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## Daring to Work Towards a World without AIDS

*In an unprecedented move, three Gladstone scientists receive a total of \$12.5 million to pursue high-impact research to fight our era's worst epidemic*

HIV, the virus that causes AIDS, has been trying to outsmart our species for nearly a century. And while we've made tremendous progress in the fight against this epidemic, there is much work left to do. Fortunately, three top [Gladstone Institutes'](#) scientists are on the front lines, and have just been given unparalleled resources with which to develop new strategies to fight this virus—and hopefully seal its fate once and for all.

The three scientists, [Warner C. Greene, MD, PhD](#), [Leor S. Weinberger, PhD](#), and [Shomyseh Sanjabi, PhD](#), come from different backgrounds and with unique perspectives, but with the same goal: to eradicate HIV from the planet. And today they are being recognized for their distinct visions of an AIDS-free planet as recipients of three separate awards from the National Institutes of Health (NIH). Together, the awards equal an approximate total of \$12.5 million over five years to advance their research goals.

Last month, the NIH's National Institute on Drug Abuse (NIDA) awarded Dr. Greene, Gladstone's founding director of virology and immunology research, a 2013 [Avant-Garde Award for HIV/AIDS Research](#). Set up to fund individual scientists of exceptional creativity who are conducting high-impact research, this award will mean approximately \$5 million in new HIV/AIDS funding.

Today, the [Office of the Director of the NIH](#) presented Dr. Weinberger with an NIH Pioneer Award of roughly \$5 million for Dr. Weinberger's highly innovative approach to HIV/AIDS research. Also today, the Office of the Director presented Dr. Sanjabi with an NIH New Innovator Award worth approximately \$2.5 million.

"The fact that the founding scientist of Gladstone's virology and immunology institute *and* two of its newest faculty have all won such awards speaks volumes about the high quality of HIV/AIDS research that's been going on at Gladstone for more than two decades," said Robert C. Gallo, co-discoverer of HIV and director of the Institute of Human Virology at the University of Maryland School of Medicine.

## Saving Immune Cells from a Fiery Death

Scientists have long thought that HIV directly killed most of the immune system's CD4 T cells, leading to the system's destruction and the onset of AIDS. But [advances by Dr. Greene and his team](#) have shown that humans respond to an HIV infection with a cycle of cell death and inflammation known as *pyroptosis*—a particularly fiery form of voluntary cell death. Further, Dr. Greene's lab has shown that this immune-system reaction underlies the progression of HIV to AIDS. And with the Avant-Garde, it is this process that Dr. Greene plans to interrupt.

To study pyroptosis, Dr. Greene's lab conducted preliminary analysis and research into the simian immunodeficiency virus (SIV), the monkey-equivalent of HIV. Some monkeys—such as sooty mangabeys—have lived and coevolved with SIV for many thousands of years, making them excellent models for studying the evolutionary response to a HIV-like virus.

Other monkeys, such as Asia's rhesus macaque monkeys, have *not* been exposed to SIV and therefore provide an ideal model for studying a more recent response to the virus. Dr. Greene's lab found that lymph-node cells from these newly exposed rhesus macaque monkeys react to SIV with the same inflammatory response as humans.

Meanwhile, lymph-node cells from the sooty mangabey monkeys did *not* respond to the virus with inflammation—implying that evolutionary adjustments are keeping SIV from progressing to the monkey equivalent of AIDS. These results led Dr. Greene and his lab to study whether they could block pyroptosis with a drug, circumventing the normal evolutionary response to HIV. Already, Dr. Greene's lab showed in human tissue that existing anti-inflammatory drugs may avert the cycle of inflammation and cell death.

Now with the Avant-Garde grant, Dr. Greene and his lab plan to launch human trials within 6-12 months to test drugs to block pyroptosis. If successful, Gladstone would be poised to help humans bypass the need to evolve a non-inflammatory response to HIV

### **Hijacking the Virus to Spread the Cure**

Dr. Weinberger is working on a bold strategy that commandeers the virus' key characteristics to incapacitate the virus and stop the spread of AIDS. His approach centers on his theory that to defeat viruses—which continually spread and mutate—an effective solution must do the same.

Dr. Weinberger will use the Pioneer award to test what he calls *therapeutic interfering particles*, or TIPs. In his laboratory, he genetically engineers TIPs by stripping out the damaging parts of HIV's DNA—while retaining HIV's characteristics of contagion and mutation.

“In a TIP, we remove the nine genes that provide the instructions to create proteins responsible for ‘building’ HIV,” Dr. Weinberger explains. “Without these genes, the TIP can not manufacture or replicate HIV. Instead, the TIP retains the virus' transmission and mutation properties—but carries no deadly payload.”

As a result, these compact TIPs would move more quickly than HIV, piggybacking on HIV and stealing cellular resources that the virus needs to thrive. Dr. Weinberger's hope is that these particles will effectively stop HIV by replicating more efficiently than the virus does. He believes that, should HIV then further mutate as viruses often do, TIPs would match that mutation and continue to be effective.

Think of HIV as a weighty dump truck carrying a toxic payload. By converting HIV into a TIP, the toxicity is dumped and the vehicle's chassis is slimmed down. So instead of a lumbering truck filled with a nasty cargo, the TIP becomes a sports car with an empty trunk. The sports car zips along its route—passing HIV on the left and right—hogging all the fuel resources at gas stations along the way.

Should Dr. Weinberger's research succeed, TIPs would amount to a vaccine that spreads on its own and evolves naturally. Based on Dr. Weinberger's projections, the seeding of TIPs with just 1% of the sub-Saharan population, which is home to nearly 70% of the world's HIV-infected people, could drop the prevalence of HIV/AIDS to less than 2%, down from current prevalence of 15-30%.

TIPs could also prove especially effective with hard-to-reach populations such as drug addicts or sex workers. If the experiments turn out as expected, Dr. Weinberger may well have developed an effective strategy to contain the outbreak of other deadly viruses, such as hepatitis, SARS or Ebola.

### **Building a Better Immune Cell**

Dr. Sanjabi, meanwhile, is building on the Nobel-prize-winning stem cell discoveries of Gladstone's [Shinya Yamanaka](#), MD, PhD, to genetically engineer laboratory animals to have human immune systems. Dr. Yamanaka's discovery of how to make *induced pluripotent stem cells*, or iPS cells, lets scientists turn adult skin or blood samples into stem cells that, like embryonic stem cells, can develop into other cell types in the body.

Dr. Sanjabi plans to use iPS cell technology to transform blood samples from HIV elite controllers—HIV-infected individuals who can naturally control the virus—into immune cells. In collaboration with researchers at Yale, the University of California, San Francisco and Gladstone, Dr. Sanjabi will be able to genetically engineer “humanized” mice that resemble the elite controllers' genetic background. Using these mice, Dr. Sanjabi hopes to identify exactly *where* latent HIV lingers in the body of elite controllers compared to those HIV-infected individuals who, without antiretroviral therapies (ARVs), succumb to AIDS. This information could lead to a way to keep HIV-infected people from developing AIDS—*without* a lifelong need for ARVs.

“We are truly gratified to see the promising work of three Gladstone investigators recognized in this prestigious manner—and in the space of just a few years,” said Gladstone President R. Sanders Williams, MD, referring to the fact Gladstone investigator, [Eric M. Verdin](#), MD, won an [Avant-Garde award in 2010](#). “We applaud their research efforts and their multi-pronged strategy in the fight to cure HIV/AIDS.”