SPOTLIGHT ON
RESEARCH

SPRING 2015

Arthritis Foundation℠

ARTHRITIS FOUNDATION RESEARCH FORUM
Inspired Science from Young Investigators

The Arthritis Foundation funds pioneering scientists with innovative ideas that have the potential to move arthritis research in new directions.

On April 23rd four of these funded researchers presented their findings at the Foundation's research forum at NYU Langone Medical Center in New York City. They included Postdoctoral Fellowship recipients: Yu Grace Qiao, PhD, Hospital for Special Surgery; Wenzhao Meng, PhD, University of Pennsylvania Medical Center; and Tanisha Jackson, PhD, Feinstein Institute for Medical Research, North Shore-LIJ Health System.

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The fourth investigator, Innovative Research Grant recipient, Jose Scher, MD, Assistant Professor of Medicine, NYU School of Medicine, and Director, NYU Psoriatic Arthritis Center, was the keynote speaker.

Stephen I. Katz, MD, PhD, Director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, was the evening's special guest.

Autoimmune diseases are malfunctions of the body's immune defenses. Instead of attacking foreign infectious agents, the immune system mistakenly attacks the body's own cells and tissues. More than 5 million Americans have some autoimmune form of arthritis. If left untreated, autoimmune diseases can damage the skin, blood, nervous system and internal organs.

The researchers examined different paths within the human body that lead to autoimmunity and inflammation. Through their research, they have learned more about the mechanisms that cause inflammation, thereby increasing the arsenal of data medical science can use to design new treatments and stop the destructive process in its tracks.

Read more about their investigations on page 3.

Featured speakers met before the forum on April 23rd. They are (left to right): Dr. Jose Scher, Dr. Yu (Grace) Qiao, Dr. Tanisha Jackson; Dr. Stephen Katz and Dr. Wenzhao Meng.

Interview with Dr. Stephen Katz

Before attending the research forum, Dr. Stephen I. Katz, Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), answered some questions for "Spotlight on Research."

Q: Have there been any changes/ trends in the way rheumatology research has been conducted over the past 10 years?

A: Over the last decade, we've seen new kinds of scientific partnerships. Collaborations have formed not only across disciplines and between basic, translational and clinical researchers, but also across sectors. The recently funded NIH Accelerating Medicines Partnership (AMP) in lupus and rheumatoid arthritis is an excellent example. It is a multi-sector effort with government, academic institutions, patient groups, private foundations, and industry working together to achieve the shared goal of identifying and validating promising biological targets for drug development. Research also has become more technology-driven. The AMP is a great example of how cutting-edge technology is advancing biomedical research.

Q: What do you feel will be three important areas of growth in rheumatology research going forward?

A: I'll mention computational biology, team science, and patient-centered research. All three play a critical role in advancing precision medicine—the ability to tailor treatment based on an individual's biology, environment and lifestyle. Promising computational and technological tools will improve understanding of biological and environmental factors that influence health and disease. But, researchers must work together to achieve maximum public benefit from those valuable resources. Efforts to incorporate patient-reported outcomes into clinical research will enhance interventions for individuals with chronic diseases. Of course, there are many other exciting opportunities. The NIAMS Long Range Plan is an excellent resource for learning more.

Q: What would you say to young scientists to encourage them to focus on research?

A: I would tell them that "you are the future!" Ensuring a robust pipeline of new biomedical investigators is one of our highest responsibilities, and we have taken several steps to support young scientists. For example, the NIAMS leads the intramural NIH Rheumatology Training Program, which was featured in *The Rheumatologist* in March 2015. Like many NIH components, we have a more generous payline for applications from new investigators. NIAMS funds extramural training and career development programs for researchers in its mission areas. This is a period of tremendous opportunity in science, technology and medicine. I would encourage young researchers to focus on what they see as the most exciting scientific questions.

Investigators Featured at April 23rd Forum

Jose U. Scher, MD

NYU Langone Medical Center • New York, NY

Dr. Scher is Assistant Professor, Department of Medicine, at NYU Langone Medical Center. He also serves as Director of three facilities: the Arthritis Clinic at NYU-Hospital for Joint Diseases, the NYU Psoriatic Arthritis Center at NYU Medical Center, and the Microbiome Center for Rheumatology and Autoimmunity at NYU School of Medicine.

A practicing rheumatologist and leading investigator, Dr. Scher's areas of expertise are psoriatic arthritis (PsA) and rheumatoid arthritis (RA). His main area of research is related to the role of the human microbiome (all microorganisms and genetic material present in the human body) in autoimmune and rheumatic disease, specifically in psoriasis, PsA and RA.

Dr. Scher's lab findings include the association between periodontitis and RA, with certain microbes in the gums only characteristic of new-onset diseased patients. He and his collaborators have found an overabundance of intestinal bacteria called Prevotella copri in the intestinal microbiome of newly diagnosed, untreated RA subjects. Dr. Scher's team also observed an absence of two gut microorganisms (known as Ruminoccocus and Akkermansia species) in patients with PsA. These two microorganisms which protect the intestines are also found lacking in patients with other related conditions such as inflammatory bowel disease. The goal of his research is to better understand these findings for diagnosing and treating patients with inflammatory arthritis.

Yu (Grace) Qiao, PhD

Hospital for Special Surgery • New York, NY

Dr. Qiao received her PhD in Immunology at the University of Michigan and later joined Dr. Lionel Ivashkiv's lab at Hospital for Special Surgery. She studied chronic inflammation and the mechanisms and regulation of proteins called interferons in an effort to better understand autoimmune diseases such as rheumatoid arthritis.

Dr. Qiao's investigation looked at macrophages, which are cells that play important roles in promoting inflammation in diseases including rheumatoid arthritis. Macrophages produce pro-inflammatory cytokines such as TNF and IL-6, that lead to tissue destruction, she explains. "The goal of our research was to better understand how the genes that encode these cytokines are regulated and we did discover new mechanisms that regulate the expression of these genes."

"We also found that DNA organization plays an important role in the control of inflammatory cytokine expression," she says. "We discovered that a pro-inflammatory environment changes DNA structures of cytokine genes such as TNF and IL-6, creating a type of 'snowball' effect. First, this type of environment sensitizes cells for faster and elevated inflammatory responses to even minimum levels of stimulation. Second, once genes are activated, they are more difficult to turn off as the DNA structure cannot be closed properly. This provides a potential explanation of prolonged cytokine production in chronic inflammation and may help us design safer and more effective new targets for drugs to treat autoimmune disorders like rheumatoid arthritis."

Investigators Featured at April 23rd Forum

(CONTINUED)

Wenzhao Meng, PhD

University of Pennsylvania, Perelman School of Medicine • Philadelphia, PA

Dr. Meng received her PhD in Biochemistry at Temple University in Philadelphia and a degree in Molecular Biology in her native China. She is currently a Research Associate of Pathology and Laboratory Medicine, Perelman School of Medicine, and Acting Technical Director, Human Immunology Core, at the University of Pennsylvania.

"B cells are an important part of the immune system as they generate the millions of antibodies that recognize and attack specific infectious agents," Dr. Meng says. "In normal immune system development, the B cells which produce antibodies that would attack the body's own cells are eliminated before they mature — but in autoimmune disorders, this selection process fails, allowing faulty B cells to fully develop and begin producing self-attacking antibodies. Therefore, a major challenge of improving the diagnosis and treatment of autoimmune diseases is first figuring out how to pinpoint the defects in the selection process that allow faulty B cells to pass through."

Dr. Meng explains that "there are millions of different B cells, and trying to find the faulty B cells is like looking for a needle in a haystack." In an important advance, she and her colleagues have developed B cell repertoire high-throughput sequencing techniques that have allowed them to identify abnormal B cells that could lead to autoimmune disorders. Specifically, Dr. Meng analyzes the genetic coding of millions of B cells and suggests that genetic coding of B cells in lupus patients differs from normal controls. "My hypothesis is that this genetic coding is differentially selected in lupus patients, and that the genetic alterations resulting in possible faulty B cells expansion may serve as candidate biomarkers for early lupus diagnosis or response to B-cell targeted therapy."

Tanisha Jackson, PhD

The Feinstein Institute for Medical Research

North Shore-Long Island Jewish Health System • Manhasset, NY

Dr. Jackson's curiosity about how the immune system is regulated drives her interest in the field of rheumatology. She received her PhD in Microbiology from the University of Alabama at Birmingham, and is currently a postdoctoral fellow in the lab of Dr. Betty Diamond at The Feinstein Institute for Medical Research. Tanisha shares with us some of the findings revealed during her Arthritis Foundation-funded study of the effect of CSK gene expression on B cell tolerance and autoimmunity.

"We have found that people with a mutation in a gene called CSK have an increased risk of developing lupus," Dr. Jackson explains. B cell activation leads to a relay of messages from the B cell receptor on the surface of the cell to molecules that perform specific functions inside the cell. CSK is a molecule that can block the relay of messages during B cell activation.

"The goal of my research was to understand how changes in CSK activity cause lupus. To study this, I used mouse models of the disease in which the mice express higher or lower levels of CSK in their B cells. My research showed that mice with less CSK produce fewer antibodies against DNA and have decreased kidney damage while increased expression of CSK leads to more hyperactive B cells and more severe disease. This suggests that reduced CSK can lessen the effects of lupus. Finding a treatment that can turn down CSK activity may reduce autoantibody production and the ensuing damage caused to organs. We hope that CSK will be a potential target for lupus therapies that will help improve the lives of patients with the disease," she says.