BREAKTHROUGH STUDY DELAYS T1D

Megan and Madeline Coder are twins who do everything together — like dancing and even raising sheep in their hometown, Battle Ground, Washington. But in the fall of 2014, when Megan was nine, she learned she had something that Madeline didn’t: type 1 diabetes (T1D).

“My mom has T1D and my sister died from T1D complications in her early 30s,” says Keri Coder, Megan and Madeline’s mom. “The T1D tools have gotten a lot better, but it was still scary when Megan was diagnosed — I couldn’t stop checking on her at night.”

Megan’s doctors recommended that her brothers and sisters get tested to see if they might develop the disease. Of the nine siblings, only Madeline had biomarkers that showed she would almost certainly get T1D. Fortunately, the Coders also learned that Madeline could join a clinical study — led by TrialNet and involving Benaroya Research Institute at Virginia Mason (BRI) — of a drug called teplizumab that could potentially slow T1D down.

This study made a breakthrough earlier this year, when TrialNet and concurrently published in the New England Journal of Medicine.

“We’ve believed that delaying T1D was possible for decades, and we finally found a way to do it,” Dr. Greenbaum says. “It’s a step toward delaying T1D for longer, and hopefully preventing it altogether.”

SLOWING ATTACKS

The teplizumab study is part of BRI’s decades-long push to predict, prevent and cure T1D. One key milestone came when data from TrialNet’s Pathway to Prevention study and studies like it identified the biomarkers that show a person will likely get T1D. The next step was finding ways to slow it down.

Teplizumab intrigued Dr. Greenbaum’s team after studies showed it could slow disease progression in those who already had T1D. The researchers wondered: Could it also help

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AIMING FOR BETTER LUPUS TREATMENTS

A few months before Toni Grimes was set to deploy to Iraq in 2007, she went out on the town with her cousin. The following morning, the Army major woke up short of breath and barely able to talk.

“I couldn’t get up,” she says, “I had to text my cousin, who was just three bedrooms away, to rush me to the hospital.”

Toni had been diagnosed with lupus a few weeks earlier, but her symptoms had been mild. Now the disease had caused so much fluid to build up around her lung that it collapsed.

“The day I went into surgery, my unit deployed to Iraq,” she says.

Toni was cleared to go to Afghanistan five months later. But her lupus got worse, ultimately causing her to retire from the military after more than 19 years.

Toni isn’t alone. Veterans and military members, especially women of color, are more likely to have lupus than the general public — possibly because they’re exposed to toxic chemicals, stress and PTSD. That’s why the U.S. Department of Defense (DOD) funds lupus research — and why it awarded grants to BRI’s Karen Cerosaletti, PhD, and Adam Lacy-Hulbert, PhD in 2018. The researchers are studying genes that play a role in lupus and are gaining insights that could improve treatment.

“We’re learning more about how and why lupus starts,” Dr. Cerosaletti says. “This will help us know who is most likely to get it so we can diagnose it sooner and develop better treatments.”

BLOCKING GENES

Dr. Lacy-Hulbert thinks that a gene called ATG5 is a promising target for new lupus therapies.

Immune cells protect us by hunting down bacteria and viruses. Dr. Lacy-Hulbert’s team found that cells that lack ATG5 never stop attacking. Eventually, they aim at healthy cells and cause lupus.

Dr. Lacy-Hulbert thinks it might be possible to stop these attacks by using medications to reactivate ATG5 and other genes. This could switch off overactive immune cells.

“This is helping us understand the mechanisms that cause lupus and moving us toward better, more personalized treatments,” he says.

NEW THERAPIES

Dr. Cerosaletti has identified a different gene involved in lupus: BANK1. This gene plays a role in immune cells called B cells. Many B cells make tiny proteins called antibodies, and some of these antibodies attack healthy cells, causing lupus.

Dr. Cerosaletti has shown that BANK1 may increase the number of B cells that make antibodies, especially in people with lupus who have a particular BANK1 variant. She is using her DOD grant to study how BANK1 spurs B-cell growth — planning to eventually test drugs that could block this process, to slow or even prevent lupus.

Toni Grimes served in the Army before lupus derailed her military career.

Karen Cerosaletti, PhD, and Adam Lacy-Hulbert, PhD

Toni has a new mission: helping people with lupus by running support groups and advocating for research funding.
“There’s only one drug that was developed specifically for lupus,” Dr. Cerosaletti says. “This research could open the door to more treatments that help more people.”

HOPE FOR A CURE

Toni is all too aware that there’s only one drug developed for lupus, because it doesn’t work for her. That’s why her new mission is helping others who have the disease.

“In the military, you always have a purpose,” she says. “Now lupus is my purpose.”

Toni leads a lupus support group in Arizona, advocates for research funding and sits on the DOD’s Peer Review Panel for lupus research.

“The people developing these drugs might not think about how a drug that causes hair loss would impact a 20-year-old, or that a medication that causes weight gain might cause a middle schooler to get bullied,” she says. “The panel lets patients like me voice these concerns.”

The DOD-fueled research gives Toni hope.

“I’m excited that there will be better treatments in my lifetime,” she says, “and maybe even a cure.”

USING VR TO SEE INSIDE CELLS

In 2016, two of BRI’s information technology experts — Garrett Wright and Tom Skillman — had a conversation that sparked a novel question: Could virtual reality (VR) headsets let scientists step inside cells and view them in greater detail than ever before?

Bill & Melinda Gates Foundation and a partnership with Yongxin (Leon) Zhao, PhD, at Carnegie Mellon University (CMU).

“This VR tool will give us new insights into autoimmune diseases, infections and more,” Dr. Stefani says, “and we’re working to make it accessible for scientists everywhere.”

BETTER THAN MICROSCOPES

Looking at cells using traditional microscopy is like looking at a 2D aerial picture of a city while knowing the city has actual 3D streets to walk on. Using the new VR software, called ConfocalVR, scientists can visually step inside tissues and cells and see things they never saw in 2D.

“We have scientists who’ve been studying the same types of proteins for 40 years, and they’re blown away when they see them in VR,” Dr. Lacy-Hulbert says.

GATES FOUNDATION GRANT

The grant and partnership arose from Skillman and Dr. Stefani presenting their software at the 2018 Grand Challenges Annual Meeting (GCAM) to the Gates Foundation and other members of the global Grand Challenges community. Scientist GCAM attendees were invited to view their own data in VR. The technology intrigued CMU’s Dr. Zhao — who has been pioneering his own brainchild, called expansion microscopy.
Right now, light microscopes can only zoom in so far before an image gets blurry and grainy. This means it’s hard to study especially tiny features of cells, particularly features of microbial cells — those that come from bacteria and other invaders. To overcome this, Dr. Zhao started using a special gel to expand microbial cells to 100 times their actual size (picture an ant becoming as big as a rhinoceros).

“This is the future of complex imaging,” Dr. Zhao says. “It’s like watching a movie in IMAX versus watching it on your phone.”

GLOBAL IMPACT

BRI is already sending cells from our biorepositories to CMU. Dr. Zhao’s team enlarges them, tags key proteins with different colors, and scans them using a special 3D microscope. Then CMU’s team sends the digital image data back to BRI for analysis.

Our team will use software being specifically developed for this project to accelerate our understanding of this data using VR.

Researchers on the frontlines of infectious disease research in Africa could then upload their data and examine it in real time with other experts around the world.

“This tool could help scientists everywhere,” Dr. Stefani says. “And it all started because BRI believes in collaboration and encourages scientists to pursue outside-the-box ideas.”

THE POWER OF PARTNERSHIPS

The VR collaboration with Carnegie Mellon is just one example of how BRI is teaming up with other top organizations to pursue discoveries. Here are two more of our latest partnerships:

**Allen Institute for Immunology**

BRI was invited to join a national research endeavor, led by the new Allen Institute for Immunology, that maps out how the immune system works. Our role is to create a detailed portrait of what a healthy immune system looks like. This baseline will help reveal how immune disorders develop.

**Parker Institute for Cancer Immunotherapy**

Jane Buckner, MD, is a principal investigator on a $10 million initiative to study diabetes in cancer patients who receive immunotherapy. This could shed new light on how type 1 diabetes develops, and on how T cells contribute to autoimmune disease.
people who don’t have the disease yet?

TrialNet recruited 76 people who were on track to develop T1D, including Madeline. She and her mom spent two weeks in Seattle, where Madeline received an infusion of teplizumab every morning. Then the pair spent the afternoons exploring the city.

Researchers found that those who received teplizumab were diagnosed with T1D a median of two years later than participants who received a placebo.

“It’s great that this drug can delay diabetes, and it also shows that we can treat people before they get the disease,” says BRI President Jane Buckner, MD. “This helps us make the argument for treating T1D earlier and opens the door to new trials that try to prevent it.”

THE NEXT FRONTIER

Madeline was eventually diagnosed with T1D but, not until she was 12 — three years after her sister.

“It’s a gift to people like Madeline because they can spend less of their lives managing T1D,” Dr. Greenbaum says.

Madeline and Megan are high school freshmen now, and they work together to manage their T1D.

“We check on each other and help each other — and that helps us be more independent, together,” Madeline says.

Still, both girls are excited about research that could make life easier for people like them.

“It gives me hope that if I ever have kids and they get diabetes, there might be a cure,” Megan says.

For BRI researchers, the study proves they can slow down immune attacks that trigger T1D — which inspires them to apply these findings to other areas of research.

“This discovery pushes us to ask the same questions about other diseases: Can we predict who will get multiple sclerosis or RA? Could we prevent them altogether?” Dr. Buckner says. “We’re going to keep pushing to answer these questions, and we won’t stop until we make our vision of a world without autoimmune disease a reality.”

Dr. Greenbaum encourages those who have a relative with T1D to get screened and see if they’re eligible for clinical trials. Learn more at Trialnet.org or by emailing Diabetes@benaroyaresearch.org.
2019 WALK TO END LUPUS NOW
What: Help end lupus by supporting the Lupus Foundation of America, which is devoted to solving the mystery of lupus.
When: Saturday, Sept. 21 at South Lake Union Park
Learn More: www.lupus.org

SAVE THE DATE: ILLUMINATIONS LUNCHEON
What: Learn how your gifts are helping accelerate progress against autoimmune disease and allergies.
When: Friday, November 8 at Sheraton Grand Seattle
Learn More: BenaroyaResearch.org/bri-events or call 206-341-0112

JINGLE BELL RUN TO END ARTHRITIS
What: Be part of the longest-running holiday-themed 12K/5K race series anywhere — and help conquer arthritis!
When: Sunday, Dec. 8 at Westlake Park
Learn More: www.arthritis.org