

TOGETHER WE DISCOVER

2024

An abstract, monochromatic illustration in shades of gray and white, set against a dark teal background. It depicts a variety of biological and chemical structures, including spherical cells with textured surfaces, some with internal details, and others with spiky or fibrous protrusions. Small, simple geometric shapes like dots and triangles are scattered throughout, suggesting molecular components or data points. The overall composition is dense and layered, with elements appearing to float or cluster together, creating a sense of dynamic scientific exploration.

Benaroya Research Institute
Virginia Mason Franciscan Health

Id agglutinin disease allergies palindromic rheumatism optic neuritis
Gögen's syndrome microscopic polyangiitis ankylosing spondylitis POEMS
syndrome pernicious anemia IgG4-related sclerosing disease stiff
person syndrome autoimmune diabetes insipidus myositis vasculitis
autoimmune polyglandular syndrome type 3 ulcerative colitis autoimmune
hepatitis primary sclerosing cholangitis rheumatoid arthritis autoimmune
retinopathy Guillain-Barré syndrome Hashimoto's disease autoimmune
inner ear disease chronic Lyme disease bullous pemphigoid uveitis
undifferentiated connective tissue disease vitiligo inclusion body myositis
IgA nephropathy paroxysmal nocturnal hemoglobinuria autoimmune
hepatitis narcolepsy psoriatic arthritis autoimmune dysautonomia
transverse myelitis hemolytic anemia Kawasaki disease multifocal
motor neuropathy mixed connective tissue disease complex regional
pain syndrome Graves' disease autoimmune oophoritis myasthenia
gravis dermatitis herpetiformis primary biliary cholangitis polyarteri
nodosa chronic inflammatory demyelinating polyneuropathy polymyalgia
rheumatica Takayasu's arteritis autoimmune myocarditis sympathet
ic ophthalmia thrombotic thrombocytopenic purpura pemphigus Behçet
disease alopecia areata Susac's syndrome relapsing polychondritis
chronic idiopathic urticaria amyloidosis juvenile idiopathic arthritis
dermatomyositis neuromyelitis optica rheumatic fever autoimmune
polyglandular syndrome type 1 neuromyelitis optica celiac disease acu
te disseminated encephalomyelitis adult-onset Still's disease pure red cell
aplasia paraneoplastic cerebellar degeneration psoriasis giant cell
arteritis hidradenitis suppurativa acquired hemophilia Crohn's disease
leukocytoclastic vasculitis retroperitoneal fibrosis granulomatous
temporal arteritis dermatomyositis polymyositis sarcoidosis IgA
vasculitis pyoderma gangrenosum multiple sclerosis reactive arthritis
Addison's disease immune thrombocytopenic purpura anti-GBM disease
antiphospholipid syndrome juvenile myositis cancer paroxysmal cold
hemoglobinuria erythema nodosum lupus Evans syndrome Cogan
syndrome infectious mononucleosis autoimmune retinopathy periodonti
tis Lambert-Eaton myasthenic syndrome CREST syndrome
autoimmune polyglandular syndrome type 2 axonal and neuronal neuropathies

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LETTER FROM BRI LEADERSHIP

Dear BRI Community,

We know the reality of the diseases we study all too well: many days full of frustrating symptoms before getting the right diagnosis. Months or even years to find the right treatment. Living every day with a disease that has no cure. This reality motivates us on our mission to predict, prevent, reverse and cure immune system diseases.

In “Together We Discover,” we share some of BRI’s biggest advances in the last year and highlight some exciting things to come. You’ll learn about research into the connection between Down syndrome and autoimmunity, explorations of how genetics and environmental factors impact the immune system, and new frontiers in tissue-specific immunology.

We chose the name “Together We Discover” because there’s one thing at the heart of every BRI discovery: a team. Collaboration is vital given the nature of the questions we ask. We will not get to the bottom of these diseases by studying one small part of the immune system. Instead, we need to understand genetics, the microbiome, and many different cell types. We need to learn more about how things like smoke, exposure to chemicals, and viruses tip our immune systems toward disease. We need technologies to measure all of these factors and expert data scientists to find meaningful patterns.

With every discovery we make, we ask the same question: What’s the next step that will move us closer to helping someone? This approach has established BRI as a world leader in human immunology. It’s how we make discoveries that change lives.

You – BRI donors, employees, collaborators, research participants, and community members – play a crucial role in our work. We have hope for a day where we can tell everyone living with chronic immune system diseases: “We finally have a cure.” We have hope for a day when we can tell someone on track to develop an autoimmune disease: “Don’t worry, we can prevent it.” This is not a future we can realize alone. But together, we just might be able to.

Sincerely,



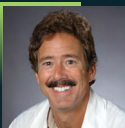
Jane Buckner, MD
President
Benaroya Research Institute



Margaret McCormick, PhD
Executive director and chief operating officer
Benaroya Research Institute

BRI ADVISORY BOARD

BRI’s advisory board is made up of community leaders and includes scientists, doctors, and people impacted by immune system diseases. Together, these individuals provide guidance and support to BRI as we work toward our vision of a healthy immune system for everyone.



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Physician



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Uli Chi, PhD
Virginia Mason Franciscan Health
Chair, board of directors



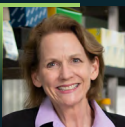
Andrew Held, MBA
J.P. Morgan Private Bank
Executive director
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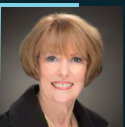
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Lund Opsahl
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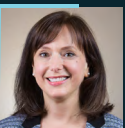
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Owner



David Williams, MBA
Security Pacific Bank
Former executive manager



Robert Williams, PhD
Amazon
Former director, Amazon Appstore

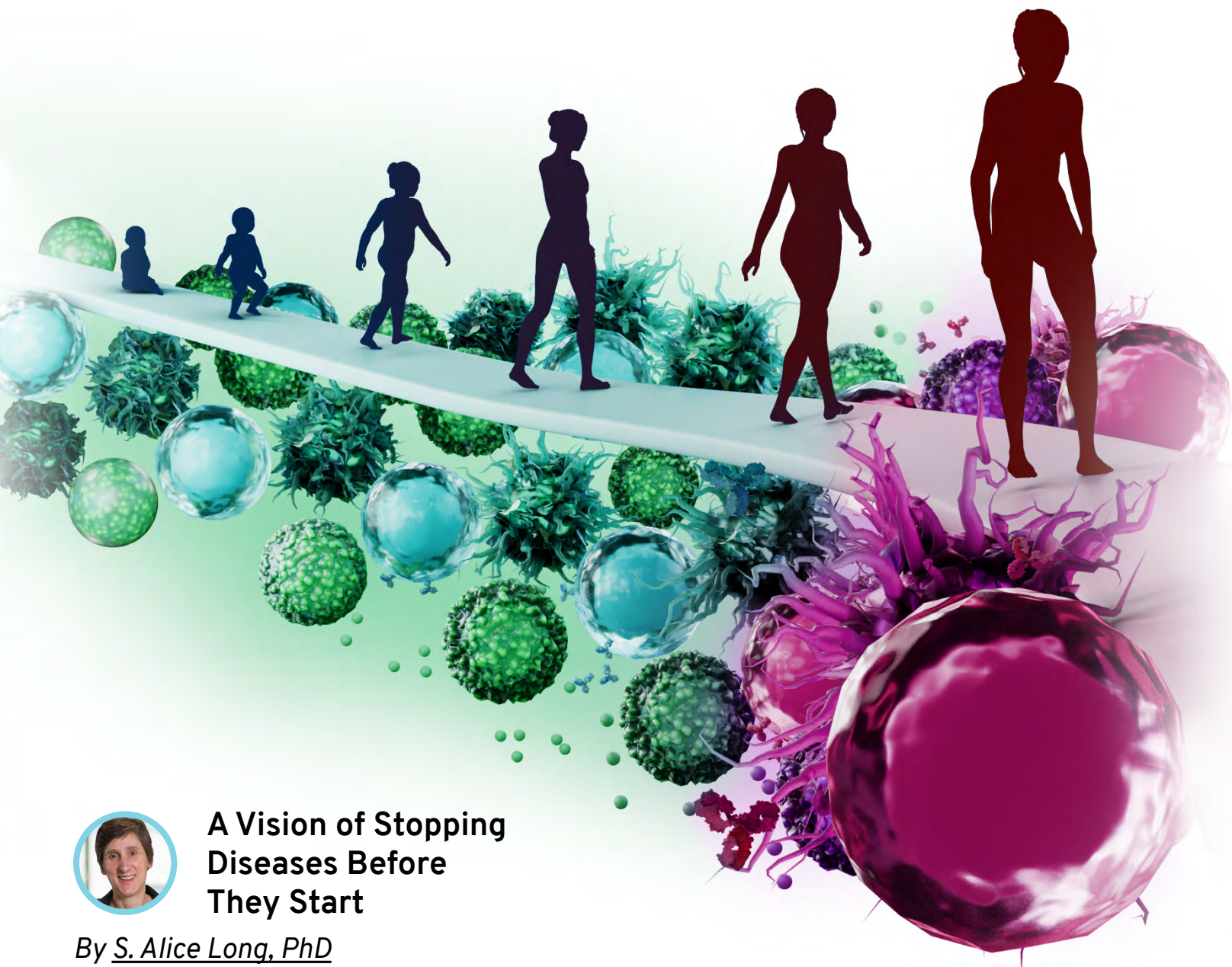


Steven Ziegler, PhD
Benaroya Research Institute
Member, Center for Fundamental Immunology
Director of external collaboration



Catherine Zimmerman
Mediator and conflict resolution coach

PRE-AUTOIMMUNITY: HOW DO WE PREDICT AND PREVENT AUTOIMMUNE DISEASES?



A Vision of Stopping Diseases Before They Start

By S. Alice Long, PhD

Our team is on a mission to predict who will develop autoimmune diseases. Most autoimmune disease research has been done on people who already have a disease. But we’re looking earlier and asking a different question: How does someone go from being “at risk” for a disease to actually

developing it? What does that transition look like? And what can we do to stop it? My lab, in partnership with several other BRI scientists and a team from the Allen Institute, is working on a new study funded by the National Institute of Health Immune Drivers of Autoimmune Disease (IDAD) grant.

My part of the project is to zero in on immune cells called naive T cells. These cells grow up to do different jobs, most of which help protect your body from viruses and bacteria. But a handful of these cells stray down the wrong path. Instead of fighting off infections, they start attacking healthy tissue, causing autoimmune disease.

Our ultimate goal is to figure out which naive T cells grow up to cause disease and if there’s a way to redirect them down a different path. This could, in theory, prevent autoimmunity – and move us closer to a day where people who are “at risk” for a disease never actually develop it.

We’re examining these cells in two seemingly unrelated groups: people with Down syndrome and people with biomarkers for type 1 diabetes (T1D). Both of these groups are very likely to develop an autoimmune disease. People with two or more specific biomarkers have a nearly 100% chance of developing T1D. Meanwhile, about one in two people with Down syndrome develops an autoimmune disease.

We hope to identify early warning signs of these cells turning into disease-causing cells, and examine whether anything within the T cells’ genetics make them more likely to cause disease.

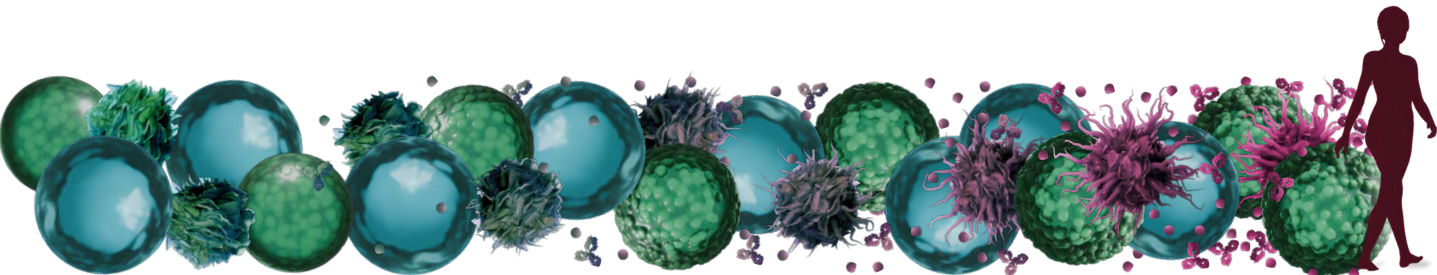
Another exciting part of this study will be working to understand how and why people develop multiple autoimmune diseases. Having one autoimmune disease makes a person more likely to develop another one, so we’re thinking about preventing not only a first diagnosis but also subsequent diagnoses. The earlier we can intervene the better. This study is a big step forward in making that possible.



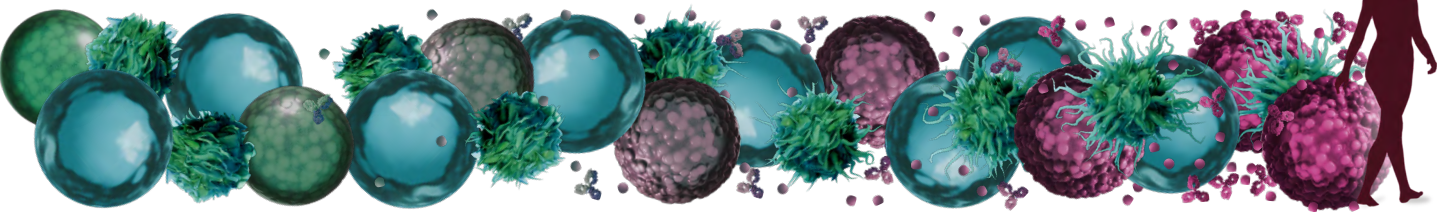
What Down Syndrome Can Teach Us About How Autoimmune Diseases Develop

By Bernard Khor, MD, PhD

I think about this IDAD study as examining early steps on the path to autoimmunity. We know that different types of immune cells – T cells, B cells, and innate immune cells – all play a role in autoimmunity. But the actual changes that lead to disease are likely different in different groups: There’s likely one version of autoimmunity that starts in T cells and another in innate immune cells.



Dendritic cell (innate immune cell)-driven autoimmunity



T cell-driven autoimmunity



Down Syndrome and Immune System Disease Facts and Stats

Nearly **50%** of people with Down syndrome will develop an autoimmune disease.

Children with Down syndrome are around **5** times more likely to develop certain types of leukemia than children without Down syndrome.

Adults with Down syndrome develop solid tumor cancers about **1/2** as often as the general population.

If we understand exactly how these diseases develop – all the different paths they might take – that could open the door to targeted medicines to treat each path to disease. This could significantly improve treatment and open the door to prevention.

My part of this project is to better understand the path to autoimmunity in people with Down syndrome: Does it look the same across the majority of people with Down syndrome or are there different paths? Can the path to autoimmunity in people with Down syndrome act as a lens to reveal people without Down syndrome who are proceeding down a similar path? And can this teach us about treating and preventing autoimmunity in people with and without Down syndrome?

I'm fascinated with learning more about how Down syndrome affects the immune system because there's so much we don't understand: like why one in two people with Down syndrome has an autoimmune disease but very few people with Down syndrome develop solid tumor cancers like breast cancer?

This project brings together experts across different types of immune cells and different disease areas. We're looking at the same problem from different angles to create a more holistic picture. That's how we'll find solutions that help people.

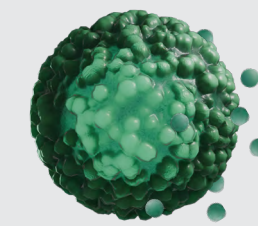
Pictured below, from left to right: Megan Olson (clinical research assistant, [BRI Center for Interventional Immunology](#)); Drew MacFarlane (outreach research assistant, [BRI Center for Interventional Immunology](#)); Bernard Khor, MD, PhD (associate member, [BRI Center for Translational Immunology](#)); and Rebecca Partridge, MD (clinical member, [BRI Center for Interventional Immunology](#)) at the 2024 Buddy Walk supporting 321 Buddy in Tacoma, Washington.



GUIDE TO THE IMMUNE SYSTEM

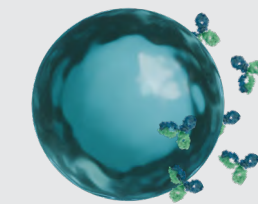
A healthy immune system protects us from infectious agents like pathogenic bacteria and viruses. It also helps keep us healthy by identifying and removing our own cells that might develop into cancer and contributing to wound healing. The immune system needs to be perfectly balanced, seeking out infectious agents and cancerous cells while avoiding our healthy tissues and our normal microbiome. At BRI, we study this balance – both how the immune system functions in health and how it changes when we develop allergy, autoimmunity or cancer.

Learn more about key parts of the immune system:

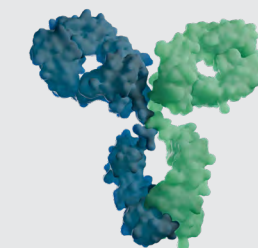


T cells are the workhorse of the immune system. There are two main types of T cells: effector T cells, which turn on an immune response and aid in immune memory, and regulatory T cells, which turn the response off when an infection has resolved. Both of these types of T cells keep us protected from viruses and bacteria but are also implicated in autoimmune disease.

● **Cytokines** are small proteins that act as physical messengers between immune cells. They allow cells to learn about what's happening elsewhere in the body, and tell the immune cells what type of response to generate.



B cells make antibodies (see below) and maintain a memory or catalog of pathogens so that your immune system can quickly respond to infections. For example, after an immunization, B cells are important in kicking off the immune response – “talking” to T cells, so that the next time you're exposed to that pathogen your immune system can act quickly.



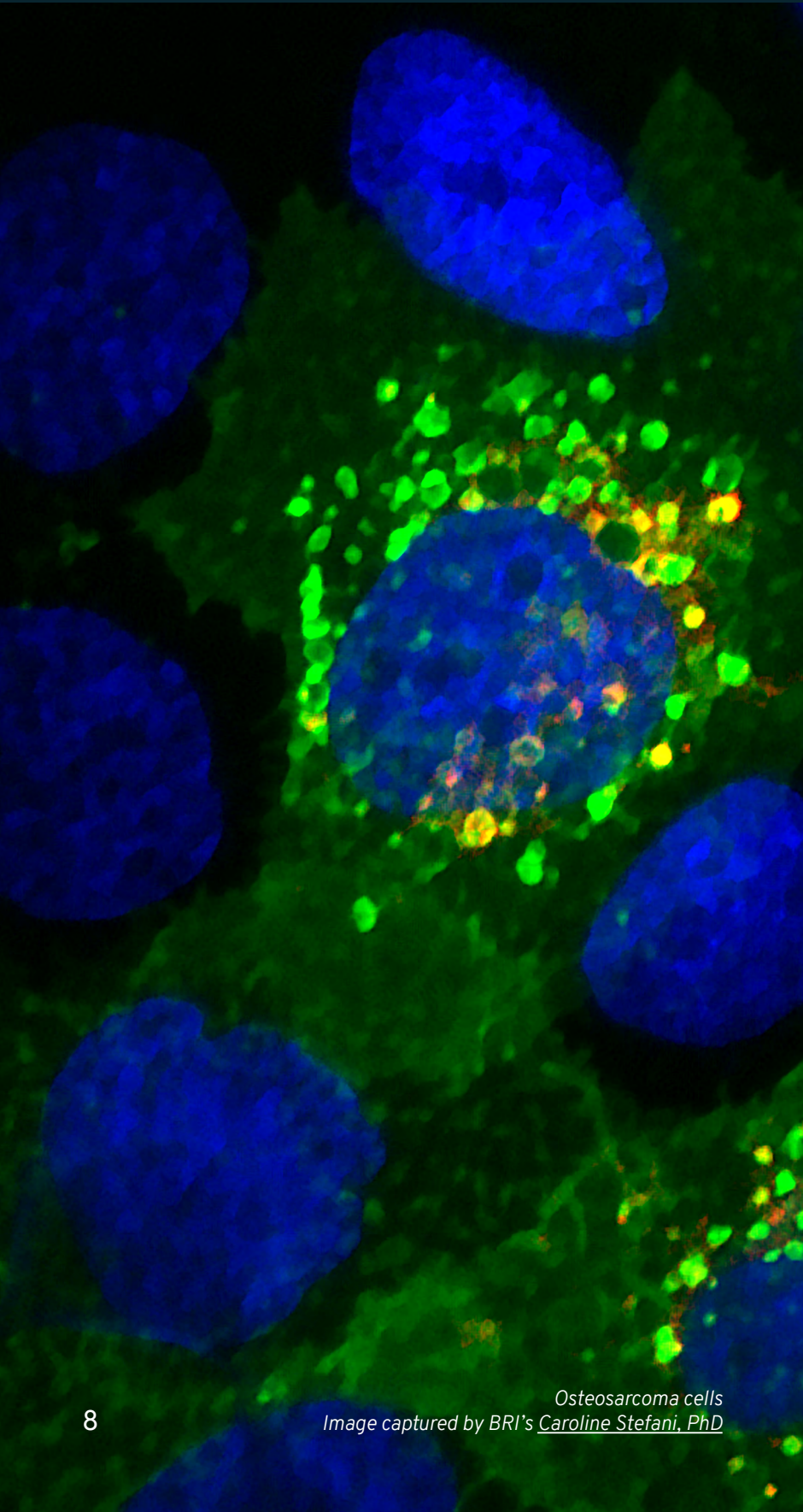
Antibodies are proteins made by B cells that act as signposts to other immune cells. They bind to targets like viruses or pollen and help the immune system recognize the presence of such targets. This is an important part of stopping infections – often before they get started. But when antibody responses go wrong, they can signal autoimmunity.

Antibodies are a powerful tool for predicting who is at risk for developing certain autoimmune diseases and are easily identified in the blood. They tell clinicians and scientists that the immune system is activated against specific tissue.



Dendritic cells are a type of innate immune cell that helps kick off immune responses by detecting and capturing pathogens and then breaking down and displaying them to other immune cells. We know that altered dendritic cell function can play a role in autoimmune diseases like systemic lupus erythematosus and inflammatory bowel disease.

STATE-OF-THE-ART MICROSCOPE ARRIVES AT BRI



Osteosarcoma cells
Image captured by BRI's Caroline Stefani, PhD



How Our Newest Technology Will Fuel Groundbreaking Discoveries

Featuring Caroline Stefani, PhD

In 2023, BRI purchased a game-changing microscope that is enabling us to see the immune system in ways we've never dreamed of – like taking real-time videos of cells interacting and testing up to 100 different treatments at the same time. This purchase was possible thanks to generous support from the M.J. Murdock Charitable Trust.

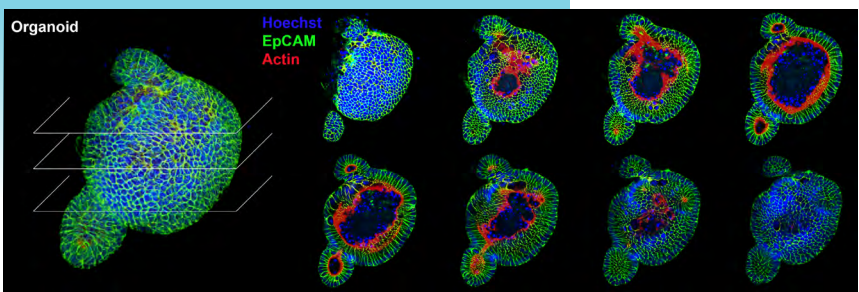
“This is now the most powerful microscope we have at BRI, and we are one of only three academic institutions in the Pacific Northwest with this technology,” says Caroline Stefani, PhD, who leads BRI’s Imaging Core. “These high-end technologies enable us to go faster, answer bigger questions, and branch out into new and exciting areas of research.”

Dr. Stefani is an expert in using advanced imaging tools to extract data from blood and tissue samples. With this new tool, she’ll partner with scientists across BRI and with external collaborators to dig deeper into existing research questions and take on new challenges in immune disease research.

Exciting ways our new microscope will advance research include:

Viewing every section of a sample

With traditional microscopes, scientists can only see two-dimensional pictures of cells. The new microscope allows us to take cross-sectional images, which provide a lot more detail. Think of it this way: The new machine could take a picture of a tomato and then create a detailed picture of individual tomato slices. This allows scientists to gather more detail and look at samples from different angles. This is particularly informative when we use it on organoids – lifelike models of human guts or lungs – and study each layer of tissue in precise detail.



Organoids stained for nucleus (blue), EpCAM (green), and actin (red). Left portion of image shows full 3D structure; right portion of image shows sequential image sections (Z-Stack). Imaged on Leica SP5 confocal microscope.

Seeing how cells behave

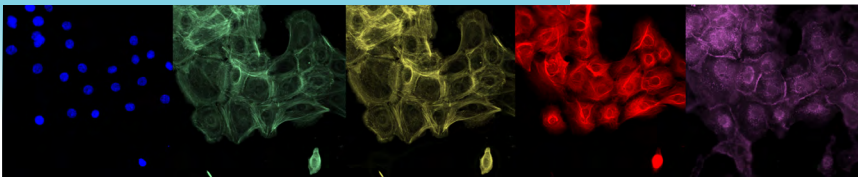
Our new microscope can image up to 384 wells at the same time. Wells are tiny separated chambers or compartments that can each be filled with different cells or medicines. They enable scientists to see how cells behave under different circumstances – for example, how they respond to different medicines or different doses of a medicine. Our new microscope can also record videos of cells over milliseconds, minutes, hours and even days, helping us understand how they respond to treatments or changes to their environment. With this additional data, we can learn how to better deliver medications and better understand diseases.



Left: wells. Right: high-throughput imaging of 384 wells containing human cancer cells treated with various drugs. Imaged on ImageXpress HT.ai 10x objective.

Getting more data out of samples

The new microscope is enabling us to study as much data as possible from every blood or tissue sample we put under the microscope. Previously, we could only gather four parameters from each sample, but the new microscope allows us to gather eight. This allows us to learn as much as we can from every blood or tissue sample we study and work more efficiently by gathering more data from each experiment.



Cell painting of skin cells stained for nucleus (blue), F-actin (green), phalloidin (yellow), mitochondria (red), WGA (magenta); imaged on ImageXpress HT.ai 20x objective.

BRI FACULTY

MEMBERS

BRI members serve as the core of our scientific staff.



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Center for Fundamental Immunology
Member



Allyson Byrd, PhD ★
Center for Systems Immunology
Assistant member



Karen Cerosaletti, PhD
Center for Translational Immunology
Director and associate member



Kurt Griffin, MD, PhD ★
Center for Interventional Immunology
Associate member



Oliver Harrison, DPhil
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Bernard Khor, MD, PhD
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Adam Lacy-Hulbert, PhD
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Director and member



S. Alice Long, PhD
Center for Translational Immunology
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Center for Interventional Immunology
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Director, BRI Clinical Research Center



Jane Buckner, MD
Center for Translational Immunology
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Daniel J. Campbell, PhD
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Director and member



Carla Greenbaum, MD
Center for Interventional Immunology
Director and member



Jessica Hamerman, PhD
Center for Fundamental Immunology
Member
Director, BRI academic affairs



Eddie James, PhD
Center for Translational Immunology
Associate member



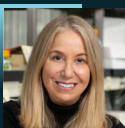
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Peter Linsley, PhD
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James Lord, MD, PhD
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Meg Mandelson, PhD
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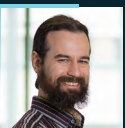
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John Ray, PhD
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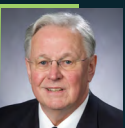
Steven Ziegler, PhD
Center for Fundamental Immunology
Member
Director, BRI external collaboration

EMERITUS

BRI's emeritus faculty are retired members who have a distinguished record of research.



Gerald Nepom, MD, PhD
Center for Interventional Immunology
Emeritus member



Thomas Wight, PhD
Emeritus member

AFFILIATE

BRI affiliate members hold appointments with a collaborating institutions and are strongly engaged in BRI's research.



Matthew C. Altman, MD, MPhil
Center for Systems Immunology
Affiliate investigator



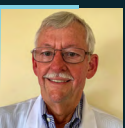
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Richard Kozarek, MD
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Rebecca Partridge, MD
Center for Interventional Immunology
Clinical member

★ Denotes an individual who has joined our faculty within the past year.

HOW DO GENETICS AND ENVIRONMENTAL FACTORS LEAD TO IMMUNE SYSTEM DISEASES?

Scientists know that genetics and environmental factors play a role in disease. But we don't know exactly how, why, or what we can do about it. BRI is conducting significant research efforts in both of these areas, working to better understand how our genetic code and the world we live in affect whether or not we develop disease – and to unravel new ways to treat and prevent it.



Unraveling the Genetic Roots of Autoimmunity

Featuring John Ray, PhD

Can one change in your genetic code alter the course of your life? Could it explain why one sibling has three autoimmune diseases and another doesn't have any? Could it be why two people with multiple sclerosis experience very different symptoms?

And if we can understand the exact role of genetics – can we target genetic changes to stop these diseases?

These are the questions John Ray, PhD, is trying to answer. His research focuses on a little-understood part of the genome called the non-coding region. He's already identified certain genetic changes in this region that are tied to autoimmune disease. The National Institutes of Health (NIH) funding he received from 2023 NIH Director's New Innovator Award helps him use state-of-the-art technologies to dive deeper into the exact role these changes play in disease and how we can stop them.



“We hope that way down the line, what we find out about the non-coding region of the genome could lead to personalized therapies, better diagnostics, or even preventive treatments,” Dr. Ray says.

The new funding will allow his team to dissect tens of thousands of genetic changes related to autoimmunity in T cells from actual people for the first time. He’ll also apply single-cell CRISPR screenings to study how those cells divide, how they move around, and how genetic variants across the genome interact to promote disease. See [page 21](#) to learn more about how BRI’s Innovation Fund helped get this technology up and running at BRI.

This is also one of the first times that any scientist has studied the role changes in the non-coding region play in symptoms of an autoimmune disease. Using samples from BRI’s [multiple sclerosis biorepository](#), he’ll examine whether genetic variants could help explain why some people have more severe disease than others.

“The more we understand about how genetic variants affect disease, the closer we get to finding ways to target those variants to treat or even prevent disease,” Dr. Ray says.



What Role Do Environmental Factors Play in Autoimmunity?
Featuring [Jane Buckner, MD](#) (left), and [Cate Speake, PhD](#) (right)

BRI recently joined a groundbreaking collaboration working to understand the role of the exposome – the sum total of everything a person has ever been exposed to in their entire life – in [autoimmune disease](#).

As the collaboration was forming, BRI’s team came to the table with a crucial question: How exactly do we do that?

That question ultimately landed Cate Speake, PhD, BRI President Jane Buckner, MD, and other BRI scientists with a National Institutes of Health grant to plan out how to study the exposome. Now, they’re mapping out the best questions to ask and how to answer them.

“We know that environmental factors play a role in health: Too much sun can lead to skin [cancer](#); air pollution is related to [asthma](#),” Dr. Speake says. “But we don’t fully understand the role of environmental factors (like air quality) and exposures (like chemicals) in autoimmunity.”

BRI’s team is working to change that, focusing on two big questions.

“We first want to understand which exposures promote autoimmunity. What flips the switch from not having an autoimmune disease to having one?” Dr. Buckner says. “And then once you have an autoimmune disease, what role do environmental factors play? How do they affect disease progression or how you respond to a treatment?”

The BRI research team wants to explore other factors too, including geographic location, diet, and social determinants of health – and even whether certain viruses during childhood can increase the likelihood of autoimmunity as an adult. It’s no small task.

14 Dr. Speake is thinking critically about which diseases might provide the most insight into the



Pictured above: Members of the EXACT network, a national research consortium that is studying how the exposome contributes to the development and progression of [autoimmune disease](#), convene in Seattle for their inaugural meeting in May 2024.

connection between the exposome and autoimmunity. She’s also forming partnerships with experts from different fields – including genetics, bioinformatics and environmental science – to help determine the best ways to measure various exposures and their impact on health.

“We’re looking to groups who are already measuring exposures for other types of research, rather than reinventing the wheel,” Dr. Buckner says. “And we’re working together to figure out where we should focus our efforts and how to start chipping away at these questions in a very targeted way.”

These groups include experts in tools that measure hundreds of thousands of chemical components from a blood sample to reveal patterns tied to disease. They also include environmental health experts who will examine data like air quality index and pollen counts to explore if and how these factors play a role in autoimmune disease.

Dr. Buckner and Dr. Speake are looking forward to answering one question in particular: How does wildfire smoke impact [rheumatoid arthritis \(RA\)](#)? This question will build on data Dr. Speake’s team collected in the Sound Life Project, which detailed changes in immune system cells in times of peak wildfire smoke.

“We know that smoking cigarettes is associated with autoimmune diseases and RA in particular, and we want to better understand if wildfire smoke may cause some of the same problems,” Dr. Speake says.

This is one of many important questions the team hopes to answer over the next several years as they carry out this research.

“There is still a lot we don’t know about how and why autoimmune diseases develop,” Dr. Speake says. “This study will be pivotal in helping us better understand the role of environmental factors, which is a crucial piece of the puzzle.”

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HOW TISSUE-SPECIFIC IMMUNOLOGY IS ADVANCING SCIENCE



Studying Tissue To Improve Inflammatory Bowel Disease Treatment

Featuring James Lord, MD, PhD

James Lord, MD, PhD, has spent the last 20 years building BRI's Inflammatory Bowel Disease (IBD) Biorepository – one of the world's most robust libraries of blood and tissue samples from people with inflammatory bowel diseases like Crohn's disease and ulcerative colitis. When asked why studying tissue samples is crucial in autoimmune disease research, he has a simple answer:

“Well, it's like when notorious burglar Willie Sutton was asked why he robs banks – he said, ‘because that's where the money is.’ The immune cells that cause disease live in our tissue, so sampling the tissue allows us to catch them in the act,” Dr. Lord says.

Traditionally, scientists have studied immune-mediated diseases by looking at blood samples. But blood samples only tell part of the story.

“We're lucky in IBD because we can safely and easily collect cells from colon tissue during colonoscopies, which are often part of IBD care,” Dr. Lord says. “Most disease areas don't have that kind of access to tissue. But because we do, we can closely study disease exactly where it's happening.”

One particularly exciting tissue-specific project is examining why a medicine called vedolizumab can lead to remission for some people with IBD. This means long periods without stomach pain, digestive problems, and other sometimes debilitating IBD symptoms. But this medicine doesn't work for everyone. And with all IBD medicines, there's no way to know which one will help which person, other than a painstaking process of trying different treatments and seeing if they work.

Experts thought vedolizumab worked by preventing circulating immune cells called T cells from migrating into the gut. But Dr. Lord's team discovered that the drug actually targets a different type of immune cell, called a dendritic cell (pictured right).

Now, with a new grant from the National Institutes of Health, Dr. Lord's team is zeroing in on dendritic cells in blood and tissue samples from people taking vedolizumab for IBD to see what is unique about the dendritic cells in people who benefit from this treatment and different from people who do not.

“We want to examine how dendritic cells interact with vedolizumab to prevent them from going to the colon in some, but not all patients,” Dr. Lord says. “This can help us predict which patients it will or won't help. It can also teach us exactly how this medicine works and thus how IBD happens in the first place.”



Pictured above: BRI's freezer farm, home to blood and tissue samples donated by biorepository participants for our scientists to study.



Moving Toward Preventing Ulcerative Colitis

By Adam Lacy-Hulbert, PhD

It's not often – if ever – that I read about a new discovery, drop what I'm doing, and run across the hall to tell my colleague James Lord, MD, PhD. But that's what happened when I read about a finding that could revolutionize the way we treat inflammatory bowel disease (IBD) and even open the door to preventing it.

The paper described a type of protein called an autoantibody (pictured right) in people with ulcerative colitis (UC). This was intriguing because first, the autoantibodies seemed to be attacking a group of proteins called alpha-V integrins, which I've studied for 25 years. And second, the autoantibody was present as much as a decade before people were actually diagnosed with UC.



An autoantibody showing up that long before a person actually develops a disease is concrete evidence that we may be able to predict UC – and possibly prevent it.

Within days, we had identified the same autoantibody in tissue samples from BRI's IBD Biorepository. Now, Dr. Lord and I are mapping out studies to better understand the role this autoantibody plays in UC and if targeting it could treat or prevent the disease. My expertise is in lab experiments and models, while Dr. Lord is a physician scientist who conducts research and sees patients. We work together to build lab models to test all sorts of variables while making sure the questions we ask are relevant to patients.

What's particularly exciting is that Dr. Lord believes an existing medicine might work to prevent UC, so we wouldn't even need to develop a new therapy. BRI has been leading prevention trials in type 1 diabetes for years, so the infrastructure to carry out this type of trial is already in place right here in our institute. This means that preventing ulcerative colitis could be a very real possibility in the near future.



Pictured above: a BRI scientist prepares a biorepository sample

BRI Biorepository Research Participants Fuel Our Next Discoveries

BRI is home to 11 biorepositories containing blood and tissue samples donated by people with and without immune system diseases. We are grateful to receive approximately 10,000 samples annually that allow our scientists and their collaborators to make new insights and faster progress toward predicting, preventing, reversing and curing immune system diseases.

If you are interested in joining a biorepository, please contact us via email at biorepository@benaroyaresearch.org.

NEW FRONTIERS IN PRECISION MEDICINE

Why Precision Medicine Matters

Here’s the reality that many people face when diagnosed with a disease like lupus, rheumatoid arthritis or ulcerative colitis: Doctors have many medicines to choose from but no way of knowing which one will work best for which person. Patients have to endure a painstaking trial and error process of finding a medicine that works for them that takes months or even years. All the while, they may experience painful and frustrating symptoms that lead to long-term damage or complications.

BRI believes in a better way: a world where doctors can identify the right treatment for each person right away, where no one has to suffer. That’s why precision medicine is one of our key focuses: developing ways to identify the best possible treatment for each patient, based on their genetics, specifics of their disease, and many other factors. Precision medicine questions BRI scientists are asking include:

- How can we better predict who will respond to which medicine for inflammatory bowel diseases like Crohn’s and ulcerative colitis so people get the best treatment for them as soon as possible?
- Why can certain medicines delay the onset of type 1 diabetes for years in some people but not at all in others?
- Would people with Down syndrome benefit from getting certain vaccinations at a younger age than people without Down syndrome?
- Why do some people develop autoimmunity as a side effect of checkpoint inhibitor therapy for cancer?



Next Generation Cancer Therapies: Why Do They Cause Autoimmunity?

Featuring Peter Linsley, PhD (left), and Ty Bottorff, PhD (right)

Some people were baffled when patients who took an innovative new cancer treatment called checkpoint inhibitors developed symptoms that looked a lot like type 1 diabetes, overactive thyroid, and other autoimmune diseases. But not Peter Linsley, PhD.

“I would have been more surprised if it didn’t happen,” Dr. Linsley says. “The immune system is like a continuum. On one end, it’s underactive and people get cancer. Go too far the other way, it’s overactive and we start to see autoimmune disease. Checkpoint inhibitor treatment ramps up the immune system to fight cancer, so it makes sense that it might become too active and cause autoimmune disease-like symptoms.”



The checkpoint inhibitor approach has given new hope to people with many types of cancer, offering the promise of a treatment that precisely targets the cancer and is less toxic than chemotherapy and radiation. But it doesn’t work for everyone. At BRI, the Linsley Lab, Long Lab, and Buckner Lab are working to learn more about what type of medicine will work best for which patients and to learn more about the side effects that develop.

Some patients only had mild side effects. Many people who experienced side effects actually had a stronger antitumor response, meaning their bodies did a better job of fighting off the cancer. But for a small number of people, the side effects were so severe that they had to stop treatment.

“Right now, there’s no way of knowing what response a person will have, so we hope examining this in the lab can generate data to help clinicians make the best decisions for their patients,” says Ty Bottorff, PhD, a postdoctoral researcher focused on bioinformatics in the Linsley Lab.

Dr. Linsley and Dr. Bottorff are examining blood from people receiving checkpoint inhibitor therapy, zeroing in on specific sequences of proteins inside T cells (pictured right). They hope to better understand when and why these cells decide to attack. Their efforts have already revealed a unique and very specific group of T cells. These T cells seem to be cross-reactive, meaning they are attacking both the cancer and healthy cells.



“We’re now taking a closer look at this very specialized subset of cells and asking why they decide to react with tumors. What is it about them that’s different?” Dr. Linsley says. “These cells could help us predict things like who is a good candidate for checkpoint inhibitors and what kind of side effects they might experience.”



Pictured above: a BRI scientist working with biorepository samples in one of our labs

Asking Questions in the Lab To Inform Precision Medicine

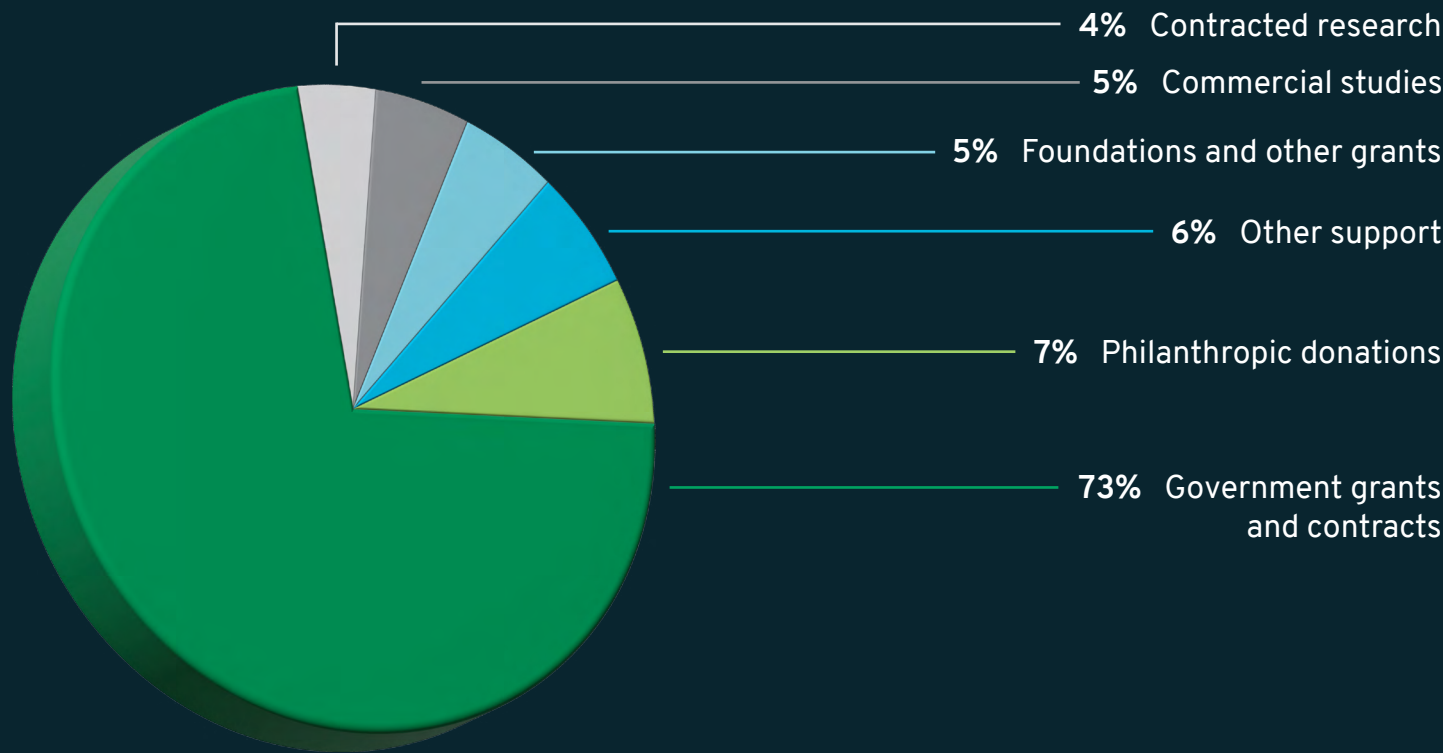
The Linsley Lab is one of many BRI labs working to drive health care toward precision medicine. This means a future where doctors know which therapy is best for a patient based on their unique biology, and patients get the treatments they need when they need them.

This research often takes patient experience and provider knowledge from the Virginia Mason Franciscan Health clinical network back to the lab. BRI bioinformaticians, fundamental immunologists, and other experts are finding answers, making new insights, and moving BRI closer to our vision of a healthy immune system for everyone.

BRI BY THE NUMBERS

For nearly 70 years, BRI scientists have been working to better understand the immune system with a vision of improving the lives of people who have diseases like type 1 diabetes and rheumatoid arthritis. From the beginning, we’ve known that we could not do it alone. Thanks to scientific partners, government support, industry collaborators, and a strong community of generous donors, we are on our way to better treatments with fewer side effects and personalized medicines that target the root cause of disease.

2024 BRI Components of Support | \$88 million



Awards and Recognition



Jane Buckner, MD
Steinman Award for Human Immunology Research
American Association of Immunologists, 2024



Carla Greenbaum, MD
Health Care Leadership Lifetime Achievement Award
Puget Sound Business Journal, 2023



Steven Ziegler, PhD
Distinguished Fellow
American Association of Immunologists, 2024



Doing Together What We Can't Do Alone

By Jessica Hamerman, PhD

I’ve wished that BRI had a fund to support innovative research ideas and new technologies for a long time. I’m thrilled to see it become a reality and especially thrilled to be part of the first team to receive an Innovation Fund award.

The Innovation Fund is allowing me and John Ray, PhD, to implement a new technology called single-cell CRISPR screening. With this tool, we can examine the cause and effect of genetic changes in more detail than ever before. We can also examine many genetic changes together rather than one at a time. Our biggest screen is looking at about 80 changes and their effects on many immune cell types.

Our study is using single-cell CRISPR screens to learn more about the role genetics plays in autoimmune disease. Our ultimate goal is to identify genetic changes that we could target to create new treatments for lupus-related kidney disease (lupus nephritis) and other autoimmune diseases.

This study would not be possible without Dr. Ray and his team. We are combining my expertise in models of lupus and his in genetics of autoimmunity and CRISPR screens to conduct research that neither of us could do alone. This type of collaboration is so valuable because it accelerates the pace of discovery by forming partnerships, rather than either of us having to stop and learn an entirely new skill. Plus, collaborating makes this work way more fun.

We’re so grateful to all of the donors who support the Innovation Fund. Your gifts have a ripple effect, because once an Innovation Fund project gets a tool up and running, it is available to scientists across BRI. My team used single-cell CRISPR to examine the genetics of cells called monocytes in lupus nephritis – but another scientist could easily use the same tool and method to study T cells in type 1 diabetes or B cells in rheumatoid arthritis. When you support this fund, you have an impact across labs and diseases that helps lay the foundation for groundbreaking advances. Thank you.



Make a donation to support BRI’s Innovation Fund by scanning the QR code to the left or [visiting bri-news.short.gy/dEZh7d](https://bri-news.short.gy/dEZh7d).



BRI’s Innovation Fund Is Powering Possibility

BRI recently launched our Innovation Fund with the goal of supporting early-stage projects and developing and implementing new tools and technologies. This funding helps keep BRI on the leading edge of research, fills a funding gap for these types of studies, and fuels innovative collaborations and discoveries.

Each project:

- Includes two or more BRI scientists, typically from different fields or areas of expertise.
- Focuses on tools and innovations that will be useful for groups across BRI.
- Supports technologies at any stage of development, from early proof-of-principle studies through implementation and validation.
- Shares findings and figures and makes them available for all BRI scientists to use when applying for grants.
- Makes tools and technologies available to investigators across BRI.

ABOUT BRI

Progress against one immune system disease is progress against them all

At BRI, we study the immune system and the wide range of diseases that affect it – including autoimmune diseases, allergies, asthma and cancer. Through our research, we're developing a detailed understanding of the immune system, in health and disease, aiming to understand how disorders start and how to rebalance the immune system back to health.

As a nonprofit research institute within Virginia Mason Franciscan Health, we collaborate with doctors and patients to accelerate the path from innovative lab discoveries to life-changing patient care.

OUR MISSION	Advance the science to predict, prevent, reverse and cure diseases of the immune system
OUR VISION	A healthy immune system for everyone
OUR VALUES	Persistent inquiry; innovation and agility; constant collaboration; integrity and respect

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