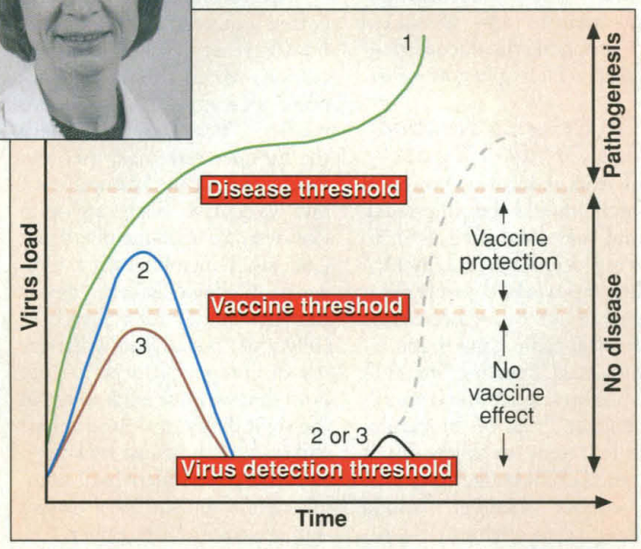
Weakened SIV Vaccine Still Kills

An AIDS advocacy group is stepping up a campaign to test "attenuated" HIV vaccines in people, but several monkey experiments suggest that achieving protection without causing disease may be hard

For the past few years, a small group of researchers has been urging the federal government to pay more attention to an AIDS vaccine strategy that, in monkey experiments, has shown more promise than any other: inoculation with a live, but weakened, version of the AIDS virus. Last week, their cause gained widespread media attention when an AIDS advocacy group stepped up its recently launched campaign for human tests of such a vaccine. The group, the Chicago-based International Association of Physicians in AIDS Care (IAPAC), parlayed an informal 25 September meeting with researchers at the National Institute of Allergy and Infectious Diseases (NIAID) into worldwide television and newspaper coverage. Yet, just as the campaign is taking off, monkey researchers have quietly been reporting evidence at scientific meetings that will heighten doubts that an "attenuated" HIV vaccine can ever safely be tested in people.



SOURCE: R. RUPRECHT, R. RASMUSSEN, P. SHARMA, AND Y. HU

Narrow window. Ruth Ruprecht *(inset)* proposes that weakened strains (2 and 3) will protect only if they replicate just enough (2); but they might become pathogenic later *(dashed line)* through mutation or loss of immune system suppression. Normal strain follows path 1.

The new data, which come from several labs, reveal that a vaccine made from weakened SIV—HIV's simian analog—can cause full-blown AIDS in adult monkeys. Researchers already had evidence that the vaccine can cause disease in newborn animals, which have immature immune systems. Now, the finding that a similar deadly progression may occur in adults has deeply worried some investigators. "To do these [human studies] makes me really nervous," says Ruth Ruprecht of the Dana-Farber Cancer Institute in Boston.

Ruprecht's group—which was the first to report that attenuated SIV can cause illness in newborn monkeys (*Science*, 24 March 1995, p. 1820)—is one of several that has seen a weakened SIV cause disease in adults. Others include Mark Lewis at Henry M. Jackson Foundation in Rockville, Maryland; Martin Cranage at the Centre for Applied Microbiology and Research in Salisbury, United Kingdom; Ruth Connor at New York City's Aaron Diamond AIDS Research Center; and Ronald Desrosiers of the New England Regional Primate Research Center in Southborough, Massachusetts.

It was Desrosiers who provided the initial impetus for the attenuated vaccine approach with a landmark study published in the 18 December 1992 *Science* (p. 1938). His lab showed that deleting the *nef* gene from SIV resulted in an apparently harmless virus—"delta-*nef*"—that was capable of protecting inoculated animals from a subsequent "challenge" with SIV. Those results, as well as Desrosiers's follow-up work and similar data from other labs, have encouraged IAPAC to push for human trials of an attenuated vaccine.

More than 50 people have volunteered for an IAPAC-organized trial of an attenuated AIDS vaccine that the group hopes to conduct beginning in 2000 (*Science*, 22 August, p. 1035). "We're not ready to go into trials tomorrow or the day after tomorrow," says Deputy Director José Zuniga, one of the volunteers. "But at some point we have to get away from pure science and look to see what happens in humans."

Jack Killen, head of NIAID's Division of AIDS, says his branch is not as gung-ho about moving the attenuated vaccine into the clinic as IAPAC would like. "Certainly, the concept of a live, attenuated vaccine is one we all agree deserves a lot of attention," says Killen. But he says that last week's meeting was supposed to be just a brown bag lunch discussion, not a formal meeting with various public health officials, as IAPAC's press releases stated. "There was a definite concern that the degree of media attention was making much more out of this meeting than we intended it to be," says Killen. Other AIDS researchers are more critical of IAPAC's proposed trial. "I don't think they've seen enough data to make an informed decision," says Lewis. "It's kind of scary."

The data now include the disturbing new monkey results. As Ruprecht first reported at a primate meeting held 3 to 6 September in Seattle, her group has inoculated 18 animals during the past 4 years with a version of SIV that they attenuated by knocking out three separate genetic parts of the viral RNA—a so-called "delta-3" SIV. Theoretically, this virus should be much weaker than the delta-*nef* SIV Desrosiers originally used. Although all of the animals initially had barely detectable levels of SIV for several months—a clear sign that the virus was weakened—four now have high levels of the virus in their blood, with one developing full-blown AIDS and another showing early signs of immunologic damage. "The triple-deleted viruses we've worked with are pathogenic," declares Ruprecht. "If they're called a vaccine, I'm highly concerned."

Lewis agrees. "It's hard for me to call this a vaccine," he says, now that he and his coworkers have had a monkey die from what looked like AIDS, 33 months after they had given the animal a delta-*nef* SIV. At Aaron Diamond, Connor says one of 20 monkeys inoculated with a delta-*nef* SIV last year now has severe immunologic damage. In the United Kingdom, Cranage says his group has seen AIDS in one adult monkey given an SIV that only had a small portion of *nef* deleted. And Desrosiers, who has given various attenuated SIVs to 45 monkeys since 1988, says he now sees high levels of virus and disease progression in two animals given delta-*nef* and in one inoculated with delta-3.

None of these labs has yet determined how

these weakened strains are causing disease. All of them have found that the virus did not simply repair its damaged genetic material, but the weakened strains did undergo genetic changes during the course of the infections. It's unclear, however, whether these changes made the virus more virulent, or whether the animals' immune systems simply could no longer contain the weakened virus. It's also possible that the animals are infected with other pathogens that compromise their immunity. "Scientifically, it's extremely interesting," says Desrosiers.

Ruprecht makes sense of all these data with what she and her co-workers call the "threshold hypothesis," which they published last year in a supplemental issue of the journal *AIDS* (see graph). According to this theory, an attenuated virus must copy itself at a high enough rate to trigger an appropriate immune response, but not so high that it causes disease. (Obvious as this theory may sound, Ruprecht notes that the weakened poliovirus used in that vaccine replicates at the same rate as wild poliovirus.) Ruprecht theorizes that the immune systems in her sick animals at first kept the attenuated SIV below the disease threshold, but then, for an unknown reason, lost control of the virus. Lewis, who holds a similar view, notes that this creates a conundrum for the attenuated AIDS vaccine strategy. "The problem is, the safer you make the virus, the less it grows and the less effective it is," he says.

Desrosiers agrees, but thinks it may be possible to find the happy medium without putting humans at too high a risk. He points out that the attenuated vaccines he's been working with lately are much weaker. "I've not been advocating for years anything that was just delta-*nef* or even delta-3," he says. Currently, his lab is testing delta-4 SIVs that he says are "considerably more attenuated than delta-3." Ultimately, he says, "it really turns into a risk/benefit equation of what is acceptable." An attenuated HIV vaccine, he notes, should only be offered to people who are at a high risk of becoming infected by the virus: "This vaccine is not for babies."

For the first human trials, Desrosiers argues that researchers must err on the side of caution: "If we're going to make any mistake, let's be too far down on the scale of attenuation." Even then, he acknowledges that the vaccine may still cause adverse events. "Is it going to be absolutely, 100% safe? Forget it. It never will be. If you put it into enough people, there will be problems. That's true of every live, attenuated vaccine." But, he says, the question boils down to what the likelihood is of the person becoming naturally infected by HIV versus becoming injured by the vaccine: "We're never going to know until we put it into humans, and that's why people have different best guesses."

–Jon Cohen

SYNCHROTRON RESEARCH

Berkeley Facility Ranks Low On Advisory Panel's List

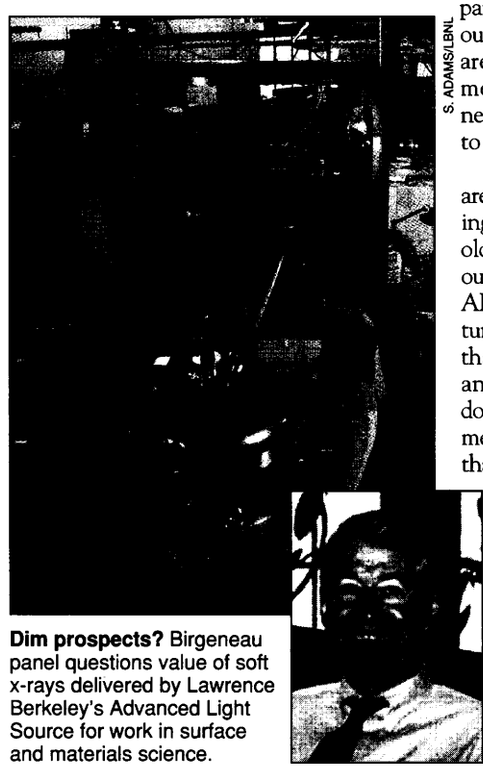
BOSTON—When a burgeoning field runs up against a stagnant budget, something has to give. Next week a Department of Energy (DOE) panel reviewing U.S. synchrotron research facilities is expected to suggest that the government put the squeeze on the Advanced Light Source (ALS) at Lawrence Berkeley National Lab in California rather than on Stanford's Synchrotron Radiation Laboratory (SSRL) and the National Synchrotron Light Source (NSLS) at Brookhaven National Laboratory in Upton, New York. The Advanced Photon Source (APS) at Argonne National Laboratory near Chicago, meanwhile, would continue operations, but without major upgrades in the near future. These and other recommendations promise to trigger a lively debate when they are aired on 8 October at a meeting in Washington, D.C.

Earlier this year, DOE asked the panel, led by Robert Birgeneau, science dean at the Massachusetts Institute of Technology, to recommend priorities for synchrotron radiation research in the coming decade. A wide array of materials, biological, and environmental researchers are clamoring to use machines that generate beams of x-rays to probe matter (*Science*, 8 August, p. 756). But given projections of a flat budget, the department faces some hard choices in deciding the proper level of support for two aging facilities—SSRL and NSLS—two expensive ones recently brought online, and initial planning for a next-generation facility.

The panel's solution is to look favorably on proposed upgrades to the older facilities, to reject immediate expansion plans by ALS and the new $812 million APS at Argonne, and to raise questions about the payoff from ALS, according to panel members who requested anonymity. They also urge DOE to spend modest sums planning next-generation machines so that it can make a decision in the middle of the next decade.

The biggest hue and cry over these conclusions is likely to be raised by managers and users of the $100 million ALS. The panel questioned the type and quantity of work there, as well as the lab's $100 million request for upgrades and a boost to operating funds. Unlike the other synchrotron sources that produce hard x-rays, ALS produces soft x-rays that are used for specialized areas such as surface science. It was built with novel applications in mind, such as industrial uses for computers and advanced optics, some of which are just getting under way. That uncharted territory, says one DOE lab official, makes it "a rich area to explore, but difficult to exploit."

It's also expensive. ALS's annual budget of $33 million is 50% higher than Stanford's, for example, while its user community of 300 is less than half the size. ALS supporters argue that it is a unique source that hasn't had a chance to demonstrate its worth. But as one panel member points out, "just because you are unique doesn't mean that you are necessarily [being put] to good use."



S. ADAMS/LBNL

Dim prospects? Birgeneau panel questions value of soft x-rays delivered by Lawrence Berkeley's Advanced Light Source for work in surface and materials science.

Panelists say they are not recommending closing the 4-year-old machine. "It's not our proposal to drop ALS out of the picture, but to reexamine that area of science and what can be done," says one panel member, who adds that other facilities like Brookhaven's NSLS are capable of producing soft x-rays. "Somehow we got the cart before the horse," the scientist adds, by building a facility without understanding the kinds and numbers of users it would draw. "I don't want to see it go away," he adds. "But we were struck by the comparison of ALS against the others, and it falls to the bottom."