New Drug Keeps HIV Out of Cells

Drugs currently approved to fight HIV wait for the virus to start trouble inside the cell before springing into action. Like a bouncer stopping obnoxious patrons at the door, a promising new drug paralyzes the virus before it ever invades.

Sixteen HIV-positive adults without any AIDS symptoms received intravenous doses of the experimental drug, known as T-20, twice daily for 2 weeks. HIV concentrations in the four patients given the highest doses dropped by 99 percent, an effect as potent as that of the drug combinations given to HIV patients today.

"The antiviral effect of the T-20 drug is really substantial," says Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases in Bethesda, Md.

"I don't think anybody, even the big supporters of T-20, expected the impressive response we saw in the highest-dose group," says J. Michael Kilby of the University of Alabama at Birmingham, lead author of a report in the November NATURE MEDICINE. "But the enthusiasm for this project isn't merely about this drug, it's about [proving] a whole new approach to therapy."

To do its damage, HIV bumps up against immune cells, binds to them, and invades. Standard medications attack enzymes the virus uses to copy itself once inside the host cell, but the new approach stops the virus from ever fusing to the cell. "The virus can't do anything if it can't get inside our cells," Kilby says.

Seeking to block that fusion, researchers from Alabama, Duke University, and the North Carolina biotechnology company Trimeris set out a decade ago to figure out the role of so-called glycoproteins that stud the outside of the virus like lollipops. When the sticky end of the lollipop bumps into an unsuspecting immune cell, the lollipop stem, a protein called gp41, releases the sticky end and reaches out to snag the cell, then pulls it close enough for the virus and cell to fuse.

To stop gp41's deadly act, the team designed the peptide T-20, a chain of 36 amino acids. The molecule attaches to gp41 and prevents it from drawing virus and cell together.

Some researchers have wondered whether blocking cell entry by this mechanism could really stop a virus from spreading. "Although the principle of blocking entry is not new, this was the first truly successful attempt," Fauci says.

Some patients in the T-20 trial experienced low-grade fevers or complained of transient headaches, but no one withdrew from the study because of side effects. The drug appears safe, Kilby says, but unlike existing HIV drugs, T-20 does not work in pill form. Stomach acid would damage its delicate chain of amino acids before it could reach the bloodstream.

Douglas D. Richman of the University of California, San Diego points out the impracticality of a therapeutic drug that can't be taken as a pill. "Working people who need drugs all their lives are going to want that," he says.

That difficulty "doesn't bother me that much," says Fauci. "If you prove the concept that you get a substantial antiviral effect, then you start working on better mechanisms of delivery."

Richman notes that it might be possible to develop a smaller, less complex molecule, just as potent as T-20, that would not be destroyed in the stomach.

Kilby's team is already testing the power of administering T-20 just under a patient's skin. "A simple shot, like an insulin shot that you could learn to give yourself at home, is getting a little closer to something that would be practical," Kilby says. Simple injections of T-20 might some day work as a "rescue regimen" for people who develop resistance to other drugs, he adds.

Kilby expects results in the next few months, but even if they're promising, researchers still need to test the drug's long-term success and its effects when combined with other drugs. It could take years before T-20 is approved for widespread use. *—S. Simpson*

Ancient Americans show metallic flair

Scientists working at an ancient ceremonial center in Peru can be forgiven if they break into a chant of "Hallelujah, foiled again." Copper and gold foil unearthed there dates to about 3,000 years ago, offering the oldest known evidence of metalworking in the New World.

Metallurgy in this region arose in what is believed to have been a relatively small society without strict social classes, assert archaeologist Richard L. Burger and geologist Robert B. Gordon, both of Yale University. Traditional theories hold that large states characterized by stark social divisions held a monopoly on technological innovations such as metallurgy.

Burger and Gordon present their findings in the Nov. 6 SCIENCE.

"This is an extremely important paper," comments archaeologist Daniel Sandweiss of the University of Maine in Orono. "It finally gives us a clear indication that metallurgy was invented independently [in the New World] and developed in ways that were similar to its beginnings elsewhere."

The Yale researchers directed excavations at Mina Perdida, located on a large, natural terrace above a coastal valley. A flat-topped, terraced pyramid dominates the site. Digging focused on two long, raised mounds arranged in a U shape and framing a ceremonial plaza.

Mina Perdida and nearby sites have already yielded remains of religious rituals and other community activities, and of households situated on their fringes. These locations were abandoned before the rise of Peruvian cultures that produced smelted copper objects by around 2,000 years ago.

Radiocarbon dating of artifacts found in the same sediment as the copper and gold-foil fragments yields an age of between approximately 3,120 and 3,020 years, Burger and Gordon report.

Metalworkers at Mina Perdida understood copper's natural properties and how to manipulate the metal in sophisticated ways, Burger holds. Microscopic analysis of foil specimens indicates that they were expertly hammered into thin foils. In some cases, a heating process was used as part of foil production. Three copper foils have folded corners and edges. Fragments of gold attached to two copper foils indicate that Mina Perdida artisans made gilded objects.

Foils may have been attached to ceremonial attire or objects in order to reflect light during ritual performances, Burger suggests. Ancient onlookers probably marveled at the capture and redirection of a natural force as significant as the sun, he says. *—B. Bower*

A bit of gold foil clings to postage-stamp-sized copper foil found in Peru.