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Unraveling the Basics of HIV/AIDS Biology

Gladstone's discovery of precise molecular mechanisms in the human body leads to a new potential therapy for our era's deadliest epidemic

December 19, 2013—To repair a racecar, it helps to know how the engine works. The same is true in biology, where research into the precise molecular mechanisms that operate the human body—in sickness and in health—can be key to finding new preventions, treatments and cures for disease.

New research from the laboratory of Warner C. Greene, MD, PhD, at the Gladstone Institutes underscores this notion by revealing the body's step-by-step reaction to an HIV infection. The lab's discovery of exactly how the body—and not the virus—kills most of the immune system's CD4 T cells has helped the lab identify a potential new therapy that may block AIDS. A Phase 2 clinical trial is being planned.

"Our studies have investigated and identified the root cause of AIDS—how CD4 T cells die," said Gladstone Staff Research Investigator Gilad Doitsh, PhD. Dr. Doitsh has been spearheading this research for years in the laboratory of Dr. Greene, who directs virology and immunology research at Gladstone, an independent biomedical-research nonprofit. "Despite some 30 years of research into the virus, this key HIV/AIDS process has remained pretty much a black box."

The research could hardly come at a more critical time, as something referred to as AIDS fatigue leads many to think that HIV/AIDS is solved. In fact, HIV infected an additional 2.3 million people in 2012, according to UNAIDS estimates, bringing the global total of HIV-positive people to 35.3 million.

Antiretroviral medications (ARVs) can prevent HIV infections from causing AIDS, but they do not *cure* AIDS. Further, those taking ARVs risk both the premature onset of diseases that normally occur in aging populations, as well as a latent version of the virus that can rebound if ARVs are discontinued. Additionally, some 16 million people who carry the virus lack access to ARVs, according to World Health Organization estimates.

The potential therapy identified by Dr. Greene's lab may offer effective solutions for all these challenges.

Building on Previous Research

As is often the case in science, this new work builds on an investigation that began years ago. Published in *Cell* in 2010, previous research that Dr. Doitsh also spearheaded showed how HIV attempts, but fails, to productively infect the vast majority of CD4 T cells. And in an attempt to protect the body from further spreading the virus, these immune cells commit "cellular suicide," killing the immune system and causing AIDS.

After that research, Drs. Greene and Doitsh began to look for ways to prevent this by studying exactly *how* the suicidal response functions. Working in the laboratory with human spleen and tonsil tissue, as well as lymph-node tissue from HIV-infected patients, they found that these so-called *abortive* HIV infections leave fragments of the virus's DNA in the immune cells.

As three lead authors—Dr. Doitsh, graduate student Nicole Galloway and Xin Geng, PhD—described in *Nature*, these DNA fragments trigger a fiery and highly inflammatory form of cell death known as *pyroptosis*. During this process, immune cells rupture and release inflammatory signals that attract still more cells to repeat the death cycle. And again, using human tissue samples, they found that an existing, safe and well-tolerated anti-inflammatory drug that may be able to block this inflammation and pyroptosis in HIV-infected people.

This discovery, in turn, made the scientists wonder how the body senses the fragments of HIV's DNA in the first place, before alerting an enzyme known as caspase-1 to launch an immune response. To identify the so-called *DNA sensor*, the scientists found a way to genetically manipulate CD4 T cells in HIV-infected tissue. In doing so, they discovered that reducing the activity of a protein known as IFI16 inhibited pyroptosis, explained Zhiyuan Yang, PhD, a Gladstone postdoctoral fellow who is one of two lead authors of a *Science* paper, published simultaneously with the *Nature* paper.

"This identified IFI16 as the DNA sensor, which then sends signals to caspase-1 and triggers pyroptosis," said Kathryn M. Monroe, PhD, the *Science* paper's other lead author, who completed the research while a postdoctoral fellow at Gladstone. "We can't block a process until we understand all of its steps—so this discovery is critical to devising ways to inhibit the body's own destructive response to HIV. We have high hopes for the upcoming clinical trial."

The Phase 2 trial being planned promises to validate a variety of expected advantages. For example, by targeting the human body, or host, instead of the virus, the drug is likely to avoid the rapid emergence of drug resistance that often plagues the use of ARVs. The anti-inflammatory may also provide a bridge therapy for the millions without access to ARVs, while also reducing persistent inflammation in HIV-infected people already on ARVs. Many suspect this inflammation drives the early onset of aging-related conditions such as dementia and cardiovascular disease. By reducing inflammation, the drug might also prevent expansion of a reservoir of latent virus that hides in the body and thwarts a cure for HIV/AIDS.

"This has been an absolutely fascinating voyage of discovery," said Dr. Greene. "Every time we turned over a 'experimental rock' in the studies, a new surprise jumped out."

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