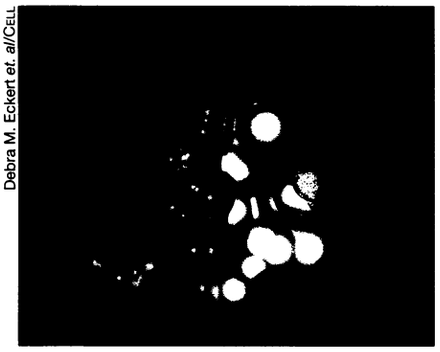
For possible AIDS drug, smaller is better

Pull the trigger on a revolver and the hammer draws back for a split second before slamming forward. Imagine stopping a deadly gunshot by quickly inserting an impediment between the cocked hammer and the bullet.

AIDS researchers are now developing drugs that perform a comparable feat, halting HIV midway through its attempt to fuse with and infect a cell. One such drug, T-20, has already entered clinical trials (see p. 236). However, because it's a large, fragile molecule that's not readily absorbed in the digestive system, T-20 must be injected.

Investigators have now taken a key step toward creating drugs that act like T-20 but are small and hardy enough to be taken orally. They've designed bits of protein, or peptides, that bind to an indentation on a viral-surface protein, gp41, that HIV uses to enter cells.



Debra M. Eckert et. al/Cell

A possible AIDS drug (green and white) fills a pocket on an HIV protein (blue).

Both T-20 and the newly discovered peptides interfere with the actions of gp41, but they attach to different regions of the protein. The pocket targeted by the peptides normally stays hidden. When the AIDS virus bumps into a cell, gp41 changes shape and exposes the pocket as it helps the virus infect the cell.

"When we saw the crystal structure of gp41 several years ago, the pocket was something that jumped out at us" as a drug target, notes Peter S. Kim of the Howard Hughes Medical Institute at the Whitehead Institute for Biomedical Research in Cambridge, Mass.

In the Oct. 1 Cell, Kim and his colleagues describe peptides—some as small as one-fourth the size of T-20—that fit snugly into the gp41 indentation. In test-tube experiments, the peptides stop HIV from infecting cells, the group reports.

"It's a very nice example of the basic science of structural biology getting translated into a potential drug," says Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases in Bethesda, Md.

To find HIV-blocking peptides, Kim's group created an artificial protein with an exposed gp41 pocket. The scientists screened a large library of peptides for ones that bound to the pocket. Using D amino acids, mirror-image replicas of natural amino acids, the researchers then made synthetic versions of the selected peptides. These forms are resistant to degradation, making them ideal for pills that must survive a bath in the digestive enzymes of a stomach.

Pills that block the ability of HIV to infect cells should complement current AIDS drugs, which target enzymes used by the virus once it's already inside a cell, says Fauci. Such new pills should make it more difficult for HIV to evolve drug resistance, he adds.

The test-tube experiments, however, suggest that Kim's peptides aren't as effective as T-20 at stopping the AIDS virus. Still, now that scientists have shown that peptides binding the gp41 pocket can thwart HIV, drug developers will rush to craft molecules that are even smaller and more potent than the ones his group identified, predicts Kim.

Moreover, his team plans to make the artificial-pocket protein freely available so that pharmaceutical and biotech companies can screen their stocks for other drugs that might stop HIV from shooting its way into cells. *—J. Travis*

Life found beneath Antarctic ice sheet

Pushing the known envelope of life to a new extreme, scientists have found evidence that viable microorganisms populate a gigantic freshwater lake hidden for hundreds of thousands of years beneath the Antarctic ice sheet.

Called Lake Vostok, the near-freezing body of water is locked in perpetual darkness beneath 4,000 meters of ice (SN: 10/2/99, p. 216). No one has yet collected samples of the trapped water, but an international drilling team has bored down to within 120 m of the lake and pulled up samples of the deep ice. According to glaciologists, ice from this level represents lake water that froze to the bottom of the glacial sheet.

"When you take this ice and melt it down, you do find some viable cells," says David M. Karl of the University of Hawaii at Manoa in Honolulu, who reported his results last week at a meeting in Cambridge, England. Originally living in the lake, these organisms became trapped in the lowermost ice as it froze, he says.

Another group, led by John Priscu of Montana State University in Bozeman, also reported observing microbes in the frozen lake water. Priscu's team, however, didn't find evidence that the cells were alive.

Karl and his colleagues used nutrients labeled with radioactive carbon to test for living microbes in the melted ice. By tracking the carbon, they demonstrated that glucose and acetate were broken down to form carbon dioxide. Living cells carry out these same reactions in a process called respiration.

"I think that was a really clever way to look at metabolism. He showed they're viable," says Priscu.

Karl notes that a similar experiment gave a positive result when it flew on the Viking spacecraft in the 1970s. In that case, researchers concluded that no organisms were involved but extreme ultraviolet radiation hitting Mars had broken down the radioactively labeled molecules into carbon dioxide. However, the Hawaiian team performed its Vostok experiment in the dark and conducted several control tests to rule out false-positive results, says Karl.

At this point, neither team can identify the microorganisms. About 1 micrometer in size, they could be either bacteria or members of a domain of life called archaea, which populates many extreme environments. Priscu's team is currently trying to sequence DNA isolated from the ice and match it against known organisms. "That will tell us if they are ancient or unique," he says.

Whatever microbes are present in the deep ice must be mini-Methuselahs. Both Priscu and Karl used radioactively labeled compounds to test whether the cells were growing, a different process from respiration. Neither group could find evidence that the organisms bulked up or reproduced. "These cells are probably growing very, very slowly," says Karl.

A French team also tested the ice but couldn't demonstrate that the cells they found were originally from the ice rather than contaminants introduced during drilling or lab studies.

To confirm the presence of living microbes in the lake itself, scientists must punch through the ice sheet and collect samples of the water, says Karl. Such a mission would also help determine how organisms can survive in such a starved environment. Some geologists have suggested there may be hot springs at the bottom of the lake spewing out nutrients. At the Cambridge meeting, researchers discussed mounting an international mission to breach the lake without contaminating the water.

That's going to be a difficult task, says Tommy J. Phelps of Oak Ridge (Tenn.) National Laboratory, who studies bacteria living within Earth's crust. "I would hate for my grandchildren to blame our generation for perturbing the lake," he says. *—R. Monastersky*