As people who are affected by lupus know, it is one of the most puzzling and complex autoimmune diseases, say Benaroya Research Institute scientists and Virginia Mason clinical researchers. Diagnosis is difficult because it can affect all the systems of the body. Current treatments haven’t effectively treated the many symptoms of lupus and they have significant side effects.

“The manifestations of the disease are so varied, there are no two people alike,” says Jeffrey Carlin, MD, head of BRI clinical research for lupus and member of the Virginia Mason rheumatology section. “But good things are on the horizon for people with lupus. Scientists are discovering much more about the disease and how it works. New drugs, currently in development, will target the immune system more specifically, making them more effective, with fewer side effects.”

BRI’s approach to research takes all the complex elements of autoimmune diseases into consideration. “We not only go broadly, but we go deeply,” says BRI President Jane Buckner, MD. “We study genetics, we develop in-depth knowledge of the immune response, we discover how the immune system operates in people with lupus compared to those without disease and we translate our knowledge to clinical trials. Our patients provide feedback that goes back to the laboratory and that improves the treatments. That’s how we do science — in a deep, extensive continuous improvement loop.”

Dr. Buckner is a rheumatologist who sees people with lupus at Virginia Mason every week. “It’s a very difficult disease, and we’re dedicated to improving the care of our patients and ultimately curing lupus,” she emphasizes. “The answer will be in finding diverse ways to rebalance a person’s immune system so it doesn’t cause lupus.”

Though the cause of lupus is unknown, scientists have discovered three different factors that play a role in triggering lupus. These are genetic risks that predispose people to lupus; hormones — the disease is nine times more common in women; and environmental factors such as a virus, smoking, UV light and drugs.

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When there isn’t an approved treatment for a disease or when a drug stops working for a patient, doctors turn to clinical research trials for options for their patients. Virginia Mason and Benaroya Research Institute are working to provide a remarkable patient experience — where medical research is an option at every step of care, from initial diagnosis to long-term follow-up.

All clinical research at Virginia Mason is overseen by BRI, uniquely combining the expertise of a world-renowned medical research institute with the remarkable care of a healthcare quality leader. Patients receive the opportunity for promising treatments before they are broadly available.

WIDE VARIETY OF DISEASES

Research led by BRI clinical investigators primarily focuses on diseases of the immune system such as type 1 diabetes, multiple sclerosis, Crohn’s, ulcerative colitis, rheumatic diseases, allergies and asthma. Together, BRI and Virginia Mason clinical researchers engage in research across a wide variety of diseases and conditions such as cardiology, cancer and urology.

More than 1,000 patients participated in over 150 clinical research studies last year. More than 150 Virginia Mason physicians from nearly every clinical department are involved in research studies.

Here are some highlighted autoimmune diseases and allergy clinical research areas of focus. Be sure to consult with your physician, who can guide you to relevant clinical research studies. Clinical trials change often. To stay informed, join the Clinical Research Registry or look online for the latest information.

**Allergy and Asthma**

The Allergy, Asthma and Immunology Department at Virginia Mason has clinical trials that may include studies on food allergies and environmental allergies such as pollen and grass. Two clinical trials are now available for peanut allergies.

**Diabetes**

Type 1 diabetes clinical research trials range from prevention trials for high-risk individuals, to studies to save insulin-producing cells in the newly diagnosed, to therapies to help manage diabetes and reduce possible disease complications. For more information on studies through BRI’s Diabetes Clinical Research Program, visit BenaroyaResearch.org/diabetes, call 800-888-4187 or email diabetes@BenaroyaResearch.org.

**Gastroenterology**

The Digestive Disease Institute at Virginia Mason has a number of clinical trials open for inflammatory bowel disease — six clinical trials are available in Crohn’s disease and two in ulcerative colitis.

**Neurology**

Clinical trials are available in the Neuroscience Institute at Virginia Mason for diverse types of multiple sclerosis — three studies are currently open.

**Rheumatology**

New clinical studies currently available in the Rheumatology Department at Virginia Mason include one in giant cell arteritis and one in scleroderma. Novel studies will be forthcoming in lupus.

**HOW TO LEARN MORE:**

**Clinical Research Registry** — The Clinical Research Registry connects people interested in clinical research with physicians at Virginia Mason conducting these studies. To join the registry, visit BenaroyaResearch.org/CRR.

**Biorepository** — People with diseases studied by BRI can contribute to research by donating blood and medical histories. People without these diseases are also needed to participate. To learn more about joining a BRI biorepository, call 877-202-5200, email biorepository@BenaroyaResearch.org or visit BenaroyaResearch.org/bio.
HOW THE IMMUNE SYSTEM WORKS

The immune system has two arms that respond when an infection such as a virus occurs. The “innate” immune system is the part that responds first and is always present and ready to fight an infection. This part sounds the alarm so the first responders — much like the firefighters — come on the scene. The firefighters then pull a major fire alarm that communicates to other cells that they need to respond. These alarms are the cytokines, and they alert the “adaptive” part of the immune system to take action. The adaptive part of the immune system eliminates the infection. In this system, the B cells produce antibodies that bind to the virus to clear it from the body, but they can’t do it without the help of the T cells. The T cells help orchestrate the B cells, telling them what to do and shutting down the immune response when the virus is gone.

FINDING WAYS TO BREAK THE LUPUS CYCLE

“The signals that turn on the fire alarm in lupus are small proteins called cytokines,” says Jessica Hamerman, PhD, BRI principal investigator. Made by cells of the “innate” part of the immune system, cytokines are usually made in fast bursts to direct the B cells to make antibodies to fight an infection. “In lupus, the cytokines don’t get turned off and they amplify the response and feed the fire,” she explains. “When the B cells make antibodies that bind to the dying cells, it causes innate cells to make even more cytokines. The cells are activated again and again by the cytokine alarm, creating a vicious cycle.”

Dr. Hamerman researches how particular cells of the innate part of the immune system, called plasmacytoid dendritic cells, produce cytokines when they see dying cells, to signal the fire alarm. In lupus, important cytokines are called type 1 interferons. “It’s hard to block the type 1 interferons once they’re released from plasmacytoid dendritic cells, so we study how these cells interpret the signals from dying cells to make these cytokines. Then maybe we can interfere in the signal so they don’t make the interferons or make less of them. That would take the oxygen out of the fire or break the cycle.”

In studying all of the signaling steps in plasmacytoid dendritic cells, Dr. Hamerman and her team discovered a novel protein that controls the production of type 1 interferon and could be a target for therapies. “We’ve studied the protein in model systems and now in human samples from the BRI biorepository with exciting results,” she says. Dr. Hamerman’s study on cytokines just happened to connect to lupus — a disease that affected her grandmother.

GENETICS PLAY A MAJOR ROLE

“Genes are an important part of lupus,” says Karen Cerosaletti, PhD, principal investigator, who has researched genetics for 20 years at BRI and who has focused on lupus. “If you have a sibling with lupus, you are 20 times more likely to have the disease compared with the general population,” she notes. “Genes affect every part of the immune system in lupus. Genes tell us the pathways that are important in lupus that we could target for treatment. Genes that are found in lupus may also be involved in other autoimmune diseases, and we can apply what we learn in lupus to other diseases.”

In Dr. Cerosaletti’s recent research, she found that the BANK1 lupus gene increases the number of B cells in your body. When these B cells go amiss, they can make antibodies that recognize dying cells, starting the cycle of immune destruction causing lupus. “This gene predisposes your body to lupus, and this pathway could be a target for treatment,” she stresses.

A recent study at BRI in collaboration with Seattle Children’s Research Institute has shown how a variation in the gene IFIH1 increases the risk of lupus, while also protecting people from viruses. “This type of information helps us to understand why these genes are so common, and also helps us create more targeted treatments for lupus,” says Dr. Buckner, a leader of the study.

DISCOVERING NEW PATHWAYS FOR TREATMENT

BRI Principal Investigators Adam Lacy-Hulbert, PhD, and Mridu Acharya, PhD, study how cells make the bad decision to attack the body’s own cells. Dr. Lacy-Hulbert studies cells of the innate immune system called dendritic cells, which organize communications. “We research how dendritic cells make the decision to react to foreign materials or the body’s own cells and how they communicate it to the immune cells,” he says.
Dr. Acharya studied with Dr. Lacy-Hulbert and applied the knowledge to B cells in lupus. They are taking the information they are learning in model systems and applying it in human samples. “The B cells of people with lupus are hyperactive, causing inflammation and damage to tissues,” says Dr. Acharya. “We have discovered a new molecular pathway in lupus that includes certain proteins that normally work together to prevent B cells from targeting a person’s own cells, but it doesn’t function properly when people develop lupus. We want to understand why these proteins fail in lupus and potential treatments to get them working properly again.”

Dr. Acharya will use the BRI biorepositories to study this in people with lupus and healthy people to see the differences. She recently was among the ten researchers who received a Novel Research Grant from the Lupus Research Alliance to pursue this line of inquiry.

**STOPPING ACTIVATION OF LUPUS**

T cells can help B cells become activated and make antibodies. To understand the role of T cells in lupus, BRI scientists in the laboratory of Principal Investigator Bill Kwok, PhD, can identify the specific targets of these T cells using a novel technology developed at BRI called tetramers.

Tetramers capture the specific T cells that recognize dying cells in the blood of patients with lupus. Scientists can then describe the distinctive features of these T cells to find out how they go amiss. Preliminary results show that lupus specific T cells grow and divide, making more disease-specific T cells in a subset of patients with lupus. Dr. Kwok’s lab is further investigating the role of these T cells in the disease process.

**TESTING NEW THERAPIES THROUGH CLINICAL TRIALS**

BRI and Virginia Mason are also on the forefront of testing new drugs for lupus. “Within the year, we should have several new clinical trials for patients that will test new drugs targeting the pathways of lupus,” says Dr. Carlin. “We are also a part of the Lupus Clinical Investigators Network.” This group works to facilitate the clinical study of new and existing therapies to treat, cure and ultimately prevent lupus. This provides more clinical trials for Virginia Mason patients with lupus to hopefully expand treatment options.

“Through our lupus biorepository, where we collect volunteers’ blood samples and medical histories, we can also learn more about the variance of lupus in different people,” says Dr. Carlin. “Some may be more affected genetically, or in B cells or T cells. If we know that, we can tailor medicine to each person.”

BRI has a Clinical Research Registry people can join to be informed of clinical trials that may be appropriate for them. Visit BenaroyaResearch.org/CRR.

People with lupus and family members without lupus can also join the biorepository to help with medical research. Visit BenaroyaResearch.org/RA-bio.

**lupus fast facts**

- **1.5 million** Americans have lupus
- Develops between **15-45** years of age
- More frequent in **women** than men **9:1**
- More frequent in **women** of African American, Asian, Latino and Native American descent
- Currently there is **no cure** and there are limited treatment options
Bernard Khor, MD, PhD, is researching how to rebalance the immune system when inflammation gets out of control, causing autoimmune diseases such as inflammatory bowel disease and type 1 diabetes. He’s using new innovative approaches that bring together chemistry, bioinformatics and clinical collaborators.

Dr. Khor and his team have discovered a chemical that may be helpful in dampening inflammation, and its protein target. This discovery may help explain the greatly increased rate of autoimmunity in patients with Down syndrome, a medically important but poorly understood facet of the syndrome. To better understand this relationship and how it applies to other patients with autoimmunity, he’s creating a new BRI biorepository for people with Down syndrome.

“However, if the inflammation is too strong or goes on for too long, it can damage tissues, causing certain autoimmune diseases. Therefore, precise regulation of the inflammatory response is essential for maintaining health.”

White blood cells known as T cells are the main regulators of tissue inflammation. Specialized T cells called regulatory T cells shut down the immune response when it’s no longer needed. “Many autoimmune and other inflammatory diseases are thought to arise, at least partially, because regulatory T cells fail to stop the inflammatory response,” says Dr. Khor. “Boosting the number or the activity of the regulatory T cells could help treat these diseases.”

Dr. Khor and his team looked for a chemical or drug that would increase the activity or number of regulatory T cells. After screening over 3,000 chemicals, including many drugs currently approved for use in humans, they focused on a chemical called harmine that potently enhanced differentiation of regulatory T cells. In model systems, harmine reduced inflammatory reactions by inhibiting a protein kinase called DYRK1A.

AUTOIMMUNE DISEASES GREATER IN PEOPLE WITH DOWN SYNDROME

DYRK1A is also thought to be one of the driver genes in Down syndrome. “Patients with Down syndrome have a 15- to 100-fold greater chance of getting autoimmune diseases such as type 1 diabetes and celiac disease, and we want to understand why,” he says. “We think it’s related to excessive DYRK1A reducing the ability to generate anti-inflammatory regulatory T cells. If we’re correct, we might improve autoimmunity in these patients by inhibiting DYRK1A. Then we can go back to the broader patient populations with type 1 diabetes and other autoimmune diseases to understand who else might benefit from DYRK1A inhibition.”

To study this effectively, Dr. Khor will be establishing a BRI Down Syndrome Biorepository to collect blood and tissue samples and medical histories from people with Down syndrome and their siblings without Down syndrome as healthy volunteers for comparison.

“People with Down syndrome and their families are really suffering as they take on the additional burden of autoimmune diseases,” says Dr. Khor. “We’d like to find ways to help them as well as translate this to other people with autoimmune diseases. BRI has the expertise to bring everything together to solve this problem.”

Dr. Khor is starting his laboratory at BRI. To learn more, visit BenaroyaResearch.org/khor-lab. To learn about the Down syndrome biorepository call toll-free 877-202-5200.
UPCOMING EVENTS

BOEING CLASSIC GOLF TOURNAMENT
What: The Boeing Classic, an official PGA Champions Tour event featuring the legends of golf 50 years of age or older. The event will benefit Benaroya Research Institute.
When: Monday – Sunday, Aug. 21-27 at The Club at Snoqualmie Ridge
Contact: For more information and ticket options, visit BoeingClassic.com.

GRAPES ON THE GREEN
What: Join us for this lively wine tasting, multicourse dinner and auction that kicks off the Boeing Classic Tournament weekend. This event benefits Benaroya Research Institute.
When: Friday, Aug. 25 at The Golf Club at Newcastle
Contact: For more information, visit VirginiaMasonFoundation.org/events, call 206-223-7521 or email Events@VirginiaMason.org.

SAVE THE DATE: ILLUMINATIONS LUNCHEON
What: Learn about the latest breakthrough research at BRI. Attend as a guest, table host or table sponsor, or become an event sponsor.
When: Friday, Oct. 27 at a new location: Sheraton Downtown Seattle
Contact: Illuminations Luncheon event manager at 206-583-6514 or email Events@VirginiaMason.org.