<table>
<thead>
<tr>
<th>CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Welcome</td>
</tr>
<tr>
<td>1 What Are Autoimmune Diseases?</td>
</tr>
<tr>
<td>2 Multiple Sclerosis</td>
</tr>
<tr>
<td>3 Type 1 Diabetes</td>
</tr>
<tr>
<td>4 Allergy and Asthma</td>
</tr>
<tr>
<td>5 Lupus and Inflammation</td>
</tr>
<tr>
<td>6 Personalized Profiles in the Future</td>
</tr>
<tr>
<td>7 Translational Research</td>
</tr>
<tr>
<td>7 Principal Scientists, Research Sponsors, Board of Directors and Administration</td>
</tr>
<tr>
<td>8 Selected Financial Data</td>
</tr>
</tbody>
</table>
Dear Friends,

New therapies for several major diseases now selectively target just the faulty parts of the immune system, instead of suppressing the whole immune system, minimizing dangerous side effects. New knowledge now speeds diagnosis and enables earlier treatment, averting progressive disability. And new discoveries are the foundation for efforts to prevent diseases and track people's immune systems to personalize the best treatments for them. These pioneering advances are no longer dreams, they are reality, and we are proud of the role that Benaroya Research Institute at Virginia Mason (BRI) is playing in this medical revolution. In this report, we introduce you to some of our research participants, physician researchers and scientists who are leaders on the cutting edge of medical research for diabetes, arthritis, multiple sclerosis, lupus, inflammatory bowel disease, allergy and several other autoimmune and immune mediated disorders, working to create a future bright with hope for conquering these diseases.

In 2011, BRI experienced a significant increase in growth and progress. Our research volume rose dramatically during the year to $37 million, as grant funding to BRI from the National Institutes of Health (NIH) increased by 24 percent over 2010. A record 6,872 people participated in our registries or clinical research trials in 2011 to advance medical science. Our researchers published more than 100 scientific papers in competitive, peer-reviewed research journals and gave 137 presentations worldwide, from Bellevue to Budapest.

Scientific programs continued to grow, with expansion of BRI's Systems Immunology Division led by Damien Chaussabel, PhD, and through increased activities at BRI for the Immune Tolerance Network (ITN), a major NIH-funded clinical research network for immunological diseases led by BRI's Director Gerald Nepom, MD, PhD. Institutional growth kept pace, and we welcomed Homer Lane as chief financial officer and chief administrative officer to lead our financial and operational functions, and Bolong Cao, PhD, as our first business development director, to implement an intellectual property management and technology commercialization strategy. Together with Virginia Mason, BRI established the Wilske Center for Translational Research to provide a supportive framework for clinic-based physicians and BRI researchers to collaborate.

In the next few pages, we celebrate our advancements and gratefully acknowledge our board members, donors, collaborators, clinical research participants and partner organizations who work with us to change dreams into reality. Thank you for your support.

Sincerely,

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

Jack Nagan, JD
Executive Director, Benaroya Research Institute
Faces of Hope — WHAT ARE AUTOIMMUNE DISEASES?

For an active young woman with a skin rash and kidney disease, it is lupus. For a mother with weakness and vision problems, it is multiple sclerosis. For an athletic teenager ready for college who must inject insulin several times each day, it is Type 1 diabetes. For Benaroya Research Institute at Virginia Mason (BRI), autoimmune diseases are more than 80 different disorders in which the body’s immune system makes a mistake and attacks the body’s own healthy tissues. Our scientists work together to study the genes, molecules, cells and function of the immune system to discover the common elements that — no matter what type of organ is affected — will explain the disease course and help identify the best approach for therapy.

CLINICAL RESEARCH: A PATH TO PROGRESS

Clinical trials are research studies conducted with volunteers who receive access to experimental new approaches often not available outside the clinical trial setting, and an opportunity to contribute to learning about and treating their disease. BRI conducts dozens of trials each year in many different diseases, through our Diabetes Research Program partnership with Seattle Children’s and the National Institutes of Health; through trials with the Immune Tolerance Network in other autoimmune diseases; and through the BRI Clinical Research Program partnership with physicians at Virginia Mason.

THE POSSIBILITIES

Researchers at BRI are keenly aware of the expression “in vivo, veritas.” Truth (veritas) in clinical research comes from testing in real life (vivo), not in test tubes. When laboratory and preclinical studies indicate a high probability of success, it is time to invite people to participate as research team members, volunteering themselves to help advance science and medicine through clinical trials, registries and studies of their blood and tissue. Whether testing a new drug therapy, studying a combination of drugs in a new way, or monitoring immune cells in response to a novel treatment, BRI’s clinical and translational research programs provide a coordinated system for the patient. Staff members help them decide if they want to enroll in a study. If they choose to participate, staff members work with them closely to monitor health, safety and changes in their disease profile.

Clinical research is not just for people with disease, but also for disease-free people who want to help advance knowledge. In a typical study, blood samples, tissue samples, medical history and other data from disease-free people are being compared with those with autoimmunity, such as Type 1 diabetes, to understand how healthy immune systems work compared with those with disease. BRI maintains registries and sample repositories allowing comparisons of thousands of individuals for a large variety of diseases, as well as healthy “control” participants.

Lawrence White regularly contributes blood samples for the registry of disease-free people. “My mom works at Virginia Mason and she joined the healthy registry group and was telling me about it,” he says. “I thought it was a great way to do my part to fight autoimmune diseases. I’m concerned about diabetes within my family and the African American population. Just giving my blood is an easy way to help the cause.” Lawrence and Sylvia White have both participated in the healthy registry for four years.

(L – R) Elise Boden, MD, Janice Chen and James Lord, MD, PhD, study inflammatory bowel disease.
In 2003, four months after her mother received a diagnosis of multiple sclerosis (MS), Molly Jo McGuire learned that she had MS, as well. Molly Jo experienced the typical numbness and fatigue with initial disbelief. “It seemed unreal so close on the heels of my mother’s diagnosis,” she says. Since then, Molly Jo’s husband discovered he too has MS, as does his sister.

Molly Jo regularly gave herself injections for the MS and then stopped when she had her children, Ivy Jane, 4-years-old, and her 2-year-old twins, Elliot and Alice. She had serious side effects when she returned to the injectable medication. Her neurologist, Mariko Kita, MD, head of the Virginia Mason Multiple Sclerosis Center, and Molly Jo discussed a clinical study as an alternative.

“I decided to join a BRI clinical research trial for a new oral MS medication,” Molly Jo says. “It seemed like a promising choice for me personally, and I also wanted to participate to help find better treatments for this disease. I feel fantastic because of the new medication and it’s wonderful to contribute to research.” Molly Jo has a full, active life with family, friends and work, but she still makes time for the research study. “Our family is committed to helping conquer MS.”

BRI’s programs in MS clinical research include trials of innovative experimental therapies that target molecules used by the immune system to penetrate and inflame the central nervous system. BRI’s MS registry connects laboratory scientists with blood samples from these research participants to advance understanding of how and why MS develops and to quickly assess how laboratory findings can predict clinical outcomes. Projects at BRI also focus on genetics to learn how particular genes can increase susceptibility for MS, and how those same genes influence the type of personalized therapy that can be offered to individuals. Investigators in the Bettelli and Buckner laboratories at BRI have homed in on three specific types of T lymphocytes that are suspects in the hunt for the best way to reverse immunological activation in MS: a cell known as “TH17” that drives the disease process; a cell known as “TREG” that tries and fails to control the disease; and a cell known as “TEFF” that resists the body’s attempts to down-regulate the damaging inflammation that destroys nerves and brain tissue in MS.
**AN ATHLETE’S STORY**

When you’re 13 years old and a high-performing gymnast, it’s bewildering to learn you have Type 1 diabetes.

“I was mostly confused, because I had no clue what diabetes really was,” says Jordan Widener, a senior at Glacier Peak High School in Snohomish. “All I knew was my life was going to change forever.”

Jordan quickly learned to be more organized. “There are no more last-minute sleepovers with my friends,” she says. “I have to plan what I’m doing each day and the next. When you’re an athlete training up to 24 hours a week, diet is really important. Diabetes helped me learn about good nutrition, which will keep me healthy throughout my life.”

Jordan joined a clinical research trial at Benaroya Research Institute that aims to preserve the cells that produce insulin as long as possible. This study is now in long-term follow-up and has shown positive results.

“The folks at BRI are awesome! They have given me so much help with controlling my diabetes,” she remarks. “My hope is that the research gives us a better understanding of diabetes and leads to a cure. I joined because I wanted to do my part.”

While it’s challenging to manage her diabetes while performing at such a high level, Jordan has reached her dream. She accepted a scholarship for gymnastics at the University of California-Berkeley for fall 2012.

For more than 20 years, Benaroya Research Institute has served as a worldwide leader in research to prevent, treat and cure Type 1 diabetes (T1D). BRI scientists have accounted for several of the substantial discoveries in the field, including the identification of diabetes susceptibility genes, descriptions of the properties of diabetes-associated immune cells, and the development of laboratory and clinical tools to study disease progression and response to therapy.

In 2011, a major clinical trial sponsored by the Immune Tolerance Network was completed by Carla Greenbaum, MD, director of BRI’s Diabetes Research Program, and her BRI colleagues, pioneering a radically new type of therapy. Instead of just interfering with the immune response that causes T1D, this trial simultaneously boosted the part of the immune response that — under normal circumstances — helps regulate overactive immune cells. BRI investigators also completed studies of another novel approach to therapy, attempting to immunize volunteers with diabetes against their disease. Using BRI’s tetramer biomarker technology, patients in this trial were studied to determine both the safety and the immunological effects of this vaccine. In a new collaborative program funded by the Washington State Life Sciences Discovery Fund, together with University of Washington stem cell researchers, BRI scientists are developing a bioengineered implantable matrix (the natural substance that holds cells together in every tissue). This matrix is designed to support the transplantation of insulin-producing cells made from advanced adult stem cells called progenitors.
If Tom Hardy eats food that contains nuts or seafood, he can feel a tingling sensation in his mouth, swelling in his throat and pain in his stomach, followed by a struggle to breathe. His food allergies and asthma have caused life-threatening events, requiring several emergency hospital visits.

“It’s scary to feel your body spiral out of control and not be able to breathe,” he explains. “I need to be extremely careful of what I eat and carry an EpiPen and Benadryl with me wherever I go.”

When Virginia Mason allergist David M. Robinson, MD, suggested Tom take part in a Benaroya Research Institute biorepository to study people with allergies and asthma, Tom was highly motivated to join.

“Now that my baby daughter, Willow, has arrived, I have even more reason to participate,” Tom remarks. “I want to help her out if she has allergies. I want to support the advancement of research to understand these diseases and help find ways to prevent them in the future.” For the last four years, Tom has provided blood samples for BRI scientists to study.

**A FATHER’S STORY**

**THE POSSIBILITIES**

Therapy for severe allergies currently requires lengthy and often dangerous allergy shots, also, progression to asthma is very difficult to control. BRI’s investigators have developed two new approaches designed to break this pattern and pioneer a novel treatment and monitoring paradigm. In one strategy, researchers led by Steven Ziegler, PhD, director of BRI’s Immunology Research Program, are investigating a key factor, termed TSLP, which helps initiate the inflammatory cascade that leads to the onset and progression of asthma and allergies. In another, a BRI team led by William Kwok, PhD, and Eric Wambre, PhD, uses BRI’s tetramer technology to detect and study the immune cells that are affected by administration of allergy shots. These studies have, for the first time, provided a clear picture of the fate of the allergic cells as they circulate in the body before, during and after therapy. By comparing these results with the clinical symptoms of patients in the studies, investigators can use these findings to develop safer, more effective and faster treatment.

*(L – R)* Eddie James, PhD; William Kwok, PhD; and I-Ting Chow, PhD, further develop tetramer technology.
In two weeks, Kammi Short gained 35 pounds, her body was swollen, a rash appeared on her face and she couldn’t find out what was wrong. Finally, an uncle recommended she visit Virginia Mason. After three days of testing, on her 24th birthday, it was discovered she had lupus. Doctors reported that she was a day away from kidney failure and a lifetime of dialysis. Lupus is a chronic autoimmune disease that can damage any part of the body — skin, joints and organs. Kammi’s lupus is characterized by inflammation of the joints, swelling and fatigue. “The worst part is not knowing one day to the next how I’ll feel,” she says. “I’ll be 100 percent going to bed and in the morning, I won’t be able to get up; my joints are so sore.”

Now 35, Kammi also suffers from two other autoimmune diseases, Sjogren’s syndrome and Raynaud’s disease. Several family members have autoimmune diseases, including Type 1 diabetes and multiple sclerosis. This is a familiar pattern to BRI scientists, who study families such as Kammi’s to search for the genes and underlying mechanisms that are common to different autoimmune diseases.

Stanford Peng, MD, PhD, Virginia Mason rheumatologist, told Kammi about a new lupus BRI clinical research trial he is conducting with a drug that may reduce the symptoms of inflammation in lupus. “I thought, if I receive the medicine and it makes me feel better it is worth it,” says Kammi. “If it helps me, it may help others, and it’ll inform researchers on what works or not.”

Kammi works at a child care center and loves working with horses, taking part in barrel races and other events. “What I do requires a lot of energy and right now I’m feeling great. I hope this trial can be part of the solution for lupus.”

Continued, p. 6
Inflammatory autoimmune diseases such as rheumatoid arthritis, lupus, scleroderma and others illustrate dynamics of the immune system that pose difficult challenges to successful therapy. BRI scientists study molecular and cellular pathways that drive the inflammation in these diseases. For example, Jessica Hamerman, PhD, investigates specific signaling molecules that control immune cell function, and Karen Cerosaletti, PhD, focuses on the genes that are specific for lupus, contrasting those with genes that are more general for other autoimmune diseases. Daniel Campbell, PhD, and Paul Bollyky, MD, PhD, study ways to regulate the large variety of inflammatory pathways inappropriately activated in patients, searching for molecular switch mechanisms that can be exploited for better therapy.

Controlling immune activation is only part of the clinical picture, however. Healing of tissue already damaged by inflammation is critical. BRI investigators in the Hope Heart Matrix Biology Program, led by Thomas Wight, PhD, study the tissue’s ability to defend itself against the inflammatory cascade that leads to eventual disease, as well as ways for the tissue to repair itself and regain function. Projects led by Margaret Allen, MD, Robert Vernon, PhD, and James Dennis, PhD, supported in 2011 by the Department of Defense, focus on tissue engineering strategies designed to repair or replace injured tissues including tendons, ligaments, muscles and blood vessels.

BRI’s Systems Immunology Division is developing a way to provide an immune system profile for individual patients, monitoring signs of immune system problems with a sophisticated molecular analysis performed from a simple blood test. Led by Damien Chaussabel, PhD, these studies create a detailed profile that represents the expression of thousands of genes; as the profile changes over time, or with treatment, it provides both an early warning of things to come and also an indication of the types of therapies that may be needed. With this profile, it is possible to envision prevention or treatment for many autoimmune and immune mediated diseases specifically tailored to each person. Indeed, any immune response can be monitored in a similar fashion, and in 2011, BRI received a $5.3 million grant from the National Institute of Allergy and Infectious Diseases to develop this blood profiling technology for analysis of emerging and re-emerging infectious diseases all over the world.
Translational Research: Interpreting and Using Scientific Discoveries

The examples of personal stories told by Molly Jo, Jordan, Tom and Kammi illustrate the power of moving discoveries from the laboratory into clinical application. BRI’s mission is to develop and accelerate this process, by combining excellence in basic science with a teamwork approach to address unmet medical needs. 2011 was a year in which numerous such advances were realized, additional partnerships were formed, and new funding was secured to enable investigators to continue this record of accomplishment.

PRINCIPAL SCIENTISTS
Margaret Allen, MD, FACS
Chris Amemiya, PhD
“Aru” K. Arumuganathan, PhD
Estelle Bettelli, PhD
Jane Buckner, MD
Daniel Campbell, PhD
Karen Ceresaletti, PhD
Damien Chaussabel, PhD
James Dennis, PhD
Carla J. Greenbaum, MD
Jessica Hamerman, PhD
Michael Kinsella, PhD
Kris Kowdley, MD
Christian Kuhr, MD, FACS
William Kwok, PhD
S. Alice Long, PhD
James Lord, MD, PhD
Gerald T. Nepom, MD, PhD
Stanford Peng, MD, PhD
Helena Reijonen, PhD
Srinath Snda, MD
Bradley Stone, PhD
Robert Vernon, PhD
Thomas Wight, PhD
Steven Ziegler, PhD

RESEARCH SPONSORS
Alliance for Lupus Research
American College of Gastroenterology
American Diabetes Association
American Heart Association
American Society of Regional Anesthesia
Amgen Inc.
Anesthesia Patient Safety Foundation
Arthritis Foundation
Asthma and Allergy Foundation of America
The Broad Institute
Cancer Research Institute
Centers for Disease Control and Prevention
Crohn’s and Colitis Foundation of America
Cumming Foundation
Department of Defense
Food Allergy Initiative
Helmsley Charitable Trust
International Anesthesia Research Society
The Ben and Catherine Ivy Foundation
JDRF
Microsoft Corporation
Multiple Sclerosis Society
National Institutes of Health
National Science Foundation
ResMed Foundation
Roche Organ Transplantation Research Foundation
Southwest Oncology Group
Theragenics Corporation
UK Ministry of Defense
U.S. Army Medical Research Acquisition Activity
Washington State Life Sciences Discovery Fund
Zymogenetics

BOARD OF DIRECTORS
Jack I. Almo
Tom Cohen
John M. Corman, MD
Carla M. Dewberry
Frank A. Dvorak, PhD
Carla J. Greenbaum, MD
Ray Heacox
Andrew D. Jacobs, MD
Ditman L. Johnson
Gary S. Kaplan, MD
Thomas J. Kelley
Robert B. Lemon, Chair
Trish Markey
Gaylia R. Meitzen
Margaret Morrow
Gerald T. Nepom, MD, PhD
Kristi Pangrazio
Judith Rising
Miriam Sevy
Dale Sperling
Christopher B. Wilson, MD

ADMINISTRATION
Kay Branz, MBA
Andrew Burich
Bolong Cao, PhD
Holly Chase
Chris Hansen
Homer Lane Jr., MBA
Iris Mondri-Kish, MBA
Jack Nagan, JD
Gerald T. Nepom, MD, PhD
Cheryl Weaver
Jason Wood

(L – R) Jun Luo, MD, PhD, and Margaret Allen, MD, study ways to improve tissue repair and functionality.
### STATEMENTS OF FINANCIAL POSITION

<table>
<thead>
<tr>
<th>ASSETS</th>
<th>2011</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cash and investments</td>
<td>$14,966</td>
<td>$15,545</td>
</tr>
<tr>
<td>Funds held at VMHS on behalf of BRI</td>
<td>$14,986</td>
<td>$16,043</td>
</tr>
<tr>
<td>Grants and other receivables</td>
<td>7,298</td>
<td>5,911</td>
</tr>
<tr>
<td>Other assets</td>
<td>1,289</td>
<td>1,533</td>
</tr>
<tr>
<td>Land, buildings and fixed assets, net</td>
<td>31,126</td>
<td>30,092</td>
</tr>
<tr>
<td><strong>TOTAL ASSETS</strong></td>
<td>$69,665</td>
<td>$69,124</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LIABILITIES</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Accounts payable, accrued expenses and</td>
<td>9,439</td>
<td>6,510</td>
</tr>
<tr>
<td>advance payments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bonds payable</td>
<td>26,116</td>
<td>26,981</td>
</tr>
<tr>
<td><strong>TOTAL LIABILITIES</strong></td>
<td>$35,555</td>
<td>$33,491</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FUND BALANCE</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrestricted</td>
<td>21,811</td>
<td>22,477</td>
</tr>
<tr>
<td>Temporarily restricted</td>
<td>3,812</td>
<td>4,697</td>
</tr>
<tr>
<td>Permanently restricted</td>
<td>8,487</td>
<td>8,459</td>
</tr>
<tr>
<td><strong>TOTAL NET ASSETS</strong></td>
<td>$34,110</td>
<td>$35,633</td>
</tr>
</tbody>
</table>

| TOTAL LIABILITIES AND NET ASSETS            | $69,665| $69,124|

### STATEMENTS OF ACTIVITIES (Unrestricted Net Assets)

<table>
<thead>
<tr>
<th>REVENUES</th>
<th>2011</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsored research</td>
<td>$31,122</td>
<td>$24,432</td>
</tr>
<tr>
<td>Contributions and net assets released from</td>
<td>1,972</td>
<td>2,900</td>
</tr>
<tr>
<td>restrictions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other income</td>
<td>233</td>
<td>251</td>
</tr>
<tr>
<td>Nonoperating activities</td>
<td>4,169</td>
<td>5,881</td>
</tr>
<tr>
<td><strong>TOTAL SUPPORT AND REVENUES</strong></td>
<td>$37,496</td>
<td>$33,464</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EXPENDITURES</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Research project costs</td>
<td>$30,713</td>
<td>$23,631</td>
</tr>
<tr>
<td>Research support</td>
<td>7,449</td>
<td>7,110</td>
</tr>
<tr>
<td><strong>TOTAL EXPENSES</strong></td>
<td>$38,162</td>
<td>$30,741</td>
</tr>
</tbody>
</table>

| INCREASE (DECREASE) IN UNRESTRICTED NET ASSETS | $ (666) | $ 2,723 |

### COMPONENTS OF SUPPORT 2011

- Biotech and Pharmaceutical Studies 6%
- Foundation Grants 16%
- Federal Government Grants 72%
- Donation and Endowment Revenue 6%