

LEAP

Johns Hopkins University
School of Medicine
Division of Rheumatology
Winter 2021

OUT OF THE DARKNESS
OF A PANDEMIC

FLASHES OF INSIGHT

LONG-HAUL LYME DISEASE

X FACTOR IN SJÖGREN'S

PETER FRAMPTON

LIGHT IN THE DARKNESS

This is an unusual time, and this year's *LEAP* reflects it well: we start with Covid-19's very sickest patients, and a Hopkins-wide team's groundbreaking efforts to illuminate an unusual response in their immune system. We end with a remarkable patient with a rare autoimmune disease: the legendary musician, Peter Frampton, who is not only raising awareness and research funding, but changing medical advice about how to preserve muscle function.

Before I tell you more about this issue of *LEAP*, I want to tell you how proud I am of the Division of Rheumatology, for how our clinicians, scientists, clinical and administrative leaders, nurses and staff have rallied during this unprecedented pandemic. They adapted on the fly: conducting clinic visits by telemedicine, providing direct Covid-19 care in hospital, continuing research online and directly on Covid in person, completely changing our teaching and instruction to an online format, and collaborating in countless Zoom meetings, while keeping our hospital patients safe with comprehensive new protocols. Our faculty and staff are caring, dedicated, and committed to helping our patients, no matter what. They are truly incredible.

In our cover story (page 2), observations made in Covid-19 patients who were so sick that they were on ventilators soon led a Johns Hopkins team to suspect an autoimmune response. We quickly discovered not only that this was not a regular autoimmune response – but it was very similar to something we had seen in patients with a type of myositis. This therapeutic insight might help patients with severe inflammatory complications of Covid-19.

We also update the pioneering work of John Aucott and Mark Soloski (see page 6) on post-treatment Lyme disease (PTLD), which doesn't get better despite treatment. They have made new discoveries – a genetic fingerprint, the metabolic response, important changes in the gut microbiome, and tendinopathy-related

causes of pain – that have the potential to transform how this disease is treated, and to offer hope to these PTLD “long-haulers.” And of course, their approach might be important for the new Covid-19 “long-haulers” who are flooding clinics.

In two stories (pages 10 and 12), we offer new insights into the events at the very beginning of Sjögren's Syndrome: Brendan Antiochos is investigating how LINE-1, a bit of misplaced genetic material, prompts an unexpected autoimmune reaction, and Erika Darrah is investigating Xist, a gene that is supposed to silence extra copies of the X chromosome before birth, but which might be abnormally activated in Sjögren's.

And finally (page 14), one of rock's greatest legends, guitarist Peter Frampton, has an autoimmune disease called inclusion body myositis (IBM). Not only has he surprised his doctor, Lisa Christopher-Stine, by maintaining his fingers' ability to play the guitar, and protected muscles in his arms, legs, and core with vigorous exercise: he has given back, raising money for much-needed research with a nationwide concert tour, and raising awareness and hope in his “fellow IBM-ers.”

Each of these stories, in its own way, sheds light and offers hope, and this is my wish for you during this challenging time: that you may find and inspire light and hope, as well.

In the words of Amanda Gorman, at the recent Presidential Inauguration:

*The new dawn blooms as we free it
For there is always light,
if only we're brave enough to see it
If only we're brave enough to be it*

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



WINTER 2021

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OUT OF THE DARKNESS OF A PANDEMIC:



Why do some people who have Covid-19 seem to have very few symptoms, while others get terribly sick and die? Hopkins scientists have discovered an answer, and it's an old nemesis: a particular set of immune and inflammatory responses that they've seen before.

Think back a year ago to early March 2020. The coronavirus, Covid-19, had already killed many thousands in China and Europe, and now it had reached the U.S. Big-city hospitals on both coasts sprang into high gear,

FLASHES OF INSIGHT

setting up triage tents, scrambling for ventilators and personal protective equipment. And the doctors taking care of the surge of patients began to notice some major differences in how this new virus affected people.

“It became clear that there was more than one phase of coronavirus,” says Antony Rosen, M.D., the Mary Betty Stevens Professor of Medicine, Director of Rheumatology, and Vice Dean for Research. “Patients got the viral phase – aching, fever, not feeling great – and then they seemed to do reasonably well, to stabilize.” The second phase, if it came, happened a week to 12 days after the first symptoms arrived, “and then they got incredibly sick. It happened very fast.”

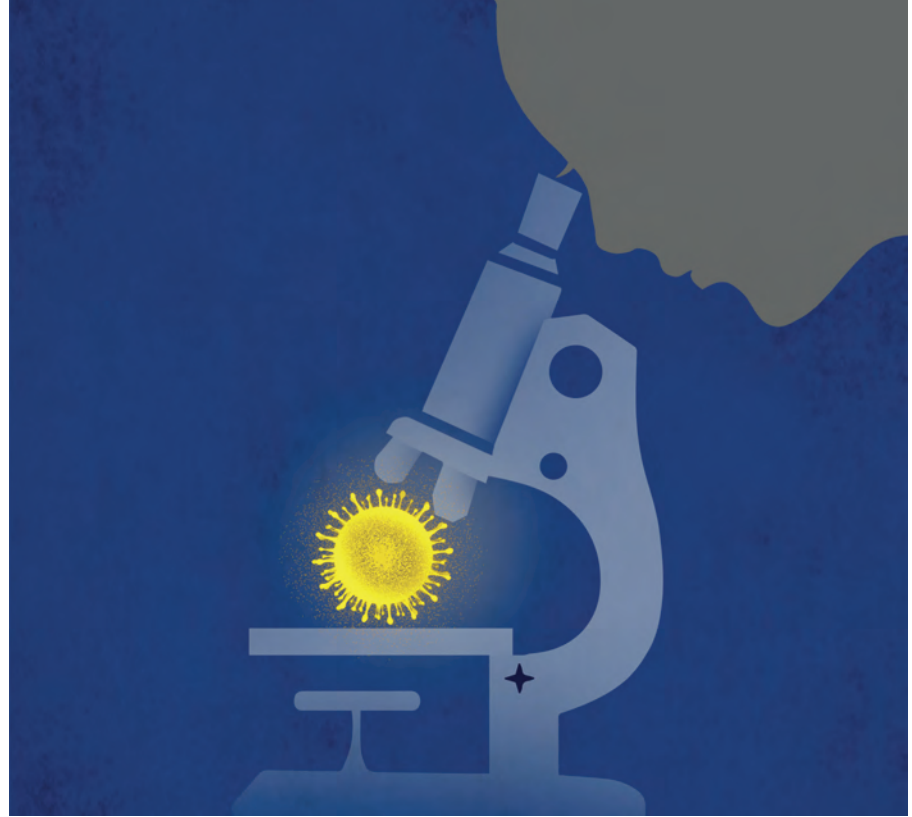
Why would people who appeared to be getting better, all of a sudden, get worse?

There were clues in the bloodwork: “they had active inflammation of all kinds; high white counts, high sed rates, high CRP levels (all markers of inflammation) and high D-dimer levels” (associated with clotting). A group of Hopkins scientists meeting to think about Covid-19 suspected the inflammation could be coming from an immune response turned on by the virus, and they quickly assembled a stellar multidisciplinary team to investigate.

By this point, scientists already knew quite a bit about the Covid-19 virus, including how it invades the body: its doorway into cells is a receptor called ACE2. “ACE2 is a protease, an enzyme that cuts other proteins or peptides,” Rosen explains. ACE2 is expressed at high levels in epithelial cells in the lungs, and endothelial cells in blood vessels, which may explain the intense respiratory and vascular symptoms in the sickest patients. The distinctive spike protein of the virus sticks to the ACE2 receptor like molecular superglue. “When they come together, they don’t come apart. If you have a viral antigen and a host protein that come together with high affinity, that’s the classic situation where autoimmunity arises; the host protein gets caught up as collateral damage.” Of note, he adds: “Many of those are single-shot autoimmune diseases. The patient gets very sick, but because the virus is the driver, as the virus gets taken care of, the autoimmune disease goes away.”

The team’s first question: Is ACE2 itself a target of the immune response?

“We are very good at looking for antibodies,” says Rosen, and the major reason for this is the world-class expertise of scientist Livia Casciola-Rosen, Ph.D. So they set to work: “We got sera from patients in the Johns



Hopkins system who had Covid,” patients who represented the full spectrum of the disease. “Some had milder symptoms, some were on oxygen, some were intubated and ventilated and survived, and some died.”

Normally, when someone gets infected with a virus, the body’s immune system responds very quickly with a surge in immunoglobulin M, (IgM) antibodies. Then the T cells – designed to kill foreign invaders – get involved, and a week or so later, the body produces a more mature host defense response: immunoglobulin G (IgG) antibodies, which are plentiful and bind very strongly to the virus. Casciola-Rosen started out looking for IgG antibodies, and she made a striking finding: there weren’t IgG antibodies against ACE2 in the sickest Covid patients. Instead, many patients who were on a ventilator or who died made *IgM* antibodies against ACE2! “About 30 percent of people in that worst category make these antibodies,” compared to only about 3 percent – ten times fewer – of patients with milder symptoms.

“This is not a regular autoimmune response,” says Rosen. “We’ve studied autoimmunity for many years. It tends to be driven by your own T cells, and it rapidly becomes an IgG response. This one gets stuck at IgM. It never goes to

IgG; it’s a T-independent immune response, a very primitive immune response.”

Here’s another startling finding: In patients who were treated with steroids, the antibodies went away and...

“Those patients got better,” says Rosen. “The patients who die keep these antibodies until the end. This suggests that it’s a highly novel mechanism whereby the virus is turning on the immune response – which is dangerous, because of what these antibodies bind to, the ACE2 receptor. IgM is a huge molecule. It’s in the circulation tumbling around, and it sees the surface of these endothelial cells and sticks to it.”

Ordinarily, he explains, endothelial cells are like smooth ice, and blood just glides right over them. But with these giant antibodies shackled to the ACE2 receptors within the lining of blood vessels large and small, “the surface of the ice gets all roughed up. Things stick to it, and it gets clotty. The microclots cause bad vessel dysfunction. Basically, the patient gets severely ill, critically low in oxygen, and needs a ventilator or dies.” In the laboratory of Dr. Felipe Andrade in Rheumatology, Dr. Maria

Isabel Trejo showed that the IgM recognizing ACE2 causes the “complement cascade” to become activated: this is a group of plasma proteins that enhance, or complement, what the antibodies, T cells, and other immune system soldiers are doing. IgM antibodies from eight out of eight patients with Covid activated the complement cascade.

Then came what Rosen describes as a “moment of wonder.”

For about 15 years, he says, rheumatologists worldwide have seen a rheumatic disease that appears seasonally, is related to dermatomyositis, and is associated with autoantibodies against MDA5, a sensor that detects viruses. Its features include a skin rash, lung disease similar to that of Covid-19, a cytokine storm – a burst of inflammation-promoting responses – and worst of all, a very high death rate. Casciola-Rosen, working with Drs. Christopher Mecoli and Lisa Christopher-Stine in Rheumatology, looked at blood samples they had collected from patients

At first, after the MDA5 syndrome was identified, when these patients with dermatomyositis went to the ICU they almost always died. “It was very frustrating and demoralizing to try to treat them,” Christopher-Stine says. Groups in Japan and China, where this illness is more common, found that calcineurin inhibitors (drugs such as cyclosporine, which activate T-cells but also suppress the immune system) produced an “amazing response. Mortality went down to 20 percent. The patients were deathly ill, but if you gave a calcineurin inhibitor, it could be miraculous.” Interestingly, these drugs seem to be very powerful at inhibiting T-independent IgM responses. This may be a therapeutic insight that might help patients overcome their severe Covid-19 infection with the inflammatory complications that lead to a high mortality.

The Hopkins team is working with other groups around the world to see whether this evidence is reproducible and present in other populations. It is possible that the vaccine will change the face of the Covid-19 pandemic before

“If you have a viral antigen and a host protein that come together with high affinity, that’s the classic situation where autoimmunity arises; the host protein gets caught up as collateral damage.”

with this similar disease. The first patient’s blood she analyzed also showed prominent IgM antibodies to ACE2. “Home run! Patients with MDA5 myositis make the same kind of antibodies that we see in the sickest Covid patients. It’s a similar syndrome, and there appear to be T-independent responses to ACE2 in that syndrome, as well. Could this syndrome be induced by a similar virus?”

sufficient evidence is available to prove the efficacy of this approach, and to apply it broadly clinically. This is one of the challenges of studying severe and complicated pandemic illnesses. But the findings are critical for understanding the severity of Covid-19 and similar syndromes (including future pandemics), and providing tools and approaches for improving patient outcomes. [↓](#)

AN ALL-STAR TEAM

In addition to Antony Rosen and Livia Casciola-Rosen, the all-star Hopkins team included David Thiemann, Felipe Andrade, Maria Isabel Trejo, Jody Hooper, Elissa Leonard, Jamie Spangler, Andrea Cox, Carolyn Machamer, Lauren Sauer, Oliver Laeyendecker, Brian Garibaldi, Stuart Ray, Christopher Mecoli, Lisa Christopher-Stine, Laura Gutierrez-Alamillo, Qingyuan Yang, David Hines, William Clarke, Richard Rothman, Andrew Pekosz, Katherine Fenstermacher, Zitong Wang, and Scott Zeger – Hopkins scientists from Rheumatology, Cardiology, Infectious Diseases, Emergency Medicine, Pathology, Cell Biology, Pulmonary and Critical Care Medicine, Biostatistics, Biomedical Engineering, and Chemical and Biomolecular Engineering, at Johns Hopkins University and the School of Medicine, the Bloomberg School of Public Health, and the National Institutes of Health. The studies were funded by the Gates Foundation, the Greene Foundation, and the Donald B. and Dorothy L. Stabler Foundation.

In addition, Rosen notes, “None of this could have been studied if we hadn’t had a strong Precision Medicine platform in place. Our colleagues were experts in data science and biostatistics, virology, myositis, complement, infectious diseases, cell biology, pathology, immunology, and biomedical engineering – a highly multidisciplinary group. I basically reached out and said, ‘We have this question. We think this is important. Would you be interested? Everybody said yes. It was just incredible!’”

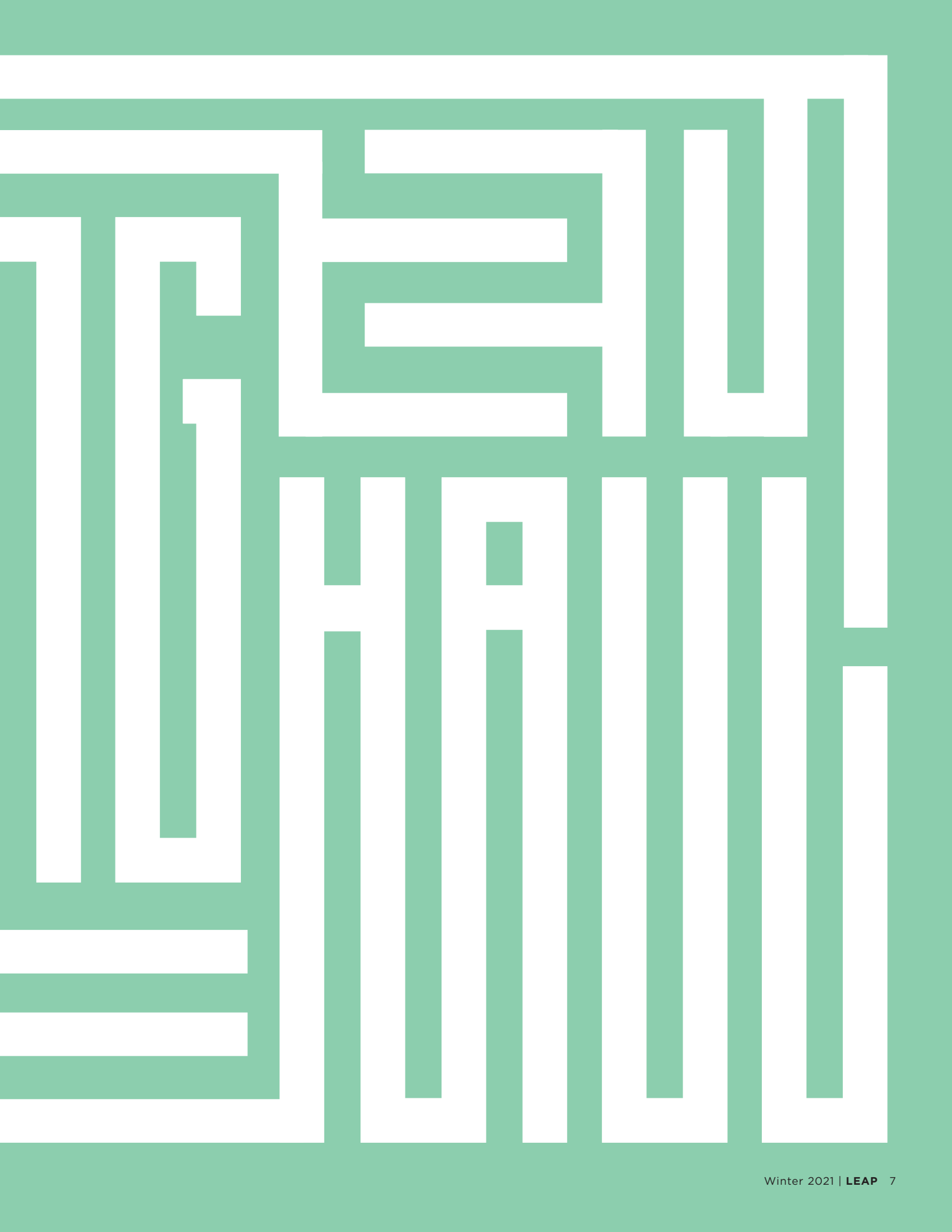
PTLD:

LONG-HAUL LYME DISEASE

Some people get bitten by a deer tick that's infected with *Borrelia burgdorferi*, develop a rash, are diagnosed with Lyme disease, take antibiotics, feel better, and get their life back to normal.

Others aren't so lucky. Diagnosed just as promptly, they take the exact same course of antibiotics. And then... they don't get better. What's happening?





John Aucott, M.D., an infectious diseases specialist and the founding Director/physician of the Johns Hopkins Lyme Disease Research Center, is a world authority on this “post-treatment Lyme disease” (PTLD), a condition he helped define. Its symptoms are persistent, and can include fatigue, pain, weakness, brain fog, and sleep disorders. He has studied and treated hundreds of patients with PTLT, who tell him things like, “I can’t get out of bed,” or “I can’t ride

It may be that reintroducing healthy bacteria into the colon could significantly improve quality of life in these patients.

my bike,” or “I’m exhausted trying to get through the work day.” In addition to feeling ill, frustrated, discouraged and even desperate for relief, these patients often must deal with a stigma – similar to that experienced by a brand-new group of patients from the pandemic, the Covid-19 ‘long-haulers,’ Aucott says. “The Covid long-haulers aren’t dying, they don’t have signs of extensive organ damage – but they have the exact same lingering, disabling symptoms that we have been pointing out for years in our PTLT patients.”

Aucott and his longtime colleague, scientist Mark Soloski, Ph.D., suspect that for the PTLT “long-haulers” – about 10 to 15 percent of people treated for acute (initial) Lyme disease – the disease process triggers persistent changes in the immune system and the autonomic nervous system. Their pioneering research program focuses on defining and characterizing changes

in the underlying molecular mechanisms that cause and perpetuate these symptoms, with the hope of finding biomarkers to help diagnose and monitor this disease, and to discover new avenues of treatment. Their areas of active study include:

The gut microbiome:

In work recently published online in mBio, Soloski, Aucott and colleagues at Hopkins, Northeastern University, and University of California-San Diego reported that PTLT patients have a distinct microbiome

“signature,” or population of bacteria in their gastrointestinal tract compared to healthy controls and to an intensive care unit (ICU) control group. The scientists analyzed fecal samples from patients in the Hopkins Study of Lyme Immunology and Clinical Endpoints (SLICE), and compared them to the healthy control group and to the ICU control group – patients who were

The metabolome – all those small molecules our cells make and pour out into our blood – is perturbed in patients with Lyme disease. The scientists have identified a “fingerprint” of metabolites unique to patients with PTLT.

also on antibiotics. “We found that the PTLT group had two distinct differences in their gut bacteria – an abundance of *Blautia* bacteria, and a decrease in *Bacteroides*,” says Soloski. “*Bacteroides* is interesting, because it produces GABA, an important neurotransmitter.” Low levels of GABA can cause anxiety and depression. In turn, an excess of *Blautia* has been found in people with obesity, Alzheimer’s disease, and multiple sclerosis. The good news about the gut microbiome is that it can be altered by many factors, including diet, medication, and even fecal transplant. It may be that reintroducing healthy bacteria into the colon could significantly improve quality of life in these patients – a compelling idea that the investigators feel is worthy of further study.

The metabolic response:

In another study, Soloski, Aucott and colleagues at Hopkins, the Centers for Disease Control, Colorado State University, and New York Medical College found significant metabolic differences in people with PTLT compared to other patients. This work was published in *Clinical Infectious Diseases*. “Basically, we found that the metabolome – all those small molecules our cells make and pour out into our blood, our signature of the metabolic activities of all the cells in the

“Everybody’s looking for the Target store sign,” but that distinctive bullseye rash only appears in 20 percent of patients. Patients and clinicians miss the other 80 percent.”

body – is perturbed in patients with Lyme disease.” The scientists have identified a “fingerprint” of metabolites unique to patients with PTLT. This might one day lead to a blood test to determine which patients with Lyme disease are at risk of PTLT, and to help monitor the course of illness in PTLT patients.

Is there a genetic fingerprint?

Soloski and Aucott are looking for epigenetic changes – small mutations in the structure of DNA – among the 20,000 or so genes in the genome. This is big-data analysis that wouldn’t have been possible a few years ago. Computers and data experts sift countless pieces of evidence, like miners sluicing for gold, looking for valuable nuggets: patterns of gene expression, particularly in immune system genes and in messenger RNA genes.

Better treatment for PTLT

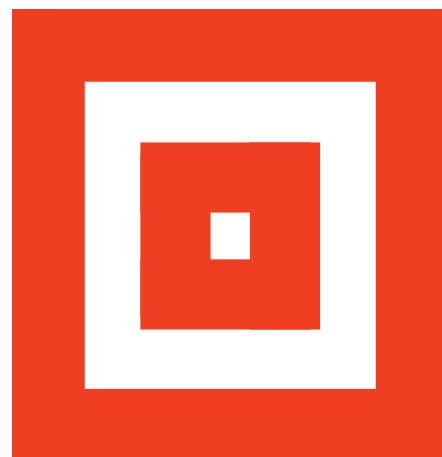
“There is no FDA-approved treatment for PTLT,” says Aucott, “so we use drugs that the FDA has approved for other indications. Treatment is very patient-specific, depending on the primary symptoms.” For example, fatigue often goes along with postural orthostatic tachycardia syndrome (POTS), a condition where the heartbeat skyrockets with a change of position – from sitting to standing, for example – that is treated by blood pressure-regulating drugs such as midodrine.

In exciting research recently published online in *BMJ Open*, Hopkins scientists Alison Rebman, Ting Yang, and Aucott, have identified six symptom factors and three potentially clinically relevant subgroups among patients with PTLT. The group’s findings may be an important step toward developing even more personalized and specific treatment plans.

Aucott has spent years working to raise physician awareness about PTLT, which “doesn’t fit into one specific disease silo” or subspecialty; in fact, the Center is the only one of its kind based in an academic department of medicine with a focus on PTLT.

New to the Center is rheumatologist John Miller, M.D., who brings expertise in joint ultrasound. “He is showing changes in our patients that are subtle,” particularly “tendinopathy-related causes of periarticular pain that nobody’s seen before, because joint ultrasound has never been done in these patients.” Miller has found enthesitis, inflammation where tendons insert into the joints that is also found in psoriatic arthritis and Reiter’s syndrome (reactive arthritis). His findings “may lead to looking at autoimmune-related drugs,” says Aucott, and the images “are opening up a whole new field of clinical inquiry. Nobody else is really doing this.” [L](#)

For more information on the Center, please go to <https://www.hopkinslyme.org>.



NOT ALWAYS A BULLSEYE

Artificial intelligence (AI) is making possible what John Aucott describes as his “pet project:” analyzing the rash that comes at the start of Lyme disease and is key to early diagnosis. “Our studies show that many people have trouble making the right diagnosis. Everybody’s looking for the Target store sign,” but that distinctive bullseye only appears in 20 percent of patients. “Patients and clinicians miss the other 80 percent. We trained the computer by AI to read cell phone images and make a better diagnosis.” Aucott was senior author on a report of this work, recently published in *Computers in Biology and Medicine*.

Could rashes even help predict which patients might be headed for PTLT, and could a better understanding of rashes lead to more effective, personalized treatments? These are possibilities Aucott hopes to explore.

A NEW CULPRIT IN SJÖGREN'S SYNDROME:

GENETIC "JUNK"

This story begins where a 2018 *LEAP* story left off: with an ordinary immune system protein called IFI-16 that goes rogue in the salivary gland tissues at the beginning of Sjögren's syndrome (SS).

Rheumatologist Brendan Antiochos, M.D., knew some of the chain of events: foreign DNA – maybe bacteria, maybe a virus – in the salivary tissue is recognized by the immune system. The immune system activates a particular protein called IFI-16, which immediately tackles the offending DNA. But then these IFI-16 proteins get carried away: instead of just attaching themselves to the enemy invader, they start sticking to each other, piling into long lines, or filaments.

Unfortunately, these filaments irritate the very tissue they were meant to help. Their presence activates an additional immune response: lymphocytes, white blood cells, arrive at the scene and begin to make holes in the membrane of nearby salivary cells. Antiochos and colleagues also have shown that these cytotoxic cells cause IFI-16 filaments to leak out of the salivary epithelial cells, and this is likely what drives the immune response and activates the cycle of autoimmunity in SS.

But what starts all this?

Antiochos and colleagues have uncovered one culprit, and it's neither bacteria nor a foreign virus. Instead, says Antiochos, a recent Greene Scholar, it's a "retro element" called long interspersed nuclear element (LINE)-1. "This is inside all of us: little segments of DNA, repeated and scattered throughout the genome. These segments have been known about for decades," but scientists believed them to be the cellular version of an old car up on concrete blocks, or dead satellites floating around in space: "basically, just junk."

But investigators have discovered that some of these retro elements are, in fact, still active and able to replicate. In fact,

Unfortunately, these filaments irritate the very tissue they came to help.



Antiochos says, they can "physically move in the genome and start a new copy of themselves somewhere else. They can copy and paste," like the "jumping genes" that scientist Barbara McClintock identified in corn plants, work for which she won the Nobel Prize in 1983. If one of these elements plunks down in the wrong place, it can cause harm. "We know of genetic diseases and cancers where LINE-1 is doing just that – landing in a bad spot."

When LINE-1 replicates, it produces "nucleic acid intermediates" – a hybrid of RNA and DNA, a molecular Liger (a cross between a lion and a tiger). The immune system can detect these pieces of nucleic acid that appear unexpectedly. The trouble with LINE-1 is that it's "somewhere between friend and foe. It's self but not quite self; it's part of us." Clearly, the immune system doesn't view it as entirely good-natured.

Researchers have also detected LINE-1 expression in the kidneys of patients with lupus, and this raises an important question: "Could this be a completely new target of therapy?" Drugs already exist to block replication of LINE-1: they are used to inhibit HIV. But before these drugs could be used to treat rheumatic diseases, notes Antiochos, "we need to know who actually has LINE-1 that's active."



Is LINE-1 only involved in the *initiation* of disease, but not the *perpetuation*? “If it’s only involved at the beginning, that would be hard to treat. But if we could link LINE-1 expression with ongoing disease activity, we might be able to limit the damage.”

There is a lot of LINE-1 out there.

“We’re looking at something that’s present in abundance in everyone. Most of these LINE-1 insertions probably aren’t doing anything; they’re genetic fossils. So, it’s really challenging to quantify how active LINE-1 is.” With hematopathologist Kathy Burns, Chair of Oncologic Pathology at Dana Farber and an expert in LINE-1, Antiochos is devising tests to measure LINE-1 activity. “There are probably just a handful of places where there’s an active LINE-1 insertion that’s capable of replicating itself. If it’s there, intact, turned on and actively replicating, it could be producing these nucleic acid intermediates that could turn on the interferon system. Interestingly, LINE-1 uses two proteins to replicate itself. It turns out that one of those proteins is actually an autoantigen, and antibodies have been found in patients that target that protein.”

What’s next? Antiochos is developing lines of epithelial cells in which he can turn LINE-1 and IFI-16 on and off, “to see whether LINE-1 activates this protein and generates the structures we saw in the salivary gland.” Although he believes LINE-1 is probably not the sole cause of SS, that there may be multiple underlying triggers, “we are moving closer to precisely identifying groups of patients with something in common, and finding precision therapy.” ↴

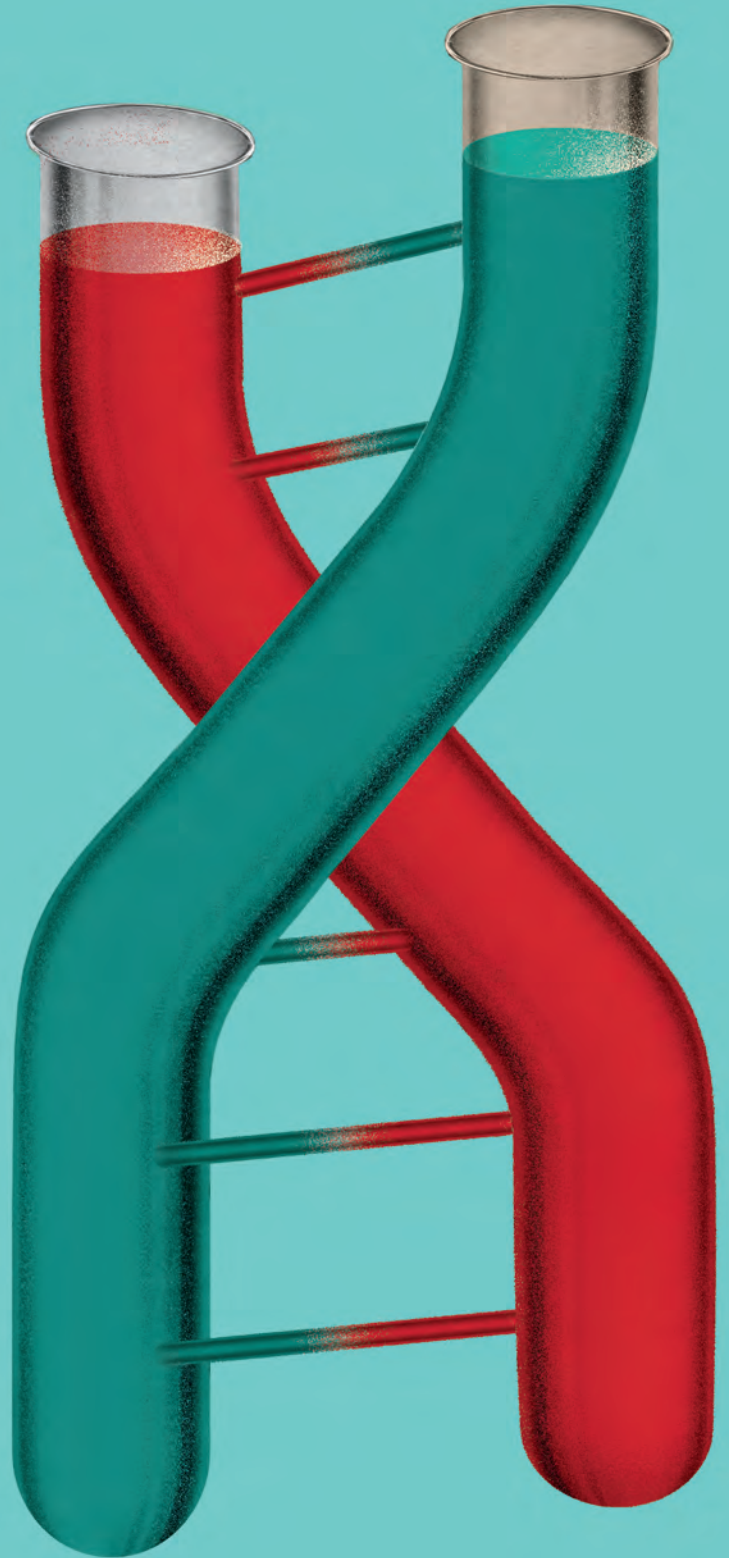


“This is inside all of us: little segments of DNA, repeated and scattered throughout the genome. These segments have been known about for decades,” but scientists believed them to be the cellular version of an old car up on concrete blocks, or dead satellites floating around in space: “basically, just junk.”



SJÖGREN'S AND THE X FACTOR

Why is Sjögren's Syndrome (SS) much more common in women than men? The answer may lie in a large RNA molecule called Xist (pronounced "exist"), whose main job is supposed to be over and done with in the womb.



Xist, in a female embryo, acts like a cover over a canary cage: it silences gene expression on one of the X chromosomes. Briefly, females have two X chromosomes, and males have one X and one Y chromosome. To prevent females from getting a massive double dose of 1,000-plus genes on the X chromosome, which would be fatal, half of the X genes are inactivated by Xist, which basically wraps a molecular blanket around the extra X chromosome's genes.

Immunologist Erika Darrah, Ph.D., a recent Greene Scholar, is exploring the role of Xist in SS. How did she zero in on this particular molecule? There has long been anecdotal information that men who have two X chromosomes and one Y (a rare condition) are more likely to get SS. And, "a lot of immune genes on the X chromosome are thought to play a role in Sjögren's. Maybe there is abnormal activation of the X chromosome."

Could Xist actually stimulate the immune system to promote cytokines, interferon, and the formation of autoantibodies? No one has ever looked.

Could Xist actually stimulate the immune system to promote cytokines, interferon, and the formation of autoantibodies? No one has ever looked.

We still don't know whether this is the chicken or egg. Is it a cause, actually leading to the development of the disease, or is it a consequence of the disease process?" The answers might lead to an entirely new way to treat Sjögren's.

Darrah began by measuring levels of the Xist molecule in blood cells in patients with SS compared to healthy donors. Her preliminary studies wouldn't have happened without funding from the Greene Foundation, "because this was a completely new hypothesis that was outside the box. It wouldn't have been funded by the NIH. But the Greene Foundation gave us the freedom to explore this very novel idea and to establish new techniques in the lab that we needed to ask the questions." One of the techniques she is using is RNA flow cytometry, which can detect RNA in single cells.

Initially, Darrah says, "we thought patients with SS would have less Xist than healthy donors, but we saw the exact opposite!" This unexpected finding led Darrah to wonder: "Does Xist have a role that no one has really explored yet as a direct promotor of inflammation that interacts with immune sensors?" In July 2020, Darrah and her colleague, Brendan Antiochos, received an NIH R-21 grant to investigate whether and how Xist affects the immune system: "Does it interact with the immune receptors, does it promote the pro-inflammatory cytokine

production that you can see in Sjögren's? Which regions of the RNA are actually interacting – can we identify the piece or pieces of this molecule that are causing the trouble? And can we find any evidence that this might interact with Ro and La, the antigens recognized by the immune system in patients with Sjögren's?"

It also remains to be learned, Darrah adds, whether some patients with SS have more Xist than others, and whether this correlates with more severe disease or a disease flare. And finally: "The question we still don't know is whether this is the chicken or egg. Is it a cause of Sjögren's, actually leading to the development of the disease, or is it a consequence of the disease process?" The answers might lead to an entirely new way of treating SS; possibly, to disrupt the inflammatory process started by the Xist molecule by blocking the factors that cause it to be expressed. [↓](#)

LEARNING FROM PETER FRAMPTON

After all these years, legendary musician Peter Frampton sounds just as good as ever. In fact (although he might disagree), to those who have heard him live or listened to some of his newer recordings, this beloved guitarist sounds even better than he did back in the days of his landmark 1976 album, *Frampton Comes Alive!* or *Fingerprints*, for which he won a Grammy in 2006.

This is remarkable for two reasons: first, he has an autoimmune disease called inclusion body myositis (IBM) that affects his muscles. And second: although he has experienced some weakness and loss of function in larger muscles, his fingers still work great!

Frampton's finger dexterity was not at all what his doctor, rheumatologist Lisa Christopher-Stine, M.D., Director of the Johns Hopkins Myositis Center, expected to find; then again, neither was Frampton himself.

Before his first appointment, Christopher-Stine says, she wondered whether he would be one of those high-maintenance, dark sunglasses-wearing celebrities. He wasn't. "He didn't have an entourage; he's just a very down-to-earth, lovely person." He is also consistently upbeat, with a can-do attitude, great sense of humor and a hearty laugh. He

has IBM, but IBM doesn't have him. "Sure, I have my darker moments," Frampton says. "But I have so much to be thankful for. We all have our battles; this is mine, but everybody has something. You walk down the street, and you've no idea what the person who just passed you is going through. This has opened me up to be more empathetic about other people's battles. Yes, mine is serious, but there are many worse ones out there."

PATIENT AND TEACHER

IBM is not the same in every patient, Christopher-Stine notes, "and it's unclear why certain muscle groups are targeted more than others." The finger flexor muscles are often specifically affected in IBM and for that first visit, Christopher-Stine's immediate concern was how badly affected they would be in the renowned guitarist. She was in for a surprise. His finger dexterity, built over decades of disciplined practice and virtuoso performance, was extraordinarily well-preserved, she says.

"I have noticed some changes," says Frampton. "They're small. I am very, very slowly losing power in my hands, so that's a little disturbing. But so far, because I've been playing all my life, as soon as I take up a guitar, they tend to know what to do."

Because of Peter Frampton, Christopher-Stine has changed her advice for patients with IBM. "In many ways, he's been a teacher as much as a patient," she says. "He taught me how important exercise and recurrent use of one's fingers are. Remarkably, his left hand, which plays the frets, is even stronger than his right hand, which is his dominant hand! I started recommending to other patients to get a guitar or piano – just start playing. I don't know that we can undo damage that was already there (in other patients), and it is unlikely



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that people who don't play at that high level would get the same benefit. But he has proven that there is a benefit in isolating our finger flexors individually; most people don't do that. We tend to concentrate on grip testing and strengthening rather than on individual finger muscles."

EXERCISE IS NON-NEGOTIABLE

In addition to practicing and playing guitar, Frampton does a one-hour workout six days a week. This is non-negotiable; even the pandemic and gym shutdowns haven't stopped him. "I'm very lucky; I do not have the swallowing problem (these muscles can be affected in IBM)," he says. With the help of a personal trainer (online during the pandemic), he exercises "every muscle that is affected," in his case, "the muscles in the legs, the arms and the hands. We mix it up: legs and core, then core and arms another day, so it's always different.

"I am aware of the very slow decline; stairs are a real problem for me. We concentrate on fall prevention: that's the way I found I out I had this, the reason I went to a neurologist in the first place. I fell twice on stage within a month. I had no idea what was going on. I knew I was losing power in my legs, but I really

"I fell twice on stage within a month. I had no idea what was going on. I knew I was losing power in my legs, but I really didn't have a clue as to what was going on. I actually thought my tight jeans were impeding my walking! The mind is a terrible thing!"

"I have noticed some changes," says Frampton. "They're small. I am very, very slowly losing power in my hands, so that's a little disturbing. But so far, because I've been playing all my life, as soon as I take up a guitar, they tend to know what to do."

didn't have a clue as to what was going on. I actually thought my tight jeans were impeding my walking! The mind is a terrible thing!"

That was six years ago. During a 10-day break in his concert schedule, Frampton went to a neurologist, who narrowed down the diagnosis to two possibilities. "He didn't tell me until after he'd diagnosed me with IBM that the first one on his list was ALS (amyotrophic lateral sclerosis, also called Lou Gehrig's disease). Because it is so slow-moving, IBM is hard to diagnose."

GIVING BACK

And because it is pretty rare, affecting maybe eight out of every one million Americans, IBM has not garnered huge research funding; neither has it been a big focus of drug development by pharmaceutical companies. Frampton is doing his best to change this, establishing the Peter Frampton Myositis Research Fund at Johns Hopkins to raise money for research. In February 2019, he went on "CBS This Morning" to announce the Fund and his 51-date U.S. Farewell Tour. "Each promotor donated a dollar from every ticket sale," he says. "The Shriners teamed up with us," selling copies of Frampton's 2019 CD, *All Blues*. "I didn't see any money from that CD: half the profit went to the Shriners, and half of it went to my fund at Johns Hopkins." So far, the tour and CD sales have raised close to \$300,000.

"The promotors had to do this themselves. They had to work out how many people were there, they had to write a check after every one of my concerts in different places, and they all sent in the money," Frampton says. "In fact, in a couple places, they gave a huge check on top of that. People were just so behind the Fund and doing as much as possible."

“SYMBOL OF HOPE”

Since he went public with his diagnosis, “he’s become a symbol of hope,” says Christopher-Stine, who gets calls and letters from patients saying that Frampton has inspired them. Frampton makes time to talk to “other IBM’ers,” on the road and online. On the Farewell Tour, “I would do a VIP meet and greet at the end of each concert, usually about 40 to 50 people,” he says, “and if there were any IBM’ers, we left them until last, so I could spend more time with them.” He remembers one couple in particular: “They didn’t say that he had IBM, they didn’t wait until the end, so we didn’t know. So I’m standing in between them, and I’m signing their stuff and getting ready to take a picture, and the wife says, ‘You diagnosed my husband.’ I said, ‘Excuse me?’ He was very quietly spoken, and he said, ‘I had been to I don’t

INHERITED RESILIENCY

Christopher-Stine says of Frampton, “I feel so fortunate to know him. He is truly a remarkable human being.” Frampton says his positive attitude is inherited. “My kids say to me, ‘Dad, how come it’s always the little, tiny things that really bother you? When something big happens, good or bad, you take it in your stride.’ I don’t know, but I’m the problem-solving optimist of the family. I got that from my parents. I was born five years after my dad came back from Germany in the second World War. I learnt so much from their stories.” His father fought in Europe and Africa. His mother survived the Blitz. Over time, “she got fed up with going to the bomb shelter in the basement, so she just stood out on the balcony and watched the bombs come down. Every day, they woke up and didn’t know if it would be their last.”

“I watched you on CBS, and everything you said, all your symptoms, I ticked them off one at a time. I just yelled at my wife, ‘Hey, come in here! Frampton just diagnosed me! I’ve got IBM!’”

know how many doctors. Nobody knew what I had, and nobody could help me. I watched you on CBS, and everything you said, all your symptoms, I ticked them off one at a time. I just yelled at my wife, ‘Hey, come in here! Frampton just diagnosed me! I’ve got IBM!’ He went to a neurologist, because that’s what I said to do, if you’ve any weakness in your leg muscles and no clue what it is.” Frampton asked the man if he was exercising now, and the answer was, “Every day.” There was proof that I had actually helped someone by talking about it on TV.”

They were glad to be alive, and so is Frampton. “I just feel like, if I’m the face of IBM, then I think you’ve got the right person, because I never give up!”

For more information on the Peter Frampton Myositis Research Fund, please go to: <https://www.hopkinsmyositis.org/gift/peter-frampton-myositis-research-fund>.



Frampton and Christopher-Stine, after a concert.



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"Some people in this industry have said that the more senior artists like myself, no one wants to hear new music from them, so don't worry about it. I get it. But that's what I do, you know? You can't just stop. So even though new music from me isn't going to **LEAP** to the Top 40 stations... it doesn't matter because it's what I do every day. I'm always creating. Whether people want to hear it or not, I'm gonna do it."

— Musician Peter Frampton, quoted in *Billboard*, 2016. Frampton is still playing at the top of his game, despite having an autoimmune disease. His dexterity has not only amazed his Hopkins doctor, Lisa Christopher-Stine, but changed the advice she gives to patients. Story on Page 14.