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Antibodies, together with viral 'inducers,' found to control HIV in mice

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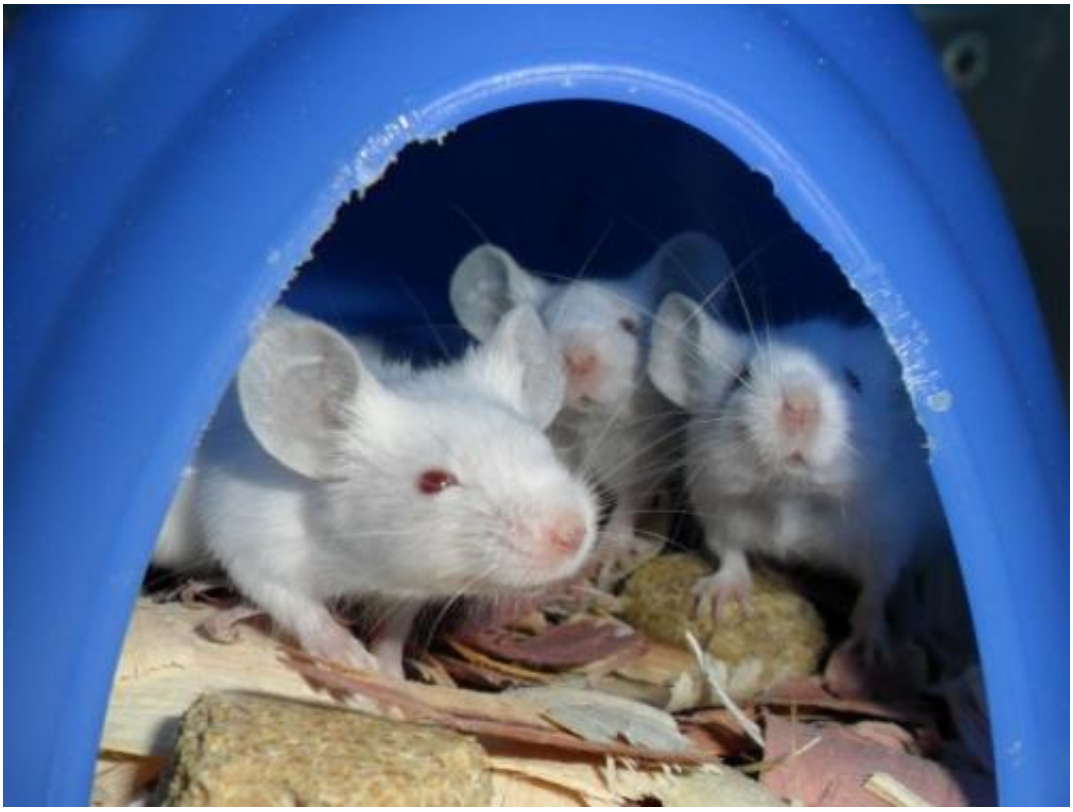

Credit: Martha Sexton/public domain

Although HIV can now be effectively suppressed using anti-retroviral drugs, it still comes surging back the moment the flow of drugs is stopped. Latent reservoirs of HIV-infected cells, invisible to the body's immune system and unreachable by pharmaceuticals, ensure that the infection will rebound after therapy is terminated.

But a new strategy devised by researchers at Rockefeller University harnesses the power of broadly neutralizing antibodies against HIV, along with a combination of compounds that induce viral transcription, in order to attack these latent reservoirs of cells in an approach termed "shock and kill." In tests on mice, 57 percent of animals treated in this way did not have the expected resurgence of virus in their blood after their treatment ended.

"This is the first time that any combination of agents has been found to prevent viral rebound in any animal model," says Nussenzweig.

Three Rockefeller labs collaborated on the study: Michel C. Nussenzweig's Laboratory of Molecular Immunology; Alexander Tarakhovsky's Laboratory of Immune Cell Epigenetics and Signaling; and Jeffrey V. Ravetch's Leonard Wagner Laboratory of Molecular Genetics and Immunology. The findings are published August 14 in *Cell*.

The problematic latent reservoirs of HIV-infected cells are established very early in the infections, possibly even before tests can detect the presence of the virus, and current drug therapies are unable to kill the latent cells.

"The latent reservoir remains the major barrier to curing HIV-1 infection," says Nussenzweig, who is the Zanvil A. Cohn and Ralph M. Steinman Professor and a Howard Hughes Medical Institute investigator. "Our finding suggests that antibodies could play a significant role in disrupting the establishment and maintenance of the latent reservoir, which is believed to be a necessary step to curing patients of HIV-1."

The Nussenzweig lab has worked for several years on broadly neutralizing antibodies, a recently discovered subset of antibodies with an unusually high ability to recognize HIV consistently despite the virus's ability to rapidly mutate. Broadly neutralizing antibodies have shown

great promise for treating HIV infection in mouse and monkey models of HIV. But by themselves they suffered the same problem that plagued other therapies: when you stop administering them, the virus rebounds.

Counterintuitively, the key to success in this instance was combining broadly neutralizing antibodies with viral inducers, compounds that prompt latent viruses to become active by promoting the transcription of their DNA. The idea is to eliminate the invisibility of the latent reservoir while simultaneously attacking the virus. More than half of the mice that received broadly neutralizing antibodies along with a cocktail of three viral inducers had no viral rebound at all, even three-and-a-half months after their last injection. (Broadly neutralizing antibodies alone, or even in combination with a single viral inducer, did not have this effect, nor did combinations of anti-retroviral drugs and viral inducers that have been attempted in the past.)

The researchers say that one reason broadly neutralizing antibodies may have succeeded where traditional drugs have failed is their ability to directly harness the power of the body's own immune system using Fc receptors, which occur on a wide variety of immune system attack cells and help them precisely target the infection.

"A big surprise in this study was the important role the Fc part of the antibody played in amplifying the potency of broadly neutralizing antibodies," says Ravetch, who is Theresa and Eugene M. Lang Professor. "Their effect in neutralizing latent reservoirs of HIV-1 was largely driven by Fc-receptor binding."

More information: *Cell*, Halper-Stromberg et al.: "Broadly Neutralizing Antibodies and Viral inducers decrease rebound from HIV-1 latent reservoirs in humanized mice." www.cell.com/cell/abstract/S0092-8674(14)00993-3

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