LEAP

Johns Hopkins University
School of Medicine
Division of Rheumatology
Winter 2024

SJÖGREN'S RESEARCH

AT THE CUSP OF BREAKTHROUGHS

GAME CHANGER:
LIQUID BIOPSY

AT LAST, AN ANSWER:
WHY AUTOIMMUNE DISEASES ATTACK MORE WOMEN THAN MEN

MOMENTUM!

"At the Cusp of Breakthroughs," "Game Changer," "At Last, an Answer." As you can tell from our headlines, so much is happening here in the Division of Rheumatology. If we had to choose one word to sum up this issue of *LEAP*, it might be momentum. We are making more discoveries and they are happening faster, because we have built a critical mass of infrastructure. Our approach is multifaceted, and is well described in our cover story about the Sjögren's Center. (Page 2). Briefly:

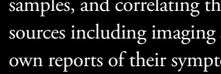
We have seven centers – for Sjögren's, Arthritis, Lupus, Vasculitis, Lyme Disease, Myositis, and Scleroderma – that, on the clinical side, bring together multidisciplinary teams with expertise in treating these diseases. On the basic science side are investigators who, using powerful technology and big data, are conducting in-depth molecular analysis of tissue and blood samples, and correlating them with millions of pieces of information from sources including imaging scans, findings from patient visits, the patients' own reports of their symptoms, and longitudinal studies. We are delivering precision medicine to our patients, helped by two impressive resources here at Johns Hopkins: our NIH-funded Precision Medicine Data Integration Core, and our Precision Medicine Analytics Platform.

In addition, our world-class clinicians and scientists are taking part in several multi-institutional research projects, including the NIH's Accelerating Medicines Partnership-Autoimmune and Immune-Mediated Diseases (AMP-AIM) Program. Such collaborations are further accelerating our research, and the results are dramatic.

Lupus affects nine women for every one man; in Sjögren's, the ratio is 19 to one. Autoimmune diseases are markedly tilted toward women – and now, for the first time, we know a major reason why, thanks to groundbreaking work led by scientist Erika Darrah and clinician-scientist Brendan Antiochos (Page 10). The implications for this research – in our understanding of many autoimmune diseases, and our hope of finding entirely new ways to treat them – are massive.

A window to the kidney: Some patients with lupus develop disease in the kidney, and until now, there has been no way to know for certain what's really happening inside the kidney except for an invasive, expensive procedure: kidney biopsy. But now, physician-scientist Andrea Fava has found biomarkers that approach biopsy-level certainty (Page 6). He is partnering with industry to develop a "liquid biopsy" urine test that will help us know if there is trouble in the kidney, and if the patient is being treated, whether the medication is working. This test may even help predict a flare before it happens.

Finally, we could not deliver excellent, compassionate care without our remarkable, dedicated staff. It is our great pleasure to introduce you to four people who work hard and with great success make life better for our patients.



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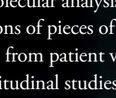

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Vice Dean for Research, JHUSOM
Chair, Executive Committee, Johns Hopkins inHealth

We are making more discoveries and they are happening faster, because we have built a critical mass of infrastructure.

WINTER 2024

LEAP

Left: Why are lupus, Sjögren's, rheumatoid arthritis, and many other autoimmune diseases so heavily tilted towards women? Physician-scientist Brendan Antiochos and scientist Erika Darrah (see Page 10), in landmark research, have cracked this huge mystery. Their research also points to completely new ways to treat these diseases.

JOHNS HOPKINS MEDICINE

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AT THE CUSP OF BREAKTHROUGHS

The Jerome L. Greene Sjögren's Center was already providing world-class care. Now, thanks to team medicine and team science, it is also leading an unprecedented surge in research.

Nearly 15 years ago, rheumatologists Antony Rosen, M.D., and Alan Baer, M.D., were asked a simple question: Could Johns Hopkins build a world-class center for treatment and research in Sjögren's disease? The question was asked by philanthropist Dawn Greene, who had a personal interest in Sjögren's.

There wasn't a comprehensive center specializing in Sjögren's anywhere – but one was desperately needed. Sjögren's is an under-recognized disease, affecting as many as four million Americans. Like many autoimmune diseases, it is complex, varies from person to person, and is difficult to treat. And worse, because its symptoms mimic those of other conditions, it is often misdiagnosed – which can result in delayed treatment and sometimes, permanent tissue damage.

Team Medicine and Team Science

Could Hopkins create the center Mrs. Greene envisioned? Could it ever! The key was, and remains, "team medicine and team science," says Baer, who specializes in treating patients with Sjögren's and has directed the Jerome L. Greene Sjögren's Center since it opened in 2009. He assembled a team of experts from "the depth of talent we already had at Johns Hopkins": top-of-their-field rheumatologists, neurologists, ophthalmologists, gynecologists, radiologists, and otolaryngologists.

Baer felt strongly that the team approach should begin at diagnosis. This in itself was a noteworthy departure from the norm. Even today, "a coordinated evaluation is unusual," says Baer. Why is this? Unfortunately, "many rheumatologists believe that an accurate diagnosis of Sjögren's is not necessary because of the lack of disease-modifying therapies. But having a correct diagnosis is *very* important to patients, who are dealing with a chronic illness marked by persistent fatigue, pain, progressive dryness of mucosal membranes, and complications including damage to the teeth and eyes, sexual dysfunction, internal organ involvement, and the risk of lymphoma."

Thus, Baer set up a Center devoted specifically to Sjögren's that offered a coordinated, multidisciplinary one-to-two-day initial evaluation. This begins with a detailed history and physical exam from Baer or rheumatologist Thomas Grader-Beck, M.D., Ph.D., and then, depending on the patient's specific symptoms, could also include a visit with: ophthalmologist Esen Akpek, M.D.; optometrist Lee Guo, O.D.; gynecologist Anne Burke, M.D.; audiologist Roni Dinkes, Au.D.; otolaryngologist Jean Kim, M.D., Ph.D., who performs a minor salivary gland biopsy; and neurologist Michael Polydefkis, M.D., Director of the Cutaneous Nerve Lab.

> "We are conducting research using a vast amount of resources at a scale that's never been attempted before."

"The delivery of complicated treatment takes a lot of time," says Baer, "and it begins with a thorough evaluation. It takes time to unravel what is happening, and what could be causing it."

Identifying Pathways and Subgroups

As Director of Hopkins Rheumatology for 20 years, Rosen championed a center-based model of patient care and research. This allows clinicians to focus on the treatment of specific rheumatic diseases (at Hopkins centers for Sjögren's, scleroderma,

lupus, arthritis, myositis, vasculitis, and Lyme disease) and also facilitates clinical research, as patients allow their clinical data – including blood, urine, tissue specimens, and imaging scans – to be studied to help improve understanding and treatment of their diseases.

Sjögren's behaves differently in women versus men, and in children compared to adults. Some patients are burdened by pain and fatigue, while others mainly experience dryness of their eyes and mouth. As many as half of Sjögren's patients have at least one other autoimmune disease, and a subset of these are at risk of developing lymphoma.

One way to begin to understand specific disease pathways is to identify subgroups of patients who have similar sets of symptoms, clinical traits, and trajectories of disease, and then to analyze blood and tissue from patients within these groups, looking for biologic pathways they may have in common. This is precision medicine. Ami Shah, M.D., Director of Rheumatology, developed and co-leads the division's NIH-funded Precision Medicine Data Integration Core. Through this Core, she says, "the Sjögren's Center can harness institutional big data from the electronic medical record (EMR) and other sources, with great potential to accelerate research and bring new discoveries back to patients."

No Scrap of Data is Too Small to Be of Potential Value

Over the past decade, rheumatology faculty have collaborated closely with biostatistics expert Scott Zeger, Ph.D, who helped develop the Johns Hopkins Precision Medicine Analytics Platform. Using a vast network of computers, this mighty platform can rapidly collect and sort millions of bits of data: records of patients' medications, laboratory tests, pathology and imaging reports, diagnoses, and findings at clinic visits. It's a computerized superhighway where millions of pieces of clinical information can be analyzed to discern patterns and predict events, such as a disease flare.

ALAN BAER, M.D.
"We are at the cusp of major breakthroughs, and the key is sharing these vast amounts of data with scientists all over the world."

Baer and colleagues have been right in the thick of this work, conducting their own longitudinal research studies using data from this platform. "What's unique about this," says Baer, "is that Johns Hopkins has created this system where you can say, 'Pull data from all the patients who have been seen anywhere throughout Johns Hopkins who have a diagnosis code for Sjögren's, or a test that would point fairly specifically to the presence of Sjögren's. Rather than only relying on the patients we are seeing ourselves in our clinic, we can study patients seen throughout the whole institution." With the Precision Medicine platform, "we can analyze data from more than 25,000 patients with suspected or known Sjögren's."

Currently, Baer and colleagues are using this platform to study more than 180 patients with Sjögren's who developed lymphoma, a potential complication of the disease.

The collection of clinical data in the Sjögren's Center has been bolstered by the use of computerized programs developed by physician-scientist Grader-Beck. He is an informational artist, and his palette is the Epic EMR system. With a grant from the Sjögren's Foundation, Grader-Beck created uniform data-collecting templates in the EMR that can be used (with the patients' identifying information and privacy protected) not only by Hopkins, but by other institutions that also use Epic – and vice versa. "Thomas has pioneered the use of Epic to collect uniform data on Sjögren's patients at Hopkins, the University of Pennsylvania and the University of Wisconsin," notes Baer. "He is looking at clinical studies across a large number of people who have Sjögren's: identifying cohorts based on what they look like clinically, grouping them and finding similarities, and starting to predict subgroups. Very quickly, you can assemble a large data set. This has cranked up the whole machine of our research!"

Grader-Beck also set up a way for Sjögren's patients to enter their own data. "When patients come to see us, they answer questionnaires on a tablet," says Baer. "This uses standardized tools to measure symptoms such as the severity of dryness and intensity of pain, and to look at the patients' functional capacity at a given time. We can graph the result: you had this much pain, more than you had last time, you're more tired. What do you think happened?" These changes often coincide with life events, such as an energetic visit from the grandchildren, or a stressful period at work.

The patients' own reports are very helpful, Baer continues. "For the physician, a flare might not be as apparent; what's happening in their bloodwork may not change very much from the last visit." In lupus, for example, "flares are much more recognizable. A patient may get a big flare with a rash, or changes in the lining of the lungs. That seldom happens in Sjögren's: instead, patients are aware they are feeling more brain fog, or having more dryness, or more pain. Sadly, physicians often don't listen to their patients to try to understand what's going on. The temptation is to dismiss it as fibromyalgia, but patients are really telling you that there's a change. Just because we don't understand it, doesn't mean it isn't important."

> "The delivery of complicated treatment takes a lot of time. It takes time to unravel what is happening, and what could be causing it."

Looking for Molecular Pathways

Analyzing the molecular underpinnings of specific subgroups of patients has been a focus of the work by world-class scientist Livia Casciola-Rosen, Ph.D., over the last 30 years. For example: Casciola-Rosen studied salivary gland tissue from lip biopsies of Sjögren's patients to define pathways that drive tissue dysfunction in the disease – "key to beginning to target the right pathway in the right patient," she says. "The exceptional tools of molecular measurement and data analysis available in this era are dramatically changing the pace and precision of discovery in this disease."

This is particularly evident in the Center's participation in a program funded by the National Institutes of Health, in partnership with pharmaceutical companies and nonprofit partners. "We are part of the Sjögren's Team in the Accelerating Medicines Partnership-Autoimmune and Immune-Mediated Diseases (AMP-AIM) Program," says Baer. "The goal is to define disease pathways that lead to inflammation and tissue damage in Sjögren's that can be targeted with specific drugs."

The research program takes advantage of cutting-edge technologies to "deconstruct" what is happening in the affected tissues and blood specimens down to the level of individual cells and then piece together processes leading to the diseased state, Baer explains. These analyses are being done by specialized teams in the AMP-AIM network who have pioneered these techniques. "Everyone in the AMP-AIM network meets weekly to discuss the scientific questions and progress made to date." As part of AMP-AIM, the Hopkins Sjögren's Center is recruiting more than 170 patients with suspected or known Sjögren's, including some with an overlap of systemic lupus, for comprehensive one-day evaluations, including rheumatology, dental, and eye exams, as well as salivary gland ultrasonography, lip biopsy, and collection of blood.

This may be the most in-depth study of Sjögren's patients ever conducted. "All materials collected from patients will be analyzed with all of the available tools." Through transcriptome analysis, "we are looking at which genes are expressed by individual cells and their neighbors, and we are identifying cell types, some of which were never known before." Through spatial transcriptomics, "we are learning which cells are next to others, how they interact, and putting together mechanisms that are happening in the tissue itself. We are conducting research using a vast amount of resources at a scale that's never been attempted before."

"There is so much potential for collaborative research, and it is a hugely powerful approach," says Baer. "All of this data will be available so other groups across the world can use it. This will greatly enhance our likelihood of finding disease pathways. We are at the cusp of major breakthroughs, and the key is sharing these vast amounts of data with scientists all over the world."

A LIQUID BIOPSY FOR LUPUS NEPHRITIS

GAME CHANGER

For patients living with lupus nephritis (LN), and for their doctors, not knowing what's really happening in the kidneys is tough. A liquid biopsy could be a game-changer.

Left: Rheumatologist **ANDREA FAVA, M.D.** "Even in the setting of a clinical trial, no more than 30 to 40 percent of patients respond to treatment. That's unacceptable!"

Living with lupus nephritis (LN) – and treating it – is a bit like walking down a foggy road. The only street light is the clarity that comes from a kidney biopsy: at that precise moment, a rheumatologist such as Andrea Fava, M.D., can see exactly what is happening in the kidney. But biopsies are invasive and expensive; patients can't undergo them every few months to get an up-to-date window on the disease. So, for years, Fava and colleagues have done the next best thing: relied on a simple test that looks for protein in the urine (proteinuria).

The Trouble with Incomplete Information

But, as Fava will tell you, this urine test is not ideal. In fact, it can even be deceiving. "Proteinuria is a useful biomarker," he says. "It's the best we've got now, but it has many limitations." Here's an example: Let's say Mary, a patient with systemic lupus erythematosus (SLE) has a positive proteinuria test. Mary gets a kidney biopsy to confirm the presence of LN, lupus in the kidney, and then is placed on one or more drugs to help calm the immune system and lower blood pressure (caused when the kidneys can't do their job of removing waste and excess fluids from the body).

Is the medication working? That's a tough one. The kidney damage, for a long time, is silent; there are no warning signs or symptoms to say, "something is not right here!" And the proteinuria test itself provides incomplete information, says Fava. If in six months or a year Mary still has proteinuria, "that doesn't tell us whether she just needs more time on the medication, or whether the treatment is failing and I need to change it." The stakes are very high: as many as 20 percent of patients with SLE develop permanent kidney damage, lose kidney function and need dialysis.

Nor does the proteinuria test tell what *kind* of inflammation is going on – and this is important, because a different medication might be more effective. The immune system has a host of players: T cells, for instance, B cells, macrophages, neutrophils, and cytokines, including one called IL-16 (more on this later). Like all rheumatic diseases, LN varies from person to person, and requires precision treatment. Someone with more T cell inflammation might respond better to one medication, someone with B cell inflammation to another, and so on. But that knowledge is hard to come by.

"What we have is not working. We are trying to save kidneys! We want to save people from dialysis."

Also: "Proteinuria cannot tell us if there is truly inflammation in the kidney," says Fava. "It can be high when there is chronic damage like scar tissue. It can be high from hypertension or diabetes. This is why we need to do kidney biopsies to figure out if the patient has LN or not – and, most importantly, if there's something we can treat or not." And there is a spectrum: "LN comes in all sorts of flavors and severity. There can be a little bit of activity or a lot of activity, and *the amount of proteinuria may have no correlation with that*."

For 20 years, Fava says, scientists have chased biomarkers, looking for a better, more specific signpost in the urine of LN patients. "But up to now, none of these approaches have produced anything that has been used in a clinical trial, and here we are, still using proteinuria."

That is about to change. In exciting news, a team of scientists led by Fava, has originated a noninvasive biomarker test – a "liquid biopsy" – now moving toward commercial development.

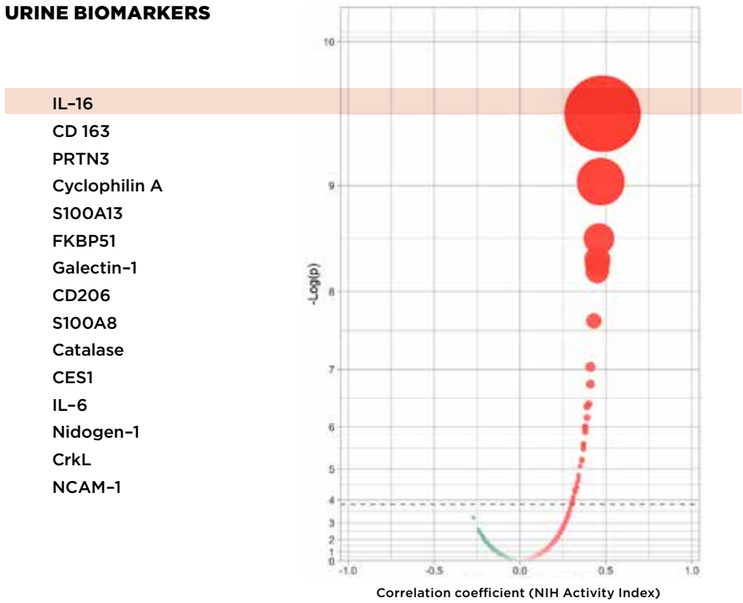
Tapping the Power of Urine Proteomics

Fava knew that the standard proteinuria test looks in the right place: the urine, which contains a wealth of information about what's happening in the kidney. So it was to the urine that he and his research team turned for better answers. The biomarker assay that they are developing uses a sophisticated approach that wasn't around 20 years ago: *proteomics* – the in-depth molecular analysis of thousands of proteins expressed by the genes within the affected kidney. The sudden difference in what can be seen is like looking at a star with a high-powered telescope after seeing it with the naked eye.

This research was done as part of the National Institutes of Health's Accelerating Medicines Partnership (AMP), a public-private collaboration involving academic centers, the Food and Drug Administration, biopharmaceutical companies, and nonprofit organizations. "We enrolled more than 200 patients with LN who had undergone a clinically indicated kidney biopsy," says Fava, and in studies of the patients' urine, "we cast a very broad net," analyzing 1,200 different proteins, "aiming to find a handful that are important."

Then they followed these patients over time. "We got other urine samples at three, six, and 12 months. Meanwhile, the patients were being treated by their own rheumatologists. The patients were then classified as being responders or non-responders after one year of treatment, based on proteinuria and preservation of kidney function." They collected data from some patients for as long as five years.

Could biomarkers predict response to treatment? Yes! Fava and colleagues did find a handful of biomarkers in the urine that, looked at together, correlate with the degree of inflammation in the kidney much better than proteinuria does. In patients who turned out, at one year, to be responders to treatment, these markers went down at three months, signaling that immunosuppression was effectively reducing inflammation in the kidney.



These selected biomarkers also provided insight into the disease itself, later confirmed by biopsy: "These are markers of cellular inflammation," Fava explains. Of the handful, among the most interesting to Fava and colleagues was IL-16, "which is one of the most common inflammatory cytokines (proteins that regulate immune response) found in LN," he explains. "We discovered it a few years ago, and it is very tightly associated with inflammation in the kidney." Moreover, "we found the cells making IL-16, and we are going to study them in more depth. This could be a new treatable target."

In addition to predicting favorable response, these biomarkers signal when extra help may be needed. "They stay elevated in those who are not responding to immunosuppression," says Fava, who envisions using this liquid biopsy as a barometer to provide more precisely tailored care for his patients.

"The sudden difference in what can be seen is like looking at a star with a high-powered telescope after seeing it with the naked eye."

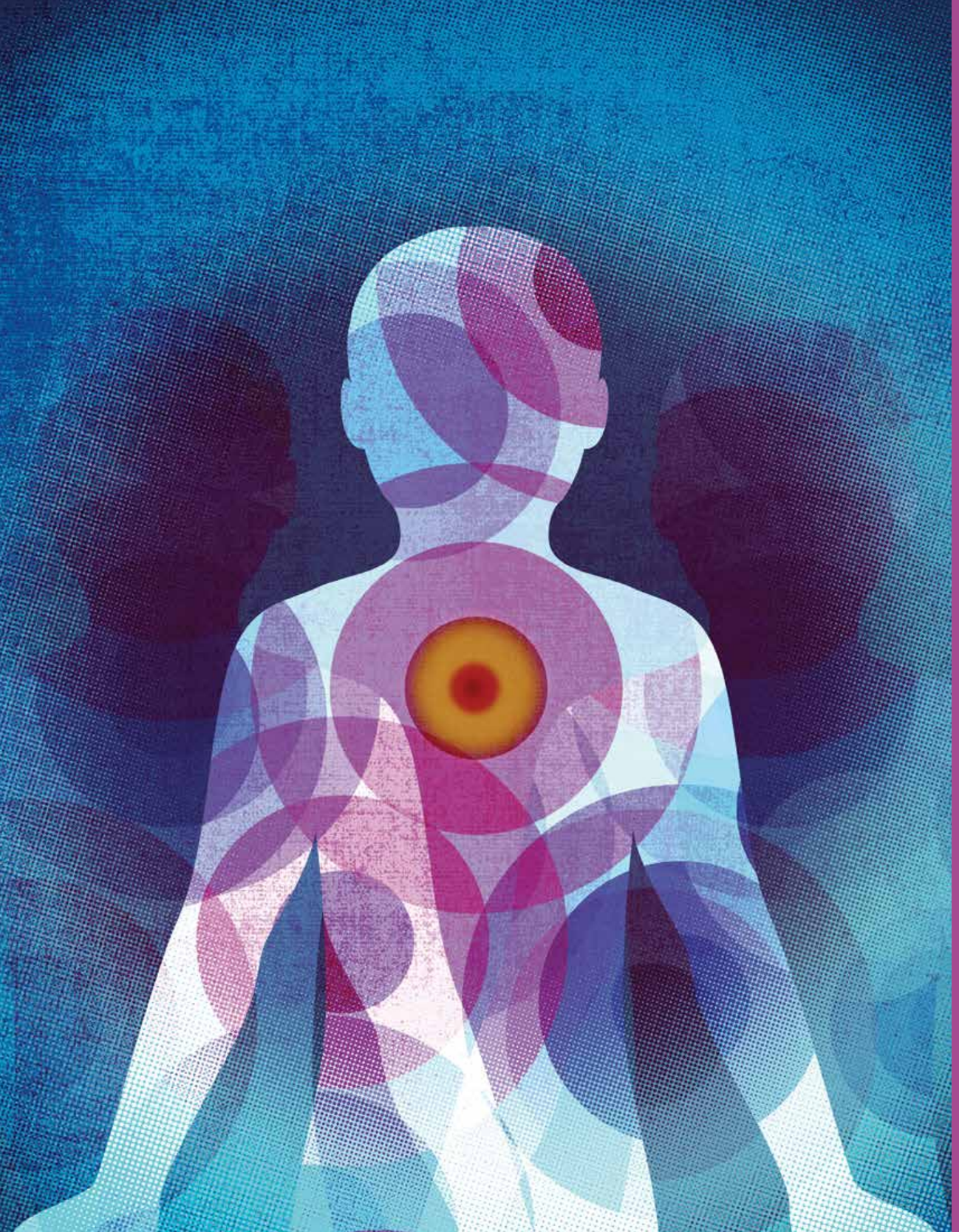
Could these same biomarkers see even farther into the future? Yes! "We said, 'let's look at least three years ahead," says Fava. "We looked at six and 12 months, and we found that the persistence of the biomarkers – in particular, IL-16 – predicted the loss of kidney function at three years. Another key question, still to be answered:

Could these or other biomarkers even predict the *onset* of LN – before hidden inflammation starts to damage the kidney? Possibly. It may be, Fava continues that "we could intervene early with less toxic drugs, and prevent damage altogether."

Fava's goal is nothing less than changing the standard of care. "What we have is not working," he states. "We are trying to save kidneys! We want to save people from dialysis." Currently, "even in the setting of a clinical trial, no more than 30 to 40 percent of patients respond to treatment. That's unacceptable! It means more than 50 percent of patients have persistent inflammation that is damaging healthy kidney tissue, and this is how people lose their kidney function over time."

Unfortunately, more than one-third of patients "despite achieving complete remission as *measured by proteinuria*, continue to acquire kidney damage. And when we do a kidney biopsy in these patients, *even though there's no proteinuria*, they still have active LN. Could biomarkers help protect these patients by detecting damage that other tests cannot? A liquid biopsy could revolutionize our treatment."

To make this happen, Fava and colleagues are working with a commercial partner to develop an assay, which they hope will be available in a few years. Fava's research has been funded by grants and awards from the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases, the Lupus Foundation of America, the Lupus Research Alliance, and support from the Jerome L. Greene Foundation and the Plank Family Foundation.



AT LAST, AN ANSWER

WHY AUTOIMMUNITY TARGETS WOMEN MORE THAN MEN

Hopkins investigators have cracked one of the biggest mysteries in rheumatic diseases, and the implications from this discovery are huge.

Lupus affects nine times more women than men, and in landmark research led by scientist Erika Darrah, Ph.D., Hopkins investigators have found a major reason why: it has to do with an RNA molecule (a messenger of genetic information) that lives on the X chromosome, and an immune system protein that reacts to it.

This alone is a major discovery, but the implications go far beyond lupus to many autoimmune diseases, in which the largest risk factor is *simply being female*.

The X Chromosome and XIST

What, on a genetic level, do women have that men don't? Well, they have twice as many X chromosomes (men have one X and one Y chromosome; women have two X chromosomes). Thus, scientists long suspected that *something* on the X chromosome was to blame for rheumatic diseases such as lupus and Sjögren's being so markedly skewed toward women. But they couldn't identify a culprit.

Darrah, an immunologist, joined this search about 10 years ago when she was a young faculty member fresh out of her postdoctoral training in the Division of Rheumatology. "I presented a journal club article about the X chromosome and the role of a molecule of RNA called XIST (pronounced "exist"). The basic job of XIST is very important, and it happens in the womb: "It inactivates one of the two X chromosomes per cell in all females," says Darrah. "It's nature's way of normalizing, so that men and women have approximately the same expression of genes on the X chromosome," instead of women getting a double dose.

Women, then, have one *active* X chromosome, and an *inactive* one, with XIST "strongly tethered" on the inactive chromosome. "It shows up as a single dot on the inactive X chromosome." But this journal club article showed that in cell tissue samples from some women, particularly in those with lupus, "XIST had left that position in the cell, or was absent from the cell altogether. That got me thinking about the X chromosome and XIST and lupus," Darrah continues. "In the paper, they measured XIST expression and where it was in the cell with some very classic, old-school methods."

> "Contrary to what we expected – that XIST was putting the brakes on inflammation– we actually saw the opposite! Women with lupus and Sjögren's actually had higher levels of XIST RNA."
>
> Erika Darrah, Ph.D.

Darrah's timing was just right to begin looking at XIST in a new way. "In the lab, we were just embarking on some interesting ways to expand flow cytometry," a sophisticated technology that uses a laser beam to analyze single cells very quickly. Darrah wondered if there was a way "we could use flow cytometry to study the expression of XIST in healthy women and in women with autoimmune diseases."

At first, Darrah thought that XIST would prove to be something of a molecular good guy: "I thought it probably played a helpful role in lupus and autoimmune diseases, that maybe XIST was protecting *against* autoimmunity by repressing genes involved in inflammation." In pilot studies funded by the Jerome L. Greene Foundation, Darrah, physician-scientist Brendan Antiochos, M.D., and colleagues measured XIST levels in blood cells from healthy participants and from patients with lupus, Sjögrens, and later, scleroderma. This was breaking new ground for flow cytometry: "It was usually used to measure proteins expressed by the cells, and here we were using it to measure RNAs."

What they found threw the team for the proverbial loop: "It was really surprising," says Darrah. "Contrary to what we expected – that XIST was putting the brakes on inflammation – we actually saw the opposite! Women with lupus and Sjögren's actually had *higher* levels of XIST RNA. This stopped us in our tracks. What could this mean?"

They expanded their studies, and "the more women we tested, the more we saw this was true," says Darrah. "It made us reevaluate how XIST fit into the bigger picture of lupus pathogenesis." Based on the preliminary data, Darrah and colleagues applied for and received an R21 grant from the National Institute of Dental and Craniofacial Research (which funds Sjögren's research). "That's where we first hypothesized that perhaps in autoimmune disease with a strong female bias, XIST might be playing a pro-inflammatory role, serving as an alarm signal, a driver of inflammation."

XIST Has an Accomplice

Could it be that, as XIST silenced the one X chromosome and drastically cut its production of proteins, the immune system identified it as a bad apple, a cause of genetic harm? Did XIST have an unwitting accomplice – an opposing agent mistakenly assigned by the immune system to attack it?

As it turns out, yes, and its name is toll-like receptor 7 (TLR7). "TLR7 is an immune protein that detects potentially harmful RNA," says Antiochos, "such as RNA made by viruses, or by injured 'self' cells (the body's own RNA). TLR7 is known to be activated in lupus. It makes a powerful inflammatory weapon: type 1 interferon."

In their most important study yet, recently published in the *Journal of Clinical Investigation Insight*, Darrah, Antiochos and colleagues provided, in effect, the smoking gun: they proved the XIST-TLR7-interferon connection. "First, we looked at whether XIST could bind to TLR7 and activate its immune response," says Darrah. "We proved that XIST did indeed strongly bind to TLR7 and trigger the production of interferon." They looked at other "potential molecules of interest," but "over and over again, XIST just blew them all out of the water." They proved that instead of protecting the body from TLR7 and interferon, XIST actually propelled the immune response into overdrive, stimulating the production of interferon and facilitating the development of lupus.

The investigators measured XIST levels in blood samples from patients at the Johns Hopkins Lupus Center and also, using publicly available data from another study cohort, measured the levels of XIST and interferon in white blood cells taken from the kidneys of patients with lupus. "We found that the levels of XIST in the kidneys of these patients correlated with higher interferon levels," says Darrah, "and also that patients with more XIST in their blood cells had more severe disease." Importantly, they showed that interferon did not increase XIST levels, "suggesting that XIST is a driver, rather than a consequence, of interferon in lupus."

"We are now seeing XIST as a danger signal related to autoimmunity," says Antiochos. This pathway is female-specific, "explaining why lupus, Sjögren's and other rheumatic diseases are so much more common in women."

But wait! Men can get Sjögren's and lupus, too. How does that work? This will be the subject of research headed by Antiochos. "It might be that other endogenous patterns are more expressed in men," he says, "or that men with these diseases might actually express XIST even though they're not supposed to."

Where Do We Go From Here?

Questions for future research: Is there a hidden control switch for XIST? Is there something upstream of XIST that influences its expression? One way to learn more, says Antiochos, would be to look at longitudinal samples from people who started out healthy and then developed lupus or another autoimmune disease. "Was XIST upregulated five years before they developed the disease? Was it already setting them up for autoimmunity?" Such a study is very doable in today's research environment, he adds, thanks to large, open-access data sets.

> "We are now seeing XIST as a danger signal related to autoimmunity, explaining why lupus, Sjögren's and other rheumatic diseases are so much more common in women."
>
> Brendan Antiochos, M.D.

How might this discovery affect the treatment of lupus and other autoimmune diseases? Instead of suppressing the *entire* immune system, it may be that knocking out XIST alone would be an effective way to stop the disease. Or maybe just knocking it *down*, not out, would work. "I don't think we necessarily need to get rid of it," says Darrah. "If it's getting into places where it shouldn't, especially if it's expressed at high levels, maybe passing a threshold, it may be that the body is sensing that extra level." One therapeutic approach, Darrah speculates, might be development of a molecular sponge to soak up the excess XIST. Another strategy might be a molecular signal jammer, something that specifically blocks the interaction between XIST and TLR7.

Another thought: Might a biomarker test for XIST help predict a flare of disease, or even identify people at higher risk of developing autoimmunity? Could such a test be used to stop disease before it starts? It is possible, Darrah says, that XIST measurements could be used as a way to stratify someone's risk of developing lupus. "It may be that some people are just born with different amounts."

Darrah is grateful for the Greene Foundation for the initial funding "for this kind of wacky, out-of-the-box hypothesis. It enabled us to grow this program from nothing to getting funding for a study that we were able to publish," and for generating much more data yet to be published.

OUR CHAMPIONS OF COMPASSION

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.

FELICIA EFE SICILIANO, C.M.A, M.S.W.
Medical Assistant/Future Social Worker

Felicia Efe Siciliano has been at Hopkins for 27 years, and has worked as a medical assistant in the Rheumatology Clinic since 2000. She has a heart for the patients she sees every day, and takes the time to listen to them as she takes their vital signs. She always wants to be encouraging to them, and to help if she can.

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"Some of these patients I've known for years – decades!" she says, and some of them need someone to talk to. "Some people need a little more time. You don't want to rush them, don't want to leave the room right away, because you see they are lonely, especially the older patients," says Siciliano.

Over the years, she began to "comprehend the unique ways patients cope with their illnesses, and to understand how social support and family support helps patients thrive and better manage their diseases. You see the difference between those who have that support, and those who don't."

Siciliano began to want to do more to help, to be "more than just a friendly face." She realized that "you can talk to a patient all day. But if they are struggling with their day-to-day living, if they're homeless, if they can't afford their medications, if they have a mental illness or other issues, if they're in an abusive relationship, how are you going to help them if they can't eat, or they're struggling to provide for their children? How can you help the person if their basic needs are not met?"

So, she went back to school and recently earned her Master's degree in social work. "Initially, I wanted to be a therapist, and I did an internship as a therapist. But I realized that I prefer case management, because I feel I'll be able to help patients more by linking them to resources."

Studying social work has helped her do her job in the clinic better. "A person may come in and be angry. Then you come to realize that you don't know what is causing that [and] that this person may be reacting to their situation – they're just coping with so much. I've had patients who just cannot afford their medications," or who are going through personal hardships "and can't really speak for themselves."

Siciliano aims to secure a position in case management, preferably at Hopkins, where she can "assist the same patients in acquiring the essential daily support they need to flourish, bringing an extra level of care."

HONG WANG, PH.D.
Research Associate

Scientist Hong Wang, Ph.D., has been conducting translational research in the Division of Rheumatology for eight years.

She is a molecular biologist, and her name has been on some important papers coming out of the Division – most recently, the *Journal of Clinical Investigation Insight* article on molecular factors such as XIST that skew autoimmune disease toward women (see Page 10). She has worked with multiple principal investigators, including Erika Darrah, Ph.D., Brendan Antiochos, M.D., and Livia Casciola-Rosen, Ph.D, on diseases including rheumatoid arthritis, lupus, Sjögren's, scleroderma and myositis.

"I have been doing research for more than 20 years," says Wang. After earning a medical degree in China, she came to the U.S. in 2000, earned her Ph.D., at Ohio State University, and worked at several universities before coming to Hopkins. "Johns Hopkins is the best place to do research, and I'm very happy to be here," she says.

If you are a Rheumatology patient, you may never see Wang, but she wants you to know that you are very much on her mind. She hopes the work she does will improve understanding of your disease – and she hopes that, if you have the opportunity to allow your blood or tissue samples to be used in clinical research, you will say yes. "The information we get from patient samples gives us a lot of insight. It helps us figure out the pathways driving these diseases, and to determine the directions for future therapy."

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Before she came to Hopkins, Wang did mostly basic research using cell cultures and animal models. But working with patient tissues "allows us to verify our hypotheses, and helps determine treatment. Patients are our partners in research! We highly appreciate their participation."

Many autoimmune diseases can be divided into subgroups of patients – which means that the availability of tissue and blood samples may be fairly limited. "Our research is focused on a very small

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population with unique combinations of biomarkers like antibodies," she says. Fortunately, "patients have been very eager to take part in our studies and have generously donated their blood to us," for which Wang and colleagues are very grateful.

"The pace of our research is getting faster and faster," she says. "In the beginning, it required very detailed, slow work, and now the computer software can handle the data in a much shorter time." Even with big data, "this research is complicated and highly demanding." It is a challenge she enjoys.

When she is not working, Wang likes to travel, and spends many happy hours tending her rose garden.

SHARDE MICHIE-MCCOY
Senior Medical Office Coordinator

Sharde Michie-McCoy has worked at Johns Hopkins for seven years, working in several clinics before coming to Rheumatology as a Medical Office Coordinator. What does she do? "I am the 911 for patients," she says. "I'm the call for anything you need: labs, prescriptions, directions, instructions within your Mychart – you name it, I can more than likely help you. I love it! I enjoy interacting with the patients. I've been doing it for so long, that patients call, 'Hey, can I speak to Sharde?' I'm a people person!"

When Michie-McCoy first came to the Rheumatology Clinic, the world was about to change, due to the Covid lockdown: "I was in clinic for a total of three days and then sent home to work remotely," she says. "This was a tad bit challenging for me!" She was just starting to match the staff faces with the name tags, "now I had to go and work from home with minimal knowledge of what exactly I needed to do! To make things more interesting, I had had just gotten engaged, so I was in the middle of planning a wedding, too – talk about a challenging time!"

But there is a saying in her family: "'To whom much is given, much is required.' It was that time for me to prove to myself that I understood those words! When it was time for us to come back into the office, it was so nice to actually be able to interact with patients face to face. To not be on Zoom calls, and to see some of the doctors and staff I had never met, but had been talking to for over a year."

As part of her job, Michie-McCoy tries hard to help patients reduce the cost of medications. "I find them different coupons, or places to get samples if the medicines are too expensive." When a patient needs something, "I always say, 'If I don't have the answer, I will find it!'" If it's taking longer than expected, she calls and says, "I didn't forget about you. I'm still working on it!" It is important to her that the patients "feel safe and heard."

Her work at Hopkins has given her "a new love for medicine," she says. "The time and dedication that it takes to save a life is endless. I am so glad to be able to be a part of this greatness, and to help patients like I would want someone to help me!"

"I am the 911 for patients, I'm the call for anything you need: labs, prescriptions – you name it, I can more than likely help you."

RHONZA HOWARD, R.N.
Clinical Nurse Coordinator

A lot of life experience has made Rhonza Howard, R.N., ready, willing, and able to go the extra mile for her patients and their families, and for the Rheumatology fellows and other doctors she works with in the clinic.

For starters, she was a "military brat" who moved a lot growing up, and she is a Navy Veteran. "I can pretty much get along with everybody; that's why nursing was made for me!" Earlier in life, as a grocery store deli manager, "I dealt with a lot of complaining customers," and she learned to listen. "Just listening to them, troubleshooting, saying, 'Hey, what can I do to make this better?' makes a difference. If you can soothe things, and be proactive instead of reactive, little fires won't turn into big fires. A lot of times people just want to be heard."

She loves people. "Each person is a story, and there's something special that they bring to the table, and it deserves to be listened to. If you don't listen, you can miss out on the best of people."

She understands all too well what patients and their families are going through, particularly those with lupus: "Lupus runs in my family. I know how serious it is; I've had relatives die from it. It's really close to my heart. I've seen people in their twenties go on dialysis. People need to know that this disease affects every organ; this affects your life. It's such a vast disease. Education is the key to working with patients and with family members who are at risk and need to get tested, but who don't take it seriously – and they should! If you can teach one, you can reach one."

Howard has four sons. One of them, now age 31, was diagnosed with a brain tumor when he was nine years old. "Astrocytoma. They said he was going to die, that it was inoperable. We went through chemo and radiation, and lots of prayer. He made it! I don't remember the doctors, but I remember the nurses. They were the ones who hugged him and hugged me. They were the ones who got us through that." This experience led her to go to nursing school. "Nurses are the soft touch between the doctors and the patients. The gentle hands, the TLC."

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She can relate to just about anything patients are going through, because she has been through it or something similar, including loss of close family to disease and to violence, dealing with serious illness herself, and living with her parents, who both have medical conditions. Life experiences, especially difficult ones, "can either make you bitter or better, more compassionate and understanding. I choose to love, because that's what helped me get through," along with her faith. "I've had nothing. I don't have much now, but I share whatever I have. I want to see people grow. I shed a lot of tears, but I also laugh and smile a lot. I choose to be here!"

Howard is fiercely devoted to the Rheumatology fellows, whom she nurtures. "I love my fellows. The fellows are the key – the future rheumatologists! We already have a shortage of rheumatologists. They can either get burned out or they can fly." She does her best to teach them the ropes, particularly how to deal with insurance companies and navigate getting prior authorizations. "They are brilliant and I learn from them. I look at the fellows as caterpillars getting ready to gain their wings. We want to keep them here, but some may fly away, following the Johns Hopkins trend of being world leaders in rheumatology – my butterflies!"

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"A quality of an inventor is imagination, because invention is a LEAP of the imagination from what is known to what has never been before."

— Thomas Alva Edison, Inventor