



University Hospitals
Case Medical Center

Cleveland | Ohio

FORGING MEDICINE'S FUTURE

DIVISION OF RHEUMATOLOGY



DEAR COLLEAGUE:

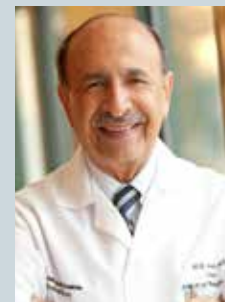
As one of just 18 hospitals named to the **U.S. News & World Report Honor Roll**, University Hospitals Case Medical Center is committed to building upon a legacy of medical discovery that began nearly 150 years ago and continues today.

UH rheumatologists, many of whom are also faculty at Case Western Reserve University School of Medicine, are forging the future of medicine through a number of programs and initiatives:

- Evaluating the role of NK cells in host-defense mechanisms in hepatitis C infection to better understand how the interferon response mechanism may work during chronic viral infection.
- Researching inflammatory transcription factors that are involved in both arthritis and inflammation disease and in preterm labor.

- Studying tocilizumab, an approved drug for the treatment of mild to severe rheumatoid arthritis, and its effect on the metabolism of cartilage.

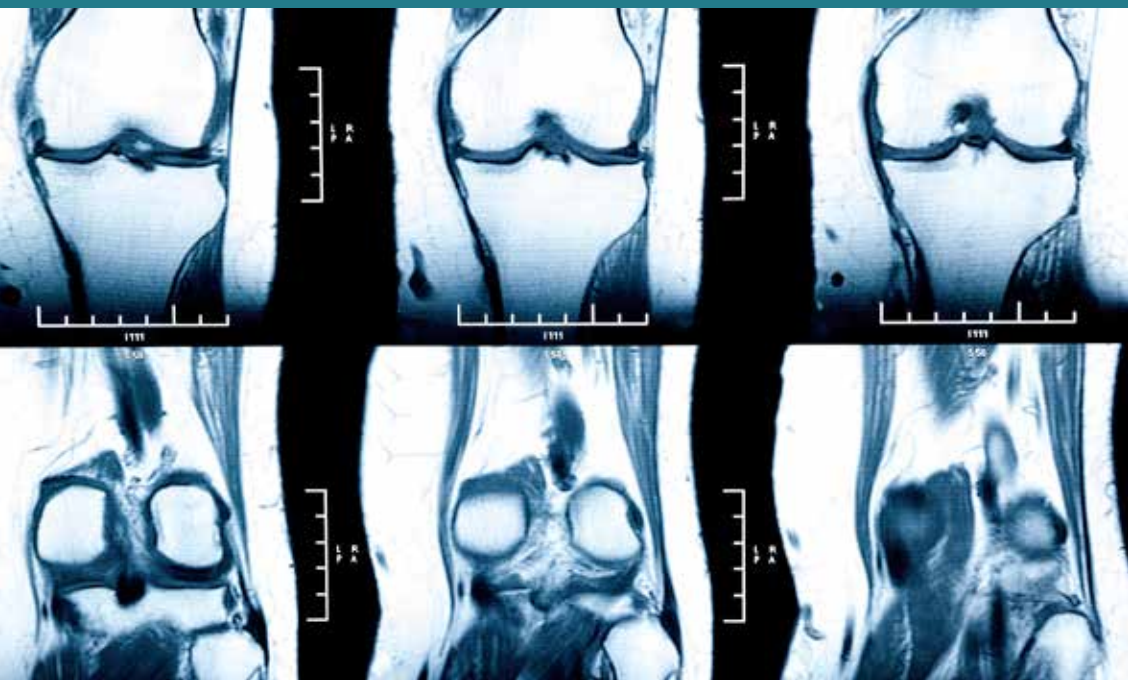
We welcome your feedback on how we can work together to further enhance research and clinical care.



ali d askari

Ali D. Askari, MD

*Chief of the Division of Rheumatology and Director of the Rheumatology Fellowship Program, UH Case Medical Center
Professor of Medicine,
Case Western Reserve University School of Medicine*



Division of Rheumatology

The Division of Rheumatology delivers the most advanced diagnostics and therapeutic treatments for personalized care of rheumatic diseases. To learn more about the division's programs, email RheumatologyInfo@UHhospitals.org.

The Division of Rheumatology at UH Case Medical Center is widely recognized as a center for superb health care, offering **unsurpassed medical training and leading-edge clinical research**. The division can provide new solutions and care to more patients in Northeast Ohio each year due to ongoing clinical expansion.

UH CASE MEDICAL CENTER

Among the nation's leading academic medical centers, UH Case Medical Center is the **primary affiliate of Case Western Reserve University School of Medicine.**

TO HEAL. TO TEACH. TO DISCOVER.

With more than 1,000 registered beds, UH Case Medical Center provides primary, specialty and subspecialty medical and surgical care. Located in the heart of Cleveland's University Circle on a beautiful 35-acre campus, UH Case Medical Center includes general medical, intensive care and surgical units, as well as three major specialty hospitals:

University Hospitals Seidman Cancer Center

University Hospitals MacDonald Women's Hospital

University Hospitals Rainbow Babies & Children's Hospital

Our physicians and researchers – who also serve as faculty at Case Western Reserve University School of Medicine – are leaders in their respective fields, and their ongoing clinical research programs push the boundaries of medical progress.

Our dedication to clinical research and education has played a major role in building UH Case Medical Center's rich legacy of medical innovation, and continues to this day. Coupled with a commitment to implementing the latest therapies and integrating with the most technologically advanced hospitals and community facilities, UH Case Medical Center offers a depth of care and scope of services unmatched by any other medical center in Ohio.

1,000+
registered
beds

35
acre
campus

3
major
specialty
hospitals



THE PRIMARY AFFILIATE OF Case Western Reserve University School of Medicine

The commitment to exceptional patient care begins with revolutionary discovery. **University Hospitals Case Medical Center is the primary affiliate of Case Western Reserve University School of Medicine**, a national leader in medical research and education, and consistently ranked among the top research medical schools in the country by U.S. News & World Report. Through their faculty appointments at Case Western Reserve University School of Medicine, physicians at UH Case Medical Center are advancing medical care through innovative research and discovery that bring the latest treatment options to patients.

Dr. Ali Askari (center) with fellows: Drs. Artan Kaso; Maya Mattar; Shernett Griffiths, Chief Fellow; Zachary Wolff; Ogechi Muoh; and Ayesha Kanwal.



Rheumatology

The Division of Rheumatology at UH Case Medical Center treats a host of rheumatic diseases, trains postdoctoral fellows and, with Case Western Reserve University School of Medicine, directs a number of local and national research projects on basic and clinical rheumatology. Services include treatment of:

- Systemic lupus erythematosus (lupus)
- Rheumatoid arthritis
- Sjögren's syndrome
- Fibromyalgia and inflammatory muscle diseases
- Common arthritic problems, such as osteoarthritis

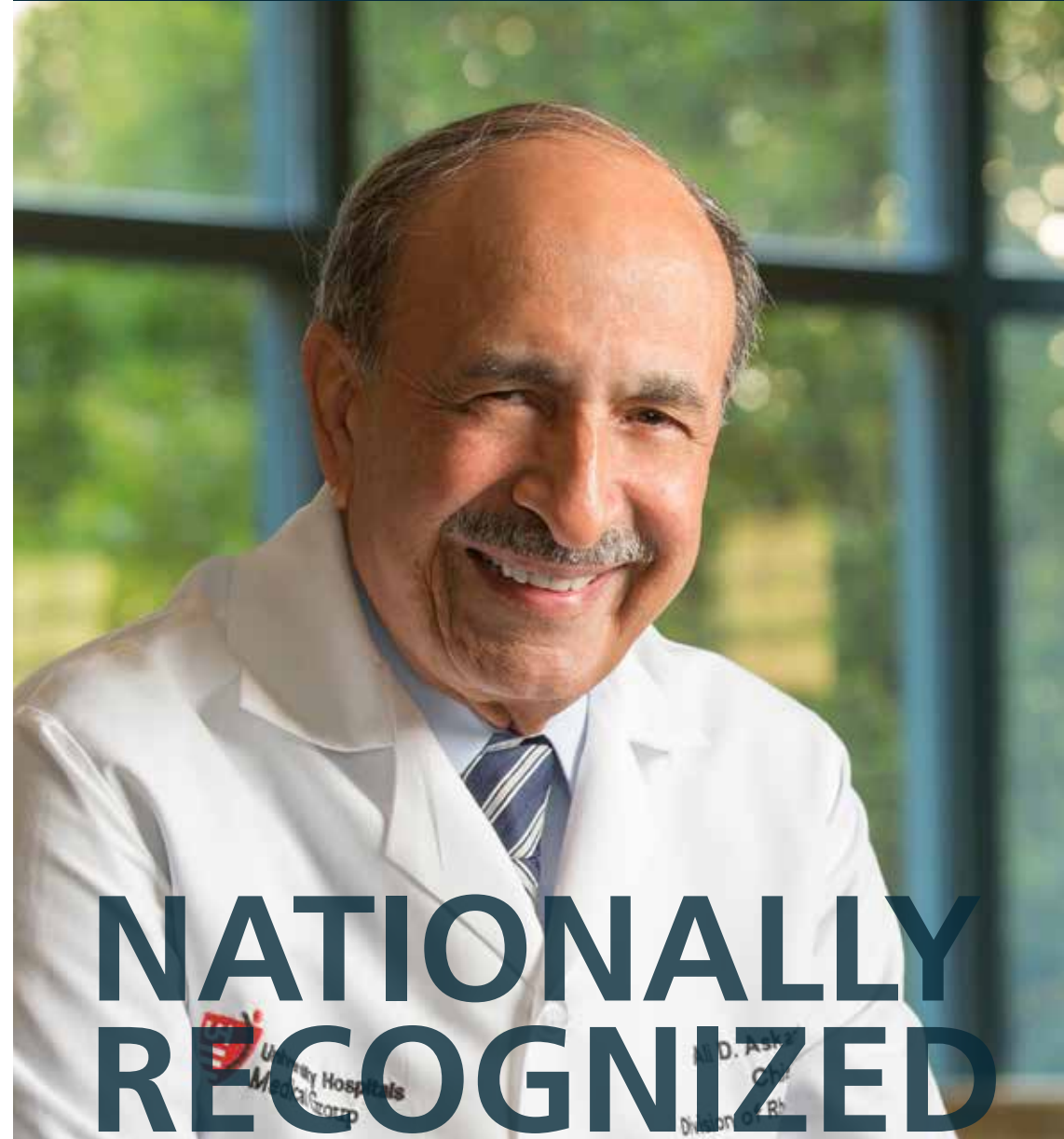
The Division of Rheumatology delivers the most advanced diagnostics and therapeutic treatments for personalized care of rheumatic diseases. The division has access to all related musculoskeletal services at the hospital, including orthopaedic surgery, physical and occupational rehabilitation, neurosciences and diagnostic radiology. In addition to offering patient care, basic research and clinical research, the Division of Rheumatology's postdoctoral fellowship program, through the Department of Medicine at Case Western Reserve University School of Medicine, is nationally recognized and fully accredited by the Accreditation Council for Graduate Medical Education.

Physician-scientists in the Division of Rheumatology at UH Case Medical Center and Case Western Reserve University School of Medicine are **internationally renowned rheumatologists, widely published researchers and respected educators.**

They are led by **Ali D. Askari, MD**, *Chief of the Division of Rheumatology and Director of the Rheumatology Fellowship Program, UH Case Medical Center; and Professor of Medicine, Case Western Reserve University School of Medicine.* Dr. Askari founded the division's Sjögren's Syndrome Center to improve treatment, build awareness of the disease and increase clinical research for future treatments.

With a special interest in the treatment of muscle diseases, Dr. Askari published a landmark study on steroid-induced myopathy, a study on cardiac involvement in polymyositis and dermatomyositis, followed by a study on phosphofructokinase deficiency, a metabolic myopathy.

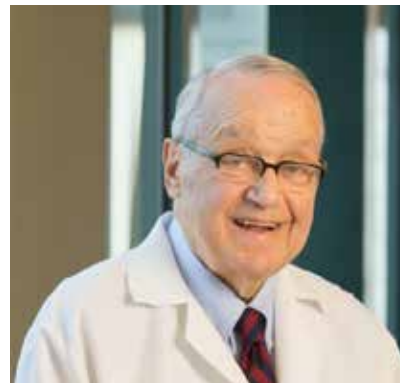
He also pioneered the innovative treatment of relapsing polychondritis with colchicines. He is president of the Cleveland-based National Sjögren's Syndrome Association and a founding fellow of the American College of Rheumatology. **In 2012, Dr. Askari received the American College of Rheumatology Master Designation**, an honor bestowed on a select few rheumatologists each year for their contributions in education, research and the well-being of patients with rheumatic diseases. Also in 2012, he published "Identification of Oral Bacterial DNA in Synovial Fluid of Patients with Arthritis with Native and Failed Prosthetic Joints" in the Journal of Clinical Rheumatology.



**NATIONALLY
RECOGNIZED
EXPERTS**

RHEUMATOLOGY

NATIONALLY RECOGNIZED EXPERTS



Dr. Roland Moskowitz



Dr. Van Warren

David Blumenthal, MD, *Assistant Professor of Medicine, Case Western Reserve University School of Medicine*, is an outstanding clinician and educator certified in internal medicine and rheumatology. Drawing from his vast experience at a number of leading medical institutions, he is a leader in the education of the fellows at Louis Stokes Cleveland VA Medical Center. Dr. Blumenthal **has been a member of the Food and Drug Administration's Arthritis Advisory Committee.**

Roland W. Moskowitz, MD, *Director of Clinical Research, UH Case Medical Center; and Professor Emeritus of Medicine, Case Western Reserve University School of Medicine*, was the division's chief from 1976 to 2001 and is a **world-renowned authority and researcher in osteoarthritis.** In 1991, Dr. Moskowitz described the first genetic defect as a cause of familial osteoarthritis through NIH-funded research. Over the past decade he has been involved in the development of models for investigation of osteoarthritis, which are used by many investigators to demonstrate the efficacy of various therapies in treatment. Dr. Moskowitz received the highest level of honor from the American College of Rheumatology, the President's Gold Medal.

Mathilde H. Piro, MD, *Director of the Rheumatology Section, Louis Stokes Cleveland VA Medical Center; Associate Director of Fellowship Program, UH Case Medical Center; and Assistant Professor of Medicine, Case Western Reserve University School of Medicine*, is a **superb educator and physician with a rich background of experience** from both the Cleveland Clinic Foundation and McGill University, where she was a lecturer for many years. Dr. Piro is certified in internal medicine and rheumatology. She was a fellow in the Royal College of Physicians in Canada.

Padmapriya Sivaraman, MD, *Instructor of Medicine, Case Western Reserve University School of Medicine*, is an outstanding clinician certified in internal medicine. Dr. Sivaraman is a graduate of UH Case Medical Center's internal medicine residency and rheumatology fellowship programs. Her special interests are rheumatoid arthritis, **osteoporosis, lupus and myopathies.**

Van D. Warren, MD, *Assistant Professor of Medicine, Case Western Reserve University School of Medicine*, is an excellent clinician and educator certified in medicine and rheumatology. He is the primary teaching faculty member involved in the fellowship program **focusing on osteoporosis and metabolic bone disease.**

All National Institutes of Health (NIH) funding for basic and clinical research is awarded to the School of Medicine at Case Western Reserve University.

CLINICAL ADVANCES

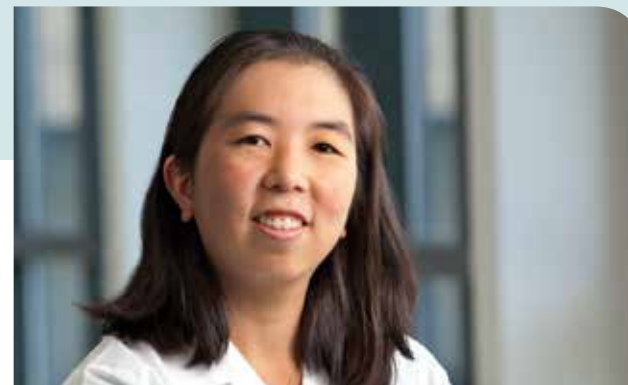
The Division of Rheumatology at UH Case Medical Center delivers the most advanced diagnostic and therapeutic treatments and personalized care for a host of rheumatic diseases. The division offers specialized treatment through its renowned centers:

- The Sjögren's Syndrome Center, which provides the highest standard of service for Sjögren's patients and created a database for information on patients. Through its multispecialty team of physicians, including staff from ophthalmology, otolaryngology, neurology, urology, dental medicine, gynecology, gastroenterology and pathology, the center helps patients to receive the highest quality of care.
- The Osteoporosis Center at UH Chagrin Highlands Health Center, which diagnoses and treats osteoporosis patients at nearly any stage. Certified DEXA Scan technologists perform bone density scans, limiting radiation exposure to just 10 percent of the radiation used during a standard chest X-ray. Bone density results are then discussed in professor rounds for final approval and increased accuracy.
- The Infusion Center at UH Chagrin Highlands Health Center, which offers advanced care for infusions of biologic agents that provide leading-edge treatment of rheumatic diseases.
- The Rheumatology Chemotherapy Treatment Clinic at the Louis Stokes Cleveland VA Medical Center, which is known for advanced care of rheumatic diseases. In addition to boasting clinical practices at 14 sites in the Cleveland metropolitan area and leading clinical research on rheumatic disorders and related conditions, education has been one of the utmost priorities of the division since its inception. Over the past four decades, more than 50 highly qualified rheumatologists graduated from this program and were certified in internal medicine and the subspecialty of

rheumatology, and most of them are now involved in academic practice or clinical research across the country. The division's postdoctoral fellowship program, through Case Western Reserve University School of Medicine, is nationally recognized and fully accredited with commendation (2005) – the highest honor – by the Accreditation Council for Graduate Medical Education (ACGME). Fellows are trained as investigative diagnosticians, leading-edge researchers and compassionate clinicians.



Drs. Ali Askari (far left) and Roland Moskowitz (third from right) with fellows: Drs. Maya Mattar; Shernett Griffiths, Chief Fellow; Artan Kaso; Zachary Wolff; and Ogechi Muoh.



Dr. Angela Robinson



Dr. Donald
Anthony Jr.

Natural Killer (NK) cells were identified in the early 1980s as being capable of killing tumors or virally infected cells without any prior exposure to the virus, differing from T or B cells in that they require no memory. Though they have long been attractive as cancer-fighting cells, harnessing their power has been elusive.

NATURAL KILLER CELLS STUDIED IN HEPATITIS C SETTING

NK Cells Hold the Key to Interferon-free Therapies

A project funded by the Veterans Affairs central office and the NIH, through Case Western Reserve University School of Medicine, led by **Donald D. Anthony Jr., MD, PhD**, *Rheumatology Section, Louis Stokes Cleveland VA Medical Center; and Associate Professor of Medicine, Case Western Reserve University School of Medicine*, is **evaluating the role of NK cells in host-defense mechanisms in hepatitis C infection to better understand how the interferon response mechanism may work during chronic viral infection.**

One of the projects is looking at the role of systemic immune activation and aging on host response to new antigens, or new pathogens, by observing how the immune system state before immunization with a vaccine predicts whether somebody will respond to the vaccine. A number of cells and cytokines are known to be involved in this, but a recent endeavor is to fully understand how prior activation of the system can make the host less able to respond. This applies to the settings of chronic viral infection as well as to autoimmune disease, where the immune system is activated either by dealing with pathogens or because of autoimmunity.

It is also known that in hepatitis C infection, specific genotypes of NK cells are associated with the ability of the human host to resolve infection on its own. Dr. Anthony believes that NK cells and interferon work together to help clear hepatitis C infection during interferon-based therapy. However, interferon therapy has many unwanted side effects. Dr. Anthony hopes that understanding how NK cells help fight viral infection will lead to the development of new treatment strategies for hepatitis C and other viral infections.

Highly morbid outcomes of some hepatitis C infections include formation of autoantibodies and vasculitis, which can lead to kidney failure, nerve problems and even death. Additional contributors to such outcomes include cold precipitable immune complexes composed of rheumatoid factors. **Another goal of Dr. Anthony's lab is to understand how these autoantibodies are produced during hepatitis C infection, so that better treatment strategies can be developed.**

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New Pathways to Treatment of Rheumatoid Arthritis and Diseased Cartilage

Approved Arthritis Drug May Protect Cartilage from Deterioration

The lab of **Charles J. Malemud, PhD**, *Assistant Director for Fellowship Research, UH Case Medical Center; and Professor of Medicine and Anatomy, Case Western Reserve University School of Medicine*, is currently involved in a study of tocilizumab, an approved drug for the treatment of mild to severe rheumatoid arthritis, and its effect on the metabolism of cartilage.

Tocilizumab is becoming more significant in the clinic because it has an important effect on moderating the biological activity of a potent pro-inflammatory cytokine called IL-6. IL-6 is an acute-phase reactant protein that is increased in synovial fluid in patients with rheumatoid arthritis.

Dr. Malemud's **first project has been looking at the effect of IL-6 on articular cartilage by studying chondrocytes**, the cells of the tissue, and the signaling pathways that modify the responsiveness of chondrocytes to this cytokine. One pathway is the IL-6 pathway, in which a group of enzymes called Janus kinases are activated, leading to the activation of signal transducers and activators of transcription (STAT) proteins, potent transcription factors that regulate the expression of genes.

This system is involved in amplifying pro-inflammatory cytokines. When this pathway is activated by IL-6 gene expression, additional pro-inflammatory cytokines are up-regulated, creating the mechanism by which the chronicity of arthritis is sustained over time. This continuous amplification is never turned off, and tocilizumab interferes with the activation of this pathway and essentially shuts down the activation of STAT proteins. This was the first example of how this mechanism might protect articular cartilage from destruction when it's used in the context of rheumatoid arthritis.

A second project addressed the Mitogen-activated protein (MAP) kinase pathway, also activated by IL-6. While the IL-6 pathway is primarily involved in the amplification in pro-inflammatory cytokine genes, the **MAP kinase pathway is involved in the production of matrix metalloproteinases, enzymes that degrade the articular cartilage**. Preliminary data supports the hypothesis that tocilizumab will protect the cartilage by inhibiting the MAP kinase pathway and the production of matrix metalloproteinases. A report of the findings were presented at Immunology Summit – 2013.

The third project addresses cell death, in which pro-inflammatory cytokines destroy chondrocytes. Unlike some other tissues, no stem cell population exists to replace chondrocytes that are lost during this process. IL-6 induces apoptosis in these cells; research is under way to determine if tocilizumab will suppress this as well.

In the past 10 years, Dr. Malemud has moved into a translational approach to research, combining the experience of 40 years and resources gathered over that time to make discoveries made in the lab significant to therapeutic applications. Other projects under way in Dr. Malemud's lab, or in collaboration with colleagues, include:

- Looking at inflammatory transcription factors that are involved in both arthritis and inflammation disease and in preterm labor
- Molecules which, if they were inhibited, could be very useful in the treatment of rheumatoid arthritis
- Treating osteoarthritis using stem cells



Dr. Charles Malemud

Dr. M. Edward Medof

Natural Development of Foxp3+ T Regulatory Cells (Tregs) Discovered

CREATION OF TREGS WITH ROBUST SUPPRESSOR ACTIVITY PRESENTS NEW APPROACH TO IMMUNE BIOTHERAPIES

M. Edward Medof, MD, PhD, Professor of Medicine and Pathology, Case Western Reserve University School of Medicine, specializes in rheumatoid arthritis, lupus and other connective tissue diseases in which the immune system is deregulated. He has been on the UH staff and School of Medicine faculty for over 20 years, serving as an expert on immune diseases for members of the Department of Medicine and receiving consults throughout the Midwest and as far away as Alaska.

Dr. Medof was previously at the University of Chicago where he directed the Rheumatology Clinical Laboratory and directed an outreach program at five community hospitals. He then joined the staff of New York University, continuing clinical

rheumatology work at Bellevue Hospital. He developed new ways to examine regulation of complement cascade, one of the key systems of the immune response. He has more than 185 peer-reviewed publications.

Dr. Medof is internationally known for the **discovery of the Decay-Accelerating Factor (DAF), a protein present on all cells that functions as a shield to protect self-cells from attack by our own immune system**, important for connective tissue disease. Dr. Medof recently discovered how Foxp3+ T regulatory cells (Tregs), master cells that protect us from autoimmunity, naturally develop in the body. Defects in Tregs are present in many autoimmune diseases, and the new knowledge of how to make Tregs is an exciting new approach for immune biotherapies.

Tregs previously have been made artificially, *ex vivo*, by taking the CD4+ subset of T cells and incubating it with a cytokine called transforming growth factor TGF-beta. But cells produced in this way are not stable and possess poor suppressor activity.

Dr. Medof's laboratory has learned how to make Tregs that possess robust suppressor activity from patients with autoimmune disease and that can be given

back to patients to shut down their autoimmunity naturally. This research was published in February 2013; the work was funded by grants from the NIH, the Department of Defense and the National Multiple Sclerosis (MS) Society. A similar protocol is in progress for lupus.



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All National Institutes of Health (NIH) funding for basic and clinical research is awarded to the School of Medicine at Case Western Reserve University.

The Harrington Project for Discovery & Development is a \$250 million national initiative to accelerate the development of medical breakthroughs by physician-scientists into medicines that benefit patients. It is a unique model that aligns, through mission and structure, nonprofit and for-profit resources into a system for drug development. The Harrington Project thereby addresses a set of major challenges in medicine that have created a development gap for promising discoveries.

The Harrington Discovery Institute at University Hospitals Case Medical Center, the nonprofit component of The Harrington Project, enables physician-scientists to translate their clinical insights and research into novel therapies that benefit patients and society. Through an annual competition, the Harrington Discovery Institute selects a group of medical innovators known as Harrington Scholar-Innovators whose projects are funded and actively guided by drug discovery experts toward the clinical realm.

HARRINGTON DISCOVERY INSTITUTE
AT UNIVERSITY HOSPITALS CASE MEDICAL CENTER

A CATALYST FOR A NEW MODEL IN DRUG DEVELOPMENT

2014 SCHOLARS The 2014 class of Harrington Scholar-Innovators selected by the institute's scientific advisory board are:

Jayakrishna Ambati, MD
University of Kentucky

Darren Carpizo, MD, PhD
Rutgers Cancer Institute of New Jersey

Garret FitzGerald, MD
University of Pennsylvania

Mark Humayun, MD, PhD
University of Southern California

John Kheir, MD
Harvard University

Rahul Kohli, MD, PhD
University of Pennsylvania

Gavril Pasternak, MD, PhD
Memorial Sloan-Kettering Cancer Center

Irina Petrache, MD
Indiana University

David Rowitch, MD, PhD
University of California, San Francisco

Jean Tang, MD, PhD
Stanford University

David Wald, MD, PhD
Case Western Reserve University

To learn more, visit HarringtonDiscovery.org.



THE HARRINGTON SCHOLAR-INNOVATOR GRANT PROGRAM: CHANGING THE STATUS QUO

*Sanford Markowitz, MD, PhD
Harrington Scholar-Innovator, Class of 2013
Case Western Reserve University School of
Medicine, Cleveland, Ohio
Colon cancer*

When Dr. Markowitz is not treating patients at UH Seidman Cancer Center, he is dedicated to understanding the genetic basis for colon cancer as the key to developing better treatments. He and his team have identified a genetic “switch” that controls cell division and tissue growth in colon cancer.

As exciting as he finds the basic research process, Dr. Markowitz is keenly aware of the need to translate scientific discoveries into commercially viable treatments – and the barriers to making that happen.

“The biggest challenge for any academic laboratory is to get beyond the lab and develop a therapy,” he explains. “By connecting academics with industry experts, the Harrington Discovery Institute is giving our ideas a fighting chance to succeed.”

Read more at HarringtonDiscovery.org/Scholar-Innovator2013.

To be notified of the next Harrington Scholar-Innovator Grant call for proposals, email Natalie.Haynes@UHhospitals.org.

In 1996, UH created a clinical trials office at what is now UH Case Medical Center. At the time of its creation, the focus and management of clinical trials was managed by a small staff. This team was charged with the fiscal management of a handful of clinical trials, as well as regulatory oversight of human subject protections. By 2000, the office became known as the UH Research Institute.

From 1996 to 2003, the clinical research enterprise at the academic medical center continued to expand, resulting in exponential growth of both the staff and the research activity managed. The institute grew into a much broader

support department and became the **Center for Clinical Research and Technology (CCRT)**, which consists of seven offices dedicated to developing a standardized platform ensuring the responsible conduct of research for patients through scientific, regulatory, legal, ethical and fiscal review.

The CCRT now provides infrastructure, programmatic, personnel and administrative support for all research activities performed at UH by UH medical or scientific staff. These medical scientists are national and international leaders in their respective fields and are committed to **identifying standards of excellence** and potential areas for improvement to promote and **facilitate clinical and translational research**.

By 2013, the CCRT activities amounted to over \$42 million at UH and \$167 million of UH activity related to the affiliation between UH and Case Western Reserve University School of Medicine. These funds emanate from nearly 1,200 active grants and contracts at UH and nearly 700 additional grants that annually fund the shared faculty of UH and the School of Medicine through nearly 2,300 active human research protocols.

To learn more about the Center for Clinical Research and Technology directly, visit UHhospitals.org/Clinical-Research, call 216-844-5576 or email ClinicalResearch@UHhospitals.org.

UH Case Medical Center **CENTER FOR CLINICAL RESEARCH AND TECHNOLOGY**

Clinical research has always driven the practice of medicine to new heights and, as such, is deeply embedded within the very mission statement of University Hospitals:

To Heal. To Teach. To Discover.

Clinicians and Scientists at UH Case Medical Center and Case Western Reserve University School of Medicine



Division of Rheumatology

Ali D. Askari, MD

Chief, Division of Rheumatology
Director, Rheumatology Fellowship Program
Professor of Medicine

Donald D. Anthony Jr., MD, PhD

Rheumatology Section, UH Case Medical Center
and Louis Stokes Cleveland VA Medical Center
Associate Professor of Medicine

David Blumenthal, MD

Rheumatology Section, Louis Stokes
Cleveland VA Medical Center
Assistant Professor of Medicine

Elizabeth Brooks, MD, PhD

Assistant Professor of Pediatrics and Medicine
Adult and Pediatric Rheumatology

Hulya Bukulmez, MD

Assistant Professor of Pediatrics
Pediatric Rheumatology Research

Douglas Flagg, MD

Assistant Clinical Professor of Medicine

Lawrence Kent, MD

Clinical Professor of Medicine

Marie Kuchynski, MD

Senior Clinical Instructor of Medicine

Armindia Lumapas, MD

Clinical Instructor of Medicine

Charles J. Malemud, PhD

Assistant Director for Fellowship Research
Professor of Medicine and Anatomy

M. Edward Medof, MD, PhD

Professor of Medicine and Pathology

Roland W. Moskowitz, MD

Director, Clinical Research
Professor Emeritus of Medicine

Mathilde H. Pioro, MD

Director, Rheumatology Section,
Louis Stokes Cleveland VA Medical Center
Associate Director of Fellowship Program
Assistant Professor of Medicine

Angela B. Robinson, MD, MPH

Assistant Professor of Pediatrics
Pediatric Rheumatology

Elisabeth Roter, MD

Assistant Clinical Professor of Medicine

Donna Sexton-Cicero, MD

Clinical Instructor of Medicine

Padmapriya Sivaraman, MD

Instructor of Medicine

Richard L. Stein, MD

Assistant Clinical Professor of Medicine

Van D. Warren, MD

Assistant Professor of Medicine

Staff

Carmelene Jefferson

Division Manager

Cindy Faciana, RN

Nurse Supervisor

Jacqueline Russell

Academic Education Coordinator

Independent Specialists on Staff

Jeffrey Chaitoff, MD

Phyllis Iannuzzi, MD

Mohammad Moayeri, MD

Senior Clinical Instructor of Medicine

Physicians receive their academic appointments and their accompanying titles from Case Western Reserve University School of Medicine.

To refer a patient or learn more
about UH Case Medical Center
Division of Rheumatology, call
1-866-UH4-CARE (1-866-844-2273) or
visit **UHhospitals.org/Rheumatology**



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