Pursuing a Revolution in IBD Treatment

Treatment options for inflammatory bowel disease (IBD) have been limited for most of Dr. Elisa Boden’s career. Until a few years ago, she and her colleagues – including James Lord, MD, PhD, and Michael Chiorean, MD – have had only a few types of medications to treat IBD. And those drugs often failed to stop the immune attacks that trigger the two forms of IBD: Crohn’s disease and ulcerative colitis.

“Only about half of IBD patients respond to those drugs – and only about 20 percent achieve remission,” says Dr. Boden, a gastroenterologist at the Virginia Mason Digestive Disease Institute and a principal investigator at the Benaroya Research Institute at Virginia Mason (BRI).

“Unfortunately, this leaves many IBD patients to endure incessant digestive problems, severe pain and other symptoms that can erode their quality of life.”

The good news is that IBD treatment options are rapidly expanding and an unprecedented number of new therapies are in clinical trials. But there’s no way to predict which one will work for a particular patient. Instead, doctors must follow a ‘trial and error’ approach, and it can take months before they find the right therapy.

That’s why Drs. Boden, Lord and Chiorean are working to revolutionize IBD treatment by pursuing a precision medicine approach that could tailor treatment to individual IBD patients. They are performing research to identify biomarkers – proteins and other molecules in patients’ blood or cells – that can predict whether they respond to a specific drug.

“The vision is that doctors could use advanced tests to pinpoint a patient’s biological profile as soon as they’re diagnosed, and then match them with the right therapy,” Dr. Lord says. “This means patients could almost immediately get the treatment that gives them the best shot at success, without having to endure symptoms or get worse while we search for the right drug.”

New Biomarker

Drs. Boden and Lord reached a key milestone last year, when they published their discovery

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of a biomarker that could potentially identify which patients respond to the drug vedolizumab.

The researchers started this study by taking blood samples from Virginia Mason IBD patients before they started using vedolizumab, and then again after they had taken several doses. Dr. Lord’s lab then carefully analyzed the immune cells in these samples.

Vedolizumab binds to a specific type of receptor on the outside of some immune cells. Drs. Boden and Lord discovered that some people who have more of this receptor respond better to the drug.

Now Drs. Boden and Lord are running a study to confirm their results.

“This could eventually open the door to a clinical real-world test that could predict which patients should receive vedolizumab,” Dr. Boden says.

WHY BIOREPOSITORIES MATTER

The vedolizumab study is just one example of how Drs. Boden and Lord are investigating biomarkers related to new IBD therapies. IBD patients at Virginia Mason have the option to participate in a BRI biorepository, a collection of biological samples and health information from volunteers with and without disease, used to advance research. Dr. Lord’s lab studies the cells in these samples to identify differences between people who respond well to a therapy and people who don’t.

“We’re extremely grateful for people who donate these samples, because it gives us what we need to study the IBD biomarkers and to investigate many other pivotal questions,” Dr. Lord says.

TAILORING THERAPY

As this research progresses, Dr. Lord envisions developing a “menu” of biomarkers that physicians can use to determine which therapies are right for which IBD patients.

The fact that patients respond differently to different treatments suggests there is a range of forms of IBD. Discovering biomarkers that can differentiate these forms of IBD might reveal what happens in different people. More importantly, the research could help uncover ways to rebalance the immune system when it turns against people to cause IBD.

“I think there’s a realistic chance we’ll cure some forms of IBD in my lifetime,” Dr. Lord says.
When people with diseases like lupus and systemic juvenile idiopathic arthritis (SJIA) are feverish and light-headed, doctors start to worry: These symptoms can indicate a life-threatening condition called macrophage activation syndrome (MAS).

MAS strikes when macrophage cells – which should eat bacteria – eat red blood cells instead. BRI principal investigator Jessica Hamerman, PhD, and postdoctoral fellow Holly Akilesh, PhD, recently discovered that a specific macrophage, which they named an “inflammatory hemophagocyte” (iHPC), is the culprit behind MAS. This could have big implications for patients with autoimmune diseases – and even for kids with malaria.

“If we can figure out how to get rid of iHPCs or keep them from eating healthy red blood cells, we might prevent MAS,” Dr. Hamerman says.

**KEY PROTEIN CHANGES**

In 2014, Drs. Hamerman and Akilesh set out to learn how normal macrophages develop in people with inflammatory conditions. Usually, cells use a protein called M-CSF to make macrophages. The researchers discovered that this is upended when cells instead use different proteins, TLR7 and TLR9. The result is a completely new cell: iHPCs that eat healthy red blood cells.

“Now that we know how this unusual cell develops, we can work toward new ways to treat and prevent MAS,” Dr. Hamerman says.

**HELP FOR KIDS WITH MALARIA**

Dr. Hamerman was curious if iHPCs play a role in MAS-like anemias in people with conditions besides autoimmune diseases. She decided to study malaria because it often leads to severe malarial anemia (SMA) – the second leading cause of death for kids with malaria.

Dr. Hamerman partnered with University of Washington malaria expert Marion Pepper, PhD, to study how SMA starts. Their findings weren’t just similar to those in the autoimmune disease study. They were identical.

“The exact same pathway and the exact same cells play a significant role in SMA,” Dr. Hamerman says. “So if we can develop therapies that prevent severe anemias in patients with autoimmune diseases, they might work for kids with malaria.”

**GOAL: REAL-WORLD TREATMENTS**

Now Dr. Hamerman and her team are moving toward real-world clinical applications.

This includes partnering with Seattle Children’s Hospital rheumatologist Susan Shenoi, MD, to collect samples from kids with MAS. The team plans to use those samples to investigate ways to inhibit the iHPC cells that cause MAS.

“We’re very excited about Dr. Hamerman’s work because knowing more about what causes MAS will help us develop better, more targeted medicine,” Dr. Shenoi says.

Dr. Hamerman is also working with the NIH’s Peter Crompton, MD, MPH, to study samples from malaria patients.

“Thanks to many collaborators at BRI and beyond, we’ve started moving our findings from the lab to the clinic to hopefully help people around the world,” Dr. Hamerman says.
In the late 1970s, Virginia Mason researchers had a groundbreaking idea: Use a portable pump to deliver insulin in patients with type 1 diabetes (T1D).

In T1D, immune cells attack the pancreas until it can't produce insulin, a hormone that regulates blood sugar. The team at the Virginia Mason Research Center — the research arm that later became BRI — created pumps that continuously delivered insulin and kept blood sugar stable in the hospital. But the doctors needed to confirm that patients could use the pumps at home and during daily activities. Enter Mary Buse, a Virginia Mason patient who had lived with T1D for decades and who quickly volunteered to test the innovative pump.

"Mary was very courageous – she put her life on the line in hopes of improving her health and making life easier for people with T1D," says her longtime friend and physician, Robert Mecklenburg, MD.

Mary's brave choice was one of many ways she supported Virginia Mason and, later, BRI. She passed away at age 92 in 2008, and her support lives on through a $400,000 gift BRI recently received from her estate.

"Thanks to the Buses, we upended the treatment paradigm by enabling patients to better manage T1D on their own," — Robert Mecklenburg, MD

Mary’s steadfast commitment to helping others inspired those around her and lives on through her philanthropy.

"She saw how one breakthrough opened the door to many more,” Dr. Mecklenburg says, “and I know she’d be happy that her gift will help us keep raising the bar on research and treatment.”

Delmer and Mary Buse helped Virginia Mason perfect the insulin pump – and their family’s recent donation to BRI could set the stage for new discoveries.

IMPROVING LIVES WORLDWIDE

Mary’s participation in the insulin pump study shows how her impact extended far beyond Seattle. She and the other research participants didn’t just wear the pumps and collect data; they also delivered valuable feedback about living with – and improving – the pumps.

“People like Mary literally helped us write the book on living with insulin pumps,” Dr. Mecklenburg says. “That shifted us from a place where T1D patients relied on doctors to call the shots to a place where T1D patients worldwide could take charge of their condition, and stay healthier and more active than ever before.”

ENABLING BREAKTHROUGHS

Thanks to the Buses, we upended the treatment paradigm by enabling patients to better manage T1D on their own.

— Robert Mecklenburg, MD

Mary was part of a groundbreaking generation of T1D patients: people born before 1920 who showed it was possible to live a long, full life with the disease.

“She wore an insulin pump, eventually one much smaller than what she first tested, for 25 years,” says Mary’s grandson, Rich Weiss. “And it helped her live a full and happy life — to travel, to spend time with family, and even to golf three times per week at age 85.”

The original insulin pumps were cumbersome, but they allowed patients like Mary Buse to lead much more active lives.

Thanks to the Buses, we upended the treatment paradigm by enabling patients to better manage T1D on their own.

— Robert Mecklenburg, MD

Mary’s contributions during her life benefited people around the world, and her extraordinary gift will help us keep finding better ways to understand, prevent and treat T1D,” says BRI President Jane Buckner, MD.
PERSONALIZING TREATMENT FOR T1D

BRI’s Matt Dufort, PhD, and Peter Linsley, PhD, led two new studies that could help doctors predict how quickly type 1 diabetes (T1D) will progress in some people, and match them with treatments that could slow it down.

“T1D moves much faster in some people than in others, and that increases their risk of long-term problems like heart disease and stroke,” Dr. Dufort says. “Our discoveries could help fast progressors get the right treatment early on. It means they could stay healthier, and it’s a step toward tailored treatments that could improve the lives of many more people with T1D.”

PINPOINTING FAST PROGRESSORS

People with T1D who are fast progressors stop making insulin – a hormone that regulates blood sugar – relatively quickly, and often at a young age. Making even a little bit of natural insulin can prevent or delay some of T1D’s long-term complications.

Dr. Dufort and his colleagues – including Peter Linsley, PhD, Carla Greenbaum, MD, Alice Long, PhD, and Cate Speake, PhD – set out to look for differences between fast progressors and patients whose T1D develops more slowly.

The researchers found that young fast progressors (under age 20) had increased numbers of B cells, a type of white blood cell, in their blood.

Dufort and his colleagues built on this discovery by finding that an immunotherapy drug called rituximab can hinder T1D’s progress in these patients by blocking B cells.

“Now we’ll work to confirm these results, and then we can hopefully move toward using a test that detects whether young T1D patients have higher B cell levels,” Dr. Speake says. “Based on those results, doctors could someday prescribe rituximab to try to slow T1D’s progression in younger patients.”

CLOSER TO TAILORED TREATMENTS

The BRI researchers made two other findings that could enable precision medicine for more T1D patients.

DuFort and his colleagues described a new way to predict how quickly T1D will progress in any T1D patient: measuring a protein fragment called C-peptide that plays a key role in insulin production.

“This could forecast how far along a patient’s T1D will be in two years, so doctors can eventually prescribe treatment based on that prognosis,” Dr. Dufort says.

Dr. Linsley led a related study that investigated how another immunotherapy drug, called abatacept, affects T1D patients. Dr. Linsley’s study showed that patients who don’t respond to the drug produce more B cells.

“If patients start taking abatacept and their doctor sees elevated B cells, they could adjust their dosage of abatacept or switch to a different treatment,” Dr. Linsley says.

LAUNCHING A CLINICAL TRIAL

These projects were funded by JDRF and NIH, and are fueling a new clinical trial that combines rituximab and abatacept for T1D.

“No one has tested these two drugs together in T1D, and we’re interested in whether this can prevent or delay the disease,” Dr. Speake says.

“It’s not enough to understand why the immune system becomes imbalanced in diseases like T1D,” Dr. Greenbaum says. “We also have to find ways to rebalance the immune system so we can improve people’s lives, and our collaborations help us do that as quickly as possible.”
Benaroya Research Institute at Virginia Mason
1201 Ninth Avenue
Seattle, WA 98101-2795

**BOEING CLASSIC GOLF TOURNAMENT**
*What:* The Boeing Classic is a PGA Champions Tour event featuring golf legends. The event benefits BRI.
*When:* August 23-25 at The Club at Snoqualmie Ridge
*Visit:* BoeingClassic.com

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