Benaroya Research Institute at Virginia Mason (BRI) is relatively small compared to large research universities, but its impact goes well beyond its size and location, accelerating scientific discovery globally. A key reason for this is BRI's “culture of collaboration,” which expands the impact of scientists’ work through engagement with numerous external investigators. This article illustrates this collaborative emphasis with a few examples of how BRI’s expertise and unique scientific resources are shared with researchers all over the world.

“In many cases these collaborations result in extended scientific interactions that strengthen both BRI and our collaborating scientists,” says BRI Associate Director Jane Buckner, MD. “It helps us move research forward.”

**STUDYING CELLS TO ELIMINATE ALLERGIES**
—Bill Kwok, PhD, and Erik Wambre, PhD, with Imperial College London

For a project on one of the major causes of allergies (Timothy grass), supported by the National Institutes of Health (NIH) and the Immune Tolerance Network, Drs. Kwok and Wambre at BRI work with Dr. Stephen Durham of Imperial College London.

“By studying the immune profiling of these cells, we expect to learn more about the cellular and molecular mechanisms that lead to successful immunotherapy,” according to Dr. Kwok. This would allow researchers to find better ways to turn off the immune systems’ reaction to allergens and eliminate allergies.

**UNDERSTANDING T1D PROGRESSION**
—Helena Reijonen, PhD, and Bill Kwok, PhD, with University of Helsinki and University of Turku

In an NIH funded project to better understand genetic susceptibility of type 1 diabetes, Drs. Reijonen and Kwok at BRI work with Dr. Mikael Knip at the University of Helsinki and Dr. Jorma Ilonen at the University of Turku, Finland. Finland has a universal health system with excellent medical records. The country is able to track the diagnosis and health history of every child in Finland.

Clinical research participants in allergy studies in London contribute blood samples that are shipped to BRI for analysis. “By studying the immune profiling of these cells, we expect to learn more about the cellular and molecular mechanisms that lead to successful immunotherapy,” according to Dr. Kwok. This would allow researchers to find better ways to turn off the immune systems’ reaction to allergens and eliminate allergies.

*Continued on page 5*
Forty-year-old Cheryl Hile runs marathons, bicycles and holds a demanding full-time job—impressive accomplishments but, on the surface, not especially remarkable in this day and age.

Cheryl, however, is remarkable. She engages in these strenuous activities despite a dropped foot, weakened thigh muscles, fatigue and a “creepy-crawly” feeling in her body—all symptoms of multiple sclerosis (MS). MS is an autoimmune disease in which the body’s immune system destroys myelin, the protective sheath that covers nerve fibers. This affects the brain and spinal cord, leading to pain and disability.

“I was so depressed after receiving a diagnosis of MS,” she says. “I didn’t know anything about the disease except that I had a co-worker in a wheelchair and thought that was my future. But I kept on running and exercising because that was my stress reliever, where I could be myself.”

In keeping with her take-charge personality, Cheryl did extensive research on the disease and the best places for treatment and research. She soon discovered Virginia Mason Medical Center and Benaroya Research Institute at Virginia Mason (BRI). In partnership with Virginia Mason, BRI’s team of expert scientists is focused on identifying causes and cures for MS and other devastating autoimmune diseases.

Cheryl and her husband moved to Seattle so that she could become a patient of Mariko Kita, MD, BRI clinical investigator, director of the Virginia Mason Multiple Sclerosis Center and head of the Department of Neurology at Virginia Mason. From their first meeting, Cheryl knew Dr. Kita was right for her.

“Dr. Kita is very compassionate and doesn’t talk down to you,” Cheryl says. “She gives me information so that I can make my own choices and doesn’t tell me what to do. And she is very willing to help keep me active and running.”

BIOREPOSITORY PARTICIPANT
Even though she has moved back to San Diego, Cheryl continues to see Dr. Kita. She also participates in BRI’s MS biorepository. A biorepository consists of blood and tissue samples linked to medical and demographic information collected from people with a specific disease or condition. Researchers use this information to better understand progression of diseases and possible therapies, accelerating the translation of discoveries from the lab to the patient.

“Through the biorepository, researchers at BRI discovered a biomarker for MS that can be used as a target for new therapies,” she says. “What I hope for is better treatments for MS and I would really like to see a cure, so if it means regularly donating a small amount of blood, then I will gladly extend my arm!”

For more information about MS research, visit BenaroyaResearch.org.

**Progress in MS Therapies**

BRI and Virginia Mason have participated in more than 30 clinical studies that have advanced MS treatment including FDA approval of new therapies shown on this chart. One of the most promising new areas of research lies in remyelination—reversing damage and growing back nerves. BRI and VM are now testing a new molecule for the first time in humans that has been shown to repair and reduce lesions.
Benaroya Research Institute (BRI) has been awarded another leadership role in type 1 diabetes research. Carla Greenbaum, MD, BRI's director of the Diabetes Research Program and Clinical Research Center, has been named chair of Type 1 Diabetes TrialNet.

TrialNet is a network of the world’s leading type 1 diabetes researchers exploring ways to prevent, delay and slow progression of the disease.

BRI now leads Type 1 Diabetes TrialNet and its Clinical Network Hub, the T1D Exchange Biobank Operations Center, the JDRF Core for Assay Validation (CAV) and the Immune Tolerance Network (ITN). BRI’s collaborations uniquely consolidate type 1 diabetes leadership at BRI in all major aspects of research including:

• Prevention (TrialNet)
• Intervention (Immune Tolerance Network)
• Biomarkers (JDRF CAV)
• Repositories (T1D Exchange Biobank)

DR. GREENBAUM ON TRIALNET

How does TrialNet help people with type 1 diabetes?
Many people are still producing small amounts of insulin at the time of diagnosis. TrialNet looks for treatments that can help extend insulin production since even small amounts of natural insulin production can decrease long-term complications and improve disease management.

For relatives of people with type 1 diabetes—who are at 15 times the risk of developing the disease—TrialNet offers a unique risk screening test that can identify those persons with the highest risk years before symptoms appear.

What is the benefit of identifying high-risk individuals?
• Those individuals found to be at highest risk may be eligible to join a prevention trial, testing ways to delay and prevent type 1 diabetes.
• When type 1 is identified at its earliest stages, it allows for early and aggressive therapy, which goes a long way toward preserving the pancreas's ability to continue making insulin. This is critical, especially in children, because it may make their diabetes easier to manage and lessen the likelihood of serious long-term complications.
• People who are diagnosed early may be able to avoid getting seriously ill. About 25-30 percent of children with type 1 diabetes are diagnosed when they are seriously ill, compared to 3-4 percent of those who participate in research studies such as TrialNet.

What prevention trials are available?
Based on screening results, individuals may be eligible to join one of three prevention trials. Each trial tests a medication—oral insulin, abatacept and teplizumab—to see if the drug can help delay and/or prevent onset of type 1 diabetes. All of the medications have shown promise in earlier studies.

What trials do you have for those newly diagnosed?
TrialNet researchers are currently testing whether a drug used alone or in combination with another drug will help those newly diagnosed (within the last three months) continue to make some of their own insulin.

A pilot study found that those who received the combination maintained insulin production for up to one year after treatment compared to the untreated group who experienced a nearly 40 percent decline.

What are your hopes for people with diabetes?
Type 1 diabetes is a complex, devastating disease that needs to be managed 24/7. With TrialNet and other research collaborations, we are making tremendous progress. We are moving to where we can intervene in the disease process prior to and during diagnosis. We hope to find ways to eliminate and prevent this disease.

How can I learn more about diabetes research studies?
Visit: BenaroyaResearch.org/diabetes-research
Call: 800-888-4187
Email: Diabetes@BenaroyaResearch.org

TRIALNET BY THE NUMBERS

15 years of dedicated clinical research and trials
17 Clinical Centers in North America and 6 International Centers
200+ screening sites worldwide (screening test kits are also available by mail)
INSPIRING FAMILY SUPPORTS RESEARCH

If you’re searching for a story of human triumph in the face of living with autoimmune diseases, look no further than the Biesold family.

In 2006, Christie Biesold, then a single mom with two children, was stopped in her tracks with stiff, painful and inflamed toes and fingers. She had difficulty putting on her clothes, couldn’t cook and clean, and required help at work for physical tasks. “I’m a very independent and mentally strong person,” she explains. “I was mortified that I needed help to do regular things like open cans of food.”

Even though he still fights pain daily and flare-ups on a monthly basis, it does not keep him from his passions, spending time with his 10 grandchildren and fishing in Alaska.

Several years ago, another medical concern entered Christie’s life. Her daughter, Courtenay Brennan, at age 15, developed painful TMJ. She also suffered from pain in her joints and full body fatigue. “I learned on the first day of my freshman year in high school that I had psoriatic arthritis too,” says Courtenay. “Because my mom was totally on top of it, we knew we needed to treat it aggressively.” Even though Courtenay quickly began the latest treatments, she missed half of her freshman and sophomore classes. After finding the best therapy for her, she was able to fully attend her junior year and have an active social life.

“We were worried that I’d have to undergo jaw reconstruction surgery but the drugs stopped the deterioration of my jaw,” notes Courtenay. “That was amazing news and a really high point in my treatment.” She is now starting her senior year. “I decided I need to be positive about this disease. It’s made me a more mature person and given me a lot of opportunities to meet people and support others who struggle with diseases. With my mom and family by my side, I can fight this, go to college and have a good life.”

A NEW CHALLENGE

The close family, who support each other so strongly, now has another challenge. Christie’s 15-year-old son, Conor Brennan, has recently developed an autoimmune disorder that also was difficult to diagnosis. He has a rare illness called PANDAS, Pediatric Autoimmune Neuropsychiatric Disorder Associated with Strep, which results in inflammation of the child’s brain. Christie worked for months trying to get a correct diagnosis, and is now working tirelessly to find the right medical care and support for her son.

“It’s just heartbreaking to have your children afflicted with these diseases,” says Christie. “No child should have to go through this pain and suffering. As an adult, I feel like I can take it, but I know what it’s like to ache all over and I know what they’re up against.”

HOW THE BIESOLDS HELP

Even though they’re dealing with several diseases, the whole family—Phyllis and Bruce Biesold, Christie and Todd Biesold, and their children Courtenay and Conor Brennan and Gill and Colby Biesold—are committed to supporting causes important to them. When they learned about BRI’s research to prevent, treat and eliminate autoimmune diseases, they supported the institute with a $10,000 gift and shared their story at BRI’s fundraising event Grapes on the Green.

For more information on giving to BRI, visit BenaroyaResearch.org.
the country who develops type 1 diabetes, as well as their siblings. Samples from these children are sent from Finland to BRI for tetramer analysis—a technology developed at BRI to study the cellular properties of the immune system. This is helping scientists to understand how the disease progresses before symptoms begin to appear. With this knowledge, scientists can figure out how to stop the immune system from attacking insulin-producing cells in type 1 diabetes.

**IMMUNE CELLS AND SKIN DISEASES**  
Adam Lacy-Hulbert, PhD, and University of Rochester

“Using models of immune responses in the skin, developed by Dr. Deb Fowell at the University of Rochester, we have together discovered that immune cells use different mechanisms to enter inflamed and normal skin,” reports BRI’s Dr. Lacy-Hulbert. “This may lead to new approaches to block autoimmune diseases that cause skin disease (such as psoriasis, pemphigus and lupus) without affecting normal immune responses.” The Lacy-Hulbert Laboratory has a number of collaborations to advance research into how the immune system balances defenses against infections while preventing autoimmune diseases.

**CELLULAR THERAPY AND T1D**  
Steve Ziegler, PhD, and Jane Buckner, PhD, with University of California, San Francisco (UCSF) and Yale University

As part of a consortium funded by JDRF, Drs. Ziegler and Buckner at BRI collaborate with Dr. Jeff Bluestone at UCSF and Dr. Kevan Herold at Yale to study regulatory T cells in type 1 diabetes (T1D). Regulatory cells are important for modulating the immune system. Studies focus on ways to modify these cells for use in cellular therapy. In clinical trials, regulatory T cells are injected into a patient to increase suppression of an immune system’s attack on the cells that create insulin. Techniques for growing and modulating these cells are jointly developed, and methods specifically developed at BRI for monitoring the cells infused into patients are used in the trial.

**CELLULAR STRESS AND T1D**  
Eddie James, PhD, and University of Pittsburgh

“In collaboration with Drs. Jon Piganelli and Meghan Marre at the University of Pittsburgh, we’re investigating cellular stress and the formation of disease,” explains BRI’s Dr. James. Cellular stress happens when target cells—such as islet beta cells in type 1 diabetes—mistakenly come under attack by the immune system or infectious agents. How the cells respond to this stress can have a major influence on whether the cells will survive. Dr. Piganelli is an expert in cellular stress and the impact it has on immune system diseases. The James Laboratory at BRI links this type of cellular stress to specific changes in the immune system that appear to be an important step in understanding how the body attacks its own islet beta cells causing type 1 diabetes.

**TRANSLATING RESEARCH TO THERAPIES**  
Jane Buckner, MD, and Gerald Nepom, MD, PhD, with Bio Design Institute at Arizona State University

When Drs. Jason LaBaer and Ji Qiu of the Bio Design Institute designed a new technology to identify autoantibodies—molecules made by the immune system that can act as biomarkers for disease—they approached Drs. Buckner and Nepom at BRI to translate this technology into medical applications. Starting with rheumatoid arthritis, and now extending these studies to relapsing polychondritis, this technology has uncovered several new potentially important molecular targets. Based on these data, the BRI lab of Dr. Eddie James is now investigating whether T cells from people with rheumatoid arthritis recognize these same molecules and could be used as targets for new therapies.

**HUB FOR IMMUNE RESEARCH NETWORKS**  
Carla Greenbaum, MD, Gerald Nepom, MD, PhD, Eddie James, PhD, Jared Odegard, PhD, and Jane Buckner, MD

BRI investigators lead two of the major autoimmune disease clinical networks, both funded by NIH. TrialNet (Dr. Greenbaum) and the Immune Tolerance Network (Dr. Nepom) involve dozens of academic medical centers worldwide. BRI also acts as the coordinating center for other major collaborative initiatives such as the JDRF Core for Assay Validation (Dr. Odegard), the Immunology of Diabetes Society T Cell Workshop (Dr. James) and the NIH-sponsored Cooperative Disease Study Group for Autoimmunity (Dr. Buckner).
ATTEND ILLUMINATIONS LUNCHEON
What: The Illuminations Luncheon is an opportunity for guests to learn firsthand about the latest in allergy research at BRI and to support immune diseases research.
When: Oct. 30, 11 a.m.–1 p.m., The Fairmont Olympic Hotel, Seattle
Contact: BenaroyaResearch.org or event manager at 206-223-7521 or email Events@VirginiaMason.org

TOUR BRI ON SCIENCE FRIDAYS
What: Attend our Science Friday Tour to learn more about BRI and immune diseases research. The event includes a light breakfast, conversation with a leading researcher and a lab tour led by scientists.
When: Sept. 25 and Dec. 4: 8-9:30 a.m.
Contact: Rachel Martin at 206-342-6519 or RMartin@BenaroyaResearch.org

JOIN US AT LIFE SCIENCES RESEARCH WEEKEND
What: This event provides an opportunity for the entire family to learn more about the exciting world of life sciences research. BRI and other research institutes will have hands-on demonstrations.
When: Nov. 6–8, 2015, at Pacific Science Center
Contact: PacificScienceCenter.org/research-weekends