In the 1860s, when the first American transcontinental railway was built, the first step in the process was to send out an advance team of scouts to identify the best route. After the pathway was mapped, a team of workers arrived to clear the roadbed by blasting rock and leveling the ground. Another group laid the tracks, and then the trains were able to proceed.

Building a railroad is an apt analogy for medical research. Before new therapies can be developed, basic scientists need to scout out a pathway for research. At Benaroya Research Institute at Virginia Mason (BRI), where basic researchers work hand-in-hand with clinical investigators, the mission is to understand diseases of the immune system and find new therapies. Therefore, basic research at BRI is centered on this question: How does the immune system work?

“You can’t lay tracks until you know where the train is going,” says BRI Director Gerald Nepom, MD, PhD. “In immunology research, that translates into discovering what the immune system cells are doing and what they do in disease.”

The Immunology Research Program team scouts a pathway for research by investigating how the immune system works.

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In March of this year, 13-year-old Lizzie Blockhus experienced a week of being very tired and not feeling well. "I woke up in the middle of night and was dying of thirst," she explains. "Then I was at my sister’s soccer game, dying of thirst again and I knew something wasn't right. My mom had me test my sugars on my sister's meter and they were high. She rushed me to Seattle Children’s Hospital." Lizzie was diagnosed with type 1 diabetes.

Even though Lizzie’s 16-year-old sister has type 1 diabetes, Lizzie didn’t think she would get the disease. "It didn’t seem real because I’m used to saying my sister has it, not me," she says.

Lizzie joined a clinical research study for people aged 12 to 45 years old who are newly diagnosed (less than three months) with type 1 diabetes. The study is through TrialNet, an international network of researchers who are exploring ways to prevent, delay and reverse the progression of type 1 diabetes. Carla Greenbaum, MD, head of BRI's Diabetes Research Program, is also the chair of TrialNet.

In the study, TrialNet researchers are testing whether a low dose of ATG (Thymoglobulin®) used alone or in combination with GCSF (Neulasta®) will help people with new onset diabetes 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.

"Many people are still producing small amounts of insulin at the time of diagnosis," says Dr. Greenbaum. "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. If this combination of drugs is successful it could be a very promising therapy."

Lizzie joined the study to help other people out. "We need a cure," she states. "I hope that the study is positive and that the medicine works and can help people in the future. I would advise people to join studies because you learn how they work. You also meet some very fun people along the way.

"Type 1 diabetes hasn't affected me that much except I have to look out for my health," says Lizzie. She attends middle school and plays soccer on elite teams. "Having diabetes doesn't stop you from anything. It just makes you a little bit more special."

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 of developing type 1 diabetes years before symptoms appear. 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. Learn more at BenaroyaResearch.org.
EXCITING ADVANCES IN MULTIPLE SCLEROSIS RESEARCH

Many new treatments for multiple sclerosis (MS), an autoimmune disease attacking the central nervous system, have been developed within the last ten years. But sometimes these drugs aren’t effective for certain people or have side effects or are difficult to administer. Scientists continue to look for better drugs and therapies as well as ways to eliminate MS. Below is a research update on a variety of studies that BRI is conducting or collaborating on with other institutions. They are tackling various scientific and immunologic questions that explore innovative ways to fight MS from the lab to clinical studies.

Can aggressive therapy halt aggressive MS?

In a clinical trial led by the Immune Tolerance Network (ITN), researchers used high-dose chemotherapy to suppress the immune system and transplanted the participants’ own stem cells to see if they could induce sustained remission in early aggressive relapsing-remitting MS. This year, the three-year interim report showed the approach to be highly effective. For this clinical trial, called HALT-MS, the ITN team at BRI leads a large multi-institutional research effort. At BRI, William Kwok, PhD, is researching the molecular details that describe immune responses in participants in this trial study.

Can abatacept stop or delay the progression of MS?

The science behind abatacept is different from other approved treatments for MS. Unlike most immunosuppressive drugs, abatacept targets a specific molecule on the surface of T cells that leads to changes in cell activation. T cells are key players in the autoimmune attack that leads to disability in MS. Because abatacept affects the immune system in a more specific way, researchers are evaluating its potential as a treatment for MS with fewer side effects than current medications. This study, called ACCLAIM, is being conducted by the ITN. BRI clinical researcher Mariko Kita, MD, enrolled patients in the study, and BRI scientists Adam Lacy-Hulbert, PhD, Jessica Hamerman, PhD, Estelle Bettelli, PhD, Dan Campbell, PhD, Steve Ziegler, PhD, and Jane Buckner, MD, are analyzing the immune system response of participants in the study.

Oral therapies are available, but are we using the right dose?

The last five years has seen the introduction of oral therapies to treat MS. Clinical researchers are examining whether the current dosing regimens are optimal and are comparing the effectiveness of two different doses of an oral drug (fingolimod) with an injectable drug (glatiramer acetate) at reducing relapses associated with relapsing-remitting MS (RRMS). Patients with RRMS have recurrent acute episodes (relapses) of neurological symptoms that are followed by a complete or partial recovery. It is hoped that reducing the number of relapses may help slow the progression of the disease. Achieving the optimal dosing schedule will help to individualize care of patients with MS. Dr. Kita is currently enrolling patients in this study.

How do some MS drugs work at a molecular level?

Dr. Bettelli, PhD, in collaboration with Mohamed Oukka, PhD, Seattle Children’s Research Institute, has been developing new experimental models to understand how the oral drug fingolimod works at a molecular level and how it is modulating different cells of the immune system. Does the drug work differently in different people and on different immune cells? Eventually this information will help clinicians to match the right drug to the right person at the right time.

Will this drug repair damage to the body?

Researchers are testing a new drug that aims to repair damage to the myelin that is destroyed in MS. The cells that make myelin can initially repair it, but as MS progresses, there is little spontaneous repair. While current treatments aim to slow the progression of the disease, there are no approved therapies that stimulate the repair or regrowth of myelin once it has been damaged. Researchers are testing rHlgM22, a drug that in preclinical studies promoted remyelination and also showed sustained improvements in motor activity. Dr. Kita is currently enrolling participants in this study.

Does MS that mostly affects the brain differ from the one that mostly affects the spine?

Joan Goverman, PhD, at the University of Washington, noticed in a system model of MS that when the disease mostly affected the brain, it was immunologically different from when it mostly affected the spine. She is collaborating with Drs. Buckner and Kita on this inquiry to see if the same thing can be demonstrated in humans. With samples from the BRI biorepository of patients with MS, they are further studying immunological signatures of those who have MS mostly in the spinal cord versus those with disease confined primarily to the brain.

How do people with MS progress over time?

Dr. Buckner and her team are using the BRI biorepository to conduct studies of people with MS to understand their response to different medications and the differences when their disease is active or not active. She is looking for changes that can be recognized in blood samples that will signal a favorable response to treatment or a sign that disease might be more aggressive in a particular individual. Such signals would help to identify patients who are not responding to treatment or who might need more aggressive initial treatment. This historical snapshot can help scientists investigate individual disease progression over time.

JOIN A STUDY OR BIOREPOSITORY

If you are interested in learning more about joining clinical studies or the BRI biorepository, visit BenaroyaResearch.org.
RESEARCH TECHNOLOGY AND TOOLS

Research is making an unprecedented leap forward as the ability to predict the onset or progression of disease is further developed. At the same time advancements are being made to intervene in the disease process in a more proactive and effective way. The springboard for this great leap is, and will continue to be, the rapid advance of technology. New tools improve the ability to devise solutions for complex diseases by quickly generating data and analysis to advance discovery.

INVESTING IN YOUNG SCIENTISTS

Science advances when bright young investigators bring their expertise, passion and enthusiasm to BRI. However, they have more difficulty getting grant funding to launch their research because they haven’t become established. BRI is committed to promising young scientists. Donations support setting up new laboratories and projects. These investments have proven successful many times over as young researchers make discoveries that improve people’s lives.

Here are some of the ways your generous donations make an impact on the fight against autoimmune and immune system diseases and improve the lives of so many:

DISCOVERY AND SEEDING INNOVATION

A critical characteristic of scientific research is that the timing and direction of discovery are uncertain. Finding the causes and cures for devastating immune system diseases must be pursued quickly and completely. Often it becomes essential to rapidly direct funds to new avenues of research and quickly explore emerging ideas.

Funding this rapid research allows BRI to respond to emerging innovations as they happen to accelerate the pace of discovery, leading to faster advances. Scientists can seed and test innovative hypotheses, build data and provide continuous project funding. This preliminary work and project continuity is key to BRI’s success rate in obtaining research awards to accelerate discovery. Because of this, BRI is much more likely to be awarded a National Institutes of Health grant based on well-supported grant applications. This allows today’s discoveries to advance into tomorrow’s clinical treatments and cures.

WHY GIVE TO BRI?

At Benaroya Research Institute, philanthropic investments have been absolutely critical to the success of scientific endeavors, innovative ideas and medical breakthroughs. Every philanthropic dollar invested at BRI for innovative research has been multiplied into additional research dollars through government grants and sponsored projects. In 2014, philanthropic investments in BRI totaled $7.1 million while more than $49 million was awarded to BRI by the government and other organizations for dedicated research activities.

Here are some of the ways your generous donations make an impact on the fight against autoimmune and immune system diseases and improve the lives of so many:

Kimm O’Brien with the latest technology Illumina machine that provides more efficient and faster study of cells.

Holly Akilesh, PhD, and Jessica Hamerman, PhD, accelerate research progress through donor contributions. Dr. Hamerman established her laboratory in part with philanthropic support.

How to Give

Contributing to BRI provides the Institute with vital funds to continue innovative research, invest in new ideas, support new investigators and buy critical equipment. Thank you for your generosity. Every gift large or small makes a difference. To give, visit BenaroyaResearch.org/support-us or return the enclosed donor envelope with your gift.
BASIC RESEARCH MAPS Route TO MEDICAL ADVANCES

Continued from front page

identifying their different roles. How committed is a cell to its process and can it be changed? Then, how can it be changed?”

BRI accelerates discovery through laboratory breakthroughs in immunology that are then translated to clinical therapies. That process begins when basic scientists ask creative questions about the immune system and how it works. They put together experiments that elicit information, and talk to other scientists at BRI and worldwide. They continually put together pieces of the immune system map. The basic scientists share their knowledge with other researchers at BRI who are experts in translating basic science into new therapies and conducting clinical research. "Having the research teams all under one roof is a very effective way of making medical advances," says Dr. Nepom.

While scientific technology and knowledge of human diseases have exploded in the last several decades, the immune system is incredibly complex and hard to map. It has evolved redundant pathways over millennia in response to diverse challenges such as infections and viruses. Its random design can be prone to mistakes causing diseases of the immune system. Scientists have also learned there are multitudes of different immune system cell types, and few are exactly alike.

“The scientists in this field are extremely creative and have to have a long-term view of where they are headed,” says Dr. Nepom. “They are rewarded when they get to experience the incredible excitement of discovering something new that was previously unknown.”

Basic research in immunology at BRI is led by Steven Ziegler, PhD, program director. Major discoveries by BRI scientists and their teams in this field include the following:

• Identification of genetic markers for disease susceptibility, particularly type 1 diabetes and rheumatoid arthritis. — Gerald Nepom, MD, PhD, and Barbara Nepom, MD.

• Descriptions of immune system genes, which provide insight into the way the immune system evolves and functions. — Steven Ziegler, PhD.

• Identification of a triggering molecule that promotes asthma and other allergic diseases. — Steven Ziegler, PhD.

• Discovery of ways the immune system cells cooperate and work together to fight infections while preventing immune attack against the body. — Adam Lacy-Hulbert, PhD.

• Descriptions of how the immune system turns on and off. — Daniel Campbell, PhD.

• Discovery of a “mirror” regulatory T cell that tells each different helper T cell how to respond. — Daniel Campbell, PhD.

• Identification of a subset of immune system cells believed to be potent inducers of multiple sclerosis and other diseases. — Estelle Bettelli, PhD.

• Definition of how external signals can react with immune system cells to change cell pathways. — Jessica Hamerman, PhD.

• Creating a topographical map of the molecular surface that initiates specific immune activation. — William Kwok, PhD, and Gerald Nepom, MD, PhD.

For more information, visit BenaroyaResearch.org.
JOIN US FOR SCIENCE FRIDAY IN 2016

You're invited to join us for a unique opportunity to learn about medical research at Benaroya Research Institute. BRI Science Fridays include the following:

• light refreshments
• overview of BRI with a lead researcher
• laboratory tour of BRI led by scientists
• discussion with board members and other guests

UPCOMING 2016 DATES

Breakfast, 8-9:30 a.m.
• Jan. 22
• March 25
• July 15
• Dec. 9

Lunch, Noon-1:30 p.m.
• May 20
• Sept. 16

Register: Reserve your seat to witness exciting immune system disease medical research. Contact Rachel Martin at 206-342-6519 or RMartin@benaroyaresearch.org.

THANK YOU!

We are grateful for the support of the 2015 Illuminations Luncheon Sponsors! The program showcased BRI breakthrough science with a spotlight on food allergy research.

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