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BIOMEDICAL RESEARCH

Disappointing Data Scuttle Plans For Large-Scale AIDS Vaccine Trial

SEATTLE, WASHINGTON—The National Institutes of Health (NIH) has decided not to fund full-scale clinical trials of the leading AIDS vaccine in its pipeline. At a closed session held here at a 5-day AIDS conference,* 60 investigators who have been evaluating the vaccine in a midsize human study learned that an interim analysis showed weaker-than-hoped-for immune responses against HIV. Even so, the U.S. military and the makers of the vaccine, in collaboration with researchers and officials in Thailand, are still planning to go ahead with a large-scale trial of a similar preparation, and Merck is working with NIH to move another vaccine into midsize trials.

Disappointed. Lawrence Corey heads the clinical trials group that would have tested the vaccine.

Researchers had pinned high hopes on the first vaccine, a concoction made by the Franco-German pharmaceutical company Aventis Pasteur that has HIV genes stitched into a harmless bird virus, canarypox. If all went well with the midsize study, they planned to launch the largest HIV vaccine trial to date, involving 11,000 people. The $60 million to $80 million trial was expected to begin in the United States, South America, and the Caribbean by the end of this year. It would have been conducted through the HIV Vaccine Trials Network (HVTN), a collaboration funded by NIH's National Institute of Allergy and Infectious Diseases that has 25 sites around the world.

But a preliminary analysis of immune responses in the midsize trial did not meet the targets HVTN researchers had set for staging the larger one. Researchers have long known that the vaccine does little to stimulate production of antibodies, which prevent viruses from infecting cells. But in some people it stimulates production of killer cells, immunologic warriors that target and destroy cells that the virus infects. The planned trial was designed to test whether these killer cells can thwart HIV. That, in turn, could help resolve a huge mystery confronting the field: No one knows which immune responses correlate with protection. "If we could find any kind of correlation of protection, that would spur the field forward more than anything else," says HVTN's principal investigator, Lawrence Corey, a leading clinician in sexually transmitted diseases at the University of Washington, Seattle.

To arrive at a statistically significant result in the large-scale study, HVTN statisticians had calculated that at least 30% of the volunteers would have to develop killer-cell responses. The preliminary analysis of the midsize trial, which involves 330 volunteers, found that the killer-cell response was about "one-third lower" than needed, says Corey: "The vaccine stimulates an immune response, but not at the level that we can analyze the correlates."

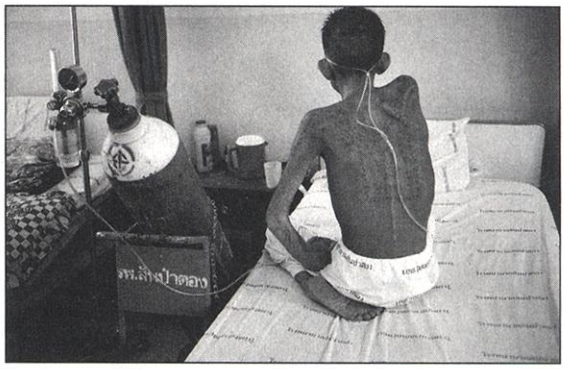
To Corey and others close to the study, the results are disheartening: "With 15,000 new HIV infections a day, anything that delays anything disappoints me." Virologist James Tartaglia, head of the global HIV program at Aventis Pasteur and a key architect of the vaccine, points out that many vaccines have come to market with scant understanding of how they work. Tartaglia says he has no quarrel with analyzing killer-cell levels, but he says the most important question is whether the vaccine provides any overall protection.

This is precisely what led the U.S. military's AIDS research program and collaborators in Thailand to design an "empirical" efficacy trial of a slightly different version of the Aventis Pasteur canarypox vaccine. The Thai trial, slated to begin in September, will combine the Aventis Pasteur vaccine with one that contains a genetically engineered version of HIV's surface protein. The second vaccine, which is made by VaxGen of Brisbane, California—and which is now in full-scale efficacy trials by itself—aims to stimulate antibody production. The Thai trial should determine whether the vaccine provides any overall protection, but it will not have the statistical power to tell which immune responses are most significant. The trial, which will cost $35 million to $45 million, will involve nearly 16,000 people.

In a twist, much of the funding for that trial may end up coming from NIH. The U.S. Office of Management and Budget in January directed the Department of Defense to transfer its AIDS research program to NIH; the agency has agreed to provide the $24 million annual budget (*Science*, 1 February, p. 781). And Corey says the HVTN may become involved with the Thai study, noting, "We're very supportive of that trial."

HVTN is also collaborating with Merck on the testing of the company's AIDS vaccines. This fall, HVTN will stage midsize studies of Merck's approach, which uses a one-two punch of a so-called "naked DNA" vaccine that carries HIV genes followed by one that uses adenovirus as the vector. This strategy also relies on stimulating production of killer cells. In preliminary data presented here by Merck's Emilio Emini, each vaccine, when used alone, appears to be at least twice as good as canarypox at stimulating this arm of the immune system. The ultimate aim of the study is to analyze the impact on killer cells when the two vaccines are combined.

Several researchers applaud NIH for pulling the plug on its lead vaccine. Immunologist John Moore of Cornell University,



Forging on. An AIDS patient in Thailand, where the U.S. military is still planning a large-scale trial.

CREDITS: (TOP TO BOTTOM) FRED HUTCHINSON CANCER RESEARCH CENTER; DARROW MONTGOMERY

* Ninth Conference on Retroviruses and Opportunistic Infections, 24–28 February in Seattle, Washington.

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The mammography wars

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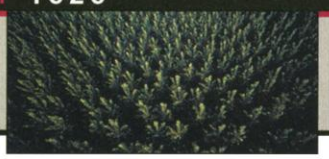
The future for transgenic trees



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DNA and the search for roots

who wrote a commentary in the 24 January issue of *Nature* that criticized NIH and the Department of Defense for planning "duplicative" trials of the vaccine, says NIH has "shown excellent judgment after reviewing the scientific data." Douglas Richman, a virologist at the University of California, San Diego, who sits on NIH's AIDS Vaccine Advisory Committee, says many of his colleagues on that panel had similar qualms. "I was very uncomfortable with the two trials," says Richman. "I can live with the one." He says he "remains skeptical" that the vaccine will work, but adds, "I'd be delighted if I were wrong." **–JON COHEN**

BIOTECHNOLOGY

Has GM Corn 'Invaded' Mexico?

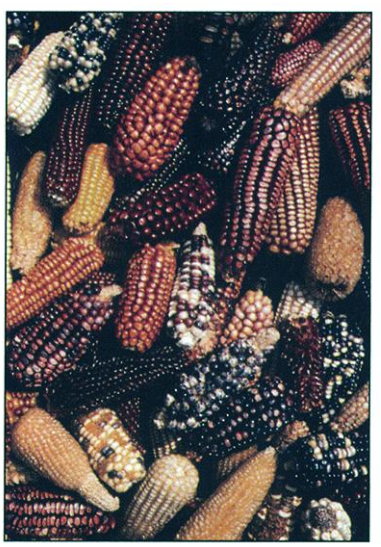
On Thursday, 21 February, the gene wars took a stunning new twist, or so it seemed. Mexican newspapers reported that two teams of government researchers had confirmed University of California (UC), Berkeley, biologist Ignacio Chapela's explosive findings: that transgenic corn was growing in Mexico, the heartland of maize diversity.

Yet even as Chapela was proclaiming this news at a Mexico City press conference, a scathing editorial in the February issue of *Transgenic Research* was crisscrossing the globe by e-mail. In it, editor Paul Christou charged that Chapela and his coauthor, UC Berkeley graduate student David Quist, had presented "no credible evidence ... to justify any of [their] conclusions." Meanwhile, *Nature*, which published the Quist-Chapela paper last November, was weighing the publication of no fewer than four biting critiques of the article. Adding to the muddle, Elena Alvarez-Buylla Roces, a biologist at the National Autonomous University of Mexico who appeared with Chapela at the press conference, insisted in a later e-mail to *Science* that Mexican investigators "still do not have definite answers towards corroborating or not [corroborating] Chapela's results."

Welcome to the "maize scandal," which is driving the battle over genetically modified (GM) crops to new heights of acrimony and confusion. Widely circulating anonymous e-mails accuse Chapela and Quist of conflicts of interest and other misdeeds. Meanwhile, 144 civil-society groups have leapt to the authors' defense, asserting in a joint statement on 19 February that the biotech industry is using "intimidatory" techniques to "silence" dissident scientists. "I've never seen anything like it," says Peggy Lemaux, a UC Berkeley molecular biologist who is one of the most public critics of the Quist-Chapela paper. "There's been a lot of fighting about transgenics, but this is something else."

Still unclear, say many scientists, is whether transgenic corn has indeed invaded Mexico—and if so, whether it poses a threat to one of the world's most important foodstuffs.

The furor began on 29 November, when Quist and Chapela reported that transgenic maize genes had introgressed—skipped from one gene pool to another—with traditional strains (landraces) of maize in remote areas of Oaxaca. The highlands of Oaxaca, Chiapas, and adjacent Guatemala are one of seven "centers of genetic diversity" that spawned most of today's crops. To protect this diversity, an invaluable resource for crop breeders, the Mexican government declared a moratorium in 1998 on planting transgenic maize anywhere in the nation. Now the *Nature* paper was claiming "a high level of gene flow" from illegally planted transgenic maize to local landraces—a process that Quist and Chapela argued could exert "a major influence on the future genetics of the global food system."



At risk? Traditional strains of maize could be threatened by GM corn.

Greenpeace and others opposed to biotechnology immediately called on the Mexican government to ban transgenic U.S. maize, the presumed source of the foreign genes. (Free-trade rules let transgenic maize be shipped into Mexico but not grown there.) "World food security depends on the availability of this diversity," Chapela told *Newsweek* in January. "Having it contaminated is something humanity should worry about."

Adding to the alarm, Quist and Chapela suggested that the transgenes were unstable. The foreign genes, they wrote, often "seemed to have become re-assorted and introduced into different genomic backgrounds." In other words, when transgenic maize hybridized with landrace maize, the novel genetic material broke up into chunks that jumped around the genome. The implications were profound: Because a gene's behavior depends on its place in the genome, the displaced DNA could be creating utterly unpredictable effects.

Activists' fears centered on the promoter sequence—usually CaMV 35S, which originates in the cauliflower mosaic virus—used to drive the activity of newly inserted genes for, say, herbicide resistance. If the promoter broke off during hybridization, it could conceivably take over other genes, with unknown consequences. "The spread of the promoter could prove to be worse than the spread of the genes for herbicide and insect resistance," says Peter Rosset, co-director of the Institute for Food and Development Policy (Food First), a research group that advocates on behalf of small farmers. "If true, this would be a red flag that would call into question every other GM crop on the market."

But Lemaux and other critics aren't buying it. "They're saying that the [hybrid and introgressed] genomes were completely unstable all the time," she says. "I've worked with transgenic corn for 10 years, and I've never seen anything like that."

To search for transgenic DNA, Quist and Chapela took sample ears of maize from two locations in Oaxaca in October and November 2000 and tested them using the polymerase chain reaction. PCR amplification detects particular snippets of DNA by multiplying them to observable levels. Unfortunately, notes molecular biologist Marilyn Warburton of the Mexico-based International Maize and Wheat Improvement Center (CIMMYT), PCR is so sensitive that minute traces of laboratory contaminants can create false-positive results. "If you get a positive result, you have to check it repeatedly," Warburton says. "And even then you need to confirm it by another method to be completely sure you're not fooling your-

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