FINE-TUNING IMMUNE CELLS TO STOP DISEASE

To understand what causes type 1 diabetes (T1D), imagine a spy novel. It starts with a hero, the T-cell, that roams your body like James Bond. The T-cell hunts down enemies — bacteria and viruses — and snuffs them out. Then something goes terribly wrong: The hero becomes a villain.

Like a double agent, T-cells can turn against your body and attack your pancreas, triggering T1D. It keeps attacking, methodically destroying your ability to produce insulin and control blood sugar. Your T1D becomes ever more debilitating.

Fortunately, there’s hope: One of BRI’s real-life heroes, Alice Long, PhD, is moving closer to a therapy that makes the enemy T-cells so exhausted they surrender. “We think it could be possible to make the T-cells say ‘we give up, we’re too tired to keep attacking the pancreas,’” Dr. Long says. “That could slow down T1D or maybe even stop it.”

This approach of manipulating T-cells to stop disease could extend far beyond T1D. That’s why Dr. Long is teaming up with other researchers, including BRI President Jane Buckner, MD, to study the machinery inside these cells more closely than ever before.

“T-cells like this one turn against the pancreas in people with T1D. Dr. Long is pursuing therapies that could exhaust these cells and stop the disease.”

“This could reveal ways to dial T-cells down to stop autoimmune disease or dial them up to attack cancer,” Dr. Buckner says. “It’s a new frontier of immune research, and BRI is excited to be at the forefront.”

T-CELL DISCOVERIES

Dr. Long has dedicated her career to finding better therapies for people with T1D. The best available treatment is to inject insulin. Even then, T1D increases the risk of serious health issues like heart disease and stroke.

“There’s a desperate need for therapies that protect the pancreas so it can keep producing natural insulin, because that helps people with T1D stay healthier and have fewer complications,” Dr. Long says.

Dr. Long believes that understanding a phenomenon called “T-cell exhaustion” could unlock these therapies. Several years ago, researchers discovered the body is home to exhausted T-cells, which are alive but have stopped attacking. Everyone has these exhausted cells. But subsequent research showed that

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Viruses like COVID-19 infect you by entering your cells. Then they trick your body into making virus copies. These copies spread through the body and make you sick.

A research team including Dr. Lacy-Hulbert, Anna Bruchez, PhD, and Lynda Stuart, MD, PhD, recently used an innovative method to study how COVID-19 infects your body. They found that some genes can put protective armor around your cells that traps the virus and makes it impossible to infect you. Turning on those genes could be a promising new way to fight off COVID-19 and other viruses. Their findings were recently published in Science, a prestigious academic journal.

“IT could be possible to develop a drug that turns on these genes so the virus can’t infect you,” Dr. Lacy-Hulbert says. “This approach doesn’t just work for COVID-19 — it works for Ebola and SARS too.”

TRAPPING THE VIRUS IN A BUBBLE

When the pandemic started, Dr. Lacy-Hulbert’s team wanted to see if an approach they’d found to curb other viruses might also work for COVID-19.

The researchers knew that viruses make you sick by inserting their genetic code into your cells. Viruses then trick your body into making a bunch of virus copies, which enables them to travel through your body and make you sick. But the team learned that a handful of cells don’t get infected: Viruses enter these cells, but they have an armor-like coating that traps them inside.

“The virus is basically trapped in a bubble,” Dr. Lacy-Hulbert says. “It can’t inject its genetic code or replicate. Eventually, your immune system clears those cells out and you never get sick.”

A VIRUS’ ACHILLES HEEL

In the early 2010s, Dr. Lacy-Hulbert’s team developed a novel screening technique to study Ebola. They learned the deadly virus had an Achilles heel: A gene called MHC class II transactivator (CIITA).

USING GENES TO FIGHT COVID-19

Viruses like COVID-19 infect you by entering your cells. Then they trick your body into making virus copies. These copies spread through the body and make you sick.

Some cells have a gene that builds an “armor” that traps the virus inside them. This prevents the virus from copying itself and spreading.

BRI researchers found that turning on this gene can trap the virus and stop it from making you sick. This could inform a new way to treat COVID-19 and other viruses.
The research team’s next steps are to run a more comprehensive screening, looking at millions of cells infected with COVID-19. They hope this will help them find additional genes that may help protect against the virus.

“The more we know about how viruses infect cells — and the more we learn about how to block those infections — the better we’re equipped to fight this virus and others,” Dr. Lacy-Hulbert says. “We hope our insights will open up new avenues to help solve this pandemic and to treat viruses that impact people around the world.”

BRI HELPS LEAD COVID-19 VACCINE TRIAL

BRI researchers are part of a nationwide team of experts leading the Pfizer COVID-19 vaccine trial. The study has enrolled over 44,000 participants with a goal of developing a vaccine that’s safe and effective for everyone.

BRI WELCOMES GENETICS EXPERT

John Ray, PhD, became BRI’s newest principal investigator on September 30. He comes to us from the Broad Institute of MIT and Harvard. His work focuses on how genetic variants turn the body’s immune system against itself.

“We all have genetic variations, which contribute to the wonderful diversity among people,” Dr. Ray explains. “But some variants lead to disease. If we can identify those, we can develop new, targeted therapies for diseases like lupus and rheumatoid arthritis.”

Dr. Ray joins our Center for Systems Immunology, which uses genomics and data analysis to identify factors important in immune system diseases such as autoimmunity. His first experiments will help find the genetic variants behind five autoimmune diseases. Of about 20,000 genetic variants associated with these diseases, only a fraction of them are likely to actually cause disease. The Ray lab will identify them by studying how these variants interact with immune cells called T-cells, which play a role in multiple autoimmune diseases.

Originally from San Diego, Dr. Ray studied and worked at the University of Washington before moving east for graduate school and his fellowship. He’s excited to be back in the Pacific Northwest and to explore some of the natural wonders he didn’t get to the first time around.

“I’d love to hike the Wonderland Trail around Mount Rainier,” he says. “Maybe in a few years — we have lots of work to do first!”
When Maggie Arnold started preschool, her mom, Cheryl, sent her off with a little purse full of all the essentials: school supplies, Benadryl and an EpiPen. The Arnolds had learned that Maggie had severe allergies to peanuts and other foods when she was just 3. Now Maggie is 16 and is always finding new ways to live well with her allergies.

Though they live 2,000 miles from BRI in Southern Illinois, they closely follow our work and are strong believers in our mission.

“When it comes to food allergies, we have a mindset of constant learning,” Cheryl says. “Learn the facts from scientists like those at BRI, use that knowledge to keep moving forward, and hope their research leads to better treatments.”

A WAY OF LIFE

Having severe peanut allergies doesn’t just mean that peanut butter makes you sneeze. Eating even the smallest trace of peanuts can cause a life-threatening reaction called anaphylaxis, where you can lose consciousness and have trouble breathing.

“I always read labels super closely and never eat at buffets and things like that,” Maggie says. “It’s just a way of life.”

For Maggie, being a kid with severe food allergies meant learning to keep her head up when she felt left out — like when she was the only one who couldn’t have cupcakes at birthday parties.

“You just need to be brave and keep pushing forward,” she says.

As a teenager, food allergies pose different challenges: bringing your own food to sleepovers and making sure anyone you date hasn’t eaten peanuts before they go in for a kiss.

But Maggie, who’s now a high school junior, deals with challenges in stride. Sometimes she feels sad or anxious, but drawing always helps her feel better. She’s learned to always be vigilant of her surroundings, taking steps like wearing long sleeves to the movie theater in case someone sitting there before her was eating peanut M&M’s.

“And when people started all the hand washing and sanitizing during COVID, that was easy,” she says. “I’ve been doing that all along.”

HOPE IN RESEARCH

Cheryl and Maggie found BRI through reading about peanut allergy research conducted by Erik Wambre, PhD. They’ve followed our blog, Autoimmune Life, and stayed in touch through social media ever since. They’re drawn to BRI because our scientists study the whole immune system, not just one disease. Maggie was recently diagnosed with postural orthostatic tachycardia syndrome (POTS). Cheryl’s sister passed away from multiple sclerosis.

“It makes you wonder: Are these things connected?” Cheryl says. “We believe in BRI because they’re not just looking for better treatments, they’re looking for the reason behind all of these conditions. And once we know that, a cure won’t be far.”
people with autoimmune disease who have higher numbers of these cells also have less severe disease and fewer complications. Then Dr. Long and Peter Linsley, PhD, made a key discovery of their own.

They showed that T1D progresses more slowly in people who have higher numbers of exhausted CD8 T-cells. They also found that a drug called teplizumab increased exhausted CD8 T-cells in most individuals. Even better, BRI researchers led a study which showed that treatment with this drug delayed the onset of T1D by approximately three years in people who were susceptible to the disease.

“Those were ‘aha moments’ — we started to think, maybe it’s possible to create a therapy that exhausts these cells and stops T1D,” Dr. Long says. “But first we needed to understand these cells in much greater detail.”

MULTIMILLION-DOLLAR GRANT

Dr. Long recently received a $2.6 million National Institutes of Health grant to investigate why CD8 T-cells become exhausted and how this influences T1D. She’s also collaborating with Dr. Buckner and Erik Wambre, PhD, on an NIH-funded project that looks at T-cells in cancer patients.

People with cancer have the opposite problem as people with T1D and other autoimmune diseases. In cancer, T-cells should attack cancer cells, but something about cancer leaves them too exhausted to attack. Drugs called checkpoint inhibitors can nudge those cells back into attack mode. But those drugs can push T-cells into overdrive until patients end up with symptoms similar to autoimmunity.

“If we can understand the process that leads to autoimmunity in these patients, it could help us understand the biological dial that controls how much T-cells attack,” Dr. Buckner says.

The BRI team’s vision is to be able to control both sides of the T-cell equation. This could enable them to adjust cancer therapies to prevent autoimmune attacks or create therapies that exhaust attacker cells and stop autoimmune disease.

“We’re getting closer to being able to turn the immune system up or down depending on a patient’s needs,” Dr. Buckner says. “And that means we’re getting significantly closer to improving the lives of people with everything from T1D to cancer — and maybe even to stopping those diseases altogether.”

SOUND LIFE PROJECT PUSHES FORWARD

Despite the pandemic, researchers are moving full speed ahead with the Sound Life Project (SLP). The SLP is the first study of its kind: Scientists are studying how aging, lifestyle and the environment impact healthy immune systems over two years. This will help them better understand what goes wrong in disease and ultimately help millions with conditions like autoimmune diseases, allergies and cancer.

Since the study began in 2019, we’ve recruited nearly 100 participants and started collecting health data and blood samples. During phase 1 of the pandemic, we continued to recruit participants and collect data remotely through an app developed for this study. Now, we’re welcoming back participants to collect samples with added precautions.

“COVID-19 has posed many challenges, but our participants are a wonderful, dedicated group helping move research forward,” says Cate Speake, PhD, project lead for the SLP. “The SLP team, including Claire Mangan and Deric Khuat, have worked tirelessly under ever-changing circumstances to make sure the study stays on track, that we collect quality data and that we continue to build strong, valuable relationships with participants.”
Fine-Tuning Immune Cells to Stop Disease  
BRI researchers received a multimillion-dollar grant to study how a phenomenon called T-cell exhaustion could help stop everything from type 1 diabetes to cancer.

Armoring Cells Against COVID-19  
Could solving the pandemic be as simple as trapping the virus in a bubble? Researchers found that this strategy could help fight COVID-19, Ebola and other deadly viruses.

Persevering Through Peanut Allergies  
Peanut allergies impact every part of life. One family — inspired by BRI’s research — shares how they persevere.