Researchers unveil new monkey model for HIV

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By altering just one gene in HIV-1, scientists have succeeded in infecting pig-tailed macaque monkeys with a human version of the virus that has until now been impossible to study directly in animals. The new strain of HIV has already been used to demonstrate one method for preventing infection and, with a little tweaking, could be a valuable model for vetting vaccine candidates.

A team of researchers led by Paul Bieniasz and Theodora Hatziioannou at The Rockefeller University showed that two pig-tailed macaques, given a common antiretroviral treatment one week before and one week after being exposed to the newly engineered HIV, had no signs of infection. "We're not saying we can save the world with antiretroviral pills. But this model will allow us to start studying the best way to administer prophylaxis and do other experiments on preventing HIV-1 infection that could not be easily done on humans," says Bieniasz, head of the Aaron Diamond AIDS Research Center Laboratory of Retrovirology at Rockefeller and a Howard Hughes Medical Institute investigator.

The findings, to be published Monday in the *Proceedings of the National Academy of Sciences*, show that the engineered virus injected into a pig-tailed macaque initially spreads almost as ferociously as it does in people and the virus remains detectable for at least six months. But it does not make the monkeys sick. Rather, it behaves as it is thought to behave in a group of HIV-positive people whose exceptional immune systems are generally able to keep the virus in check. These fortunate few are called

long-term nonprogressors.

The animal model grew out of years of research into the molecular cloak-and-dagger fight between HIV and the cells of the host it infects. In particular, Bieniasz, who is also a scientist at the Aaron Diamond AIDS Research Center, Hatziioannou and colleagues have studied two groups of rapidly evolving genes, APOBEC3 and TRIM5, which produce unusual classes of defensive proteins with distinctive capabilities to fight retroviruses such as HIV. These genes, shared by humans and their simian forebears, have evolved mutations specific to each species' unique history of retroviral battles. In most simians, the APOBEC3 and TRIM5 proteins actually kill HIV on sight, making it impossible for researchers to study the virus in an animal model. Instead, they have studied HIV's cousin, simian immunodeficiency virus (SIV), which causes an AIDS-like disease in certain monkey species. But SIV shares only about half of its amino acid sequence with HIV, making it a very imperfect substitute for testing anti-HIV drugs and vaccines. Several labs have engineered hybrids called SHIVs — SIVs that contain pieces of HIV DNA — but these have problematic differences, too.

Now, Bieniasz and Hatziioannou, working with Vineet KewalRamani and Jeffrey Lifson at the National Cancer Institute in Maryland, have developed a strain they call simian-tropic HIV-1 (stHIV-1), which shares about 95 percent of its genome with the human version. It differs only in the one HIV-1 gene that fails to deal with the pig-tailed macaques' APOBEC3 defenses. (The scientists did not need to overcome their TRIM5 defenses because macaque TRIM5 proteins are extremely unusual and not effective against HIV). The new research marks a major advancement of experiments the Bieniasz and Hatziioannou team published in 2006 that showed that HIV engineered to hide from both the APOBEC3 and TRIM5 proteins in rhesus macaques could grow in their cells, at least in a test tube. But that strain's growth was poor, and it failed to take root in the actual animals.

The new virus, stHIV-1, spreads almost as quickly after injection as HIV-1 initially does in humans and it persists for several months, after which it is controlled. Bieniasz and colleagues showed that that control is in part thanks to a specific class of immune system T cells that if blocked, allow a resurgence of the virus. The team demonstrated the use of the model by showing that a commonly used antiretroviral drug combination taken briefly before and after an injection of two million infectious units of stHIV-1 effectively protected the monkeys from the virus.

Though the work is an important advance, for stHIV-1 to be useful for testing vaccines, the scientists must modify the protein envelope that surrounds the virus so that it targets the same set of immune cells in monkeys as it does in humans. In addition, says Hatziioannou, an assistant professor at ADARC, they want the infection to run its full course and cause disease, to make it as faithful to HIV-1 as possible. "This model, even as is, should be useful for studying pre- or postexposure treatments," she says. "But to have a really authentic model, we need to make it pathogenic, to make it hotter."

Source: Rockefeller University