Pediatric AIDS Vaccine Trials Set

A particularly vulnerable population—HIV-infected mothers and children—could provide some quick answers to crucial questions in AIDS research

Preventive and therapeutic AIDS vaccines have been tested in humans since 1986. But to date, no vaccine trial has attempted to stop transmission of HIV from mothers to infants or treat infected children. That's all about to change. In the next 6 months, six trials are set to begin in just those populations. And not only do those trials hold the promise of preventing infection and disease in children, many researchers hope they may tease out the answer to the most baffling question facing AIDS vaccine developers: What must the immune system do to foil HIV?

Though there is scant animal data suggesting that AIDS vaccines might prevent transmission from mother to child or provide therapeutic benefits to infected children, these trials have already been broadly endorsed by AIDS researchers and activist groups alike—and have received strong support from Congress. It may seem surprising that there has been no outcry over the ethics of testing AIDS vaccines in these vulnerable populations. After all, infants can hardly give informed consent. But, in fact, many researchers argue that it would be unethical not to conduct the planned studies, since they offer one of the few glimmers of hope for infected mothers and children.

Pregnant women and children also turn out to be ideal subjects for trials that aim to determine whether an AIDS vaccine works. To gather sound data quickly, investigators need a population that shows high infection rates and falls ill soon after becoming infected. Otherwise, it would take many years (or a huge number of subjects) to get results. The highest-risk populations in the industrial countries, however, rarely have infection rates above 2% per year, and the lag time before disease is generally 10 years. But the picture is different among the very youngest victims: Some 30% of the 6000 children born to infected women in the United States each year become infected, and if those children were not treated, 50% of them would progress to AIDS within 2 years.

Given those statistics, and the paucity of treatments available, the research community has decided to press ahead with mother-and-child studies. The main sponsor is the National Institute of Allergy and Infectious Diseases (NIAID), which will launch five placebo-controlled trials in the next 6 months. The Walter Reed Army Institute of Research and the National Cancer Institute also plan a trial in infected children. These small initial tests will focus on safety and immune responses; demonstrations of efficacy will come later. Yet the promise of this approach is such that John Sullivan of the University of Massachusetts, who heads the pediatric vaccine working group of the AIDS Clinical Trials Group (ACTG) at NIAID, predicts that "the first studies that will show efficacy of any HIV vaccine will be in perinatal care."

Timing is everything

If the trials hold so much promise, why didn't they begin years ago? One reason is that many researchers felt it was unethical to conduct trials in pregnant women and children until animal and human studies had proven the vaccines safe and capable of stimulating immune responses. Vaccine manufacturers also say they were concerned about being sued by the women or their children if the experimental vaccine causes—or is perceived to cause—harm. To protect themselves from liability concerns, manufacturers lobbied for legal protection (*Science*, 10 April, p. 168). In addition, from a scientific vantage point, some researchers felt too little was known about how HIV and the immune system behave in pregnant women or children. Some researchers were also skeptical that results based on an infant's immature immune system—which differs significantly from that of an adult—could be generalized to the population at large.

Several factors have now combined to overcome many of these hesitations. One is data from human trials suggesting experimental AIDS vaccines are safe and in some cases can augment the immune response (though whether that translates into actual protection is not known). Concerns about liability have been relaxed a bit because two states that are home to vaccine makers—Connecticut and California—have indemnified companies making vaccines for trials.

Political muscle has also been applied. Senator Orrin Hatch (R–UT) weighed in last March by introducing an amendment to the NIH 1992 reauthorization bill that mandated trials in infected pregnant women and children within a year. Hatch became interested in the issue after being lobbied by Shepherd Smith, head of the nonprofit group Americans for a Sound AIDS/HIV Policy (ASAP), who says he sought Hatch's clout because the trials hadn't "received the attention we would have liked." (Congress passed the bill, but President Bush vetoed it because it contained a provision overturning a ban on federal funding of research involving fetal tissue from elective abortions.)

Further campaigning came from Lt. Col. Robert Redfield, an Army AIDS researcher who is now under investigation by his employer for allegations that he overstated the significance of some early therapeutic AIDS vaccine data. Redfield says he was concerned over the Public Health Service's lack of "a comprehensive strategy" for pregnant women and children infected with HIV. He spoke with Surgeon General Antonia Novello, and Novello held meetings with NIH and Food and Drug Administration (FDA) leaders to push for vac-

Maternal and Pediatric AIDS Vaccine Trials

	Company	Vaccine	Patients	Earliest Start
	Pregnant Women			
1.	MicroGeneSys	gp160	24	Jan. 1993
2.	Genentech	gp120	24	Spring 1993
3.	Biocine/Chiron	gp120	24	Spring 1993
	Comparative Trial in Newborns (0-3 days)			
4.	Genentech	gp120	60	Spring 1993
	Biocine/Chiron	gp120	60	
	Comparative Trial in Children (1 month-12 years)			
5.	MicroGeneSys	gp160	30	Jan. 1993
	Genentech	gp120	30	
	Biocine/Chiron	gp120	30	
	Children (2 months-18 years)			
6.	MicroGeneSys	gp160	60	Jan. 1993

NIH Panel OK's Vaccine Test–in a New Form

At an extraordinary public meeting at the National Institutes of Health (NIH) on 23 November, a blue-ribbon panel convened by NIH Director Bernadine Healy concluded there are not enough hard data to justify a large-scale trial of a therapeutic AIDS vaccine made by MicroGeneSys Inc.—a trial for which Congress recently added $20 million to the Defense Department appropriations bill after being lobbied by the company. But, after looking the gift horse in the mouth, the panel decided the money was too tempting to pass up. It voted that the $20 million be used to stage a large-scale trial, not of the MicroGeneSys vaccine alone, but of several therapeutic vaccines going head-to-head.

The controversial appropriation, which was criticized by many researchers as an attempt to do an end-run around peer review, came with one proviso: The trial of the MicroGeneSys vaccine would not go forward if the NIH director, the commissioner of the Food and Drug Administration (FDA), and the secretary of defense all specified in writing that it should not. Healy took that as an invitation to form her panel. When Congress "opened the door, we gave them our best advice," Healy told the panel, which included FDA commissioner David Kessler, two NIH institute directors, and leading AIDS activists. "They can take it or leave it."

AP/WIDE WORLD

Sounding board. Bernadine Healy addresses her blue-ribbon panel.

In sharp contrast to the panel's first meeting 2 weeks earlier, which was marked by a rambling agenda, last week's gathering rarely strayed from pertinent issues and provided an overview of the trials that have been conducted using the MicroGeneSys vaccine, gp160. The verdict was that the political process hadn't served science well. "It confirmed my suspicion that lobbying is not the way to set important trials," Healy told *Science*.

Principal investigators from MicroGeneSys trials in the United States, Canada, and Sweden presented data from small studies designed to assess safety and immune responses. There were hints from these studies that the vaccine may have positive effects on the immune system's population of CD4 cells and even reduce or stabilize the amount of HIV. Yet almost every hint of that kind was followed by caveats noting that the data were not statistically significant, the trial had no placebo control, or the experiment included too much "noise" to arrive at a meaningful conclusion.

Better answers could come from two placebo-controlled trials, with a total of nearly 900 patients, that are already under way. But those trials will take several years to show significant effects. The largest, involving 600 patients, is being headed by Lt. Col. Robert Redfield of the Walter Reed Army Institute of Research. Redfield, who presented his preliminary findings at the meeting, said the trial may not be over until 1997. What's more, Redfield noted that it is designed to evaluate the vaccine's effect on "surrogate markers" such as changes in CD4 counts and viral levels, rather than clinical symptoms. And that helped lead the panelists to the conclusion that the $20 million would be best spent on a large, comparative trial (including as many as 30,000 people) of several therapeutic vaccines that focused on clinical endpoints such as death and specific opportunistic infections.

At the meeting, NIAID director Anthony Fauci asked representatives of the vaccine companies present to discuss product availability and their willingness to help pay for a large trial—which could cost more than the $20 million Congress approved. Representatives of Genentech, Chiron, and the Austrian company Immuno said they had vaccine available, would consider contributing money, and would provide vaccine free. Franklin Volvovitz, the president of MicroGeneSys, was at the meeting but did not respond.

That evening, MicroGeneSys issued a press release saying Volvovitz was "delighted" with the panel's decision. The press release contended that the MicroGeneSys vaccine is the "principal drug to be tested" in the trial. "Volvovitz," the release said, "emphasized the importance of caution in the design of clinical protocols for inclusion of other vaccines in the trials." The MicroGeneSys product is "farthest along the development path," the release argued, and "unless additional funding is available to enlarge the study endorsed by the NIH advisory panel, inclusion of other vaccines will dilute the power of the study to arrive at a definitive answer."

Both Healy and Fauci took strong exception to the release. Fauci, who chaired the panel, stressed that the group's recommendation was not for a test of the MicroGeneSys product, but for a comparative trial of several vaccines. Healy called the claim that MicroGeneSys is further along than the others "preposterous," adding that "no one product seems to deserve preference over another." As for the claim about diluting the power of the study, Fauci said, "One could say that the danger of picking out the wrong product over the others is a greater danger than diluting the study." The panel's recommendations will be forwarded to the NIH Director's Advisory Committee for final approval.

–J.C.

cine studies in mothers and children.

These efforts have led to the formation of an informal coalition urging mother-and-child AIDS vaccine trials. "Everyone feels that the disease is of such dread consequence that legitimate, safe studies are warranted," says Samuel Katz of Duke University Medical Center.

That sentiment was seconded at a recent meeting on HIV vaccine therapy (see box on this page) by FDA commissioner David Kessler, who urged that trials in children "be brought into synch" with ongoing trials in adults. "When you're dealing with kids who have a life-threatening disease," Kessler told *Science*, "I think that we have to be able to allow them to have access....I think it would be unethical *not* to do that."

Much of the enthusiasm for the preventive trials in pregnant women stems from successes with hepatitis B. When given at birth to the infant of an infected mother, hepatitis B vaccine (combined with hepatitis B antibodies) can prevent chronic infection in infants more than 85% of the time.

Yet HIV is far more complex than hepatitis B virus. Hepatitis B is almost always transferred at birth and can be neutralized by a known antibody. In contrast, half of all HIV infections may occur in utero, and no one

knows whether antibodies (which latch onto free-floating virus), killer cells (which clear infected cells), or a mixture of the two can stop HIV. Against this background of ignorance, there are a few signs that fetal and infant immune systems can fight off infection stemming from the mother: 70% of the children born to HIV-infected mothers remain virus-free. "If there's any immunologic component," says Katz, there is a "great hope" that a strategy based on the one that succeeded with hepatitis B could do the job.

A successful vaccine to prevent maternal-fetal transmission might work in several ways. A vaccine could lead the immune system to reduce the mother's "viral load"—the total amount of virus in her system—thereby reducing the amount of virus that crosses the placenta. Alternatively, if antibodies from the mother can reach the fetus, vaccinating her could expand the fetus' antibody repertoire. New data from Gene Shearer of the National Cancer Institute also suggest that uninfected newborns may mount effective killer cell responses.

To be of general significance, of course, vaccines tested in pregnant women would have to be able to protect not just fetuses but those living outside the womb. And that's a possibility. Art Ammann, director of the Pediatric AIDS Foundation, says if vaccines lower maternal transmission rates, "it might turn out that we learn what actual protection is." Says Ammann: "If immunologic studies correlated an increase in neutralizing antibodies or [killer cells] with protection, then you'd expect the same thing might work in adults."

The trials aimed at infants and children have two slightly different strategies, depending on the age of the offspring. One study involves vaccinating newborns within 3 days of birth. "This assumes that a significant proportion of transmission occurs perinatally [during or shortly prior to birth]," says Diane Wara of the University of California, San Francisco, who chairs the ACTG pediatric committee for NIAID. Researchers hope the vaccine can prevent infection by stimulating the immune system to mop up HIV before a reservoir of virus can build up. Failing that, the vaccine might "kick start" the immune system so soon after infection that the disease would be less virulent. Another strategy is contemplated for therapy in children with established infections; there the idea is to expand the immune response and keep the virus in check, delaying or even preventing the onset of disease.

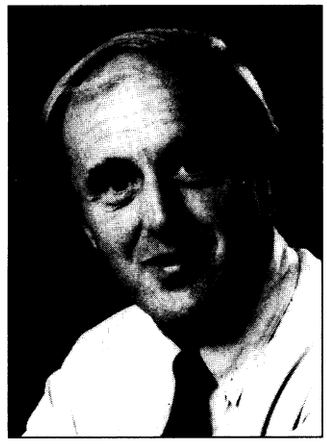
NIAID's Patricia Fast, a pediatrician at the Division of AIDS who helped design the mother-and-child trials, thinks they could validate the merit of vaccine therapy, which some researchers regard skeptically. "If it works in babies, I'd be extremely optimistic that the approach would work in adults," says Fast. Whether the upcoming trials in pregnant women and children offer a workable vaccine or not, however, they promise to speed the race for answers to scientifically crucial questions. And that alone provides reason for hope.

–Jon Cohen

BIOTECHNOLOGY

Scripps Signs a Deal With Sandoz

Thirteen years ago, the Scripps Research Institute raised eyebrows when it signed what was then an unusual agreement with Johnson & Johnson (J&J), giving the drug company first rights to license the results from Scripps' research in return for about $120 million. It wasn't long before other nonprofit research institutes and universities rushed to follow suit—or risk being left behind in the high-stakes world of biomedical research. Now, Scripps is about to up the ante again: This week, Scripps president Richard Lerner was expected to announce that he has signed what he calls a "landmark" deal with the Swiss firm Sandoz Pharma—by far the largest research agreement ever struck between a U.S. research institute and an industrial partner.



New security. Richard Lerner.

The deal involves cash payments of several hundred million dollars and exchange of researchers over 16 years starting in 1997, when the J&J agreement expires. In return, Sandoz will get the first right of refusal to license any research from Scripps. "This is our underpinning, our endowment," says Lerner. "This money goes to underwrite partial salaries, to recruit young scientists, to do some risky problems that no one wants to pay for. It gives us security." And Lerner isn't the only one who is jubilant: "This billion-dollar project will create jobs for Californians," says California governor Pete Wilson. "If we are to ensure California's economic health, it will be as a result of such partnerships."

This high-profile partnership was a match made in Wall Street. Lerner says investor William J. Gedale, president and chief executive officer of General American Investors, acted as the "match maker," introducing Lerner to Max Link, chairman of Sandoz Pharma. In the months that followed, Sandoz sent over a team of its top scientists to Scripps and the two groups checked out each other's scientific capabilities.

They found a remarkable compatibility: "We have more than 70% overlap in research," says Stephan Guttmann, a chemist who is head of worldwide research and development at Sandoz Pharma. Sandoz, the world's seventh largest drug company, is known for its "academic" style of research in immunology—including the development of the drug Sandimmun, or cyclosporin, which is used to prevent organ transplant rejection. It also has strong research programs in autoimmune diseases, the central nervous system, neuroendocrinology, and cardiovascular and respiratory disorders—and a newer interest in gene therapy and retroviruses. Sandoz was attracted to Scripps because "we like their extremely high quality people," says Guttmann, noting that Scripps has the largest concentration of people in the world working in the fertile area at the boundary of chemistry and molecular biology.

So Sandoz made an offer that Scripps' board of trustees couldn't refuse: In return for licensing rights, the company will give Scripps $300 million between 1997 and 2007, with a built-in mechanism to offset inflation. It has promised to renew the contract at a higher, to-be-negotiated rate for another 6 years. In addition, Sandoz will pick up the tab for developing teams of scientists to work with Scripps researchers, bringing the value of the whole package to about $1 billion.

Guttmann says the agreement is part of Sandoz's "Go West strategy" to "strengthen our presence in the United States." The company already has about 1000 R&D associates at its New Jersey subsidiary and a dozen U.S. ties, including a $100 million licensing agreement in oncology research with Harvard's Dana-Farber Cancer Institute.

Scripps senior vice president William H. Beers says Scripps scientists have reacted "positively" to the deal, but with one caveat: "They don't want people to think we're so rich, we don't need NIH money." For that reason, Lerner is quick to put the sum into perspective: "The amount of money (coming from Sandoz) is really no more than the state would put into an academic department or an endowment from Stanford University, for example, to pay people's salaries." And, like the earlier agreement with J&J, Lerner expects this agreement will be copied by other academic research institutes. "You can be sure there will be dozens of these," he says.

–Ann Gibbons