Immune therapy is one of the biggest medical breakthroughs in decades: It can cure some cancers by telling the immune system to find and kill cancer cells. But when doctors started using immunotherapies called checkpoint inhibitors, some patients had a puzzling side effect — their immune system also attacked healthy tissue. The reaction is strangely similar to autoimmune disease. And it caught the attention of BRI President Jane Buckner, MD, and other scientists, including Peter Linsley PhD, Lynn Rose, PhD and Erik Wambre, PhD.

“Some patients have reactions that look like rheumatoid arthritis or type 1 diabetes (T1D),” Dr. Buckner says.

Our team recently launched two studies investigating this connection. The research could help doctors predict who will respond to checkpoint inhibitors and match patients with treatments that are most likely to work. It could also provide clues on what triggers autoimmunity.

“There’s a connection between checkpoint inhibitors and how autoimmunity starts,” Dr. Buckner says. “The more we know about what causes autoimmunity, the closer we get to therapies that stop it.”

**CUSTOM TREATMENT**

The immune system is equipped to hunt down cancer cells. But some cancers send signals that put the brakes on. Checkpoint inhibitors release that brake so the body can attack tumors.

These therapies are far less toxic than chemotherapy and have sparked remission of melanoma and other solid tumors. Still, they only work for 20 to 30 percent of patients. The National Cancer Institute recently awarded BRI a $4.5 million grant to pinpoint why checkpoint inhibitors only work for some patients and why they can lead to autoimmunity.

“It might seem unusual that BRI is getting cancer research grants, but we have decades of experience figuring out why immune cells malfunction, so it makes sense to apply that expertise to cancer,” Dr. Buckner says.

BRI scientists will study blood samples from patients receiving checkpoint inhibitors by working with oncologists at Virginia...
In April 2017, Steve Gordon and his daughter, Callie Triller, hiked to Machu Picchu in Peru. Seven months later, Steve started experiencing severe joint pain and learned he has rheumatoid arthritis (RA). It’s been a long journey to find a medication that gets him back to hiking, skiing and other activities.

“I’ve tried five medications in about two years,” Steve says. “Some drugs cost over $50,000 a year, so it’s very frustrating when they don’t work.”

Aside from Callie and one sister, Steve’s three siblings and three children all have autoimmune diseases.

“Whenever I have an unexplained illness or pain, I fear that it’s the start of an autoimmune disease,” Callie says. “And I have the same worries when my son gets sick.”

Eddie James, PhD, is working to help people like Steve and Callie. Scientists can predict who will get RA: people with certain markers in their blood and who have a family member with RA. But they can’t predict when — some people will get it in their 20s while others won’t until their 60s.

Dr. James and BRI President Jane Buckner, MD, led a study examining T cells involved in RA and discovered a key indicator to predict the disease. Dr. James recently presented this research at the American College of Rheumatology Annual Meeting.

“This research will help us treat RA earlier, before it progresses, and help us find ways to prevent it,” Dr. James says.

**KEY CELL CHANGES**

This project was part of the Targeting Immune Responses for the Prevention of Rheumatoid Arthritis (TIP-RA) study, which monitored over 100 patients’ immune systems for three years.

Researchers studied samples from people who had antibodies for RA — meaning they had a nearly 100 percent chance of developing the disease. Some participants developed RA during the study, and scientists pinpointed key cell changes among those participants.

Researchers believe that screening patients for these cell changes could help doctors know when RA will start, opening the door to improving treatments.

“Knowing that someone will develop RA soon after these changes means we can start treating them when medicines are most effective,” Dr. James says.

**AIMING TO PREVENT RA**

BRI’s researchers’ next steps include testing medicines that could prevent or delay RA.

Autoimmune disease research at BRI has inspired Steve to donate to our biorepositories — and he’s recruited his family to donate too.

“BRI is trying to create better, more individualized treatments, and I’m happy to give a simple blood donation to support that,” Steve says.

Callie’s son Noah turned 1 in 2019, and BRI’s work gives their family hope for the future.

“If scientists could determine if Noah was at risk and treat him preventively, that would be incredible,” Callie says. “BRI’s progress makes me think that he may never have to worry about autoimmune disease.”
ANOTHER LANDMARK T1D DISCOVERY

When some people are diagnosed with type 1 diabetes (T1D), the disease progresses so quickly that their pancreas stops making insulin within a year. For others, the process is slower and this can make their T1D easier to manage. But what if we could identify these fast progressors early and match them with treatments that help them stay much healthier for much longer?

Alice Long, PhD, and her BRI colleagues have made a discovery that marks key progress toward this goal and opens the door to potential new treatment strategies. For example, her team found that slow progressors have higher levels of exhausted CD8 T cells — cells that are worn out from attacking the pancreas.

Their discoveries could lead to a test that helps doctors identify when someone’s T1D will progress quickly. And the study is already informing research into new potential treatments.

“We’re closer to being able to tell someone ‘you’re a fast progressor, and we can give you a treatment that’s going to slow down or stop the attacker cells,’” Dr. Long says.

DECODING THE DATA

To study the differences between fast and slow progressors, Dr. Long’s team started by using tetramer technology as a molecular magnet to find the cells that cause T1D in each population.

“There are only about 1 of those cells in every 10,000 white blood cells,” Dr. Long says.

Then Peter Linsley, PhD, and BRI’s bioinformatics staff helped Dr. Long’s team analyze an unprecedented amount of data from these cells.

EXHAUSTED ATTACKERS

This teamwork enabled the researchers to identify higher numbers of exhausted CD8 T cells in slow progressors.

“These cells have been trying so hard to attack the pancreas that they get tired and say ‘nope, we’re not doing that today,’” Dr. Long says. “That means they leave the pancreas alone so it can function.”

Dr. Long envisions doctors someday using a test to determine how many exhausted CD8 T cells are in a T1D patient’s blood.

“If they don’t have many exhausted cells, the doctor could know they’re a fast progressor and put them on medication that preserves pancreas function for as long as possible,” she says.

INNOVATIVE TREATMENTS

“Next, we want to study these cells more closely and look for unique markers we could use to identify and target them,” Dr. Long says.

Dr. Long and her colleagues are already investigating whether innovative therapies can cause more CD8 T cells to become exhausted.

“Those therapies might be able to slow T1D down in certain patients,” she says.

Dr. Long also recently received funding to investigate why these cells become exhausted in the first place.

“It could be possible to design treatments that go in and exhaust the cells,” she says. “They’d stop attacking the pancreas so people with T1D could live longer, healthier lives.”
BRI has a bold vision: a healthy immune system for everyone. We need your help to make that possible.

We recently kicked off a potentially game-changing partnership with the new Allen Institute for Immunology. Fueled by a $125 million gift from the late Paul G. Allen, this partnership aims to learn more about how the immune system works from health to disease. BRI’s role includes creating the most detailed portrait yet of healthy immune systems. To do this, we’ll study blood samples from donors over time.

“We’ll be able to see how healthy immune systems change as people age, and how lifestyle and environmental factors alter immune systems,” says BRI President Jane Buckner, MD. “This will help us understand which changes are normal and which ones contribute to disease.”

When you volunteer to participate in research, you play a critical role in moving science forward. Scientists will use samples from donors to learn more about the immune system and how to predict, prevent and ultimately cure life-changing diseases that impact us all.

Breakthroughs start with people like you!

HOW IT WORKS

Eligible volunteers will:

- Share health information and donate blood samples at 10 in-person visits over 2 years
- Use phone app — developed at BRI — to report and track lifestyle information, in addition to in-person visits
- Receive free parking and a stipend for each visit
- Help to advance research that leads to future treatments and cures

WHO CAN PARTICIPATE

The Sound Life Project is looking for people in the Seattle area who are 25-35 or 55-65 years old who are generally healthy and have no chronic or major medical conditions. If that doesn’t sound like you, please feel free to sign up anyway — BRI has many other studies you might qualify for, whether you have an immune-related disease or not. Please share this opportunity to participate in research with friends and family. Learn more and sign up at Soundlifeproject.org/signup.
CANCER HOLDS CLUES TO AUTOIMMUNITY

Continued from front page

Mason Cancer Institute, Seattle Cancer Care Alliance and the University of Texas Austin. Then they can examine these samples, looking for biomarkers that indicate who responds to immunotherapy.

"Patients can lose valuable time trying therapies that might not work," Dr. Wambre says. "Our goal is to help doctors know when checkpoint inhibitors will be effective, so they can match patients with the best therapy from the start."

DAMPENING IMMUNE RESPONSE

The research team is also using patients’ cells to look for clues about why some patients have autoimmune reactions.

“We’re interested in this common factor that turns the immune system on and off,” Dr. Rose says. “Knowing more about that could lead to therapies that turn down the immune response in people with autoimmune disease.”

CLUES ABOUT T1D

Dr. Buckner and Dr. Wambre are investigators in a separate collaborative project looking at the development of insulin-dependent diabetes in patients taking checkpoint inhibitors. This $10 million project is funded by the Parker Institute for Cancer Immunotherapy, JDRF, and The Leona M. and Harry B. Helmsley Charitable Trust.

Researchers suspect that immunotherapy wakes up a type of T cells that attacks healthy tissue.

“We’re studying patient samples to see if these special T cells are activated,” Dr. Buckner says. “We expect that immunotherapy patients who have activated cells will develop autoimmunity.”

She hopes this research will help predict which cancer patients might react to immunotherapy with a T1D-like response. It could also lead to broader insights about T1D.

“If we can figure out why the immune system attacks the pancreas in people who take checkpoint inhibitors, it could help us understand why these attacks happen in other people too,” Dr. Buckner says.

GOAL: HEALTHY IMMUNE SYSTEMS

This research is the latest step in BRI’s quest to uncover common links among many immune system diseases, in hopes of sparking a new era of treatment.

“We’re getting closer to figuring out why the immune system overreacts or underreacts in many diseases,” Dr. Buckner says. “And that means we’re closing in on therapies that bring immune systems back to health.”
WHAT’S INSIDE

Searching for Autoimmunity’s Roots
When cancer patients started having autoimmune attacks, it gave BRI a new chance to study a longstanding question: How — and why — does autoimmunity start?

What If We Could Prevent Rheumatoid Arthritis?
A new discovery brings us closer to predicting when rheumatoid arthritis will strike, which means doctors could treat the disease earlier, and maybe even prevent it.

Another Step Toward Breakthrough Type 1 Diabetes Treatments
Is it possible to “exhaust” attacker cells and stop T1D in its tracks? A BRI team is on a quest to transform treatment.