Dr. Hans-Peter Kiem Awarded amfAR Grant for Research on HIV Gene Therapy

Potential cure strategy builds on unexpected findings about hematopoietic stem cells.

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The most meaningful HIV cure will be not only safe and effective but also widely accessible for the 39 million people infected worldwide, no matter who they are or where they live.

Hans-Peter Kiem, MD, PhD, is pursuing such a cure in the form of in vivo gene therapy that confers HIV resistance to a specific subset of a patient's hematopoietic stem cells, or HSCs, the building blocks of our blood and immune systems. He was awarded $480,000 by amfAR, The Foundation for AIDS Research, to support the next stage of his work.

"This grant gets us one step closer to in vivo gene therapy for HIV as well as sickle cell disease and other genetic diseases," said Kiem, who holds the Stephanus Family Endowed Chair for Cell and Gene Therapy. He is also deputy director of the Translational Science and Therapeutics Division. "I think this will have very wide implications for the field,"

The two-year amfAR grant will fund research to test delivery of gene-editing enzymes in an animal model using engineered virus-like particles or eVLPs. eVLPs function as envelopes that can efficiently and safely carry tools for gene editing inside their shell and carry molecules that target particular cells of the body — in this case, CD90+ HSCs — on their surface.

Upon delivery to a CD90+ HSC, the gene-editing enzymes are meant to introduce a mutation known as CCR5-delta32. This mutation, which occurs naturally in a small number of people, prevents HIV from entering and infecting cells. Introduction of the CCR5 mutation is the only cure for HIV to date.

This approach made Timothy Ray Brown, known as the Berlin patient, the first person ever to be cured of HIV after he received an allogeneic stem cell transplant for leukemia using cells from a donor born with the CCR5 mutation.

Because the mutation is rare and a stem cell transplant is a risky, expensive procedure requiring access to sophisticated medical infrastructure and special expertise, the approach that cured

Brown is not easily scalable worldwide. Nor is an ex vivo, or outside-the-body approach, such as removing HSCs from an HIV-infected person, genetically modifying the cells for resistance and then returning them to the patient.

Today, about 25% of people living with HIV don't even have access to the antiretroviral medicines that can hold the virus at bay.

To cure HIV, especially in low- and middle-income countries where it's most prevalent, it's essential to develop a "portable gene therapy" or "gene therapy in a syringe," Kiem said, that can be packaged, shipped and administered in an outpatient setting as an injection that works on the patient's HSCs in their own body.

Why CD90+ HSCs make a great target in HIV

Earlier animal studies showed that in vivo gene therapy could work, but researchers needed to identify the most effective subset of cells to modify in order to stop HIV while causing little to no off-target effect.

"The questions we had to answer were, 'What is the best cell population to target in patients, and how can we get at that population?' In other words, we needed to characterize the blood stem cell we ought to target and then develop the best platform to target it," said Kiem, an international leader in this approach to curing HIV.

It turns out CD90+ HSCs, in particular, make a worthy target for HIV gene therapy because they're instrumental in creating new blood cells.

Stefan Radtke, PhD, senior staff scientist in the Kiem Lab, and his collaborators reported in a recent issue of the journal *Blood* that CD90+ HSCs contribute significantly to both short- and long-term multilineage repopulation of blood cells after myeloablative conditioning (high intensity chemo and/or radiation) and transplantation.

Historically, HSCs have been thought to be quiescent, not to expand symmetrically and not to play a role in short-term post-transplant recovery. However, Radtke's research found the opposite: that after transplant CD90+ HSCs are active; they create identical copies of themselves in massive quantities, forming pools; and contribute to recovery in as little as two weeks. As early as 50 to 60 days after transplant, they are the main source of new blood cells in the body, and their role is long lasting.

For the *Blood* paper, the researchers dug deeper into data from their earlier work which found that CD90+ HSCs were active early in the repopulation of blood cells after transplants in large animal models. Next, they built mathematical models of the cells' behavior which predicted pools of HSCs would form. Then, they performed a CD90+ HSC transplant in an animal model and checked the bone marrow to see if the pools predicted by the model were present, which they were.

Radtke acknowledges these findings upend what many physicians and scientists believe about HSCs. In fact, the results go against much of what he was originally taught. "But we have the

data," he said.

He attributes the unexpected findings in part to the fact that his team was able to take many more samples from their study subjects and to start taking samples much earlier after transplant than researchers can from humans during transplant recovery. In addition, methods to detect HSC activity have become more sensitive over time, so they can now reveal dynamics not as easily detectable in the past.

"The results confirmed for us that we are on the right track with genetically modifying these specific HSCs. They do everything, and they do it better and faster than previously reported. Now that we know CD90+ stem cells are a great target, we know we can succeed in vivo. A major concern has been addressed," said Radtke.

Another step toward bringing cures to patients

Besides having an appropriate target, researchers must deliver the gene-editing enzymes to that target — and only that target — which is where eVLPs come in.

With technology from the Liu Lab at Harvard, Kiem's team has successfully designed CD90-targeting molecules into viral envelopes, which they'll use in the amfAR-funded study.

"We have a target, we have a tool, now we need to test it," said Radtke. "Everybody's working on gene therapy for various diseases. It's this amazing technology. But we need to bring it to the patients who can really benefit from it. That's what we're moving toward with this project."

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