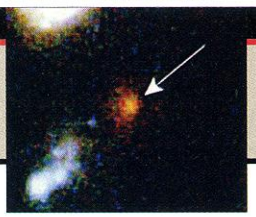

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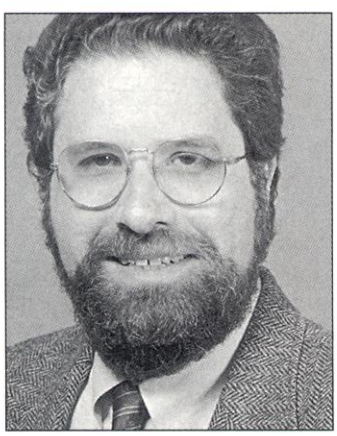
AIDS RESEARCH

Merck Reemerges With a Bold AIDS Vaccine Effort

KEYSTONE, COLORADO—Over the past few years, scientists from Merck & Co. have quietly built an AIDS vaccine research program that has fundamentally altered the landscape of this beleaguered field. In separate presentations at a scientific meeting* here this week, Merck researchers Emilio Emini and John Shiver described some of the first results of this ambitious effort: a comparison of various AIDS vaccine approaches in more than 100 monkeys. The work indicates that Merck is banking more heavily than any other vaccine maker to date on the so-called "monkey model" to select the most promising strategy for human tests. But what most dazzled researchers here is the sheer scale of the company's AIDS vaccine effort, an endeavor that has attracted scant interest from other big pharmaceutical companies.



Return engagement. Emilio Emini leads Merck's renewed effort.

As Merck scientists and others stressed, huge obstacles stand between monkey results and a vaccine that works in humans. Merck's successes in monkey experiments also closely resemble the positive results reported recently by several other groups. Still, Merck's single-minded pursuit of vaccines that ignore antibodies and instead boost what is known as the "cellular" arm of the immune system impressed many of the 300 researchers who attended the gathering. "I think their studies are terrific and very energizing," says David Watkins, a primate researcher at the University of Wisconsin, Madison. "I'm delighted that they've made such a comprehensive effort." Douglas Richman, a virologist at the University of California, San Diego, emphasizes that academic groups simply don't have the resources to conduct such extensive, systematic studies.

Shiver first described a head-to-head comparison of five different vaccines that represent an about-face for the company. In 1986, Merck launched what became a leading AIDS vaccine program based on the idea that antibodies, which prevent invaders from infecting cells, would hold the key to a successful AIDS vaccine. Disappointed with the difficulty of stimulating potent antibodies, Merck scuttled that approach in 1992 and all but disappeared from the field. Shiver explained how the company has since designed vaccines to stimulate cellular immunity, which eliminates those cells the virus has managed to infect.

Specifically, these five vaccines exclude the gene that codes for the envelope protein of the AIDS virus—the focus of Merck's earlier effort—because it stimulates production of antibodies and it also varies greatly among viral strains. Instead, these vaccines each contain one gene from SIV (the simian cousin of HIV) called *gag*, which codes for an internal protein of the virus that is highly conserved in different strains. The comparison essentially asked which carriers, or "vectors," best deliver *gag* and stimulate the highest levels of "killer cells."

Three of the vectors in this study were variations of a bacterial plasmid, a ring of naked DNA. Another vaccine stitched *gag* into a version of the smallpox vaccine, modified vaccinia Ankara (MVA). The fifth vaccine used a crippled version of adenovirus, Ad5. After immunizing 15 animals, three with each vaccine, the researchers found the best killer cell response with Ad5 and a DNA vaccine that included a novel potentiator, or adjuvant, polyoxyethylene. They then "challenged" the vaccinated animals by injecting them with SHIV 89.6P, a hybrid strain of SIV and HIV that quickly causes immune destruction and death in monkeys. Six unvaccinated controls also received an injection of SHIV 89.6P.

The challenge virus infected all of the animals; 8 months later, five of the six controls had AIDS-like illnesses, and several of the vaccinated animals also had high levels of virus in their blood. In contrast, the animals that received Ad5 and the DNA vaccine with the novel adjuvant had low viral loads and suffered no immune damage.

Other groups have reported comparable protection with similar strategies, including the authors of a paper published in this issue (see p. 69). But Merck has taken these leads a step further. Emini described how the Merck team—which includes no fewer than 48 lab chiefs—analyzed HIV-infected humans to see which viral proteins triggered the strongest killer cell responses. This led them to add the genes *pol* and *nef* to their vaccines. Next, they injected dozens of monkeys with different vectors and at different doses to optimize killer cell production.

Merck now intends to challenge monkeys that have been immunized with their best DNA vaccine followed by two shots of the Ad5 vaccine. One possible problem is that roughly 50% of humans have antibodies against adenovirus, which might

VACCINE CHALLENGE STUDIES PRESENTED AT KEYSTONE

Presenter	Vaccine	Challenge strain
Dan Barouch, Harvard	DNA plus IL-2	SHIV 89.6P
Jay Berzofsky, NCI	Peptides	SHIV-Ku2
Shane Crotty, UCSF	OPV	SIVmac251
Paul Johnson, Harvard	Attenuated SIV	SIVmac239
Philip Johnson, Ohio State	AAV	SIV E660
Robert Johnston, UNC	VEE	SIV E660
Harriet Robinson, Emory	DNA/MVA	SHIV 89.6P
John Shiver, Merck	DNA, MVA, Ad5	SHIV 89.6P
David Watkins, Univ. of Wisc.	DNA/MVA	SIVmac239
David Weiner, Univ. of Penn.	DNA	SIVmac251

* "AIDS Vaccines in the New Millennium," 28 March to 3 April.

CREDIT: (TOP) MERCK

hamper the vector's ability to deliver HIV genes. Several researchers also cautioned that SHIV 89.6P might not accurately reflect how HIV behaves in humans.

HIV typically causes AIDS after 10 years, while SHIV 89.6P can destroy the immune system of monkeys in as little as 3 weeks. "People picked that because they thought that it was setting the bar high: If you could protect against this, you knew your vaccine was good," explains Mark Feinberg of Emory University in Atlanta. But paradoxically, SHIV 89.6P "may be easier to contain," says Feinberg. Answering this question with certainty, however, is tough because researchers are using a dizzying array of challenge strains, making it nearly impossible to compare experiments from different groups (see table). In addition, no one has yet tested the same vaccine against SHIV 89.6P and other strains. Merck's Shiver says company scientists now plan to do just that.

Small human studies have begun with Merck's DNA and Ad5 vaccines; even so, the best guess is that figuring out whether this approach works will take at least 5 years. Either way, says University of Pennsylvania virologist Neal Nathanson, the recently retired head of the Office of AIDS Research at the National Institutes of Health, Merck's comprehensive studies represent a "landmark." "For those of us who have followed the field, we're beginning to see light at the end of the tunnel."

–JON COHEN

CLINICAL RESEARCH

Fred Hutchinson Cancer Research Center Under Fire

One of the most respected U.S. clinical research centers—the Fred Hutchinson Cancer Research Center in Seattle—has been engulfed for the past month in a media investigation of alleged conflicts of interest and ethical problems in clinical trials conducted there in the 1980s. Now, partly as a result of this news coverage, "the Hutch" has been hit with a class-action lawsuit by the husband of a cancer patient who volunteered for experimental therapy in 1985.

The controversy began when *The Seattle Times* ran a five-part investigative series on 11 to 15 March charging that the Hutch had exposed subjects to undue risks in bone marrow transplantation trials in the 1980s and 1990s. The *Times* report claimed that researchers had failed to inform subjects properly about alternative therapies and neglected to tell them of potential financial conflicts of interest among the staff. Members of the Hutch, who were testing monoclonal antibodies in cancer therapy, had invested in a biotech company that was trying to develop monoclonal antibodies for biomedical use. Hutch officials insist, however, that the monoclonals developed and used in the clinic were not of interest to the company.

Center president Lee Hartwell, who was not in charge when these trials were done, immediately rejected the *Times*' allegations in a series of newspaper ads and accused the *Times* of spreading "blatantly false" information. Two weeks later, the Hutch was rattled by an aftershock. William Lee Wright Sr., the husband of a patient who had died in a bone marrow transplantation experiment, sued the center and named families of other participants as fellow plaintiffs. Hutch officials say the suit has no merit but declined comment while the litigation is pending.

The suit follows on the heels of a similar case handled by the same attorney who is representing Wright—Alan Milstein of the Pennsauken, New Jersey, firm of Sherman, Silverstein, Kohl, Rose & Podolsky. Last year, Milstein won a significant settlement from the University of Pennsylvania (the amount is undisclosed) on behalf of the father of Jesse Gelsinger, a young man who died in a gene therapy trial in 1999.

Milstein says he learned of the Seattle case "from the newspapers." The Wright suit, filed on 26 March in Kitsap County court, names as defendants the Hutch, a cofounder, several physicians, and a biotech company, alleging that they violated federal guidelines, committed fraud, and subjected patients to "battery" in the pursuit of a clinical breakthrough. The suit focuses on "protocol 126," a series of experiments begun at the Hutch in 1981 and modified seven times over the following 12 years. The protocol's objective, according to comments the Hutch has posted on its Web site, was to improve the survival rate of leukemia patients receiving bone marrow transplants by blocking a dangerous graft-versus-host immune response (www.fhcrc.org). The experiments sought to do this initially by using monoclonal antibodies to target and deplete T cells in donor marrow.

The experiments did not lead to a successful therapy, and Hutch officials concede that about 17 of the 82 patients appear to have died of graft failure. In retrospect, they say, it was clear that T cell–depleted marrow did not engraft as well as untreated marrow. *The Seattle Times*—and the lawsuit—claims that patients who enrolled in later stages of protocol 126 were not adequately informed of earlier failures and might have fared better on "standard" therapy (which was also pioneered at the Hutch). The Hutch insists that each stage of protocol 126 was a unique trial, "conducted separately," with specific risks and benefits—and that patients were fully informed and gave proper consent at each stage. In addition, the Hutch points out that the experiments were peer-reviewed at the National Cancer Institute twice, in 1981 and 1986. Hartwell has appointed an outside panel—chaired by Seattle University chancellor Father William Sullivan—to take another look at all these issues.

Defending "the Hutch." Center president Lee Hartwell (left) and clinical chief Fred Appelbaum face the press.

CREDIT: ANNA MIA DAVIDSON/AP

Milstein, meanwhile, appears to be targeting other clinical research projects. He says he represents more than 10 clients in a suit against the University of Oklahoma's Health Sciences Center in Tulsa. Outside investigators faulted members of the Tulsa staff for errors in obtaining consent from human subjects, including being too optimistic in descriptions of the possible benefits of an experimental cancer vaccine (*Science*, 4 August 2000, p. 706). Milstein says he plans to announce another big suit involving clinical research "in about a week."

–ELIOT MARSHALL