

**Johns Hopkins University School of Medicine** Division of Rheumatology Winter 2014

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## **VICIOUS** CYCLE

## WELCOME TO LEAP

The people who work here in the Division of Rheumatology are truly exceptional. In addition to being very good at what they do, they are dedicated and caring, and every one of them brings something to the job that is distinctive and special.

All of us know that when you are sick, coming to the clinic or hospital can sometimes feel intimidating or even scary and confusing, especially if you are in pain or if you are here to help a friend or family member who is sick, and you're worried. And so, we thought that it might help for you to get to know us. Recently, I asked all of the faculty and staff in the Division to tell you about three things: Their background, their experiences, and an object that is meaningful to them and helps crystallize why they are here. The responses have been amazing, and I want to share some of them with you.

I also want to explain the title of our magazine: We decided on the name, "Leap," for several reasons. First, because the verb itself is one of progress; it is not stagnant. Neither are rheumatological diseases, and neither is our work in treating them. "Leap," to us, suggests hope, and faith, and joy. A leap is not a tentative baby step; it is bold and purposeful. We have so much hope here. We hope and believe that we can improve the lives of our patients. We have faith in our scientists, whose discoveries are bringing about better treatments for the challenging diseases our patients face, and in our staff, who are here because they want to be, because they want to make a positive difference in your life.

Antony Rosen, M.D. Director, Division of Rheumatology

## WINTER 2014

- 4 Vicious Cycle
- 8 Lupus and the Arteries
- 14 Different as Snowflakes

## 10 Photo Essay: The Story Project

"Recently, I asked all of the faculty and staff in the Division to tell you about three things: Their background, their experiences, and an object that is meaningful to them and helps crystallize why they are here. The responses have been amazing, and I want to share some of them with you."

- Antony Rosen

Additional responses to the Story Project initiative are included on pages 7, 16, and 17.



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DISCOVERY

IN THE VERY WORST RHEUMATOID ARTHRITIS, IT TURNS OUT THAT WHAT'S DRIVING THE IMMUNE SYSTEM AND HURTING THE BODY IS...THE IMMUNE SYSTEM

It's a difficult and frankly odd concept, and scientists are just starting to grasp it, but it opens up some exciting possibilities for diagnosing and treating the most severe rheumatoid arthritis (RA): The engine driving severe RA is the immune system, which makes antibodies that stimulate the body to make antigens - proteins that, in turn,

stimulate the production of more antibodies.

Thanks to a discovery made at Hopkins, scientists have a new and very important clue as to what produces the often debilitating symptoms of RA. And now that they know what to look for - a biomarker that can be spotted in a blood test - they hope to identify the patients who have it the worst before the disease takes its toll on the joints. Even more exciting: This discovery of something no one knew existed may lead to new ways to treat the most aggressive cases of RA - and perhaps limit or prevent devastating joint damage altogether.

It all started with some antibodies. Scientist Erika Darrah, Ph.D., was studying some enzymes, called peptidylarginine deiminases (PADs for short), known to play a role in RA; in particular, she was studying an enzyme called PAD4. Then she noticed something unexpected: Some patients with RA had antibodies to this enzyme in their blood. "Normally in autoimmune diseases, antibodies are thought to be passive bystanders that just mark damage to

## WHAT ARE PADS?

PAD enzymes are involved in a process called citrullination. Citrulline is an amino acid that is normally present in the body and is important for many of the things our cells routinely do; basically, PADs modify specific proteins in the body. For reasons that are still unclear, the immune system in patients with RA often attacks a specific set of proteins that contain citrulline - proteins that have been modified by PADs. "This phenomenon is really specific to RA," says Erika Darrah, "and doesn't appear to happen in other autoimmune diseases that we know of."

## "[Antibodies] may be driving RA...by turning on enzymes, amplifying the immune response, and perpetuating the cycle of damage."

specific tissues," Darrah says. But it turns out that these particular antibodies are anything but passive. In fact, they bind to the PAD enzymes. What should happen next is that the enzymes would be cleared from the body, their function effectively handcuffed. Instead, these enzymes get turned by the antibodies into super-efficient machines that then modify thousands of other molecules. The antibodies jump-start the PAD enzymes, says Darrah, "and it is an almost irreversible event." Darrah's finding, and the investigation this immediately sparked, suggest a whole new way for scientists to think about antibodies: "They may be driving RA in these patients by turning on enzymes, amplifying the immune response, and perpetuating the cycle of damage." In the initial study, Darrah and colleagues looked at blood samples from 44 patients with RA; of these, 18 percent had the PAD antibodies. In a second study, they looked at 194 samples, and found the antibodies in 12 percent of patients. In both studies, howev-

er, the antibodies showed up in people with

need of innovative approaches to treatment.

extreme cases of RA – the people most in

Darrah, Rosen, and colleagues published

currently part of our approach at all,"

this work in Science Translational Medicine.

"Looking for these antibodies is not

says Antony Rosen, M.D., the Mary Betty Stevens Professor and Director of Rheumatology at Johns Hopkins. But identifying subgroups of patients with specific features and treating them as individually as possible has been one of Rosen's aims for Rheumatology; he has also led a larger drive toward more personalized medicine throughout Johns Hopkins. What "personalized medicine" means is that if you have RA, it's not the disease, but your disease that counts. What's most important to the doctors treating you is the details of your disease - what's causing your pain, how best to treat the inflammation in your bones and joints, and how to give you the most mobility and best quality of life. In recent years, scientists have learned that these factors can be very different from one patient to the next.

"To develop a test that allows physicians to determine what type of disease patients have, what treatments they'll respond to best, and what side effects they'll have that's really our goal," says Darrah. "Right now, physicians have a lot of tests they can run to diagnose and even predict who's at high risk to develop RA. But there is currently no information to figure out ahead of time what type of RA they're going to develop. We can't yet tell a patient, 'over

the next five years, your disease is going to be relatively stable and mild,' or 'your RA is going to be really aggressive and it will require aggressive therapy.""

For now, RA is "a big umbrella," says Darrah. "Likely there are different subgroups of patients who get to this disease in various ways, and if we can learn more about the disease as a whole, we can identify the specific pathways or arms of the immune system that are active in one patient versus the next, and tailor our therapy to that individual."

The ability to distinguish those who are in for a more severe course of RA would be of great help to patients and doctors. The test is still being validated and is not yet ready for clinical use; Darrah, Rosen, and colleagues are exploring with a biotech company the possibility of developing a clinically available test.

What Darrah and colleagues have found, basically, was so unexpected that they're still trying to understand all of the repercussions that this discovery may hold. There are so many questions: "What we know so far," says Darrah, "is that some people with RA continue to accumulate damage over time. Our data suggest that in the people who develop this biomarker, their disease really takes off and becomes much worse. Even though they may have had RA for a long time, once they develop this biomarker, they tend to develop severe

"We want to know exactly when this biomarker appears in relation to clinical symptoms..."

disease that is hard to control. We don't yet know all the nuances."

The timeline will be very important to figure out, and to do this, the Hopkins team will need to study longitudinal samples of blood – samples, taken over the course of years, of the blood of people with RA, or from people in long-term medical studies who go on to develop RA - to determine the answer to questions like these: Was this antibody there the whole time? Was it there before RA was even diagnosed? If not, do people somehow just develop this antibody - and if this just spontaneously happens, could it be that a virus, or infection, or some other factor leads up to it? "That's the next step," says Darrah. "We want to know exactly when this biomarker appears in relation to clinical symptoms, to understand if there's a good window of time to identify people with the biomarker, to intervene and maybe prevent damage."

Another critical question: If scientists can figure how the antibody turns the enzyme on, can they figure out a way to turn it off? "If we can learn how these antibodies are interacting with these PAD enzymes, exactly how they're pushing the disease forward, maybe this will lead to the development of an inhibitor that can intervene in a specific part of the immune system that's dysregulated, and actually

stop this." L



## THE STORY PROJECT

Julie Paik, M.D. Instructor in Medicine, Division of Rheumatology

I was reminded of thick Korean thread at my son's first birthday party. This is a big celebration in Korean tradition. The highlight is a game where the child chooses an object which foretells his future. If he chooses thread, it means he is destined for a long life. To me. this thick thread characterizes my relationship to work because I have had a long connection to Hopkins. The initial thread would be the fact that I attended college at Johns Hopkins and then returned here for fellowship. The additional tiny threads that make up this larger thread are all the people I have met through work - my amazing mentors, colleagues, coordinators and staff at this division. Because of this intertwined network, this thread only gets thicker and stronger and contributes to my growth as a clinician and researcher.

## INSIGHTS

# **IIIII AND** THE H H

NEW HOPE FOR FIGHTING **ATHEROSCLEROSIS** 

For people with lupus in the Western world despite so many advances in treating autoimmune disease — accelerated atherosclerosis remains a bitter enemy.

For people with lupus in the Western world – despite so many advances in treating autoimmune disease - accelerated atherosclerosis remains a bitter enemy. The fact that atherosclerosis ("hardening" of the arteries, with the buildup of fat and cholesterol that form plaque deposits) kicks into high gear in these patients and is the major cause of death has long troubled physicians and researchers like Michelle Petri, M.D., M.P.H., and Adnan Kiani, M.D., M.P.H. "The survival of patients with lupus has not improved since 1980," says Petri. "We can treat lupus nephritis better, we have better antibiotics and better medical care in general – but we haven't made any progress in preventing the accelerated atherosclerosis."

But fresh insights by Petri and Kiani and an exciting collaboration with Hopkins cardiologist Armin Arbab-Zadeh, M.D., offer new hope - not only for treating lupus, but for treating atherosclerosis in general.



Look at all the green in this CT image of an artery. That's the soft, noncalcified plaque, and it's full of inflammation, very unstable. The pink is an established, hardened deposit of plaque. The orange is the remaining opening within the artery for blood to flow through.

## **Getting Beyond Traditional Risk Factors**

Petri, Director of the Lupus Center and of the Hopkins Lupus Cohort, identified multiple factors that predict the risk of complications from accelerated atherosclerosis; with biostatistician Larry Magder, she published them in the American Journal of Epidemiology. "These include hypertension and cholesterol and also some lupus-specific factors, such as lupus anticoagulant and low complement," Petri says. "But we are treating the traditional cardiovascular risk factors and we think we're treating lupus." So why haven't the statistics changed? Petri and Kiani carried out the Lupus Atherosclerosis Prevention Study, a twoyear clinical trial, actively targeting the atherosclerosis with high doses of a statin drug, atorvastatin (Lipitor). "We were so sure that statins would help," she says, but "to our unhappy shock, atorvastatin did not reduce progression of atherosclerosis in lupus," even though statins have been proven to lower the "bad" LDL cholesterol and reduce inflammation. "I don't think very many people believed our study, until the same thing happened in a pediatric lupus trial. The final nail in the coffin was that statins didn't even work in the lupus mouse model to prevent atherosclerosis.

We were quite discouraged." Clearly, there had to be more going on

"When our trial was negative," says Kiani, "we starting looking at the noncalcified plaque" - plaque in an early, "soft" state before it hardens. "Noncalcified plaque is more active, has an inflammatory component, and it's more unstable. We started looking at the prevalence of this noncalcified plaque in lupus patients. To our surprise, there was about a 50-percent presence of noncalcified plaque among lupus patients." The next goal is to follow these patients and see how this softer plaque progresses. Kiani and Petri will also be looking at immunologic markers, medications, and disease activity, to see if they correlate with any changes in the noncalcified plaque buildup. "This type of study has not been done in any of the rheumatologic fields," notes Kiani.

Cardiologist Arbab-Zadeh, director of Cardiac Computed Tomography, is developing a scoring system for noncalcified plaque, comparable to the system used to evaluate hard plaque deposits. "Noncalcified plaque has been studied in HIV," notes Petri, "where there's also an increase in accelerated atherosclerosis. A chronic inflammatory state seems to be a way to activate atherosclerosis - whether it's an infection like HIV or an autoimmune disease like lupus."

Petri and Kiani are conducting follow-up scans for noncalcified plaque in patients with lupus whom they had evaluated a couple of years ago. "We're hoping that we will have so much more information over the next couple of years," Petri says, "that might enable us to try again for an intervention study. It may be that something could work at this very early level of noncalcified plaque."

Petri and Kiani believe that this research could lead to whole new ways of treating inflammation and soft plaque in many groups of patients. "The insights we get in a terribly inflammatory disease like lupus," Petri says, "may have payoffs in the general population." L

# THE STORY PROJECT

MEET SOME OF THE PEOPLE DEDICATED TO MAKING OUR PATIENTS' LIVES BETTER. IN OUR STORY PROJECT, CARRIED OUT WITH MUCH HELP FROM MATT ROSEN AND ALLAN GELBER, M.D., PH.D., M.P.H., WE ASKED FACULTY AND STAFF TO TELL US A LITTLE ABOUT THEMSELVES AND ALSO TO DESCRIBE AN OBJECT THAT IS PERSONALLY MEANINGFUL AND HELPS CRYSTALLIZE WHY THEY ARE HERE.



This is a picture of my son. He is my personal connection to the rare disease community. He is a reminder why doctors and researchers do what they do. Had a lab in the Netherlands never taken an interest in Schinzel-Giedion syndrome, we would never know the genetic mutation that causes it. The same can be said for the Scleroderma Center and the Division of Rheumatology. If none of us, or the doctors we work for, had ever taken a scientific interest in these diseases, we would not make progress into understanding them. Each of our patients is a father, mother, son, or daughter, who wants better treatments and a cure for their disease just as I hope for my son. My family is a reminder that I, too, am a patient of Johns Hopkins and I want to treat each of our patients the way I want my son to be treated – with sincerity, dignity, respect, and understanding.

ADRIANNE WOODS, RESEARCH PROGRAM COORDINATOR

About seven years ago, I started at the brand new Myositis Center with nothing more than a folding table and a trash can. I realized that this disease was malicious and I really felt that I had to do everything I could to help the patients get the care they needed to get well. For the first time in my life, I felt that I was a part of something important - like really important - and I was making a difference. This was probably the most rewarding experience, not just of this job, but of my entire career thus far. After a few years and a couple of thousand patients later, I was promoted to Clinical Supervisor of the General Rheumatology Clinic at Good Sam and, more recently, I was promoted to oversee the Bayview and Good Sam clinics. As a young woman, mother, college student and an ambitious career woman, I am so grateful to be a part of a Division that values equality and family while recognizing its employees for a job well done and encouraging growth.

SHANNON BISHOP, CLINICAL SUPERVISOR

My mission is simple: to build a better world. I believe that we all partake in this common pursuit to enrich the world. I take joy in my work, as if I were a Rockette: watching young people find their vocation, providing encouragement (as well as a few home-cooked meals) along the way, and being there for such milestones as graduation; enhancing my skills as a clinician educator in Rheumatology; caring for patients as they deal with rheumatic diseases; and inspiring others as I have been inspired.

The world – including Rheumatology – has changed significantly in the years since I came to Hopkins. I believe that I am one of the "living stones" in our Division. "Living stones" are not just an inert foundation, but a vibrant assembly – embodying always the best, unyielding in service, co-creating a better world. Others may choose to sit it out. We will dance!

CAROL ZIMINSKI, M.D., ASSOCIATE PROFESSOR OF MEDICINE





If I had to choose something that represents how I feel about my work, it would be my hiking boots.

Walking long distances and up mountains is hard work, and it reminds me of many aspects of being a rheumatologist: That getting to the summit requires hard work and perseverance, that the journey is not always comfortable and easy but the struggle makes the achievement that much more meaningful. That one's partners along the path are so crucial to the enjoyment, meaning and memories of the journey. And that failure to reach the summit the first time often means trying again using a different path, or preparing better for the journey.

So, too, with our work here. We have a destination, we have a walking team. Many people have different skills and strengths to get us over the terrain and to reroute as needed. We know the pain and reward of effort, and how our journey brings us near to the spirit and mystery of our universe which animates and calls us.

ANTONY ROSEN, M.D., DIRECTOR, DIVISION OF RHEUMATOLOGY

I am a postdoctoral fellow in the Division. I was born and raised in Berlin, Germany. I grew up in a city that was free and yet surrounded by a death strip. Every Christmas, for the first years of my life, I passed tanks lining the streets on our way to see my grandparents. When I was 5 years old, my father gave me a chisel and took me to an endless wall. That wall, the Berlin Wall, was the means of dividing a whole nation and the symbol of a world divided. That day, I knocked the tiniest piece of concrete out of it. Insignificant by itself. But so did thousands of others that came together determined to tackle this obstacle too big for any individual to overcome. They did.

Fifteen years later, I studied medicine at Humboldt University of Berlin, a birthplace to modern pathology, microbiology and immunology, right behind the cobblestones that now mark the Wall that is no more. I first came to the Division in 2009, fascinated by systemic autoimmune diseases and inspired to learn at a place that has greatly shaped our current understanding of rheumatic disease mechanisms. I brought the story of a city, my story, with me.

MAX KÖNIG, M.D., *POSTDOCTORAL FELLOW* 



Winter 2014 | **LEAP** 13

RESEARCH

# -HKSNOWFLAKES

NEW DISCOVERIES HELP EXPLAIN WHY RHEUMATIC DISEASES LIKE SJÖGREN'S ARE DIFFERENT IN EACH PATIENT, AND POINT THE WAY TO NEW FORMS OF TREATMENT

Like snowflakes, rheumatic diseases manifest themselves in unique ways. For example: Two patients with Sjögren's syndrome might seem to have identical symptoms, but have dramatically distinct complications. Finding effective treatment is not easy.







## THE STORY PROJECT

Mark Soloski, Ph.D. Professor of Medicine

A Mobius strip, also called a twisted cylinder, comes to mind. I've always been fascinated by interesting objects that stimulate thought; the works of M. C. Escher come to mind. The Mobius strip has no real end, no matter where you begin on the strip as you traverse the surface, you never come to a stopping point. I believe science is much like this - when it is done well. we do cover much around but when we do so, we keep generating new questions that need to be unraveled. It is a job never completely done, a job we keep passing on.

Research led by Hopkins scientists has shed new light on why patients fall into various subtypes of rheumatic disease: It's because what's causing the same outward clinical signs and symptoms can involve completely different molecular pathways from person to person. In a recent study, the scientists looked at the two types of interferon that are active in the salivary gland tissue of Sjögren's patients. Their findings, published in the journal, Proceedings of the National Academy of Science (PNAS), also have important implications for people with lupus and other autoimmune diseases.

Genetic studies have shown that many interferon pathway genes are triggered in several rheumatic diseases, including Sjögren's and lupus, "and this has led to the hope that targeted treatment could turn off specific types of interferon and be of benefit to patients," says rheumatologist Alan Baer, M.D., co-author of the study. But as the scientists found, "it's not quite as simple as we thought. There's more than one type of interferon that's activated in these patients – and simply turning off one form of interferon may leave other forms activated, which may perpetuate the disease. So it's really provided an extra layer of complexity to our understanding of what's going on in these patients."

In this study, scientists looked at type I and type II interferons, which switch on similar – often overlapping – genes.

Previous studies looking at gene expression had suggested that type I was the major form of interferon active in Sjögren's patients. "But those earlier analyses were kind of like watching a horse race," says study co-author, John Hall, Ph.D., "and concluding that the horse that's leading at mid-track is the one that wins the race." Instead of looking at a snapshot of gene activity - a single analysis at four or maybe 12 hours – the investigators looked at the equivalent of a time-lapsed photo, following interferon patterns in genes for 48 hours.

Early on, many genes appeared to be specifically activated by type I (alpha) interferon. However, over time it became apparent that these same genes were also highly activated by type II (gamma) interferon. "This is important," says Hall, "because when you look at a picture of diseased tissue, you don't know whether the events you're capturing occurred 30 minutes ago, 30 hours ago, or days ago. So by analyzing the signatures at only one time, you've missed the whole story. Kinetics is very important." How important? Interferon type I can be made by many cells, but the presence of interferon type II suggests that particular immune cells - T cells, for example – are active in the diseased tissue.

"We think this work is fundamental because it may enable the molecular pathways that are directly active to be identified and precisely defined" with biomarkers, says

"...turning off one form of interferon may leave other forms activated, which may perpetuate the disease."

## "...we hope to be able to tailor therapies that will specifically interfere with the key molecular pathways active in individual patients."

study co-author Livia Casciola-Rosen, Ph.D. "It could help choose which therapies are going to be effective in any one patient. In Sjögren's syndrome and many autoimmune diseases, good biomarkers are lacking."

The scientists spent years doing preliminary studies, first looking at the expression of interferon-regulated genes and then interferon-regulated proteins in cultured cells, Casciola-Rosen says. "We spent a lot of time and effort choosing and then validating and optimizing the most precise and best probes to report on the distinctive interferon pathways. It sounds simple, but it actually took a lot of time and very detailed work - and at the end, we knew what probes to use to see whether type I or II, or both, were active." The reason for such painstaking groundwork, she explains, is that in Sjögren's disease, "patient samples are rare and very precious. We have tiny amounts of tissues to work with. We wanted to be sure that when we got them, we would do the right experiment." The probes paid off: In some samples, mainly Type I was shown to be active; in others, mainly Type II, and in a few, both types of interferon were active. "That was really interesting, because if you use a therapeutic drug on a patient that targets Type I interferon activity, and that patient has Type II, that therapy won't work effectively." The next step, she adds, is "to look at a bigger group of tissue

## **Precision Medicine: Tailoring Treatment to Fit the Patient**

This work would not have been possible,

"The remarkable discovery here is that there is considerable heterogeneity among patients with Sjögren's," says Baer, "and understanding that heterogeneity is very important." Ideally, molecular markers will characterize the disease picture beforehand and help the doctor come up with subtypespecific treatment. This kind of "precision medicine" is already happening in cancer therapy, Baer notes. "That's really the hope of the future. In the past, we've relied primarily on just clinical characterization; patients come in with certain clinical findings and we've labeled that as Sjögren's. But now we hope to be able to tailor therapies that will specifically interfere with the key molecular pathways active in individual patients. Without question, it's very complicated and there's still a lot more work to be done, but this is a very exciting time." Baer adds, without the Jerome L. Greene Foundation, which established the Sjögren's Syndrome Center at Johns Hopkins and helped fund this research. "We wouldn't be able to do these types of studies without their tremendous support." L

samples to make sure our findings really are robust, and then work on trying to take this to the therapeutic level. We hope this is really going to help people."



## THE STORY PROJECT

Ami Shah, M.D., M.H.S., Assistant Professor of Medicine

A spark: Sometimes when I am pursuing a research question, I make a discovery that is completely unexpected, but highly interesting. In this situation, it is like a spark that stimulates me to dig deeper and motivates me to share what I have learned.

Hopkins Rheumatology is known for outstanding clinical research, compassionate care and teaching, exceptional training, a robust basic immunology program, and an environment where our scientists and clinicians work together to solve problems.

> The Johns Hopkins Hospital opened. Its first Professor of Medicine, Sir William Osler, made some of the earliest contributions in treatment of rheumatic disease in the U.S.

We have 6 disease-specific Centers: Arthritis, Lupus, Myositis, Scleroderma, Sjögren's Syndrome, and Vasculitis The Johns Hopkins Division of Rheumatology has been ranked #1 in the nation in the annual *U.S. News & World Report* Best Hospital rankings for 9 consecutive years. We would not be here without the hard work of our entire team of faculty,

researchers and staff.

WE SEE PATIENTS WITH MORE THAN 200 TYPES OF RHEUMATIC DISEASES FROM ALL OVER THE WORLD.



I love to laugh. I grew up watching comedies and when I was old enough, started to do some acting myself. We work in an often-serious profession, and sometimes my lightheartedness had to be put on hold during my training. As I've grown older, I realize that we heal people in ways that have nothing to do with medicine. Bringing joy to a patient can be equally beneficial. Why do we heal people if not for them to go on and enjoy life? Levity and humor are key to my life philosophy and they've become key to my role as a physician.

LAURA CAPPELLI, M.D., POSTDOCTORAL FELLOW



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## "We must walk consciously only part way toward our goal, and then leap in the dark to our success."

— Henry David Thoreau