Frontiers of MEDICAL Research

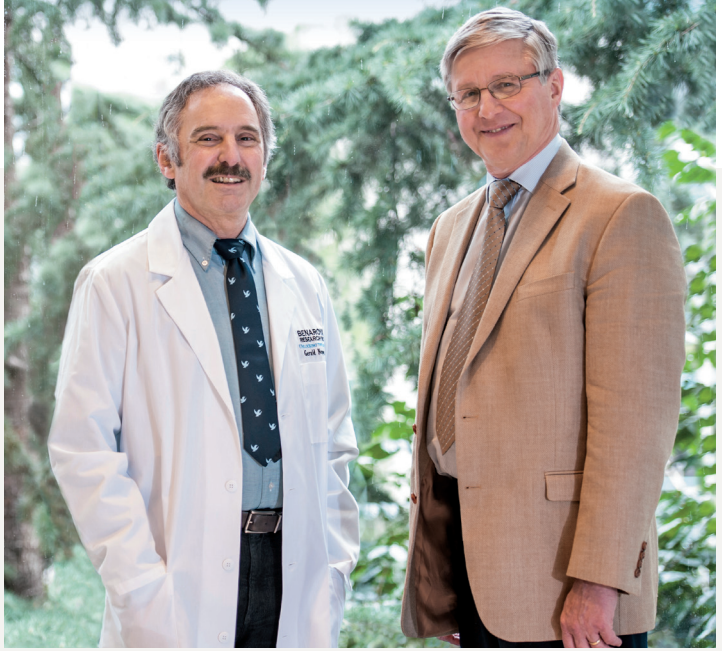
BENAROYA RESEARCH INSTITUTE VIRGINIA MASON

CONTENTS

Karen Cerosaletti, PhD,
BRI research assistant member

2012

Welcome to Benaroya Research Institute
Frontiers of Medical Research



From left: Gerald T. Nepom, MD, PhD, director; Homer W. Lane, Jr., executive director, Benaroya Research Institute

Dear Friends,

In 2012, more than 4,000 individuals participated in research studies at Benaroya Research Institute at Virginia Mason (BRI). It's a remarkable number and reflects the important partnership BRI scientists have with our participants and volunteers. We're all after the same thing: New knowledge leading to improved treatment for autoimmune diseases — Type 1 diabetes, multiple sclerosis, rheumatoid arthritis, systemic lupus — and the more than 80 other disorders caused by mistakes made by our immune systems. And because autoimmune diseases are connected through these related mistakes, so is the way we're fighting them. BRI has a unique and focused philosophy of collaboration between researchers and physicians, across clinical trials and across scientific disciplines, designed to connect laboratory research to medical needs. The progress we make against one disease can help advance progress against them all.

Jane Buckner, MD

Lynn Rose, PhD

In this report, we highlight a few of the stories from 2012 that illustrate our dedication to transformative research: linking our genetic inheritance to disease susceptibility, using this information to guide development of new therapies, creating molecular probes that serve as miniature tools for improving diagnosis and prognosis, and discovering fundamental new insights into how immune cells make their fateful decisions. It's been an exciting and fruitful year, supported by more than $20 million from the National Institutes of Health (NIH), as well as major financial support from numerous foundations, companies and individual donors.

In addition to our scientific growth in 2012, BRI also grew through increased collaborative relationships and additions to the institutional leadership team. BRI investigators are increasingly involved in the pioneering clinical trials sponsored by the Immune Tolerance Network, a large NIH-supported international program led by BRI, and the number of collaborations with the pharmaceutical industry increased substantially, accelerating our impact on drug development. In 2012, BRI's Chief Financial Officer Homer W. Lane, Jr., was promoted to executive director of BRI; Jane Buckner, MD, director for BRI's Translational Research Program, was named associate director of BRI; and Lynn M. Rose, PhD, joined BRI as the first director of scientific administration.

Progress in our research is now reflected every day in improvements in people's lives. We're extremely grateful to the community of supporters who are engaged with us, financially or through our studies, and who continue to help us transform hope into reality.

Sincerely,

Gerald T. Nepom, MD, PhD
Director
Benaroya Research Institute

Homer W. Lane, Jr.
Executive Director
Benaroya Research Institute

Progress Against One Autoimmune Disease is Progress Against Them All

ONE IN 20 AMERICANS suffers from an autoimmune disease — Type 1 diabetes, multiple sclerosis, Crohn's disease and rheumatoid arthritis are just a few. Because all autoimmune diseases are connected in the way the immune system attacks the body, Benaroya Research Institute at Virginia Mason (BRI) scientists aren't focused on eliminating one or two autoimmune diseases — they are taking on many more. As a world leader in scientific innovation, BRI's discoveries are having significant impact on people living with autoimmune diseases today — by improving the ability to predict disease risk, decreasing disease progression and making therapies safer and better.

Autoimmune diseases strike one in 20 Americans

As a world leader in scientific innovation, BRI's discoveries are having significant impact on people living with autoimmune diseases today.

What is BRI's formula for success?

EXPERIENCE — BRI's researchers have been making scientific discoveries for more than 25 years. They've discovered why some people are more susceptible to certain diseases than other people. They've learned how and why some people's immune systems attack and destroy their own cells and tissues. They've been able to create tests to figure out better therapies for these diseases.

EFFICIENCY — The institute shares a common focus, core resources and infrastructure that frees scientists to focus on pioneering ideas.

COLLABORATIONS — Scientists and clinicians in Seattle and beyond come to BRI for innovative technology, expertise and partnerships.

LEADERSHIP — BRI leads boldly. Organizations such as the National Institutes of Health, JDRF and the Helmsley Trust have funded BRI to develop significant new programs.

Adam Kerr (right) with Coordinator Marli McCulloch-Olson, Diabetes Clinical Research. Adam participated in a trial aimed at halting progression of newly diagnosed Type 1 diabetes.

Prototype of a tissue-engineered replacement for blood vessels that have been damaged or lost through disease or injury, developed by Robert Vernon, PhD, and Thomas Wight, PhD. The Wight Laboratory has found a novel way to induce cells to produce the rubber-like protein elastin to provide resilience in engineered cells, which include replacements for blood vessels. This finding led to BRI's first spin-off biotechnology company Matrexa, which arose out of research from Dr. Wight at BRI and Mervyn Merrilees, PhD, at the University of Auckland, New Zealand. The goal is translate this discovery into therapeutic applications for a variety of tissues, including skin and artery replacements.

Discovery Starts in the Laboratory

ONE OF THE UNIQUE QUALITIES OF BRI is the close integration of three types of medical research — laboratory research, translational research and clinical research — to improve people's lives. "Our scientists can address both the basic science issues and clinical applications," says BRI Director Gerald T. Nepom, MD, PhD. "That is the best way to design studies with the highest potential for success."

The laboratory provides a controlled environment to discover the unknown, test theories and develop new ideas.

BRI's significant laboratory advances in 2012 include:

- **A breakthrough discovery of how allergy shots steer the immune response** to prevent allergies. These findings open new horizons for understanding allergic disease and improving safety and efficacy of current allergy shots. Scientists Erik Wambre, PhD; William Kwok, PhD; and David Robinson, MD, led this work.
- **Decoding how a common change in a gene called PTPN22 may predispose children and adults** to develop autoimmune diseases including Type 1 diabetes, rheumatoid arthritis and lupus. Jane Buckner, MD, BRI associate director, and colleague David Rawlings, MD, Seattle Children's Research Institute, now lead a team testing how this gene may help predict the people who are at risk for autoimmune conditions and whether a therapy can be developed to compensate for this genetic change.
- **Finding a new complexity in the immune system** — a "mirror" regulatory cell for each kind of helper T cell to tell it how to respond. "Now when we want to target a certain group of cells to correct the immune system when it makes a mistake, we need to find the right regulatory T cells to target," says Daniel Campbell, PhD, principal investigator of this work.
- **Discovery of a molecular pathway to regulate macrophages** — cells in the immune system that are some of the first responders at sites of injury, infection and inflammation. This work was performed by the laboratory of Jessica Hamerman, PhD.

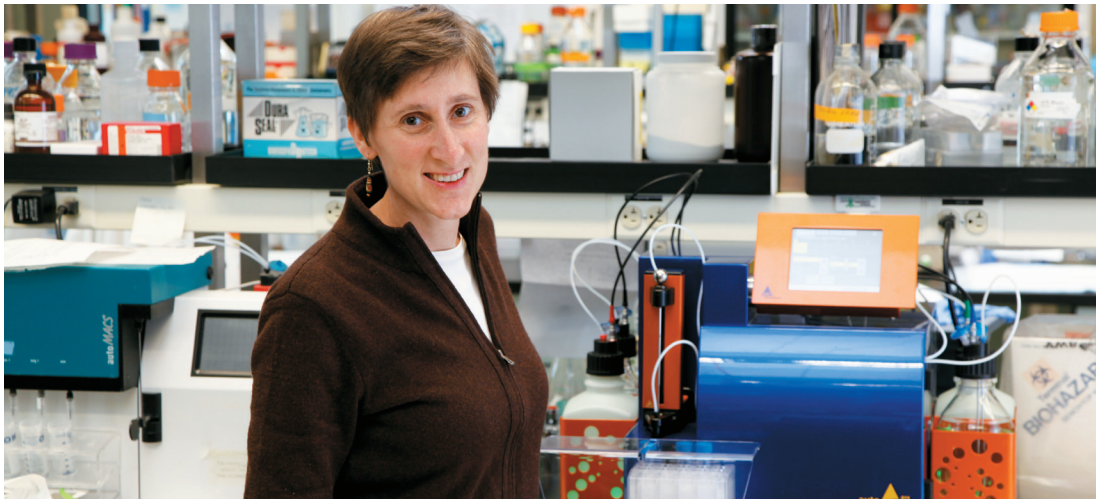
Erik Wambre, PhD (center), with his colleagues, discovered pioneering information about allergy shots and how the immune system works.

Translational Research and Biorepositories

TRANSLATIONAL RESEARCH is the link between laboratory research and clinical research, built upon an exchange of materials and information between these two disciplines. BRI scientists and collaborators work together to study blood and serum samples along with medical and demographic data collected from people with autoimmune and immune-mediated diseases. These include multiple sclerosis, Type 1 diabetes, lupus, rheumatoid arthritis, inflammatory bowel disease, allergy and asthma. BRI maintains an extensive biorepository with samples dating back to 2000, including 11 disease categories and a biorepository of healthy people for comparison purposes.

Advancements in 2012 also include the following:

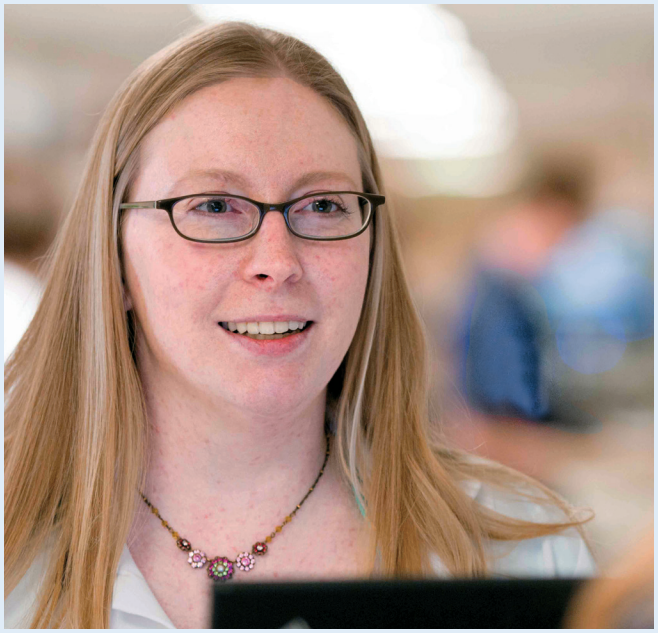
- **BRI established a new translational research core laboratory** — the Human Immunophenotyping Core. Scientists use this core to identify the underlying mechanisms of disease and develop biomarkers of disease, says Alice Long, PhD, manager of the core. The core is also a designated laboratory for the Immune Tolerance Network (ITN). BRI Director Gerald T. Nepom, MD, PhD, serves as the director of the ITN, one of the largest government-funded clinical research networks in the nation working to accelerate new treatments for diseases of the immune system.
- **The BRI Diabetes Research Program, under the direction of Carla Greenbaum, MD, received a $4.4 million grant** from The Leona M. and Harry B. Helmsley Charitable Trust to establish the T1D Exchange Biobank Operations Center. Dr. Greenbaum serves on the Joint Steering Committee for the T1D Exchange®, which consists of a clinic network, the online community called Glu and the biorepository.
- **BRI scientists began new partnerships with several biopharmaceutical companies** to potentially speed up translational research of diagnosis and treatment of autoimmune and immune-mediated diseases.



Alice Long, PhD, manager of BRI's Human Immunophenotyping Core laboratory, evaluates biomarkers for immunological changes associated with disease status and response to experimental therapy.

PARTICIPANT PROFILE: SUMMER ENGLER

Despite suffering from three autoimmune diseases, Summer Engler maintains her enthusiasm serving patients as a general medical intern at Virginia Mason. Her goal is to become a rheumatologist to treat musculoskeletal diseases like hers and continue her dedication to medical research. She is enrolled in the rheumatic diseases biorepository at Benaroya Research Institute. She joins more than 200 scleroderma participants volunteering for research to better understand how the immune system fails in autoimmune diseases.



PARTICIPANT PROFILE:
MICHELLE MUNRO

A red nose during the holiday season was the first sign that Michelle Munro had an uncommon autoimmune disease. Relapsing polychondritis (RP) occurs when the immune system attacks cartilage throughout the body. It most often affects the ears, nose, joints, spine and trachea, though other body parts can be affected. With constant pain and worsening symptoms, Michelle enrolled in a new clinical trial to test a drug that blocks one of the major signaling systems used by the immune system in autoimmune diseases. After six months of study treatments, Michelle is reclaiming her life. "I've appreciated the ability to be a team member with Virginia Mason and BRI in this research and move ahead in a positive way," she says.

Michelle Munro (left) with her partner, Jeaneen Watkins and assistance dog, Hayden, at the Grapes on the Green event to benefit BRI.

Clinical Trials Bring Research Results to Patients

CLINICAL RESEARCH STUDIES are conducted with volunteers who participate in experimental medical approaches not available outside the clinical trial setting, and play a major role in pushing the boundaries of knowledge about their disease and new therapies.

BRI conducts nearly 100 trials each year in many different diseases: through a Diabetes Research Program partnership with Seattle Children's, TrialNet and the National Institutes of Health; trials with the Immune Tolerance Network; and the BRI Clinical Research Program with physicians at Virginia Mason.

Exciting advancements in 2012 include:

- **Multiple sclerosis research.** Participation in clinical trials led to the FDA approval of a second oral agent (teriflunomide) for multiple sclerosis and a third anticipated in 2013. Studies in 2013 will focus on the possibility of remyelination as well as impact of treatment on brain volume measurements. Translational work also remains active with exploration of biomarkers to guide treatment decisions.
- **Rheumatology research.** Led by Stanford Peng, MD, PhD, BRI was part of the pivotal trials for the first drug in a new class of immunotherapies called JAK inhibitors. This is the first oral medication to be approved in a number of years and the only major drug approved for rheumatoid arthritis in 2012.
- **Type 1 diabetes research.** Clinical trials included the study of an artificial pancreas *(see box on page 8)*, new experimental drugs to modify the immune response, whether vitamin D can change how immune cells function, better ways to measure insulin secretion and how best to monitor patients at risk of developing Type 1 diabetes.

Prevention of Diseases

ONE OF THE IMPORTANT LESSONS learned in BRI's quest to diagnose, better treat and cure autoimmune diseases is that earlier intervention is better than later intervention. And the ultimate goal of early diagnosis and therapy is prevention — before autoimmune diseases become a clinical problem.

Several pioneering advancements at BRI in 2012 focused on prevention:

- **Calculating an individual's risk for the development of Type 1 diabetes** — the publication of a practical algorithm by Carla Greenbaum, MD, and collaborators at TrialNet. With this discovery, at-risk people can be closely monitored and have opportunities to enter a prevention trial.
- **Exploring how to interrupt the immune process** that causes the destruction of insulin secreting beta cells in the pancreas during the "pre-diabetic" state and thereby prevent or delay the onset of Type 1 diabetes. BRI is participating in an experimental drug therapy prevention trial sponsored by TrialNet offered to relatives of people with diabetes who are themselves at very high risk for developing the disease.
- **Researching how to restore balance between "good" and "harmful" cells** involved in initiating disease, by regulating the immune response. Jane Buckner, MD, will lead a $2.6 million study to understand how the immune system becomes unbalanced and how it might be manipulated in people with autoimmune diseases.
- **Looking for the genetic roots of Type 1 diabetes.** Three different research strategies are being used together to follow the precise molecular steps that are caused by susceptibility genes associated with Type 1 diabetes, in a new $4.3 million grant to BRI investigators.
- **Identifying key infectious triggers and regulators of a molecule called TSLP**, a key component of the early immune response in the lung airways leading to asthma and allergies. Immunology Research Program Director Steven Ziegler, PhD, leads the laboratory team.

PARTICIPANT PROFILE: HANNAH MILLARD

Hannah Millard, a 12-year-old from Anacortes, Wash., tested as very high risk to develop Type 1 diabetes and entered the teplizumab prevention trial, headed at BRI by Carla Greenbaum, MD. She received infusions every day for two weeks to test if the drug can help stop or slow down the immune reaction that causes Type 1 diabetes. "When I felt stressed during the study, I thought that I'm helping a lot of people and this is worth it," says Hannah.

Hannah Millard (right) with her mom, Kristin Glenn

Personalized Medicine

"OUR VIEW OF THE IMMUNE SYSTEM continues to evolve, and we continue to be surprised by its complexity," stresses BRI Director Gerald T. Nepom, MD, PhD. "The good news is that there are multiple opportunities for targeted intervention — for disease prediction, prevention, intervention and therapy — based on the knowledge we gain."

Immunology research is driving toward individualized treatment for each person with autoimmune and immune-mediated diseases. "Each person's genetics, environment and immune system mechanisms are unique," Dr. Nepom emphasizes. "People react to therapies differently and their responses may change over time. The optimal approach will be to individualize health care for each person and offer the right treatment at the right time."

BRI is leading several worldwide efforts to personalize medicine:

- **Damien Chaussabel, PhD, and his Systems Immunology Division team are developing a way to provide an immune system profile** for individual patients. The profile will detail the expression of thousands of genes over a person's lifetime. The goal is to provide an early warning of things to come and an indication of what treatments might be needed. In 2012, the development of a low-cost genomic fingerprinting assay enabled the team to generate immune signatures of hundreds of patients with infectious and autoimmune diseases. Such an assay may one day make its way to the clinic where tools for evaluating immune health are critically needed.
- **William Kwok, PhD, and his team developed new biomarkers to allow individualized studies of responses** to vaccines and food allergies in 2012. They also developed a new biomarker to study individuals with the highest level of risk for developing Type 1 diabetes. BRI serves as the inventor and international leader for the production and application of biomarkers that have brought about a broad array of scientific advances, including the study of individual immune responses to better understand disease and how to personalize treatment.

PARTICIPANT PROFILE: CLARK WEBBER

Clark Webber, 23, was diagnosed with Type 1 diabetes 11 years ago. The Diabetes Research Program has a full spectrum of studies for participants throughout the disease process. Research ranges from prevention trials for high-risk individuals to studies for the newly diagnosed working to save insulin-producing cells, and therapies to help manage diabetes and reduce possible disease complications. Clark is participating in a clinical research trial to test an artificial pancreas that automatically calculates and dispenses insulin based on real-time changes in blood glucose levels. The hope is this would relieve adults, children and their families from the arduous 24/7 manual maintenance of their diabetes. "The artificial pancreas looks to be the next big, decisive innovation in diabetes management and care," says Clark. "It will bring a newfound level of freedom to people like me."

Dana VanBuecken (left), ARNP, with participant Clark Webber

PRINCIPAL SCIENTISTS

Margaret Allen, MD, FACS
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Estelle Bettelli, PhD
Jennifer Bollyky, MD
Jane Buckner, MD
Daniel J. Campbell, PhD
Karen Cerosaletti, PhD
Damien Chaussabel, PhD
James E. Dennis, PhD
Carla Greenbaum, MD
Jessica Hamerman, PhD
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FISCAL YEARS ENDING DEC. 31 (000s omitted) (UNAUDITED)

STATEMENTS OF FINANCIAL POSITION

ASSETS	2012	2011
Cash and investments	$ 15,153	$14,966
Funds held at VMHS on behalf of BRI	16,668	14,986
Grants and other receivables	8,013	7,298
Other assets	2,318	1,289
Land, buildings and other fixed assets, net	33,377	31,126
TOTAL ASSETS	**$ 75,529**	**$ 69,665**
LIABILITIES		
Accounts payable, accrued expenses and advance payments	9,884	9,439
Bonds payable	30,547	26,116
TOTAL LIABILITIES	**$ 40,431**	**$ 35,555**
NET ASSETS		
Unrestricted	21,450	21,811
Temporarily restricted	4,737	3,812
Permanently restricted	8,911	8,487
TOTAL NET ASSETS	**$ 35,098**	**$ 34,110**
TOTAL LIABILITIES AND NET ASSETS	**$ 75,529**	**$ 69,665**

STATEMENTS OF ACTIVITIES (Unrestricted Net Assets)

REVENUES	2012	2011
Sponsored research	$ 33,210	$ 31,122
Contributions and net assets released from restrictions	2,530	1,972
Other income	1,599	233
Nonoperating activities	5,946	4,169
TOTAL SUPPORT AND REVENUES	**$ 43,285**	**$ 37,496**
EXPENDITURES		
Research project costs	$ 32,258	$ 30,713
Research support	8,168	7,449
TOTAL EXPENSES	**$ 40,426**	**$ 38,162**
Refinancing of Debt	($ 3,220)	
Change in Unrestricted Net Assets	($ 361)	($ 666)

COMPONENTS OF SUPPORT 2012