AIDS VACCINE RESEARCH

U.S. Panel Votes to Delay Real-World Vaccine Trials

After a daylong debate about staging a test of HIV vaccines in thousands of uninfected people, a federal advisory panel last week appeared evenly split on the pros and cons of the trial. But in a late-hour move, as those supporting the trial realized they couldn't sway those with deep misgivings about the vaccine products, the panel unanimously decided to nix the plans. As a result, the first real-world tests in the United States of AIDS vaccines could be delayed for several years, and some vaccine developers are searching for ways to change the decision.

The immediate future of the federal government's AIDS vaccine program, which is largely run by the National Institute of Allergy and Infectious Diseases (NIAID), was foretold on 17 June in the aptly named Crystal Ballroom of a Bethesda, Maryland, hotel. There, 21 members of the congressionally mandated AIDS Research Advisory Committee (ARAC) and seven from NIAID's advisory council decided—after 7 hours of debate—that the two vaccines furthest along in animal and human tests had too slim a chance of working to justify large-scale tests. In particular, the panel was unconvinced by data from these tests that the vaccines trigger the type of immune responses needed to outwit HIV.

"What they favored in the end was postponing until there were products they felt better about, but not stopping the program development in its entirety," said the meeting's chair, Ashley Haase of the University of Minnesota Medical School. And NIAID director Anthony Fauci, who has the final say, swiftly backed the recommendation.

The two vaccines both contain a genetically engineered version of gp120, a protein on the surface of HIV. Made by Genentech Inc. and Biocine Co., the vaccines have prevented small numbers of chimpanzees from becoming infected and have proven safe and capable of stimulating immune responses in small human trials. But to date, no study has tried to answer the critical question: Can these vaccines actually can prevent humans from becoming infected with HIV?

A number of researchers have argued it was high time the question was answered. The advisory groups' decision, in fact, starkly contrasted with one made in April by an NIAID-organized "working group" of leading AIDS vaccine researchers (*Science*, 20 May, p. 1072). That group, uneasy about the expense of a full-fledged efficacy trial, suggested it was time to move to a mid-sized trial—about 4500 people over 2 years—because it was the most effective way to truly learn whether the vaccines work.

DARROW MONTGOMERY

Delays and disappointments. HIV vaccines aren't ready for large efficacy trials, says NIAID chief Anthony Fauci.

Fauci said that the two recommendations were the result of different perspectives. "The vaccine working group considered the scientific rationale for going forward. The [joint meeting] considered a variety of things," he said.

One consideration was the potential difficulty in recruiting volunteers for such a trial. A flier from New York's AIDS Coalition to Unleash Power (ACT UP) distributed at the meeting threatened "a massive boycott" of efficacy trials and charged that "going ahead with these trials is not only premature, but extremely unethical and dangerous." The group has grave doubts about these vaccines, which they fear may actually enhance people's susceptibility to infection (*Science*, 17 June, p. 1660). ARAC member Martin Delaney, founding director of San Francisco's Project Inform, also points out that "everyone in the community has grown very frustrated with mediocre answers and mediocre products. And we'd hate to start vaccines the same way we've been doing antivirals for the last 8 years."

The advisory groups also raised grave doubts about the study design. The April recommendation to stage a 4500-person trial came about because the working group decided the design could determine whether a vaccine was extremely effective or flatout didn't work. Short of efficacy, the researchers hoped the trial would tease out which immune responses correlated with protection. But new calculations presented to the advisory groups show that the 4500-person design was so statistically underpowered that it might dismiss a partially effective vaccine as useless and shed little light on immune correlates.

Yet despite the community opposition and scientific limits of the trial, several advisers said they thought it was worth staging. "I'm inclined to believe this might be the right time to start doing it and warn the public that we don't have any grandiose expectations," said ARAC's R. Palmer Beasley, an epidemiologist at the University of Texas at Houston. And for a while it appeared as though there might be a split vote on whether to proceed using this design. "We were debating for several hours [over] whether that was something the group could decide upon," said Haase. "They basically couldn't."

So the groups abandoned the divisive question. Instead of forcing members to vote on the present design, they brought to the table a slightly different, more general motion: to proceed with efficacy trials only when there were more compelling data. This quickly passed without dissent. "Given that the scientists were somewhat divided and that Martin Delaney was saying, 'Wait a minute, wait a minute, let's back off,' it would have been difficult to move forward in the direction of [a mid-sized trial]," said one ARAC member who asked not to be identified.

Fauci said he would take this advice to hold off, a move that rankles Genentech and Biocine. "It's a terribly unfortunate decision," said Genentech's Donald Francis. "It certainly slows things down." Francis also says he's confident that Fauci's decision won't hold, noting that Genentech plans to take its case both to Congress and the executive branch. "We've got a vaccine that deserves to be tested," he says.

The advisory groups stressed that current tests on any potential AIDS vaccines should continue and that the present decision should not impede efficacy trials in other, harder hit countries, several of which hope to launch real-world tests soon. But in this country, Fauci estimates that it will be at least 2 to 3 years before another HIV vaccine—or new data from the Genentech and Biocine vaccines—reopens the question of efficacy trials sponsored by NIAID.

–Jon Cohen