin disease of psoriasis vulgaris, the inflammatory genes and pathways in psoriasis vulgaris lesional skin differ from psoriatic arthritis lesional skin. Many of the differentially expressed genes are associated with joint tissue or bone metabolism. This would likely be the first study to show that inflammation linked to joint tissue and bone formation and resorption could be ascertained from skin biopsies. Common inflammatory pathways may exist in skin, joint tissue and blood. These findings could lead to the discovery of key pathogenic molecules suggesting new therapeutic targets, or to biomarkers in skin lesions or blood that can predict the onset or severity of psoriatic arthritis.



Elana J. Bernstein, MD, MSc

Columbia University College of Physicians & Surgeons

Outcomes of Lung Transplantation in Autoimmune Diseases

Autoimmune diseases are chronic, complex, multisystem diseases. The pulmonary parenchyma and pulmonary vasculature are frequent targets of many autoimmune diseases, including polymyositis, dermatomyositis, systemic sclerosis, systemic lupus erythematosus, mixed connective tissue disease, Sjogren's syndrome, and rheumatoid arthritis. Adults with these diseases are at risk for developing interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH). Although therapies for ILD

and PAH have advanced over recent years, they remain limited in their ability to control disease progression. Therefore, many adults with autoimmune disease related ILD or PAH progress to end-stage lung disease requiring lung transplantation. Although lung transplantation can be life-saving, many transplant programs are hesitant to offer lung transplantation to those with autoimmune diseases due to concerns about extra-pulmonary involvement that might affect short- and long-term survival. However, outcomes data in lung transplantation candidates with autoimmune diseases are extremely limited, and even absent for some diseases. The overall objectives of this project are to evaluate mortality rates in adults with autoimmune disease who have undergone lung transplantation in the United States since implementation of the lung allocation score system in 2005, and to identify predictors of poor outcome following lung transplantation in adults with autoimmune diseases. The rationale that underlies this proposed research is that identifying and addressing modifiable risk factors in adults with autoimmune diseases before and after lung transplantation will improve their survival.



Ashira D. Blazer, MD New York University

Arterial Dysfunction Related to IFN in Carriers of APOL1

Systemic lupus erythematosus patients have a 2-3 fold increased risk of cardiovascular events compared to the general population. With higher prevalence of renal disease, cardiovascular disease, and hypertension, African American (AA) SLE patients experience accelerated damage accrual and increased cardiovascular morbidity and mortality. Recent genome wide association studies have identified mutations in the Apolipoprotein L1 (APOL1) gene which associate with non-diabetic renal disease and CVD in homozygous carriers. These risk variants (RV) have high allelic frequencies in individuals of African heritage

as they confer the evolutionary advantageous ability to resist African sleeping sickness. As an innate immune factor, APOL1 expression is highly regulated by inflammatory factors including interferon, TNF, and toll like receptor ligation. Based on preliminary data demonstrating an association between hypertension and RV, including heterozygous carriers, this project leverages a US AA and Ghanaian SLE cohort to address the hypotheses: a) clinical phenotypes associated with APOL1 RV are a consequence of a genetic propensity towards endothelial dysfunction b) APOL1 cytokine-dependent transcription is amplified in SLE resulting in a more penetrant phenotype in heterozygous carriers. In Aim 1, the association between the candidate genotype and clinical/laboratory variables associated with endothelial dysfunction including hypertension, pulse pressure, and biomarkers (vWF, e-selectin, endothelial protein C receptor) will be explored. In Aim 2 it will be determined whethe high IFN alpha signature modifies these associations in patients carrying at least one RV. In Aim 3, in vitro experiments will address APOL1 RV mediated functional consequences to the endothelium. The long-standing history of poorer outcomes in AA SLE patients emphasizes the importance of risk stratification in this group.



Pravitt Gourh, MD National Institutes of Health

Unraveling the Genome of Scleroderma in African-Americans

African-Americans have a higher incidence and prevalence of systemic sclerosis (SSc; scleroderma) than European-Americans. African-Americans develop SSc at an earlier age, with a more severe phenotype, interstitial lung disease and an increased risk for mortality as compared to European-Americans. Family studies and twin studies point towards a significant genetic effect in SSc pathogenesis. Majority of the African-Americans derive their ancestry from Western Africa and Africans have a SSc phenotype that is very similar to African-Americans and different from European-Americans. Thus, the African-American SSc population is an ideal target population to understand SSc pathogenetics. We are utilizing this fact and adopting a comprehensive approach of testing common and low frequency/rare variants and applying admixture mapping to identify SSc associated loci. We hypothesize that the higher prevalence and severe phenotype of SSc in African-Americans is due to the genetic variants derived from their African ancestry. We will collect samples under a multicenter consortium, GRASP (Genome Research in African-American Scleroderma Patients) across US and controls will be tested for ANA by indirect immunofluorescence. Whole exome sequencing and genotyping will be performed to identify rare and common variants leading to SSc susceptibility. Identifying genetic loci associated with African-Americans SSc will help identify pathways involved in SSc susceptibility that could potentially be targeted therapeutically.



Shanthini Kasturi, MD Hospital for Special Surgery

Feasibility and Validity of PROMIS in SLE Patients

The accurate measurement of patient reported outcomes (PROs) is a priority for healthcare delivery, research, and policy arenas. PROs, especially health related quality of life, are particularly important in systemic lupus erythematosus (SLE), a heterogeneous disease in which similar constellations of symptoms can have disparate impact across patients. Current PRO instruments do not address several themes relevant to SLE patients, do not allow comparisons between SLE and other diseases, or are difficult to administer at the point of care. Patient Reported Outcomes Measurement Information System (PROMIS), an initiative funded by the National Institute of Health, offers validated item banks and dynamic computer adaptive tests (CATs) to precisely and efficiently measure PROs in a variety of domains. PROMIS is domain rather than disease specific, enabling comparisons across a range of chronic conditions. PROMIS CATs are promising new modalities for assessing patient centered domains in adult SLE patients.

Our work aims to: 1) assess the feasibility of administering PROMIS CATs to SLE outpatients at the point of care and remotely; 2) assess the psychometric properties of PROMIS CATs compared to existing PRO instruments win SLE patients; and 3) assess the relationship between PROMIS CATs and existing SLE disease activity and organ damage measures. We hypothesize that PROMIS CATs will strongly correlate with existing PRO instruments and will offer increased precision and measurement efficiency. Validating PROMIS in SLE patients and demonstrating feasibility of its use in clinical care will promote both patient-centered care and effective clinical research in this population.



Chan Kim, MD Boston University School of Medicine

Biomechanical Disturbances and Hip Osteoarthritis

Hip OA (osteoarthritis) is a significant source of morbidity in the United States, and more than 231,000 total hip replacements are performed each year in the United States. Despite this, not much is known about the etiology, pathophysiology, and risk factors of hip OA. Furthermore, none of the risk factors studied with hip OA is particularly strongly associated. This project will use data from the Multicenter Osteoarthritis Study (MOST) to explore the association between hip OA and biomechanical risk factors. MOST, a multicenter, longitudinal community based study of 3026 subjects, was originally conducted to study knee OA, but long limb films were also acquired which can be used to assess hip OA. Biomechanical risk factors play a more integral role in the development of knee OA than previously recognized. We hypothesize that this is true for hip OA as well. Biomechanics are likely strongly interrelated between the hip and the knee.

The overall goal of this project is to examine the relation of risk factors with biomechanical consequences on the occurrence of hip OA in the MOST cohort. We will examine the association of femoroacetabular impingement and hip OA. We will examine the assocation between radiographic knee OA and hip OA. Leg length inequality has previously been shown to increase the risk of knee OA in the MOST cohort, so we suspect this is true for hip OA as well. We will also determine the association of vibratory sensory deficit and hip OA.



Konstantinos Loupasakis, MD Hospital for Special Surgery

Mechanisms Driving Sustained NF-κB Signaling in RA FLS

Chronic synovial inflammation is a hallmark of Rheumatoid Arthritis (RA). The exact mechanisms leading to perpetuation of synovitis are not known but synovial fibroblasts (FLS) have emerged as important contributors. TNFα-exposed FLS display sustained activation of NF-κB pathway, leading to joint damage via unrestrained production of pro-inflammatory and tissue-degrading mediators. NF-κB pathway is controlled by homeostatic negative feedback loops and transcriptional regulators that effectively terminate its signaling. Sustained response of RA FLS leads us to hypothesize that these cells lack important signaling "brakes" and transcriptional repressors, thereby failing to achieve effective NF-κB signaling termination following exposure to TNFα. Our preliminary studies suggest that A20, an important signaling "brake", may lack a functionally critical phosphorylation, whereas ABIN3, a partner of A20, is not expressed in RA FLS. In addition, a group of pathogenic genes, which are known to be repressed by transcriptional regulator Bcl3, are highly expressed in TNFα-stimulated RA FLS, whereas Bcl3 is not inducible by TNFα in these cells. The specific aims of this project are: 1) to examine how the lack of ABIN3 induction by TNFα affects NF-κB signaling in RA FLS; 2) to investigate the phosphorylation status of A20 and its impact on NF-kB activity in RA FLS, 3) to assess how Bcl3 regulates the expression of pathogenic NF-κB-target genes in TNFαstimulated RA FLS. We will address these questions using primary human FLS from RA or Osteoarthritis patients and monocytes/ macrophages from healthy donors and RA patients. Expression and complex formation by A20 and ABIN3 will be evaluated with qPCR, immunoblotting and co-immunoprecipitation. Bcl3 expression, regulatory complex formation and binding to NF-KB-target pathogenic gene promoters will be assessed by qPCR, immunoblotting, co-immunoprecipitation and chromatin immunoprecipitation. These results will markedly expand our understanding of RA pathogenesis and will set the stage for the development of novel, FLS-targeting therapies.



Jonathan J. Miner, MD, PhD Washington University in Saint Louis School of Medicine

Mechanisms of IRF5-mediated SLE Pathogenesis

We propose to address the mechanism by which Irf5 affects to systemic lupus erythematosus (SLE) pathogenesis using several novel approaches. First, we will study the cell type-specific contributions of Irf5 during SLE pathogenesis using tissue-specific Irf5 knockout mice. We expect that deletion of IRF5 in one or more specific leukocyte subsets will limit cytokine production and/or immune cell activation, resulting in protection from SLE. Understanding cell type-specific effects of IRF5 has implications for patients with IRF5 polymorphisms, since it might suggest ways to individualize future therapies (e.g., B-cell-targeted therapies versus cytokine blockade in patients who over-express IRF5). We also propose to define the role of the IRF5 CGGGG indel risk haplotype using models of SLE and yHV68 infection. We will generate Irf5 CGGGG indel knock-in mice using CRISPR/Cas9 technology, a recently developed, rapid approach for genome editing. This will give us novel mechanistic insight into ways in which this risk polymorphism contributes to SLE pathogenesis.



Grant S. Schulert, MD, PhD Cincinnati Children's Hospital Medical Center

MicroRNA and Abberant Monocyte Polarization in SJIA

Systemic juvenile idiopathic arthritis (SJIA) is an autoinflammatory disease characterized by high fevers, rash, lymphadenopathy, serositis and arthritis. Children with SJIA are at significant risk of developing macrophage activation syndrome (MAS), a potentially life-threatening episode of overwhelming inflammation, characterized by activation and expansion of CD8-positive T cells and hemophagocytic macrophages. In children with SJIA, the predominant effector cells are mononuclear phagocytes; however, these cells appear to have a distinct phenotype from that of healthy children or patients with other subtypes of JIA, and it is highly likely this phenotype contributes to the pathogenesis of SJIA and the risk for MAS. Historically, activated macrophages are divided into general classes of classically or alternatively activated based upon stimuli and their resulting polarization. However, SJIA monocytes exhibit a novel activation phenotype, and we hypothesize that this activation state contributes to disease pathogenesis. MicroRNAs (miRNAs) are small non-coding RNAs that post-transcriptionally regulate gene expression programs, and are an important contributor to the generation of polarized monocyte phenotypes. Growing evidence also suggests that microRNA dysregulation contributes to the pathogenesis of rheumatic diseases. Our preliminary data suggest that monocytes from patients with active SJIA demonstrate profound alternations in miRNA expression as compared to normal control samples, and we hypothesize that these alterations contribute to the activation phenotype of macrophages in children with SJIA.

Data obtained from these studies will significantly advance our understanding of SJIA and the risk for developing MAS, a major cause of morbidity and mortality in pediatric rheumatology. Specifically, our studies address a critical knowledge gap as to the precise phenotype of monocytes in SJIA, and the contribution of microRNA to monocyte polarization. This emerging area has the potential to reshape our understanding of the molecular mechanisms controlling macrophage activation and differentiation. Our long term objective is to enhance the understanding of the cellular mechanisms underlying innate immune dysfunction leading to rheumatic disease in children, and to inform the rational design of novel diagnostics and therapeutic strategies.



Runsheng "Bridget" Wang, MD

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Evolution of Inflammatory Back Pain

Inflammatory back pain (IBP) is a key symptom of spondyloarthritis (SpA) and a component in the classification criteria of ankylosing spondylitis (AS), and axial SpA. It is the most frequent and predominant symptom in the early stage of disease, and has been widely used for diagnostic purposes in clinical practice. Studies of patients with AS suggest that it can take up to 10 years for patients with IBP to develop radiographic sacroiliitis. However, the natural history of patients with IBP has not been well characterized, because representative cohorts of patients who present with IBP have not been followed long-term. Therefore, the specificity of IBP for a future diagnosis of AS or axial SpA is unknown. Although non-radiographic axial SpA was initially proposed as the precursor stage of AS to facilitate an early diagnosis, it is not clear whether all patients develop radiographic sacroiliitis, and if so, over what time frame.

To address these questions, a population-based, prospective, longitudinal study that followed patients with new-onset IBP or non-radiographic axial SpA for 10 to 15 years would be needed; however, it is not feasible given the time, cost and potential for loss of follow-up. So I proposed a retrospective study using data of the Rochester Epidemiology Project (REP). REP is a unique medical records-linkage system established in 1966 that includes detailed medical records of the entire population in Olmsted County, Minnesota. It allows study of a population-based, retrospective cohort of patients followed from symptom onset to final diagnosis.

This study will provide new knowledge of long-term outcomes of patients with incident IBP and of prognostic value of this symptom, particularly its specificity for progression from IBP to SpA and AS. It will assess the specificity of non-radiographic axial SpA criteria for progression into AS. Ultimately, results of this study will help clinicians estimate the risk of developing AS in the future in patients with IBP, ensure correct diagnosis and appropriately utilize health care resources, such as referral to a rheumatologist, MRI of pelvis and/or spine and use of biologics.



Lehn K. Weaver, MD, PhD The Children's Hospital of Philadelphia

Myelopoiesis Drives Sustained TLR9-Mediated Inflammation

Monocytes are myeloid cells important for the initiation of inflammation, and have been implicated in the pathogenesis of chronic rheumatic diseases. Monocytes interact with their environment through the expression of cell surface, endosomal, and cytoplasmic pattern recognition receptors, including Toll-like receptors (TLRs), which are capable of responding to endogenous and exogenous 'danger' signals. Persistent activation of TLRs is an important contributor to the development of chronic inflammation in multiple rheumatic diseases. However, cell-intrinsic mechanisms to control inflammation during chronic TLR stimulation, including TLR tolerance, are thought to restrain inflammatory responses in the face of chronic TLR stimulation. Therefore, the generation of sustained inflammation in TLR-driven rheumatic diseases must bypass cell-intrinsic TLR tolerance mechanisms to perpetuate chronic inflammation. Using a murine model of repeated TLR9 activation, I have shown that repeated



Ming Zhang, PhD Tufts Medical Center

Development of a Fast Knee OA Cartilage Damage Index

Osteoarthritis (OA) is the most common form of arthritis, causing substantial disability in the general population. Cartilage morphometry on MRI may become an acceptable outcome measure for clinical trials among patients with knee OA. However, obtaining accurate and reproducible cartilage data is burdensome. It may take up to 6 hours to measure the medial and lateral compartments of one knee. Furthermore, operators who use cartilage segmentation software often need extensive training. To conduct large clinical trials it will be vital to create an efficient, sensitive and reproducible method to assess cartilage morphometry. In a previous study, I designed and validated a rapid cartilage quantification method, cartilage damage index (CDI) on medial cartilage compartment. The purpose of this study is to expand and validate CDI to detect cartilage damage in the lateral cartilage compartments, and to study the relations between medial and lateral CDI.

There are 3 specific aims: 1) To expand the CDI method to lateral cartilage. 2) To validate the CDI method on the lateral cartilage. 3) To study the difference and relations of medial and lateral cartilage.

The method can be deployed into the Osteoarthritis Initiative (OAI) which includes 4800 participants' 7-years MRI scans. The results can be used to improve our understanding of osteoarthritis, especially in a large cohort.

I have a combination of expertise in computer-aided image analysis and clinical research into osteoarthritis. I developed several methods and software to measure OA biomarkers on MRI, such as bone marrow lesion (BML), bone volume fraction (BVF), effusion, cartilage denudation, cartilage volume, cartilage mean thickness, and cartilage damage index (CDI).

TLR9 stimulation in vivo leads to heightened systemic inflammation rather than tolerance, and discover an accumulation of TLR9-responsive monocytes in peripheral tissues of inflamed mice. Although inflammatory monocytes undergo cell-intrinsic TLR9 tolerance normally, the generation of new TLR responsive inflammatory monocytes is increased during TLR9-mediated inflammation maintaining a continuous stream of TLR responsive cells to perpetuate inflammation in the presence of repeated TLR9 stimulation. Interestingly, inflammation-induced myelopoiesis does not occur in the bone marrow, but rather correlates with an increase in extramedullary myeloid progenitors in peripherally inflamed tissues. As extramedullary myeloid progenitors have been found in patients with rheumatoid arthritis, systemic lupus erythematous, scleroderma, dermatomyositis, and psoriasis, it is intriguing to speculate that extramedullary myelopoiesis may be a critical factor driving systemic inflammatory responses in multiple rheumatic diseases. The results of my research will inform future attempts at rational, targeted therapeutic interventions for pediatric rheumatic diseases, as well as determine fundamental regulatory mechanisms that initiate and perpetuate chronic inflammation and autoimmunity. This is of particular interest in the pediatric population I treat where there may be an early window for intervention to reverse and/or cure rheumatic diseases if we develop a better understanding of early disease pathogenesis.



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

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



Pui Y. Lee, MD, PhD Boston Children's Hospital

Discovering Novel Pathways of Monocyte Development

Monocytes are essential to innate immunity but also propagate the inflammatory response in autoimmune arthritis and other rheumatologic diseases. Understanding the basic biology of monocyte development is therefore central to unraveling disease pathogenesis and, potentially, to identifying new therapeutic targets.

This project exploits a novel system we have developed to identify key steps in monocyte ontogeny. The differentiation of inflammatory monocytes (Ly6C-hi CCR2+) and residential monocytes (Ly6C-low CX3CR1+) from murine bone marrow precursor cells remains an enigmatic process. Using reversible overexpression of the transcription factor Hoxb8, we have generated novel CCR2-RFP/ CX3CR1-GFP dual-reporter cells that remain immortalized at the myeloid precursor stage until induced to differentiate into Ly6C-hi CCR2+ inflammatory monocytes, followed by maturation to Ly6C-lo CX3CR1+ residential monocytes. This system represents the first in vitro recapitulation of monocyte development. Using a chemical inhibitor screen, we identified a novel role of mechanistic target of rapamycin (mTOR) in steady-state monocyte development, but find that mTOR-independent pathways can be engaged under specific conditions. Recognizing that these observations may illuminate both normal and disease-associated monocyte function, we propose two specific aims:

In Aim I, we test the hypothesis that the mTOR complex 1 is essential to steady-state monocyte development, using primary bone marrow myeloid progenitors and animals with inducible deletion of mTOR complex components.

In Aim II, we test the hypothesis that the mTORC1 pathway can be bypassed in vitro and in vivo by inflammatory stimuli including M-CSF, TNF- α , IL-1 and Toll-like receptor signaling, and use a chemical inhibitor screen and CRISPR/ shRNA technology to dissect relevant pathways.

These studies will therefore incorporate in vitro and in vivo approaches to expose novel pathways of monocyte development. We expect to uncover key differences in monocytes develpment in steady-state and inflammatory conditions that will have important implications for the optimal targeting of monocytes in rheumatic diseases.

2015 AWARD RECIPIENTS | PAGE 35

Education and Training Awards

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 RECIPIENTS

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.





Uzma J. Haque, MD Johns Hopkins University

Web-based Rheumatology Curriculum for Medicine Residents

Musculoskeletal (MSK) disorders are a leading cause of pain and disability and account for a guarter of ambulatory clinic visits. Internal Medicine (IM) residents often receive limited and unpredictable exposure to rheumatology during IM training. This deficit is reflected in low selfconfidence in rheumatology reported by IM residents and low rheumatology scores in IM Certificate examination. In clinical practice, this skill and knowledge deficit impacts early disease recognition and referral of rheumatic diseases. This delay can hinder new treatment paradigms, which require prompt diagnosis and treatment and collaboration between primary care providers (PCP) and rheumatologists. We hypothesize that a rheumatology curriculum focusing on competencies in evaluation of common ambulatory MSK disorders, indications for referrals and new treatment paradigms will enhance rheumatology knowledge, cognitive and problem solving skills in IM residents and translate into improved clinical evaluation of common rheumatic disorders.

In our project, we will:

a. develop an interactive web-based rheumatology
curriculum for IM residents to improve knowledge and
skills in evaluation and management of arthritis and
common musculoskeletal disorders.
b. publish this curriculum on a highly utilized educational
website with great national penetration.
c. assess the impact of this curriculum with rigorous
outcome metrics.

Our curriculum will be published on Johns Hopkins Physician Education & Assessment Center (PEAC), an established web-based ambulatory curriculum, currently utilized by nearly 200 IM programs and 11,000 IM residents in the United States. This platform incorporates case-based modules linked to didactics. It also incorporates unique evaluative component which allows rigorous outcome assessment. There are: 1) pre-and post-tests and 2) satisfaction surveys built into the modules evaluating knowledge gained and content clarity. We will use learner feedback and satisfaction surveys to further improve the modules. These outcome metrics and performance data will be used to assess change in rheumatology knowledge with use of rheumatology modules during IM training. We will also track rheumatology scores in In-Training and ABIM examinations. Anticipated outcomes include improved post-test scores, rheumatology scores on IM Boards and scholarly publications on the impact of this curriculum in the field of on-line rheumatology education.



Beth L. Jonas, MD The University of North Carolina at Chapel Hill

An Innovative Pre-Clinical Curriculum for Rheumatology

The goal of this project is to utilize two novel educational methods, Spaced Education and Blended Learning, to develop an innovative curriculum dedicated to the rheumatic diseases at UNC School of Medicine. The undergraduate curriculum is comprised of three phases: The Foundation phase, the Application phase, and the Individualization phase. This curriculum will be delivered during the Foundation Phase.

Online Spaced Education will be used to highlight concepts important to the understanding of rheumatic diseases that are presented within each of the organ blocks during the first 16 months of the preclinical curriculum. Students receive clinically relevant questions via email at selected intervals. Questions are answered online and the learner receives immediate feedback with the correct answer and the rationale. The same questions are sent to the learner using a customized adaptive algorithm to enhance knowledge acquisition and to assure the retention of knowledge over time.

The final block of the Foundation Phase is a new course entitled Multi-Organ Synthesis (MOS), and will emphasize multisystem diseases with a focus on the rheumatic diseases. wThe spaced education intervention will help prepare students for understanding the pathogenesis and treatment of rheumatic diseases that will be emphasized within the new MOS course. Blended learning modules will be developed in selected systemic rheumatic diseases to be presented during this final block of the Foundation Phase. An educational product available for dissemination will include the spaced education questions and rationales and the material developed for the blended learning modules.



PEDIATRIC VISITING PROFESSORSHIP RECIPIENTS

The Pediatric Visiting Professorship provides support for a board-certified professor of pediatric rheumatology to visit an academic institution, ensuring that medical students and residents gain valuable exposure to pediatric rheumatology.

Funding for this award is made possible through an endowment provided by Amgen, Inc.



Timothy Beukelman, MD, MSCE to visit Florida Hospital Medical Center

Megan L. Curran, MD to Marshall University School of Medicine

Thomas B. Graham, MD, MS to University of Tennessee College of Medicine at Chattanooga

Philip J. Hashkes, MD to Miami Children's Hospital

Sandy D. Hong, MD to University of Kansas at Wichita

Rita S. Jerath, MD, ChB to Morehouse School of Medicine

Carol B. Lindsley, MD to University of New Mexico

Jay Mehta, MD to SUNY Downstate Medical center

Lakshmi N. Moorthy, MD to visit Howard University

Barry L. Myones, MD to visit Our Lady of the Lake

Heather A. Van Mater, MD to visit Carilion Clinic- Virginia Tech Carilion SOM

FELLOWSHIP TRAINING AWARD RECIPIENTS

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

Baylor College of Medicine Fellowship Training Award

Cincinnati Children's Hospital Medical Center Fellowship Training Award

Columbia University Fellowship Training Award

Johns Hopkins University Fellowship Training Award

MedStar Washington Hospital Center Fellowship Training Award

University of California, Los Angeles Fellowship Training Award

University of California, San Diego Fellowship Training Award

University of California, San Francisco Fellowship Training Award

University of Mississippi Medical Center Fellowship Training Award

University of Nebraska Medical Center Fellowship Training Award

University of North Carolina at Chapel Hill Fellowship Training Award

University of Pennsylvania Fellowship Training Award

University of Washington

Paula De Merieux Fellowship Training Award Funding for this award is made possible through an endowment from the estate of Paula de Merieux, MD.

Albert Einstein College of Medicine Amgen Fellowship Training Award

Brigham & Women's Hospital Amgen Fellowship Training Award

The Children's Hospital of Philadelphia Amgen Fellowship Training Award

Duke University Amgen Fellowship Training Award

Feinstein Institute for Medical Research Amgen Fellowship Training Award

Indiana University Amgen Fellowship Training Award

Massachusetts General Hospital Amgen Fellowship Training Award

New York University School of Medicine Amgen Fellowship Training Award

Oregon Health & Science University Amgen Fellowship Training Award

Stanford University Amgen Fellowship Training Award

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Tufts Medical Center Amgen Fellowship Training Award

University of Chicago Amgen Fellowship Training Award

University of Michigan Amgen Fellowship Training Award University of Minnesota Amgen Fellowship Training Award

Washington University Amgen Fellowship Training Award

Funding for the Amgen Fellowship Training Awards is made possible through the financial support of Amgen, Inc.



MEMORIAL LECTURESHIPS

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

Edmund L. Dubois, MD, Memorial Lectureship Presented by: Amr H. Sawalha, MD

Oscar S. Gluck, MD, Memorial Lectureship Presented by: Laurie H. Glimcher, MD Paul Klemperer, MD, Memorial Lectureship Presented by: Daniel L. Kastner, MD, PhD

Memorial Lectureship in Honor of Dr. L. Emmerson Ward Presented by: V. Michael Holers, MD

Annual Meeting Awards

Annual Meeting Awards recognize scholarship among aspiring rheumatology professionals and provide them the opportunity to attend the premiere scientific meeting in the field.

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

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



Pui Y. Lee, MD, PhD Boston Children's Hospital



Sian Yik Lim, MD Massachusetts General Hospital

PEDIATRIC RESEARCH AWARD RECIPIENTS

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

Karen James, MD The Children's Hospital of Philadelphia

Hanna Kim, MD National Institute of Arthritis and Musculoskeletal and Skin Disease



MEDICAL AND PEDIATRIC RESIDENT RESEARCH AWARD RECIPIENTS

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

Monique Bethel, MD Georgia Regents University

Catherine Donnelly, MbBchBAO University of Cincinnati

Dewan K. Fahima, DO Monmouth Medical Center

Ryan Jessee, MD Duke University Irene Lazarus, MD Texas Tech University

David Leverenz, MD Vanderbilt University

Elena Myasoedova, MD, PhD Mayo Clinic

STUDENT ACHIEVEMENT AWARD RECIPIENTS

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

Desiree R. Azizoddin, BA, MA Loma Linda University

Samantha A. Chalmers, MS Albert Einstein College of Medicine

Brian W. Coburn, BS University of Nebraska Medical Center

Gautam Edhayan, MSE University of Michigan Arielle W. Fein, BA Columbia University

Mary Louise Fowler, BA Boston University School of Medicine

Jennie A. Hamilton, BS, MS University of Alabama Birmingham

Dennis J. Wu, BS University of California, Davis

STUDENT AND RESIDENT ACR/ARHP ANNUAL MEETING SCHOLARSHIP RECIPIENTS

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

Caleb Anderson, MD Tripler Army Medical Center

Madison Andrews University of Oklahoma Health Sciences Center

Sherridan Bigg, BS Medical University of South Carolina

Ashley Blaske, MD Vanderbilt University Medical Center

Kierstin Bockelman, BS Medical University of South Carolina

Sedrick Bradley University of Mississippi Medical Center

Kaityn Bryant University of Arkansas for Medical Sciences

Kimberly Cooper, BS, BA, DO Our Lady of the Lake Regional Medical Center

John Fritzlen University of Kansas Medical Center

Erin Gaffney, BS Medical University of South Carolina Nathaniel Hayward, MD Banner University Medical Center

Laura Howe, MD Banner University Medical Center

Kelly Jensen Tulane University

Rebin Kader, DO University of Arizona

Manjinder Kaur University of Arizona

Day Lennep University of Mississippi Medical Center

Rufei Lu University of Oklahoma Health Sciences Center

Heather Michalak, BS Medical University of South Carolina

Luke Monteagudo, MD Tripler Army Medical Center

Amanda Moyer University of Oklahoma College of Medicine Sun Jung Oh Georgia Regents University

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Arshiya Rana, MD University of Nevada

Amanda Schnell, MD University of Kansas

Travis Sizemore, BDO, MPH University South Carolina

Ellen Snyder, MD, MS Tulane University School of Medicine

Douglas VonHerzen, MD Roger Williams Medical Center

Sarah Yale, MD Medical University of South Carolina

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.

EPHRAIM P. ENGLEMAN ENDOWED RESIDENT RESEARCH PRECEPTORSHIP RECIPIENT

The Ephraim P. Engleman Endowed Resident Research Preceptorship encourages residents to consider a career in rheumatology research by supporting a full-time, in-depth research experience with an established rheumatology professional. *Funding for this award is made possible through an endowment from Dr. Ephraim P. Engleman.*



Monica Crespo-Bosque, MD

Preceptor: Tuhina Neogi, MD, PhD Boston University School of Medicine



RESIDENT RESEARCH PRECEPTORSHIP RECIPIENTS

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



Margaret H. Chang, MD, PhD

Preceptor: Peter A. Nigrovic, MD Boston Children's Hospital Denver



Ali Duarte Garcia, MD

Preceptor: John Wong, MD Tufts Medical Center



Alicia M. Hinze, MD

Preceptor: John P. Atkinson, MD, PhD Washington University School of Medicine



Brian Le, MD

Preceptor: Laura Carbone, MD Georgia Regents University



Scott Matson, MD

Preceptor: Kevin Deane, MD, PhD University of Colorado Denver



Nicole Yang, MD

Preceptor: Anthony Reginato, PhD, MD The Warren Alpert Medical School at Brown University

MEDICAL AND GRADUATE STUDENT PRECEPTORSHIP RECIPIENTS

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.

Kelly Jensen, BA Preceptor: Lesley Ann Saketkoo, MD, MPH Tulane University

Amit Lakhanpal, PhD Preceptor: Ernest Brahn, MD University of California, Los Angeles

Minhui Liu Preceptor: Basia Belza, PhD University of Washington

Ashley A. Peterson, BS Preceptor: Alfred Kim, MD, PhD Washington University School of Medicine Tiffany Phanhdone, BS Preceptor: John Varga, MD Northwestern Feinberg School of Medicine

Melanie H. Smith, PhD Preceptor: Lindsey A. Criswell, MD, MPH, DSc University of California San Francisco

Giancarlo Valiente Preceptor: Wael Jarjour, MD The Ohio State University Wexner Medical Center

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

MEDICAL STUDENT CLINICAL PRECEPTORSHIP RECIPIENTS

The Medical Student Clinical Preceptorship introduces students to the specialty of rheumatology by supporting a full-time clinical experience.

Stephanie Fong, BS Preceptor: Jay Persselin, MD VA West Los Angeles Healthcare Center

Melissa Rafferty, BSN Preceptor: Bonita S. Libman, MD University of Vermont

Michael Skelton, BS Preceptor: Laura Carbone, MD Georgia Regents University Megan B. Sanborn Preceptor: Diane Kamen, MD, MSCR Medical University of South Carolina

John U. Wright, BS Preceptor: Natasha M. Ruth, MD, MS Medical University of South Carolina

MEDICAL STUDENT RESEARCH PRECEPTORSHIP RECIPIENTS

The Medical Student Research Preceptorship introduces students to the specialty of rheumatology by supporting a full-time research experience.

Rachel Carlson, BS Preceptor: Ralph Budd, MD The University of Vermont College of Medicine

Laura Easton, BS Preceptor: James N. Jarvis, MD University at Buffalo

Linh Ho Preceptor: Kristen Demoruelle, MD University of Colorado School of Medicine

Susanna K. Jeurling, BS Preceptor: Michael Pillinger, MD NYU School of Medicine

Deepa Patel Preceptor: Neal Roberts, MD University of Louisville Christopher Rice, BS Preceptor: Laura Carbone, MD Georgia Regents University

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

Janice Tiao Preceptor: Victoria Werth University of Pennsylvania School of Medicine

Thanh Tran Preceptor: Susan Boackle University of Colorado School of Medicine

Surabhi Vinod, BS Preceptor: Stanley Bridges, MD University of Alabama at Birmingham

HEALTH PROFESSIONAL RESEARCH PRECEPTORSHIP RECIPIENTS

The Health Professional Research Preceptorship introduces students to rheumatology-related health care by supporting full-time research by a graduate student in the broad area of rheumatic disease.

Solomon Agere, M.Sc. Preceptor: Salahuddin Ahmed, M.Sc., PhD Washington State University

Brian Fissel Preceptor: Antonis Aliprantis Brigham and Women's Hospital

Milena Gianfrancisco Preceptor: Lindsey Criswell, MD, MPH The Regents of the University of California, San Francisco

Calliope Holingue Preceptor: Lindsey Criswell, MD, MPH The Regents of the University of California, San Francisco Allison Kosir, BS, DTP Preceptor: Jennifer Stevens Lapsley, BA, MPT, PhD University of Colorado Denver

Brian Loyd Preceptor: Jennifer Stevens Lapsley, BA, MPT, PhD University of Colorado Denver

Alyssa N. Van Denburg, B.A. Preceptor: Francis J. Keefe PhD Duke University

Alexandra Wink Preceptor: Kevin Gross, MPT, MSc, ScD Boston University School of Medicine

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Rheumatology Research Foundation

Advancing Treatment | Finding Cures

Rheumatology Research Foundation 2200 Lake Boulevard NE Atlanta, GA 30319 Phone: 404.365.1371 Fax: 404.633.1870 E-mail: Foundation@rheumatology.org www.rheumresearch.org