Plotting the end of Lyme disease

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Internationally known Lyme researchers Sam Telford, a Cummings School professor, and Linden Hu, a professor at the School of Medicine, demonstrate how fabric flags are used to collect ticks for studies. Credit: Alonso Nichols

As people weary of being cooped up during a pandemic winter look forward to a summer outside, residents across the northeastern United States are once again confronted with a familiar virulent pathogen

lurking in the woods and fields. Unlike coronavirus, however, this dangerous microorganism doesn't float through the air—it enters the body through the bite of a tick.

Lyme disease has been a constant scourge since it was identified five decades ago on the Connecticut coastline, before spreading across the New England and Mid-Atlantic states. Caused by the bacterium Borrelia burgdorferi (and its cousin Borrelia mayonii), the disease has long baffled scientists with its strangely stealthy manifestations.

While Lyme can sometimes be diagnosed early from its telltale bullseye-shaped rash, it often goes unnoticed for weeks in a person before it starts leading to complications including arthritis and—in severe cases—attacks on heart and brain tissue. While it can often be resolved with antibiotics, some 10 to 20 percent of patients see infections persist, with fatigue, joint pain, and mental impairment lasting months and even years. Sometimes doctors who treat such long-suffering patients aren't even able to definitively pinpoint Lyme as the cause. All of those complications make the mission of the new Tufts Lyme Disease Initiative even bolder: "Eliminate Lyme Disease by 2030."

"Many of our approaches are currently designed to see if we can get rid of Lyme disease at its source," said physician Linden Hu, the Paul and Elaine Chervinsky Professor of Immunology at Tufts University School of Medicine and one of the initiative's two co-directors. That means bringing together a multidisciplinary team of scientists who can deal with all aspects of the disease, from animal behavior to human health. "Our work spans a range that includes ecology, epidemiology, population health, genetics, and clinical intervention," said Sam Telford, an epidemiology professor at Tufts Cummings School of Veterinary Medicine and a board member of the initiative.

If any institution can unravel the intertwined mysteries of Lyme, it is

Tufts, which has been on the forefront of study and treatment of the disease for nearly half a century. Among the pioneers who first identified Lyme disease in the mid-1970s were David Snydman, an infectious disease specialist at the Centers for Disease Control, and Allen Steere, a rheumatoid physician at Yale University, who believed that such illnesses could be traced back to bacterial infection. When a cluster of several dozen supposed cases of juvenile rheumatoid arthritis broke out in Lyme, Connecticut, they were skeptical of the diagnosis, believing it may have been caused by a pathogen instead. Eventually, they were among the scientists who helped identify the tick-borne Borrelia as the cause of the disease.

Snydman became chief of geographic medicine and infectious diseases at Tufts Medical Center and a professor at Tufts School of Medicine. Steere became chief of rheumatology at the medical center and a professor of rheumatology and immunology at the School of Medicine, positions he held until 2002. During that time, he gathered a team of doctors and scientists around him to study the strange new disease, creating a nucleus of knowledge that would eventually grow into the current initiative. Hu was recruited by Mark Klempner, an infectious disease physician who made early discoveries on the biology of Borrelia; Hu found studying the pathogen the perfect intersection between basic science and clinical work. John Leong, now Edith Rieva and Hyman S. Trilling Professor and chair of Molecular Biology & Microbiology at Tufts School of Medicine, was a postdoctoral fellow at the school with Professor Ralph Isberg when he started studying Lyme and was recruited by Steere to Tufts Medical Center. He was joined by rheumatologist Robert Kalish, now associate professor of medicine at Tufts and director of the medical center's Lyme Disease Clinic, and Jenifer Coburn, now at the Medical College of Wisconsin and a recognized leader in the study of Lyme.

"It's not just Linden and me—the institution should be proud of its place

in the history of Lyme disease," said Telford, who began working on Lyme at Harvard School of Public Health before coming to Tufts in 2002. "People who have done work here in the past have been involved in all of the seminal discoveries," added Hu, "of the disease, of the bacteria, of a vaccine, of tests—it was all Tufts or Tufts people."

Wipe It Out in the Wild

Any effort to snuff out Lyme disease has to start with its eight-legged bloodsucking hosts. "Until you get rid of it in the environment, you've got to keep investing in prevention in humans," Hu said. "Whereas if you wipe it out in the wild, it's one and done, right?" Eradicating Lyme in the ecosystem, however, is easier said than done. While the bacteria that cause the disease live in ticks, the ticks don't pass it down to their offspring directly—instead, they feed on a vertebrate host, such as a white-footed mouse, and pass the pathogen to it. When another tick feeds on that same host, it too picks up the bacterium.

Many of the efforts by Hu and other scientists have been focused on breaking that chain. One promising technique Hu developed, for example, was to vaccinate mice by leaving out vaccine-infused food for them. The oral vaccine contained a virus that would express a Borrelia antigen that would make the mice immune to Lyme. "The idea was to feed it to mice in the wild, and have fewer infected mice, which would translate into fewer infected ticks, and fewer human cases," Telford said. While the scientists insist the technique is safe, however, it's been held up by the U.S. Department of Agriculture, which is leery about releasing a virus in a world beset by a pandemic. "We got stuck in regulatory purgatory," Hu said. "No one wants to put a live virus out in the wild right now."

Another technique Hu has proposed is putting an antibiotic—the standard treatment for Lyme— into mouse food left at bait stations.

Doxycycline, for example, has been shown in mice to get rid of more than 90 percent of the pathogen. While those studies were done more than a decade ago, however, that technique too has been stalled, for fear that disseminating an antibiotic widely used in humans could lead to more antibiotic-resistant bacteria, reducing the drug's effectiveness. "No one is willing to take that risk," said Hu.

He and Telford recently received a $3.8 million grant from the National Institutes of Health (NIH) to explore the use of a more narrow-spectrum antibiotic, which would target only Borrelia and a small number of similar bacteria. Along with Kim Lewis of Northeastern University, Hu's lab has identified a handful of compounds that could do the trick, including one that, he said, "looks very, very promising," and which he hopes to begin field studies on in Maine and Massachusetts soon.

One potential complication to all of these techniques is pinpointing just which vertebrate species carry the Lyme bacteria in the wild. "If you look at all the literature, it's all white-footed mouse, white-footed mouse, white-footed mouse," said Telford. A new technique developed by his wife and collaborator, Heidi Goethert, J93, however, calls that dogma into question. Goethert, who majored in biology at Tufts, met Telford while she was completing a doctorate at Harvard School of Public Health, where the two often partnered on monitoring field sites for ticks on Nantucket and Martha's Vineyard. "When you spend two nights at every field site from April to October, you get to know a person quite well," she said.

She joined him at Tufts, where she is now an assistant research professor at Cummings. Goethert argues the reason Lyme is so often associated with white-footed mice is that they are relatively easy to catch compared to other animals. Instead of looking for Lyme in rodents, she has gone straight to the source, catching ticks and grinding them up to examine what they've fed on. The technique has been used with mosquitos and

malaria for decades, allowing scientists to identify bits of animal DNA from mitochondrial genes in their stomachs. Ticks, however, eat much less frequently than mosquitos. "You're trying to find bits of digested DNA from a host a tick might have fed on a year ago," Goethert said. Instead, she searches for retrotransposons, remains of ancient viruses that are distinct for each species and prevalent in the genome, maximizing chances that enough copies will remain to detect. "With this new technique, you are actually measuring what a tick has fed on, instead of making an assumption," she said.

Her data, published in January, shows that in some years and at some sites, ticks are feeding on white-footed mice 100 percent of the time. At others, however, they are feeding on shrews, voles, squirrels, chipmunks, and even birds—all of which can harbor the Lyme infection and pass it on. "A lot of the control measures people are investing in are focused on white-footed mice," said Goethert, who hopes her findings will help ecologists cast a wider net. "It helps to know what you are actually trying to target so you can develop appropriate techniques."

One animal that has been targeted successfully to stop Lyme disease is deer. While they don't contract the disease, they serve as an abundant food source for ticks, which attach themselves to their hides by the hundreds. "I am the nation's biggest advocate for killing deer as a means of controlling tick abundance," Telford sighs, "but sadly, killing deer is a very sociopolitically difficult thing to convince people to do." He's achieved some success in working with Robert Smith, an infectious disease physician who has led a Maine research team focused on Lyme and other tick-borne diseases since1988. Smith is now a professor of medicine at Tufts, as well as director of the Vector-Borne Disease Laboratory at Maine Medical Center Research Institute, and the other co-director of the Tufts Lyme Disease Initiative.

Together, Smith and Telford conducted studies on Maine islands that

were then just beginning to report cases of Lyme; it was a way to better understand the progression of the disease in the environment. "By coupling studies and comparing northern and southern New England, we can learn a lot from ecological differences in the northern emerging area versus the more established southern area," Smith said. They were able to show the importance of deer to the tick's life cycle with a project on Monhegan Island, 12 miles off the coast. Deer were not native to the island, and when island residents decided to eradicate them, researchers showed the tick population also crashed.

"We learned on Monhegan that without the deer, the ticks don't do well," said Smith. While most communities are reluctant to kill deer, the Monhegan research has led to other experimental methods of severing ticks from the deer they need to survive—such as feeding stations equipped with insecticide-coated rollers. "It's like a deer car wash that rolls the pesticides onto the deer as they feed," Smith said. While such techniques aren't the sole answer, they could be part of a multipronged effort to fight the disease in the wild. "There is no magic bullet, but the hunt is on to find and combine methods to get at the ticks on rodents, deer, and in the environment to see if we can break the cycle and stop the disease."

The Vaccine You Never Knew About

A more direct way of controlling Lyme disease, of course, would be to vaccinate people to stop the infection from jumping from ticks to humans. Telford and Smith were both involved in studies in the early 1990s, led in part by Allen Steere, to create a vaccine called LYMErix. It worked by spurring the body to create antibodies to Borrelia's outer surface protein lipid A (OspA)—a technique shown in trials of around 15,000 patients to be about 80 percent effective in preventing Lyme infection. "It would have prevented hundreds of thousands of cases," Telford said.

The vaccine ran into several hurdles, however. For starters, it was difficult to administer, requiring three separate doses to be effective. At the time, Lyme was also a much rarer disease, and so the company making it was concerned about its ability to make a profit. "It was looked at as something that would be nice to have, but not really essential," Smith said. The biggest problem, however, came from the community of people with Lyme. Some patient advocates complained about side effects from the vaccine, even claiming it was causing Lyme disease in people who received it, and sued the company, which stopped production in 2002. "They looked at it and said, we're not making any money on this, and we don't want to defend ourselves, we're just withdrawing it from the market," Telford said.

In part, that skepticism by patients may have stemmed from the frustration that many of them were initially misdiagnosed. Lyme disease is difficult to distinguish from other, similar ailments. "The disease is a chameleon, and can even change day to day or week to week," said Robert Kalish, a rheumatologist at Tufts Medical Center who worked on Lyme disease with Steere in the 1990s, when he participated in a follow-up study of some of the original patients from Lyme, Connecticut. The one telltale sign of a Lyme disease infection is a bullseye-shaped rash. However, not all infected people have that symptom. "One person gets a rash but feels great otherwise," said Kalish, who currently runs a Lyme disease clinic, "another doesn't get a rash, but has chills and severe fever and headache and meningitis; the next person is fine until suddenly their heart goes slow and they have heart block," a problem with the heart's electrical signaling.

Some 20 years ago, Smith led a study looking at the rashes of patients who were proven to have early Lyme disease, and found a wide variation even in that marker. At the same time, diagnostic tests for the disease work well four to six weeks after infection, but are often ineffective before that. "They're only about 50/50 in the first couple of weeks,"

Smith said. The other problem with diagnosis is that once a person has tested positive for the disease, they tend to stay positive. "You can't tell if someone has been cured, and you can't tell if somebody has been reinfected," said Hu. That means doctors must often rely on guesswork and intuition to diagnose the disease, based on clues and past experience. "Lyme causes a large array of symptoms that differ from person to person," Kalish said. "So it's a disease that can look like other things and be missed."

The good news is that once Lyme disease is diagnosed, it is usually treatable with just a short round of doxycycline, which can clear up the infection in as little as 10 to 14 days. A small number of people take longer to get over the disease, requiring several months to recover. A smaller subset of those, however, develop a more chronic syndrome—sometimes called Post-Treatment Lyme Disease Syndrome to distinguish it from the active infection by the pathogen. Kalish compares it to chronic fatigue syndrome or fibromyalgia, a chronic musculoskeletal condition accompanied by fatigue and cognitive issues.

"About 15 percent of people will have prolonged symptoms for years," Hu said. "The most controversial part of Lyme disease is just what is causing symptoms in these people." In animal studies involving mice, dogs, and monkeys, biologists have shown that Borrelia DNA can be found in tissues long after antibiotic treatment is complete—implying that some part of the bug lingers on in the patient whether or not live bacteria are there. "People argue over the meaning of these animal studies," said Hu. "No one has been able to show that you can pull out live bacteria." At the same time, the biggest contributor to Lyme disease symptoms seems to come not from the bacteria itself, but from the body's own response.

"Borrelia as an organism doesn't produce toxins," said Hu. The body, however, usually responds with inflammation in an attempt to eliminate

the intruder. In most people, that inflammation eventually goes away. "Over time, all the symptoms go away, even if you don't treat it," Hu said. In the small percentage of people who develop a chronic syndrome, however, something seems to go wrong with the immune system, which continues attacking the remnants of the bacteria.

"One of our theories is that patients who continue to have symptoms have a genetic difference in the way they are able to control their own inflammatory responses and disengage from attack mode," Hu said. "So they continue to have immune responses, whether it's to live bacteria, or to dead parts of the bacteria after it's been cleared."

Among the projects of the Tufts Lyme Disease Initiative is a deep dive into just how the bacteria operates within the body in hopes of finding a way to prevent the body's over-the-top responses. Hu, along with Klemen Strle of the Wadsworth Institute, recently received a $3.1 million grant from the NIH to examine how genetic mutations affect the body's ability to develop tolerance for Lyme pathogen. "We've been asking, how do the bacteria adapt to their hosts? And how do the hosts adapt to the bacteria? And what goes wrong that could be responsible for the people who have persistent symptoms?" said Hu.

Skirting Immune Defenses

Borrelia belongs to a class of bacteria called spirochetes, named for their long, spiral shape that makes them look like microscopic fusilli pasta. For the past 30 years, microbiologist John Leong has been investigating how they infiltrate and colonize the body using a range of clever tricks to skirt the immune system's defenses. A first line of that defense is known as the complement system. "It consists of a large set of proteins devoted to killing microbes in the blood," Leong said. Those proteins recruit leukocytes, which also kill pathogens. The spirochete is able to disarm this process, however, by using surface proteins that attract the body's

own proteins that signal the complement system to stand down. The body thinks, "Hey, we don't need to worry about these, because they've got this regulatory protein on the surface," said Leong.

About 10 days after infection, the adaptive immune system kicks in, sending out specialized T- and B-cells that attack what should be now-recognized intruders. Borrelia has other ruses to confound these assailants, however. One is through a technique called rapid antigenic variation, where the bacterium creates a constantly shifting terrain of highly variant proteins on its surface, preventing antibodies from latching onto any particular target. "That's one reason why you can get Lyme disease one season, and then the next season, go out and get Lyme disease again," Leong said.

Once the spirochete evades the immune system, it can attach and invade the walls of blood vessels to take up root in different areas of the body—often the joints, but in more serious cases the heart or brain. Which system it attacks has to do again with its unique surface proteins. Collaborating with Medical College of Wisconsin's Jenifer Coburn and George Chaconas of the University of Calgary, Leong has manipulated those proteins through genetic modification. "We've identified two or three of these proteins that if you tweak the sequence, it alters which sites they colonize in the body," he said.

Understanding how Borrelia defeats the body's defenses and takes root in tissues could eventually help biologists develop more specialized treatments to fight it and eradicate it, he said. By identifying these components of the Borrelia spirochete, Leong said, we might develop treatments that target specific proteins, both neutralizing the harmful effects of the bacteria and promoting its clearance from the body.

One such treatment is being investigated by Tanja Petnicki-Ocwieja, a research assistant professor of molecular biology and microbiology at

Tufts School of Medicine, who has studied the receptors produced by Borrelia that allow it to evade the innate immune system. "If we could translate this research into a treatment, we'd find a way to modulate the immune system response," she said. "Ideally we would want to select for inflammation that is useful to get rid of the pathogen but limit the type of inflammation that is going to do damage to ourselves."

Recently, she obtained a $160,000 grant from the Global Lyme Alliance to examine the use of ozone, which has seemingly helped some longtime sufferers of post-Lyme syndrome, who administer it intravenously. Ozone, she explains, can create reactive oxygen species, molecular compounds that have been shown to modulate immune system response. "If people are using this as a treatment, we should give them a scientific basis for it—and if it doesn't work, we should let them know that as well," she said. So far, her preliminary data has shown some support for the treatment, suggesting it calms the immune response, which could lead to a resolution of symptoms.

Long-haul Lyme

Sufferers from untreated Lyme disease can eventually develop Lyme arthritis, in which joints get inflamed. "The knees can get truly damaged, to the point where they can suffer from early deterioration and potentially require knee replacement," Kalish said. Another serious complication is Lyme carditis, seen in less than one percent of patients, in which a change in heart rhythm called heart block can lead to dizziness and fainting. "It's probably the rarest but most serious complication of Lyme disease," said Smith, who recently completed an observational study of some 20 people who have suffered from the condition, which can require use of a temporary pacemaker to regulate heart rhythm. "The biggest takeaway is the importance of being aware of the disease and making the correct diagnosis early on," he said. "These cases could have been prevented by a diagnosis of early Lyme disease

when they first walked through the door."

Unfortunately, there is no clear treatment for long-term cases of post-Lyme syndrome, said Kalish, who compares it to the new phenomenon of long-haul COVID. "Whenever you have people suffering—which they truly are—you want to say, here's something that will make this better," he said. "But we can't just make things up and say there's a treatment when there's not." Sufferers have tried everything from long-term courses of antibiotics to high doses of vitamins and supplements in an attempt to flush the disease from their system. "It's open to both honest efforts that are not going to be the answer, and quackery," Kalish said.

The most important thing, he said, is for practitioners to validate to patients that the syndrome is real, and not just something they are imagining. "The worst thing is when patients are sent home and told they don't have Lyme anymore and not provided with alternate explanations for their symptoms and guidance on steps they might take that might help their condition," said Kalish. Secondly, he stresses the importance of staying healthy while the body continues to fight the disease. "It's healthy living, physically and emotionally—getting good sleep, exercising, treating depression, making sure your family and loved ones understand what you are going through," he said. "Anything you can do to live healthy is going to slowly help you gradually get better."

Hu said the narrow-spectrum antibiotic he is developing to kill Borrelia in the wild might also be used in humans to better clear the infection when it first appears, with less disturbance to "good bacteria." "It's the exact opposite of how drug companies have tried to develop antibiotics for the last 50 years," he said, noting that usually pharmaceutical firms create antibiotics to attack as wide a spectrum of germs as they can. "Although they aren't as profitable as broad spectrum antibiotics, narrowly targeted drugs may cause less resistance among other bacteria

and may be the wave of the future as we work to combat antibiotic resistance."

Giving doctors and scientists more hope, a new vaccine, VLA15, is also under development by the French company Valneva, targeting both North American and European versions of Lyme disease. "Ironically, it's almost the exact same vaccine we worked on 20 years ago," Telford said. With the growth of Lyme disease as a threat and the increased public confidence in vaccines to tackle COVID, scientists hope this time a vaccine might succeed in the market within three to five years. At the same time, former Tufts Medical Center doctor Mark Klempner, who is now executive vice chancellor of MassBiologics at UMass Medical School, is among those developing another treatment—an injection of antibodies that can provide prophylactic protection against Lyme.

Such treatments, combined with other techniques to disarm the pathogen's potency, new treatments for current sufferers, and ongoing efforts to remove it from the wild, could finally give scientists the upper hand on the insidious disease, and accomplish the Tufts Lyme Disease Initiative's ambitious goal to eradicate it entirely. If and when that happens, it could make all of us heading outside breathe a little easier.

Provided by Tufts University

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