Fred Hutch Cancer Center Researchers Receive R01 Grants to Study HIV, PrEP, CAR-T Cells and COVID-19

NIH awards allow scientists to explore how PrEP to prevent HIV influences levels of antibodies, and other questions.

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Three Fred Hutch Cancer Center research groups recently received prestigious R01 awards from the National Institutes of Health. These multi-million-dollar grants provide up to five years of support for large, multi-year investigations with clear outcomes and high potential for public health benefit.

This crop of awards highlights the biostatistical chops in Fred Hutch's Vaccine and Infectious Disease Division, or VIDD. The scientists, who all received R01 funding from the National Institute of Allergy and Infectious Diseases, will use biostatistical methods to explore questions ranging from the factors governing the reservoir of cells that harbor HIV long term, how pre-exposure prophylaxis may influence antibody clearance and what this means for vaccine efficacy, and how to use a vaccine's immunogenicity to estimate its effectiveness.

Biostatistician Yunda Huang, PhD, and immunologist Maria Lemos, PhD, MPH, will study whether use of oral daily pre-exposure prophylaxis (PrEP) pills against HIV influences how the body handles antibodies. The work could inform the dosing amount and schedule of antibodies to protect against HIV, as well as those of various vaccines, in people who take oral PrEP.

Biostatistician Bo Zhang, PhD, is working to develop biostatistical methods that will enable scientists to transform a vaccine's immunogenicity (or ability to stimulate an immune response) into a concrete estimate of its effectiveness. A second method will leverage off-target endpoints to better estimate vaccine efficacy over time, even for trials that are not randomized.

Cellular immunotherapy expert Karsten Eichholz, PhD, focuses on developing novel immunological approaches to attempt to cure HIV infection. He said he was excited to receive his R01 on the first try, just a few years after receiving a K01 career development award from the National Institutes of Health.

"It's very competitive, and we are more used to hearing a no then a yes when we send our

proposals out for review," he said.

How PrEP affects antibody pharmacokinetics

Oral PrEP is the most widely used HIV-preventive medication in the world: by 2024, nearly 8 million people had initiated the regimen. Despite new, long-acting versions, oral daily PrEP remains the version that's easiest to access around the world, so this number will only grow, said Huang, an associate professor in VIDD's Biostatistics, Bioinformatics and Epidemiology Program, or BBE, and Fred Hutch's Public Health Sciences Division, or PHS.

Huang and Lemos' latest investigation of how oral PrEP influences antibody levels grew out of observations of men participating in clinical trials that tested whether cocktails of long-lived anti-HIV monoclonal antibodies can prevent HIV infection. When measuring the pharmacokinetics of the antibodies — how their levels wax and wane within the body — the researchers saw that the levels of the infused monoclonal antibodies decayed 14% faster in U.S. men on PrEP.

"Our original interest was to see if there would be any differences between the people who are on PrEP and the people who are not on PrEP," said Lemos, an immunologist and staff scientist in VIDD's McElrath Lab. HIV vaccines are currently experimental, but many potential participants take PrEP.

"Some people on PrEP may be interested in taking a vaccine against HIV," Lemos said. "Because vaccine immunity takes time to develop, they might get vaccinated while on PrEP. So we need to know how antibodies are affected by PrEP."

The team found that faster antibody decay was associated with increased intestinal permeability. The new R01 will support efforts to extend these investigations to a different population: in this case, South African women at risk of HIV. The researchers will also look at whether oral daily PrEP affects clearance of vaccine-induced antibodies in addition to passively received antibodies.

If Huang, Lemos and their team find similar results in women, the insights could inform monoclonal antibody dosage or vaccine schedules. The findings could also have implications beyond HIV, Huang said. In addition to looking at whether oral PrEP affects how women's bodies clear infused monoclonal anti-HIV antibodies, the team will also examine whether PrEP affects the clearance of monoclonal antibodies targeted to other conditions (such as arthritis) as well as naturally formed antibodies (in this case to vaccines against HIV and hepatitis B).

The work could also help people on oral PrEP make the best risk-management decisions for themselves, the researchers said.

"Oral, daily PrEP remains the standard of care for people who want to prevent HIV, and we want to make sure they can make the best decision about whether the medication applies to them or not," Lemos said.

The scientists also want to begin unraveling the mechanism behind any PrEP-induced changes in antibody levels, as well as to assess which antibodies are most likely to be effective against HIV. An antibody's effectiveness relies in part on whether it reaches the right tissues; in the case of HIV, antibodies must reach mucosal tissues to block infection. The team has access to mucosal tissue samples donated by trial participants, which are rarely studied, making their inclusion in a pharmacokinetic model quite novel, Lemos said.

The team plans to develop advanced models that predict antibody levels in mucosa based on their levels in blood, for different antibodies. Such a model would help researchers select the most effective antibodies for HIV prevention.

This part of the project is made possible by a close collaboration with the HIV Vaccine Trials Network, or HVTN, which has systematically collected and archived the specimens, Huang said.

"It's an excellent example of how a clinical trials network did the research and collected the data and specimens, and opened it up to the [research] community to have access to answer questions that are related, but not exactly what they originally planned for," Huang said. "It took a little bit of creativity to make this link, but it's just an excellent resource."

Using CAR T cells to investigate the HIV reservoir

A major hurdle standing in the way of curing HIV is the virus' reservoir, the immune cells in which proviral DNA — ready to birth new viruses — hides out. Many of the cells harboring HIV DNA express a molecule called PD-1. These include follicular T helper cells, a type of immune cell that supports antibody-making cells during an infection. They get their name from their function (helping) and area of the lymph node where they spend their time, a region dubbed the follicle.

Critical players in normal immune responses, T follicular helper cells are vulnerable to HIV infection because they express one of the molecules, CD4, that the virus uses to slip into target cells. The HIV reservoir cannot be reduced or eliminated without clearing out T follicular helper cells.

"These cells are particularly difficult targets for the immune system, as the area is 'immune privileged,'" which means that many immune cells, including the cytotoxic T cells that can kill HIV-infected cells, don't usually go there, said Eichholz, a staff scientist in VIDD's Corey Lab.

The lack of immune oversight allows HIV to hide out in the T follicular helper cells, which particularly congregate in the germinal center, where these helper cells aid antibody production during infection.

The work grew out of a prior project, in which Eichholz and his collaborators used CAR T cells, a type of cellular immunotherapy, to removed follicular T helper cells in a preclinical model of HIV infection. These CAR T cells recognize a molecule called PD-1, which T follicular helper cells express at high levels.

“We successfully depleted the T follicular helper cells, which was then associated with lower viral replication in the germinal centers,” Eichholz said.

It was the first time that the elimination of this tissue reservoir of HIV had been reported, but there was a downside. Many cytotoxic T cells also have some level of PD-1 and the CARs cleared these as well. The HIV reservoir shrank — but without killer T cells to tamp down the remainder, viral levels rebounded and disease progressed. The CAR T cells that had created this immunodeficiency persisted for about three months.

“We realized two things,” Eichholz said. “We realized that the anti-PD-1 CAR is not super specific, and that CAR T-cell persistence is something we want when treating cancer, but not for this.”

Eichholz aims to update the CAR T cells to overcome this barrier. He plans to use these updated anti-PD-1 CAR T cells in the same preclinical model of HIV to study how removing PD-1-positive helper T cells affects the dynamics of the HIV reservoir.

“We want to try to develop two different technologies, and then bring them also together,” he said.

In the current project, Eichholz and his team plan to develop CAR T cells that are controllable and also more specific. The idea is to restrict their function to a smaller set of cells (mostly T follicular helper cells and other PD-1-expressing helper T cells) and to a shorter, more-defined timeframe. The goal is to make the window long enough to wipe out HIV-harboring T follicular helper cells, but short enough to prevent sustained immunodeficiency.

To shorten the time frame of CAR T-cell activity, Eichholz addded a drug-controlled on/off switch to the anti-PD-1 CAR. The CAR T cells depend on the drug to work, so it acts as a remote control to turn them on or off: With the drug, the CAR T cells function; without the drug, they don’t.

“The idea is that by giving or withholding the drug, we can control for how long the CAR T cells are active,” Eichholz said.

To make the CAR T cells more specific for PD-1-expressing helper T cells (and make them ignore cytotoxic T cells that may also express PD-1), Eichholz added a signaling circuit that restricts which cells the CAR T cells will respond to based on which molecules the target cells express.

“Over the past few years, new CAR signaling circuits have been created that basically make cells choose how to respond by checking multiple surface proteins,” Eichholz explained.

Traditional CAR T cells spring into action as soon as they bind a single target molecule.

“These newer CAR circuits check for two different targets first, which helps make them more specific,” Eichholz said.

By choosing a second molecule that is common on helper T cells and uncommon killer T cells,

Eichholz can make the updated CAR T cells focus on the right group of T cells and ignore the wrong group. Ultimately, he hopes the two approaches can be merged to create a cell therapy that's more specific and easier to regulate.

These new CAR T cells will open new avenues for studying HIV reservoir dynamics, Eichholz said. In the short term, the novel CAR T cells will allow the scientists to better understand how the HIV reservoir is maintained and how the immune system recovers after T follicular helper cell depletion. In the much longer term, Eichholz said, similar CAR T cells may one day be a component of a combination therapy approach to HIV cure.

Improving estimates of vaccine efficacy

Zhang, an assistant professor in BBE and PHS, is working to help scientists address the lack of randomization in some vaccine trials, especially trials of boosters or vaccine updates.

"Our goal is to try to make the science a little more rigorous. That's mostly what biostatisticians do," he said.

In general, trials of vaccine updates and boosters are not randomized.

"People come in to receive the booster of their own free will," Zhang said. "Some people receive it earlier, some people receive it later. Maybe the people who choose to receive the booster are more careful in general. If you see a lower rate of COVID, it could be attributable to something other than the vaccine."

Timing, on top of who decides to get vaccinated, can also influence efficacy and durability of vaccine protection. To develop a predictive model that overcomes this lack of randomization, Zhang and his team are leveraging the widening scope of diagnostics and what are called "off-target endpoints."

When people get an experimental vaccine for a respiratory virus, they get screened for that virus when they experience symptoms. But today's technology makes it easy to include screens for other respiratory viruses. So a participant in a COVID-19 booster trial with a runny nose could get screened for influenza and RSV on top of SARS-CoV-2.

Infection with, say, RSV, would be an "off-target endpoint" for a COVID-19 vaccine trial. Rates of RSV shouldn't be affected by SARS-CoV-2 vaccination, but you would expect that masking or staying away from crowds would influence rates of both respiratory infections.

"The first aim is to leverage the off-target endpoints to estimate the durability of vaccine effectiveness over time in randomized or even non-randomized studies," Zhang said.

In a separate aim, Zhang will develop methods to support immune-bridging studies. These studies use (well-validated) immune biomarkers as proxies for vaccine effectiveness. Immune-bridging

studies are smaller, faster and cheaper to run than vaccine trials that look at endpoints like rates of infection. They're likely to be used if an already-tested vaccine is getting an update.

"Given the historical trial with everything collected and given this new immune-bridging studies where we only collect the biomarkers, we want to estimate if we keep running this trial, what would be the risk of infection associated with the new vaccine?" Zhang said.

His models will allow scientists to estimate that risk, transforming a vaccine's immunogenicity (and implied protectiveness) into a more concrete number, he said: "So we can essentially say, what is our estimated confidence interval around the infection risk if you implement this new vaccine in a certain population."

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