

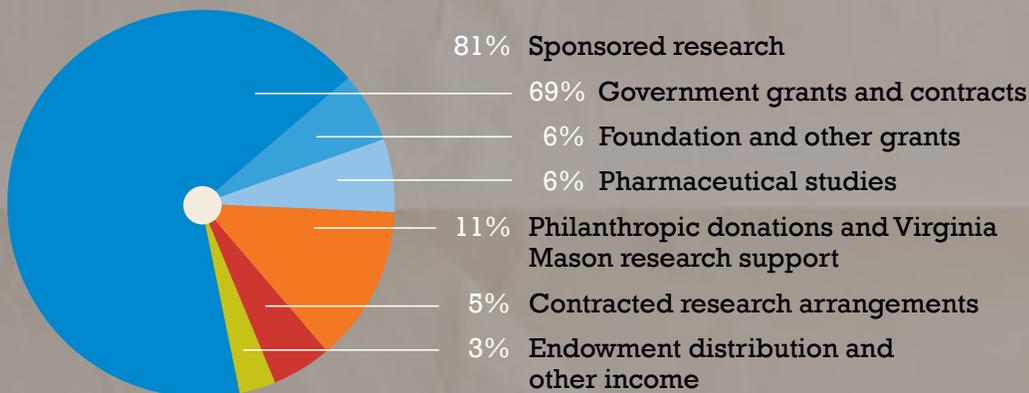


**BENAROYA  
RESEARCH  
INSTITUTE**  
**2014 ANNUAL REPORT**

**BRING IT ON.®**

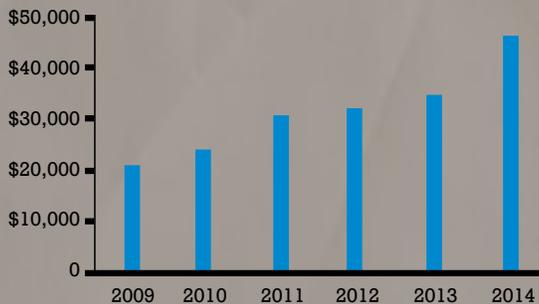
# BRING IT ON.<sup>®</sup>

## 2014 COMPONENTS OF SUPPORT \$61.5 million



## BRI SPONSORED RESEARCH FUNDING

(\$ in THOUSANDS)



BRI's funding from the National Institutes of Health (NIH) increased 170 percent in six years despite a national reduction of NIH funding during this same time.

**Cover:** Circos plot generated by the Linsley Laboratory using next-generation sequencing technology to understand the destructive cells causing immune diseases.

**Benaroya Research Institute at Virginia Mason (BRI) is an international leader in autoimmune disease and immune system research translating laboratory discoveries to real life applications. BRI is one of the few institutes in the world dedicated to finding causes and cures to eliminate autoimmune diseases.**

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### **BRI IS:**

- a nonprofit medical research institute in Seattle with 275 scientists and staff members.
  - unique in bringing together three arms of medical research—laboratory research, translational research and clinical research. Translational research takes laboratory discoveries from the bench to the bedside and back again.
  - the leader of the Immune Tolerance Network (ITN), a collaborative network for clinical research focused on the development of therapeutic approaches that lead to immune tolerance.
  - a center of innovation for other significant consortia projects including the NIAID Autoimmunity Prevention Centers, NIDDK Type 1 Diabetes TrialNet, JDRF Core for Assay Validation and the T1D Exchange Biobank.
  - funded through research grants awarded by the National Institutes of Health, JDRF, The Leona M. and Harry B. Helmsley Charitable Trust, the National Multiple Sclerosis Society and a variety of other national and regional foundations, as well as by individual philanthropic gifts.
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### **PRIMARY AREAS OF RESEARCH**



Type 1 Diabetes



Lupus



Multiple Sclerosis



Rheumatoid Arthritis



Crohn's & Colitis



Allergies & Asthma

**And many more.**

To see a full list, visit [BenaroyaResearch.org](http://BenaroyaResearch.org).

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## LETTER TO OUR SUPPORTERS

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Dear Friends,

**2014 was an exciting year** for Benaroya Research Institute at Virginia Mason (BRI), our research participants and our collaborating biomedical community. In our Diabetes Research Program led by Carla Greenbaum, MD, BRI received new NIDDK TrialNet Hub and Northwest TrialNet Center grant awards, and again expanded our clinical trial activity of immune therapies for prevention and treatment in type 1 diabetes. Through analysis of metabolic and immunological profiles, Dr. Greenbaum and colleagues created new algorithms to track and predict the clinical course of type 1 diabetes in children, essential for developing innovative prevention and islet preservation therapies. Clinical trials in hepatitis C also achieved major breakthroughs, with new anti-viral therapies resulting from multicenter studies led in part by Kris Kowdley, MD, at BRI and Virginia Mason Seattle Medical Center. And the clinical trial and research activities of the Immune Tolerance Network (ITN), directed by Gerald Nepom, MD, PhD, were reorganized under BRI administration to tackle challenging strategic initiatives in transplantation, autoimmunity and allergy therapies.

**Laboratory studies also prospered**, particularly in discovering new biomarkers and mechanisms of diseases across a broad scope of immunological dysfunction—for example, studies in the Wambre and Kwok Laboratories identified important specific molecular signals in people with allergy to shrimp and to grass pollen, which will enable personalized monitoring of people with these conditions. In addition, studies in the Chaussabel Laboratory reported several innovative transcriptional profiling studies, including analysis of sepsis and systemic lupus. Peter Linsley, PhD, identified a novel profile for melanoma that correlates with poor clinical outcomes related to the immunological response to the tumor, and Eddie James, PhD, working with other BRI colleagues, characterized a new type of immunological recognition in patients with rheumatoid arthritis and type 1 diabetes. In our Immunology Research Program, the Campbell Laboratory described complex interactions within T lymphocytes that determine cell lineage and fate, a balance required for normal homeostasis and immune response.



Homer W. Lane Jr. and Gerald T. Nepom, MD, PhD

**BRI continues to grow** to support these exciting research advances, as our research volume exceeded \$60 million for the year, and we launched a new Computing Cluster for data-intense projects, with expanded capabilities for analysis and storage. We are proud that numerous funding agencies have selected BRI to be a center for coordinating and conducting international research for eliminating diseases of the immune system. This vote of confidence for an institute of our size is an honor and makes our impact global. But more importantly, it represents a challenge and responsibility to facilitate and lead research around the world to improve the lives of people with devastating and chronic diseases for which there is no cure, such as type 1 diabetes, Crohn's disease, rheumatoid arthritis, multiple sclerosis and many more. Thanks to your support, our investigators and their staffs are well equipped to accomplish this task and keep BRI at the forefront of innovations in medical research. We are discovering advanced ways to predict, diagnose and treat disease that confirm our theme: "Progress against one autoimmune disease is progress against them all."

Sincerely,

**Gerald T. Nepom, MD, PhD**

Director  
Benaroya Research Institute

**Homer W. Lane Jr.**

Executive Director, Chief Financial Officer  
Benaroya Research Institute

# LEADERSHIP

# 2014



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# 2014 HIGHLIGHTS



## LEADING TYPE 1 DIABETES RESEARCH GLOBALLY

Up to 3 million Americans have type 1 diabetes, and the worldwide incidence of the disease is growing. Type 1 diabetes, once called juvenile diabetes, usually occurs in children or young adults. It is a lifelong autoimmune disease in which the body's immune system attacks and destroys the beta cells in the pancreas that make insulin.

People with type 1 diabetes must inject themselves daily with insulin in order to stay alive. They must carefully monitor their blood sugar, and also balance their food intake and exercise.

Long-term complications of type 1 diabetes include disabling or even life-threatening organ damage, such as heart disease, kidney disease, blindness and nerve damage.

BRI is dedicated to seeking ways to eliminate this disease, while at the same time looking for therapies to

prevent, reverse and intervene in the disease at all stages. BRI is an international leader in type 1 diabetes research and has investigated it for more than 30 years, starting with identification of a genetic marker for the disease.



Clinical research participant Ellery Rather with Marli McCulloch-Olson, Diabetes Clinical Research Coordinator.

“We’re passionate about making lives better for people with type 1 diabetes,” says Carla Greenbaum, MD, BRI Director of the Diabetes Research Program. “This is a complex, devastating disease that needs to be managed 24/7, and we want to do everything possible to prevent and ultimately eliminate it.”

“We’re very proud that an institute of our size

has been selected to lead many international laboratory, translational and clinical research programs in type 1 diabetes,” says Gerald Nepom, MD, PhD, BRI Director. “In this role, BRI can work collaboratively to accelerate discovery, finding causes and cures for this disease.”

### BRI LEADS:

**TrialNet** In 2014, BRI became the TrialNet Hub and in June 2015, Dr. Greenbaum will become chair of the TrialNet Network, supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health (NIH). The network includes 21 Clinical Centers working in cooperation with more than 200 screening and clinical research sites throughout the United States and seven other countries. TrialNet is dedicated to the study, prevention and early treatment of type 1 diabetes. Clinical trials have identified markers for risk and disease progression in diabetes and are testing therapies to intervene prior to onset of clinical symptoms, by blocking the immune attack on pancreatic beta cells that produce insulin.

**T1D Exchange Biobank** BRI leads the operations center for the T1D Exchange Living Biobank. By centralizing thousands of biological samples—together with clinical, demographic and study-derived information—the T1D Exchange Biobank aims to be a world-class



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Seven-year-old Emma Reinert with Carla Greenbaum, MD, BRI Director of the Diabetes Research Program, has participated in TrialNet since 2008. She joined the Pathway to Prevention study to determine if she was at risk for diabetes, and was later found to be eligible for the TrialNet Oral Insulin Study to see if the medication helps to delay or prevent diabetes. She was recently diagnosed with type 1 diabetes and is now in the TrialNet LIFT study, a long-term follow-up study. She lives in Redmond, Oregon, and makes the trip to Seattle to help with medical research.

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resource for innovative “real-time” clinical research, and a catalyst for the exchange of knowledge and collaboration. BRI manages several international biorepositories for type 1 diabetes and shares information with scientists internationally to accelerate discoveries. BRI uses biorepositories to better understand biomarkers associated with the progression of type 1 diabetes and to identify targets for new therapies.

**JDRF Core for Assay Validation (CAV)** The CAV is located at BRI, where teams of scientists are working to isolate type 1 diabetes biomarkers. These will be used to identify people at risk for the disease, predict progression rates and assess how well treatments are working. The CAV is a hub for numerous projects throughout the international biomarker research community. Consortium investigators can use BRI expertise to help validate biomarkers so they become more repeatable, accurate and robust. BRI scientists are also working to develop composite biomarkers in a way never before attempted involving multiple biomarker measurements to better predict the clinical course of type 1 diabetes. Scientists can request samples from type 1 diabetes biorepositories, further develop

candidate biomarker assays and share their progress and data in real time through the CAV LabKey website.

**Immune Tolerance Network** BRI leads the Immune Tolerance Network (ITN), a large international clinical research consortium supported by the National Institute of Allergy and Infectious Diseases of the NIH. The Network conducts clinical trials and studies in transplantation, allergy and autoimmunity. ITN’s mission is to accelerate the clinical development of immune tolerance therapies. The aim is to reprogram the immune system so that disease-causing immune responses are stopped while maintaining the immune system’s ability to combat infection. For type 1 diabetes, the ITN designs and conducts clinical and preclinical studies. They are designed to extend people’s ability to produce insulin when they are newly diagnosed with type 1 diabetes by rescuing beta cells from immunological attack.

### **PROGRESS TOWARD PERSONALIZED MEDICINE**

In clinical trials, not all individuals respond in the same way to particular immunological therapies. In the laboratory, BRI scientists are investigating the molecular mechanisms of the type 1 diabetes

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autoimmune response, and of immune interactions with each therapy, to better understand disease progression and uncover new approaches to treatment. These studies are also developing methods to better predict a person’s disease risk and provide earlier diagnoses so that patients can begin treatments earlier, at a time when more beta cells remain and more of the insulin production function can be saved.

Teams of BRI investigators, led by Alice Long, PhD, and Peter Linsley, PhD, are developing “discovery pipelines” for analysis of clinical trial samples to better understand the way different individuals respond to different therapies through interrogation of transcriptional and phenotypic properties of individual immune cells. This information is a cornerstone for tailoring therapy specifically to individuals—the right treatment for the right person at the right time.

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# DISCOVERING A BIOMARKER TO IMPROVE ALLERGY TREATMENT

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One in five people or 50 million Americans suffer from allergies. They occur when the body's immune system overreacts to a foreign substance (an allergen), such as pollen or animal dander, and although they can be mild, for some people they can compromise quality of life and even be life-threatening.

In 2014, scientists at BRI received a \$2.2 million grant from the NIH to study a unique biomarker that initiates and drives allergies. This grant expands on previous discoveries that led to the isolation of a rare type of white blood cells that show up only in people with allergic disease and is a key initiator of the allergic response.

"We hope to identify a biomarker

at the top of the allergic chain reaction that will predict the onset of allergy and will lead to novel vaccine approaches," says Erik Wambre, PhD, BRI principal investigator for the grant. "Our aim is to develop a simple blood test to predict the likelihood of resolution of an allergy during therapy and to identify people who will develop an allergy before the first symptoms are experienced. This is especially important in at-risk people such as children with a life-threatening food allergy."

Allergen specific immunotherapy (allergy vaccine therapy) remains the primary treatment for certain types of allergies. "This approach doesn't always work, is only limited

to a few allergens at a time and it can take two to five years to build up immunity," says Dr. Wambre. "Part of the reason for this is that researchers still don't fully understand the precise mechanism of how allergies work in the body. If we can identify the biomarkers at the beginning of the allergic chain reaction, we can get ahead of the symptoms and try to find a therapy that will eliminate the allergy at the first step."

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## TYPES OF ALLERGIES

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### Skin contact

Poisonous plants  
Latex  
Animal dander

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### Ingestion

Medications  
Shellfish and nuts  
Milk

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### Injection

Medications  
Bee stings

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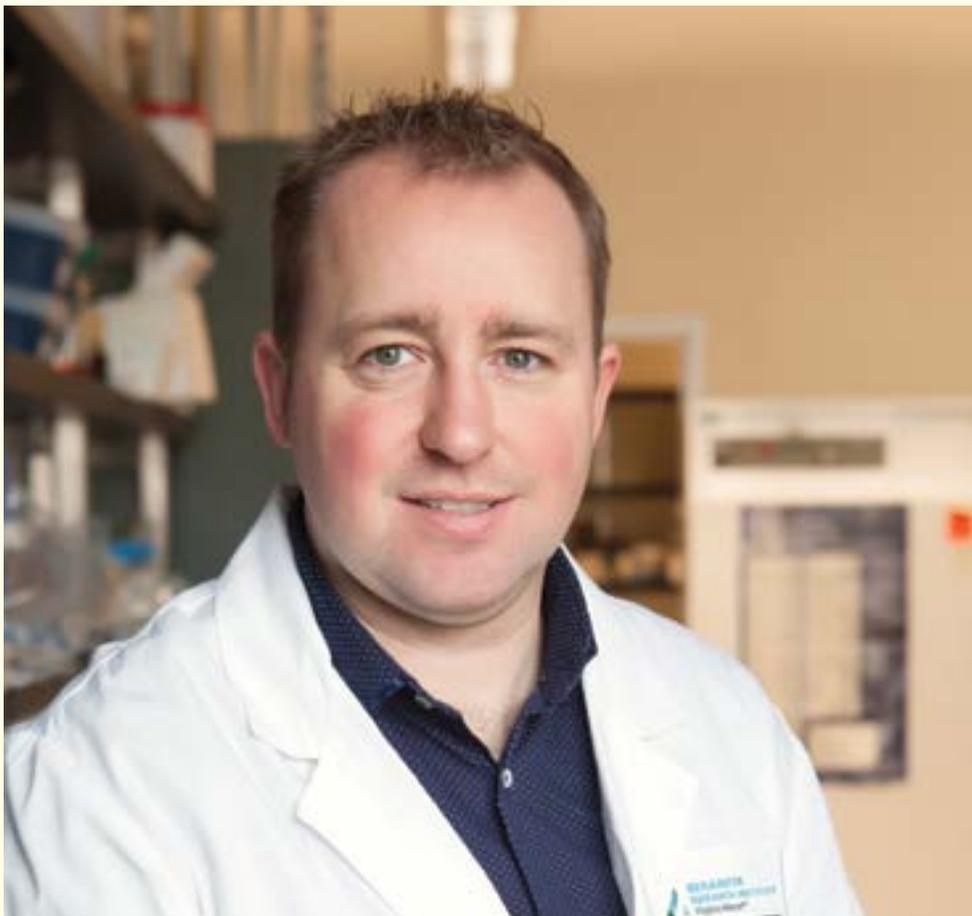
### Inhalation

Mold  
Pollen  
Dust  
Animal dander

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Erik Wambre, PhD, is principal investigator of a new grant to study a unique biomarker that initiates and drives allergies.

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BRI Associate Director Jane Buckner, MD, with Tetramer Core Laboratory Manager Eddie James, PhD.

## IDENTIFYING CELLS THAT CAUSE RHEUMATOID ARTHRITIS



In 2014, researchers at BRI used cutting-edge tetramer technology developed at BRI to find rare T cells in the immune system that drive rheumatoid arthritis (RA). “By using tetramer technology, we were able to examine whether T cells in people with rheumatoid arthritis were increased in number or were unique in other ways,” says BRI Associate Director Jane Buckner, MD, who led the study with BRI Tetramer Core Laboratory Manager Eddie James, PhD. Tetramers are a molecular toolkit originally developed at BRI that detects individual T cells in blood samples that are specific for particular disease-associated targets of immune attack.

This tool now allows scientists to study how RA starts, how current therapies may impact the immune response directed to the joint and how to specifically target these cells therapeutically. “For the first time, we were able to demonstrate that T cells that recognize proteins in the joint were increased in the blood of people with

RA and that these cells had a unique set of markers,” says Dr. Buckner. BRI is an international leader in developing tetramer technology, which allows scientists to isolate cells that are difficult to pinpoint, often compared to finding a needle in a haystack.

“RA is a debilitating disease affecting men and women of all ages including children,” says Dr. Buckner. “We used to see people with RA in wheelchairs and needing joint replacements, but during the last 15 years we have seen incredible progress in new therapies. If people are appropriately diagnosed and treated, they can work full time and be healthy, active adults. But they can still suffer and need medications that have risks and side effects. The

drugs can be costly and sometimes they don’t work or eventually stop working. If untreated, the disease will permanently destroy joints and cause pain. We would like to find ways to treat people early and target only the cells that cause the disease and eventually prevent this disease.”

**“For the first time, we were able to demonstrate that T cells that recognize proteins in the joint were increased in the blood of people with RA and that these cells had a unique set of markers.”**

—Jane Buckner, MD

## MAKING NEW THERAPIES POSSIBLE

In 2014, BRI was awarded a \$27 million grant annually over the next seven years to manage and lead the Immune Tolerance Network (ITN), a research consortium funded by the National Institute of Allergy and Infectious Diseases, part of the NIH. The ITN develops, coordinates and implements international clinical trials for novel therapies in transplantation, allergy and autoimmune disease. The ITN grant is one of the largest NIH awards made to any institution and is a significant recognition of the stature of BRI in the research community.

The ITN aims to advance knowledge and develop clinical therapies that will direct the body’s immune response toward repairing tissue damage and reversing and preventing disease. “The ITN program conducts game-changing clinical research studies that are unique,” says Director of BRI and the ITN, Gerald Nepom, MD, PhD. “The aim is to achieve ‘immune tolerance,’ which means that we are testing new therapies that will stop the immune system from attacking the body’s own tissues and redirect the immune system so it will tolerate its own tissues.”

The ITN program is also a leading innovator in clinical transparency, as well as data and sample sharing through ITNTrialShare.org, an online resource that provides access to underlying data, analyses and samples from ITN’s clinical trials. In 2014, ITN TrialShare received the National Academies of Sciences “Data and Information Challenge” Award recognizing ITN’s leadership in using data for the public good.

# THANK YOU DONORS

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Benaroya Research Institute gratefully acknowledges the support of our donors who made contributions in 2014. Philanthropic support totaled \$7.1 million and was used for clinical research trials, state-of-the-art equipment and pilot studies to achieve additional grants. We extend our heartfelt thanks.

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## 2014 DONOR EVENTS



### Grapes on the Green

The Grapes on the Green dinner auction was held at The Golf Club at Newcastle on Aug. 22. A record \$555,000 was contributed for BRI. Pictured from left to right: Mary and Chuck Kastner, Trish Markey, BRI Director Gerald Nepom, MD, PhD, Kristi Pangrazio and Stacy Lill.



### Illuminations Luncheon

BRI's Illuminations Luncheon was held on Oct. 31 and raised nearly \$100,000 thanks to the generous support of guests, donors and sponsors. Speakers included BRI Director Gerald Nepom, MD, PhD, Dillon Berg, Alexandra Grier, MC Steve Raible, Toni Berg and BRI Diabetes Research Program Director Carla Greenbaum, MD.

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## MAJOR GIFT DONOR



### Ann Ramsay-Jenkins

Philanthropist Ann Ramsay-Jenkins reconnected with an old grade school friend, Tom Wight, PhD, Director of BRI's Matrix Biology Program. She asked for a tour of his lab and was so impressed she wanted to support his work. With a \$300,000 gift, Ann created the Ann Ramsay-Jenkins and William M. Jenkins Fellowship for Matrix Biology.

"We will use the generous fellowship to ensure bright young scientists with great potential can have an opportunity for support while they begin their research careers," says Dr. Wight. "This is a tremendous boost to our program and will help accelerate our research. We greatly appreciate Ann's gift."

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## NAMED ENDOWMENT FUNDS

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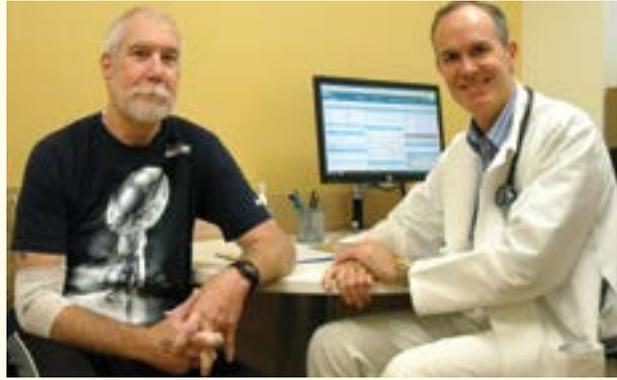
Chris Wood is a research participant in a clinical trial for axial spondyloarthritis, an immune-mediated rheumatic disease.



Adam Holcomb (left), with his father, Reid, and older brother, Isaiah, is participating in a clinical trial aimed at preventing or delaying the onset of type 1 diabetes.



Aaron and Justin Newton with their lifesaving supplies for peanut allergies. They contribute to the BRI Allergy and Asthma Biorepository.



Barry Thys (left) is a research participant in an inflammatory bowel disease (IBD) study led by James Lord, MD, PhD, BRI Clinical Investigator (right).

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Benaroya Research Institute at Virginia Mason

1201 Ninth Avenue

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