FINDINGS

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A Mother's Quest

COULD OMRF PROVIDE THE ANSWERS MELISSA CAIN SO DESPERATELY SOUGHT ABOUT HER DAUGHTER'S ILLNESS?


That more may live longer, healthier lives
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Chartered in 1946, OMRF is an independent, nonprofit biomedical research institute dedicated to understanding and developing more effective treatments for human disease. Its scientists focus on such critical research areas as cancer, diseases of aging, lupus and cardiovascular disease.

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COVER PHOTO: Brett Deering

Protecting Oklahomans From the Virus

New OMRF grant to study Covid-19 in state's different ethnic populations

As the coronavirus sweeps across the U.S., it's hit Black, Hispanic and Native American populations hardest, with members of these communities dying at higher rates than whites. "There's an urgent need to develop strategies to better identify patients who are likely to experience mild versus severe symptoms of this disease to optimally allocate healthcare resources," says OMRF immunologist Dr. Linda Thompson. "A key factor in understanding this lies in knowing how immune response varies in different ethnic groups."

In June, Thompson and OMRF colleague Dr. Mark Coggeshall secured a two-year federal grant to study the immune system's response to the virus and how it differs among people of different ethnicities. The project also aims to understand if the immune response is protective against future infections—or if it might worsen them.

That work will build upon studies OMRF scientists have been conducting for more than a decade as part of an ongoing effort to understand another potentially deadly pathogen. "Our existing research on anthrax has a developed infrastructure to study immune response to a serious viral infection," Thompson says. "So, we were set up to start this project without having to develop new methodology."

The new funding comes as a supplement to a grant awarded to OMRF to study the immune system's response to anthrax bacteria as part of the National Institutes of Health's Cooperative Centers for Human Immunology. That anthrax project will serve as a launchpad for working with Oklahomans eager to help combat the coronavirus.

"OMRF has a strong history and wonderful partnerships throughout the state," says Thompson, who holds the Putnam City Schools Distinguished Chair in Cancer Research. "That should enable us to quickly obtain blood samples from those who have been exposed to or infected by the coronavirus."

The researchers will analyze blood donated by volunteers to understand individuals' differing immune responses to the virus. They'll search for biological clues that might identify those individuals most likely to experience a severe response to coronavirus infection.

The project will also study the roles and reactions of antibodies that form in the immune response to infection to the virus known


Dr. Mark Coggeshall


Dr. Linda Thompson

"All research efforts right now should be on SARS-CoV-2 and Covid-19."

technically as SARS-CoV-2. "Specifically, we need to know if antibodies help fight the virus," says Coggeshall, the Robert S. Kerr Jr. Endowed Chair in Cancer Research at OMRF. Work will focus on a phenomenon called antibody-dependent enhancement, where instead of protecting people from future infections, antibodies could actually make them worse.

"We have to understand all aspects of the body's immune response and which ones correlate to good health outcomes, and we also need to know how these vary in different ethnicities," says Thompson. "This knowledge gap needs to be filled quickly to inform vaccine trials, some of which are already underway."

She also sees a chance to harness OMRF's expertise in immunology to benefit populations who stand particularly vulnerable to the impact of the virus. "We wanted to do something in Oklahoma that nobody else could do."

Coggeshall, for one, relishes the opportunity to undertake the new project. "Our anthrax work is promising and important, but all research efforts right now should be on SARS-CoV-2 and Covid-19," he says. "There is no more urgent issue to study in the world, and we will do everything we can to help."

OMRF is actively recruiting individuals for Covid-19 antibody testing, especially people with health conditions that put them at high risk for severe complications, those with Native American heritage, and those who know or suspect they have recovered from the virus. If you're interested in participating, please call 405-271-7745 or email Jackie-Keyser@omrf.org.

Photo by Brett Deering

A Battle That Never Ends

Renita Lewis fights lupus, which takes an outsized toll on African Americans

For most people, sunshine and warming temperatures serve as welcome heralds of summer. But for Renita Lewis, they can trigger life-threatening disease flares.

"People say, 'You look too good to be sick,'" says Lewis, 51, of Midwest City. But Lewis, a nurse, suffers from lupus, an autoimmune illness that strikes African Americans like her at disproportionate rates.

Lupus occurs when the immune system becomes unbalanced, leading to the development of antibodies and chronic inflammation that damage the body's organs and tissues. Sufferers experience periodic disease flares, affecting organs that can include the kidneys, lungs, skin and joints, as well as the cardiovascular system.

According to the Lupus Foundation of America, more than 1.5 million Americans suffer from the disease. Studies have found it strikes African Americans at roughly five times the rate it affects European Americans.

"We still have a great deal to learn about why African American women are at greater risk of lupus and at greater risk for major organ damage and early death from lupus than other races," says OMRF Vice President of Clinical Affairs Dr. Judith James. "We have investigators who are working on genetic and genomic factors, as well as our work which has focused on differences in the body's major defense system—the immune system. In all likelihood, it's probably a complicated combination of these factors, and we will keep working until we figure this out."

Lewis' first symptoms appeared when she was in her 20s: aching muscles, swollen fingers, skin rashes. But she wasn't diagnosed until a decade later,

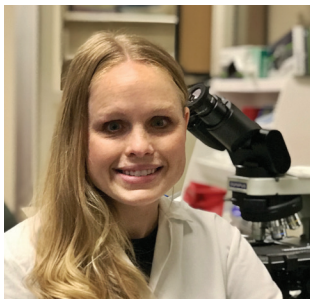
For information on treatment or participating in one of OMRF's studies or trials, please call 405-271-7745 or email clinic@omrf.org.

by which time she also suffered from shortness of breath, fatigue, asthma, stomach issues and inflammation around her heart. "I don't have kidney problems, but pretty much every other one of my organs is affected," she says.

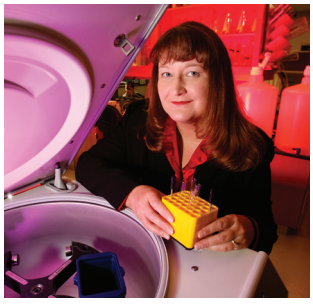
She began daily doses of prednisone, hydroxychloroquine, aspirin and anti-inflammatory medications to control her symptoms. Still, over time, lupus has exacted an increasing toll on her body. In March, after a bout of pericarditis—swelling of the membrane surrounding her heart—hospitalized her, she was forced to take short-term disability until she was well enough to return to work.

For more than a decade, physicians and clinical staff at OMRF, which has been named one of only 10 of the nation's Autoimmunity Centers of Excellence by the National Institutes of Health, have helped Lewis manage her condition. "They're on the cutting edge of research, especially on autoimmune disease, and they really care about me and want me to have as normal a life as possible," Lewis says.

As a lupus patient and a healthcare professional, Lewis recognizes the importance of participating in research studies on the disease at OMRF. "By donating blood and taking part in studies, I hope I can help researchers develop new treatments," she says. If scientists are able to understand why the condition exacts such a heavy toll on African Americans, "that would be a total game-changer."



Drs. Samantha Slight-Webb and Judith James



Renita Lewis and her daughter, Taraya

"I never want my daughter to go through this."

In a study published in May in the *Journal of Allergy and Clinical Immunology*, an OMRF research team led by James moved closer to answering this question. The scientists found that African Americans with certain risk factors for lupus had elevated activation levels in T cells, which are known to be important in lupus. Meanwhile, European Americans with similar risk factors did not.

That may be a reason at-risk African Americans are more likely to develop the disease, says OMRF's Dr. Samantha Slight-Webb, lead author on the study. And the findings could prove key to helping allay the suffering of patients like Lewis.

"Identifying this protective T-cell response could be pivotal in identifying therapeutic targets and potential drugs that may prevent people from transitioning into the disease," says Slight-Webb. "It would also help us look at drugs—and dosages—differently based on ethnicity to improve outcomes for African American patients, who are at highest risk for severe disease."

Lewis would welcome any findings that could help improve her quality of life. Still, she's more interested in developments that could benefit her daughter, Taraya, 19.

Lewis' only child, Taraya previously tested positive for antinuclear antibodies, or ANA, an indicator of lupus and autoimmune disease activity. Taraya also has several relatives on her father's side who suffer from lupus. "So, when she says she doesn't feel good, I worry," says Lewis.

Like all mothers, Lewis wants more than anything to protect her child. "If researchers could find a way to prevent lupus from starting, that would be a dream," she says. "I never want my daughter to go through this."

ASK DR. P

Old Drugs, New Tricks

Dear Dr. Prescott,

I worry about taking new medications for fear of unknown side effects. I see that we're starting to use older drugs in new ways more often these days. What are the advantages to this trend?

Larry Hawkins
Oklahoma City

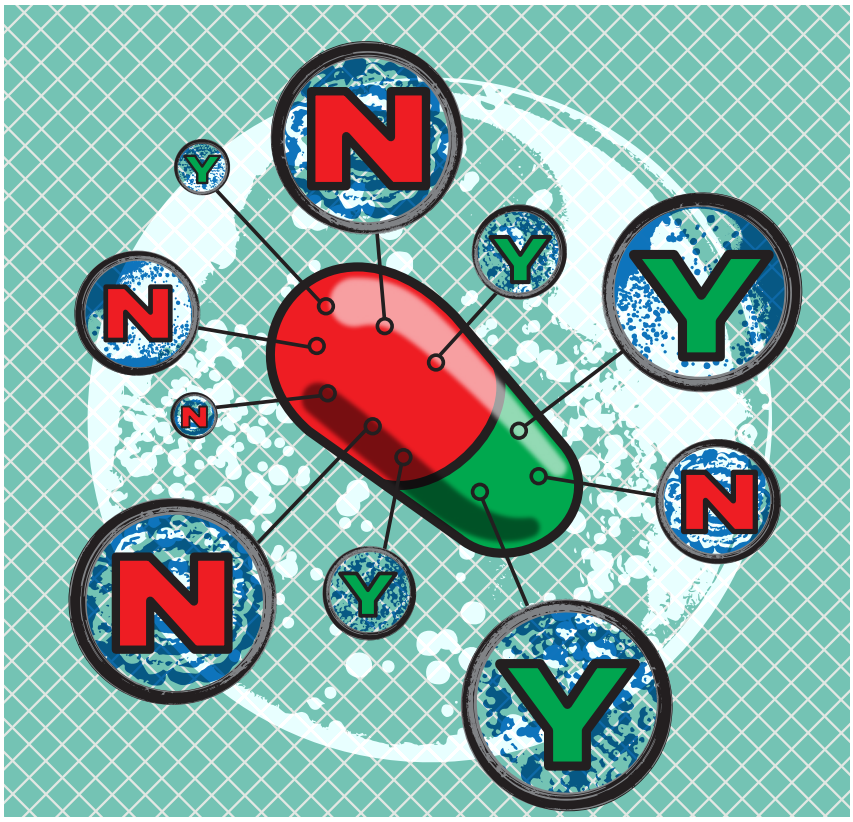


Illustration by Brad Gregg

Dr. Prescott Prescribes

Existing drugs are typically less expensive than medications that have recently arrived in pharmacies and clinics. This is because the modern research, development and testing process is considerably more complicated, time-consuming and, as a result, pricey.

Newer drugs don't yet have an extensive track record developed by use in clinical practice. But the Food and Drug Administration's approval process requires at least three (and, increasingly, four) phases of testing in which scientists monitor experimental medications for potential side effects. So, even if they have only recently become available to most patients, these drugs have undergone a years-long surveillance process.

That process, though, has involved a limited number of patients. So, when larger numbers of people receive the drug, new issues might emerge. And when scientists have more extensive pools of patient data to analyze, they might also find a pattern in adverse events previously thought unrelated to the drug.

However, I don't want you to think new drugs are dangerous. To the contrary, the medications we develop today are based on scientific understanding that was unthinkable even a decade ago. These therapies are not "blunt instruments" that physicians once used. Instead of hitting a swath of biological targets, their aim is laser-focused. As a result, this limits collateral damage.

While older drugs have been in use longer, the testing processes they underwent were much less probing. Indeed, the oldest drugs—those that came on the market before 1938—never received FDA approval. They were simply "grandfathered" in based on prior availability.

While we think of these drugs as safe, they often don't have the same rigorous testing history as newer entrants to the medical marketplace. As a result, when we repurpose (or, technically, reposition) them for use in new conditions, we can see unexpected or amplified side effects.

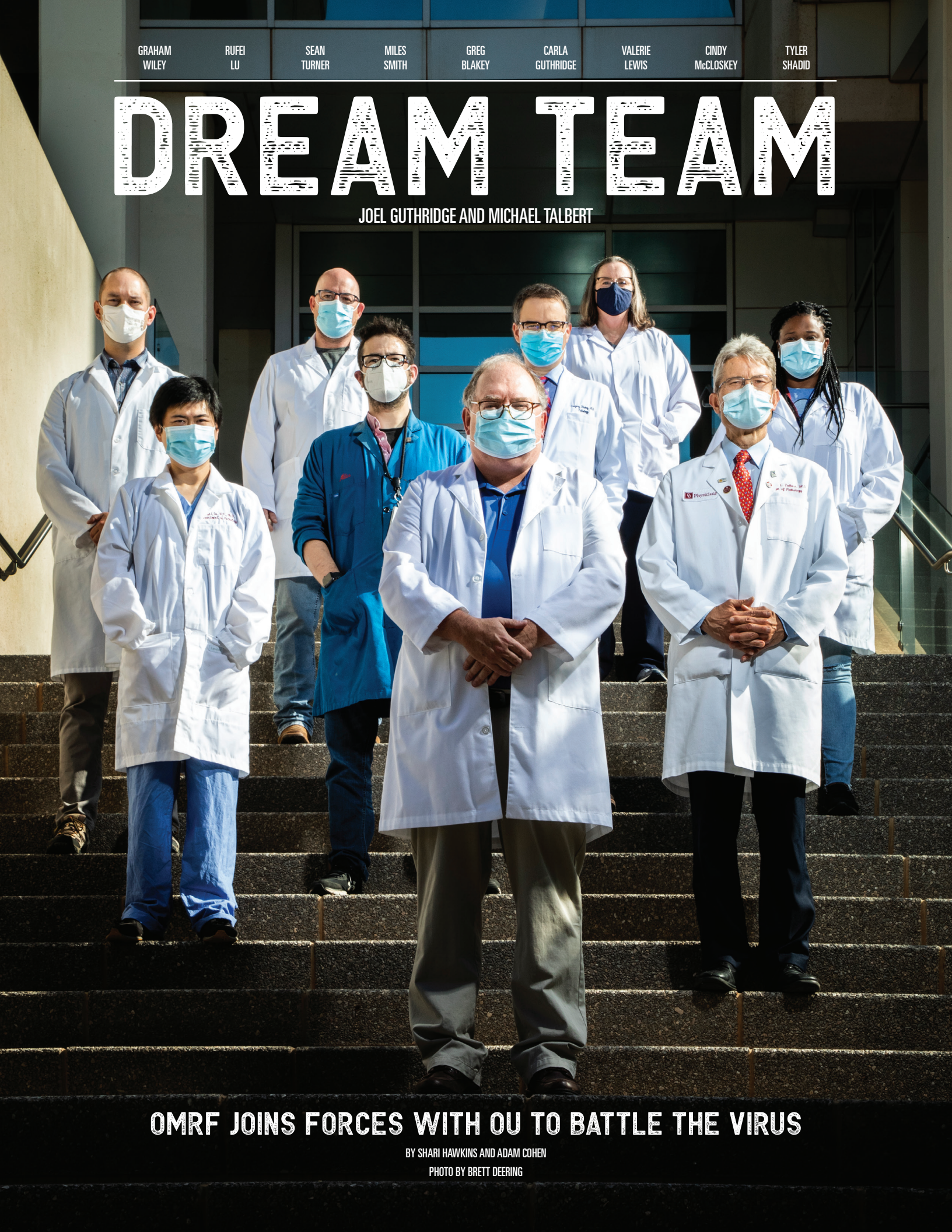
A case in point is the drug hydroxychloroquine. Doctors used it for more than a half-century as a treatment for malaria and, more recently, for autoimmune diseases like lupus and rheumatoid arthritis. But after physicians began prescribing it much more frequently as a potential treatment for Covid-19, the drug was tied to increased numbers of a potentially fatal heart arrhythmia. While hydroxychloroquine was considered generally safe in most patients, doctors now fear its potential to cause abnormal heart rhythms—a known risk—could prove especially dangerous for severely ill Covid-19 patients, who may have organ damage from the virus.

Legally, doctors can prescribe existing medications for "off-label" use as they see fit. Still, clinical trials represent the most effective way to test whether an existing medication might safely treat additional illnesses. As a patient, before I use any medication old or new, I feel best knowing it's undergone that process for the specific condition I'm suffering from.

I was always obsessed with science. I knew I wanted to be a physician, because I enjoyed seeing scientific concepts applied to improve people's lives. But my exposure to cutting-edge biomedical research as an OMRF Fleming Scholar helped me realize I wanted to be a physician-scientist. Research gave me an outlet to not only ask why but to learn how to answer questions that weren't known.

Dr. Lee Bockus

After his summer as a Fleming Scholar, Bockus earned an M.D. and also completed his Ph.D. studies at OMRF. Now a busy cardiology fellow at the University of Washington, he and his wife, Mia, also enjoy hiking, biking, scuba diving, spearfishing and kayaking.



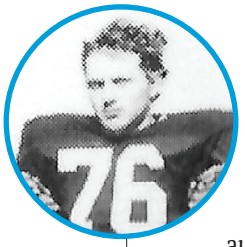
DREAM TEAM

JOEL GUTHRIDGE AND MICHAEL TALBERT

OMRF JOINS FORCES WITH OU TO BATTLE THE VIRUS

BY SHARI HAWKINS AND ADAM COHEN

PHOTO BY BRETT DEERING



Long before he ever set foot in a research laboratory, Dr. Joel Guthridge understood what it meant to be team player.

In the late 1970s and early 1980s, he strapped on pads as an offensive and defensive tackle on his Iowa high school football team. Listen to your coach. Practice hard. Come game day, you do your job—whether that means throwing a touchdown pass or, for Guthridge, battling in the trenches so your quarterback can make that winning toss.

But whatever that job is, you bring your A game.

Guthridge later transitioned from player to coach, using that team-first mindset as a mentor, judge and state tournament organizer for high school robotics competitions. "In robotics, everyone had a set of skills that had to be managed and focused toward a common goal," he says. "'Gracious professionalism' was our motto. Work and compete furiously, but graciously. In other words, work to better everyone, even your competition, because you could be competitors in one match and teammates in another."

Although Guthridge didn't know it at the time, those experiences would help prepare him for perhaps the biggest challenge of his scientific career: creating a dedicated, high-volume clinical testing laboratory for Covid-19.

On New Year's Eve 2019, Chinese health authorities confirmed they were monitoring a new and unknown virus. Within days, they announced the first death from the novel coronavirus in the Wuhan Province of central China. Japan, South Korea and Thailand soon reported cases, and in late January, a Washington state man exhibited symptoms after returning home from a trip to Wuhan.

The U.S. reported its first death on Feb. 29, and by mid-March, many Oklahoma businesses, including OMRF, issued work-from-home orders to employees. Schools closed, and restaurants and shops went dark as citizens hunkered down.

Like most Americans, Guthridge followed news on the virus known as SARS-CoV-2. A specialist in genetics and bioinformatics, he'd spent two decades studying lupus and other autoimmune diseases at OMRF. With the pandemic, Guthridge saw a way to help.

Scientists like Guthridge have used polymerase chain reaction, or PCR, testing equipment in their laboratories for years. First developed in 1984, the technology is the cornerstone for much of the genetic testing available today. With it, researchers can take a tiny DNA sample and amplify it millions of times, enabling them to identify even minuscule amounts of infectious agents.

PCR testing revolutionized forensic science and also allowed researchers to gather vast amounts of data from small quantities of sample materials. A special technique called reverse transcription PCR, or RT-PCR, added further power, enabling researchers to detect the presence of even a single particle of a virus deep inside a sample.

Guthridge had employed the process to study autoimmune diseases like lupus, multiple sclerosis and Sjögren's syndrome. Now, in the pandemic, he envisioned a new use.

"We knew we had technology that could be used, but it needed some adaptation to do large-scale clinical testing," says Guthridge. "We realized it was time to offer our assistance in the testing effort."

When the pandemic hit Oklahoma, the state had only minimal testing options available. In most labs with standard equipment on hand, technicians could only complete a few dozen tests per day. So, they limited testing to those exhibiting virus symptoms, those with a known exposure to the virus, healthcare professionals and first responders. As cases multiplied, health authorities realized things had to change.

"This was a major unmet need," says OMRF Vice President of Clinical Affairs Dr. Judith James, who worked with Guthridge to formulate a plan. "Everyone recognized we had to have more testing."

Guthridge also started talking with Dr. Graham Wiley. As director of OMRF's next-generation DNA sequencing facility, Wiley knew what it took to perform genetic testing on a large scale. Like Guthridge, he believed that scientists could employ "high-throughput" methods like RT-PCR to significantly increase testing capacity. "Talking about doing thousands of samples at a time didn't sound scary to me," Wiley says.

Guthridge, James and Wiley compiled spreadsheets with the equipment and supplies they'd need to process clinical tests. With those in hand, Guthridge and James reached out to the OU Health Sciences Center.

OMRF and OUHSC are neighbors; 13th Street separates the two campuses in northeast Oklahoma City. And while they're frequent collaborators, the two institutions can find themselves as competitors for grant dollars and philanthropic funding.

Here, though, any sense of rivalry disappeared. "We shared a single goal: to help Oklahomans in an unprecedented time of medical need," says OMRF President Dr. Stephen Prescott.

At OUHSC, Guthridge and James reached out to Dr. Michael Talbert, Lloyd E. Rader Professor and Chair of the Department of Pathology, to help lead the effort. They also enlisted Dr. Rufei Lu, a third-year pathology resident who'd trained at both institutions.

"Rufei was our secret weapon," says James, who heads OMRF's Arthritis & Clinical Immunology Research Program and also holds the Lou C. Kerr Endowed Chair of Biomedical Research at the foundation. "He's a computer whiz with a degree in chemical engineering. Plus, knowing OMRF's strengths helped make the collaboration possible."

Troubleshooting and brainstorming sessions helped Guthridge and his colleagues draw up a plan. They talked immunology and virology, but also engineering, robotics and logistics. Each team member brought unique skills. "None of us could tackle this challenge alone," says Guthridge. He acted as strategist, facilitator and organizer, a coaching role long familiar to him.

The team conferred with the Oklahoma State Department of Health and the Oklahoma City-County Health Department to organize the test flow.


Dr. Joel Guthridge

Both had already established drive-through testing centers around the state. The new OU Medicine lab would need to develop a system to collect the samples for processing and return the results to patients and healthcare providers. The faster the turnaround, the better to isolate and treat infected individuals—and to identify potential viral hotspots before they got out of hand.

Talbert, who also serves as chief of pathology and laboratory director for OU Medicine, identified empty space that could serve as the testing lab's home. Under his guidance, an OU Medicine facilities crew renovated the space to accommodate the personnel and specialized equipment the effort would require. "We made fast changes," Talbert says. "We even put up a wall in one day."

Then Guthridge turned to OMRF staff for the next part of the process: moving essential pieces of scientific equipment from the foundation to OU Medicine.

The centerpiece of the effort would be an RT-PCR testing system called the Fluidigm Biomark HD. Purchased by OMRF for $300,000, the Biomark would provide key advantages over testing platforms other labs were utilizing.

"WE SHARED A SINGLE GOAL: TO HELP OKLAHOMANS IN AN UNPRECEDENTED TIME OF MEDICAL NEED"

In the pandemic, labs were consuming unprecedented amounts of reagents, the chemicals needed to process tests. As a result, supply chains for reagents were drying up.

The Fluidigm system, though, relies on different reagents from standard PCR machines. And it employs a technology known as "microfluidics," minimizing the amounts of those reagents required to run tests. The Biomark also possesses the ability to process multiple samples at once, meaning that it holds the potential to deliver many times more results on a daily basis than a standard testing system.

"Think about microfluidics like a computer chip," says Mark Lynch of Fluidigm. "Back in the day, computer chips were massive. You couldn't have a laptop, only a desktop PC. What we've been able to do is take a laborious, time-consuming, labor-intensive process and automate it with a microfluidic chip."

Led by Guthridge, Wiley and Sean Turner, a lab manager at OMRF, the foundation's biomed staff powered down the equipment needed for the testing lab: the Biomark, another PCR processor, and other machines that would assist in the process. They swaddled everything in bubble wrap, and then—along with carts full of reagents, lab supplies and a new $35,000 robot OMRF purchased to accelerate the testing process—moved it to OU Medicine.

At OU, though, the team faced a challenge much greater than simply unpacking the equipment and plugging it back in. OMRF's Guthridge and his colleagues had used the Biomark to process and analyze biological samples donated by patients suffering from autoimmune diseases. Now, they aimed to transform it into the backbone of a high-throughput coronavirus testing lab that would run thousands of tests to diagnose the coronavirus each week.

"It was a completely novel idea to use the equipment this way," says Talbert, who oversees testing operations at OU that generate a total of approximately 5 million results each year. "No one had ever done this."

That meant reconfiguring and reprogramming equipment for its new use, then running batches of validation tests to ensure the results they produced were accurate. When data didn't pan out—as measured by Guthridge's exacting standards—the team readjusted the machines and retested. Again and again and again.

"In medical testing, you have to prove you can do it right, over and over." Wiley says. "Your mindset has to be methodical and thorough."

For weeks, the team lived this Groundhog Day-like existence, routinely pulling shifts of 12 hours or more. "They worked night and day, 7 days a week, and often didn't even know what day it was," says James. OU Medicine provided pathologists and staff for the new facility, and the team—which included OMRF's Guthridge, Wiley and Turner, plus Drs. Valerie Lewis, Miles Smith and Carla Guthridge (Joel's wife) and OU's Drs. Rufei Lu, Cindy McCloskey, Ken Jones and Greg Blakey, as well as Sarah Jonas-Bond, Tyler Shadid, Phil O'Neill, Leena Suppiah and Andrew Gross—trained them to operate the equipment.

Smith, a virologist, teamed with Lu and McCloskey, pathologists, to do much of "the heavy lifting in the viral lab," says Joel Guthridge. "They drove the science at many steps of the process."

As cases in Oklahoma kept mushrooming, the group felt increasing pressure to get the lab up and running. Still, even a single false negative could send an infectious person back out into the world, triggering a cluster of new cases. They had to get this right.

Wiley formulated a mantra of sorts that summed up the team's ethos: "Move fast, but don't be rushed."

While the team plowed ahead, across the street, OMRF remained in a state of suspended animation. Like many businesses, the foundation drastically altered operations with the arrival of the coronavirus. In mid-March, OMRF sent

Dr. Michael Talbert

most of its staff home to work virtually until cases in the state subsided. For the next two months, the foundation operated in what came to be known as "skeleton crew" mode, with only a handful of clinical staff and other personnel onsite.

Against this backdrop, few would have faulted employees who voiced a reluctance to join the effort to set up the testing lab. Especially because—in the midst of a life-threatening pandemic—the very nature of the work prevented social distancing.

"To move equipment, two people had to lift it together," Turner says. "We put protective gear on, always wore gloves, masks and disposable lab coats and kept hand sanitizer everywhere. We just tried our best." Still, he says, "If you're teaching someone else how to do something, they can't be six feet away. They need to see what you're doing."

Nevertheless, the team members didn't flinch.

"On a personal level, I felt like if I could help, I should," Turner says. "I was honored to be asked."

For Wiley, the decision to participate was really no decision at all. "I'm dedicated to OMRF's mission to help people live longer, healthier lives," he says. "So, when the call came to help, I stepped up."

Until recently, if a manufacturer wanted to utilize a novel clinical testing method, it first had to receive formal approval from the Food and Drug Administration. Scientists prepared reams of documentation demonstrating the accuracy of the test, and the FDA typically took almost a year to complete its review process. Even a designation of Priority Review, the fastest track available, only guaranteed the agency would render a decision within six months of submission.

Then came the coronavirus.

In February, the FDA created an Emergency Use Approval process for Covid-19 tests. This expedited track allows the release of novel Covid-19 tests—like the one Guthridge had devised—in just a fraction of that time.

On June 30, the OU-OMRF team filed its application with the FDA to launch the new testing operation. "We had to submit quite a bit of proof that the test actually works as we describe it," says Talbert. "In fact, we went beyond what they wanted."

In the wake of the filing, the team continued to make refinements. "Normally, we'd have about six months to prepare the lab, so there were issues we still needed to work out," Talbert says. Those included hiring and training additional laboratory personnel and, under the guidance of Carla Guthridge, integrating robotics into the process. Rather than requiring a pair of technicians to perform certain tasks, he says, "Now we only need one. It's a wonderful thing."

Although Talbert described the early days as "training mode," the operation continues to ramp up. Each day, couriers deliver samples collected at OU Medicine facilities and at "swab pods" in Oklahoma City, Tulsa and Norman. Technicians then prepare and load batches of samples, up to 186 at a time, into the Biomark, where each run takes about six hours.

During that time, says Guthridge, the machine tests each sample five times, which ensures accuracy. And because the Biomark utilizes RT-PCR technology, it has a high rate of "sensitivity," detecting infections other commercially available tests—especially the ones that deliver rapid results—can miss.

Most samples arrive in the afternoon. In a time when testing backlogs often force patients to wait a week or more to learn whether they have Covid-19, the lab typically reports results the following day. Sometimes, they're able to deliver results that same day.

Still, the team is not resting on its laurels. While continuing to fine-tune methods and add staff, Guthridge, James and Talbert are also looking for ways to supercharge the number of samples they can process in a day. Specifically, they're working on a concept called pooling, which would enable them to run four samples in the testing "wells" that currently hold one specimen. This change could quadruple the lab's daily testing capacity—without using any additional reagents.

In addition, the group is investigating the use of saliva samples instead of mucus to test. If successful, this could substitute a simple spit-in-a-cup for the current nasopharyngeal swab, an uncomfortable process subjects have described as akin to "getting poked in the brain."

Despite the fact that the collaboration arose in response to an unparalleled health crisis, Talbert says he can't help but describe the process of working with his OMRF neighbors as "amazing" and "fun." He's also got one eye to the horizon, hoping to find new projects that can benefit from their collective talents. There is, he says, "so much expertise to tap at OMRF."

James heaps praise on each member of the team and the respective institutions—OUHSC, OU Medicine, OMRF—that have made the effort possible. But, she says, others deserve credit as well.

"Our donors don't think when they're giving $20 or $40 in memory of a loved one that it's going to support cutting-edge science not done anywhere else in the world," says James. "However, without that kind of ongoing philantrophic support, this new testing facility wouldn't exist."

Like James, Guthridge is quick to credit a host of people for getting the lab up and running. "Please make sure to mention the work the biomed shop did in moving and recalibrating the equipment," he says. "And don't forget purchasing and accounting. They helped us get supplies in an environment where that was far from easy."

He keeps going, rattling off names and singing their virtues. Not once, though, does he mention himself.

Because, of course, there is no I in team. Every good coach knows that.


Illustration by Anna Heigh

The Mystery of MADISON

By Shari Hawkins & Adam Cohen

She was tiny with brittle bones and a body that rejected food. Could OMRF provide the answers a family desperately sought about their young daughter's unknown illness?

Some kids collect baseball cards. Others fill their shelves with stuffed animals. Madison Cain? She loves her beads.

A 7-year-old whose bubble-gum-hued glasses frame a cherubic face, she's decorated her bedroom walls with yards of beads in a riot of colors and shapes. She enjoys showing them off and, on occasion, donning them as necklaces or bracelets.

Some are green or blue. Others red, orange or purple. A few are larger than others.

She smiles and holds up a strand longer than she is tall. "I get different ones from different doctors," she says.

Every pea-sized memento represents a page of her medical history. The hospital that cares for Madison awards her these minuscule trophies as part of its "beads of courage" program. In an era where privacy laws lock down every imaginable tidbit of information about a person's well-being, the elementary schooler from Broken Arrow can literally wear hers on her sleeve.

Hundreds upon hundreds of tiny pieces of plastic and glass. Each standing in for an MRI or a blood draw. A stick with an IV needle. A visit to one of her many physicians. An X-ray. An infusion with a new medication. A surgery.

Already, in her young life, Madison had endured so much: broken bones, impaired mobility, cataracts, stunted growth, crippling digestive issues. Yet her doctors could find no answers.

Her case seemed like the beads, strewn across the floor of a child's room. Madison suffered from a mishmash of symptoms, with no ascertainable link or organizing principle. But, surely, there had to be something that made sense of it all.

Then, one day, one of her physicians found a study in a medical journal from a scientist at OMRF. The language was extremely technical, but Madison's mother—a nurse practitioner—did her best to decode it. And when she did, she had a powerful realization.

This, she thought, could be the string that pulls everything together.

Melissa Cain's pregnancy was uneventful. Although Madison was small at birth, no one voiced concerns. When, at 15 months, she seemed to stop growing, Melissa and her husband, Clifton, took their daughter to an endocrinologist. "They checked her heart and kidneys and did labs," says Melissa. "They finally said she was just small for her age."

But Melissa suspected something more was going on.

Madison lagged behind her peers in learning to crawl and walk. When she eventually started toddling around the house, her mother noticed a slight limp and an uneven gait. An orthopedic specialist diagnosed Madison with hip dysplasia, a condition where the joint doesn't function properly, leading to a cartilage breakdown and chronic pain.

Madison underwent surgery just after she turned 2, and doctors placed her in a cast that ran from her chest to her knees and immobilized both hip joints. Melissa did her best to keep the toddler occupied with wagon rides and lots of coloring and play time.

One day, as they played, Melissa noticed that one of Madison's eyes looked cloudy. In each eye, an ophthalmologist found cataracts, one so severe it rendered the eye sightless. Two operations removed the cataracts—and restored Madison's vision.

Despite extensive testing, her pediatrician could offer no insight as to why a 2-year-old might have issues with her bones and growth, along with an eye malady that typically strikes senior citizens. "Maybe science hasn't come far enough to know what's going on," the doctor told Melissa. "We'll just keep watching her."

Madison suffered from chronic constipation and didn't absorb nutrients from the food she ate, and she failed to potty-train. More lab work yielded little more than a bruised arm and beads for her collection. Despite a diet packed with calorie-dense foods like cream cheese and coconut oil, she couldn't seem to put on weight.

Melissa noticed a marked decrease in Madison's strength. Even after physical therapy sessions, she couldn't run or jump. She was falling behind on her motor skills, unsteady on her feet and failing to grow. At age 5, she tripped and suffered a complete break of both the large bones in her forearm.

Melissa grew desperate for answers. She scheduled session after session with specialists. To each visit, she'd bring a green, three-ring binder of Madison's

medical records. The notebook swelled as Melissa added new X-rays, MRIs and the results of every test and examination her daughter underwent.

"I got more and more assertive with doctors," she says. "My medical friends and I spent hours and hours looking up what was happening and scouring the internet." Still, "Everything we came up with, every result, said there was nothing we could do."

Madison couldn't stay awake in kindergarten. She was sleeping 14 or 15 hours a day. "She had zero energy," her mother says.

A pediatric GI specialist installed a port called a MIC-KEY in Madison's abdomen to enable extra feedings. "I'm a girl, so mine's a Minnie, not a Mickey," she says. Although regular doses of liquid packed with fats and sugars helped her gain a little weight, doctors still couldn't understand why her body continued to flush out the lion's share of those calories.

The GI specialist recommended that Madison undergo a specialized form of genetic testing. Known as exome sequencing, the technique isolates and analyzes that small part of the genome—less than 2 percent of the 3 billion nucleotides or "letters" that make up DNA—that tells cells how to build all the proteins in the body. It's in this precious real estate that errors leading to genetic diseases typically occur.

"Up until exome sequencing, you'd have to do other, less specific tests," says

Photo by Brett Deering

Madison Cain's short life has been marked by trips to the doctor, which has put the profession atop the 7-year-old's "what I want to be when I grow up" list.

Dr. Patrick Gaffney, who heads the Genes and Human Disease Research Program at OMRF. Even when those results pointed to a genetic culprit, physicians often could not be sure. "But with the advent of exome sequencing, you could conclusively identify mutations."

The test was a Hail Mary. It also wouldn't be covered by insurance. But the Cains saw no other path forward.

Madison's test results revealed that her genetic code differed from others' in one fundamental way. She had a mutation—an alteration—in a gene known as MBTPS1.

Melissa puzzled over this information. What, exactly, did it mean?

She asked a geneticist to review Madison's results. But even with her years of specialized training, the physician struggled to deduce their relevance. She'd never encountered this mutation in her years of practice. She scoured the medical literature to educate herself; all she found was a study involving a single patient who shared this same genetic mutation.

"There's one published paper on this," the geneticist told Melissa, "but it's not what Madison has."

When Melissa got home, she jumped on the internet and found the paper. Like most articles in scientific journals, its language rendered it borderline inscrutable. But having spent her career in healthcare, Melissa was more equipped than most to unravel it.

As she deciphered the jargon, her excitement grew. "I'd been waiting and looking for years," says Melissa. "It wasn't a perfect match, but I knew there was something to it, some connection."

She decided to email the scientist who'd written the article. When she found the author's contact information, she experienced another jolt. His lab was just down the Turner Turnpike, less than 100 miles away.

Dr. Lijun Xia treated patients suffering from blood disorders before joining OMRF to focus on medical research. In the lab, his interests expanded. In particular, he developed an expertise in the workings of a group of sugars known as glycans. These sugars seemed to play a key role in the function of certain enzymes at the heart of a mysterious condition afflicting Sydney Rutz, a Yukon girl.

Two of Xia's colleagues—Gaffney and Dr. Klaas Wierenga, a pediatric geneticist then at the University of Oklahoma Health Sciences Center—had sought Xia's help to get to the heart of Sydney's case. Like Madison, she suffered from bone deformities, cataracts and growth deficits. And she also had a mutation in the MBTPS1 gene.

Why would this genetic mutation cause Sydney's problems?

Xia wanted to help, but was going to have difficulty taking on the project. He leads OMRF's Cardiovascular Biology Research Program, where he oversees the work of more than 50 scientists and their staffs. As the Merrick Foundation Chair in Biomedical Research, he also has several National Institutes of Health grants of his own, none of which had anything to do with Sydney's condition.

However, as luck would have it, a new post-doctoral fellow had recently joined Xia's lab. With a freshly minted Ph.D. from Nagoya University in Japan, Dr. Yuji Kondo needed an assignment that would allow him to get his feet wet and familiarize himself with lab operations.

"We thought this would be a simple project," says Xia. "I estimated it would require a maximum of three months to finish." Instead, it took three years.

The project became more and more complex as it unfolded. Xia, Kondo and Dr. Jianxin Fu, another scientist in Xia's lab, discovered that Sydney's genetic mutation had caused a failure in the cellular machinery responsible for bone growth. The malfunction centered on collagen, a protein the body creates as one of the building blocks for bones and connective tissues.

For Sydney, "at the age of 6 or so, the bones accelerated their growth," Xia says. The body kicked into overdrive, producing more collagen. But because of the genetic mutation, her body couldn't utilize the collagen, which triggered a series of damaging cellular events. "As a result, she essentially stopped growing."

The scientists invited the Rutz family to OMRF to explain what they'd discovered about Sydney's condition. They told Sydney that, as far as they knew, she occupied a unique position in the world. She was the only person whose genes were this way.

"I'm special," she said.

The researchers explained that Sydney was so special they were going to write a paper about her. When they published it in the scientific journal *JCI Insight* in 2018, the paper created a new disease classification: spondyloepiphyseal dysplasia, Kondo-Fu type (or SEDKF).

When Melissa Cain discovered this paper in 2019, she emailed Xia. She explained that, like Sydney, Madison had

a mutated MBTPS1 gene and suffered from skeletal dysplasia. "If you are able to converse or share any information, I would be so grateful," she wrote. "We are willing to help in any way needed."

Xia responded immediately, inviting the Cains to OMRF. If Madison really was SEDKF patient number two, he needed to learn all he could about her. And he wanted to figure out if there was any way to help her.

Melissa clutched her green binder as she entered the conference room in OMRF's research tower, joined by Clifton, Madison and Madison's younger brother, along with both of the children's grandmothers. "This was a big deal, and I wanted to share the moment with our family, since it might have the potential to change Madison's care," she says.

She helped Madison climb onto the grownup-sized chair beside her. As they sat across from Xia, Gaffney and other scientists who'd worked on Sydney's genetic mutation, Melissa told her daughter's story. Xia and Gaffney asked lots of questions and scoured the medical records Melissa had brought.

"Once you see the patient, you see the need, and it makes you think how your research can solve the problem."

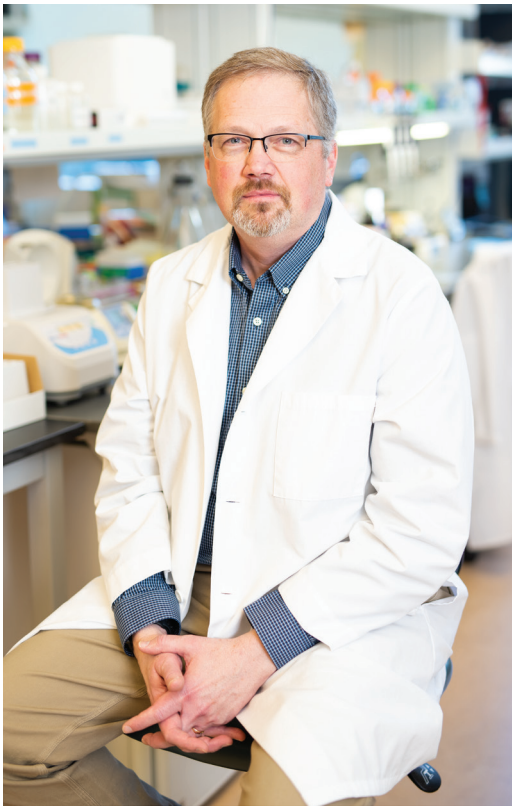
When the kids grew restless, the grandmothers took them to OMRF's cafeteria so they could play and wait for the grownups to finish talking. Before long, Xia and Gaffney accompanied Melissa and Clifton to the cafeteria to take a closer look at Madison. The pair sat with Melissa and her, asking questions about her legs, her eyes, her abilities. They analyzed her gait, her balance, her strength.

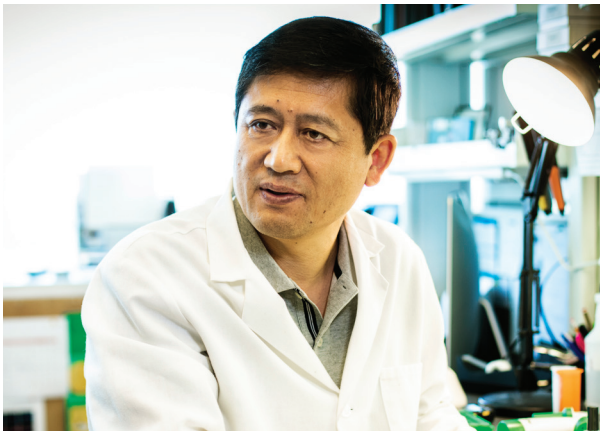
"Talking to patients, with that physical exam and conversation, is one of the most important things you can do," says Gaffney, who holds the J.G. Puterbaugh Chair in Medical Research at OMRF. "That's where you really learn a lot more than lab test values show."

But, as scientists, they need lab tests, too. In OMRF's clinic, a nurse drew blood from Madison, her mother and father. Gaffney, Kondo and Xia would then analyze those samples, doing a deeper dive to understand precisely how Madison's genetic makeup differed from her parents, and why that might matter.

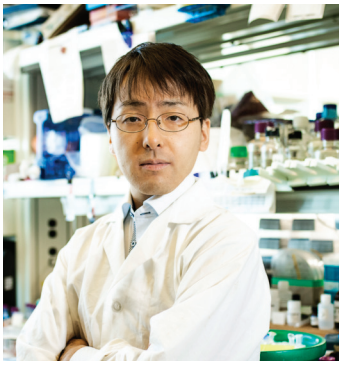
That bloodwork would represent a key component to Xia's understanding of a condition that, until he'd met Madison, he'd believed was unique to Sydney. That personal encounter—putting a face and a beating heart to a set of symptoms—can make all the difference to a scientist.

"You work in a lab with mice and test tubes, and sometimes you forget the real need. You sort of become desensitized to the real problem," says Xia. "But once you see the patient, you see the need, and it makes you think how your research can help solve a real problem. It gives you more motivation."





Dr. Lijun Xia (right) worked with fellow OMRF researchers Drs. Yuji Kondo (lower right) and Patrick Gaffney (left) to solve the genetic riddle at the heart of Madison's condition.



Melissa Cain has assembled a bulging notebook of medical records that she takes with her to all her daughter's doctor's visits, each of which yields a new "bead of courage" for Madison's collection.

With genetic diseases, he says, the need for therapies is especially profound. "These patients will live with their conditions for life." And because they can pass from parent to child, these illnesses can haunt families for generations.

Xia knew that he had his work cut out for him.

Since that day at OMRF, Xia's research paper has helped identify more SEDKF patients, with physicians, families and researchers reaching out to him. "Last year, we only knew of two: Sydney and Madison," he says. "Now we have confirmed eight cases—from Germany to Brazil to San Francisco and beyond—and we're working to confirm even more."

Xia has launched a website for physicians and families to use as a resource. He's also assembled a working group of scientists and physicians to review case information as it arrives. Misdiagnosis of rare diseases is common, he says, and often triggers the wrong treatment. It can also lead to severe complications, so the more information he and his colleagues can gather and share, the better.

"We've come together to try to see if we can identify more patients with this same genetic problem in the gene," says Gaffney. "Our work has expanded to more than one gene. We're now looking at a molecular pathway, and that's blossomed out of some detective work and publicly available papers."

At first, Sydney seemed unique. "But Madison was one of the first to make us think this might not be that rare," Gaffney says. "Now we might be able to create a database, and that could be the first step toward a clinical trial."

Xia would like to test an existing medication he believes—based on work he's done in his lab at OMRF—might help SEDKF children like Madison. But, he says, "Trials aren't cheap. We're probably talking about $1 million at minimum to start."

To generate statistically reliable results, the trial would need at least 20 patients to participate. That means finding more cases. The fact that the handful of identified cases are spread around the globe presents further logistical challenges to organizing a clinical trial.

Although Xia thinks the therapy currently on the market could improve bone development in young SEDKF patients, he doesn't believe physicians should prescribe the drug until scientists can assess its efficacy and safety in those children in a rigorous, controlled way. "We'd like to treat them right now, but we can't," he says.

He knows that means Madison and her family must wait. But, he says, it's too dangerous simply to give her a drug that hasn't been tested in her condition and see what happens. "We have to do clinical trials first."

Photos by Brett Deering

"It's a relief not trying to piece things together anymore. It really helps emotionally."

Madison's diagnosis has led to a friendship with Sydney Rutz, who carries the same rare genetic mutation.

In the meantime, Madison has been receiving infusions every three months with a drug to help improve her bone density. These IV treatments had initially proven quite challenging.

"At first, she kind of lost it," says Melissa. "So then, she'd sit in my lap, and I'd help hold her down." But at her most recent visit, Madison volunteered to sit in the infusion chair all by herself. Each time Melissa asked her daughter if she should come over and help, Madison shrugged her off. "She sat there for the whole time, no problem," says Melissa. "That was a big accomplishment."

This past fall and winter, though, Madison grew chronically listless and fatigued. She suffered from prolonged bouts of vomiting, forcing her to miss dozens of days of school. Finally, following a battery of tests and several months of struggles, her physicians uncovered a bacterial condition, which they successfully treated with antibiotics and probiotics.

As she recovered, Madison began to seem her old self, regaining energy and weight. By the end of the school year, she weighed 44 pounds—a half-dozen more than when she'd begun. She'd also grown to 3 feet, 6 inches tall, adding an inch over the course of the year. "So, she's still growing!" says Melissa. "We got really excited about that."

Madison spent a lot of the summer at her grandmother's pool, swimming with her younger brother, Maddux. (While nearly three years younger, he is now taller than his sister.) The two of them like to play Monopoly Jr. and eat ice cream and popsicles.

Madison is excited to get back to school. She's about to turn 8 and will be a second grader at Anderson Elementary in the Tulsa Union district. However, with the pandemic and possibility of virtual attendance, there's no telling how long before she'll get to enjoy her favorite part of school: joining her best friend on the playground at recess.

In the past year, Madison has realized she's different from other children. "She

knows that not all kids have tube feeds, go to infusion therapy, and can't run," says Melissa. "But it doesn't seem to bother her." So, the Cains are doing their best to enjoy the moment.

"Right now, she's not isolated from her peers. They don't seem to notice," Melissa says. "When she hits her teenage years, that's going to change."

As they imagine their daughter's future, Clifton and Melissa worry about disease progression, too. "At some point is Madison not going to be able to walk without assistance?" Melissa wonders. Will she eventually need hip replacement? Knee replacement? "We don't know exactly what this looks like."

However, they have accepted a hard truth: "She's never going to be completely independent. She may always need some help from us."

Still, receiving a diagnosis has made a big difference. "It's given us a certain element of peace," Melissa says. "Now I don't feel like there's this huge thing we're missing." No longer must she play medical detective. "It's a relief not trying to piece things together any more. It really helps emotionally."

That diagnosis has also brought another, unexpected benefit—a new friend for Madison.

With Xia's help, the Cains connected with the one family in Oklahoma who could understand what they were going through: the Rutzes. Since then, the two families have gotten together on several occasions, and Sydney—now 14 and an incoming freshman at Yukon High—has taken Madison under her wing.

"Sydney is so sweet to Madison," says Melissa. And, she says, that friendship has helped Madison recognize something about herself. "I think she understood much more about her condition once she met Sydney. She was able to identify a person who was like her," Melissa says. "Even at her young age, she knows she is the smallest person in her grade and does not physically keep up with people. Sydney shares that with her."

Knowing she is not alone, says Melissa, will help Madison. And watching as Sydney navigates the obstacles of teenage life, like driving and high school, will provide a preview of what lies ahead for Madison.

"Mary"—Sydney's mother—"wants Sydney to be an independent person," says Melissa. "We want the same thing for Madison."

To that end, the Cains have done their best not to shelter their daughter. "We basically let Madison do what she wants to do," says Melissa. "Now, we may not let her climb to the top of something. But we try to keep her daily function as normal as possible."

That normal still involves many trips to see different doctors. But, with each trip, there's an upside: more beads for Madison's collection.

Not long after her visit to OMRF confirmed Madison's SEDKF diagnosis, she received some new ones. "They're my favorite," she says.

Unlike her others, these beads are designed to be strung in a specific order. And when they are, they reveal a key piece of information about the little girl who treasures them.

They spell M-A-D-I-S-O-N.

Melissa and Clifton Cain both carried recessive mutations in a gene that led to Madison's condition, but her brother, Maddux, didn't inherit that mutation.

Photos by Brett Deering

Broadcast News

Amidst the pandemic, OMRF scientists work with the media to ensure the public receives reliable health information

Dr. Stephen Prescott had received standing ovations before. Just not on the set of a local morning news show. And not from the production crew who had just filmed his appearance.

"It was pretty unexpected," says OMRF's president. "But then again, we were navigating a landscape that was all new to us."

Earlier that week, Prescott had been booked as a Thursday morning guest on the Oklahoma City ABC affiliate, KOCO. He'd already made a similar appearance at the beginning February to talk about the new virus that had appeared in the U.S. It was now the second week in March, and producers had asked him back for further on-air discussion as the virus starting taking hold across the country.

The night before Prescott's appearance, the Oklahoma City Thunder abruptly cancelled their game at the Chesapeake Arena with the Utah Jazz. A few hours later, the National Basketball Association suspended its season after announcing that Jazz forward Rudy Gobert had tested positive for SARS-CoV-2. This news confirmed what state health officials had for months dreaded: The coronavirus had arrived in Oklahoma.

When Prescott came onto the set next morning, he sat down on a studio couch across from anchor Maggie Carlo. Unlike in previous appearances, there was no handshake, only an elbow bump. After calling Oklahoma City "ground zero" for the coronavirus in light of the NBA's cancellation, Carlo proceeded to quiz Prescott about topics that would soon become second nature to him: viral spread, precautions, travel and quarantine.

Although guests are usually ushered from the set once a commercial break arrives, Carlo asked Prescott to stay for another segment, during which he fielded questions from viewers. "The virus had been on the edge of many people's consciousness for a little while, but now there was no disputing it was here. And, understandably, that rattled just about everybody," says Prescott.

When the interview finished, Prescott rose to leave the set. As he did, the camera operators, sound technicians and on-air personalities all rose—and applauded. "It was touching," Prescott says. "It really hammered home how much people appreciated the access to reliable medical facts and guidance in a time of such uncertainty."

In the months that followed, Prescott and other OMRF scientists would make scores of similar appearances on local news stations. Dr. Eliza Chakravarty, who did almost two dozen interviews for various coronavirus stories, believes she and her colleagues play a crucial role as honest brokers of information during health crises in today's world. "These days, the media is full of all sorts of 'information' with relative degrees of veracity that makes it extremely confusing for non-scientists to understand," she says. "It's important that scientists take the time to review the actual data, distill it down so it's more easily understandable, and then work with the media to make it available to the public."

In addition to local media, OMRF scientists appeared in national outlets like *Vice* and *The Los Angeles Times* and also fielded inquiries from *CBS This Morning* and *The Wall Street Journal*. On the eve of President Donald Trump's campaign rally in Tulsa, Prescott appeared live on CNN's *Anderson Cooper 360*, discussing the wisdom of packing thousands of people into an indoor arena as new cases surged in Oklahoma.

"It's important that scientists take the time to review the actual data, distill it down so it's more easily understandable, and then work with the media to make it available to the public."

Meanwhile, Chakravarty, an immunologist and rheumatologist, spoke with news outlets about topics that ranged from evolving guidance on mask-wearing to President Trump's use of hydroxychloroquine, a drug she uses to treat her lupus patients. "The media helps to come up with the relevant questions folks are worrying about, and we can help with the answers as best we know them." With a never-before-seen virus, she says, delivering those answers in real time can help people adapt behaviors as our understanding of the virus grows and changes. "I worry when information or predictions about the virus or treatments or timelines is presented as absolute. That's just not how biological science works."

Although social distancing has brought numerous downsides, Chakravarty, for one, was glad when news stations pivoted from in-studio interviews to using Zoom to talk to her from her home. "It removes the driving time to the studio and then waiting for the segment." Instead, she can keep working on grants and publications until moments before going live on camera.

Plus, she says, "I can have plenty of Diet Pepsi and snacks right off camera for reinforcement. And wearing sweatpants instead of a skirt and heels is always a bonus."

Illustration by Chris Gash/Brian Taylor

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Groundbreaker

Marguerite DeVonne-French became the first Black member of OMRF's Sir Alexander Fleming Scholars Program in 1957, the second year of the foundation's summer science initiative. She and her fellow scholars appeared on NBC's Today Show, where they met another guest: President Dwight D. Eisenhower. French went on to earn her M.D. and practice psychiatry in Kansas City, Mo., but she returned to OMRF in 2016 to celebrate the Fleming program's 50th anniversary with fellow alumni like Dr. Clarence Wiley (Fleming '68).