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A Macaque Model of HIV Infection

Researchers have taken a major step toward developing a better animal model of human AIDS. Such a model could greatly improve researchers' ability to evaluate potential strategies for preventing and treating the disease.

Researchers have lacked a reliable animal model in which to study HIV infection, because the virus replicates poorly in most other animals. But now a team assembled by Howard Hughes Medical Institute (HHMI) investigator Paul D. Bieniasz of the Aaron Diamond AIDS Research Center (ADARC) has genetically modified the human virus so that it can infect a species of rhesus monkeys. Viral infection in the monkeys mimics the early stages of HIV infection in humans.

Bieniasz and his colleagues, Theodora Haztiioannou (also at ADARC), Jeffrey Lifson, and Vineet KewalRamani (both at the National Cancer Institute at Frederick), also demonstrated that three antiviral drugs that can be combined in a single daily pill prevent HIV infection in the monkeys. The team's work is published in the March 2, 2009, early online edition of the *Proceedings of the National Academy of Sciences*.

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- Paul D. Bieniasz

"In practical terms, it would be very useful to have an animal model where you infect the animals with HIV, and the animals then recapitulate what happens in HIV-infected humans," said Bieniasz. But HIV is highly specific for humans and generally does not infect or cause disease in other species. Over the last two decades, researchers have created genetically engineered forms of HIV, but, as with the native virus, none of those altered viruses could infect monkeys.

In the absence of an animal model of HIV infection, researchers relied on surrogate viruses -- strains of the simian immunodeficiency virus (SIV) or SIV/HIV chimeric viruses -- to study acquired immunodeficiency in chimpanzees, rhesus macaques, and other primates. However, SIV contains

only about 50 percent of the genetic code of HIV. Hence, testing drugs and vaccines on SIV-infected animals provides limited information about whether those therapies would be effective against the human immunodeficiency virus. “If you want to make a vaccine against HIV, then the vaccine you’re going to use in humans almost certainly will not work against SIV in animals,” said Bieniasz. “You have to make a parallel vaccine based on SIV to test in the animals, and then take a leap of faith that you can extrapolate that to HIV.”

To circumvent that shortcoming, Bieniasz and colleagues performed a nifty feat of genetic engineering – and got an assist from evolution. The evolutionary arms race between viruses and the host defense system equipped mammalian cells with proteins that sabotage viruses. In many monkey species, two of these proteins help reject HIV. One of these proteins, called TRIM5, inactivates incoming particles of HIV. Last year, Bieniasz and Hatzioannou discovered that pigtail macaques, a species of medium-sized monkeys from Southeast Asia, carried a mutant form of TRIM5 that fails to inactivate HIV.

“This was a key insight,” said Bieniasz. “This mutation stops TRIM5 from preventing HIV infection. So with pigtail macaques, unlike other monkey species, one of the major barriers to HIV infection is missing.”

With evolution clearing one barrier, Bieniasz and Hatzioannou set about surmounting the second -- a gene called *Vif*. *Vif*, which is found in different versions in both HIV and SIV, evolved to defeat a host defense protein called APOBEC3. The version of *Vif* found in HIV defeats the human APOBEC3, while the SIV form of *Vif* defeats the monkey APOBEC3. The team knew they could help HIV circumvent the monkeys’ APOBEC3 by equipping it with the SIV version of *Vif*. And that’s exactly what they did.

“The SIV *Vif* gene is fully effective at defeating APOBEC3 in monkeys, allowing the virus to replicate in the animals,” said Bieniasz. “So the obvious thing to do was replace the HIV *Vif* protein with the SIV version.”

Bieniasz and Hatzioannou engineered HIV to carry the *Vif* gene from SIV. Then Lifson and KewalRamani infected four pigtail macaques with this hybrid virus and found evidence that the virus invaded the monkeys’ cells as well as HIV invades human cells. Within a week or two, the animals carried between 100,000 and one million copies of HIV per milliliter of blood, approaching the same amount seen in early human infections.

However, the monkeys did not become sick with AIDS. Eventually, their immune systems kicked in and suppressed the virus. After about six months, the virus was contained. “We can quite accurately recapitulate the early stages of infection. The later phases in the monkeys look more like an atypical group of people we call long-term non-progressors,” Bieniasz explained.

To demonstrate the usefulness of the new monkey model, Bieniasz and colleagues gave three anti-HIV drugs -- tenofovir, emtricitabine, and efavirenz -- to two monkeys for a week. They then injected the animals with the virus, continued to administer drugs for a week, and then stopped the treatment. Neither of the animals became infected.

Bieniasz said the results show that a single pill containing the three drugs -- such as the commercial product Atripla -- has the potential to prevent HIV infection in macaque monkeys, and perhaps humans. "Given the great difficulty developing a vaccine against HIV, the idea of protecting people with anti-retroviral drugs is gaining a lot of traction," he notes.

"The bottom line is, the equivalent of one pill a day protects the monkeys from infection by a very high dose of virus injected straight into the blood," Bieniasz said. "If the practical difficulties -- such as lack of access to health care in much of the world -- could be overcome, then effective prevention does not seem impossible."

As the team refines the engineered virus to more faithfully replicate HIV infection in people -- and hence serve as a model for vaccine development -- they foresee researchers using the monkey model to probe other questions. "Could anti-retroviral drugs work when administered rather like a morning-after pill? What's the best timing and dose to prevent infection? You can't easily do clinical trials in people to investigate these things. But those questions can now be approached with an animal model."