Developing new gene therapies for patients with bleeding disorders

Hemophilia affects 1 in 5,000 male births in the United States, and Versiti Blood Research Institute Senior Investigator Robert Montgomery, MD, has spent his career treating patients with Factor VIII deficiency in hemophilia A, as well as von Willebrand disease.

Factor VIII (FVIII) is a protein in the blood that is essential for blood clotting. FVIII is carried by von Willebrand factor (VWF), the gene that causes von Willebrand disease, which is the most common bleeding disorder. VWF sticks to platelets, collagen and other things underneath the blood vessel wall. When a healthy person cuts themselves, the cut creates a hole in that wall. VWF sticks to it, which increases the concentration of FVIII and platelets, thereby causing the blood to clot. However, if someone lacks VWF, FVIII disappears rapidly, and they continue to bleed.

One of Dr. Montgomery’s current research topics is to study how VWF hands off FVIII at the local level, where it is needed to stop bleeding.

Normally, when physicians treat patients with hemophilia A and von Willebrand disease, they use recombinant FVIII, or FVIII that has been developed in a laboratory, which helps normalize the coagulation process. Sometimes, these patients’ bodies identify recombinant FVIII as a foreign substance and develop an antibody to it, which prevents it from working the way it is intended. Sometimes, it’s possible to trick the patient’s immune system into thinking recombinant FVIII is a good thing, by giving them overwhelming amounts of it. However, some patients cannot tolerate it at all, and must then receive recombinant Factor VIIa, an expensive substitute.

Dr. Montgomery and his colleagues sought a better, more accessible, way to treat these patients. “We have developed a gene therapy approach for hemophilia that targets patients who have inhibitory antibody,” he says. To accomplish this, he and his colleagues sought to remove the entire FVIII gene – something that has never been done before – in a model of hemophilia A. When they attempted to do this, rather than removing the gene, they flipped it, which caused it to be ineffective. Based on this, they realized that 50% of hemophilia patients have hemophilia that is based on an inversion of the FVIII gene. “Now, we’ve created an inversion that can be studied,” Dr. Montgomery said, giving new hope to patients who require alternate treatment options.
Are T Cells the Key to Fighting Solid Tumors in Cancer Patients?

The immune system has a big job: every day, it helps to protect us from harmful bacteria and viruses. One component of the immune system, T cells, usually protect us from short-lived illnesses, like viral and bacterial infections. But for some reason, they lose their fighting power when it comes to prolonged diseases like cancer. Versiti Blood Research Institute investigator Wei Guo Cui, MD, MD-PhD, is studying T cells to better understand why they experience T cell exhaustion, and why that causes them to lose their ability to fight cancer. If investigators can understand why T cell exhaustion occurs, they may be able to figure out a way to restore or re-energize these cells, causing them to regain function and fight tumors.

“… fighting a tumor is like running a marathon; it’s a long-lasting process that eventually leads to T cell exhaustion.”

“It’s like running a marathon compared with a 100-meter sprint,” Dr. Cui says. “When you get the flu, you’re running a sprint; you have a highly energized immune system. But fighting a tumor is like running a marathon; it’s a long-lasting process that eventually leads to T cell exhaustion.”

Dr. Cui and investigators at Versiti Blood Research Institute recently developed a method that can convert dysfunctional, tumor-fighting T cells into functional, bacteria-fighting T cells. Each T cell has a unique T cell receptor (TCR) that recognizes a specific antigen – it could be a virus like the flu or a tumor like cancer. By isolating T cells with specific receptors from a patient’s tumor, researchers can grow these cells in a lab.

The ultimate goal is to simultaneously trans fuse a cancer patient with dual-specific T cells and a vaccine that matches the “tails” bacteria. Because attacking something like bacteria energizes cells and puts them into “sprint” mode, these two-sided T cells will recognize the bacteria first and attack it. Then, they will migrate to the site of the tumor and attack those cancerous cells, clearing the tumor.

This novel therapy, which is unique to Versiti, is still a couple years away from clinical trials. However, Dr. Cui is confident that he and his team are poised to make a big impact in the fields of immunology, cellular therapy and cancer research.

Genetic Sequencing May Be the Key to Innovative Cancer Treatment Options

Many investigators at Versiti Blood Research Institute (BRI) focus their work in one of two ways: either in a laboratory or clinical setting. But Associate Investigator Sid Rao, MD, MD-PhD, is one of a few unique researchers who conducts work in both areas – he has a lab at the BRI and he is a practicing pediatric bone marrow transplant physician at Children’s Hospital of Wisconsin. At the BRI, Dr. Rao’s lab focuses on better understanding acute leukemias, predominantly high-risk acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL) in children.

To better understand the genetics behind leukemia, Dr. Rao and his team use next-generation sequencing, which takes small bits of a patient’s DNA and sequences millions of fragments of it, with the hope of shining a light on which genetic mutations cause leukemia to develop. “My lab focuses on genetic interactions of different mutations,” Dr. Rao said. “How do you combine mutation A and mutation B, and do those two alone cause cancer? Do you need a third or fourth?”

Dr. Rao likens it to trying to play a movie in reverse. At the end, you know that one character falls in love with another. But what happened to get them to that point? The principle is the same in leukemia research. Investigators like Dr. Rao use experimental systems to try to recreate a patient’s history. They try mutation A, mutation B and so on down the line to figure out what caused cancer to develop. “If we understand how the tumor develops, then we can figure out ways to target it,” he said.

However, this research – which has the potential to affect patients of all ages, not just children – is still in its infancy. Though investigators are confident they know what the key “players,” or mutations, are, they need to figure out the sequence in which they interact to cause cancer to develop. And the more mutations a certain type of cancer has, the more difficult it is to discover how they work together to cause disease. It will take many years to better understand these mutations and how and why they cause cancer. But Dr. Rao is perfectly poised to do so at Versiti Blood Research Institute.

“It’s a very collaborative environment with world-class scientists,” he said. “I like the opportunity to work somewhere where I can bring a unique expertise in terms of both leukemia biology and next-generation sequencing approaches.”

Community Beacon of Hope

Robert Manegold

Each year, the Virginia Brooks Jefferson Award is given in recognition of an individual, group, corporation or foundation whose outstanding volunteer leadership supports Versiti’s mission to advance patient care by providing life-saving solutions grounded in unparalleled medical expertise. This year’s winner, Robert Manegold, began his service to Versiti when he joined the BloodCenter of Wisconsin Board of Directors in 2006. He has served on both the Versiti Blood Center of Wisconsin board and the Versiti Blood Research Institute Foundation board, where he served as inaugural chair from 2015-2018. Rob’s passion for the organizations he supports is contagious; he gives freely and generously of his time and philanthropy, and our community is better for it.

You Can Make a Difference

To make a gift or learn more, contact Versiti Blood Research Institute Foundation Office at 414-937-6799