LEADING A BIOMARKER CENTER: TO FIGHT TYPE 1 DIABETES

Biomarkers are key tools for scientists studying autoimmune and other diseases. A biomarker is a measurable characteristic that reflects a normal biological process or disease state. Researchers perform measurements on accessible tissues such as blood, urine or saliva and look for how the results can be used to track the disease process. Currently, biomarkers are used to identify people at risk for diseases, predict progression rates and assess how well treatments are working.

Recognizing an unmet need in the clinic, JDRF, an international organization funding type 1 diabetes (T1D) research, hosted a workshop in 2012 to focus on the identification and utilization of robust biomarkers for the disease. Gerald Nepom, MD, PhD, director of the Benaroya Research Institute at Virginia Mason (BRI), served as chair of this meeting, where leaders in the field from academia, government and industry shared ideas. Springing from this workshop was a newly formed Biomarker Working Group, developed to foster collaboration and data sharing among researchers in the international diabetes community.

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Jared Odegard, PhD, Cate Speake, PhD, and Gerald Nepom, MD, PhD, are leaders of the new BRI-designated JDRF Biomarker Core and Assay Validation Center.

An integral component of the Biomarker Working Group is the Core and Assay Validation Center (CAV), housed at BRI.

Through the leadership of Carla Greenbaum, MD, director of the Diabetes Clinical Research Program at BRI, the Institute is in a pivotal position to drive collaborative T1D research by virtue of both its internal diabetes patient registry and sample repository, its role as Operations Center for the multisite T1D Exchange Biobank, and now as the JDRF Biomarker Working Group CAV. Dr. Nepom is the principal investigator and Jared Odegard, PhD, is co-investigator of the CAV program supported by a $1.4 million three-year grant from JDRF. Cate Speake, PhD, serves as the operations manager of the CAV.

“The working group will help advance additional biomarkers from the lab to the clinic,” says Dr. Odegard. “Unlike some other cases, such as cancer, any individual biomarker in type 1 diabetes, taken in isolation, may not give us enough information to make individual treatment decisions. However, if we can combine different measurements into a kind of composite score, we expect it to dramatically increase the predictive value of these assays, so there is a real synergy in the group members working together.”

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A common myth about type 1 diabetes is that it skips generations. Eleven-year-old Adam Holcomb’s family learned the hard way that this is not true. Three generations of the family now have type 1 diabetes. Adam’s grandfather was diagnosed at age 12, his father, Reid, at age 29, and his older brother, Isaiah, at age 9. When Isaiah was diagnosed, his mother, Jenifer, began investigating if there was a way to keep Adam and his little sister, Rosie, from developing diabetes.

She learned that Type 1 Diabetes TrialNet was testing relatives of people with type 1 diabetes to determine if they are at increased risk. Benaroya Research Institute is the Type 1 Diabetes TrialNet Northwest Clinical Center. TrialNet, sponsored by the National Institutes of Health, is a network of 18 clinical centers that conducts prevention and intervention studies for type 1 diabetes.

When asked if it was a hard decision to have Adam and Rosie tested (knowing that there was no approved treatment to prevent diabetes), Jenifer replied, “It was an easy one for us. We wanted to try to get them into a prevention study if they were at risk.” TrialNet testing showed that Rosie was not at increased risk, but Adam did show autoantibody risk markers. Relatives with two or more antibodies will eventually develop diabetes. About 1 out of 3 will develop type 1 diabetes within five years.

Although Adam was scared to learn that he is at risk for type 1 diabetes, he was willing to try a research study that would “help people not have diabetes, and maybe keep me from having diabetes.”

Adam entered a prevention study testing abatacept. The drug was first approved by the U.S. Food and Drug Administration in 2005. It is now approved for use in people ages 6 and older who have rheumatoid arthritis or polyarticular juvenile idiopathic arthritis, which are also autoimmune diseases. TrialNet tested abatacept in people who had recently been diagnosed with type 1 diabetes. The people who received abatacept kept producing insulin longer than people who did not get abatacept. The hope is that the treatment will be even more effective in people who have not yet been diagnosed with diabetes.

Adam will receive infusions of either the medication or placebo every month for a year. Meanwhile, he enjoys hockey, skiing and playing his guitar.

What is Jenifer’s advice to other parents? “It is better to know if your child is at an increased risk so parents can be prepared, be vigilant for symptoms, and know what to expect. I would highly recommend checking into the prevention studies.”

To learn more about risk testing and prevention trials, please call 800-888-4187 or visit trialnet.org.

THERAPEUTIC STRATEGY FOR TYPE 1 DIABETES

Type 1 diabetes is an autoimmune disease in which the body’s immune system attacks and destroys the beta cells in the pancreas that make insulin. The destruction of the beta cells may continue for months or years prior to the clinical diagnosis of diabetes, giving researchers an opportunity to test ways to delay or prevent type 1 diabetes. For people who already have the disease, scientists look for therapeutic interventions to reduce complications and progression of type 1 diabetes.
HOPEFUL PROGRESS IN MULTIPLE SCLEROSIS RESEARCH

Multiple sclerosis (MS) affects more than a million people worldwide including 15,000 in the Northwest. It affects women twice as often as men. MS is the most common medical cause of neurological disability in young adults ages 20-40. Usually MS happens in multiple attacks. This can cause loss of vision; loss of sensation; or debilitating weakness, dizziness or pain.

Mariko Kita, MD, Benaroya Research Institute clinical investigator and director of the Virginia Mason Multiple Sclerosis Center, provides an update on the latest research in MS.

WHAT CAUSES MS?
We still don’t know. It may be caused by environmental factors such as viruses or a lack of vitamin D, and it has a strong genetic component. At BRI, Steve Zeigler, PhD, director of the Immunology Research Program, is researching whether an individual’s genetic code controls the development of MS.

WHAT TREATMENTS ARE THERE?
The first disease modifying therapy for MS became available in 1993 and today there are 10. These treatments are oral, self-injected or infusions. They reduce relapses and slow progression of neurologic disability.

WHAT ARE THE TYPES OF MS?
People have relapsing-remitting MS (RRMS), secondary progressive MS, primary progressive MS or progressive relapsing MS based on whether they have relapses/exacerbations, a stable level of functioning between relapses or if they are slowly getting worse. We have learned that these categorizations aren’t very helpful in treating people.

What’s important is what is happening behind these relapses and progression. In healthy people there is a balance between the inflammatory part of our immune system (when we are fighting infection, etc.) and the anti-inflammatory part of the immune system (when we calm down that inflammation). In MS, this is out of balance and we think the inflammation that causes lesions, scars, MS attacks and disability is being driven by Th1 cells. Our treatments tend to target calming down this inflammatory Th1 response or augmenting the anti-inflammatory Th2 response.

We have now learned about another important immune cell called Th17. It may play a role in the pro-inflammatory phase of the disease, causing relapses in people with MS. This research will help us classify MS according to an immunological basis such as a Th1- or Th17- driven disease.

At BRI, Estelle Bettelli, PhD, is characterizing Th17 disease. It may cause more motor deficit and respond to therapies differently. We have an upcoming clinical trial of a new treatment specifically targeting Th17.

HOW DO YOU KNOW HOW SEVERE A PERSON’S MS WILL BE?
At BRI, Jane Buckner, MD, associate director, and her colleagues have been studying patients with more active MS compared to those who have more benign MS. T cells, which are part of the immune response, are typically kept in check by regulatory cells. Dr. Buckner’s group has shown that in more aggressive RRMS, the T cells are able to evade regulation and they cause lesions. Her research also found how this could be reversed. When treated, T cells respond to the regulatory cells.

HOW DO YOU DETERMINE THE RIGHT TREATMENT?
Currently, we don’t have any mechanism for predicting how a person is going to respond to disease-modifying therapies. At BRI, Damien Chaussabel, PhD, director of Systems Immunobiology, and his colleagues are looking at gene activity in forms of the disease. With a small blood sample he is able to detect different profiles of gene expression and virtual genetic signatures of a disease. Once these signatures are established, he can then see the effect of treatment on the genetic signatures. We hope to predict soon after initiating treatment whether a person might respond to that treatment.

IS THERE ANY WAY TO REPAIR THE DAMAGE?
The new frontier of MS is reversing damage. The current therapies are only doing damage control. One of the most promising areas of research right now lies in remyelination, reversing damage and growing back nerves. Through the partnership between Virginia Mason and BRI, we are testing a new molecule for the first time in humans that has been shown in system models to remyelinate and repair the lesions and reduce lesions. This is beyond exciting and reflects the robust clinical trials research program at BRI. We’ve participated in more than 30 clinical studies that have advanced MS treatment.

For more information on MS clinical research, visit BenaroyaResearch.org.

• MS is an autoimmune disease in which the body’s immune system mistakenly attacks myelin, the fatty substance that surrounds and protects the nerve fibers in the central nervous system, including the brain and spinal cord.

• When the myelin is damaged, the nerve impulses are not transmitted as quickly or efficiently, resulting in symptoms such as numbness in the limbs, fatigue, dizziness, paralysis and/or loss of vision.
As a young man, Frank Dvorak had set his sights on a career in aviation. He was in his senior year at the Royal Military College of Canada when he received the life-changing diagnosis: type 1 diabetes. Because of his disease, he was grounded from flying. “It was awful news to get,” Frank recalls. “That was a really black time.”

FACING THE CHALLENGE

“I refused to let diabetes slow me down,” Frank says. He switched gears following graduation and enrolled in the University of British Columbia, where he studied for his master’s degree in mechanical engineering. That’s also where he met his future wife, Vivien, who was pursuing her bachelor’s degree in philosophy.

In 1967, Frank earned his PhD in aeronautical engineering from Cambridge University. The Dvoraks moved to the Seattle area, and Frank joined Boeing. He left a few years later to help form Flow Research (now Flow International) and then founded Analytical Methods, Inc., with Vivien serving as office manager.

THE PROMISE OF A CURE

A long-time patient of Virginia Mason, Frank feels “very fortunate” regarding the care he’s received through the years. He has had diabetes for 53 years and began treatment by mixing his insulin and using a glass syringe with a stainless steel needle. Eventually he was able to use the insulin pump. Today he also uses a continuous blood glucose monitor that is being used in the BRI artificial pancreas study. “The next level of treatment will be some form of pump, continuous glucose monitor and computer combinations that will communicate with each other to form an artificial pancreas,” says Frank. “BRI’s study will go a long way in making this happen in the not too distant future.”

In 2008, he was introduced to the Benaroya Research Institute and its world-leading work. His interest and involvement in BRI deepened, and in 2011, he enthusiastically joined the board of directors. “BRI holds the promise of a cure for not only type 1 diabetes, but for all autoimmune diseases,” he says.

The Dvoraks recently extended their generous support of BRI with an estate gift to total $2 million. “The executive committee had been talking about creating chairs in specific research settings, and we really liked that idea,” Frank says. “BRI has done so many great things. We want to provide leadership by example.” The couple’s gift will establish the Frank and Vivien Dvorak Chair in Diabetes, funding BRI researchers in perpetuity.

In addition to a love for travel, Frank and Vivien are passionate about boating. Together they have cruised thousands of nautical miles. And for more than three decades, they have been proud and active members of the United States Power Squadrons, a non-profit organization focused on boating education.

“We’re big on volunteering,” Frank says. “Giving time is important.” Married 50 years in December 2013, the Dvoraks celebrated their golden wedding anniversary with friends on a Caribbean cruise.

While type 1 diabetes is a serious, chronic disease, “You can’t let it hold you back from what you want to do,” Vivien says. “You just have to work around it.”

For more information on giving to BRI, please visit BenaroyaResearch.org.
ASK THE RESEARCHER

Q: What causes inflammatory bowel disease (IBD)?

A: Inflammatory bowel disease (IBD—not to be confused with irritable bowel syndrome, or IBS) is a chronic state of intestinal inflammation, manifesting as either Crohn’s disease or ulcerative colitis. While we do not know for certain what causes it, three factors play a major role:

1) The genes a person inherited from their parents (called a genotype)
2) The bacteria that live in the gut (called the intestinal microbiome)
3) An overactive immune system (called immune dysregulation)

Putting these three factors together, IBD probably results from the immune system overreacting to gut bacteria, particularly in people who have genetic differences affecting the immune system’s interactions with bacteria. Much of this information is very new, so the details of this interplay are still being deciphered. However, the rate at which we are increasing our understanding of IBD is quite exciting and promising.

There have also been epidemiological observations suggesting environmental factors contributing to IBD. For example, IBD is more common in places that get less sunlight, or fewer infections, suggesting that those factors may be protective. However, such correlations have not been proven to cause IBD. Other exposures that would seem like obvious factors, such as diet or stress, have not actually shown a clear correlation with IBD in population studies. One environmental factor that has been proven to affect IBD is smoking—people who smoke are more likely to develop Crohn’s disease than those who do not.

JAMES LORD, MD, PHD
BRI RESEARCH ASSISTANT MEMBER
GASTROENTEROLOGIST, VIRGINIA MASON MEDICAL CENTER

Genetic Connections in Autoimmune Diseases

This illustration shows the connection between common genes in autoimmune diseases. These genes are common in two, three or four diseases. As BRI looks for new therapies to affect these genes in one disease, they can be applied to others.

Biomarker

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Dr. Odegard further describes how this work could impact patient care. “For example, if our biomarkers can determine how fast type 1 diabetes is going to progress in a person, we can determine whether to manage the disease with either standard or more intensive insulin therapy, or even experimental immunosuppressive drugs. By the same token, biomarkers could make our trials of new drugs in recent-onset patients both more cost-effective and more likely to succeed.”

For more information on type 1 diabetes research, visit BenaroyaResearch.org and TIDBiomarkers.com/BWG.

CAV CENTER IS A HUB FOR THE BIOMARKER RESEARCH COMMUNITY TO:

- Request samples from diverse TID biorepositories, including from BRI, the TID Exchange, TrialNet and the Immune Tolerance Network; further develop candidate biomarker assays; and share their progress and data in real time through the JDRF Biomarker LabKey website.
- Use BRI expertise to help consortium investigators validate biomarkers so they become more repeatable, accurate and robust.
- Develop composite biomarkers, in a way never before attempted, to assemble signatures involving multiple biomarker measurements to better predict the clinical course of type 1 diabetes.
BRING IT ON.

Benaroya Research Institute at Virginia Mason
1201 Ninth Avenue
Seattle, WA 98101-2795

Boeing Classic Golf Tournament
What: The Boeing Classic, an official PGA Champions Tour event featuring the legends of golf 50 years or older, will benefit Benaroya Research Institute.
When: Aug. 18–24 at TPC Snoqualmie Ridge
Contact: For more information and ticket options, please visit BoeingClassic.com.

Executive Women’s Day
What: Executive Women’s Day at the Boeing Classic is an opportunity for women business leaders to learn from each other and network in an exclusive and engaging forum. The event includes a behind-the-scenes tournament tour.
When: Aug. 19 at TPC Snoqualmie Ridge
Contact: For more information and ticket options, please contact Michelle DeLancy at Michelle@BoeingClassic.com.

Grapes on the Green
What: Join us for wine tastings from premier wineries, a multicourse dinner and a live auction featuring exclusive travel opportunities and rare wine lots. This event benefits Benaroya Research Institute.
When: Aug. 22 at The Golf Club at Newcastle
Contact: For more information and ticket options, please visit virginiamasonfoundation.org/grapes-on-the-green.

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BRI is a world-renowned nonprofit medical research institute in autoimmune diseases. For more information, visit BenaroyaResearch.org or call 206-342-6500.