LEAP

Johns Hopkins University
School of Medicine
Division of Rheumatology
Winter 2022

AUTOIMMUNITY AND CANCER

THE TRUTH EMERGES

UNDERNEATH THE BIG UMBRELLA

UNSUNG HEROES

CARRYING ON, WITH GREAT HOPE

Despite a very difficult year for all of us, remarkable things are being accomplished at Johns Hopkins Rheumatology, and I hope you will see that this issue of *LEAP* is full of hope and excitement, of discoveries, research and care as we work to transform the understanding and treatment of rheumatic diseases.

We continue to make great progress in defining the connections between autoimmunity and cancer. In our cover story (Page 2), you can see that what we have learned about dermatomyositis might lead to entirely new tactics for treating cancer, as well.

For years, we have been working to apply precision medicine to rheumatic diseases. Our scientists, caregivers, and our patients themselves know that there are very few cookie-cutter diseases in Rheumatology. That's because, while not all patients are the same, some of them have similarities in symptoms, severity of illness, and trajectory, and we can custom-tailor our treatments to these subgroups. Rheumatology is one of the leaders in precision medicine at Johns Hopkins (story on Page 6).

We are so proud of our Greene Scholars (Page 10), and grateful for this funding that helps launch the research careers of our young investigators. We profile three of them in this issue, and as you will see, they all are looking to rewrite the standards of care for their specialty diseases: lupus nephritis, psoriatic arthritis, and antiphospholipid syndrome.

I truly hope you will come to know, as I do, what amazing people we have working in the Division of Rheumatology. In addition to their excellence at what they do, they are distinguished above all by their care and compassion for our patients, and for each other. They are kind, they are diligent, and what they do is way more than a job. I am proud to introduce you to four unsung heroes (Page 13), whose commitment helped us carry on during the shutdown. And I give equal thanks to all the others who are not featured this year.

What I hope this issue conveys most of all is that we are a family here. And like many families in recent months, we have lost loved ones. One of them you may recall from a previous issue of *LEAP*: Estelle Williams (pictured at right), who was our Clinic Patient Service Coordinator for more than 15 years. Estelle was a nurturing person, who cared deeply for the patients she came to know in our Scleroderma Center. In her words: "We try to maintain a level of service that can make them feel comfortable, from the time they enter the clinic to when they leave. I want them to know that I'm here for them, I will do whatever I can within my power to make the visit pleasant, and I know that a lot of them are very emotional when they come. Everyone has a different situation, and we've got to be alert to identify it and work with it."

Estelle is greatly missed, and so is another dear friend, Nancy Hellman Bechtle, the Chair of our Advisory Board, who was an inspiration to us, and whose obituary appears on Page 17.

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

WINTER 2022

LEAP

JOHNS HOPKINS MEDICINE

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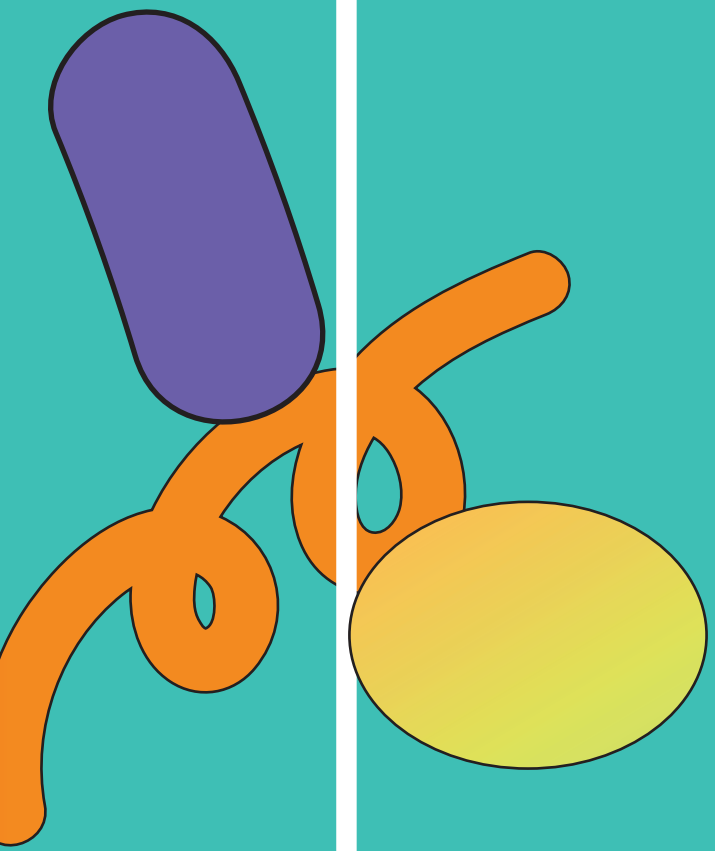
THE



“It is a riddle, wrapped in a mystery, inside an enigma; *but perhaps there is a key*.”

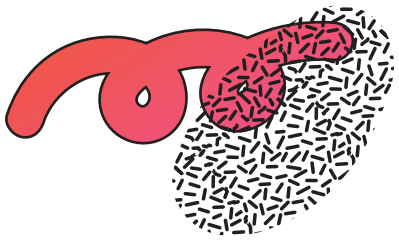
Winston Churchill, 1939

AUTOIMMUNITY AND CANCER EMERGES

Autoimmunity is a phenomenon so complicated and nuanced, with so many variables, that deciphering its origin has been like trying to chisel a delicate figure out of a giant boulder. But the truth is emerging.

Nearly seven years ago, a Johns Hopkins team made a landmark discovery: Autoimmunity is the unfortunate casualty of war – collateral damage from the body's struggle to fight off cancer. In a few patients who developed scleroderma and cancer at about the same time, the scientists traced a chain of events: cancer mutated a normal gene that produced an autoantigen (a protein that caused an immune response), which led to scleroderma. That initial study, published in *Science,* was small, but its impact was large – upturning old theories about autoimmunity, and stretching to encompass other rheumatic diseases.

Now, scientists from Hopkins and Stanford have uncovered more links in the peculiar chain connecting autoimmune disease – this time, dermatomyositis – and cancer. What they have learned will be practice-changing for the treatment of



dermatomyositis. It might also lead to entirely new tactics for treating cancer.

This project, led by scientist Livia Casciola-Rosen, Ph.D., began with some intriguing questions. For example: What causes, in some patients, a window of time where cancer and autoimmunity *both* emerge? This phenomenon is called cancer-associated myositis, or CAM. They had a partial answer: "We knew that CAM is much more likely to occur if specific autoantibodies are present,"

"What's the relationship to cancer? Long story short, the more kinds of autoantibodies the patient produces, the more immunodiversity, the less likely it is that cancer is going to emerge."

says Casciola-Rosen. In particular, TIF1-γ (an autoantibody, pronounced "Tif-one-gamma"), is found in about 60 percent of all CAM. "Dermatomyositis patients who have an antibody against TIF1-γ have the highest risk that a cancer will emerge." Even so, she adds, "only 30 percent of people who have TIF1-γ antibodies manifest a cancer. Why not the others?"

Another question, "and we didn't know what to make of it," says Antony Rosen, M.D., Director of Rheumatology, Vice Dean for Research, and co-author of the study, "is that some people with these TIF1-γ antibodies get the cancer and dermatomyositis nearly simultaneously, within the same year. In others, it's delayed three to five years. And some people *never get cancer at all!*"

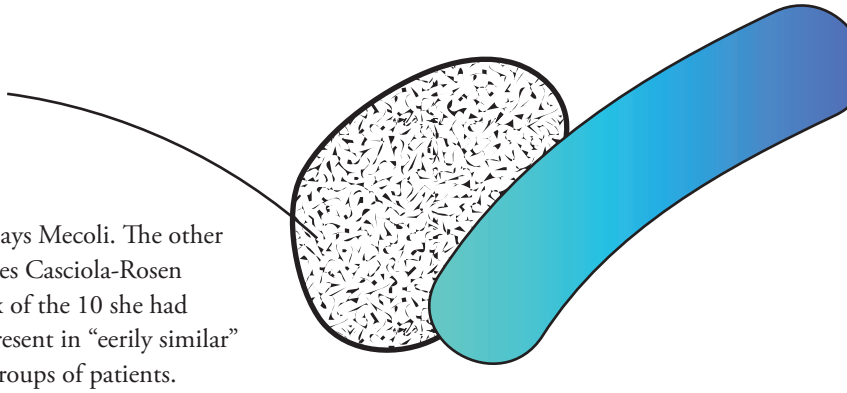
The scientists' earlier research in scleroderma with Dr. Ami Shah and colleagues, hinted at what might be happening: patients who made antibodies against a molecule called POLR3 were more likely to develop cancer close to the onset of scleroderma. "Not all patients with those antibodies got the cancer," says Casciola-Rosen, "and we found another antibody that helped us identify those patients with POLR3 antibodies who were less likely to develop cancer. We wondered whether the same could be true here, as well."

They began looking for new antibodies that might be lurking in the shadows of CAM, previously overlooked with the spotlight on TIF1-γ. Working with longtime collaborator David Fiorentino, M.D., Ph.D., of Stanford University, the Hopkins team initially studied biodata from 36 Stanford myositis patients with TIF1-γ antibodies. Half developed cancer within three years, and half never developed cancer.

Casciola-Rosen plunged into the data, laboriously poring over immunoprecipitations – basically, readouts of all the antibodies present in each patient's blood. Each readout is a black-and-white, difficult-to-decipher, very complicated fingerprint of autoimmunity, and it just so happens that Casciola-Rosen is probably the best in the world at looking at these and discerning patterns with the naked eye. As she compared the patterns between patients who developed cancer and those who did not, she noticed that the fingerprint "was more flamboyant in the group that did not get cancer. But that was the first impression, actually just visual." Casciola-Rosen then turned to a computational signal processing analyst, Matthew Rosen.

Matthew Rosen's analysis confirmed what Casciola-Rosen had seen: that patients who didn't get cancer had much more complicated patterns, indicating a more robust immune response in general. He also showed that as the number of immunoprecipitation bands increased (showing the stronger immune response) the time between cancer onset and dermatomyositis got longer. The more bands, the longer the interval. The longer the interval, the less aggressive the cancer.

Casciola-Rosen then went back to the 18 patients who did not get cancer, selected five of them, and conducted a more expensive, state-of-the-art analysis using proteomics and mass spectrometry. She was looking for new antigens that those patients might have in common, and she hit paydirt: a list of 23 candidate antibodies. "Most of them had never been

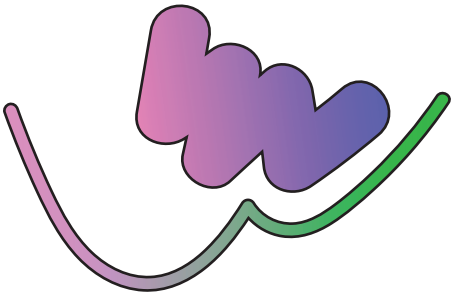


reported as antibodies before." But that was just a first step. "When you do mass spec, not all the hits are real. Determining which ones are real takes a lot of time, and if you don't do it thoroughly, you can get things pretty wrong!" she explains. She prioritized 13 candidate antibodies for re-evaluation, eliminated three of those and validated 10. "Of those 10, we then took 110 patients in the Stanford cohort, all of them TIF1-γ-positive, some with cancer and some without cancer, and looked for these antibodies." About a third of these patients had an antibody against a molecule called CCAR1. (Of the handful of other antibodies that showed up in these patients, CCAR1 was by far the most common.)

To validate these findings, they looked at biodata from a larger group: 142 patients with TIF1-γ antibodies in the Johns Hopkins Myositis Cohort, directed by rheumatologist Lisa Christopher-Stine, M.D., M.P.H., with the analysis done by rheumatologist Christopher Mecoli, M.D., M.H.S. "Very strikingly, the CCAR1 antibodies were present in our group, with basically the same prevalence as in the Stanford group – about one-third," says Mecoli. The other candidate antibodies Casciola-Rosen had identified – six of the 10 she had validated – were present in "eerily similar" numbers in both groups of patients.

Mecoli continues: "What's the relationship to cancer? Long story short, the more kinds of autoantibodies the patient produces, the more immunodiversity, the less likely it is that cancer is going to emerge." Furthermore, immunodiversity "shifts that time to the right." If cancers do occur, they appear later and have very rarely spread beyond the primary site. "Most patients who had a lot of immunodiversity had stage 0-1 cancer, compared to people with only the single TIF1-γ antibody response, who often developed aggressive, stage 4 cancer within one year. We could see that spectrum, the dose relationship between immunodiversity and the aggressiveness and likelihood of cancer."

"I think these diseases are going to teach us how to take care of cancer. They're solving the problem themselves."



Practice-Changing Knowledge

One exciting implication of this work is better, more personalized care for patients with dermatomyositis. "Currently, we screen everybody with dermatomyositis, and we keep screening them," says Antony Rosen. "Now we have markers that can tell a patient, 'Your chance of cancer is very high,' and those we really need to screen aggressively. And we also can tell a patient, 'You have markers that say your chances of getting cancer are very low.'"

Adds Mecoli: "There's a cost to PET scans and CT scans," and it's not just financial. "Patients worry about getting cancer, but they also worry about the cumulative dose of radiation they are receiving." Another worry is false positives. "With TIF1-γ myositis patients, any little thing that looks abnormal, you're going to go after and biopsy it because you don't want to miss the cancer." Although the biopsy is usually negative, he says, "you still need to undergo an invasive procedure.' Today, if a new patient sees us, we say, 'You have TIF1-γ myositis, I'm going to evaluate you like every TIF1-γ myositis patient.' This research is an additional stepping stone toward a more precision-medicine approach" to follow-up and treatment.

"This has been an amazing collaboration" says Casciola-Rosen. "It illustrates the power of the interface between clinical and translational research insights and patients who are really well-phenotyped, and clinicians working closely with those patients. We could not do this work without the clinicians we work with. We are very blessed to have people who work so well together." L

IMPLICATIONS FOR CANCER?

Could antibodies like CCAR1 and TIF1-γ someday be part of a cancer-fighting arsenal for everybody? It's quite possible, says physician/scientist Antony Rosen, M.D. "We're actively working on that." What's happening in dermatomyositis, scleroderma, and other rheumatic diseases appears to be *cancer immuno-editing.* "Basically, when a cancer arises because of these genetic changes in the genome of the cancer, the natural immune response is very robust, and keeps it at bay. In some people, the cancer is fully eliminated. Because the cancer is genetically plastic, if the immune response does not completely kill the cancer, the immune response will select for cancers that are no longer fully controlled over time, and cancer will emerge. We think these rheumatic diseases are giving us a window into the natural process whereby humans are forming cancers," and in some cases, treating themselves without ever needing surgery or medication. "I think these diseases are going to teach us how to take care of cancer. They're solving the problem themselves."

The key to treating very complicated diseases is precision medicine. It's understanding that under the large umbrella of a disease are mini-umbrellas: more precise subgroups, known as phenotypes.

PRECISION MEDICINE

UNDERNEATH THE BIG UMBRELLA

Some diseases are pretty straightforward; patients are all managed with the same basic treatment, and they all respond about the same. No roadbumps, no subtleties, no surprises.

Very few rheumatic diseases are like this.

"We've taken care of over 4,000 patients with this disease. How can we harness data from all of them to more accurately calculate this individual patient's risk in real time?"

That's why, for the last two decades, groundbreaking research at the Johns Hopkins Division of Rheumatology has focused on finding ways to make sense out of diseases that:

- aren't simple at all;
- can manifest vast differences in symptoms, organ involvement, trajectory and prognosis from patient to patient;
- and whose great complexities require the physician's art, as well as the science, of medicine to treat.

The key to treating very complicated diseases is precision medicine. It's understanding that under the large umbrella of a disease are mini-umbrellas: more precise subgroups, known as phenotypes (see side story). In years past, these subgroups were not so clearly defined, but an experienced rheumatologist could get an idea of where disease might be heading in a patient, and could guide treatment based on other patients evaluated with similar characteristics.

Traditionally, says rheumatologist Ami Shah, M.D., Co-Director of the Scleroderma Center, "a physician could say, 'Based on my prior experience, I think this patient's risk of an adverse event is X.' But that estimate is highly variable and based on a physician's prior experiences. Instead, one could ask, 'We've taken care of over 4,000 patients with this disease. How can we harness data from all of them to more accurately calculate this individual patient's risk in real time?'"

Under the leadership of Antony Rosen, M.D. Director of Johns Hopkins Precision Medicine Initiative, and co-leadership with biostatistician Scott Zeger, Ph.D., Hopkins has established more than two dozen Precision Medicine Centers of Excellence (PMCOE). Two of them are housed in Rheumatology: one for scleroderma, and one for myositis. Through inHealth, the Hopkins analytic platform, "we have transformed how we collect research data," says Shah.

The PMCOEs are able to harness and analyze millions of bits of data: results of patient-reported outcome measures, information from novel sources including "wearables" (such as Fitbits and at-home spirometers), office notes from patient visits recorded in the electronic medical records (EMR), results of radiographic images, diagnostic tests, and findings from research studies.

What happens to this pipeline of clinical data? It goes to Division of Rheumatology researchers and clinician-scientists, and then their findings go right back into improving patient care, completing the circle. "Through inHealth, we are using revolutionary tools of measurement, data science, and connectivity to discover clinically relevant and biologically anchored subgroups," Shah explains. "The idea is continuous learning: clinicians provide longitudinal data from their patients. Scientists look for patterns and clues, and bring discoveries back into delivery of patient care to improve outcomes for patients."

The Division has received a P30 grant from the NIH to establish the Rheumatic Diseases Research Core Center, led by Rosen and Clifton "Bing" Bingham, M.D. As part of this federal award mechanism, Shah and Bingham are co-leading the Precision Medicine Data Integration Core. "We are developing personalized medicine strategies, using an individual data visualization tool to understand

MINI-UMBRELLAS: WHAT MAKES A SUBGROUP?

Subgroups may be based on risk factors, clinical symptoms, the presence of certain antibodies, or all of the above. Looking at lung disease in scleroderma, for example, doctors look at risk factors: being of African American or Native American descent. They study disease specifics: lung disease is more likely to develop in the early years of scleroderma, and in patients who experience rapid, diffuse skin changes. They can also look for the presence of certain biomarkers, such as anti-topoisomerase-1 antibody positivity. They can look for other biomarkers that can predict aggressive disease. And they can look for key findings on HRCT and FVC tests.

Because scleroderma is a heterogeneous (varies from patient to patient) disease, some patients have a milder form, and others a more severe disease. Not everyone needs the same monitoring, tests, and medication. Defining subgroups allows the right patients to get the right treatment at the right time.

If Mary is at higher risk of having an event, she and Shah will come up with a plan for increased monitoring and intervention, including a possible change in medication. But if she is at lower risk, Mary can have some peace of mind.

a patient's trajectory across multiple organ systems in a way we couldn't easily visualize before. We can compare patients to other patients who are most like them." The Core will soon be applying these analytic resources to other rheumatic diseases, including rheumatoid arthritis, vasculitis, and Sjögren's.

Let's say that Shah has a patient, Mary, who has scleroderma. Using this tool, she can show Mary the longitudinal trajectory of her disease across multiple organ systems. Shah is concerned that Mary, who was diagnosed two years ago, might develop interstitial lung disease (at greatest risk of developing within the first three years). Mary can see a graph of her lung function over time, as measured by a forced vital capacity (FVC) test, and high-resolution CT (HRCT) scan images. Mary can see when she began taking different medications, and their results. She can see her predicted lung function. She can see patients across the spectrum – in the 10th, 50th, or 90th percentile, for instance – in the entire Johns Hopkins cohort of patients with scleroderma, and she can also see the trajectories of patients most like her. She can see snapshots of mileposts like diffusion capacity, skin scores, GI disease, muscle weakness, and lab results. She can see her estimated risk, based on multiple biomarkers, of having a major event in the next six months, one year, 18 months, and two years. If Mary is at higher risk of having an event, she and Shah will come up with a plan for increased monitoring and intervention, including a possible change in medication. But if she is at lower risk, Mary can have some peace of mind.

Shah and colleagues are studying the tool with their patients, who have provided "excellent suggestions" for ways to improve it. "Seeing their trajectory helps them understand,

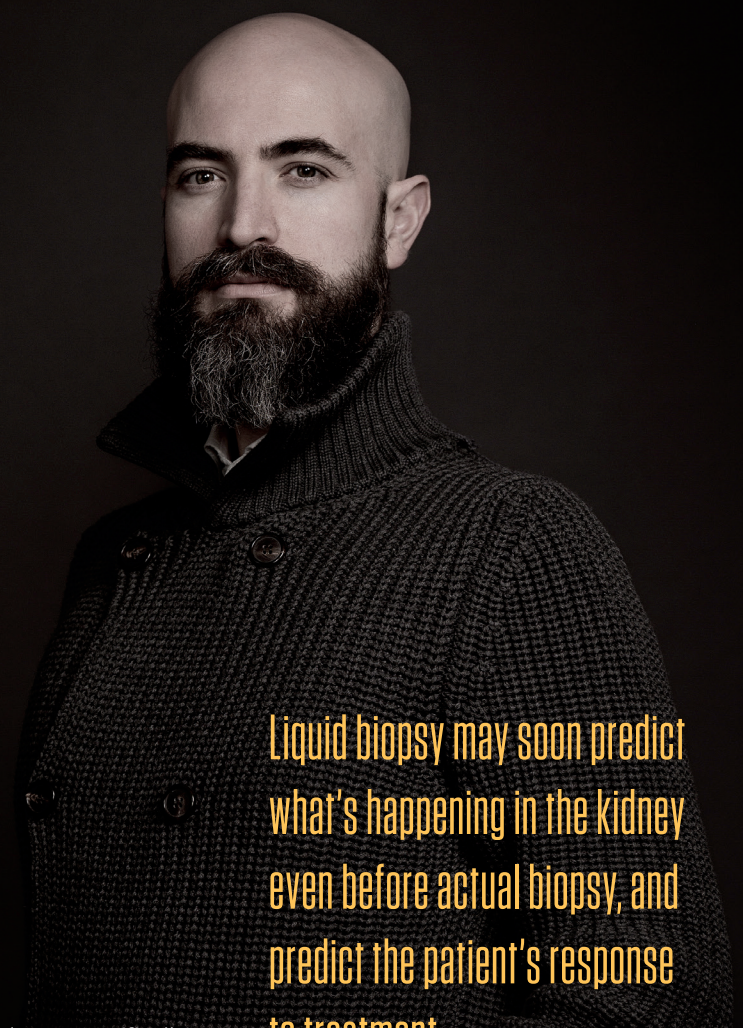
"The idea is continuous learning: clinicians provide longitudinal data from their patients. Scientists look for patterns and clues, and bring discoveries back into delivery of patient care to improve outcomes for patients."

'This is why my doctor is suggesting X, Y, or Z.' or 'This is why I don't need treatment with this drug,' or 'This is why I need this test.' It communicates the thought process behind complex treatments and can facilitate shared decision-making. Patients can see where their disease is now, and where it's likely to go."

In other research, Shah and colleagues are investigating the role of the data visualization tool in helping physicians manage and predict risk in patients with complicated diseases. "We would expect the physician's experience plus the tool to be greater than each one alone," says Shah. Using the tool may be of especial help to trainees and community physicians who do not see very many patients with scleroderma. "Because it's Web-based, this could potentially be disseminated and embedded into other hospitals' EMR systems," says Shah. "We are intentionally designing it to be used beyond Johns Hopkins."

THE GREENE SCHOLARS

Meet three young physician-scientists who are working to transform the standard of care for lupus nephritis, psoriatic arthritis, and antiphospholipid syndrome, with support from the Jerome L. Greene Foundation.



ANDREA FAVA, M.D.
Instructor of Medicine,
Division of Rheumatology

"The way we diagnose and manage lupus nephritis (LN) is not good enough," says rheumatologist Andrea Fava, M.D. "We have the technology: let's learn to do better!"

People with LN are at risk of developing chronic kidney disease, and "in 10 to 20 percent of patients, this can lead to permanent kidney damage and dialysis." Unfortunately, Fava notes, kidney disease in LN is not always easy to detect and monitor. "When patients come to the clinic, we screen for protein in the urine," a sign of kidney damage, "and if we see that, we get a biopsy of the kidney. If that shows damage, then we go ahead and treat. Depending on what we see, we may be more or less aggressive with treatment."

What if, six months or a year later, that patient still has protein in the urine? "It doesn't explain whether the patient just needs more time, or the treatment is failing." Nor does the standard urine test shed light on which particular inflammatory cells are involved. "We have drugs that are targeted very specifically to one inflammatory cell or another," says Fava. "The issue is in selecting the patients correctly." For example, some people have B cell inflammation, and some have macrophage inflammation. "Being able to separate the kind of inflammation would allow us to personalize the treatment." Newer types of kidney biopsies may provide that information, but biopsy is an invasive, painful, and expensive procedure. "We can't subject patients to repeated kidney biopsies every few months!"

What's the next best thing to biopsy? Liquid biopsy, sophisticated molecular analysis of those same kidney cells as they are shed into the urine. This is what Fava is working to develop, with funding from the Greene Foundation and the Accelerating Medicines Partnership. Using novel approaches such as urine proteomics, and looking at the genomics of single inflammatory cells, Fava and colleagues are tracking "an incredible amount of information" – the patterns of more than 1,200 proteins in the urine at the time of kidney biopsy, and then at three, six, and 12 months. In a recent study, they found one protein, called interleukin 16 (IL-16), that is "very tightly associated with inflammation in the kidney. By measuring this protein in the urine, we are able to predict the amount of activity of LN." IL-16 may also be "a new treatable target," he adds.

> Liquid biopsy may soon predict what's happening in the kidney even before actual biopsy, and predict the patient's response to treatment.

Fava hopes this powerful technology will soon predict what's happening in the kidney even before actual biopsy, predict the patient's response to treatment, and monitor the kidney's recovery. Even more exciting: He hopes liquid biopsy will allow doctors to follow patient-specific trajectories in real time, classify new subgroups of patients, "and provide some precision medicine that is definitely lacking in lupus."

MAXIMILIAN F. KONIG, M.D.
Instructor of Medicine,
Division of Rheumatology

Cancer and autoimmune diseases are like two sides of the same coin. In cancer, the soldiers of the immune system don't adequately fight off harmful cells, and new oncology treatments involve immunotherapy: ramping up the immune system to kill cancer. In rheumatic diseases, the opposite is true: these soldiers are overzealous. They mistake the body's own cells for enemies and declare war on normal tissue.

Rheumatologist Maximilian Konig, M.D., is uniquely poised to study both immunotherapy and autoimmunity: he did two postdoctoral fellowships, one in Rheumatology, and one in Immuno-oncology at the Ludwig Center for Cancer Genetics and Therapeutics. During this time, he became fascinated with the idea of adapting CAR-T cell therapy – immunotherapy that involves engineering the body's T cells (powerful white blood cells) to kill specific targets – to treat rheumatic diseases.

In first-in field research, with support from the Greene Foundation, Konig is developing immunotherapies for patients with antiphospholipid syndrome (APS), an autoimmune disease that can cause dangerous blood clots, with devastating complications. In APS, "self-reactive B cells make autoantibodies," says Konig. "These antibodies are pathogenic. If you transfer them into healthy mice, they have miscarriages, just like patients with APS, and they become prone to arterial and venous blood clots. That's exactly what happens to patients with APS. Stroke, heart attacks, deep venous thrombosis, emboli – they're all driven by activation of the clotting cascade." In CAR-T cell therapy, the patient's own cells are collected, re-programmed, and then put back into the body.

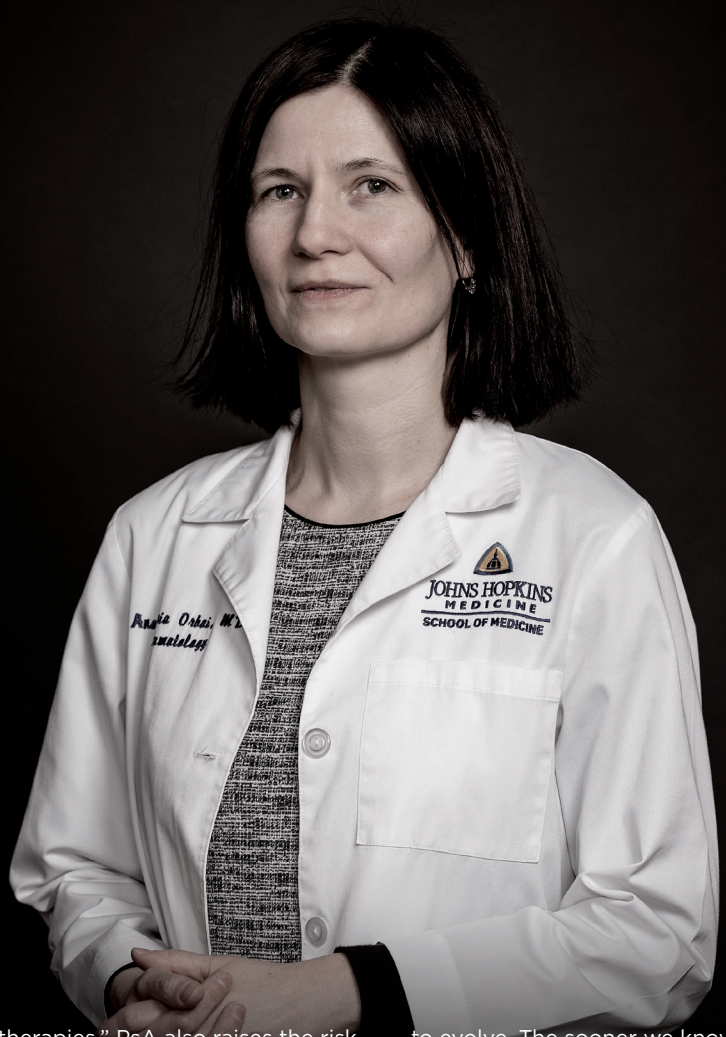
Konig's goal is to eliminate the cells that make these harmful antibodies "without touching any of the good cells, the immune cells we need to fight infection and cancer." He is creating what he calls "antigen-specific personalized immunotherapy," using gene-editing technology called CRISPR-Cas9. "Basically, we're genetically re-programming a patient's own T cells to only recognize these self-reacting B cells and to kill them. If we get it right, the reward is huge: instead of keeping someone on blood thinners for life, with all the complications that come from that plus all the risks of APS, we will be able to reset the immune system without interfering with day-to-day immune responses. That's kind of the Holy Grail of Rheumatology – a very lofty goal!"

Konig's goal is to eliminate the cells that make these harmful antibodies "without touching any of the good cells, the cells we need to fight infection and cancer."

Konig's team includes his oncology mentor, Bert Vogelstein, M.D., and Kenneth Kinzler, Ph.D. – both world-class molecular scientists. "If this works out just like we envision, it should be ready for prime time in the next couple of years."

And then, Konig hopes, this technology can be applied to other autoimmune and rheumatic diseases. "Now that we have these new tools, we can develop precision therapies – tailored to the disease and patient – to target what we want to target and leave the rest alone. It's just a matter of time!

"The status quo doesn't have to be what it is. I think the future of treating these patients will change, based on our findings."



ANA-MARIA ORBAI, M.D., M.H.S.
Assistant Professor of Medicine, Division of Rheumatology

"It's a very difficult quest, because we're starting with nothing," says rheumatologist Ana-Maria Orbai, M.D., M.H.S., who directs the Psoriatic Arthritis Program. "There's no biomarker for psoriatic arthritis (PsA), no blood test to tell with certainty if somebody has psoriatic arthritis, or if someone with psoriasis is at risk for progressing to psoriatic arthritis."

Around 4 percent of American adults have psoriasis, and of those, a third are at risk of developing psoriatic arthritis. "The problem is, the diagnosis is clinical," because of the lack of a specific blood test, and this means that PsA is often misdiagnosed – which can have serious consequences. "It's a painful form of arthritis," Orbai says, "it has a definite impact on function, and within six months, it can cause irreversible joint damage, something we are trying to avoid with current therapies." PsA also raises the risk of developing other conditions, including heart disease, diabetes, and cancer.

With funding from the Greene Foundation, Orbai and Hopkins scientist Livia Casciola-Rosen, Ph.D., are looking for biomarkers in blood samples from 500 people with psoriatic disease, with the hope of being able to predict who is at risk of developing PsA and other health conditions. "We're following inflammatory markers that are elevated in half of the patients." With basically "nothing to hang onto," she says, "we're trying to match the clinical course – how their health is evolving," and to spot molecular changes that reflect the signs, symptoms, and severity of disease.

"Our goal is to classify patients into smaller groups that make sense. This will determine their treatment, how we follow them, and how their disease is likely to evolve. The sooner we know which trajectory they belong to, the better we will be able to treat our patients from the beginning – instead of trial and error. The status quo doesn't have to be what it is. I think the future of treating these patients will change, based on our findings."

The complexity of Rheumatology is part of what drew Orbai to this specialty. "The immune system is fascinating," she says. "Rheumatology in general is fascinating, because of the diversity of manifestations, and the intricacy of putting patterns together. When you get it – when you've done it right – there is great satisfaction that you are able to help your patients and improve their quality of life."

UNSUNG HEROES

During the pandemic, many unsung heroes worked tirelessly behind the scenes and handled unforeseen circumstances with grace. Meet four remarkable people who have helped keep Rheumatology going during challenging times.

DON MENDELL
Ambulatory Services Manager

Don Mendell's job, in a nutshell, is to keep all the Johns Hopkins Rheumatology clinics running smoothly. He accomplishes this by constantly planning for the "what ifs."

Before Covid, "We were never set up to work from home," say Mendell. That changed in a matter of days. "We had to shut down all ambulatory clinics. Everyone had to work remotely, and all appointments had to be rescheduled to telemedicine." This meant getting new equipment for off-site use, including laptops and headsets. It meant figuring out how to route faxes, emails, and "snail mail" to faculty and staff at their homes and for Mendell, it meant coming to work in the midst of the shutdown. "I was here every day."

At first, he recalls, "our biggest hurdle was the telephone." With no one able to answer the phones, many patients left multiple messages. "There was a huge bottleneck of calls," until – through communication software Mendell implemented – phone calls that came into a Johns Hopkins line could be answered on a faculty or staff member's laptop at home. "That was a lifesaver. "

"You always have to figure out a way."

Today, many providers remain on a hybrid schedule, working from home two days a week to lower the number of patients in the clinic at any given time. Challenges remain; for example: to protect immunocompromised patients in Rheumatology, everyone (staff as well as patients) must wait 20 days after testing positive for Covid before being able to come to the clinic. There is a Hospital-wide shortage of Medical Assistants (MAs). "Yesterday, I should have had five MAs; I had two. Every department that sees patients is going through this." Mendell gets emails every day from Hopkins colleagues: "'Help! Do you have any MAs you can send over right away?' It's that bad."

MAs see the patients before the doctors; they go through their family history and medications, take vital signs and administer EKGs. "Their role is not easily filled." Without them, Mendell must juggle. His current solution is "to get more doctors to do telemedicine to alleviate some of that pressure. Any MAs assigned to home duty can see patients via telemedicine. "You always have to figure out a way."

In his free time, Mendell goes for stress-reducing runs, and when he can, he travels.

She talked patients through home-tech challenges including logging into EPIC, recovering lost passwords, and getting set up for telemedicine visits. "My job expanded to 'Help Desk.'"

SHATEMA GUINYARD
Senior Medical Office Coordinator, Sjögren's Center

Shatema Guinyard starts every day by planning ahead. "I see what's on my plate for the day and actually make a physical checklist," she says. "It feels so good to check something off and then cross it off: when I cross it off, I know it's done!" She uses colorful Post-It notes to distinguish what is urgent – to be done within the hour – from what needs to be completed by the end of the day.

An average day's work includes responding to patient messages, helping patients get prescriptions, initiating prior authorizations (for biologic therapies) with insurers, scheduling patients, compiling big packets of information for new patients, and generally helping the clinic run smoothly. In this position, you have to multi-task."

Guinyard is one of the few who worked onsite throughout the pandemic. New patients at the Jerome L. Greene Sjögren's Syndrome Center may see as many as a half-dozen specialists for diagnostic testing, including a dry eye exam, ultrasound, EMG-NCV (electromyography and nerve conduction velocity study, to assess the health of muscles and nerves), and skin biopsy. Guinyard schedules those appointments and then assembles hefty, nearly 20-page packets of appointment letters and forms.

During the shutdown, "no one else was here. Our floor was completely empty, and it was very quiet. It was very difficult not having coworkers and other people around." But she had plenty of opportunities to talk by phone to patients – many of whom had trouble setting up telemedicine appointments on their home computers. Guinyard talked them through challenges including logging into EPIC (the patient portal), recovering lost passwords, and figuring out how to use the microphone and camera on their computer for the telemedicine video visit. "My job expanded to 'Help Desk.'"

In the fall of 2021, more people came back to work and "we were almost back to normal," but "as Covid is ramping up again, we are converting patients back to telemedicine," and Guinyard is once again fielding calls from people needing tech support.

When she's not working, Guinyard is… well, she's working! Every other weekend, she is a front desk receptionist for a nursing rehab center, where her mother also worked for many years. Guinyard has had that job for five years, ever since she moved from Los Angeles (where she used to surf) to Baltimore to be closer to her family. "When I do have downtime, I like to read, and I'm a big movie buff." Guinyard is expecting her first baby in early Spring.

KENDRA JOHNSON
Senior Grants and Contracts Analyst

Kendra Johnson manages all of the external funding ($10 million in research grants and clinical trials sponsored by the NIH and private foundations) that Rheumatology uses to support its basic science and clinical research. With the help of her colleague, Kevin Stark, she has kept these grants moving forward, enabling Rheumatology faculty to remain funded, to continue doing research throughout the pandemic, and to apply for new grants. Her work is crucial to the mission and financial viability of the Division.

Before the shutdown, Johnson's projects were spread out over two computer monitors at her desk. Then for one year, working remotely, she condensed all that work into one laptop. "It wasn't until after that first year that I was able to go onsite and get my monitors. That was the greatest feeling!"

As many who work from home discover, it is difficult to leave the office. Johnson is used to pushing herself. She has a degree in finance from West Chester University, and spent summers working for her father's company. Her dad has high expectations and is her role model, she says. "I quickly had to learn to keep up with him!"

One of her greatest challenges during the pandemic has been to achieve a work-life balance. "I felt like I was constantly working, knowing things needed to get done." She had to set a cut-off time "to *not* work," she says. "Being in lockdown for that long of a period, I really underestimated how it would take a toll. It's definitely been a learning experience, understanding the importance of mental health, seeing how important it is to create schedules and break down the time so I'm not constantly churning out work every moment."

Setting work limits for herself has helped tremendously. Being able to go back to church has made an important difference, as well; so has spending time with her family – her father and mother, four sisters, and her brand-new nephew. In her down time, Johnson enjoys jigsaw puzzles, knitting, listening to music, and watching movies – particularly, musicals, many of which she knows by heart. Her favorites are "Gypsy!" and "The Sound of Music."

One of her greatest challenges during the pandemic has been to achieve a work-life balance. "I felt like I was constantly working, knowing things needed to be done."

JACQUELINE WORRELL
Senior Medical Office Coordinator, Myositis Center

"I remember like it was yesterday," says Jacqueline Worrell. It was March 2020, and she had just returned from vacation. Before she left, everything was normal. When she came back, there was a global pandemic, Hopkins was shutting down, and Worrell was going to have to work remotely. "I didn't want to. I'm a people person! I didn't want to be stuck at home!"

In August 2021, Hopkins started to open up, and "I was the first one to come back," Worrell says. "I didn't have transportation. I was taking public transportation to get in. The buses ran, the subway ran, but it was limited; there were a lot of delays. I made myself accountable to get up earlier so I wouldn't be late, even though there was nobody to see me. To me, it was an honor, a goal, to get to work on time."

Working from home is not for everyone, and Worrell struggled. "It literally had me in tears. I can't explain the feeling; I felt so undone." When the shutdown started, she recalls, she would get up, "take a shower, wash my face, eat breakfast go into my home office, and cry, because that's not where I wanted to be." One day, "on lunch break, I ran to my old car, which wasn't working, and called my parents. I remember getting in the car, locking the door, and saying, 'I need to be in the office.' Everyone thinks it's a joy to work from home," but Worrell missed her coworkers, and she missed the patients, many of whom she has grown to know. "We've cried together, the patients and I. We've prayed together."

In the clinic, Worrell schedules hundreds of new patients and follow-up visits for four physicians: Christopher Mecoli, Eleni Tiniakou, Tae Chung, and Andrew Mammen. She sends out patient letters and emails, answers chart messages, and helps however she can. "The doctor is Batman, and I am Robin!"

She is also a kind and caring voice on the phone for patients. "Many of them are afraid and in pain, wondering, what's going to happen to me? When you hear that on the phone, you do the best you can."

In her free time, Worrell is active in her church, loves Zumba, loves reading, and is a regular at her local library.

"I made myself accountable to get up earlier so I wouldn't be late, even though there was nobody to see me. To me, it was an honor, a goal, to get to work on time."

A GOOD FRIEND

Johns Hopkins Rheumatology has lost a good friend: Philanthropist Nancy Hellman Bechtle, head of our Rheumatology Advisory Board, beloved wife, mother, and grandmother, who died of metastatic lung cancer in November 2021. She was 83.

When someone dies, people who don't know her wonder, "What did she do?" In the case of Nancy, a better question might be, "What *didn't* she do?" Among other things, in her full and remarkable life, Nancy was president of the Board of Governors of the San Francisco Symphony for 15 years. She was a longtime member of the Board of Directors for the Charles Schwab Corporation and for Tahoe's Sugar Bowl Resort.

She was a world-class skier, for whom the steepest and longest run at Sugar Bowl is named: Nancy's Couloir, after a notoriously difficult run in Jackson Hole that Nancy was the first woman ever to successfully ski. "She used to race in college," says her husband, Joachim Bechtle. "She was the most beautiful powder skier, until last year."

Nancy's openness about her scleroderma brought hope to many struggling with this disease.

Nancy was a huge part of San Francisco's Hardly Strictly Bluegrass Festival, founded by her late brother, Warren Hellman. By popular demand, she started her own Bluegrass band, Nancy & the Lambchops – and even recorded an original song, "Don't Sweat the Small Stuff." Her last performance was in 2019.

In 2000, Nancy developed scleroderma, which was first misdiagnosed. Unable to find helpful treatment in San Francisco, she and Joachim came to Hopkins. Immediately, they felt they had made the right decision.

Wigley's treatment was so innovative that Nancy's home doctor refused to follow it, until "finally, Fred said, 'You've got to do it, because that's the only way," says Joachim. Wigley prescribed CellCept, a drug originally designed to prevent organ rejection after transplant. "Nancy was the sixth person in the world on CellCept. It was clearly against the advice of her doctor – and it worked! I massaged Nancy every day, and her skin was absolutely tight." One day, Joachim felt a little bit of softening of the skin on her foot. "From there, everything improved." Wigley continued to treat her over the years. When in doubt, we called Fred. He clearly saved her." In appreciation for Wigley and for Antony Rosen, who was involved in Nancy's care "from the get-go," the Bechtles gave back to Hopkins.

"We became friends with a common mission: to cure scleroderma," says Wigley. "Nancy was a brilliant businesswoman and quickly realized that I desperately needed help to build a world-class Scleroderma Center of Excellence. She arranged for the consulting firm, McKinsey & Co., to meet with me. They provided the guidance, and Nancy and Joachim provided incredible support to give us the opportunity to prosper. In fact, Joachim (at age 60) ran three marathons, challenging their

friends to donate funds to our Center if he won the race in his age bracket – which he did, every time!"

Nancy's openness about her scleroderma brought hope to many struggling with this disease. "Everyone here told her that this disease was the end of her activities," says Joachim. "But after Fred treated her, she actually went back to a very active physical life," that included scuba in Belize, skiing in Antarctica "with a number of first ascents," and mountaineering near Mont Blanc. She was appointed by President (George W.) Bush to the National Park Foundation, which she chaired, and also appointed by President Bush and reappointed by President Obama to the Presidio Trust, which she also chaired. She was amazing." And she is greatly missed.

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"One cannot LEAP a chasm in two jumps."

— Winston Churchill