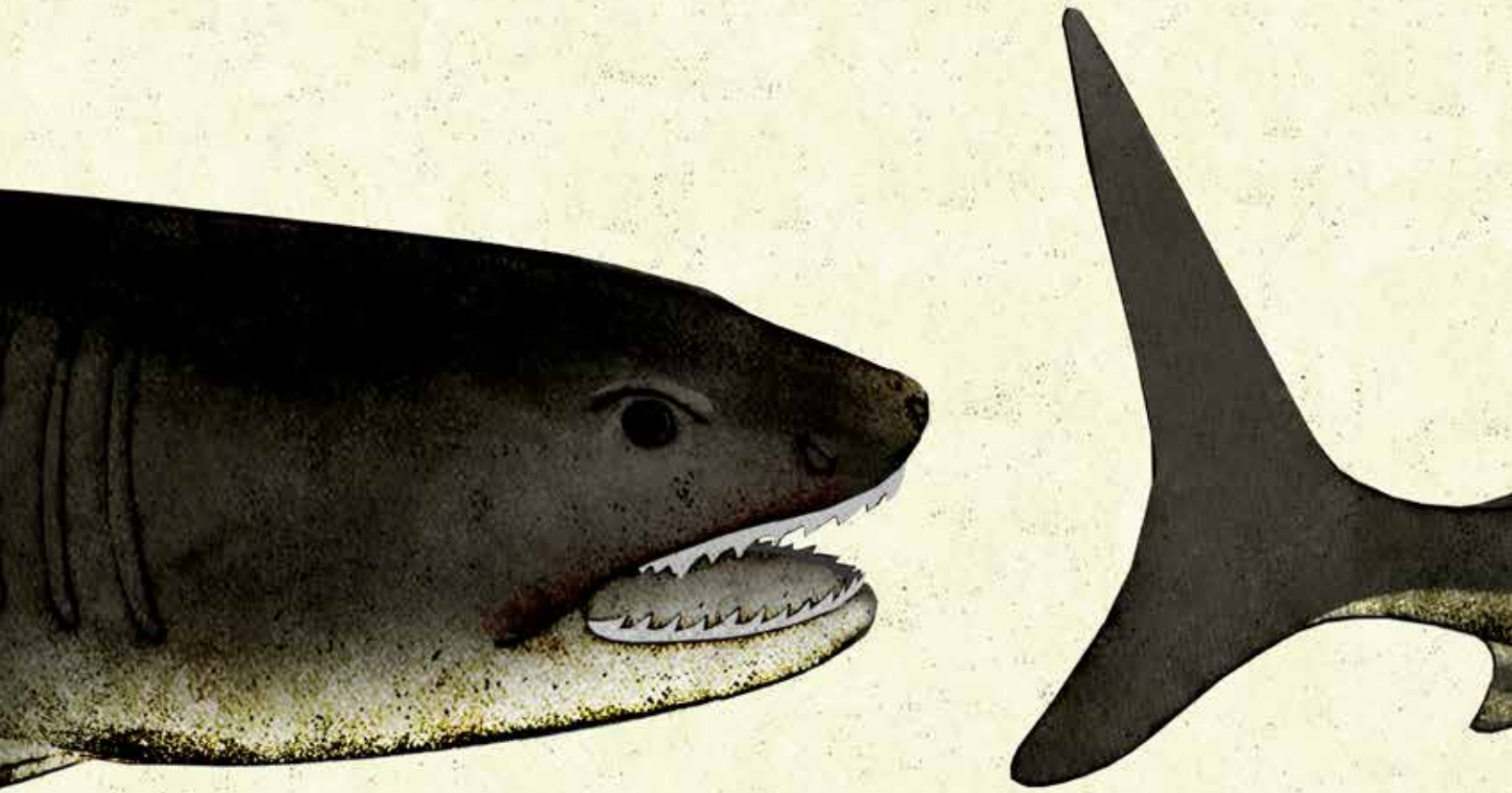
LEAP

Johns Hopkins University
School of Medicine
Division of Rheumatology
Holiday/Winter 2015



CONNECTIONS

AUTOIMMUNITY AND CANCER

"IT'S SUCH A BLESSING"

WHEN THE BODY TURNS ON ITSELF

POINTS OF CONNECTION

This issue of *Leap*, although autoimmunity is on the cover, is actually about the many points of connection here in the Division of Rheumatology. First, of course, is our connection to our patients. It's not just physicians, nurses, and staff. It's also our scientists, working to discover how these diseases start and how they might be stopped.

Our cover story is on the remarkable discovery that autoimmunity in some patients with scleroderma begins when the body successfully fights off cancer. This landmark research, published in *Science*, has the potential to revolutionize how we think about both autoimmunity and cancer.

In other exciting research we see how, for the first time, certain immune system components called IFI-16 proteins respond to pathogens: They form structures that orchestrate the attack against foreign invaders. Jungsan Sohn, a basic scientist in Biophysics, is studying these proteins in the laboratory; meanwhile, Livia Casciola-Rosen and Brendan Antiochos are studying them in the tissue of patients with Sjögren's syndrome. These scientists have teamed up, and their work may lead to new ways to treat Sjögren's and other autoimmune diseases.

We understand that really exciting discovery comes from points of connection, as people with different ways of thinking and expertise approach problems from different angles. Investing the funds provided by our donors to encourage collaboration at these points of connection is producing exceptional results.

This issue also features another way that we want to connect with you: our Story Project. A while back, I asked our faculty and staff to answer a question about their background, their experiences, and an object that is meaningful to them and helps crystallize why they are here. I thought their responses were amazing, and many of you wrote to tell me that you did, too.

We are making great progress in our understanding of autoimmune diseases, and we have great hope for the future. We are proud to share that with you, our partners in discovery and hope.

Antony Rosen, M.D.
Director, Division of Rheumatology
Vice Dean for Research

AMI SHAH AND LIVIA CASCIOLA-ROSEN: BREAKTHROUGH IN UNDERSTANDING AUTOIMMUNITY, STORY ON PAGE 4.

HOLIDAY/WINTER 2015

LEAP

Who We Are: The Story Project

Our Story Project Initiative is continued on pages 7, 11, and 13.

JOHNS HOPKINS MEDICINE

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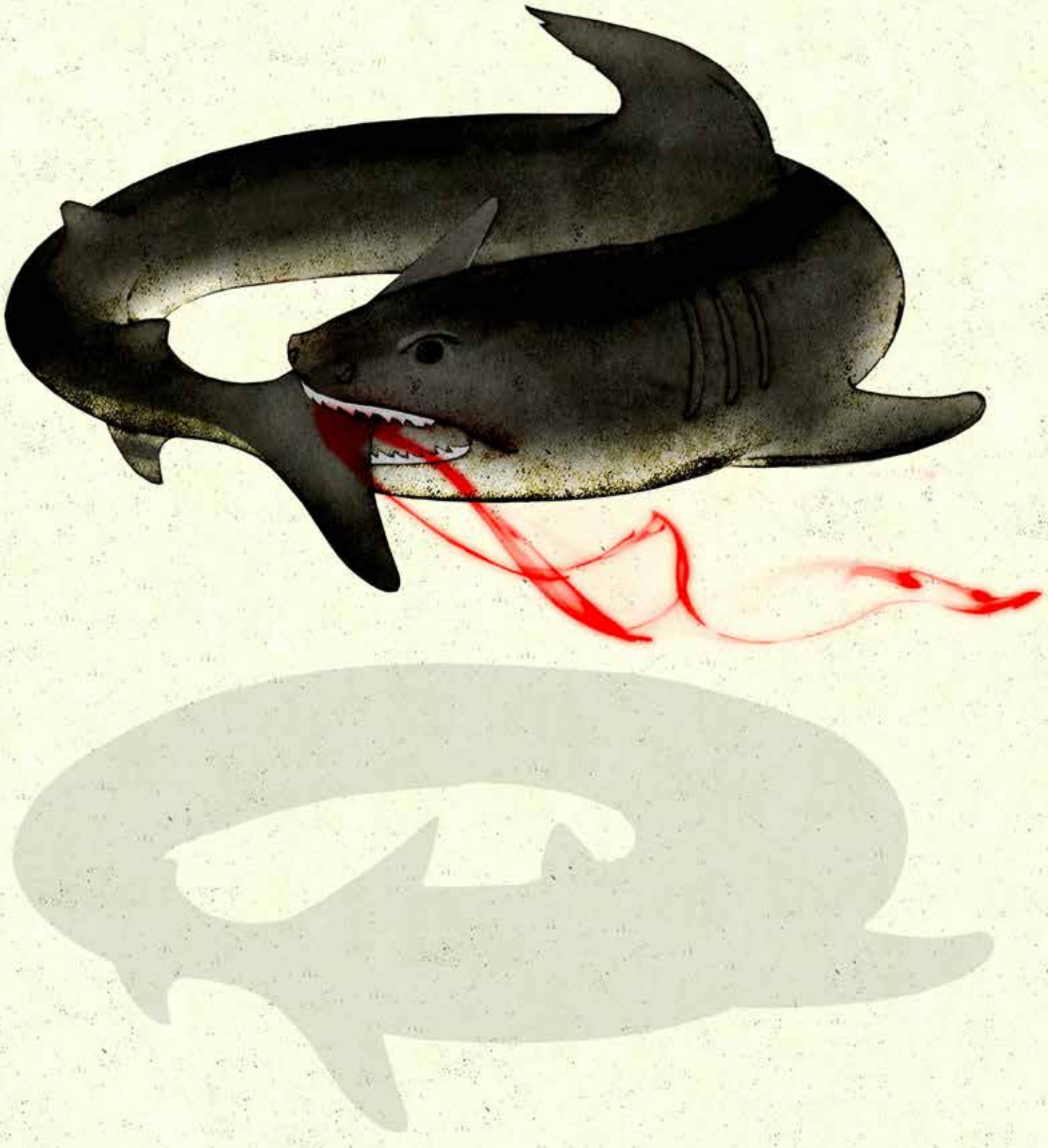

AUTOIMMUNITY AND CANCER

NEW DISCOVERY GENERATES POWERFUL NEW IDEAS ABOUT TREATING BOTH

Scleroderma is a devastating autoimmune disease characterized by hardening of the skin. Now, Hopkins scientists have discovered that it's also something else: the unfortunate consequence of the body's ferocious battle to fend off cancer. It's a casualty of war. The implications of this — for treating other autoimmune diseases, and also for using the body's own weapons to fight cancer — are profound.

Just think about it: What if most of the people – hundreds of thousands, all over the world – who develop an autoimmune disease such as rheumatoid arthritis, lupus, vasculitis, myositis, or scleroderma, actually get sick because their immune system is so amazing that it successfully attacked and killed off a cancer? "This is a powerful notion," says rheumatologist and Vice Dean David Hellmann, M.D., "and it is potentially changing how we think about how cancer develops, and how autoimmunity develops and how to treat it."

This finding, published in the January 10, 2014, issue of *Science*, has been hailed as a landmark. Some commentators have suggested that the study will stand on its head the current notion of cancer and of autoimmunity – that it could revolutionize both fields.

"This changes our view of how autoimmunity may begin. It also changes our view of what the therapy for autoimmunity may need to be. If it's induced by a cancer, maybe we should be trying to find and cure the cancer rather than fighting the autoimmune system."

WHAT'S HAPPENING

Some patients develop scleroderma and cancer at around the same time. What they have in common is that they make antibodies specifically against one particular molecule, called RNA polymerase III. The people who have this immune response also develop a very aggressive form of scleroderma. The immune system fights against a form of RNA polymerase III that's in the patient's cancer — and this response cross-reacts with the patient's normal tissue, and causes scleroderma to begin. A collaborative group of clinicians, biochemists, immunologists and cancer geneticists teamed up to address this idea, and showed that mutations in self molecules in cancer turn on the immune response in some forms of scleroderma, which fights against the cancer and damages some normal tissues.

The *Science* study was small, and it only involved patients who had been diagnosed with both scleroderma and cancer at around the same time. But in these patients, scientists found the same cascade of events: Cancer mutated a normal gene that produced a protein that caused an immune response that led to scleroderma.

Striking Similarities

Like most revolutions, this one began quietly, with some clinical observations that piqued the interest of a veteran rheumatologist. Fred Wigley, M.D., Director of the Johns Hopkins Scleroderma Center of Excellence, has cared for thousands of people with rheumatic illnesses, particularly scleroderma, over the years. Wigley had seen cancer and autoimmunity before; it is well known, particularly in myositis, that people who develop an autoimmune disease are at higher risk of developing cancer. But two patients, who came to the clinic in 2006 and 2007, had some striking similarities. "They had new-onset scleroderma, really aggressive disease, and had been diagnosed with cancer within a few months of getting their scleroderma symptoms," says rheumatologist Ami Shah, M.D., a co-investigator on the study.

Antony Rosen, M.D., Director of Rheumatology and Vice Dean for Research at the Johns Hopkins University School of Medicine, had "for a really long time been thinking that maybe cancer itself is a trigger for the development of rheumatic diseases," Shah notes. "Fred said, 'I know Antony's going to be interested in these patients. Now let's figure out how we can partner with our patients to study the biology.' The idea was that if we could get their clinical data, obtain cancer tissue to study, and figure out what the timing was trying to tell us, then we could understand this better."

Meanwhile, scientist Livia Casciola-Rosen, Ph.D., in other research, had found that the same molecules targeted in myositis also show up in higher quantities in cells that are repairing muscle injury: the same signature of antigens is expressed in cancer tissue, but not in normal tissue. "Maybe," says Antony Rosen, "the immune response starts against the cancer and then cross-reacts against muscle tissue, which gets injured and is in the process of repairing.

Maybe the muscle is an innocent bystander of an immune response that was initiated against the cancer."

To see if something similar was happening in scleroderma, Shah and her colleagues in the Scleroderma Center recruited patients with scleroderma and cancer, and obtained their blood samples and cancer tissue specimens for further study. That work, done along with Casciola-Rosen, Rosen, Wigley, and Laura Hummers, M.D., was published in *Arthritis and Rheumatism* in 2010. "In that study, we found something which was incredible and unexpected," says Casciola-Rosen. "Ami found that the time interval between cancer and scleroderma is quite variable, but – something that had never been noticed before – there's a subgroup of people in whom cancer and scleroderma occur at the same time."

And what those people had in common was that they made antibodies specifically designed to fight one particular molecule, called RNA polymerase III. "The people who have that immune response against this molecule have an incredibly fulminant, aggressive form of scleroderma. This led up to the idea that maybe the immune response was targeting a form of the molecule that is present in the patient's cancer – that this turns on the response, which subsequently cross-reacts with the patient's normal tissue and causes this process we recognize as scleroderma."

Adds Shah: "When we looked at the tumors, we saw that this molecule was really enhanced in these cancerous cells. We didn't see that in tumors from people who had other antibodies, so we didn't think it was a general cancer effect. We thought, 'Wow, this is really specific,' that we're seeing this antigen expressed in the cancer, we're seeing somebody making an antibody response to this antigen, and we're seeing that they're getting these two diseases close together in time."

The next step was to team up with geneticists with expertise in studying the cancer side of the equation. Fortunately, because this is Johns Hopkins, two of the best in the world happened to be right in the neighborhood: Bert Vogelstein, M.D., Clayton Professor of Oncology and Pathology, and Kenneth Kinzler, Ph.D., Professor of Oncology. The results of this collaboration became the *Science* paper. Vogelstein and Kinzler sequenced the key gene, called POLR3A, in tumors from eight patients who had the antibodies to RNA polymerase III. They also sequenced "a bunch of other autoantigens in cancers from patients with scleroderma with a variety of immune responses," explains Rosen. "We chose people with other antibodies as controls. They discovered that RNA polymerase III was mutated in three out of the eight cancers from patients who make those antibodies. But it was not mutated in cancers from patients with scleroderma with any other immune response."

The rheumatology group then took those observations and showed that the immune response in scleroderma is initiated

Cancer mutated a normal gene that produced a protein that caused an immune response that led to scleroderma.

THE STORY PROJECT

Ana-Maria Orbai, M.D., M.H.S.
Instructor in Medicine, Division of Rheumatology

I can't think of anything better than a garden, a garden with lots of different interesting vegetation spots, fascinating colors, and noises, that I can explore. It is the variety of activities that my work entails – doing research, reading, asking questions, applying new knowledge and new ideas, caring for patients, thinking of their results, explaining their results, watching them, trying to understand them and respond to them – that inspires me and gives me a feeling of freedom. Freedom and the passion of endlessly exploring can take me a long way through the garden.

by the mutation in RNA Polymerase III. In other words, the POLR3A gene was mutated by the cancer, the mutated form was then recognized by the immune system as an enemy. Then, the original form was also recognized and attacked, as well – suggesting that once this response has been activated, it attacks the protein in both cancerous and normal tissues.

They also found that there were RNA polymerase antibody patients who did not have a POLR3A mutation detected but who had lost their second copy of the POLR3A gene. "This is very exciting," says Rosen, "because it suggests that the immune response was editing the cancer – that the immune response was able to select against cancer cells expressing the mutation."

Of the patients with the antibodies, only 20 percent ever manifested a cancer throughout the course of their lives; some of these people were followed for two decades. "Only 20 percent get cancer and it's always early," says Rosen. What about the other 80 percent? In those people, the vast majority, "this immune response is successful – it gets rid of the cancer or keeps it under control," and by the time they have developed scleroderma, the cancer is long gone. "But the self-sustaining tissue injury remains."

Implications and More Questions

If this hypothesis proves correct, "our view of autoimmunity as an abnormality of the immune response may be wrong," says Rosen. "Autoimmunity, in fact, may be an immune response doing a task that is absolutely critical to the survival of the host – and that is, getting rid of the cancer." And then, on relatively rare occasions, that immune response misfires, cross-reacts with self tissue and creates a separate problem such as scleroderma. "This changes our view of how autoimmunity may begin. It also changes our view of what the therapy for autoimmunity may need to be. If it's induced by a cancer, maybe we should be trying to find and cure the cancer rather than fighting the immune system."

It may be that there is a "golden window," right when scleroderma symptoms first begin; that cancer is there, too, actively being fought off by the body. And this may be the critical time when scleroderma is vulnerable, and curable.

An even broader implication: If the immune system is a powerful force, able to edit tumors and keep them under control, the autoimmune response – if it could somehow be tempered to avoid the debilitating side effects of scleroderma and other rheumatic diseases – "may in fact be life-saving," says Rosen "and may represent a potent anti-tumor mechanism that we may be able to harness."

Will it be possible to find evidence, in the 80 percent of the people with scleroderma who didn't seem to have a cancer, that there used to be one? "It's possible that in those 80 percent, cancer triggered their autoimmune disease, but their immune response was so robust that they eliminated or somehow immunologically controlled their cancer so that it didn't emerge clinically," says Shah. "Could it be that treating an underlying cancer could actually be effective scleroderma therapy? If the cancer is the trigger and you treat that, do you treat the downstream disease that develops? If this is indeed the case, it could revolutionize the way we treat scleroderma."

The huge potential for finding new immunologic weapons to treat cancer is very exciting, Shah agrees, but that's not what she's thinking of right now. "At the end of the day, I want to help people with scleroderma. That's what's really interesting to me as a rheumatologist."

It may be that there is a "golden window," right when scleroderma symptoms first begin; that cancer is there, too, actively being fought off by the body. And this may be the critical time when scleroderma is vulnerable, and curable. "We're very interested in studying patients with new-onset scleroderma," says Shah, "because those patients may still have evidence of an underlying tumor. If we study patients with longstanding disease, they may have mounted a really good immune response and eradicated an underlying cancer. But those patients who are fresh in the disease process may hold the key to telling us whether there could be a hidden cancer that we could treat, and improve our patients' quality of life." ⊥

In addition to Rosen, Shah, Wigley, Vogelstein, Kinzler, and Casciola-Rosen, these authors also contributed to the *Science* paper: Christine Joseph, Ph.D.; Erika Darrah, Ph.D.; Andrew Skora, Ph.D.; Francesco Boin, M.D.; Andrea Fava, M.D.; Christopher Thoburn, B.S.; Isaac Kinde, B.S.; Yuchen Jiao, M.D., Ph.D.; and Nickolas Papadopoulos, Ph.D.

INTERPRETING THE FINDINGS

Antony Rosen, M.D., Director of Rheumatology and Vice Dean for Research, has wondered for a long time whether cancer was a trigger for autoimmune disease. His hunch has just been proven. Now what?

This work is shaking up how we think about autoimmune diseases. What's most interesting to you about this right now?

This really strengthens the hypothesis of immune surveillance — that all of us are developing cancers throughout our lives, and our immune system kills most of those, and it's only when the cancer escapes immune system destruction that a tumor actually develops. A subset has an immune reaction to the tumor, and that response may kill the tumor and not cause an autoimmune disease — that's Pathway 1. Pathway 2 is that the immune response doesn't kill the tumor, and the same response to the cancer causes the autoimmune disease, as in the patients in this story. The third pathway is that the immune response kills the cancer but also causes an autoimmune disease, and that's the patient with scleroderma who doesn't have cancer.

This research also seems to be fusing different specialties as doctors think about approaching cancer from an immune system standpoint, and perhaps autoimmune diseases from an oncological standpoint.

We are definitely evolving in our focus. An analogy would be the idea of Continental Drift. For example, the Drakensberg Mountains of South Africa share unique species of flora and fauna with the Tipuis off the north coast of Venezuela. Genetically and evolutionarily, these regions are incredibly similar, yet they're far apart. So if you only focused on one, you might study that and think that's the way it's always been. But in fact they were once present in one site, in the primordial land mass; and although they separated and evolved independently, they represent a single origin, and their separation is a single event. The same concept is true potentially of cancer and autoimmunity. That is, we end up studying autoimmunity separately and cancer separately, but it's also possible that at the origin, cancer and autoimmunity were connected, and that autoimmunity represents the single event that happened when the two were connected.

The value of focusing on rare events — like where the two land masses were connected — is that they may help you understand the connection and the origin. Even though the majority of scleroderma and cancer cases have already moved apart, if you can find the few, where the land masses are still connected, sometimes trailingly connected, you can potentially infer what led to that separation.

You have talked about the body "editing" cancer. What does that mean?

What we can see here is that when a cancer gets a mutation in a gene like RNAP3, the powerful immune response is able to push the cancer down. So you get a cancer, there's an immune response that specifically recognizes the cancer, and it fights the cancer. Sometimes the immune response is highly effective and it eliminates the cancer. But cancer is not stupid; in fact it's dynamic and plastic and mutable. When the immune system is negatively selecting against the cancer, the cancer doesn't just sit idly by. Our work has shown evidence of immuno-editing — that when the immune system attacks a component in the cancer that it recognizes as an enemy, the cancer loses that component.

The cancer jettisons certain features, and streamlines itself, like the Apollo rockets?

Yes. The concept is that the cancer is continuously trying to evolve away from whatever the immune system is throwing at it. And the immune system is constantly following. A highly plastic dance is being set up, where cancer leads, and the immune system follows and knocks it down. That dance probably can go on for a long time. The immune system doesn't eliminate the cancer, but it's able to keep it under control, sometimes for many years.

Over time, the cancer does something that the immune system just can't follow. Or, it could happen at the immune system's end — it becomes suppressed, gets old, it starts to lag behind, meanwhile the cancer keeps moving forward.

What does this mean for immunotherapy?

There's a new group of drugs that is changing the whole field of immunotherapy. They are called "checkpoint inhibitors." These are checkpoints. The tumor puts up immune checkpoints that say, 'Stop fighting against me.' But with these checkpoint inhibitors, patients are responding in ways no one could have conceived before. The immune system is able to break through the shield the cancer puts up. My prediction is that with time, our ability to effectively immune-target tumors is going to improve dramatically.

"IT'S SUCH A BLESSING"

CREATIVE FUNDING HELPS YOUNG INVESTIGATOR LAUNCH RESEARCH

What can the thyroid teach us about how autoimmune disease begins? Quite a lot, believes Jenna Mammen, M.D., Ph.D.

She is studying an induced model of autoimmunity, exposing thyroid tissue samples to a drug that causes an immune reaction, and then watching tissue damage develop. "Her insights will be highly relevant to other forms of autoimmunity," says Antony Rosen, M.D., Director of the Division of Rheumatology, "where you don't control the timing and you don't know where and what kind of problem will emerge."

Her approach, using the thyroid as the model, has a couple of advantages: "First, autoimmune disease in the thyroid is incredibly common," she says. "Up to 20 percent of older white women end up with thyroid antibodies." Second, because thyroid biopsies are fairly plentiful, tissue is available for culture studies. In early research, Mammen obtained tissue and grew the primary thyroid cells in culture. "We're

"Being a clinician is an important part of being a good medical researcher: you're seeing the real problems people encounter, and that's where the inspiration comes from."

now in the second phase, and my work moving forward is developing experiments to understand the interactions between the immune system and thyroid cells."

How Mammen has gotten to this point is a testament to her own perseverance, to support from Rosen and other colleagues and mentors, and to a number of individuals who have given money to fund autoimmune disease research at Johns Hopkins – whose gifts of hundreds or thousands of dollars, bundled together, have enabled Mammen to do the groundwork she needed to secure larger funding from the National Institutes of Health.

"Developing the tools we need to ask interesting questions requires a lot of trial and error," she says. The answer to each question takes a certain amount of money to pay for experiments and to buy time on expensive equipment, such as a microarray, owned by other Hopkins labs. This early, foundation-laying work is "speculative development, as it were, that the NIH requires before it will give you a bigger grant," Mammen notes. "If you go to the NIH and say, 'I would love to be able to ask questions, and I think I can accomplish this if I put these things together,' they'll say, 'Well, put those things together and get back to us.'"

Using these other discovery funds, all from private sources, Mammen developed assays to figure out which tests will prove most helpful in investigating the autoimmune process in the thyroid. Government funding agencies tend to regard such effort as risk-taking, and in an era when grant money is so tight, are reluctant to fund work that isn't already primed for success. But Mammen regards her early studies "not so much as taking risks, as just doing things that have never been done before."

Some of her early funding came from the Division's Ira T. Fine Discovery Fund. "These funds allow faculty to protect their research time," says Mammen, "and they are invaluable. It used to be that if you did a day of clinic, that might pay for two days of lab research. Now, a day of clinic pays you for a day of clinic. Being a clinician is an important part of being a good medical researcher: you're seeing the real problems people encounter, and that's where the inspiration comes from." But clinical work doesn't pay for any time in the lab. "If you're in clinic 20 percent of the time, you've got to support 80 percent of your salary with grants. That protected time is crucial, especially if you're a junior investigator and you don't have a lab full of postdocs and technicians. You need protected time because you're the one in the lab or at the computer, doing the project. It's not like this money pays for a staff; these small grants pay the actual creative time for the young doctors. It's such a blessing for us."

THE STORY PROJECT

Jessie Werner
Research Assistant, Myositis Center

I think I would bring in a bicycle chain. A bicycle chain contacts all parts of the bicycle. It cannot operate independently, and the bike cannot operate without it. Similarly, Hopkins is a huge institution with lots of working parts, but everyone must collaborate to make it run effectively. As a Research Assistant for the Myositis Center I work with numerous departments, hospitals and individuals. In the same way that a bicycle chain moves through all parts of the bicycle, I have had the opportunity to interact with many parts of Hopkins. Finally, the chain does not steer the bike, but it keeps things running smoothly. I like to think that I contribute to the Myositis Center in a similar way.

WHEN THE BODY TURNS ON ITSELF

THE BEGINNINGS OF AUTOIMMUNITY

The battlefield is tiny, and the soldiers are fierce, dedicated, and efficient. They form squadrons and quickly surround and dispatch the enemy. But sometimes, the soldiers are overzealous, and their friendly fire — causing the immune system to attack normal cells instead of viruses or bacteria — can result in an autoimmune disease such as lupus or Sjögren syndrome.

Basically, the proteins form strands – think of army ants, or Roman soldiers locked in shield formation.

The skirmishes take place on the molecular level, and the soldiers are members of a class of protein called "IFN inducible protein-16," or IFI-16. Like firemen and paramedics, they are first responders, rushing to the scene as soon as they detect a pathogen. Now we know, because biophysicist Jungsan "Jay" Sohn, Ph.D., has managed to take the first-ever pictures of these little warriors, that they don't strike until the enemy reaches a critical mass. By knowing this, and by discovering specifically how these proteins attach themselves to intruders – binding to DNA and forming a scaffold – Sohn and his research team are poised to figure out ways to modulate this mechanism.

Sohn works on the Johns Hopkins University campus, and his work is focused at the molecular level – using a high-powered electron microscope and careful biophysical measurements to study and photograph interactions between these proteins and bits of DNA. Meanwhile, at the Johns Hopkins Bayview Hospital, in the Division of Rheumatology, cell biologist Livia Casciola-Rosen has been working separately on the same IFI-16 protein, coming at it from a different angle – particularly, how its actions result in the damage to the salivary glands and tear ducts in people with Sjögren syndrome. They didn't know about each other's work until Antony Rosen, M.D., Director of Rheumatology, happened to ask Sohn what he was working on. "I told him that I was working on this protein called IFI-16, that it forms these gigantic structures of DNA, and he was smiling," says Sohn. "I asked him what was going on, and he told me that they had been working on this for years, having seen unusual structures in the salivary glands of Sjögren syndrome patients. I had no idea." Now, the three scientists, together with Brendan Antiochos, M.D., discuss their work frequently, share reagents, and are collaborating on some projects. "A lot of traditional biophysicists don't have an opportunity to collaborate or work in a system at the patient level. We talk about atoms and molecules and how the protein moves, but we don't have the means or knowledge about how the functional protein exactly works in certain diseases. We can read about it. My work is looking at how IFI-16 responds to DNA at the molecular level under noninfectious conditions. Livia and Brendan are looking at

THE STORY PROJECT

Victoria Ruffing, R.N., CCRC
Nurse Manager

If I could bring an object to work which best describes me, I think it may be Silly Putty. I have to bounce from task to task. Silly Putty is bouncy: I have to be able to change shape and mold into the role of counselor, educator, manager, colleague, writer, social worker, case manager, and student. Silly putty is claylike: Most importantly I have to stay current in rheumatology and transfer the skills I learn to what I teach and share – just as pictures are transferred to the Silly Putty, when you rub it on the funnies page.

patients with Sjögren's. I'm excited that our work has relevance to the general public and that we can do something in the future to help people with these conditions, where dysfunction may be amplified by IFI-16."

What Happens

Like smoke detectors, IFI-16 proteins are sensors. "These guys go after viral or bacterial DNA, and they form these structures around the DNA," says Sohn. "In turn, this switches on the immune system, mostly interferons, and triggers an inflammatory response – aches and pains, fever – but at the same time, that cures the infection by getting rid of those pathogens." Basically, the proteins form strands – think of army ants, or Roman soldiers locked in shield formation. Other proteins do this, too, "completely unrelated to IFI-16, by completely different mechanisms," which suggests that forming these scaffolds, or filaments, of DNA is "some sort of universal defense mechanism."

In a recent study, published in the *Proceedings of the National Academy of Science*, Sohn and his team genetically engineered IFI-16 from bacteria and – picture gladiators entering a microscopic arena – put them in close proximity to synthetic DNA sequences. They asked a very smart question: Did length matter? And as it turns out, length does matter quite a bit. The IFI-16s don't get alarmed until the foreign DNA reaches a certain length, more than 60 base pairs. "Length seems to play a key role. When the DNA reached 70 to 100 base pairs in length, the IFI-16 molecules got switched on," and started to surround the DNA.

Sohn believes that the length of the DNA strands could be the key to understanding why this system usually works so well, and why the body usually doesn't attack itself. "Naked" DNA is DNA that is not accompanied by proteins, which regulate it, protect it, and sometimes turn it off or on. Apparently, short strands of naked DNA don't set off alarms. When the DNA is long enough – like a strand of virus, for example – the IFI-16 proteins link up to form even longer chains, "filaments that merge and elongate."

How do they link up? Sohn's team found that there are three parts to the IFI-16 proteins. One of them is called PYD, and this seems to be the tie that binds the chains together. In experiments, when the scientists broke up the PYD, the IFI-16 proteins did not connect. "Knowing that the PYD domains interact to form this scaffold really helps us," Sohn says. "This is a very specific interaction, and that makes it a great potential target for a drug. If we could prevent, or inhibit, or completely disintegrate these structures, we might be able to alleviate the symptoms of autoimmune disorders." Of course, the reverse might also be true: Making this interaction even stronger might boost immunity and help in other diseases, maybe even in fighting cancer.

"Our approach is to figure out how this works exactly, so we can have an intelligent way to manipulate the function of this protein," says Sohn. "Once we figure this out, Livia will have an easier time doing in-vivo experiments that can help patients." L

"This is a very specific interaction, and that makes it a great potential target for a drug. If we could prevent, or inhibit, or completely disintegrate these structures, we might be able to alleviate the symptoms of autoimmune disorders."

— Jungsan "Jay" Sohn, Ph.D

ABOUT THOSE SQUADRONS

When the IFI-16 proteins line up, they're doing what the body does very well: Attacking a perceived enemy. "The body has very potent ways to recognize invading organisms at very low concentrations," says rheumatologist Brendan Antiochos, M.D. The IFI-16 proteins focus on components of these organisms, and render the cell a hostile environment for these pathogens to replicate. Usually, this is the right thing to do. But "under some conditions, this process can become autonomous, causing chronic cell and tissue dysfunction."

Other authors of the paper were Johns Hopkins scientists Seamus Morronea, Tao Wang, Leeza Constantoulakis, Richard Hooy and Michael Delannoy.

THE GREENE SCHOLARS

WITH SUPPORT FROM THE JEROME L. GREENE FOUNDATION, THESE HIGHLY CREATIVE FACULTY ARE ESTABLISHING THEIR RESEARCH CAREERS, MAKING THE TRANSITION TO INDEPENDENT NIH SUPPORT.

My presence at this Division resulted from a spur-of-the-moment decision, one that changed my life irrevocably. I grew up in the town of Pedavena in northern Italy, a picturesque village nestled in the folds of the Dolomites. My father, like me, was a doctor, and it was from him that I first learned the critical importance of compassion in administering patient care. In Italy, students choose their profession straight out of high school, so I chose to enter medicine, in the field of immunology. The immune system, along with the unique connection between physician and patient, drew me to medicine – something about the existence of an immensely complicated, infinitesimal world within the human body enchanted me, as much then as it does today.

FRANCESCO BOIN, M.D.
ASSISTANT PROFESSOR,
DIVISION OF RHEUMATOLOGY
JEROME L. GREENE SCHOLAR

I went to medical school at the National University of Mexico, and did my residency in Internal Medicine and my fellowship in Rheumatology in Mexico City. Then I came to Johns Hopkins to get my Ph.D. in immunology, to better understand how changes to the immune system affect the development of human rheumatic disease. After returning to Mexico City to further develop my career as a scientist, I opted to return again to Baltimore, where exciting collaborative research opportunities were available, enabling me to work in the laboratory to identify targets for new therapies to help people with rheumatoid arthritis (RA). From my training and the patient care I did in Mexico, and from the exceptional environment for collaboration between clinicians and scientists here in the Division, I always have the patients in mind. Currently, I'm investigating two components of the immune system, called perforin and complement. We believe that they initiate and maintain inflammation in RA. Because of the unique enterprise that brings molecular rheumatology together with clinical rheumatology here at Hopkins, I expect that we will see direct applications of this work to patients with RA. My goal is to help create the next generation of treatments for patients with RA.

FELIPE ANDRADE, M.D., PH.D.
ASSOCIATE PROFESSOR,
DIVISION OF RHEUMATOLOGY
JEROME L. GREENE SCHOLAR

I have been told on several occasions throughout my life that I am not what people think of when they think of a … fill in the blank. The first word that comes to mind is "valedictorian." With black clothes, purple hair, and a high school graduation speech about the pitfalls of conformity, I suppose I can see where they were coming from. The second word that comes to mind is "scientist." As the daughter of two hard-working non-doctors, the wife of a Baltimore city firefighter, and a professional woman with interests outside of the lab, I don't seem to fit that mold either. Truth be told, I wouldn't have it any other way.

ERIKA DARRAH, PH.D.
ASSISTANT PROFESSOR, DIVISION OF RHEUMATOLOGY
JEROME L. GREENE SCHOLAR

DARRAH'S WORK ON RHEUMATOID ARTHRITIS WAS FEATURED IN THE LAST ISSUE OF *LEAP*, AVAILABLE ONLINE: WWW.HOPKINSRHEUMATOLOGY.ORG

I am a basic scientist-biochemist. We study how our innate immune system distinguishes "self" from "non-self" at the molecular level. Specifically, we investigate how human interferon-inducible protein 16 (IFI-16) selectively binds DNA from pathogens and assembles into polymers to initiate inflammatory responses. Although essential in defense against a number of viruses and bacteria, IFI-16 is also associated with a number of autoimmune disorders such as Sjögren's syndrome. Thus, understanding its normal function would provide insights into how IFI-16 might become rogue and promote diseases.

Being at Johns Hopkins University provides a one-of-a-kind research environment. The depth and breadth of both the basic and medical scientific communities are top-notch. Thus, it may not be surprising for a starting junior faculty member like me to collaborate with world experts like Drs. Livia Casciola-Rosen and Antony Rosen, who also happen to study IFI-16 and its disease mechanism. Because our approaches are quite different, the outcome of such collaboration is incredibly synergistic, and for me, eye-opening.

JUNGSAN SOHN, PH.D.
ASSISTANT PROFESSOR, DEPARTMENT OF BIOPHYSICS AND BIOPHYSICAL CHEMISTRY, JEROME L. GREENE SCHOLAR

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.

10

NUMBER OF CONSECUTIVE YEARS THE DIVISION OF RHEUMATOLOGY AT JOHNS HOPKINS HAS BEEN RANKED #1 BY *U.S. NEWS & WORLD REPORT* MAGAZINE.

4

Simple lifestyle changes that can make a big difference if you have myositis:

EXERCISE
REST
GOOD NUTRITION
REDUCTION OF STRESS

88 PEOPLE: **28 FACULTY** AND **60 STAFF** IN THE DIVISION OF RHEUMATOLOGY DEDICATED TO MAKING LIFE BETTER FOR OUR PATIENTS.

4 MILLION

Estimated number of Americans living with Sjögren's Syndrome

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The publication of LEAP is made possible through a grant from the Jerome L. Greene Foundation

JLGreene

"A great accomplishment shouldn't be the end of the road, just the starting point for the next **leap** forward."

— Harvey Mackay, bestselling author of
Swim With The Sharks Without Being Eaten Alive and
Beware the Naked Man Who Offers You His Shirt