Using Glycobiology to Stop Inflammation

A new approach to treating sickle cell disease has broader potential

Sickle cell disease, a genetic disorder that affects millions of people worldwide, causes enormous suffering. In healthy people, red blood cells are round and flexible, moving easily through the vascular system. In people with sickle cell disease, red blood cells are rigid and sickle-shaped. They periodically clog blood vessels, resulting in vaso-occulsion, which impedes the flow of blood and causes pain and inflammation. Over time, this may damage tissues and organs, engendering premature death.

Because of the disease, patients with sickle cell are also more at risk of complications after surgery. To prevent perioperative sickle cell-related complications, patients require meticulous clinical care after an operation.

Researchers have long been searching for a way to prevent vaso-occulsion and inflammation in sickle cell disease, with little success. "The traditional view was that the sickle cell itself was the complete source of pathology in this disease," says Richard Cummings, PhD, Vice Chair of Basic and Translational Research in the Department of Surgery and Director of the Harvard Medical School Center for Glycoscience. For example, the only FDA-approved drug, hydroxyurea, works by reducing the number of sickle cells circulating in the bloodstream.

"Often the simple explanations for things in biology turn out to be wrong," Dr. Cummings says. "And it turned out it wasn't the sickle cell itself that was causing problems, it was that it becomes highly adhesive. That is what triggers the inflammation."

A key target in preventing inflammation is P-selectin, a protein expressed in the endothelial cells that line blood vessel walls. Once activated, P-selectin initiates a multistep process that promotes adhesion of sickle cells, white blood cells (leukocytes), platelets, and other cells to blood vessel walls. Other researchers had tried developing P-selectin inhibitors, but they were clinically ineffective.

As one of the world's leading experts in glycobiology, Dr. Cummings understands the potential of using glycans — sugars and other carbohydrates — to develop new therapeutics. More than a decade ago, he and two colleagues, Richard Alvarez and Rodger P. McEver, MD, at the Oklahoma Medical Research Foundation, thought there might be a way to use an understanding of glycan recognition to engineer a better P-selectin inhibitor. They formed a new company, Selexys Pharmaceuticals, that began developing antibodies to prevent activation of P-selectin.

One of the antibodies they developed, SelG1 (crizanlizumab), was evaluated in the SUSTAIN trial, a Phase 2, randomized controlled trial published in the *New England Journal of Medicine* in February. Investigators at 60 sites tested SelG1 against placebo in 198 patients with sickle cell disease. During the year-long study, the antibody reduced the number of painful crises by 43.5 percent. Moreover, patients who received the antibody went without a pain crisis for an average of 4 months, nearly three times longer than those on placebo.

"This work has much broader implications," says Elliot Chaikof, MD, PhD, Chairman of the Department of Surgery at BIDMC. "The P-selectin pathway contributes to many diseases that involve inflammation and tissue damage, such as blood clots, heart disease, and inflammatory bowel disease."

Dr. Cummings, Dr. Chaikof, and others are now collaborating in research to determine how to use insights from glycan recognition to develop small molecules that can efficiently target P-selectin to treat many other types of inflammation. This translational research may lead to additional therapeutics.

"Glycobiology can suggest solutions at complete variance with the standard way of thinking," Dr. Cummings says, "but great science requires risks." And he intends to keep taking them.