UCHealth CENTRAL INSIDER

UNIVERSITY of COLORADO HEALTH

Volume 8 | Issue 13 | January 20, 2015

Holers Puts Mono, Lupus, and More in Treatment Crosshairs

By Todd Neff

The immune system is a double-edged sword. We would die quickly without it, but its problems make us ill and can even kill us: Think lymphoma, lupus, asthma, rheumatoid arthritis, and so many other autoimmune-related diseases.

V. Michael Holers, MD, head of rheumatology at the University of Colorado School of Medicine, has generally attacked immune-system disorders on their autoimmune flanks. But his latest work, which has led to several recent patent awards, may have a bigger short-term impact on diseases with their roots in viral attacks on the immune system.

Michael Holers, MD, CU School of Medicine rheumatologist, and one of the world's top minds in the complement system's function in immune response.

An ongoing research effort Holers launched in the late 1990s has yielded compounds that, while still in the petri-dish stages of development, show promise in outwitting one of the immune system's great viral nemeses. That's Epstein-Barr virus, which causes infectious mononucleosis (a.k.a. "kissing disease") and increases the risk of cancers (Hodgkin's and Burkitt's lymphomas among them), as well as autoimmune diseases ranging from multiple sclerosis, rheumatoid arthritis, and lupus.

Epstein-Barr is also behind lymphoproliferative disorder (LPD), which attacks children who receive transplanted organs. The disorder is particularly hard to treat given the immunosuppression required for transplant itself, Holers says.

Invasion. Epstein-Barr virus works by attacking the immune system itself – hence the swollen lymph nodes among those with mono. More specifically, the virus fools B lymphocytes (also called B cells) into allowing them to bind with a certain receptor – called complement receptor type 2, or CR2 – on the surface of B cells. Like all hosts, the breached B cells then become virus factories.

Holers and colleagues have for 15 years been on a quest for a vaccine capable of stiff-arming Epstein-Barr's B-cellular advances. The recently issued U.S. Patent number 8,858,945 B2 is one indication of his success thus far; another is the 2011 acquisition, for $111 million, of Taligen Therapeutics by Alexion Pharmaceuticals.

"Mike's innovation and intellectual property were the core assets and value drivers for that acquisition," said Rick Silva, the University of Colorado Technology Transfer Office's senior director for the Anschutz Medical Campus.

"We've been working for a long time to understand the structure of the protein-protein binding interaction and to use our understanding of that structure to develop inhibitors that can be used for autoimmune and other diseases," Holers said. "That process continues today."

Holers and his research team's efforts orbit around the complement system, which is made up of a few dozen distinct blood-plasma proteins that react with one another to destroy pathogens and induce a series of inflammatory responses that help to fight

Continued

infection. (The complement system's operations are complex to the point that even simple explanations beg for a reasonable foundation in the lingo of immunology. For an introduction, check out this animation).

Fine-tuning. The work of Holers and his eight-person research group and other collaborators has involved a range of tools, including nuclear magnetic resonance imaging, X-ray crystallography, peptide inhibitors, mouse models, and patient samples (for in-vitro testing), among others.

It's painstaking work. For one thing, the CR2 receptors on a B cell bind with three other molecules (C3d, interferon alpha and CD23, familiar to immunologists), yielding productive outcomes. So even if researchers figure out the receptor's shape and a compound perfect for binding to it, which Holers and colleagues managed to do, you don't want to blindly take CR2 receptors out of commission.

And so more recent work has focused on developing molecules – inhibitors – specific to C3d, as well as the Epstein-Barr virus, to "really fine-tune our therapeutic approach," Holers said.

"We're also working to determine what human diseases these therapeutics might be useful for beyond those Epstein-Barr-related diseases – lupus, rheumatoid arthritis, and other autoimmune diseases," Holers said.

He can't say when someone with infectious mononucleosis might be able to get a shot or two and be effectively treated. The technology covered in the most recent patent was part of the Alexion acquisition, so it's up to the company to decide what's next. Holers says his team has gotten a potential therapy to within two years of safety testing and within three or four years of therapeutic trial.

Silva says Holers is recognized as a leader in the field of complement system research and in the translation of that research into potential therapies, and that his ongoing efforts have "significant translational and commercial relevance."

"His personal scientific and clinical understanding of the biology and the patient populations is unique," Silva said.