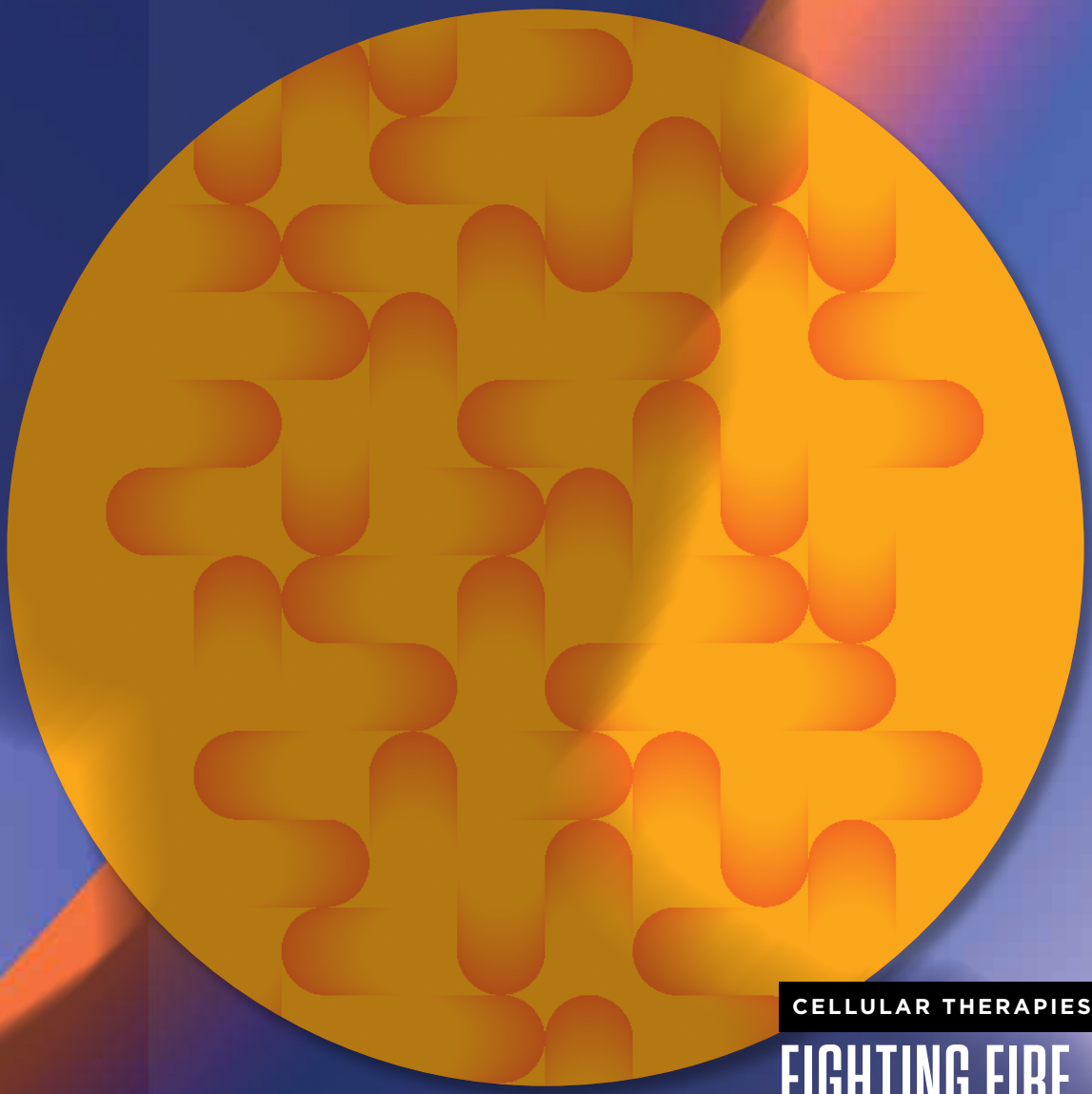
LEAP

Johns Hopkins University
School of Medicine
Division of Rheumatology
Winter 2025



CELLULAR THERAPIES

FIGHTING FIRE WITH FIRE

PARTNERING WITH OUR PATIENTS IN SCIENTIFIC DISCOVERY

In the Division of Rheumatology, we have a deeply ingrained philosophy that our patients are at the center of all we do — that their clinical and life experiences help frame the critical questions in our field and that they hold the keys to helping us unlock these complex and debilitating diseases. Our physician-scientists are extraordinarily committed to providing unparalleled patient care while partnering with our patients in scientific discovery. It is by forging close relationships together, taking the time to fully engage, listen attentively and observe wholeheartedly, that we arrive at the key questions that unlock scientific breakthroughs — breakthroughs that ultimately come back to improve our patients' lives.

While biomedical discovery is undoubtedly a long game, we're pleased to share in this issue of *LEAP* exciting stories of patient-informed innovations that are already bearing fruit in big ways.

Consider the newly launched Johns Hopkins Cellular Therapy Program for Autoimmunity, led by physician/researcher Maximilian Konig (p. 2). Dr. Konig and his team are investigating therapies that have potential to "reset" the immune system and knock out severe autoimmune disease. While current cellular therapies in clinical trials have great promise, he and his collaborators in the lab are also developing next-generation immunotherapies to target disease-causing immune cells more precisely, but without the current increased risk of infection.

Brit Adler has been driven to pursue research aimed at improving care for those living with POTS (postural orthostatic tachycardia syndrome). This debilitating condition has for too long gone under recognized, as Dr. Adler observed while treating patients in the Johns Hopkins General Rheumatology Clinic. She has found that many patients with POTS have an overlapping autoimmune disorder — knowledge that is guiding her research and informing clinical trials within the Johns Hopkins POTS Program.

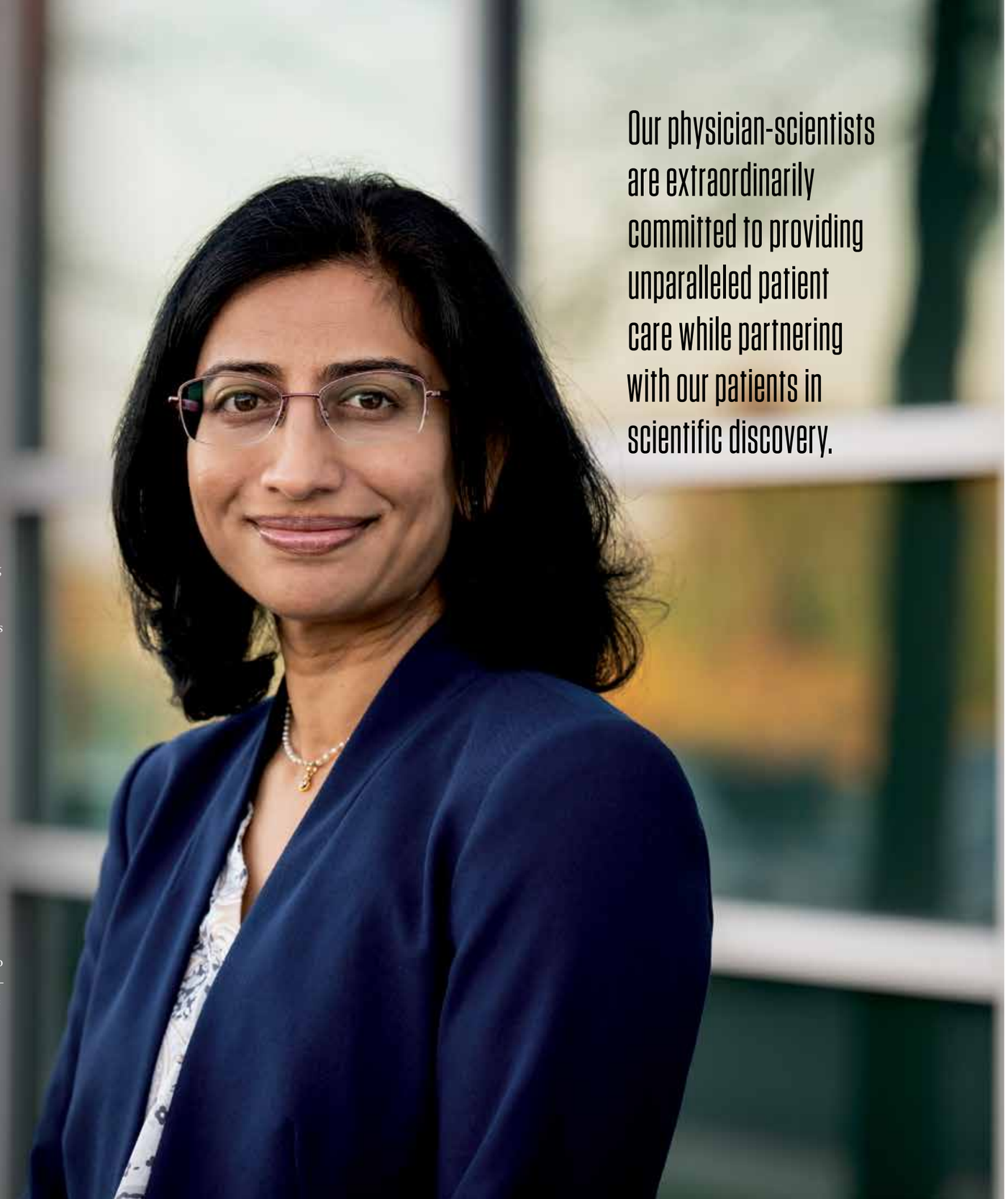
While Felipe Andrade and Eduardo Gómez-Bañuelos now devote their full-time energies to advancing research in lupus at the molecular level in the lab, both of these dual trained M.D./Ph.D.s have treated patients with the condition, which helps them frame the critically important questions that can improve care for patients. They have jointly discovered a new biomarker to identify patients with lupus at high risk of heart attack or stroke.

In this issue of *LEAP*, we also celebrate four of our talented and dedicated staff members, who are committed to nurturing our patients and trainees along their journeys with us and fostering important scientific discoveries.

It is this ongoing partnership, of engaged patients, astute clinicians and scientists, and dedicated staff working in tandem, that makes me so proud to be a part of the Johns Hopkins Division of Rheumatology — and so hopeful for a future marked by transformational breakthroughs in treatments for patients with autoimmune disorders.

Ami A. Shah

Ami Shah, M.D., M.H.S.
Director, Division of Rheumatology
Professor of Medicine



Our physician-scientists are extraordinarily committed to providing unparalleled patient care while partnering with our patients in scientific discovery.

WINTER 2025

LEAP

Left: Ami Shah

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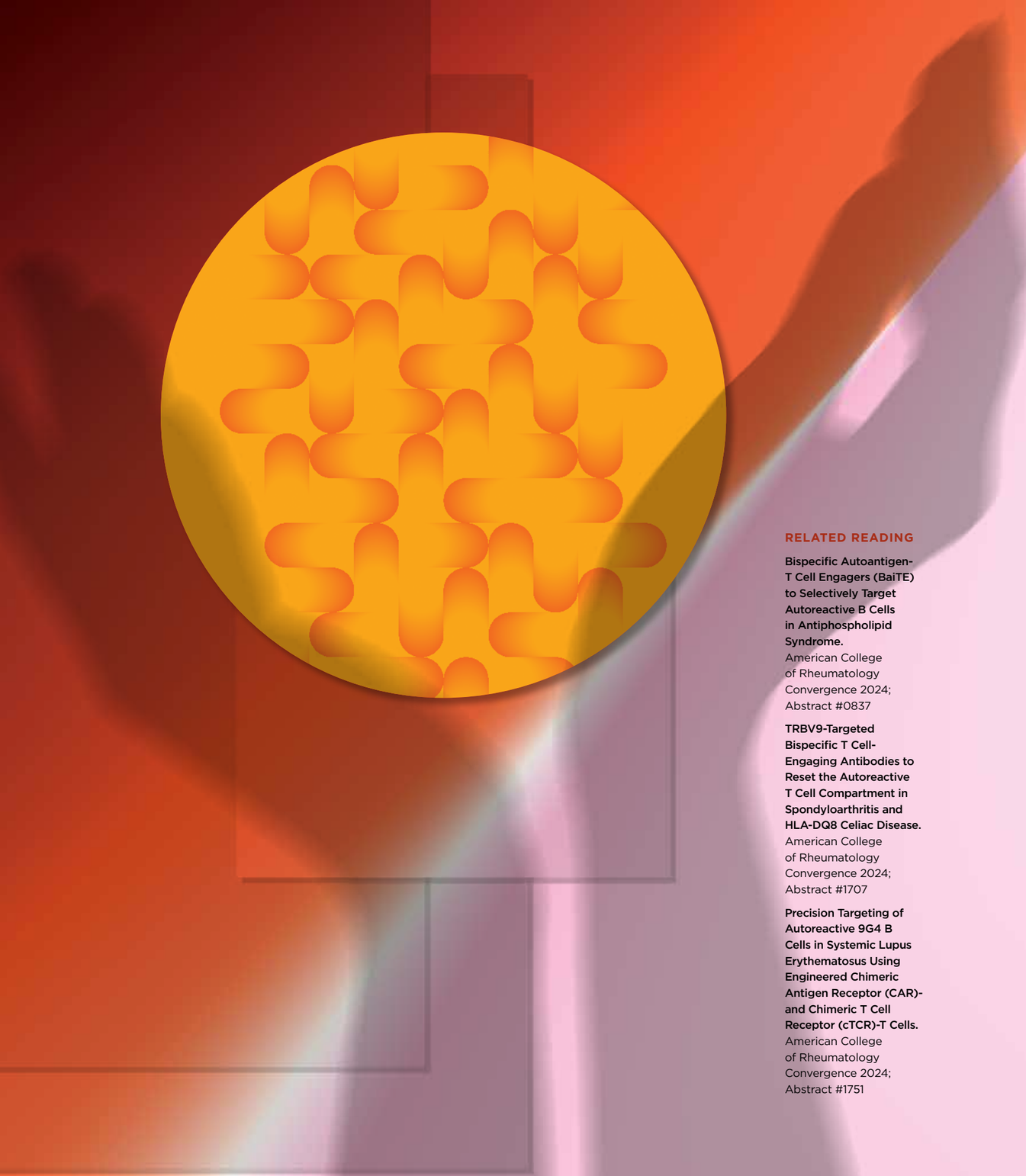

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American College of Rheumatology Convergence 2024; Abstract #1751

There is a revolution brewing for patients with severe autoimmune diseases — a revolution that promises to be nothing short of "transformative," asserts **Maximilian Konig, M.D.**, assistant professor of medicine.

Konig is leading the charge at Johns Hopkins to develop and deliver immune effector cell therapies — borrowing from strategies that have become the standard of care in treating blood cancers — to achieve long-term remission, and even a functional cure, for patients with severe rheumatic diseases ranging from lupus to myositis to antiphospholipid syndrome (APS).

Konig is guiding the launch of the Johns Hopkins Cellular Therapy Program for Autoimmunity, which is expected to enroll its first patients in clinical trials in 2025. Housed within Rheumatology and Medicine, the program is believed to be the first in the United States that is operated independently of an oncology unit.

"We have created a dedicated infrastructure for a program that specializes in treating patients who have autoimmune and rheumatic diseases using engineered T-cell therapies and bispecific antibody approaches," Konig says. "We hope this program will serve as a model for a future where rheumatologists are empowered to take care of these patients and become proficient in managing the unique side effects of cell therapies."

Unlike existing treatments for rheumatic diseases, which may bring debilitating — even deadly — side effects because they leave the patient at long-term risk of infection, immunotherapies like the ones being offered in the new Johns Hopkins Cellular Therapy Program work by harnessing the body's own immune cells to identify and vanquish dangerous cells that cause autoimmune tissue damage, through a one-time procedure.

"Consider a 30-year-old woman with severe lupus whose disease is hard to control and prognosis poor: She might die from infection, complications of renal failure and dialysis, or other organ damage from uncontrolled lupus," says Konig. "Through cell therapy, we have a chance to 'reset' this patient's immune system to the extent that, for all intents and purposes, you can't tell she had lupus. Her symptoms may disappear and — if all goes well — she no longer needs to be on medication."

These cell therapies, he says, "are transformative in their potential."

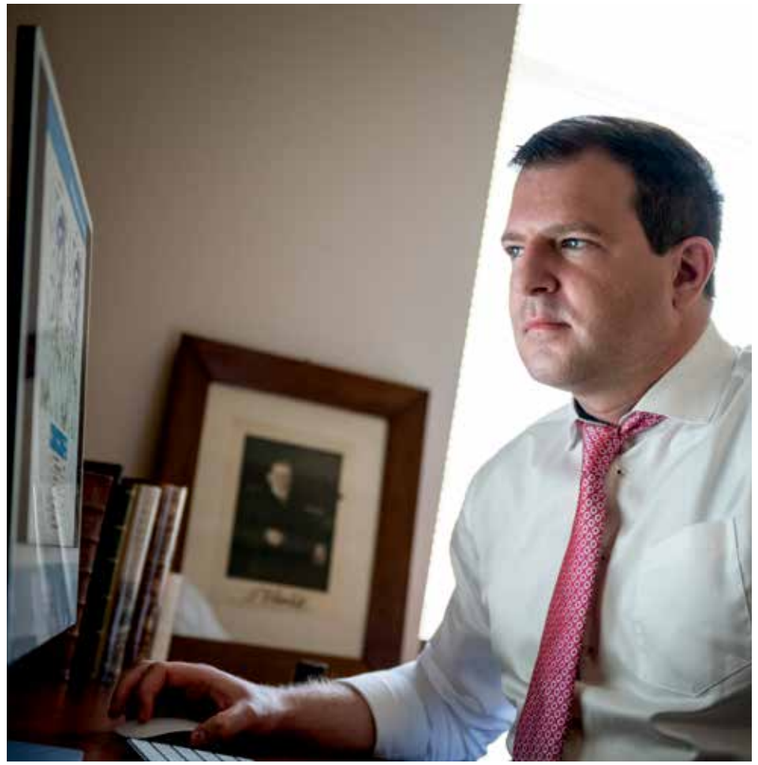
Eliminating Enemies Within

Chimeric antigen receptor (CAR)-T cells are a type of "living drug" immunotherapy that has been successfully used to treat patients with B cell-driven blood cancers. But now the same therapy is being applied to patients with severe rheumatic diseases: The approach depletes B cells with remarkable results, achieving drug-free disease remission in many patients.

B cells are a type of white blood cell that makes infection-fighting proteins called antibodies. In rheumatic disease, some "bad actor" B cells emerge; in effect, they "go rogue," attacking the body's own tissues and causing the damage we associate with a given autoimmune disease.

"Over the last several years, a whole new area has emerged in how we can treat autoimmune diseases," Konig explains. "If we can deeply deplete the patient's B cells, we can force the body to reconstitute its missing B cell pool. When that happens, we see untrained [naïve] B cells emerge that no longer recognize self-proteins as foreign — the bad actors are gone. In effect, the patient's immune system is forced to forget that it had previously started to attack the body."

The treated patient's previously active and potentially life-threatening autoimmune



MAXIMILIAN KONIG
"The program we have built, and are building, is putting us ahead of the curve."

disease can completely disappear, he says. Engineering and equipping the body's own "killer" T cells, through expression of a CAR, to rid the patient's body of these bad B cells is key to this success.

So just what can patients with rheumatic diseases expect when they begin treatment within the new Johns Hopkins Cellular Therapy Program for Autoimmunity?

CAR-T cells are currently given as part of clinical trials, Konig explains, and details differ between types of therapy and specific protocols. Patients generally begin by first providing their white blood cells (containing the T cells) in a process known as apheresis, a prerequisite for all "autologous" (patient-derived) cell therapies. The collected cells are then shipped to a specialized lab to be engineered, he says.

During the days to weeks the patient's T cells are being engineered to make CAR-T cells, the patient undergoes a course of conditioning therapy (called lymphodepletion therapy) to reduce their immune cell numbers and provide the right environment for the CAR-T cells to engraft. Then, the patient returns to Johns Hopkins to have the newly engineered CAR-T cells infused. Patients who receive CAR-T cells are closely monitored in the hospital over the next 7–14 days by Konig and other clinicians. Then they return home but continue to be monitored closely to pick up on any potential complications (typically related to the very active T cells).

While autologous CAR-T cell therapies require patients to provide their own blood cells to be engineered, Konig says that many researchers see a bright future in "allogeneic" approaches: Using healthy donor cells that are engineered in bulk and can be banked. The idea here is that a healthy donor donates cells that are specifically modified (requiring some additional engineered steps to disarm them and avoid immediate rejection when infused into another human) and then frozen. When needed for a patient with rheumatic disease, these cells could be "pulled off the shelf," thawed, and then infused.

In contrast to the individual manufacturing with autologous cell therapies, banked cell products are premanufactured from a healthy donor's T cells, which may enable more predictable behavior across patients. The result: streamlined manufacturing, reduced costs and faster treatment for patients. Konig, including his own lab, is a strong proponent of this approach, and an ongoing CAR-T cell therapy trial (GLEAM) for patients with severe lupus and ANCA-associated vasculitis offered at Johns Hopkins uses such allogeneic CAR-T cells.

In addition to providing T-cell therapies that require cell engineering, the Johns Hopkins program will offer an alternative strategy using bispecific T cell-engaging antibodies ("bispecific antibodies"). These can target and latch onto two different target molecules, and thereby engage and redirect the patient's own T cells to bind and kill B cells. The end effect is an off-the-shelf therapy that shows comparable potency to CAR-T cells without requiring any apheresis, cell engineering or conditioning therapy. Bispecific antibodies are similarly infused (typically multiple times) and require an inpatient stay and close follow-up monitoring since they show similar side effects to CAR-T cells, Konig explains.

While using cellular therapies to treat autoimmune diseases is still in its early days, the results so far have been encouraging, Konig says: "These therapies have created much excitement. Many patients are emerging from this one-time treatment with no signs of disease. It is too early to say they are 'cured,' but if we can allow patients to live drug free, accruing no further damage to their organs for five, 10, or 15 years, we have already won."

> "We're opening pathways for the large population of our patients to receive these kinds of transformative treatments."
>
> Maximilian Konig

A New Model

As the number of patients eligible for these off-the-shelf therapies is expected to grow rapidly in rheumatology in the next years, the team at Johns Hopkins is looking to rheumatologists to meet the need. "The program we have created, and are continuing to build, is putting us ahead of the curve," Konig says. "We're opening pathways for the large population of our patients to receive these kinds of transformative treatments."

Key to the new cellular therapy program is an experienced and closely knit team, including senior research nurse **Liana Boccio**, who brings deep experience in using CAR-T cell treatment from oncology to rheumatology; **Gwendolyn Leatherman**, a research nurse manager with extensive experience in clinical trials; and physicians in hospital medicine, **Margueritta El Asmar** and **Michael Cammarata**. The program also capitalizes on the expertise of staff members in the clinical trial units, colleagues in oncology, and the deep expertise of the Division of Rheumatology's Centers of Excellence.

The new Cellular Therapy Program at Johns Hopkins, Konig believes, "can be an innovative model to show hospitals across the country that cellular therapies can be made widely available to patients with autoimmune diseases by putting them in the hands of rheumatologists." L

ON THE HORIZON: PRECISION IMMUNOTHERAPIES

Even as Maximilian Konig and his team build out the new Cellular Therapy Program at Johns Hopkins, he and researchers in his lab are hard at work in their quest to shape the future of immunotherapy for rheumatic diseases. The goal: controlling disease without increasing the risk of infection.

Only a very small percentage of B cells in patients with a rheumatic disease are "bad actors" and cause tissue damage. Getting rid of just this small number of rogue B cells could get patients into remission or even cure. "Our current approaches, whether CAR-T cell therapy or monoclonal antibodies, however, take a 'sledgehammer' approach, depleting all of the patient's B cells to get rid of the few rogue disease drivers — and it works," he says. "But this brute force approach comes at the cost of the patient losing the ability to fight infection effectively."

In his lab, Konig's research team and collaborators are working to develop precision immunotherapies that selectively target and eliminate the rogue cells, leaving the 95–99% of the patient's immune system that protects from infection and cancer intact. By combining the potency of current immune effector cell therapies with therapeutic precision, says Konig, "we hope we will be able to achieve lasting disease remission with minimal risk to patients."

At the 2024 American College of Rheumatology Convergence meeting, his group unveiled four precision immunotherapy approaches that were developed at Johns Hopkins that have the potential — through further development — to become the first tailored therapies for patients with lupus, antiphospholipid syndrome, ankylosing spondylitis and celiac disease, Konig says.

Capitalizing on his lab's findings in preclinical models and blood samples donated by rheumatic disease patients seen at Johns Hopkins, the team has begun collaborating with Baltimore-based accelerator Blackbird Laboratories to move some of these precision-based strategies forward. The goal, Konig says, is to begin clinical trials in humans within five years.

Looking ahead, Konig says, "There's a lot of hope. And a lot of work to be done."

TAKING A SHOT AT POTS

For her first 40 years, physician Madeline Brown, M.D., enjoyed an active lifestyle. When she wasn't seeing patients or teaching medical residents, she and her physician husband loved hiking and skiing near their Colorado home, and traveling the globe.

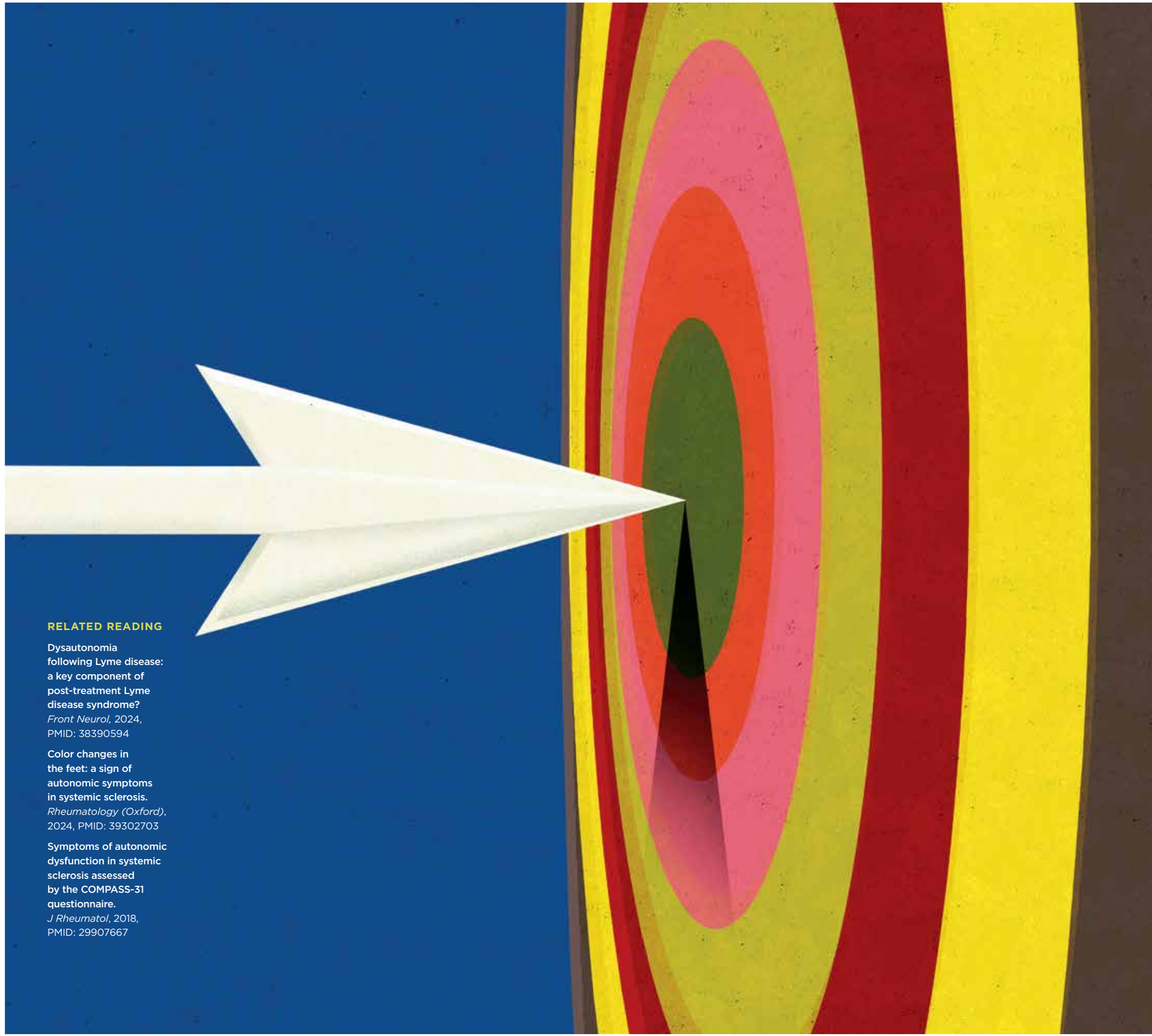
But that all began to change for her in 2018. "I started developing bad skin rashes and extreme photosensitivity to sun and experiencing joint pain and weakness in my muscles to the point that I couldn't hold positions in yoga," she recalls. After visiting her local rheumatologist, she was diagnosed with dermatomyositis, which is marked by muscle weakness and a skin rash, and Sjögren's syndrome.

By early 2020, she started struggling with new symptoms and couldn't get off the sofa. Bouts of brain fog made it difficult for her to focus. Her joints ached horribly and episodes of searing nerve pain became the norm. She felt so dizzy that it was difficult to stand up.

"I'm a doctor, so I knew there was something wrong with me. I went from being completely healthy to basically being bedridden," Brown says. "But when I went to different doctors, I had trouble getting them to take my symptoms seriously."

Eventually, in June 2022, Brown landed at Johns Hopkins and found a rheumatologist who could provide some answers: **Brit Adler, M.D.** After examining Brown and running a series of tests including a "tilt table test," which monitors the heart and nervous system's response to changes in position, Adler told her patient, "I think a lot of the weakness and brain fog you are experiencing is coming from something called POTS, or postural orthostatic tachycardia syndrome." Adler was about to join the clinical team in the POTS Program at Johns Hopkins. Brown, who by then lived in Pennsylvania, jumped at the opportunity to be treated by Adler and her team.

> "While POTS has been around for decades, it's largely been ignored by our medical system."



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Symptoms of autonomic dysfunction in systemic sclerosis assessed by the COMPASS-31 questionnaire.
J Rheumatol, 2018, PMID: 29907667

BRIT ADLER
"I saw an opportunity to make a meaningful impact by focusing my clinical care and research on POTS."

"For me, the stars aligned perfectly," says Brown. "Dr. Adler is so smart and so easy to talk to, and the fact that she was transitioning to the POTS clinic — that was exactly what I needed."

Largely Ignored Until Now

Currently, there are only a few POTS programs at hospitals around the country. Among them, the Johns Hopkins POTS Program is unique in including a rheumatologist on the multidisciplinary clinical team, which is housed within the Department of Physical Medicine and Rehabilitation. Given patients' varied needs, the program also offers access to experts in cardiology, hyperhidrosis (excessive sweating), neurology, adolescent medicine and physical therapy.

Adler, who completed her rheumatology fellowship in the Johns Hopkins Division of Rheumatology and joined the faculty in 2018, first saw patients in the Myositis Center and focused her basic research on scleroderma. It was while completing a research project on autonomic dysfunction in scleroderma that she was introduced to POTS and its symptoms, and the profound impact POTS has on patients' quality of life.

"I started looking for these symptoms when evaluating patients in my general rheumatology clinic, and I discovered that POTS is incredibly common and often overlooked," she says. "I saw an opportunity to make a meaningful impact by focusing my clinical care and research pursuits on POTS. I hope to utilize my background in rheumatology to identify different subgroups of patients with POTS whose mechanisms of disease are immune-mediated and may respond to immune treatments."

The syndrome most frequently impacts women between the ages of 15 to 50 years. Many come in with symptoms including fast heart rate, lightheadedness and fainting, brain fog, and muscle pain and weakness.

"While POTS has been around for decades, it's largely been ignored by our medical system. Historically, the response has been to dismiss these symptoms as being due to women's 'anxiety,' and to them being 'overwhelmed,'" Adler says. "But many of these patients are very sick. They are young, and the vast majority have had to cut back on school or work, or even take a medical leave because of their symptoms."

Adler's role as a rheumatologist in the POTS clinic is critical: She is finding that many patients diagnosed with POTS have overlapping autoimmune disorders, which can be debilitating and further complicate treatment. Some patients come in with Sjögren's syndrome or dermatomyositis. Other patients have scleroderma, lupus, chronic Lyme disease or celiac disease.

Says Adler, "I am also seeing a lot of overlap with Ehlers-Danlos syndrome (EDS)," an inherited group of disorders that affect connective tissues in the body, causing hypermobility and potentially life-threatening complications. "We still don't understand why EDS puts patients at risk of developing POTS," she says. "It's a big area of research."

But what's really driven an "explosion" in POTS cases, Adler says, has been the COVID-19 pandemic. Before COVID-19, an estimated 500,000 to 3 million patients in the United States were believed to suffer from POTS. Since the pandemic, that number has risen dramatically.

"We've seen a large increase in patients who develop POTS after COVID-19," she says. "There just aren't enough doctors to evaluate and treat them. It's a huge public health problem."

A Very Heterogenous Syndrome

Patients with POTS can struggle for months or even years, seeing specialist after specialist to no avail, Adler says.

When new patients do find their way to Adler at the Johns Hopkins POTS Program, she usually starts by assessing them on the tilt table. They lie flat as the table is lifted from a horizontal position to almost upright, while their heart rate and blood pressure are monitored. Many (though not all) patients with POTS will experience an increase in heart rate when upright, and/or feel lightheaded or faint. Some will also experience weakness, fatigue, sweating or nausea.

The problem in some cases appears to lie in the sympathetic vasomotor system. When a healthy patient stands up, the blood pools in the legs due to gravity; the blood vessels are supposed to squeeze and pump the blood up to the brain where it needs to go. "But in some cases of POTS, that fails to happen. The blood vessels fail to constrict and patients get blood pooling in their legs," Adler explains.

Treatment for POTS often begins with making lifestyle changes, Adler explains. These include increasing fluid and salt intake to expand blood volume and improve blood flow to prevent dizziness and fatigue; the use of compression stockings; and physical therapy, which is aimed at building muscle strength and improving conditioning for better blood circulation.

> "We are at the forefront of this emerging field, which has become a hot area of study since the pandemic. It is a very exciting time for research."
>
> Brit Adler

But lifestyle changes alone are often not sufficient. "A number of my patients need to take medications to improve their circulation or lower their fast heart rate," she says. "Our goal is to give people their function back — and we are able to do that in many cases." While some of her patients do recover fully, she says it's more common for the disease to wax and wane, causing flares over time, and many patients must see multiple specialists to manage concurring conditions.

Finding the right medication plan can be a trial-and-error affair, Adler says, undoubtedly due to the fact "that POTS is a very heterogenous syndrome." She's seen some perfectly healthy patients who have developed POTS after a head injury, and others in the months after having a baby. "The causes could be infectious — such as COVID or chronic Lyme — or POTS may have an origin in autoimmune dysfunction, such as lupus or Sjögren's syndrome. And then there are potential nonimmune causes, like concussions or EDS."

"There's probably dozens of different causes of POTS," says Adler, "and we don't have a biopsy or single diagnostic test to guide us."

An Emerging Field

In her research, Adler is pushing to gain a better understanding of the immunologic basis of POTS in distinct subgroups of patients.

Given the heterogenous causes of the syndrome, "there is a lot of work to be done to identify subsets of patients who behave similarly or have a similar underlying trigger," Adler says, which will ultimately enable doctors to fine-tune treatments based on an individual's disease course and related illnesses. A person who develops POTS after COVID-19, for example, will probably require a different treatment plan than someone like Brown, whose POTS arose in the wake of her autoimmune disorders. "We suspect that distinct clinical and laboratory biomarkers may associate with different POTS subgroups, and this is an active area of investigation by our group," Adler says.

She is working closely with infectious disease specialist **John Aucott, M.D.**, director of the Johns Hopkins Lyme Disease Research Center, to examine how POTS develops after Lyme disease, in addition to after COVID-19.

One key to finding answers that will benefit all patients with POTS, Adler says, lies in building a clinical database and biobank of patient samples (blood, urine and saliva) that will enable clinical researchers like her to parse varied causes and patterns of progression — work that she has already begun at Johns Hopkins — and to launch clinical trials to better understand the effectiveness of various treatments for different subgroups of patients.

"Despite how common POTS is, there have been few longitudinal studies that look at long-term outcomes," Adler says. "We are at the forefront of this emerging field, which has become a hot area of study since the pandemic. It is a very exciting time for research," she says. "For too long, doctors dismissed patients with POTS. It's very clear at this point that POTS is something very real and I am hopeful that we will start to unravel this complex disease." L

PARTNERS IN LUPUS RESEARCH

Felipe Andrade, M.D., Ph.D., below, and Eduardo Gómez-Bañuelos, M.D., Ph.D., right.

"We need to distinguish between patients who may look clinically identical to understand why one patient will go on to have a better outcome than another."

Felipe Andrade

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American College of Rheumatology Convergence 2024; Abstract #1607

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Nat Commun, 2023 PMID: 36941260

More than 1.5 million people in the United States are living with lupus, a chronic autoimmune disorder that affects mostly women and causes the body's immune system to attack healthy tissues and organs.

Beyond that stark statistic lies a condition that devastates lives, and a clinical research field abounding with unknowns: Why do some patients with skin rashes respond well to available lupus treatments while others with similar symptoms go on to develop additional symptoms like arthritis…and still others progress to kidney failure? What puts some patients with lupus at higher risk of having a heart attack or stroke? Just how does lupus progress in each individual patient — and what does that mean for how treatments could be tailored earlier on to stave off future damage?

These are among the vital questions driving the research of Division of Rheumatology faculty members **Felipe Andrade, M.D., Ph.D.**, and **Eduardo Gómez-Bañuelos, M.D., Ph.D.** The two researchers are moving ever closer to finding answers, thanks to recent advances they've made in their lab at the Johns Hopkins University School of Medicine.

"Lupus comprises distinct subgroups that may have similar clinical manifestations but are driven by different cellular mechanisms," explains Gómez-Bañuelos, assistant professor of medicine.

"That is why it is so important for us to focus on better understanding, at the molecular level, what the different drivers of the disease are," adds Andrade, an associate professor of medicine. "We need to distinguish between patients who may look clinically identical to understand why one patient will go on to have a different outcome than another."

In their research efforts to identify and define these new patient subsets, and to better understand various pathways of the disease, they rely heavily on a treasure trove of consented patient data, including blood and tissue samples, developed by **Michelle Petri, M.D., M.P.H.**, professor of medicine in the Division of Rheumatology. Since 1987, she has led the Johns Hopkins Lupus Cohort, a longitudinal study that has followed more than 3,000 patients with lupus.

"This incredible characterization of patients, going back decades, and the availability of research-grade data and samples has been a huge advantage to our work today," says Andrade.

Investigating Lupus Together

While Gómez-Bañuelos has been fascinated by lupus since his days as a medical student in Guadalajara, Mexico, Andrade, who trained in Mexico as a rheumatologist, devoted the first 15 years of his research career at Johns Hopkins primarily to investigating rheumatoid arthritis.

"But I'm not a single-disease scientist, and lupus was always in my sights as a disease that I wanted to study," Andrade says. "Then, about seven years ago, Eduardo joined our group as a fellow; I saw in him a path to start exploring lupus more fully. He was a driver for me to make the jump. Now, we work very closely together."

During Gómez-Bañuelos' rheumatology fellowship in Mexico, he treated patients with lupus before he moved full time to medical research at Johns Hopkins. "That experience with patients helps me understand better what all those clinical variables mean, and the weight they should have for patients," says Gómez-Bañuelos, whose wife, **Marta Escarrà-Senmartí, Ph.D.**, is also a researcher in the Andrade lab (see p. 17).

Gómez-Bañuelos splits his time between the "wet lab" (bench research) and the "dry lab," analyzing data on the computer. "Both methods are complementary and one informs the other," he says. "Going back and forth is very exciting."

Through their detective work in the lab, the two researchers are shedding light on the pathogenesis of lupus and its intersection with the unique course of disease in each patient, which could guide clinicians in providing better tailored therapies.

Interacting Interferons

One of their recent projects opens an exciting new window into the role that interferons play in various forms of lupus. Interferons are a family of cytokines, which are key proteins in the body's immune response to invaders. In recent years, lupus specialists have prescribed medications targeting interferon type I (IFN-I) in an effort to stem symptoms.

"Many patients with lupus have increased levels of IFN-I, so the paradigm has been to provide drugs that block the IFN-I pathway to control disease," says Gómez-Bañuelos. "The problem is that only about one-half of patients with high IFN-I have some degree of response to anti-IFN-I treatments. Our question was: Why?"

Some, but not all, of the downstream effects of the interferons are shared — making it challenging to know exactly which interferon is causing clinical problems in patients with lupus. In their study, published in the May 2024 issue of *Cell Reports Medicine*, the two researchers therefore cast a wider net, looking at the role played by additional types of interferon: specifically, IFN-II and IFN-III. They used a unique assay to precisely measure the independent activity of each IFN type in patients' blood samples and tapped into the extensive clinical, laboratory and whole blood transcriptional data available in the Johns Hopkins Lupus Cohort.

Previous research by scientists had found that IFN-II and IFN-III levels were elevated in patients with lupus, "but there was no analysis of how these different types of interferons were interacting," says Andrade. "Our approach was to analyze all three types at once, in every patient."

Zeroing in on the interactions proved key. The scientists found, for example, that patients with IFN-I involvement alone mainly had skin disease, clarifying why this subset of patients responds very well to IFN-I blocking agents. Conversely, patients with kidney disease, one of the most severe manifestations of lupus, showed activation of IFN-I, IFN-II and IFN-III. "So, blocking IFN-I may not be enough for these patients," says Gómez-Bañuelos.

By offering new insights into interacting effects between IFN families, as well as IFN-independent mechanisms, Andrade and Gómez-Bañuelos are moving the field closer to providing more effective, targeted therapies for lupus.

"We anticipate that these findings will be important in identifying those patients who will respond better to IFN-I blocking agents, as well as useful for designing clinical trials that target the right therapeutic mechanisms to the appropriate patient subgroup," says Gómez-Bañuelos.

A Biomarker for Thrombosis

Andrade and Gómez-Bañuelos also have a strong focus on understanding how the autoantibodies made by lupus patients serve as markers of the type of disease that the patient gets, and understanding the mechanisms underlying those clinical associations. In a promising area of study, the duo has discovered a novel autoantibody that identifies patients with lupus who are at higher risk of thrombosis leading to heart attack or stroke — specifically in the group of lupus patients who have antiphospholipid antibodies, some of whom develop blood clots.

"The antibody biomarkers for this syndrome [antiphospholipid antibodies, or aPL] have been known for years and they have a strong diagnostic value," says Andrade. "However, not all patients who have aPL antibodies go on to experience clots. And not all patients who develop thrombosis will have aPL antibodies. Here again, we wondered: Why?"

In their work in the lab and analyzing data at the computer, the researchers zeroed in on a protein that resides in the cell's mitochondria. They ultimately identified TFAM (transcription factor A mitochondria) as a target of antibodies in about 30% of patients with lupus. Moreover, they discovered that these antibodies were associated with thrombosis and antiphospholipid syndrome (APS) *independently* of aPL antibodies.

> "We have opened the door to showing that mitochondrial damage is associated with thrombosis events in lupus."
>
> Eduardo Gómez-Bañuelos

"So, we've found an entirely new biomarker that can help identify which patients with APS have a high risk of developing a heart attack or stroke, or experiencing a deep vein thrombosis," says Gómez-Bañuelos.

Moreover, says Andrade, "when both anti-TFAM antibodies and lupus anticoagulant — a marker of APS — are present, the chances of thrombosis increase up to 10 times."

In addition to better defining lupus patients at higher risk of thrombosis, says Gómez-Bañuelos, "we have opened the door to showing that mitochondrial damage is associated with thrombosis events in lupus. Understanding how this might be further exploited in studying SLE [systemic lupus erythematosus] and its prevention and therapy is a high priority."

Exploring the Origin of Antibodies Targeting DNA in Lupus

In their work on autoantibodies in lupus, the duo made another surprising finding. "We discovered a new autoantibody that is directed against DNase1L3, an enzyme whose function is to destroy DNA," says Gómez-Bañuelos.

DNase1L3, which is secreted by specific immune cells, helps break down DNA released from dying cells, preventing it from causing an autoimmune reaction. If DNase1L3 does not work correctly or is blocked by antibodies, this leftover DNA can cause harmful autoimmune responses, such as producing anti-DNA antibodies, resulting in lupus symptoms.

In a recent paper in *Nature Communications*, they show some patients have antibodies that target DNA and DNase1L3 at the same time. "We were never expecting this!" says Andrade. "We know that anti-DNA antibodies are a hallmark of lupus. But not every anti-DNA antibody is equally dangerous. Some may be harmless, while others target the kidneys or the brain, causing lupus nephritis or neuropsychiatric lupus, respectively. The reason why anti-DNA antibodies are so diverse is not fully understood."

Andrade notes that patients who harbor this subset of double reactive antibodies to DNA and DNase1L3 have a higher risk of developing more severe disease than those with antibodies that only target DNA. "It is like having two pathogenic antibodies in one," he says. Through further investigation, the scientists found that during lupus development, antibodies that initially target DNase1L3 mutate and gain reactivity to DNA, explaining the origin of double reactive anti-DNase1L3/DNA antibodies.

Insights like these into the progression of the autoimmune response, the scientists say, could help clinicians recognize which patients are at higher risk of developing a severe inflammatory response, so that steps could be taken earlier in the disease to prevent such progression before damage to organs and other body systems occurs.

"We think specific antibody subsets can be informative about which pathogenic pathways are more active in different groups of patients," says Gómez-Bañuelos.

He and Andrade are encouraged by discoveries like these — and excited to continue investigating the sea of unanswered questions that remain in their quest to develop personalized treatments for patients with lupus and other autoimmune disorders.

"As we make new discoveries, instead of finding immediate solutions, sometimes we add to the complexity," says Andrade. "But that's OK! We know that any new information we can generate, if not applied today, can be used to improve the lives of future generations of patients."

It is our pleasure to shine a spotlight on the remarkable individuals within the Division of Rheumatology. Meet four dedicated professionals with diverse roles but a shared goal: to make life better for our patients.

A 'FAMILY FEEL' IN RHEUMATOLOGY

ANGEL CHAMBERS
Senior Medical Office Coordinator
Johns Hopkins Scleroderma Center

When patients are coping with scleroderma, which causes hardening of their skin and connective tissue, they often live with a range of challenging health concerns, which can impact their heart, lungs, kidneys and muscles.

The condition can require frequent visits to Johns Hopkins' vaunted Scleroderma Center — visits managed by Angel Chambers, one of the center's three coordinators. Compassionate and friendly, Chambers brings empathy to every patient encounter.

"We are the first line of communication for patients who need to schedule an appointment, or follow-up tests. It's important for me to stay calm and on an even keel and offer a kind ear," says Chambers. "When patients first get a diagnosis, sometimes they are scared or sad and they just want to talk to someone. It's important to be sensitive. I encourage them to talk and to vent, and to share whatever is on their mind, if they wish."

Chambers, who joined the Division of Rheumatology in 2013, is a Baltimore native who began her career as a certified nursing assistant working with patients who have dementia. After a few years, she transitioned from working with patients who have cognitive impairment to begin work as a medical office assistant at

"I really like my patients. You develop a bond with them and feel like you are really helping them."

Johns Hopkins. She spent time with two different departments before landing in the Division of Rheumatology. She says she couldn't be happier.

"Rheumatology definitely has a family feel about it," says Chambers. "In previous departments where I worked, you had your role and you stayed within it. You didn't connect a whole lot with those outside your station. Here, it's different. Whether you're a coordinator, or a fellow or an attending doctor, everyone clicks and is joined together. When you see someone in the hall, you stop to say, 'Hi,' and engage."

She particularly enjoys the division's twice annual faculty/staff get-togethers, which take place in early summer and over the December holidays. "Just last June, we had a really fun gathering at the Guinness Open Gate Brewery in Halethorpe, Maryland. Everyone hung out together. It was really great," says Chambers.

A self-described homebody outside of work at Johns Hopkins, she says she enjoys visiting historical sites and meeting up with her niece to catch up over coffee.

Over her decade-plus with the Division of Rheumatology, Chambers has gotten to know some of her patients very well. "I really like my patients. You develop a bond with them and feel like you are really helping them," she says. "During the holidays in December, some of them send cards and include little notes. It's so fulfilling to get to hear about them and their families."

ENSURING SMOOTH SAILING FOR FELLOWS

KELLY HUETER
Academic Program Administrator

In her 17 years with the Division of Rheumatology, Kelly Hueter filled a variety of roles before she landed in her current spot as academic program administrator.

"When I first started, Dr. Ami Shah was a fellow and now she is director of rheumatology," says Hueter. "It's been so amazing to see how everybody in the department has grown — and they've seen how I advanced."

Hueter joined the division as a temporary employee in 2007 and was hired full time as medical records coordinator in March 2008 to transfer the paper charts into the new electronic records system. "I loved my job," she says.

Over the years, she says, "I would always fill in when needed and I loved being able to learn everyone else's job, whether it was scheduling patients, or processing patient checkout." Her next position was as senior medical office coordinator for the Jerome L. Greene Sjögren's Disease Center. She worked in that role for about 10 years under the leadership of rheumatologist Alan Baer.

In her current role with the fellowship program, which she assumed in summer 2019, Hueter handles administrative tasks aimed at ensuring smooth operations for rheumatology's nine fellows in the Accreditation Council for Graduate Medical Education (ACGME) program and four fellows in the Non-Standard Training ACGME Equivalent for the Lupus and Myositis Fellowships, as well as for Johns Hopkins trainees, and visiting medical students and visiting residents.

"I take care of all of them, to make sure they have a great learning experience. But I make sure my fellows are taken care of first," says Hueter, whose typical day includes completing paperwork and scheduling for the fellows as they rotate through the division's many specialty clinics. She also coordinates submission of multiple grants, compliance with ACGME

"We have fellows come from all over the country and around the world. Currently we have fellows from Germany, Canada, Japan and Thailand. It's important for me to check in on them to make sure everything goes well."

requirements, and, in general, keeps connected with visiting trainees to ensure their time in Baltimore unfolds seamlessly.

"We have fellows come from all over the country and around the world. Currently we have fellows from Germany, Canada, Japan and Thailand," says Hueter. "It's important for me to check in on them to make sure everything goes well."

When she isn't working, Hueter enjoys time with her husband, Dan, and their 3-year-old son, Ari — particularly outings on their boat.

Hueter is grateful for the mentoring she has received over the years from faculty leaders and administrators in the division, particularly from Myma Albayda, Uzma Haque, Ami Shah, Allan Gelber, Phil Seo, Alan Baer and Kwisha Patel.

"I cannot say enough nice things about Dr. Albayda, Dr. Haque, Dr. Shah, Kwisha and the support they show me in the work I do," says Hueter. "We all take a lot of pride in our work and are really more like a family. It's so important to have a great connection between all of us; it takes all of us working together to make a strong team."

As a mother, Hueter says work-life balance is important to her — and she's found it to be important to division leaders as well. "Last summer, Dr. Shah made a point of encouraging me to take vacation," says Hueter. "I truly needed to hear that. When I got back, I was so refreshed and ready to start a whole new academic year."

MAXIMIZING EFFICIENCY

KWISHA PATEL
Senior Administrative Manager

As a key member of the rheumatology division's senior leadership team, Kwisha Patel's role is wide-ranging and crucial to ensuring smooth day-to-day operations and the financial health of the division.

"Everyone here in Rheumatology is committed to working as a part of a team, which makes this role both exciting and rewarding," says Patel, who was working as an executive fellow at Hartford HealthCare in Connecticut before she joined the division in July 2022.

One of Patel's primary roles is to manage a group of budget analysts who work closely with principal investigators (PIs) to make sure that individual budgets are met and funding is used within stated guidelines.

"It is essential that our PIs have up-to-date insights into their accounts, so they are not overspending or underspending," she says. "I lead our analysts' efforts to make sure every dollar is wisely allocated, and we foster synergy between our clinical teams and our administrative teams."

To optimize efficiency, Patel recently led a restructuring of the budget analysts' work model. "In the past, analysts focused on specific types of grants," she explains. "Now, we've implemented a system where all the analysts are prepared to work on any grant type. So if one of them is away from the office on leave, it will be easy for someone else to step in. This cross-functional approach ensures continuity in managing these significant amounts of sponsored funding we receive through the federal government, foundations and other funding sources."

Patel also coordinates strategic planning, business development and operational activities, and managing annual budgets. This involves creating data-driven dashboards to track and improve operational and financial performance, ensuring key metrics are met across the division.

> "Everyone here in Rheumatology is committed to working as a part of a team, which makes this role both exciting and rewarding."

When Rheumatology leaders want to recruit a new faculty member to join the division, Patel also works behind the scenes to analyze data and compile a business plan to present to departmental and school leaders to support the hiring.

Reflecting on the diverse and complex nature of her role as administrative leader, Patel says, "Our faculty members are renowned in their research and clinical care, but they need a support system. I truly appreciate that [our] faculty members value teamwork. That's what excites me to come into work every day."

Once her workday ends, Patel likes to unwind by spending time in the kitchen. "I love cooking, particularly the comfort foods my grandma used to prepare," she says. Whether whipping up an old favorite or exploring a new recipe, Patel says, "I enjoy the beautiful colors of fresh produce and the aroma of spices. That's what puts me at peace after a stressful day. That's my Zen."

ADVENTURES IN BASIC RESEARCH

MARTA ESCARRÀ-SENMARTÍ, PH.D.
Research Associate

Born and raised in Barcelona, Spain, Marta Escarrà-Senmartí says she was "always curious about Latin America." So after completing her master's in organic chemistry at the University of Barcelona, she decided to pursue a Ph.D. in immunology in Mexico at the University of Guadalajara.

It was there that she met her husband, Eduardo Gómez-Bañuelos, today an assistant professor in the Division of Rheumatology (see p. 10). The couple lived and worked in Mexico for about seven years. "Our first daughter, Clara, was born there," says Escarrà, whose research focused on the role that NK ("natural killer") cells play in cancer and autoimmune disease.

"Autoimmune responses and cancer are interconnected, so during my Ph.D. studies, I worked on some projects with Eduardo," who had some overlapping research interests, she says.

The couple moved to the United States in 2018, when Gómez-Bañuelos joined the Johns Hopkins lab of Felipe Andrade (see p. 10) as a postdoctoral fellow and Escarrà began work in the pathology department as a research specialist. "I have always been interested in the way the immune system works, particularly in cancer," she says.

After a few years, she moved to join Andrade's lab, as a postdoctoral fellow focusing on better characterizing the "partners in crime" of the enzyme PAD4, which is responsible for "hypercitrullination" in rheumatoid arthritis. More recently, her research has examined the origin of anti-citrullinated protein antibodies (ACPAs). She has demonstrated that these are mutated antibodies resulting from somatic hypermutation that originally recognized carbamylated antigens.

> "I like basic science because it is always an adventure!"

Escarrà says she loves the life of a bench scientist. "I have lived in different countries during my life and I am an adventurer and I like challenges," she says. "I like basic science because it is always an adventure!"

In November, Escarrà transitioned to being a research associate in Andrade's lab. "I am so excited and grateful to continue working with Felipe," she says. In her new role, she will be more involved in leading work in the flow cytometry core at Johns Hopkins Bayview Medical Center, serving researchers from a variety of specialties who are investigating problems related to immune-based human diseases. She has utilized flow cytometry (which uses lasers to analyze the physical and chemical characteristics of cells) throughout her research career and is well prepared to provide guidance and counsel to fellow researchers.

Outgoing and upbeat, Escarrà says she values the collegial culture at Johns Hopkins and the shared excitement that comes with discovery. "In basic science research, I have to say there are more lows than highs," she says. "But when we have a high, it's the best!"

When she's not in the lab, Escarrà stays busy with Clara, now 7, and Mar ("Sea" in Spanish), age 3. "I have two jobs. During the day I am a researcher. During the late afternoons and evenings, I am Supermom!" she says, laughing.

It's not unusual for work to carry over into her family's home life — in a positive way. "Eduardo and I are a good team, and we both work in autoimmune areas so we have a lot of conversations about science," Escarrà says. "Our daughters have learned all these 'strange' words that other children their age don't know, like antibodies and proteins. Clara is already saying she wants to be a scientist when she grows up."

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"A problem is really a springboard for a LEAP into the unknown."

— Ralph E. Gibson, distinguished scientist