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Gene-Editing: The Potential Key to Eliminating HIV

Dr. Turck:
Scientists at Temple University's Lewis Katz School of Medicine have identified a novel gene-editing strategy aimed at eliminating HIV-1 infection with no adverse effects on cell mortality. So what is this new approach? And how does it work?

Welcome to *Clinician's Roundtable* on ReachMD. I'm your host, Dr. Charles Turck. And joining me today to discuss his team's research is Dr. Kamel Khalili, who is the Laura H. Carnell Professor in the Department of Neuroscience and Chair of the Department of Microbiology, Immunology, and Inflammation.

Dr. Khalili, thanks for joining us today.

Dr. Khalili:
My pleasure. Thank you very much for the invitation.

Dr. Turck:
Let's start with some background, Dr. Khalili. The strategy we'll be discussing targets a gene called mannosyl oligosaccharide glucosidase, or MOGS. So what is MOGS? And why is it important in this case?

Dr. Khalili:
MOGS is a cellular protein which produces in almost every cell, and that product of this MOGS gene is a production of the protein glycosylate cellular genes that needs to be cellular protein, and they need to be glycosylated in order to exert the function in the cells. So we noticed that based on the earlier notion that maybe MOGS can glycosylate the HIV protein that is responsible for the interaction of the virus with the host receptor and then on coreceptor and eventually the virus genome enters into the cells and then basically infect the cells. So we thought that if we can use CRISPR technology to alter expression of the MOGS by manipulating the gene responsible for the production of the MOGS, we can make the cell basically become MOGS free, and as a result, the virus which enters into that cells will not be able to produce outcoming virus with potential for infecting other cells. In other words, we are disabling infected virus, which is coming out from the infected cells, to enter other cells, and it seems that the strategy with which we thought it's working in the cell culture and the elimination of the MOGS results in the production of outgoing virus from the cells noninfectious.

Dr. Turck:
And I was wondering if you would talk a little bit more about how that CRISPR gene-editing strategy alters MOGS.

Dr. Khalili:
Basically, there are two ways we use in order to inactivate MOGS gene. One was that you can basically stop complete production of the MOGS by manipulating the nucleotide sequence within the MOGS gene, which is responsible for the production of the MOGS, and that's one way. And the other way is that we excise a segment of the MOGS gene from the host chromosome, and as a result, the cell is making a truncated portion of the MOGS protein which is inactive. The outcome of both approaches is a lack of production of the MOGS

in the cells. So once the MOGS is not produced in the cells, any virus which is replicating in that particular cell line or cells become noninfectious, so that is the way you can prevent spread of the virus to the other cells.

Dr. Turck:
For those just tuning in, you're listening to *Clinician's Roundtable* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Kamel Khalili about a novel gene-editing strategy for HIV.

Now, Dr. Khalili, does this discovery get us closer to a cure for HIV?

Dr. Khalili:
Yes, it takes us one step closer. We already have developed a strategy for the elimination of the virus from the infected cells by a gene-editing strategy, and that story is in the clinical trials right now, but we are also developing this additional strategy, basically second generations of the cure of HIV using elimination of the virus and also prevention of the spread of the virus, and for prevention of the spread of the virus, we are using the MOGS gene for editing with CRISPR.

Dr. Turck:
And at the research level, I was wondering what the next steps are that you're taking. I think you got into it a little bit, but I thought I'd ask for a little bit more detail there.

Dr. Khalili:
For us, the next step is implementing the same strategy in the preclinical stage. It means that preclinical could be a small animal model or large animal model, and the model for the HIV in the small animal is a mouse model, which is humanized. It means that circulating in the body of the mouse is a human cell which is infected with HIV, so these are immunosuppressed mice, which instead of the mouse gene's cellular, the blood cells, it does have a human cells, and those human cells are infected with HIV. In the large animal, we are using nonhuman primate that were infected with SIV. SIV is a cousin of HIV which infects Rhesus monkey. So in order to get into the clinical trial with a combination therapy of the mouse and the HIV, we need to perform some preclinical studies for showing the safety and efficacy of that, so that's what we would like to do that as a next step: take this cell culture studies to preclinical levels; and hopefully, based on the result of some of that preclinical studies we might be able to enter into the clinical stage for the clinical trials.

Dr. Turck:
Now before we close, are there any final thoughts you'd like to share with our audience today?

Dr. Khalili:
Yes. HIV has been with us for more than 40 years, and there has been a lot of information about the virus and how the virus interacts with the host and how the virus is leading to the disease progression. And current therapy, which includes antiviral therapy, or ART, has done a terrific job but has not been able to eliminate the virus, so every time that the patients stop taking the antiretrovirus therapy, the preexisting virus in the body rebounds, reactivates, and then puts the patient at risk for the development of the disease.

Our strategy is to eliminate the virus from the host genome, and by doing that, the individual does not need to take any antiretroviral drugs for HIV and then permanently cure the disease by eliminating your virus. One thing that I didn't mention, it's important to note that when the cells become infected with HIV, viral genome incorporate in the host gene, and they remain at the silent stage until it replicates, which frequently it replicates, and the result of that is killing the human immune cell, T-cells and the myeloid cells, so we look at the virus at that stage the pace of the virus and host changes. The virus become like a genetic disease, a disease that once was an infectious disease becomes like a genetic disease because of the viral genome is now incorporated in the host gene, so in order to permanently eliminate the virus from the cells, we must use a genetic approach and gene therapy, and then gene editing, which includes the use of CRISPR, provides an excellent tool to achieve that goal. And I think that we are entering the time after 40 years that we learn that gene editing can serve as a potential tool for the elimination of the infectious diseases, including HIV, by manipulating the structural organization of the viral genome and making them become inactive.

Dr. Turck:
Well, this has been such an interesting look at some exciting research aimed at the elimination of HIV infection, and I want to thank you, Dr. Khalili, for joining me today and for sharing your team's research with us.

Dr. Khalili:
Many thanks. Thank you very much.

Dr. Turck:
For ReachMD, I'm Dr. Charles Turck. To access this and other episodes in our series, visit ReachMD.com/CliniciansRoundtable, where you can Be Part of the Knowledge. Thanks for listening.