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DIVISION OF RHEUMATOLOGY AND CLINICAL IMMUNOLOGY

Inside This Edition

Rheumatic Disease, Pregnancy, and Family Planning

Rheumatic diseases may have profound effects on women of childbearing age, the consequences of which extend to issues of family planning, fertility and conception, and health during pregnancy and the postpartum period, and even the decision to become or not become pregnant and how best to achieve those goals.

"We need to develop a framework that clarifies what the roles and responsibilities of rheumatologists are in relation to family planning."

Mehret Birru Talabi, MD, PhD

Systemic lupus erythematosus, Sjögren's syndrome, and other rheumatic conditions may increase the risk of pregnancy complications. For women with these conditions, pregnancy itself and the physiological and hormonal changes that occur during pregnancy can accelerate disease activity and symptoms. Some women with rheumatic diseases may experience high-risk pregnancies and complications such as preeclampsia, fetal loss, and others. Further complicating the picture for pregnant women are the toxicities and side effects of some of the medications used to treat their underlying rheumatic condition. Several of these medications may have consequences with regard to fertility and the ability to safely conceive and carry a child to full-term birth, as first line treatments such as methotrexate carry teratogenic risk.

These aspects of family planning and pregnancy for women with rheumatic conditions are the focus of research for **Mehret Birru Talabi, MD, PhD**, one of the newest faculty members in the UPMC Division of Rheumatology and Clinical Immunology. "My research in the area of family planning and pregnancy for women with rheumatic disease focuses on the creation of a family planning framework in rheumatology that can guide the care and treatment of these patients," says Dr. Birru Talabi.

The Need for a Cohesive Care Framework

The current lack of a good framework for these patients is the product of many historical factors. In the past, some of these patients simply did not live long enough for pregnancy to be an option. The medications and treatments that are now in use and have greatly improved the health, quality of life, and lifespan for many patients did not exist. In prior decades, the prevailing approach was to simply advise patients, for their own health, to never become pregnant.

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Today, because of the advances in treating many autoimmune diseases, the landscape is much more complex for these patients, and part of the reason Dr. Birru Talabi is advocating for a more coherent and coordinated approach, not only to patient care, but to education and counseling, and the training that rheumatologists receive in relation to family planning discussions. "We need to develop a framework that clarifies what the roles and responsibilities of rheumatologists are in relation to family planning. Many patients will have successful pregnancies, and we must communicate that positive news. We also need to develop ways to educate patients about the risks and possible complications of pregnancy — short- and long-term. Understanding what pharmacological agents are safe to give patients who do want to become pregnant is critical. So, too, is determining what medications are safe to use to keep the disease controlled during pregnancy. While most contraceptive methods are safe to use among women with rheumatic diseases, estrogen-containing methods may exacerbate disease activity among certain patients with antiphospholipid antibody syndrome and/or systemic lupus erythematosus. It's incumbent upon us to know how to prescribe safe contraception to women with these diseases, or to communicate with the patient's providers who are doing the prescribing, especially if we note that a patient is on a contraceptive method that could worsen her disease activity."

Patient Education Is Critical

Dr. Birru Talabi insists that rheumatologists must take an active approach to patient education as many patients may lack knowledge about aspects of their disease in relation to pregnancy and family planning. "We cannot assume that our patients really understand that if they are on a potentially teratogenic medication they need to be on contraception, or if they don't want to be on contraception perhaps we need to rethink what medications they are taking. We also cannot assume that a patient's other providers are guiding them through their family planning decisions. Some providers may not be comfortable giving counseling because of the complex nature of these patients. Many primary care providers or gynecologists simply are not trained in rheumatology. They are rightly concerned about harming the patient, so some may expect the rheumatologist to fully manage these aspects of the patient's care, even when we as rheumatologists feel that some of these issues may best handled by primary care and obstetrics-gynecology. Some patients are unclear about which provider is responsible for managing their family planning care and counseling, and these patients may be especially vulnerable to not receiving the reproductive health care that they need."

Education and planning make for better outcomes for those individuals who decide to pursue a pregnancy. While the current literature is limited, it suggests that women with autoimmune diseases who plan their pregnancies tend to have better outcomes. They have better outcomes from a pregnancy perspective and a fetal perspective. "Almost 50 percent of all pregnancies in this country are unplanned. Among our patients, we want to avoid a surprise pregnancy, if possible, so we first can make sure their diseases are well-controlled and they're on safe medications. So, we have to educate patients about the importance of pregnancy planning, why and how it is relevant, not only to their disease but also to their health and that of their baby. If patients can work with their rheumatologist and other providers to get their disease quiescent, and stable on safe medications for several months prior to pregnancy, we believe that their outcomes are going to be better than if their disease is active and they are using potentially teratogenic drugs. Unless explicitly counseled, a patient may not know that pregnancy planning may be important to help them to achieve the reproductive outcomes that they want," explains Dr. Birru Talabi.

Filling in the Gaps in Knowledge: Patients and Providers

In order to devise ways to best counsel women with autoimmune diseases about their reproductive health, one has to first understand what the patient understands. This is one aspect of Dr. Birru Talabi's current research. She is trying to ascertain from a cohort of 150 current patients with autoimmune conditions what knowledge they have about family planning issues surrounding their condition. This research seeks to understand their level of knowledge about how their disease may impact fertility, whether or not there is a genetic predisposition to pass along their condition to any children they may have, what they should do if they become pregnant, what they understand about fertility and preconception planning, and other aspects.

Dr. Birru Talabi also is interviewing rheumatologists across the United States about their attitudes and behaviors regarding family planning to tease out what barriers may exist to these patient conversations and what gaps exist in their knowledge base. "I'm interested in understanding from my fellow rheumatologists how they are conducting or providing advice for family planning. What content areas are included in those conversations? What do providers want their patients to know, and what are they concerned about when it comes to caring for these women? I want to understand where they are getting the information they use in these conversations, so we can figure out what resources rheumatologists find are most helpful. Or, are there resources they wish they had? Again, where I am right now is trying to understand what it will take to build a framework for the care of these patients in relation to their family planning goals. We know it's important, we know we have to do it, but how and what is needed to construct this framework is the question I'm trying to answer."

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IL-17 Cytokine Signaling and Biology in Autoimmunity

Inflammatory mediators called cytokines are responsible for coordinating the inflammatory events that prevent infections. However, when dysregulated, they can trigger bystander inflammation that is a major contributor to autoimmune diseases. Many successful drugs used to treat auto-immunity act by reducing the activity of such cytokines.

"In fact, when IL-17 was first discovered and sequenced, it was not immediately apparent that it was a cytokine because of its structure."

Sarah L. Gaffen, PhD

The discovery of the cytokine IL-17 and its corresponding receptors as a unique family of inflammatory cytokines in the 1990s opened up many exciting avenues of research for investigators examining the scientific basis of autoimmune diseases. **Sarah L. Gaffen, PhD**, professor of Rheumatology and holder of the Gerald P. Rodnan Endowed Chair, has made a career of studying IL-17 and its signaling mechanisms, using molecular and biochemical approaches as well as mouse models of IL-17-dependent diseases. Her laboratory's long-term objective is to better define the role of IL-17-mediated signals in driving immune responses and disease pathogenesis. Understanding these molecular processes is expected to provide the foundation for targeted intervention for clinical benefit.

Dr. Gaffen and her lab were one of the first groups to take on the challenge of dissecting the biology of IL-17, starting in 1999 when she established her independent laboratory. "In fact, when IL-17 was first discovered and sequenced, it was not immediately apparent that it was a cytokine because of its unusual structure. It did not look like other cytokines, such as IL-6 or tumor necrosis factor (TNF). I became interested in IL-17 because of these differences and the possible implications for autoimmune diseases," says Dr. Gaffen. "I proceeded with the assumption — or at least the hope — that elucidating IL-17-driven molecular events would not only help us determine how the immune system operates but also enable us to find better ways to intervene."

Accordingly, the persistent theme in Dr. Gaffen's research is answering the following questions: What does IL-17 do in the immune system, for good or for bad? What are the molecular pathways that the IL-17 receptor activates? How do different cell types interpret the presence of IL-17 in different circumstances? Clinically, all of this is important because IL-17 pathways could potentially be altered or harnessed to suppress destructive hyper-active signals leading to inflammation and autoimmunity.

Indeed, in 2016, drugs to block IL-17 were approved for treatment of psoriasis and psoriatic arthritis, and are under evaluation for other autoimmune conditions as well. "Of course, IL-17 did not *evolve* to give us autoimmune disease," points out Dr. Gaffen. "Any time you use drugs to suppress part of the normal immune system, you run the risk of infection. It is only recently that we've come to appreciate that IL-17's main function appears to be to control certain kinds of fungal infections."

2017 NIH MERIT Award Recipient

Oral thrush is an opportunistic infection caused by a fungal member of the commensal microbiota called *Candida albicans.* Oral thrush is a common infection associated with HIV infection, where T cells are depleted to dangerously low levels. IL-17 is primarily manufactured by T cells, specifically "type 17 T helper" (Th17) cells. Dr. Gaffen's lab was the first to show a connection between IL-17 and oral thrush. Her student Dr. Heather Conti (now an assistant professor at the University of Toledo) infected mice genetically engineered mice to lack the IL-17 receptor and found them very susceptible to infection with *Candida albicans;* in other words, the mouse equivalent of human oral thrush. Humans were later discovered with chronic oral thrush not due to HIV; some of these individuals carried mutations in the IL-17 receptor, demonstrating that the immune events discovered by Dr. Gaffen's group in mice accurately mirrored human disease.

A key conundrum, however, remained. Most humans never develop oral thrush, so what is the fungal trigger that causes the immune system to produce IL-17 in order to prevent oral thrush from developing? One reason that *Candida albicans* is able to establish opportunistic infections is its ability to convert from a single cell yeast form to a multi-cellular filamentous "hyphal" state. Only hyphae are able to penetrate the surface epithelial cells of the mouth.

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Lupus Research: TLR Signaling Pathways and Their Role in Disease Expression

New systemic lupus animal model research by **Jeremy Tilstra, MD, PhD**, in the laboratory of Mark Shlomchik, MD, PhD, UPMC endowed professor and chair of the Department of Immunology, is working to better understand the pathogenesis of lupus and lupus nephritis and the roles of Toll-like receptor (TLR) signaling, specifically the TLR9 and TLR7 pathways, on the disease.

"The focus of my research going forward is how toll-like receptor signaling is implicated in lupus."

Jeremy Tilstra, MD, PhD

Dr. Tilstra completed both his MD and PhD training at the University of Pittsburgh, followed by a clinical fellowship in Rheumatology that he completed in 2016 before subsequently joining the Division as assistant professor. "I've always had an interest in autoimmune and inflammatory diseases, and actually started out my research investigating inflammatory signaling pathways and macrophage signaling in inflammatory bowel disease in the lab of Scott Tabe. As my clinical training progressed in medical school and residency, I began to gravitate toward rheumatology, the pathogenesis questions with many of the rheumatic conditions, and specifically with lupus," says Dr. Tilstra.

As the timing would have it, Dr. Tilstra's interests and work on the rheumatology and lupus front, and his fellowship in rheumatology, coincided with the arrival of Dr. Shlomchik at the University of Pittsburgh, and he began to work in Dr. Shlomchick's lab. "Having a scientist of the caliber of Dr. Shlomchik become my mentor in studying a disease that he also had an interest in made it an easy choice to continue my research into lupus."

TLR Signaling in Lupus Murine Models

One of the major features of lupus is the formation of autoantibodies that work against cell proteins. The vast majority of these antibodies can work against either DNA or RNA. "Work that had been done far prior to when I started in Dr. Shlomchik's lab showed that the antibodies were mediated by toll-like receptors. Interestingly, in our lupus murine model, TLR7 recognizes single-stranded RNA and is actually responsible for the anti-RNA antibodies. Conversely, TLR9 is responsible for double-stranded DNA anti-DNA antibodies."

TLRs are implicated as a central factor in the pathogenesis of lupus. In prior years and experiments in the field, it appeared that both TLR9 and TLR7 signaling pathways behaved in a similar manner when looked at through in vitro cell cultures. However, murine models showed completely dichotomous results. Murine lupus models deficient in TLR9 manifested a much worse disease indicating a mediating effect of TLR7. Conversely, "When TLR7 is knocked out in the model, we saw a slight improvement in disease. However, when both TLR9 and TLR7 are knocked out, the mouse models became much better in terms of their disease. The complex interaction between TLR7 and TLR9 was unexpected and not seen before in previous models of the disease," says Dr. Tilstra.

Dr. Tilstra explains that they have several hypotheses for why there is a beneficial effect when both TLR9 and TLR7 are knocked out in the animal model. One hypothesis is that the signaling pathways act in different cell types, or that there may be cell-specific effects. This led Dr. Tilstra to explore how TLR9 functions in different cell types. In order to test this approach, Dr. Tilstra and colleges analyzed cell specific knockouts of TLR9 in several cell types in the lupus murine model. This experiment showed that only in B cells was there a noticeable acceleration of disease.

The research team then conducted a unique experiment with a mouse model that over-expressed TLR9. These mice actually saw an improved disease state, suggesting that a response can be mediated in both ways with TLR9: with it knocked out you see worse disease, and with overexpression you see improved disease.

Using these different genetic models to tease apart how toll-like receptor signaling is implicated in disease, Dr. Tilstra and his colleagues hope to find to what degree cell specificity matters, and the different kinetics of that pathway. Ultimately, we want to know if these pathways are something we can target through one method or another to suppress or reverse aspects of lupus development and progression," says Dr. Tilstra.

Research Into Tissue and Cellular Interactions in Lupus

Another research interest of Dr. Tilstra that is currently in progress seeks to better understand the interaction between the tissue parenchyma and infiltrating cells in lupus murine models. The science related to how cells act in the periphery is becoming better understood. However, there is currently much less knowledge about how cells behave when they enter into tissues. Recently completed research by Dr. Tilstra and his study collaborators has uncovered several novel, and unexpected, findings in this area of research. Their work is currently in submission for publication.

Lupus and the Microbiome

Dr. Tilstra is part of a University of Pittsburgh Department of Medicine-wide project that is collecting prospective tissue samples and data on patients with a variety of conditions and subpopulations of these patients. He currently heads up the lupus registries initiative that is part of this project which is collecting both genetic and microbiome data to be used in disease-state comparisons in an effort to find any associations between the microbiome and various conditions.

"This work is somewhat analogous to my research into how cells act in the tissues that lupus is causing damage and disease in. It's really trying to understand how the body acts in the natural environment, and what these upper level associations may be between the billions of bacterial cells in, on, and around us." Other members of the Division of Rheumatology and Clinical Immunology are contributing to the broader project with other diseases, including rheumatoid arthritis, myositis, and scleroderma.

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IL-17 Cytokine Signaling and Biology in Autoimmunity *Continued from Page 3*

Candidalysin is a peptide toxin secreted by *Candida albicans* only in its hyphal state, and was discovered in 2016 by Drs. Julian Naglik of King's College London and Bernhard Hube of Friedrich Schiller University Jena in Germany. Dr. Gaffen spent her sabbatical in Dr. Naglik's lab in London in order to define this connection. Dr. Gaffen and some of her Pittsburgh team, led by postdoctoral fellow Dr. Akash Verma, showed that the Candidalysin toxin played an essential role in stimulating IL-17 production during the initial immune response, and therefore served as the missing *Candida*-derived IL-17 trigger. Additional experiments showed that IL-17 and Candidalysin behave in a synergistic manner to further amplify antifungal signals in the oral cavity. These studies thus revealed some of the essential circuitry that maintains *Candida albicans* as a commensal organism in the mouth even in the face of a normal immune system.

In 2017, Dr. Gaffen and Dr. Naglik received a prestigious NIH "MERIT" (Method to Extend Research In Time) Award for their research into the IL-17 signaling pathway and its relationship with oral candidiasis. Dr. Gaffen is one of only a handful of researchers at the University of Pittsburgh to have received a MERIT Award from the NIH, and one of only six people to have received one from NIDCR. Dr. Gaffen and her group are continuing their research into how *Candida albicans* interacts with the immune system. The long-term goal of Dr. Gaffen's MERIT award is to understand how Candidalysin generates the IL-17 signaling response in oral immunity from a biochemical and molecular standpoint.

Current Grant Support

Dr. Gaffen's research is currently supported by the following NIH-funded grants:

Host and Fungal Regulation of Type 17 Immunity to Oral Candidiasis. Project Number: R37-DE022550. Funding Body: National Institute of Dental and Craniofacial Research. *Principal Investigator: Sarah L. Gaffen.*

Negative Control of IL-17R Signaling: Implications for Fungal Immunity. Project Number: R01-AI107825. Funding Body: National Institute of Allergy and Infectious Diseases. *Principal Investigator: Sarah L. Gaffen.*

IL-17 Isoforms in Organ Specific Autoimmunity. Project Number: R21-AI128991. Funding Body: National Institute of Allergy and Infectious Diseases. *Principal Investigator: Sarah L. Gaffen.*

IL-23/STAT3 Mediated Regulation of Immunity to Oral Candidiasis. Project Number: R01-DE023815. Funding Body: National Institute of Dental and Craniofacial Research. *Principal Investigator: Sarah L. Gaffen.*

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Systemic Sclerosis Research: New Translational Investigations

The consequences of systemic sclerosis (SSc) are severe, mortality is high, and there are no approved treatments for the disease. The pathogenesis of the disease is not fully understood at this time due to the complexity of the condition from an underlying genetic and gene expression perspective, the complex signaling pathways and mechanisms involved in the disease, and the heterogeneity of the disease as manifested in individuals.

"Part of this study, and a novel approach at that, is the derivation of human tissue samples from lung transplant and pulmonary hypertension catheterization procedures."

Robert A. Lafyatis, MD

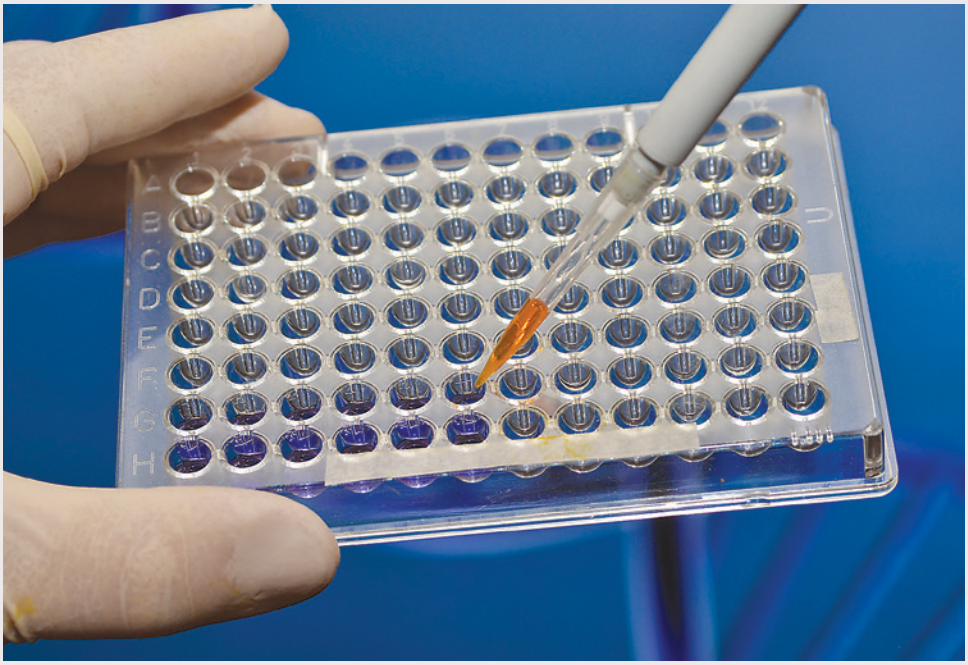
In 2017, **Robert A. Lafyatis, MD**, professor of medicine and director of the UPMC and University of Pittsburgh Scleroderma Center received P50 funding[1] from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) for translational research into the pathogenesis and identification of novel targeting pathways in systemic sclerosis. The current NIH grant is a continuation of the P50 research Dr. Lafyatis has been conducting on systemic sclerosis since 2011, and builds upon many of the findings of his research to date, which includes the discovery of biomarkers associated with skin and interstitial lung disease (ILD) in SSc.

Dr. Lafyatis is an internationally recognized expert and research leader in the field of systemic sclerosis with a focus on the pathogenesis of the disease, as well as the identification of biomarkers associated with aspects of SSc and translational investigations of potential new therapeutic agents. Prior to joining UPMC and the University of Pittsburgh in 2015, Dr. Lafyatis held appointments at Boston University.

The ultimate goal of this continuing research is to translate research findings into potential new therapies for patients with SSc. "There are a number of aspects of this grant that are novel, such as the use of human samples harvested from lung transplant patients and derived from pulmonary hypertension arterial catheterization procedures, and new technology and biochemical approaches," says Dr. Lafyatis.

Research Details and Project Components

Dr. Lafyatis' current grant is a multifocal project consisting of three separate yet related lines of investigation. Multiple departments and laboratories at the



University of Pittsburgh are collaborating on the studies, as are several of Dr. Lafyatis' former colleagues at Boston University.

The first aspect of the project will examine a variety of prognostic biomarkers related to disease pathogenesis and progression or manifestation of skin fibrosis and interstitial lung disease in SSc. Prior work by Dr. Lafyatis has implicated several genes and their expression in mesenchymal cells in the progression of both skin and lung fibrosis. Dr. Lafyatis also is interested in the role of transforming growth factor beta in disease pathogenesis and its effect on regulating myofibroblast differentiation. Using the relatively new technique of single-cell RNA sequencing, Dr. Lafyatis' colleagues will be able to probe the variations between mesenchymal cells in normal skin and that of fibrotic skin in SSc. The research also will examine the effects on myofibroblast differentiation and gene expression regulating the process by selectively blocking or knocking out the suspect genes in disease models or in human tissues.

In the second study, Dr. Lafyatis and colleagues at Boston University are further examining the role that oxidative stress and mitophagy plays in T cells in relation to pulmonary arterial hypertension (PAH) in systemic sclerosis. "Part of this study, and a novel approach at that, is the derivation of human tissue samples of the pulmonary artery from patients undergoing pulmonary arterial catheterization procedures. This approach will allow the researchers to collect these tissues and afford the ability to characterize those cells using the single-cell RNA sequencing technology we are using in other aspects of our research," says Dr. Lafyatis. A second aspect of this research into pulmonary arterial hypertension in SSc will examine the efficacy and effects of a newly approved agent, dimethyl fumarate[2] (which has been used in the past to treat plaque psoriasis and more recently multiple sclerosis) on pulmonary arterial endothelial cells.

The final aspect of the current P50 grant is devoted to better understanding interstitial lung disease in SSc. Collaborating with the University of Pittsburgh Division of Pulmonary, Allergy, and Critical Care Medicine and its chief, Rama K. Mallampalli, MD, Dr. Lafyatis and coinvestigators from the Division are examining the role of ubiquitin ligase (UL) proteins in ILD, an area of investigation for which the Division has significant expertise. UL proteins regulate numerous biochemical processes, and their role in SSc-ILD is now coming to light. Because of the history, size, and expertise of the lung transplant program at the University of Pittsburgh, a unique aspect of this part of the study will be the harvesting of lung tissues from transplant patients who have systemic sclerosis. Using lung explant and ex vivo lung perfusion models, researchers will have access to what would otherwise be extremely difficult tissues to obtain.

"This particular grant is really designed to use human materials and apply a variety of exciting new technologies and biochemical approaches to help us find new therapies for SSc," says Dr. Lafyatis.

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[2] Dimethyl Fumarate in Systemic Sclerosis-Associated Pulmonary Arterial Hypertension. Project Number: 5R21AR069285-02. Funding Body: National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). Principal Investigators: Robert A. Lafyatis and Paul M. Hassoun.

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ABOUT THE DIVISION

The Division of Rheumatology and Clinical Immunology has a tradition of excellence in patient care, education, and research for more than fifty years. Our clinical activities emphasize care of both common and rare rheumatic diseases. We have outpatient clinics devoted to all types of autoimmune diseases and musculoskeletal disorders. Our faculty have a clinical and research interest in rheumatoid arthritis, systemic lupus erythematosus, myositis, vasculitis, and scleroderma.

We are committed to a mission of providing the highest quality care for patients with arthritis and autoimmune diseases, and mentoring and training medical students, residents, fellows, and young faculty. Our research mission is to better understand arthritis, autoimmune, and other connective tissue diseases in order to improve diagnosis and therapies, with the ultimate goal of finding a cure or preventing these disorders. Faculty members are involved in both clinical and laboratory research. Our research programs are centered in the clinical areas noted above and include the disciplines of clinical epidemiology, health services, and laboratory research. Our research includes collaborative efforts with other programs in the University of Pittsburgh School of Medicine and the Graduate School of Public Health.

Remarkable advances in drug discovery, mechanisms of disease, epidemiology, outcome research, and other related fields make a career in academic rheumatology an exciting career opportunity. The University of Pittsburgh and UPMC have a long tradition of multidisciplinary collaboration. The faculty in the Division of Rheumatology, combined with cutting-edge clinical, educational, and patient care resources, provide for ongoing success of rheumatology at the University of Pittsburgh.

To learn more about the UPMC Division of Rheumatology and Clinical Immunology, please visit **UPMCPhysicianResources.com/Rheumatology**.

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