Innovative research is paving the way for better treatments and care for rheumatoid arthritis, eosinophilic esophagitis and multiple sclerosis.

An Unprecedented Way to Study Rheumatoid Arthritis

The first symptoms Linda Sloate experienced were aching hands and pain that shot up her arms. She had carpal tunnel surgery in both hands. Then she felt pain in her feet while she was teaching kindergarten and running around after her three children.

“I was diagnosed with rheumatoid arthritis (RA) and I said ‘Huh? I’m 30.’ I thought only older people got RA,” Linda says. “RA is a battle. Your whole body feels achy, destroyed. Sometimes every bit of you hurts from the top of your head down to your toes.”

She started seeing rheumatologist Jeffrey Carlin, MD, who was eventually able to enroll her in a trial of a then-new therapy — etanercept (sold under the brand name Enbrel). Linda still remembers the morning after starting the medication.

“I woke up and felt normal, the way I was supposed to feel,” she says. “I just looked up to God and said, ‘Thank you.’ Then I brought Dr. Carlin flowers and a latte.”

Linda has been on that therapy for decades and it’s helped her live with less pain. But RA has still taken a toll: She can only use three fingers on each hand. She’s had numerous hand surgeries and multiple foot surgeries. And when she couldn’t bend her arms to hug her grandkids, she had two elbow replacements.

Most recently, she had a knee replacement — and opted to donate her tissue to a BRI study led by Eddie James, PhD. His team is studying tissue samples to gain unprecedented insight into how and why RA happens. The goal is to inform treatments that target RA at the source, slowing long-term joint damage and reducing symptoms.

T CELLS AND PROTEINS

RA happens when immune cells called T cells mistakenly attack proteins in the joint. Scientists are typically only able to study immune cells from blood to learn more about how and why this happens. But thanks to participants like Linda, our team is among the first to study the T cells from joint tissue to identify the exact proteins involved in RA.

CONTINUED ON PAGE 2
Key Questions About Immune Cells and Proteins
CONTINUED FROM FRONT PAGE

The researchers aim to answer two questions: What causes certain T cells to attack specific sections of proteins in the joints? And which peptides (small fragments of proteins) are they attacking?

They’re studying attacker T cells in precise detail – cataloging thousands of peptides, working to pinpoint which ones are recognized and attacked in RA. Then, researchers will re-create a joint in a Petri dish, putting the T cells and proteins together to confirm how cells attack and which peptides are being attacked.

“This would give us ironclad evidence that specific T cells attacking a specific peptide sequence is central to the disease,” Dr. James says.

TARGETING RA AT THE SOURCE
Down the road, this research could inform game-changing RA treatments — like antigen-specific therapies, which teach your immune cells to stop attacking.

“If you know which peptide is being attacked, you can teach the body to ‘tolerate’ it and stop attacking,” Dr. James says. “That could reduce the intensity of disease or move patients into remission.”

Knowing more about attacker cells could also inform better therapies that use “designer regulatory T cells” to slow down the attack.

“Once we know which peptide a T cell recognizes, we can basically fish that cell out and create an artificial version of that cell that responds to the same peptide but has the opposite effect: It suppresses the immune response that’s hurting the joints,” Dr. James says.

NEW RESEARCH, NEW HOPE
The research team is just over one year into this four-year project, and they’ve already collected some key data. If their approach proves effective in RA, it could also provide insight into other autoimmune diseases like multiple sclerosis.

As for Linda, she’s now retired and enjoys sewing and spending time with her family. She does everything she can to support RA research.

“Who would ever think your cells would be famous?” Linda says. “All of this research and new tools are so wonderful. I think back to the famous artist Auguste Renoir in 1892, who developed debilitating RA, and I feel lucky to live in this time with all of the scientific research. You have to have a positive outlook with this disease RA. When I was diagnosed 30 years ago, it was really isolating – they didn’t know much about RA, there weren’t many people to talk to. But this work leads to new treatments and new hope, and it’s just so much better.”

Creating a joint in a Petri dish to study RA

RA happens when certain T cells attack specific parts of proteins. Using advanced tools, researchers can extract the exact T cells and exact parts of proteins involved in RA. Then, they can create a joint in a Petri dish to better understand how and why RA happens.
Testing a New T1D Therapy

BRI recently launched the Type 1 Diabetes (T1D) TrialNet TOPPLE study, investigating an exciting new approach to treating T1D. This trial is testing a plasmid-based therapy, which uses tiny rings of DNA that can be engineered to carry information into cells to change what they do. Scientists splice genes encoding proteins and other information into plasmids that can teach immune cells to stop targeting insulin-producing cells. This could enable the body to keep making insulin.

“We are trying to retrain the immune system, by telling certain immune cells to stop attacking the pancreas,” says Carla Greenbaum, MD, director of BRI’s Diabetes Research Program and director of TrialNet Hub. “This is the first time that industry has partnered with TrialNet for first testing of a brand-new drug and recognizes that TrialNet sites like BRI are key to accelerate moving therapies to clinical practice.”

TOPPLE is a Phase I trial, which tests the therapy in a small number of people to assess its safety, look for side effects and determine the right dosage. Researchers are recruiting participants between ages 18 and 45 who have been diagnosed with T1D in the past four years.

“We’re extremely grateful for our research participants,” Dr. Greenbaum says. “You play a crucial role in scientific advances, helping us move closer to better treatments and prevention for T1D.”

BRI has many trials for people living with T1D and their family members. Learn more or get involved in the TOPPLE Study: Contact us at 800-888-4187 or Diabetes@BenaroyaResearch.org.
Understanding EOE: New Studies Shed Light on Complex Condition

Megan Lavin’s son started showing signs of food allergies at just 2 months old. When they started introducing solid foods, a doctor recommended feeding him yogurt.

“So I did — and he went into full blown anaphylaxis,” says Megan, who prefers to keep her son’s name anonymous. “He was vomiting and turning beet red, his eyes rolling back into his head. I ran into the ER with him in my arms being like, ‘help, help, help!’ It was terrifying.”

They got his reaction under control and did initial allergy testing.

“Everything was coming up positive,” Megan says. “I remember bawling driving home thinking, ‘What am I going to feed him?’”

Several doctor’s appointments later, they found only 10 foods her son wasn’t allergic to. And his blood work pointed to either leukemia or eosinophilic esophagitis (EOE), a rare immune system condition that’s connected to food allergies and causes serious inflammation in the esophagus.

“They did a biopsy and confirmed it was EOE,” Megan says. “I’d never heard of it. It was scary because it was so unknown.”

EOE affects about 10 of every 100,000 people, children and adults, and it’s becoming more common. This inspired a BRI research team, led by Karen Cerosaletti, PhD, and Steven Ziegler, PhD, to launch a study asking some key questions about EOE.

“It’s clearly related to an allergy, but there’s a lot we don’t know,” says Dr. Cerosaletti. “EOE can lead to real quality of life issues, and treatments are not ideal. Patients have to follow strict diets and sometimes use steroids, which have long-term side effects, especially for kids.”

A MYSTERIOUS IMMUNE SYSTEM DISEASE

The research team aims to answer some of the biggest questions about EOE: How do allergies start the chain reaction that causes this condition? Why does the immune system cause such severe inflammation?

Studying samples from EOE patients, they found evidence of an unusual immune system response called an interferon signature that hasn’t been documented before in EOE.

“This tells us that there’s more immune system processes involved in EOE than we previously thought,” she says. “Knowing more about this immune response might bring new insights to understanding how the disease is manifested and possibilities for alternative treatments.”

Karen Cerosaletti, PhD, and her team are working to better understand what causes EOE and to find better, more targeted treatments.

Raising one son with EOE and another with multiple food allergies has inspired Megan to write blogs and cookbooks for families with food sensitivities. Photo credit: Photos by Karly.

Raising one son with EOE and another with multiple food allergies has inspired Megan to write blogs and cookbooks for families with food sensitivities. Photo credit: Photos by Karly.
TEAMING UP TO LEARN MORE

Now, BRI is teaming up with researchers from Children’s Hospital of Philadelphia to learn more about this interferon signature and the role it plays in disease.

First, they plan to study the esophageal tissue in precise detail using a cutting-edge method called spatial transcriptomics. This new technique allows researchers to measure gene expression by the cells of the esophagus in their tissue setting, so the team can learn which cells are causing inflammation and influencing neighboring cells.

Next, they’ll look at immune cells in precise detail to understand why they’re not working properly. Because about 70 percent of children with EOE have a dairy sensitivity, they’ll look for the specific T cells that react to milk proteins to possibly gain insight into why the disease starts.

“If we could find the specific cells that react, and figure out the exact part of the milk protein they attack, we may be able to teach the body how to ignore that protein — and we could do that for other allergy triggers too,” Dr. Cerosaletti says.

They’ll also ask if the disease-causing cells in the tissue can be found in the blood.

“If it turns out that these cells are also in the blood and mimic what is happening in the esophagus, you may be able to diagnose the condition or understand if treatment is working by taking a blood sample instead of needing a biopsy,” she says.

WHAT IS AN INTERFERON SIGNATURE?

An interferon signature is like a fingerprint left behind by interferon, a substance that your cells make during an immune response. Interferon’s job is typically to “interfere” or fight off something harmful like a virus entering your body. But it can also be released by cells under other conditions like autoimmune disease, where the immune system attacks healthy tissue. And when it’s released, it causes other genes in cells to be expressed, creating an interferon signature.

Researchers are using a cutting-edge method called spatial transcriptomics to gain new insight into EOE.

INFORMING TREATMENTS AND CARE

For families who live with this condition, advances like not needing biopsies could make a huge impact.

“Our son is such a trouper but he is so sick of being scoped,” Megan says.

A decade after his diagnosis, Megan’s son can eat more foods than ever and manages EOE with diet alone. But it’s not easy.

“He’s on a strict diet and he can never cheat,” Megan says. “Food is so central, it’s a big part of so many things and he never gets to participate.”

Megan supports her son through validating his feelings about being left out and celebrating the foods he can eat. Inspired to support others, she now runs a blog called Allergy Awesomeness and writes cookbooks for families with allergies. And sometimes she lets herself dream about a world without EOE.

“I pray that someday this will be a thing of the past and my son will tell people, ‘Can you believe what I went through?’” she says. “I dream that one day, it will be like polio — a stretch of the imagination that’s far in the past.”
Hope for MS Powers Support for BRI

Debra Smith first learned about BRI when a friend invited her to the Boeing Classic Golf Tournament in the early 2010s. BRI’s work became personal when she was diagnosed with multiple sclerosis (MS) in 2013.

“Not long after, my then 28-year-old daughter Sofia was also diagnosed with MS, and I was absolutely shattered,” Debra says.

Though owning and running a real estate company keeps her busy around the clock, Debra did what she could by making financial donations to BRI. Then she started volunteering with BRI in 2020, helping rally support as part of our Ambassadors Council. Her motivation to give back is simple: Our groundbreaking science gives her hope.

“I remember being at Illuminations with my husband when it was in person – he kept giving me this look when I raised my paddle again and again,” she says. “I just told him, ‘this is for Sofia.’ I don’t know how much this research will help me, but I firmly believe that it will help my daughter.”

BEAT-MS Trial Tests Promising New Approach to Treatment

The Immune Tolerance Network (ITN), a global research consortium led by BRI, recently launched a trial called BEAT-MS, evaluating a potentially groundbreaking new way to treat relapsing MS.

The research team will examine whether an autologous hematopoietic stem cell transplant (AHSCST), a type of stem cell transplant that uses a patient’s own cells, can provide a new approach for patients with relapsing/remitting MS. This trial involves over 20 different academic centers. Patients with MS will be randomized to
Estelle Bettelli, PhD, leads much of BRI’s fundamental immunology research, working to understand how MS starts and investigating potential ways to stop it.

receive either AHSCT or the best available alternative therapy — immunomodulators that are FDA-approved for MS. Subjects in the trial will be studied over several years for clinical symptoms, radiological and laboratory changes, and quality of life assessments.

“The purpose of AHSCT is to ‘reboot’ a person’s immune system,” says ITN Director Jerry Nepom, MD, PhD. “The prospect of successful AHSCT also offers the possibility of avoiding the need to take drugs long-term.”

This study is building on the success of other trials — including the ITN’s HALT-MS trial — that showed the promise of this approach in a smaller group of patients.

“In HALT-MS, a large proportion of subjects completed the five-year trial without any episodes of MS relapses or evidence of disease progression by MRI scans,” Dr. Nepom says. “The BEAT-MS trial is positioned to provide the type of convincing evidence we need to make this treatment available to large numbers of patients.”

Learn more about the BEAT-MS study: Beat-MS.org.

“The purpose of AHSCT is to ‘reboot’ a person’s immune system. The prospect of successful AHSCT also offers the possibility of avoiding the need to take drugs long-term.”

— ITN Director Jerry Nepom, MD, PhD
What’s Inside

A New Way to Study RA

BRI researchers are among the first to study tissue samples from people with rheumatoid arthritis (RA) using a promising new method. Learn how their work could inform RA treatment.

Understanding EOE

Eosinophilic esophagitis (EOE) is a rare and little-understood immune system condition. See how our team is working to better understand EOE.

Advances in MS

Read about an innovative new drug trial for multiple sclerosis (MS), and learn what inspired one family’s support for MS research at BRI.