2019 UPDATE: Division of Rheumatology and Immunology



THE OHIO STATE UNIVERSITY COLLEGE OF MEDICINE • THE OHIO STATE UNIVERSITY WEXNER MEDICAL CENTER





<u>Welcome</u>

Dear Friends and Colleagues,

As I look back on 2018, I feel incredibly grateful. It's been an exciting, fulfilling year here at the Division of Rheumatology and Immunology at The Ohio State University. I welcome the opportunity to step back and consider all that we have accomplished together.

Year after year, I marvel at how – when you bring bright, passionate and dedicated individuals together – the whole really is greater than the sum of its parts. Each is uniquely gifted, but even more so as part of our dynamic team.

This teamwork impacts the field of rheumatology and the lives of patients who turn to us for care. We're making remarkable strides – as scientists, physicians, faculty and leaders – while setting the stage for a phenomenal year ahead.

Perhaps most momentous, in September we filled the Rheumatology and Immunology chair established to honor my distinguished colleague **Ronald Whisler, MD**, former division director, who remains active in our division.

This monumental event helped us to recruit a nationally and internationally renowned researcher, **Song Guo Zheng, MD, PhD**. Dr. Zheng joins Ohio State as Professor of Internal Medicine and Director of Rheumatology and Immunology Research. You'll learn about his pioneering career and enthusiasm for joining Ohio State colleagues as a research and faculty leader.

Other highlights include:

- In May, the Scleroderma Foundation recognized our multispecialty scleroderma clinic directed by Ali Ajam,
 MBBS. The foundation designated our clinic as a trusted site for exceptional scleroderma research, education and care. It's a major step forward in building a multidisciplinary program. It reflects Dr. Ajam's work orchestrating specialties toward superb care for patients with this devastating disease. There are few clinics like it in the region or country.
- Dr. Ajam also provides responsive care for patients with autoimmune diseases in his new role as Infusion Center Director. Demand at our CarePoint East Infusion Center was high so we collaborated with Ohio State Wexner Medical Center, to open a second Infusion Center. Now, our patients can access these important therapies through Ohio State's Internal Medicine and Pediatrics site at Hilliard.
- Collaboration continues with Nationwide Children's Hospital one of the nation's best programs. Our colleague,

Dr. Veronica

Mruk, was awarded the Nationwide Children's Quality and Healthcare Leadership Fellowship. The clinical fellowship begins in July and





Song Guo Zheng, MD, PhD

Veronica Mruk, MD

her Ohio State Master's program begins in November.

- You'll also read about Stacy Ardoin, MD, in her role as Nationwide Children's Pediatric Rheumatology Chief. A faculty member in our division for the past 10 years, Dr. Ardoin is an exceptional rheumatologist for adult and pediatric patients and an outstanding physician leader. I look forward to continued work with Dr. Ardoin to advance rheumatology at Ohio State for patients of all ages.
- Breakthroughs in my lab include research spearheaded by William Willis, PhD. You'll read about the HMGB1 protein studied in inflammation for years. We've identified a new form of this protein that is present in lupus. We describe the molecule, its formation and the enzyme catalyzing formation of these large molecular weight complexes. We're eager to differentiate the functional roles of these complexes compared with the monomer to better understand lupus pathogenesis.
- Our division participated in a cross-disciplinary study led by **Mireia Guerau, PhD**. Her group found that the CD38 glycoprotein is a reliable biomarker of human inflammatory macrophages. These findings show promise for improved lupus diagnosis and treatment.

Division research encompasses many spheres – from bench research into disease mechanisms to translational, bench-tobeside applications and, ultimately, clinical studies of leading therapies. We also study transitional care from pediatric to adult rheumatology, as featured in Dr. Ardoin's story. Other research documents patients' perspectives, as mentioned in **Alexa Meara, MD**'s, exploration into inflammatory conditions in cancer patients given lifesaving immunotherapy.

Thank you for letting me share these milestones. I am inspired by my colleagues and the patients we're privileged to care for. I encourage you to send me your comments or questions by e-mail at Wael.Jarjour@osumc.edu.



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Wael N. Jarjour, MD, FACP Martha Morehouse Chair in Arthritis and Immunology Research Director, Division of Rheumatology and Immunology The Ohio State University College of Medicine The Ohio State University Wexner Medical Center

Dr. Song Guo Zheng Selected as Ohio State's Ronald L. Whisler Endowed Chair

Research Pioneer Advances Understanding of Autoimmune Diseases

In a ceremony this spring, The Ohio State University College of Medicine will formally install Song Guo Zheng, MD, PhD, as the Ronald L. Whisler, MD, Endowed Chair in Rheumatology and Immunology. Dr. Zheng comes to Ohio State from Penn State University's Milton S. Hershey Medical Center where he was a professor and director of rheumatology research. He joins Ohio State as Professor of Internal Medicine and Director of Rheumatology and Immunology Research on February 1, 2019.

The university established the \$2 million endowed chair in November of 2017 to support world-class autoimmune research and scholarship. The Whisler chair is a tribute to the renowned career and contributions of former Rheumatology and Immunology Division Director Ronald L. Whisler, MD, an active division member.

"We are honored to have Dr. Zheng join us," says Dr. Whisler. "He brings an excellent immunology and rheumatology research program to the division."

Director Wael Jarjour, MD, notes that Dr. Zheng carries on work begun years ago by Dr. Whisler. "He exemplifies Dr. Whisler's research attributes," says Dr. Jarjour. "Dr. Zheng will further Dr. Whisler's work to unravel the complicated autoimmune diseases that affect our patients.

"Dr. Zheng studies both lupus and rheumatoid arthritis," says Dr. Jarjour. "His work will bring new therapies to the clinic."

"Holding the Whisler chair is a great honor," says Dr. Zheng. "I know Dr. Whisler. In addition to his career as an outstanding rheumatologist, leader and physician, he is a productive researcher."

Dr. Zheng's expertise includes the pathogenesis, cytokines and immune regulation of autoimmune, allergic and inflammatory disease. He and his colleagues discovered "TGF- β -induced regulatory T cells – a milestone published in the October 2002, Journal of Immunology. Dr. Zheng also studies gingiva-derived mesenchymal stem cells (GMSC) and immunoregulation.

Shared Interests

Dr. Zheng is interested in Whisler's research into aging and autoimmunity. "Dr. Whisler found that aging T cells produced poor IL-2 and patients with autoimmune diseases usually have low IL-2 levels," Dr. Zheng says. IL-2 is interleukin-2 – an immune-system cell-signaling molecule. "My study first reported that IL-2 is crucial for Treg cell induction and expansion. Reduced IL-2 in an aging population could contribute to autoimmune diseases."

Dr. Zheng looks forward to joining the Ohio State team. "Ohio State is an exceptional research environment with excellent faculty and collaborators," says Zheng. "Dr. Jarjour and I have known each other many years. We share interests in Treg cells in autoimmunity, including the role of gender.

"Our labs will address these and other questions such as Treg and T Helper 17 (Th17) cell development and stability," says Dr. Zheng.

Cancer models in mice indicate that Th17 and Treg cells play a role in tumor immunology. Dr. Zheng envisions clinical studies and novel approaches to cancer. He is also interested in regulatory/suppressor cells in therapies to prevent organ transplant rejection.

A Distinguished Career

Dr. Zheng earned his Immunology PhD at University of Orleans and French National Center for Scientific Research following his MD and MS in China. He completed postdoctoral studies at UCLA and University of Southern California, where he was an assistant professor before joining Penn State as professor and research director.

He is editor-in-chief of the American Journal of Clinical and Experimental Immunology in addition to editorial roles with other journals. He has received numerous national and international honors, is principle investigator of multiple NIH grants and has published more than 120 papers. Dr. Zheng is an Elected Member of the Henry Kunkel Society.

Left to Right: Wael Jarjour, MD, Song Guo Zheng, MD, PhD, and Ronald Whisler, MD



On the Cover: Top: Rheumatology Experts BACK LEFT TO RIGHT: Kevin Hackshaw, MD, Clark Anderson, MD, Ali Ajam, MBBS, Ronald Whisler, MD and Hareth Madhoun, DO MIDDLE LEFT TO RIGHT: Latha P Ganesan, PhD, Beatrice Kenol, MD, Stacy Ardoin, MD, Song Guo Zheng, MD, PhD, and Sheryl Mascarenhas, MD FRONT LEFT TO RIGHT: Wael Jarjour, MD, Alexa Meara, MD, Zhanna Mikulik, MD, and Crystal Losambe, CNP BOTTOM LEFT: Sheryl Mascarenhas, MD MIDDLE: Ali Ajam, MBBS RIGHT: Lai-Chu Wu, D. Phil.

Patient Care

National Foundation Designates Ohio State Clinic as a Scleroderma Center



Thanks to a new national designation, more people with a rare autoimmune disease can find answers and options from specialists. In May 2018, the Scleroderma Foundation designated the Scleroderma Clinic at Martha Morehouse Medical Plaza on Ohio State's campus as a Scleroderma Center. The multispecialty center

Ali Ajam, MBBS

is one of only three in the state recognized for advanced scleroderma research, education and care.

The national nonprofit Scleroderma Foundation supports those affected by the disease. Its medical and scientific advisory board reviews designated centers to ensure exceptional research, patient care and outreach for patients, physicians and the public. The partnership spotlights Ohio State's leading approaches to scleroderma and related conditions such as Mixed Connective Tissue Disease (MCTD).

The national designation includes collaborative opportunities and a presence on the foundation's website. "It's easier for people to find us now, because there are only a few scleroderma centers," says clinic director Ali Ajam, MBBS, assistant professor of Internal Medicine. "Scleroderma is a rare condition involving many organs, including skin, lungs and gastrointestinal function. There aren't too many places or people who see scleroderma."

Ohio State's clinic helps patients find care in one place. The clinic enlists specialists in rheumatology, dermatology, nephrology, gastroenterology, cardiovascular care, pulmonology, physical therapy and other disciplines. "We have designated providers interested in helping patients with scleroderma," says Dr. Ajam.

Dedicated Care for Diverse Challenges

The clinic team coordinates care since scleroderma can affect skin, lungs, kidneys or other tissues and organs in varied ways. Hardened tissue can leave hands bent in a claw-like shape or limit overall movement and flexibility. Circulatory disorders can cause red spots on the face or Raynaud's syndrome, which restricts blood flow to fingers and toes.

Dr. Ajam notes that diagnosis is typically clear through clinical symptoms and bloodwork. Specialists may use imaging and biopsies.

"Over the years, people have told me their doctors weren't familiar with scleroderma or said there was no treatment," says Dr. Ajam. "There is a lot of misinformation or just not enough information."

Although it has no cure, scleroderma is manageable. "It's important for patients to know that," says Dr. Ajam. "There are many therapies, and we're getting more and newer treatment options."

Expanding Research and Reach

The Ohio State team investigates scleroderma and educates others. In addition to clinical studies at Ohio State and international collaboration, doctors maintain a scleroderma registry. Volunteers contribute blood and urine samples or skin biopsies. "Most of our patients want to sign up for the registry," says Dr. Ajam.

Dr. Ajam has gone to hospitals, held phone conferences and made presentations to the Scleroderma Foundation to raise awareness.

The Scleroderma Center reaches patients in Ohio and surrounding areas. "We have treated individuals from as far as Texas and Florida," says Dr. Ajam. "It's a challenging condition, but the outlook has improved in leaps and bounds. There's a lot of hope out there."

Rheumatology Leader Dr. Stacy Ardoin Helps Young Patients Find Care

Programs Partner for Greater Awareness and Reach



Stacy Ardoin, MD

Adult and pediatric rheumatology programs at Ohio State and Nationwide Children's Hospital enjoy a close relationship under the leadership of Stacy Ardoin, MD. She has served as pediatric rheumatology division chief at Nationwide Children's since March, 2017. The partnership increases knowledge about pediatric conditions and enhances care – from infancy through adolescence and the transition to adult care.

"It's a wonderful relationship," says Dr. Ardoin whose career path combined adult and pediatric rheumatology fellowships. "We have doctors who've done adult and pediatric fellowship training, which brings the programs together. We collaborate on research and quality improvement and do dual training."

Ohio State's adult rheumatology fellows gain pediatric experience at Nationwide Children's Hospital. They see

conditions ranging from neonatal lupus to juvenile idiopathic arthritis (JIA) – the most common rheumatic condition treated at Nationwide Children's.

Dr. Ardoin sees adult patients at Ohio State where she treats lupus, arthritis, scleroderma, myositis and other conditions. In addition to clinical and research activities, she is associate professor in Ohio State's Rheumatology and Immunology Division and associate professor in pediatric rheumatology at Nationwide Children's.

Expanding Expertise

Throughout the country, pediatric rheumatologists are rare, and only a few adult rheumatologists are familiar with pediatric conditions. Although nearly 300,000 U.S. children have juvenile arthritis, there are only about 350 pediatric rheumatologists.

"Pediatricians don't always think about childhood arthritis," says Dr. Ardoin. "It often gets missed. We help doctors become comfortable seeing those patients."

Helping Kids Feel Better

Dr. Ardoin enjoys helping children. "It's hard to see a child with arthritis who can't run and play," she says. "It's rewarding to make kids feel better! We also help parents, families and caregivers coping with the challenges of a chronically ill child."

Her team includes pediatric rheumatologists, social service and psychology experts, nurse practitioners and fellow trainees. "Each has a niche," says Dr. Ardoin. "My interests include lupus. In our lupus clinic we collaborate with nephrology, psychology,

<u>Research</u>

pharmacy and neuropsychology specialists. Other areas of focus within our practice include musculoskeletal ultrasounds to spot inflammation and a hypermobility [double-jointedness] clinic."

Teens and Transitions

Dr. Ardoin's team eases patient transitions from pediatric to adult care. "I love caring for teenagers," she says. "They face changes and challenges on top of a complicated illness."

It's common for adolescents to move for college, work or marriage, or change insurance and doctors. "There are developmental changes, decision-making and occasionally denial," says Dr. Ardoin. "We reduce barriers so things go smoothly."

Improving Outcomes

Pediatric colleagues collaborate to improve care. They're active in groups such as the Pediatric Rheumatology Care and Outcome Improvement Network (PR-Coin). "Through this participation, plus quality-improvement infrastructures, we've increased the percentage of JIA patients in remission or inactive disease," Dr. Ardoin says. "Over four years, we've improved that rate from 11 percent to over 44 percent."

Other partnerships include the Childhood Arthritis and Rheumatology Research Alliance (CARRA). "Our registry includes over 10,000 children," she says, "and ongoing research projects."

Dr. Ardoin's team plans to increase translational research. "We're studying complement genetics, which affects immune response," she says. "We'll expand research and improve outcomes for JIA and other diseases like lupus."

Revolutionary Cancer Immunotherapy Raises Questions About Autoimmune Effects Dr. Alexa Meara Explores a Cross-Disciplinary Response



Alexa Meara, MD

Immunotherapy harnesses the immune system to fight cancer with unparalleled precision. These drugs have worked wonders for patients with certain types of cancer. However, potential risks include the development of autoimmune conditions that warrant a closer look.

In the November, 2018 issue of RheumNow, Ohio State

rheumatologist Alexa Meara, MD, discusses autoimmunelike diseases – or rheumatic immune-related adverse events (irAEs) –associated with immune checkpoint inhibitors (ICIs). She emphasizes the importance of research and cooperation across disciplines as rheumatologists encounter patients with irAEs.

"The immune system has normal regulatory checkpoints – like checks and balances," Dr. Meara explains, "When you have an infection your immune system turns on initially and off after a while. You get sick and then you get better." ICIs block regulatory checkpoints in two pathways; CTLA-4 and PD-1/PD-L1. "Basically, they block the immune system ability to turn itself off," says Dr. Meara, "so patients develop an immune response to their cancer cells. It's amazing – your body can then fight the cancer itself."

Benefits and Risks

ICIs help some patients avoid harsh chemotherapies. They treat certain lung cancers, melanoma, renal-cell carcinoma and other cancers. "ICI drugs help people to live longer," says Dr. Meara. "They're here to stay."

Despite their success, Dr. Meara warns that autoimmunity is the Achilles' heel of checkpoint inhibitors. "The therapy allows T cells, or your immune system, to go unchecked which is by definition how you get autoimmune diseases. These irAEs are not typical antibody associated autoimmune rheumatic diseases," she says. "Patients are getting inflammatory arthritis, colitis, pneumonitis and endocrine disorders. They don't follow normal patterns and don't necessarily respond to the same drugs." Balancing the benefits and risks creates dilemmas. "It's an interesting juxtaposition," says Dr. Meara. "Cancer patients survive but might have a chronic disease requiring monitoring and management. We need to better understand irAE treatments."

"In my practice, we work with the oncologist, the gastroenterologist if there's colitis, or dermatologists for psoriasis or unusual rashes that can happen with ICIs. Multidisciplinary care is important."

ICIs adverse events range from mild conditions to rare but serious diseases such as pituitary disorders and inflammatory heart conditions. Questions remain about patients with active cancers and pre-existing autoimmune diseases or autoantibodies.

"We don't want to tell patients they can't have a lifesaving cancer drug," says Dr. Meara. "We want to be able to inform them of the risks and to provide the best care in the event of an irAE. These conditions are all intertwined – we just need to learn more and do a better job of talking to each other."

Dr. Meara plans to look at data retrospectively and prospectively in partnership with other institutions. "Then we can create guidelines," says Dr. Meara. In addition, I'm investigating the patient experience to help health care providers and others to better address patient concerns."

Study Finds New Form of Proinflammatory HMGB1 Protein Complex and Enzyme that Catalyzes its Formation

Findings Shed Light on Lupus and Other Rheumatic Diseases

Ohio State's William Willis, PhD, joined colleagues to test a hypothesis that first arose when he defended his doctoral dissertation. Now, he is a post-doctoral researcher in the Division of Rheumatology and Immunology at The Ohio State University Wexner Medical Center. His subsequent research in Ohio State's Jarjour Laboratory was based on tissue samples from patients with lupus and healthy controls. The group's findings were published in the Journal of Biological Chemistry in June of 2018.

Dr. Willis received NIH funding to investigate high-mobility group box 1 (HMGB1), a protein in the nucleus of most cells. Previous research shows that – in response to stress or injury – this versatile protein leaves the nucleus, alerts the immune system and promotes inflammation. Dr. Willis and colleagues suspected that an enzyme called transglutaminase 2 (TG2) contributed to forming new, high molecular weight protein complexes of interest in patients with lupus and other immune disorders.

"The HMGB1 protein that we investigated has been studied in inflammation for a number of years," says senior author Wael Jarjour, MD, Director of Ohio State's Division of Rheumatology and Immunology. "Over a decade ago we observed that PBMC from lupus patients had a surprising presence of large proteins that were not found in healthy subjects, but we did not know the nature of these proteins. Our current project demonstrates that a previously unrecognized form of HMGB1 is, at least in part, the culprit."



William Willis, PhD

Dr. Willis and colleagues investigated the nature and formation of HMGB1 complexes (HMGB1c) in lupus. They also found that HMGB1c levels were higher in samples from patients with lupus than those who did not have the disease.

After exhaustive analysis, the group identified important details about the size and nature of these complexes. Their work could lead to enhanced inflammation-managing therapies.

Coincidence, Collaboration and Clues

Dr. Willis' 2013 dissertation focused on lung fibrosis and TG2. He and a faculty member speculated that HMGB1c could be a TG2 substrate – the compound acted upon by the TG2 enzyme.

At the time, Lai Chu Wu, PhD, associate professor in Ohio State's Division of Rheumatology was collaborating with colleagues to study the role of exercise in inflammation and bone remodeling. Dr. Wu's group was surprised to find that certain mouse cells yielded high-molecular HMGB1 bonds when subjected to exercise-mimicking stress.

"At that time, coincidentally, I served on the dissertation committee and found the observation of stable HMGB1 complexes interesting," said Dr. Wu. "I invited Bill [Dr. Willis] to join our groups as a postdoctoral fellow to test the hypothesis that TG2 contributes to HMGB1c formation." By 2018, Dr. Willis and colleagues had confirmed their hypothesis.

"The stars aligned for this project," says Dr. Willis. "The right people were in the right place at the right time."

"Mission accomplished!" says Dr. Wu. "Bill not only showed that TG2 catalyzed the formation of HMGB1, he identified lysine residues in HMGB1 that could be substrates of TG2 and crosslinked."

Dr. Jarjour adds, "This high molecular weight form of HMGB1 has functional roles that need to be delineated and differentiated from what has been previously described." After in vitro lab studies, the group hopes to investigate the complexes in living organisms.

"We want to identify the composition and function of covalent HMGB1 protein complexes in vivo," says Dr. Willis. "If they facilitate the loss of immune tolerance to self-proteins, that would be an important result and promising therapeutic goal."

Discovery of Elevated Disease Marker May Guide Lupus Treatment

CD38 Protein Induced in Human Macrophages in Inflammatory Conditions

Ohio State researchers collaborated across disciplines and divisions to study a biomarker of inflammatory immune activity in systemic lupus erythematosus (SLE). The group aimed to see whether earlier findings in mice would extend to human cells. Data confirmed that the CD38 glycoprotein is a reliable biomarker of human inflammatory macrophages – important immune cells that pave the way for managing inflammation. The team's findings show promise for better lupus disease activity markers and novel therapeutics.

"The search for biomarkers in lupus is an ongoing quest that laboratories across the country have been working on," says Division of Rheumatology and Immunology Director Wael Jarjour, MD. "Identifying a protein that maybe a biomarker for lupus disease activity found on macrophages is a significant step forward in this field."

Mireia Guerau, PhD, assistant professor, Ohio State's College of Medicine, Department of Neuroscience, Health and Rehabilitation Sciences, led the study. Dr. Guerau directs Ohio State's Applied Immunology Laboratory. The CD38 study involved specialists from Ohio State's Medical Laboratory Science, Rheumatology and Immunology, and Microbial Infection and Immunity Divisions within Ohio State's College of Medicine and College of Veterinary Medicine.

"This highly collaborative effort brought macrophage, monocyte and SLE expertise together to improve our understanding of SLE," said Dr. Guerau. "Following CD38 in SLE patients may allow us to determine whether the therapy a patient receives is reducing disease activity without waiting for additional clinical signs," she says. "We hope to better match patients with the therapies that work for them."

A Closer Look at CD38 Proteins

Various types of immune cells contribute to inflammation and autoimmunity. "Macrophages and their monocyte precursors

Education

Continuing Medical Education Conference: Clinical Applications: Ultrasound for Rheumatoid Arthritis, Psoriatic Arthritis and other Musculoskeletal Diseases

Hareth Madhoun, DO, will lead a two-day, intensive workshop on May 31 - June 1, 2019, featuring experts in musculoskeletal ultrasound from academic medical centers across the country. It includes more than 10 hours of hands-on training in small groups, and learning ultrasound-guided injections on cadavers.

Registration opens in early 2019. For information or to register, please visit **ccme.osu.edu**. You can also visit our website at **internalmedicine.osu.edu/rheumatology**.

mediate innate immune responses," Guerau explains. "They can promote varied responses ranging from proinflammatory to proresolving."

By identifying changes in lupus patients' immune cells, researchers can see how they contribute to disease development. Biomarkers help diagnose or predict disease activity and suggest treatment adjustments.

"Currently, there are no good biomarkers of disease activity in lupus patients," says Dr. Guerau. "We previously identified CD38 as a robust marker of inflammatory macrophages in in vitro and in vivo mouse models. In humans, CD38 is expressed in certain cancers and HIV infection. However, we did not know whether CD38 was a human inflammatory macrophage marker."

To find out, investigators compared samples from healthy controls and patients with lupus with low versus high disease activity. The group followed CD38 expression in resolving versus inflammatory macrophages and examined precursor monocyte cells.

The CD38 glycoprotein is encoded by the CD38 gene. Glycoproteins, which require sugar to function, adhere to cell surfaces. Scientists often use them as surface markers. High CD38 expression reveals inflammatory activity.

"CD38 is a reliable marker of human inflammatory macrophages while other more resolving macrophages do not express it," says Dr. Guerau. "We also found that certain monocytes express high CD38 levels in patients with active SLE versus inactive patients or healthy controls."

The findings when validated provide new tools to follow disease activity in SLE patients or others with autoimmunity. Researchers hope to repeat these results in a larger cohort and understand CD38's contribution to inflammation.



Rheumatology Fellowship Program

BACK LEFT TO RIGHT: Yue Ding, MD, Jacob Seymour, MD, Bryan Coniglio, MD and Veronica Mruk, MD FRONT LEFT TO RIGHT: Lydia Cortes-Betancourt, MD, Kevin Hackshaw, MD, Program Director, Sheryl Mascarenhas, MD, Assistant Program Director, and John Fleming, DO



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A selection of journal articles from the impressive list of publications authored or co-authored by our faculty:

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