Researchers reverse HIV latency, important scientific step toward cure

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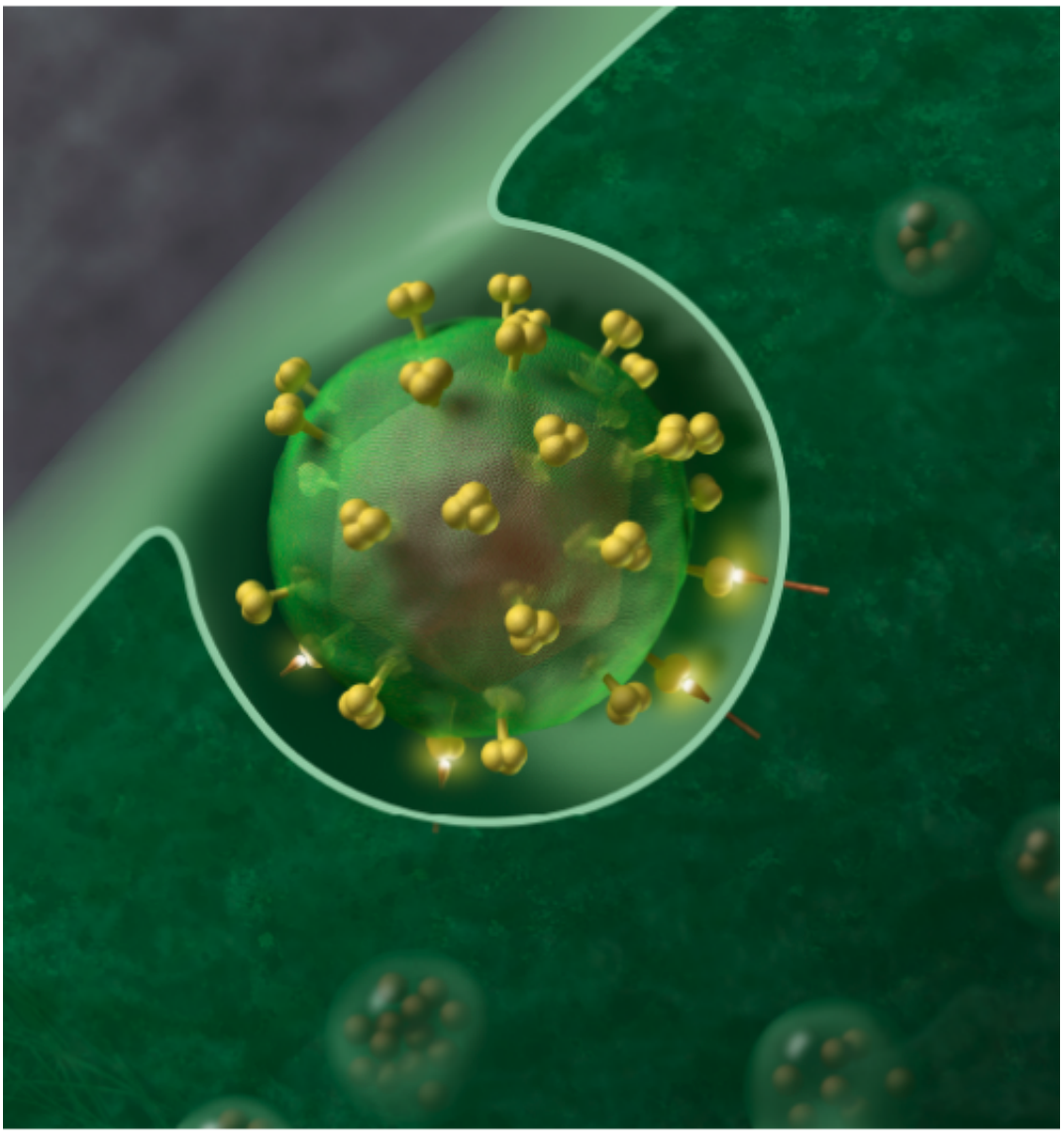

HIV-1 Virus. Credit: J Roberto Trujillo/Wikipedia

Approximately 38 million people are infected with HIV worldwide, about 1.1 million people in the United States. Currently, people with HIV take antiretroviral therapy (ART), which can suppress HIV to undetectable levels in blood, but the virus persists throughout the body in latently infected resting CD4+ T cells. The immune system cannot recognize these cells and no current therapies can eliminate them. When ART is stopped, viral loads spike in blood. This is why people with HIV must take ART continuously, and this latent reservoir is considered the greatest obstacle to a cure.

Now, scientists from the University of North Carolina at Chapel Hill and Emory University used a compound called AZD5582 to activate latently infected CD4+ T cells at impressive levels in blood and many different tissues with no or very little toxicity.

Published in *Nature*, this seminal work was accomplished at the UNC School of Medicine in ART-suppressed mouse models with fully functioning human immune cells, the kind typically infected with HIV in humans. Importantly, this research was then extended in a longitudinal, multi-dose study at Emory University in ART-suppressed rhesus macaques infected with Simian Immunodeficiency Virus (SIV). Qura Therapeutics, a partnership between scientists at UNC-Chapel Hill and ViiV Healthcare, conducted the basic science investigations that expedited the work in animal models. More research is needed before testing could begin in humans, but this work is considered a significant scientific step toward developing curative therapies.

"Previously, no one had successfully tested a latency reversal molecule in humans or in an animal model with human cells demonstrating systemic HIV induction in peripheral blood, in resting CD4+ T cells from multiple tissues, and then replicated this success in a completely different species infected with a different virus," said co-senior author J. Victor Garcia, Ph.D., director of the International Center for the

Advancement of Translational Science, professor of medicine and microbiology & immunology at the UNC School of Medicine.

Ann Chahroudi, MD, Ph.D., associate professor of pediatrics at Emory and director of the Center for Childhood Infections & Vaccines at Emory and Children's Healthcare of Atlanta, is co-senior author. "AZD5582 was remarkable in its ability to reactivate latent SIV from resting CD4+ T cells, and to induce continued virus production in the blood when monkeys were still receiving daily antiretroviral therapy," she said. "This is an exciting scientific achievement, and we hope this will be an important step toward one day eradicating the virus in people living with HIV."

This work was made possible by the Collaboratory of AIDS Researchers for Eradication (CARE) housed at UNC-Chapel Hill and part of the Martin Delaney Collaboratories for HIV Cure Research—the flagship HIV cure research program supported by the National Institutes of Health (NIH) - the Emory Consortium for Innovative AIDS Research (E-CIAR) in Nonhuman Primates, also supported by NIH, Qura Therapeutics, and ViiV Healthcare.

For several years, scientists have been trying various latency reversal agents to induce HIV out of latency so it becomes visible to the immune system, allowing an antiviral immune response to kill the virus-infected cells. Some agents focused on activating the canonical NF-kB pathway in CD4+ T cells to drive infected cells out of latency. But triggering that pathway involved many hundreds of genes, making such an aggressive approach too toxic.

Scientists at Qura Therapeutics—a partnership between UNC-Chapel Hill and ViiV Healthcare—turned their attention to the non-canonical NF-kB pathway in CD4+ T cells.

Co-senior author Richard Dunham, Ph.D., lead investigator at Qura Therapeutics, led studies with patients' cells necessary to show that AZD5582, a mimetic of the Second Mitochondrial Activator of Caspases (SMACm), could serve as an effective latency reversal agent. AZD5582 provides a gradual but persistent activation of the non-canonical NF-kB pathway while triggering fewer human genes than other latency reversal agents, potentially making it much less toxic.

"We are excited that we now, for the first time, have a simple, tractable tool to test the long-standing hypothesis that activating latent HIV can expose the viral reservoir to clearance," said Dunham, Director of HIV Cure at ViiV Healthcare.

UNC scientists led by Garcia, an Oliver Smithies Investigator and member of the UNC Center for AIDS Research, then tested AZD5582 in vivo using ART-suppressed mouse models that contain human CD4+ T cells in tissues throughout the body. Garcia and colleagues documented increases in viral RNA expressed in blood and nearly all tissues, including lymph nodes, thymus, bone marrow, liver, lung, and brain. In some cases, the viral RNA increase was more than 20 fold.

At Emory, Chahroudi and colleagues tested AZD5582 in ART-suppressed, SIV-infected macaques and found similar results, this time with multiple, weekly doses. They observed a spike in RNA expression in lymph nodes and blood of the primates, marking the first time a latency reversal agent accomplished this feat with little toxicity in both animal models used to study HIV.

In a second paper in the same issue of *Nature*, Emory researchers led by Guido Silvestri, MD and Chahroudi in collaboration with UNC researchers, accomplished latency reversal in a different way. They injected an antibody into nonhuman primates with ART-suppressed SIV infection to deplete CD8+ T cells, which are very important for

controlling the infection. Then the researchers administered an altered version of the cytokine IL-15 to show that this combination pushed viral RNA to appear in blood and tissue where it previously had not been seen. Garcia and UNC colleagues confirmed these results for HIV in the same type of mouse model in which AZD5582 was tested.

While it is not yet clear if the strategy of depleting CD8 cells could be translated into humans, this result opens new ways to understand how HIV is controlled, and how its expression might be manipulated. .

Taken together, these findings demonstrate the power of science conducted across teams, across institutions, and between industry and academic partners. The *Nature* studies show that HIV can be pushed out of hiding—confirmed across different model systems—and the studies open a range of possibilities for the development of new therapies that might one day lead to a cure for HIV.

More information: Systemic HIV and SIV latency reversal via non-canonical NF-κB signalling in vivo, *Nature* (2020). DOI: 10.1038/s41586-020-1951-3 , nature.com/articles/s41586-020-1951-3

Robust and persistent reactivation of SIV and HIV by N-803 and depletion of CD8+ cells, *Nature* (2020). DOI: 10.1038/s41586-020-1946-0 , nature.com/articles/s41586-020-1946-0

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