HIV researchers show virus the door

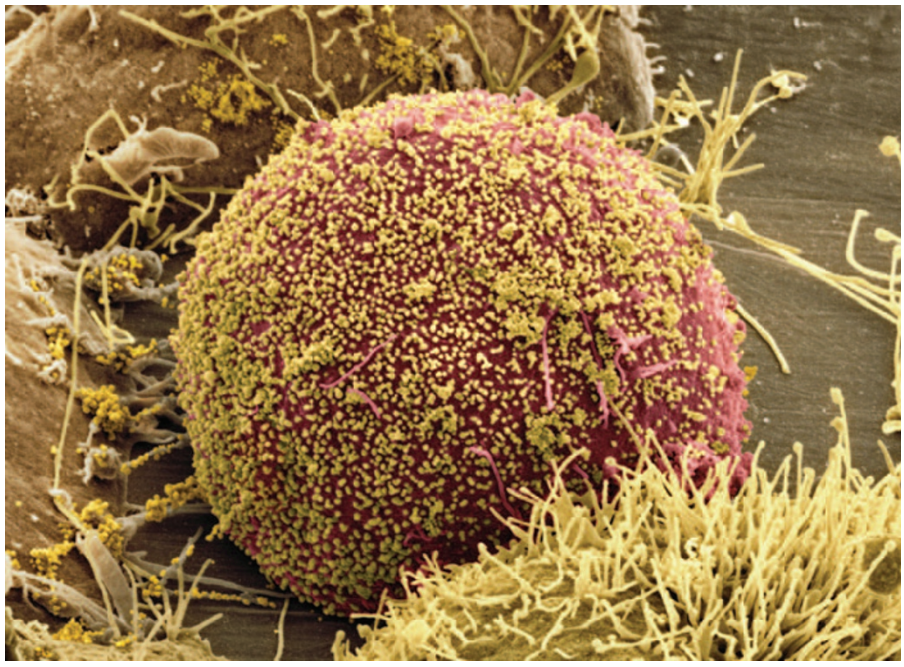
SEATTLE — Currently, HIV-infected individuals must stay on antiretroviral therapy for their entire lives, as the virus almost invariably reemerges when the drugs are withdrawn. Now, with an eye to purging the virus from its cellular hideouts, scientists here at the International Conference on Retroviruses and Opportunistic Infections (CROI) meeting in March have found new ways to lure HIV out of latent immune cells—a first step toward a long-term, drug-free functional cure.

"In the past, you did not say [the word 'cure'] because you were hyping the field," says Nathaniel Landau, a virologist at the New York University Langone Medical Center. "But it's gotten to the point where it's no longer taboo to talk about."

The most promising clinical data came from David Margolis, a molecular virologist at the University of North Carolina School of Medicine in Chapel Hill. Margolis is leading a small trial involving the drug vorinostat, a histone deacetylase inhibitor approved for treating a type of leukemia. In cell culture, vorinostat, which is marketed as Zolinza by New Jersey–based Merck, has previously been shown to activate HIV by loosening up the tightly coiled DNA that keeps the virus silent. Reporting at CROI, Margolis and his colleagues observed a similar effect in people: all of the six subjects in his trial experienced a spike in HIV transcripts in their resting $CD4^+$ T cells, indicating that the virus had become reactivated.

"This is the first indication *in vivo* that these drugs do what we think they do," says Sharon Lewin, an infectious disease researcher at Monash University in Melbourne, who is also testing vorinostat in a group of ten HIV-infected men in Australia. "The Margolis study is kind of step one; now we need to work out what comes next."

Part of what comes next is figuring out a way to eliminate the newly awakened virus-laden T cells after treatment with vorinostat or a similar drug. Many researchers had assumed that the cells might be killed automatically by the immune system or might even self-destruct as they spew HIV. But results presented by Liang Shan suggest otherwise.



Thomas Deerinck, NCMIR / Photo Researchers, Inc.

Latent bloomer: A leukemia drug helps bring HIV out of its hiding places.

A killer approach

Shan's cell-based study—which was published online in *Immunity* on the same day as his talk—found that vorinostat-treated $CD4^+$ T cells remain alive (doi:10.1016/j.immuni.2012.01.014, 2012). To destroy them, Shan, who works in Robert Siliciano's lab at the Johns Hopkins University School of Medicine in Baltimore, had to deploy 'killer' T cells stimulated with bits of HIV protein. If the findings hold true in people, drugs that flush out HIV may have to be combined with other treatments, such as vaccines that stimulate killer immune cells, to destroy the cells left behind. "We will need multiple targets," says Douglas Richman, director of the Center for AIDS Research at the University of California–San Diego. He also notes that vorinostat might not be the ideal drug; for instance, it may act on multiple genes in the body, raising safety problems.

With such concerns in mind, the field is pursuing multiple strategies to awaken the body's immune system against latent viruses. For example, several research groups are targeting a T cell receptor called programmed death-1 (PD-1) that is known to help maintain latency. Three years ago, a team led by Vijayakumar Velu, an immunologist at the Emory University School of Medicine in Atlanta, reported that an antibody that blocks PD-1 bumped up the immune response and prolonged survival in macaques infected with simian immunodeficiency virus in the absence of antiretroviral drugs (*Nature* **458**, 206–210, 2009). In follow-up work presented at CROI, Velu's team treated the macaques with the PD-1 inhibitor after withdrawal of antiretroviral therapy and showed that the approach kept viral loads down in three of six monkeys tested. According to Velu, the antibody may also help kill latent cells once they awaken and start producing HIV.

Irrespective of the specific agents under development, the basic strategy being advanced still rests on a core assumption: that existing antiretroviral therapies can completely quash HIV replication throughout the body once the virus is coaxed from its $CD4^+$ T cell lair. This assumption is supported by numerous previous studies. But if it's not true, then activating latent virus will "just create more infectious cells," warns Margolis. New findings from Courtney Fletcher, a pharmacologist at the University of Nebraska Medical Center in Omaha, stoke this concern. His work, presented at CROI, suggests that some antiretroviral drugs are at such low concentrations in certain regions of the body, such as the lymph nodes, that they may not stop HIV replication completely.

Given such uncertainties, "it's a long way from the Margolis study to saying we can actually eradicate the virus," cautions John Coffin, a virologist at Tufts University in Boston and the chair of the meeting's scientific program committee. "These are really baby steps."

Charlotte Schubert