RHEUMATOLOGY RESEARCH
UPDATE

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DIVISION OF RHEUMATOLOGY AND CLINICAL IMMUNOLOGY

Inside This Edition

Kidney-Infiltrating T Cells and Lupus Nephritis

In late-2018, lupus basic science researcher **Jeremy Tilstra, MD, PhD**, published major new findings in the *Journal of Clinical Investigation* on T cell exhaustion in animal models of lupus nephritis. This newly published work, in collaboration with Mark Shlomchik, MD, PhD, Greg M. Delgoffe, PhD, and others, points to the heretofore unknown ability of the kidneys to suppress kidney-infiltrating T cell function through metabolic exhaustion of the cells thus preventing damage.

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 an assistant professor. "I have always had an interest in autoimmune and inflammatory diseases, and started my research investigating inflammatory signaling pathways and macrophage in inflammatory bowel disease in the lab of Scott Plevy. As my clinical training progressed throughout medical school and residency, I began to gravitate toward rheumatology and questions of disease pathogenesis, specifically with lupus," says Dr. Tilstra.

Fighting Back Against Autoimmunity

Dr. Tilstra's current work focuses on how organs, such as the kidney, interact with immune cells. Organs affected by autoimmune disease could be fighting back by "exhausting" immune cells that cause damage using methods similar to those used by cancer cells to escape detection. This is the main, and first-of-its-kind finding uncovered by Dr. Tilstra and colleagues' research.

In murine models of systemic lupus erythematosus (SLE), the findings could account for the delay or extended periods over which autoimmune diseases damage organs in the body such as the kidneys, liver, and heart. Dr. Tilstra's findings may also explain how specific cancer immunotherapy agents can lead to harmful autoimmune side effects.

In lupus nephritis, a large number of kidney-infiltrating T cells (KITs) were thought to be activated, causing damage over time. Wondering how exactly these cells cause kidney damage, Dr. Tilstra began to study them in three different mouse models of lupus nephritis.

As expected, there were millions of KITs in the kidney, but they were not nearly as active as had previously been thought.

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UPMC LIFE CHANGING MEDICINE

Kidney-Infiltrating T Cells and Lupus Nephritis *Continued from Page 1*

"It was the exact opposite. The T cells were there but were sluggish, ineffective killers that did not proliferate well, which was completely unexpected," says Dr. Tilstra.

Experiments showed that these KITs did not respond to stimulation like normal T cells — they neither released characteristic inflammatory proteins, nor did they reproduce very well. The cells also took up and used much less energy, displaying signs of metabolic exhaustion.

Interestingly, the exhausted KITs were quite similar to T cells found inside tumors. The affected kidney cells also resembled tumor cells in certain ways, as they expressed higher levels of a protein called PD-L1, which cancer cells use to suppress T cells that enter the tumor.

"Tissue samples that are affected by autoimmunity have the same kind of protective responses that we thought was limited to possibly cancer or infectious states. T cell exhaustion has been observed in chronic viral infection and cancer, but what we show, for the first time, is that normal tissues, the kidney in this instance, but possibly other tissues also have this suppressive quality. In fact, what the tumor is doing in cancer may be just a maladaptation of a process or function that all tissues maintain to protect themselves from chronic damage," says Dr. Tilstra.

Dr. Tilstra and colleagues' research may be able to tell us if cancer is maladapting this process while also giving us specific targets in autoimmunity.

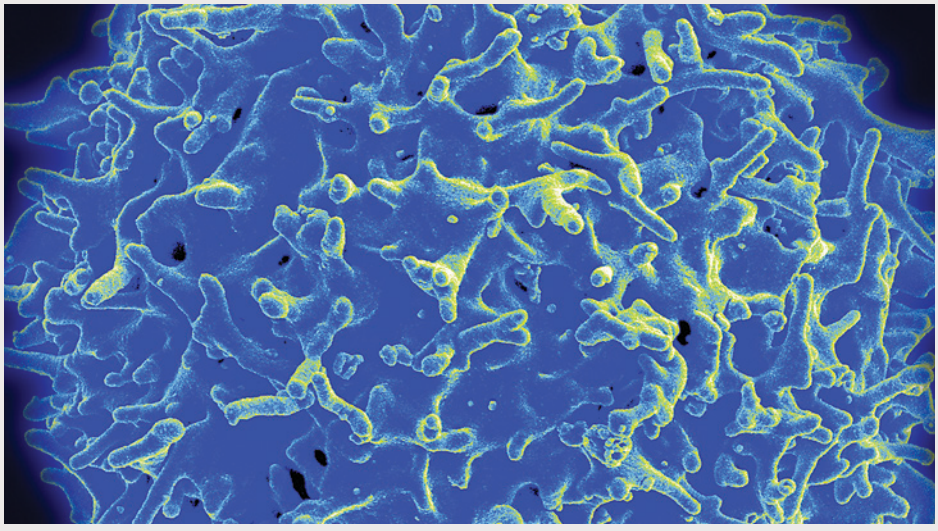
By understanding how this process occurs, the researchers hypothesize that they may be able to either amplify the process or even target those cells that have changed once they enter the kidney leading to a very targeted therapeutic process.

"We know these cells have many surface receptors accumulated during the process that may give us various pathways to target. If we can better understand these cells, which we still think are likely causing some damage to the organ, albeit slowly, this may bring about new targets for therapy," says Dr. Tilstra.

This exact work is part of a new grant Dr. Tilstra secured from the Lupus Research Alliance shortly after the publication of his T cell paper.

New Lupus Research Alliance Grant

In October 2018, Dr. Tilstra was awarded a Novel Research Grant from the Lupus Research Alliance to help continue his novel and potentially ground-breaking studies into T cell exhaustion in the kidneys in cases of lupus and lupus nephritis.



The three-year, $300,000 grants are handed out by the Lupus Research Alliance each year to support novel, promising new research into various aspects of lupus with the goal of accelerating effective treatments or cures for the disease.

"This grant will help expand on the findings we published recently on T cells and lupus nephritis by working to uncover more of how the process occurs and if it is isolated to just the kidney which would allow us to potentially target numerous tissues in the body that are affected by disorders of autoimmunity. Beyond the animal model work, this grant will support some human research aspects related to translatability and either prognostic or therapeutic modalities," says Dr. Tilstra.

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Rheumatoid Arthritis and Osteoporosis in Men: A Hidden Consequence and New Research

While osteoporosis typically affects women, nearly a third of all newly diagnosed cases occur in men, with most diagnoses occurring in individuals over the age of 50. However, individuals with rheumatoid arthritis (RA) are more likely than the general population also to have osteoporosis — both men and women. Furthermore, patients with RA are more likely to develop osteoporosis at an earlier age.

The chronic inflammation of RA, coupled with the side-effects of certain pharmacological therapies, and even lifestyle factors such as poor diet and a lack of weight-bearing exercise, can combine to cause or accelerate the loss of bone density leading to osteoporosis and an increased risk of fractures.

Division of Rheumatology and Clinical Immunology Chief **Larry W. Moreland, MD**, has opened a new line of research in his laboratory to more closely examine the interrelated nature of RA and osteoporosis, specifically in the male population.

In broad terms, Dr. Moreland's research interests are translational for a variety of conditions, including rheumatoid arthritis, vasculitis, lupus, and seronegative spondyloarthropathies, and he has extensive experience in clinical trials and long-term registries for patients with autoimmune diseases. He has extensive collaborations with colleagues at the University of Pittsburgh, as well as with numerous investigators at other academic institutions. In addition to being Division chief, Dr. Moreland is the director of the University of Pittsburgh and UPMC Rheumatoid Arthritis Center and The Vasculitis Center.

This new research investigating RA and osteoporosis in men has the potential to influence clinical practice and help to establish or modify guidelines on screening.

Guidelines for osteoporosis screening in women are established — for the general population and those more at risk due to their RA profile. However, screening recommendations and protocols for men are less well-defined because there has been a lack of research conducted on the subject.

Research Abstract at ACR 2018

In October, 2018, at the American College of Rheumatology Annual Meeting, Dr. Moreland and his study colleagues presented initial findings of their first retrospective analysis in an abstract[1] examining the prevalence of osteoporosis in men with rheumatoid arthritis, the frequency at which these individuals are being screened for osteoporosis, and what risk of future fractures may exist in this cohort.

Dr. Moreland's research identified 1,970 male patients between the ages of 50 and 70 who have RA and were seen in an outpatient clinic during a seven-year period. The research examined a number of clinical findings in the patient charts, but was notably examined for the number of bone-mineral density tests (DEXA scans) and how many of these individuals experienced any fracture.

Within the cohort and time period, Dr. Moreland's research uncovered 488 DEXA scans. Two hundred thirty-one patients were shown to have osteopenia, while 67 had osteoporosis, and 61 percent of the nearly 2,000 individuals in the study showed a decrease in their bone mineral density.

"This preliminary data is pretty clear from our perspective and warrants further research and clinical attention. The findings of osteopenia and osteoporosis in the bone density scans, particularly in those individuals with positive rheumatoid factor and anti-cyclic citrullinated peptide results, point to less than optimal bone density screening in these men. We can effectively treat osteoporosis in these individuals, and cut down on fracture risk, but we must find them first, and that means a change in clinical practice. More research is needed to clarify our preliminary findings, but we are actively pursuing research on this front," says Dr. Moreland.

Future Research

According to Dr. Moreland, additional research is needed to determine how frequent actual generalized bone damage is in men with new onset RA. If bone damage is found to occur with relative frequency, then the current screening guidelines for these patients may need to be modified. In order to make this determination a larger, prospectively collected cohort of data in men with new onset RA will be needed to establish the true frequency and severity of their bone health.

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Welcome Newest Faculty Member: Dana P. Ascherman, MD

Joining the Division of Rheumatology and Clinical Immunology in December 2018 is physician-scientist **Dana P. Ascherman, MD**, professor of medicine.

"Looking at alternative pathways in this model system may suggest new therapeutic strategies in human disease which are more selective and efficacious than present approaches involving global suppression of the immune system."

Dana P. Ascherman, MD

Dr. Ascherman comes to UPMC and the University of Pittsburgh after an eight-year appointment in the Division of Rheumatology at the University of Miami Miller School of Medicine. This is not, however, Dr. Ascherman's first faculty position at the University of Pittsburgh and UPMC. From 1998 to 2010, he was a faculty member in the Division of Rheumatology, and for eight years, served as associate director of the fellowship training program.

Dr. Ascherman has a clinical interest in idiopathic inflammatory myopathy (myositis), as well as the overlap between interstitial lung disease (ILD) and systemic autoimmune disorders such as myositis and rheumatoid arthritis (RA). He has a very active research program with several ongoing investigations, including a recently awarded R01 grant from the National Institutes of Health (NIH) (see below) that focuses on an animal model of autoimmune myopathy.

While Dr. Ascherman is heavily involved in the clinical care of patients with myositis, he also has a number of collaborations with members of the pulmonology community in treating patients who have autoimmune disease-associated ILD (AILD). While at the University of Miami, Dr. Ascherman co-founded and co-directed a multidisciplinary clinic involving pulmonary medicine and rheumatology to care for patients with AILD, an approach that he is actively working to replicate at UPMC.

Research Priorities

Dr. Ascherman's research follows two fundamental lines of investigation. The first is oriented toward basic immunology with the development of disease models to study mechanisms of autoimmunity in inflammatory myopathies. This work has been the basis of several publications over the past decade and has led to his current R01 grant investigating the contribution of innate immunity to the pathogenesis of myositis in an animal model Dr. Ascherman developed in his laboratory.

The second major area of Dr. Ascherman's research is translational, focusing on the connection between interstitial lung disease and other autoimmune conditions, such as rheumatoid arthritis. Much of Dr. Ascherman's translational research deals with biomarkers of rheumatoid arthritis-associated interstitial lung disease (RA-ILD). These studies include proteomic analyses investigating inflammatory cytokines and remodeling proteins associated with both RA and ILD.

Biomarker Research: Recent Findings and Investigations

Much of Dr. Ascherman's biomarker research in recent years has focused on the discovery of antibodies targeting post-translationally modified proteins (including those proteins undergoing citrullination). As Dr. Ascherman explains, it is known that rheumatoid arthritis is characterized by B cells targeting a range of citrullinated proteins. To harness this unique characteristic of RA, Dr. Ascherman has therefore developed a method that he refers to as reverse immunophenotyping, a technique that can generate a "fingerprint" of proteins targeted by citrullination and other post-translational modifications in relatively inaccessible tissues, such as the lung.

"Since it is difficult to obtain lung biopsy specimens to look directly for proteins that have been modified by citrullination, we are taking advantage of unique autoantibody responses in rheumatoid arthritis to track those changes and link them to interstitial lung disease," says Dr. Ascherman.

Essentially, reverse immunophenotyping compares the autoantibody profiles of RA patients with and without lung disease to detect autoantibody/autoantigen combinations uniquely associated with RA-ILD. Using this approach, Dr. Ascherman and his laboratory have identified citrullinated Heat Shock Protein 90 (citHSP90) as a candidate autoantigen that can distinguish RA-ILD patients from those with RA alone.

"Ultimately what we want to do is examine tissues in selective patients to see if those proteins are present and are specifically altered or modified by the citrullination process. The broader application of this approach examines the overlap in proteomic and serologic biomarkers that we define for RA-ILD and other conditions like idiopathic pulmonary fibrosis, which, at least clinically and epidemiologically, overlaps with RA-ILD," says Dr. Ascherman.

Modeling Myositis

Beyond these translational biomarker studies, Dr. Ascherman and his laboratory have developed two animal models of myositis over the last decade. The first model is a conventional antigen/adjuvant-induced model that is based on immunization with the known autoantigen histidyl-tRNA synthetase (HRS), also referred to as Jo-1. Because mice immunized with the combination of HRS and adjuvant develop lung as well as muscle inflammation, this model replicates several cardinal features of the anti-synthetase syndrome in humans.

Despite these observations highlighting the importance of "adaptive" immune responses targeting HRS, Dr. Ascherman has looked to develop alternative model systems. As Dr. Ascherman states, "Traditionally, in myositis, as well as other diseases like lupus and rheumatoid arthritis, we tend to focus on adaptive immunity. About 10 years ago, some interesting data emerged from other labs looking at nonconventional properties of HRS, one of which is that it can act as a so-called chemokine capable of recruiting lymphocytes or immature dendritic cells into tissues where it is aberrantly expressed. We then began to think about less conventional contributions of HRS to disease pathogenesis, including initiation of innate immune signaling pathways."

To refine this system and look more directly at the immune-activating properties of HRS, Dr. Ascherman therefore developed a second model involving direct intramuscular immunization of mice with recombinant HRS in the absence of traditional adjuvants.

This approach yields a very robust phenotype of muscle inflammation in multiple, genetically disparate strains of mice. Importantly, because the myositis phenotype can be replicated even in mice with a transgenic T cell receptor (TCR) that is specific for ovalbumin, these studies suggest that HRS can trigger innate immune signaling pathways that are not dependent on TCR recognition of HRS itself. Examination of various "knockout" strains lacking critical components of innate immune signaling pathways have subsequently highlighted the ability of recombinant HRS to activate multiple Toll-like receptors (TLRs), particularly TLR2 and TLR4.

Current Project Highlights: Examining MyD88 Pathways

After defining the significant role of Toll-like receptors, Dr. Ascherman's laboratory began to think about the role of MyD88, a signaling intermediate that functions downstream of a number of different Toll-like receptors.

"When we look at knockout mice lacking MyD88, they do not get myositis. Whatever upstream receptor of the innate immune system is involved, there is an absolute requirement for MyD88 signaling, which normally results in nuclear translocation/activation of NF-κB and triggering of pro-inflammatory cascades," says Dr. Ascherman.

Intriguingly, although knocking out MyD88 eliminates myositis in this model system, other markers of the adaptive immune response such as autoantibodies against HRS are left largely intact.

"This is another key piece of evidence showing the importance of the innate immune response in myositis," says Dr. Ascherman.

Overall, the goals of this NIH-funded project are not only to define the operative mechanisms in HRS-induced myositis, but also to assess the therapeutic impact of inhibiting relevant innate immune pathways through the use of MyD88 or NF-κB inhibitors — a novel approach that is not currently used in the treatment of human disease.

As Dr. Ascherman concludes, "Looking at alternative pathways in this model system may suggest new therapeutic strategies in human disease which are more selective and efficacious than present approaches involving global suppression of the immune system."

"We are pleased to have Dr. Ascherman rejoin the Division to continue his exciting and novel research in autoimmune diseases," says Division Chief, Larry Moreland, MD.

Further Reading

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New Director of Pediatric Rheumatology to Join UPMC Children's Hospital of Pittsburgh

Amr Sawalha, MD, has been appointed director of the Division of Pediatric Rheumatology at UPMC Children's. Dr. Sawalha will join UPMC in April after having served as professor of medicine and the Marvin and Betty Danto Research Professor of Connective Tissue Research at the University of Michigan.

At UPMC Children's, Dr. Sawalha will establish and lead a new Autoimmune Genomics Research Center. In addition, Dr. Sawalha has been appointed director of the comprehensive Lupus Center of Excellence that spans the clinical and research enterprises of UPMC and the University of Pittsburgh.

Dr. Sawalha is recognized internationally for his work in the genetics and epigenetics of complex autoimmune and inflammatory diseases. He earned his medical degree from Jordan University of Science and Technology and completed his internship and residency training in internal medicine at the University of Oklahoma Health Sciences Center, followed by fellowship training in rheumatology at the University of Michigan.

Dr. Sawalha's research focuses on elucidating genetic and epigenetic contributions to the pathogenesis of systemic autoimmune and inflammatory diseases. His research applies state-of-the-art genomic, epigenomic, and bioinformatics methodologies, and subsequent functional studies using in vitro and in vivo systems to identify and characterize genetic loci and pathways involved in the pathogenesis of immune-mediated diseases. Using clinical phenotyping and extensive national and international collaborations, Dr. Sawalha seeks to discover genomic and epigenomic markers of disease progression, specific organ involvement, and responses to therapies.

Dr. Sawalha has published more than 130 manuscripts, book chapters, and review articles and is on the editorial board of several journals. He has served in numerous key roles in the American College of Rheumatology (ACR) and other organizations. Dr. Sawalha is a member of the Medical-Scientific Advisory Council of the Lupus Foundation of America and the Vasculitis Foundation Medical and Scientific Advisory Board. Dr. Sawalha has received numerous awards, including the Edmund L. Dubois, MD Memorial Lectureship Award from the ACR in recognition of his work on lupus, and he is an elected member of the American Society for Clinical Investigation.

UPMC Physician Resources

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Presented by Terence W. Starz, MD

Dr. Starz gives a presentation on the mechanisms of inflammation on rheumatic diseases, such as initiation, stopping, and persistence.

Rheumatoid Arthritis: From the Clinic Back to the Bench

Presented by Larry W. Moreland, MD

Dr. Moreland speaks on rheumatoid arthritis, a systemic immune-mediated inflammatory disease, and recent major breakthroughs in targeted immunotherapies.

A Year in Review: Rheumatology

Presented by Ghaith Noaiseh, MD

Dr. Noaiseh presents on new trends and predictors of disease progression. His lecture includes a discussion of MRI and ultrasound for predicting synovitis, outcomes from several high-impact randomized trials, and recently approved biosimilars to manage rheumatoid arthritis.

Sjögren's Syndrome: Key Concepts for Internists

Presented by Ghaith Noaiseh, MD

Dr. Noaiseh discusses this complex syndrome, its complications, and the clinical spectrum on which it presents.

Spondyloarthropathies

Presented by Thaddeus Osial, MD

Dr. Osial presents on spondyloarthropathies and reviews the history, spectrum of diseases, distinguishing characteristics, pathogenesis, and treatment. This course teaches the varied manifestations as they relate to peripheral arthritis and inflammatory back disease, which extra-articular findings are associated with the spondyloarthropathies, and symptomatology.

Polymyalgia Rheumatica and Giant Cell Arteritis: From Etymology to a Clinical Understanding

Presented by Terence W. Starz, MD

Dr. Starz reviews the clinical manifestations, approach to diagnosis, pathophysiology, and management of polymyalgia rheumatica and giant cell arteritis.

News From the Division

Selected Recent Publications

Moghadam-Kia S, Oddis CV, Aggarwal R. Anti-MDA5 Antibody Spectrum in Western World. *Curr Rheumatol Rep.* 2018 Oct 31; 20(12): 78.

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Recent Grants, Awards, and Faculty Updates

Sarah L. Gaffen, PhD, and **Partha Biswas, BVSc, MVSc, PhD**, received NIH funding in the form of an R21 grant along with funding from the Rheumatology Research Foundation for a study on the mechanisms of IL-17 signaling in autoimmune damage of the kidney.

Partha Biswas, BVSc, MVSc, PhD, was elected to the Council of International Cytokine and Interferon Society, and he was named Deputy Editor at the *Journal of Immunology.*

Rohit Aggarwal, MD, MS, received an NIH/NIAMS R01 grant to support new myositis patient-centered tele-research designed to demonstrate that a patient-centered, observational cohort using smart technology and tele-research is an efficient way of conducting clinical studies in myositis. The grant also will validate novel outcome measures including a PRO (PROMIS-PF) and PAM in myositis.

- Dr. Aggarwal also received the 2018 Institute for Clinical Research Education Distinguished Mentor Award.

Mehret Birru Talabi, MD, PhD, was named one of 10 Distinguished Fellows by the American College of Rheumatology in 2017 for her focus on women's health in rheumatic diseases.

Robyn Domsic, MD, MPH, is a co-investigator on a new award examining how autoantibodies define scleroderma subgroups with distinct relationships to cancer.

Patrizia Fuschiotti, PhD, is studying the T cell-mediated immune responses in SSc skin disease, as well as the molecular mechanisms underlying IL-13 over-production by specific skin-resident T cell subsets in SSc patients with active disease. This research has led to a publication in 2018 (Cascio et al.)

Robert Lafyatis, MD, is leading an R21-funded clinical trial investigating the efficacy of dimethyl fumarate (Tecfidera) in systemic sclerosis-associated pulmonary arterial hypertension.

Kimberly P. Liang, MD, is continuing as a co-investigator on an R01 award to Dr. Shanmugam Nagarajan at the University of North Carolina to study the impact of Fc gamma receptor signaling on lupus-induced atherosclerosis.

- Dr. Liang also received continued R21 funding from NIH/NIAMS for her SEDRA study ("Does Sildenafil Improve Endothelial Dysfunction in Rheumatoid Arthritis?"), a six-month crossover randomized double-blind placebo-controlled trial.

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200 Lothrop St.
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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 50 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 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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Larry W. Moreland, MD

Chief, Division of Rheumatology and Clinical Immunology

Margaret Jane Miller Endowed Professor of Arthritis Research

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Division of Rheumatology and Clinical Immunology
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