

BRING IT ON.®

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NEW APPROACHES TO ELIMINATING RA

Benaroya Research Institute at Virginia Mason (BRI) is waging a comprehensive fight against rheumatoid arthritis (RA). “During the last 15 years, treatments for RA have improved enormously with new therapies,” says BRI President Jane Buckner, MD, who is leading this work. “But it is a chronic disease and

and side effects and may stop working. We want to find ways to treat people early and target only the cells that cause the disease and, eventually, prevent the disease.”

RA is an autoimmune disease caused when the immune system mistakenly attacks the membrane that lines the joints. About 1.3 million people in the United States have the disease—almost 1 percent of the nation’s adult population.

PREVENTING DISEASE

“To prevent disease, you need to know who is going to get the disease, when will they get it and how will they get it,” says Dr. Buckner. Since 2002, BRI has collaborated with the University of Colorado, Denver, on SERA (Studies of the Etiology

of Rheumatoid Arthritis), which is focused on understanding how RA starts and progresses. Scientists study relatives of people with RA who volunteer to give their blood and medical histories and follow those who have genes and autoantibodies (ACPA and RF) that are highly

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Jane Buckner, MD, (left) leads the rheumatoid arthritis research at BRI, looking for new ways to treat and eliminate the disease.

if left untreated results in pain and permanent disability. There is no cure. Current treatments are expensive, may have risks

BRI works with a group of collaborators—all top experts in RA:

- Karolinska Institute, Stockholm, Sweden
- University of Denver
- Stanford University
- University of Arizona
- University of Minnesota
- University of California, San Francisco

They research rheumatoid arthritis from various angles including prevention, matching patients with the right treatment early on and discovering who will respond to a certain drug and who won't.

VOLUNTEERING TO FIGHT RHEUMATOID ARTHRITIS

A day prior to her 51st birthday last year, Aline Keller fell in the shower. “Within one week I had so much pain and swelling in my hands and joints that I could barely walk,” she says. “I went through rigorous testing to see what was going on.” A couple of months later she was diagnosed with rheumatoid arthritis (RA).

Aline suffered with extreme pain and swelling in her shoulders, elbows, hands, knees and feet. “I was having problems with sleeplessness, crankiness, moodiness and depression,” she explains. “Getting dressed in the morning was a chore, and taking a shower, getting into my car and driving to work was hard to face.”

Her physician in Yakima, Wash., sent her to Virginia Mason Medical Center as soon as he received her test results. “I decided to come to Virginia Mason because of the medical center’s reputation in the RA field,” she notes. “When all of this started I did not think life would ever be normal again. I think that if I would have gone anywhere else, I wouldn’t have had the same positive results.”

At Aline’s first visit with her rheumatologist, Jeffrey Carlin, MD, he told her about Benaroya Research Institute and suggested that she would be a good candidate for joining the rheumatic disease biorepository. “I met with Mohammad Pourmandi from the biorepository, who is very nice and informative. He is always there to meet me before my visits,” she explains. Aline has a blood draw every three months for her lab tests and the biorepository at the same time.

LEARNING ABOUT RESEARCH

The rheumatic disease biorepository is a confidential list of people with rheumatic diseases who are willing to donate a blood sample and provide health information to support scientific research. Donated samples and personal and family health information are used by scientists in the laboratory and in analysis to help scientists better understand the causes and long-term health effects of rheumatic and immune-mediated diseases, as well as to explore better treatment options that can be used by physicians in patient care.

“I hope this research will eventually help people so they don’t have to go through the pain and suffering I have gone through this past year,” says Aline. “I hope that someday in the future the research will help people to be cured before the disease starts.”



Aline Keller participates in rheumatoid arthritis research to help others. She enjoys spending time with her children and grandchildren.

With various medications and new immunotherapy drugs, Aline eventually began to feel better. “I resumed some of my daily activities like walking my dogs, fishing and hiking,” she says. “My life is not 100 percent like it was, and I still take pain medications and muscle relaxers as needed. But I have a lot more to look forward to on a daily basis than before I started my weekly injections.”

To learn more about biorepositories at BRI or to join, please visit [BenaroyaResearch.org/biorepositories](https://www.BenaroyaResearch.org/biorepositories) or call toll-free 1-877-202-5200 or e-mail biorepository@BenaroyaResearch.org.

Scientists at Benaroya Research Institute recently discovered a critical pathway in peanut allergy that may extend to other food allergies. The pathway is triggered by Interleukin 33 (IL-33), a protein that helps drive the immune response that promotes allergic reactions to a substance, such as peanuts, that in most people is generally harmless.



Steven Ziegler, PhD, and Karen Cerosaletti, PhD, received a \$2.9 million grant to expand their food allergy research.

“If we understand more about how IL-33 works, we can find the best ways to modify the pathway and hopefully stop food allergies,” says Steven F. Ziegler, PhD, BRI’s director of Academic Affairs and the Immunology Research Program.

Dr. Ziegler and co-investigator Karen Cerosaletti, PhD, BRI research assistant member and manager of the Genotyping Core, recently received a \$2.9 million grant to expand this research. Collaborators will include Virginia Mason, Stanford University Medical School and Asthma Inc.



“By studying blood samples of people with peanut allergies and building model systems of food allergic responses, we’ve discovered that IL-33 is critically important throughout the development of peanut allergies and perhaps all food

allergies,” says Dr. Ziegler. “It’s very exciting that currently therapies are being developed to target IL-33 in other allergic diseases.”

BRI is conducting a variety of research studies aimed at preventing and finding new treatments for potentially life-threatening food allergies. The prevalence of food allergies has increased in the past several decades and affects an estimated 5 percent of children and 3-4 percent of adults in industrialized countries.

Food allergies occur when people have an immune response to food that releases chemicals that cause sneezing; itching in the nose, eyes and ears; diarrhea; and in rare cases the life-threatening reaction anaphylaxis. Currently there are few available treatments to either prevent or cure food allergies, and available medications only treat symptoms following the onset of the allergic response. Given the public health and economic impact of food allergies, there is an urgent need to identify new targets for the

development of therapies for treatment as well as potential diagnostic tools to treat this debilitating condition.

The discovery of the role of IL-33 began when Dr. Cerosaletti analyzed the blood of research participants in a clinical study of peanut allergies. She looked for

the key genes which promote the inflammatory responses seen in allergies. These genes included Thymic stromal lymphopoietin (TSLP), IL-25 and IL-33, all of which have been studied by BRI in the past.

“We are almost full circle in putting together the elements that explain how allergies occur,” says Dr. Ziegler. He previously identified TSLP as a new factor triggering the onset and progression of asthma and allergies.

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If it wasn't for the Murdock Trust helping us with essential pieces of equipment and new technology for over 30 years, we wouldn't have been able to achieve our cutting-edge research advancements," says BRI President Jane Buckner, MD. "Jack Murdock's belief in scientific knowledge as a key to solving the challenges of our world has made an enormous difference to us."

ESSENTIAL NEW TECHNOLOGY

The Murdock Trust has granted BRI with more than \$3 million over 30 years for state-of-the-art core equipment to support the research labs. These include several flow cytometers, histology



"Aru" K. Arumuganathan, PhD, director of the BRI Flow Cytometry Core, manages use of several of the machines purchased in part with grants from the Murdock Trust.

core laboratory equipment and the CyTOF mass cytometer machine. Recently, the trust granted BRI \$308,000 toward a new flow cytometer.

"Fundamental to the success of BRI is directly studying cells from patients with autoimmune diseases and other immune-mediated disorders," says Adam Lacy-Hulbert, PhD, a BRI principal investigator who will be using the new flow

cytometer. "The new flow cytometry machine will greatly increase our capacity to sort and analyze patient samples, and provide high levels of biological containment, as recommended by the National Institutes of Health. This will allow us to expand our research to use new patient groups and techniques, including novel studies into how infections affect the immune response, and keep BRI at the leading edge of basic and translational immunology."

"Our new machine will provide us with high efficiency cell sorting based on expression of up to 22 different parameters at speeds of up to 25,000 cells per second," says "Aru" K. Arumuganathan, PhD, director of the BRI Flow Cytometry Core. "The equipment will support the scientific labs at BRI and 19 current grant projects that we're conducting. We're grateful to the Murdock Trust for their ongoing significant support."

CELEBRATING ITS 40TH ANNIVERSARY

The Murdock Trust is celebrating its 40th anniversary this year. Jack Murdock lived an inspiring life with many interests and a dedication to community. He was born in Portland, Oregon, in 1917. Upon graduating from high school, he purchased a shop, with the help of his parents, for the sale and service of radios and electrical appliances. Jack and his technician Howard Vollum eventually founded Tektronix, one of the world's prominent electronic instrumentation companies.

In 1960, Jack was elected chairman of the board of Tektronix, a position he held until his untimely, accidental death in 1971. In his will, Jack established The M.J. Murdock Charitable Trust. Since its formation on June 30, 1975, the trust has focused most of its grant-making efforts in the five states of the Pacific Northwest: Alaska, Idaho, Montana, Oregon and Washington. A historical emphasis in the trust's grant awards has been in higher education, scientific research and development, human social services, health care and the arts. Over the years nearly \$850 million has been given, placing the trust within the top five largest private foundations in the Pacific Northwest.

To learn more about core laboratories, visit BenaroyaResearch.org. To learn more about the Murdock Trust, visit murdock-trust.org.

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related to RA. Researchers found the disease begins years before clinical signs and symptoms are apparent and is initiated through activation of certain proteins in the joints.

“Our findings suggest that we could intervene in this disease before it develops,” says Dr. Buckner. “We are now studying which cells would be good targets for preventing disease or providing early therapy. This sets the stage for clinical research trials in preventing RA.”

KNOWING THE RIGHT TREATMENT

“Physicians now have the tools to make a good diagnosis of RA and we have many choices for medications,” says Dr. Buckner. “But our difficulty is choosing the right drug for the right person. We are sometimes guided by patient preference, cost or contraindications, but with the majority of patients we just select a drug based on our experience, and if it does not work we move to another medication. This can take time, time in which patients continue to suffer with arthritis. We want to be able to pick the most effective drug early on. This would prevent further destruction of the joints and alleviate pain more quickly.”

Through earlier research, BRI discovered the destructive T cells that drive RA. Scientists are now studying these specific T cells in the joint to see

how they change with disease activity and therapy. “If we can observe the patient’s immune response to a drug soon after a therapy starts, we can determine if it’s working or not,” says Dr. Buckner. BRI, Virginia Mason Medical Center and the Veterans Administration Puget Sound Health Care System are studying a broad population of individuals with RA in this study.

PREDICTING DRUG RESPONSE

There are six classes of RA drugs, and some people respond to the medications and some people don’t. Some will work for a limited time and then become ineffective. Physicians, scientists and the pharmaceutical industry are joining together to predict patient drug responses ahead of providing treatment. This would allow physicians to prescribe the right drug before treatment even begins.

JOINING A BIOREPOSITORY

All of this work is supported with samples from the BRI Rheumatic Disease Registry and Biorepository. Thank you to our volunteers who donate blood samples and provide health information to support research.

For more information on RA, biorepositories and BRI’s research, visit BenaroyaResearch.org.

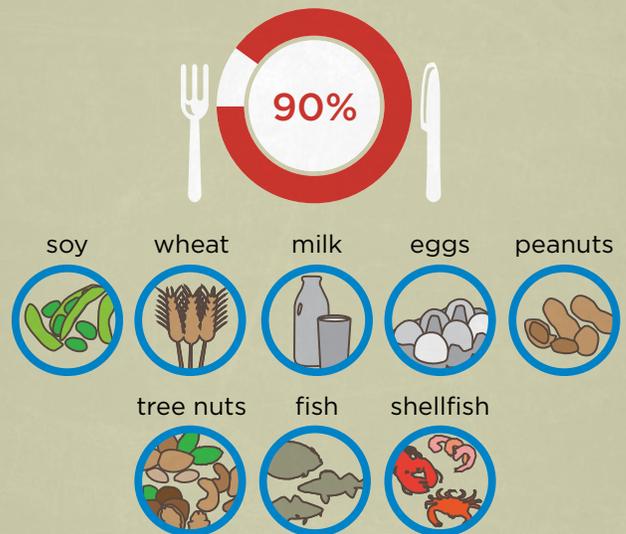
PEANUT ALLERGY

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Using model systems, Dr. Ziegler tested these proteins throughout the allergic immune response and found that IL-33 is critically important for both sensitization to allergen in the skin, as well as in the response following oral consumption. Research studies support the theory that allergies in children can develop following sensitization through the skin, leading to possible anaphylactic responses after oral consumption.

“Our new grant will allow us to replicate and expand our investigation of IL-33 and other proteins and genes in larger groups of people with food allergies, through the BRI biorepositories and research participants at Stanford, Virginia Mason and Asthma Inc.,” says Dr. Cerosaletti.

Eight top allergens cause 90 percent of food allergies



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ATTEND ILLUMINATIONS LUNCHEON

What: The Illuminations Luncheon is an opportunity for guests to learn firsthand about breakthrough discoveries spotlighting advances in diagnosing and treating and even preventing autoimmune diseases. BRI President Jane Buckner, MD, will be the featured presenter.

When: Friday, Oct. 28, 11 a.m.–1 p.m., expo, lunch and program, The Fairmont Olympic Hotel

Contact: Visit VirginiaMasonFoundation.org/events, call 206-583-6514 or email Events@VirginiaMason.org.



TOUR BRI ON SCIENCE FRIDAYS

What: Attend our Science Friday Tour to learn more about BRI and our unique approach to medical research. The event includes light refreshments, conversation with a leading researcher and a laboratory tour led by scientists.

When: Sept. 16: Noon–1:30 p.m., Dec. 9: 8–9:30 a.m.

Contact: Rachel Martin at 206-342-6519 or RMartin@BenaroyaResearch.org.

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BRI is a world-renowned nonprofit medical research institute focused on diseases of the immune system. For more information, visit BenaroyaResearch.org or call 206-342-6500.

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