HIV Eradication: One Step Closer

Hopes for HIV eradication have been stymied by the current crop of antiretroviral drugs’ inability to get at the reservoir of inactive HIV-infected CD4 cells that hide in the body. Now, Robert Siliciano, MD, PhD, from Johns Hopkins University says not only that it’s possible to get at these cells, but that his lab is already on track to identifying drugs that can wake up these cells. The discovery represents a significant step on the path to ultimately curing HIV.

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Not everyone has given up hope about developing a cure for HIV, and one researcher in particular has just moved us one step closer. Working with scientists at Johns Hopkins University in Baltimore and Howard Hughes Medical Institute in Chevy Chase, Maryland, Robert Siliciano, MD, PhD, has accomplished something that others believed impossible: a way to develop a drug that can get at the stubborn reservoir of HIV that currently goes unscathed by antiretroviral (ARV) therapy.

This recalcitrant reservoir consists of long-lived CD4 cells that harbor latent HIV throughout the body, ultimately keeping the virus archived for decades. These hideaways proved to be the downfall of eradication hopes back in the mid-1990s. While the ARVs used then could drive down viral reproduction to near zero, even for several years, they simply weren’t enough to completely purge HIV from the body. As soon as ARV therapy is interrupted, even if using today’s more powerful agents, the tiny amount of tucked-away virus is enough to reignite viral replication with full force.

Siliciano thinks there are at least two reservoirs of latent HIV. One of them is still a bit of a mystery, but the other is a collection of CD4 cells called memory cells. These cells are usually in a quiet state but have been infected with HIV at some point. An example: CD4 cells created after a child has a bout of chicken pox—cells that silently wait in the adult body for a new exposure to the herpes virus responsible—that end up becoming infected with HIV.

These HIV-infected memory cells aren’t producing major proteins or replicating, so the HIV DNA inside them isn’t doing much of anything. The cells need to be activated before HIV’s DNA can begin the process of churning out copies of itself. ARVs are only able to target HIV’s genetic machinery when it is in the active stage of entering and fusing with a cell or producing progeny when the cell is active. As a result, the drugs are futile against CD4 cells that have already been infected but aren’t active.

The only way to get at this virus is to activate the resting memory CD4 cells, but turning them all on at the same time could be deadly. So how can you turn on only the cells that are infected?
This seemingly impossible task is exactly what Siliciano and his colleagues set out to tackle. Using a line of cells that they've developed, researchers can determine whether various chemical compounds can activate resting CD4s infected with HIV. They've already found a handful of compounds that can selectively activate infected cells. While none of these are likely to be safe enough for human use, Siliciano’s group is going to keep looking, and their accomplishment represents a significant step forward in the search for a cure.

“I’d always been pretty pessimistic about this whole approach,” Siliciano says, “but in looking at about 4,000 drugs, we got nine ‘hits.’ It wasn’t actually that hard to find these drugs.”

Siliciano says his newfound optimism is shared by not only his colleagues, but also drug companies. However, he warns that the other mystery reservoir is still there and it could potentially hold out against a drug that successfully activates the reservoir of latently infected CD4 cells. It’s also going to take a while to turn his method of screening promising compounds into a medication that can be studied in clinical trials. But Siliciano is determined, and with other scientists engaged in the search for a cure, each new discovery brings us that much closer.

The Road to Success

Activating the reservoir of latent HIV-infected cells has been attempted a number of times, but not successfully. Siliciano says this is because the only drugs we’ve tried thus far are designed to turn on all the latent memory cells. This is not only inefficient—about one in a million latent memory cells carries HIV—but also dangerous.

“If you want to activate latent HIV,” he explains, “you’ve got to activate all the host [cells] that have latent virus in them. Since you don’t know which ones are infected, the approach taken in the past has basically been to activate all CD4 [memory] cells.”

However, he says, “the immune system is not designed to work with every cell getting activated at the same time. People go into shock basically. It’s called a cytokine storm. So that’s not a good way [to activate latent HIV], because people can die.”

The screening model developed by Siliciano’s group automatically picks drugs that activate latent HIV without causing global CD4 cell activation. “We can see both of those things in our screen—activation of just latent HIV versus global activation—so we pick drugs that turn on the virus without turning on the cell,” he explains. “We can’t tell from our screen whether there will be other toxic effects, but at least this way we can quickly hone in on drugs that seem to do the right sort of thing.”

Siliciano’s group published their work in The Journal of Clinical Investigation earlier this month.

Next Steps

Siliciano is working on building a partnership between his lab and a pharmaceutical company,
which will give his group access to a library of millions of different chemical compounds to test. But this is just the beginning. Once the promising compounds are identified, they have to be tested for possible human toxicity in both test tubes and animals and then turned into drugs that can work effectively in the body. This could take a number of years, and it’s not the only obstacle to viral eradication.

“The big worry for me is that there’s another reservoir that [won’t be] affected by a particular drug,” Siliciano says. “We have pretty good evidence now that there are at least two major reservoirs for HIV that contribute on an ongoing basis to viral persistence, and one of them is clearly not in CD4 cells. It’s in a different cell type, and the mechanism and biochemistry may be different. So that’s a big worry to me, and unfortunately, we haven’t identified the second reservoir yet.”

Siliciano knows, however, that many thought it would be impossible to figure out how to activate the reservoir of HIV-infected CD4 cells we do know something about. If we can do that, he figures, it should also be possible to eventually get at the other reservoir.

Siliciano hasn’t always been so hopeful. “I’m much more optimistic than I used to be about this whole thing,” he says, “and the good news is that there’s a lot of interest in this. [Noted AIDS researcher] Doug Richman had a piece in Science a couple of months ago suggesting a major scientific effort to tackle this problem. There are a lot of companies and a lot of scientists who are interested in tackling this now, whereas before people thought this was going to be very, very difficult.”

Siliciano has reason to believe that HIV might one day be curable. “There are a lot of people working on it as hard as they can,” he says, adding that there’s “increasing interest in the possibility that this can be done.”