makes sense to boost these patients' immune systems with an HIV vaccine. "Before you stop the drug, wouldn't it be wise to enhance the immune response?" asked Ho.

John Coffin, a leading retrovirologist from Tufts University, didn't think so, sparking the hottest debate of the meeting. Coffin argued that while such vaccinations might hamper any remaining HIV's attempt to spread, they could not prevent it. "You're not going to eradicate the virus with an immune response," Coffin contended. "So far that hasn't been good enough to remove the infection from a single individual." Ho countered with a calculation suggesting that in patients who only have latently infected cells, a few cells—50 to 75—come out of latency each day and produce HIV. Vaccinating, he proposed, would give the immune system enough punch to clear that small number of producing cells and, over time, eradicate the infection.

"The issue is answering the question: Is eradication possible?"

—David Ho

But several researchers suggested that complete eradication of HIV from the blood may be the wrong target in any case. Instead, they asked, why not enlist the immune system—rather than drugs—to control the virus for extended periods? That goal, Scripps's Mosier proposed, could be achieved by cycling patients with both undetectable viral loads and waning HIV immunity off therapy, and then cycling them back on when their virus reemerges. Several studies, he noted, have shown that such "treatment holidays" do not allow the virus to develop resistance to the drugs. And this repeated exposure to the virus would keep boosting immune responses to it. "It surprises me that you're even actually thinking about vaccines [to boost immunity] when you have got the natural infection of immunized people to begin with," said Mosier.

Brain drain. Even if HIV can be eliminated from the blood, however, it might not be possible to rid the body of it altogether because of the virus's propensity for skulking around the central nervous system. "I'm very worried that there's a viral reservoir in the brain," said Stuart Lipton, who studies HIV neuropathogenesis at Harvard's Brigham and Women's Hospital. There's no accurate way to measure levels of HIV in the brain, where it can stimulate the production of toxins that produce dementia. But it seems to be protected there by the so-called "blood-brain barrier," which keeps both drugs and immune cells that might fight the virus out of the brain.

Anti-HIV drugs that do reach the brain are a double-edged sword, warned immunologist Angela McLean of Oxford University in the United Kingdom. Only low concentrations of the drugs likely make it past the blood-brain barrier, she noted, and "suboptimal" levels of anti-HIV drugs allow the virus to develop resistance to the agents. "The last thing you want is intermediate drug levels," cautioned McLean.

To make matters worse, the brain is but one "sanctuary site" for HIV. Other areas of the body that have similar barriers include the testes, the eye, the thymus, and the spinal cord. And even less is known about HAART's impact on HIV in these sites. "The sanctuary issue is still up in the air," said Ho.

The think tank participants proposed a practical way to learn much more about the impact of anti-HIV drugs on these remote compartments: autopsies of relatively healthy, HIV-infected people. Although many autopsies have been done on people who have died from AIDS, by definition they have failed treatment and their bodies hold no clues to how HAART affects viral levels in the brain and other hard-to-access sites. Retrovirologist Ashley Haase of the University of Minnesota Medical School in Minneapolis suggested that researchers make a concerted effort to find HIV-infected people who have died from car accidents and other traumas. "One thing that might come out of this meeting is the need to develop such a tissue bank," said Haase.

In the end, researchers could not agree whether eradication is possible, but they clearly are nowhere done thinking about it.

–Jon Cohen

BIOSENSORS

Getting an Inside Look at Cells' Chemistry

New microscopic sensors can size up the chemical status of a living cell. Unveiled early this month in New Orleans at the Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy by a group at the University of Michigan, Ann Arbor, the sensors fit inside the cell and monitor its changing chemistry on the spot. Among other things, they could help researchers understand how an individual cell responds to a dose of drugs or toxins.

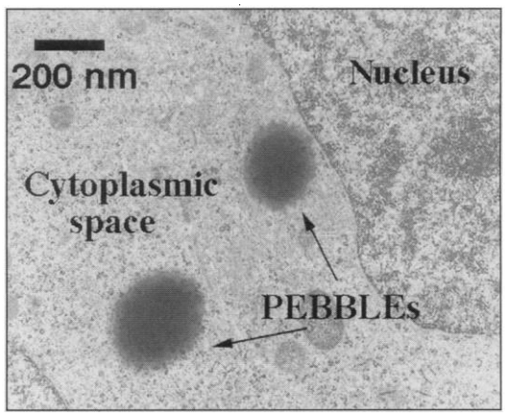
Cells constantly adjust their level of ions such as calcium or potassium in response to external stimuli. Biologists usually measure these changes by injecting dyes into a cell or poking it with electrodes. But Michigan chemist Raoul Kopelman and his colleagues wanted to find a less invasive method.

The key turned out to be a class of molecules, called ionophores, which normally latch onto positively charged ions and help pull them across the cell membrane. Kopelman and his grad student Heather Clark packaged ionophores specific for different ions into the surfaces of particles less than 100 nanometers across, made of a plasticlike polymer. As each ionophore sucks up its target positive ion, it compensates by releasing positively charged protons, which activate a fluorescent dye embedded in the particle.

To test their minisensors, dubbed PEBBLEs (Probes Encapsulated By BioListic Embedding), the researchers injected them into brain cells or mouse eggs with a "gene gun," which is normally used to shoot DNA into a cell via a puff of helium. The brightness of the PEBBLEs' glow revealed the concentrations of the ions they were tailored to detect. Cells don't seem to mind the PEBBLEs, says Kopelman, probably because they take up little space—each occupies only a millionth of an average cell's volume.

"I think it's beautiful," says Stephen Weber, a chemist at the University of Pittsburgh. He notes that because PEBBLEs are used with a microscope, researchers can determine the exact three-dimensional position of each sensor as well as its readout. Says Kopelman: "You can now follow chemistry on a single-cell level and see how any change affects it within seconds, minutes, or hours."

–Kevin Boyd



UNIV. OF MICHIGAN

Inside job. Polymer-encapsulated sensors spy on ions within the cytoplasm of a cell.

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