AIDS RESEARCH

Vaccine Drought Spurs NIAID Plan to Improve Industry Ties...

WASHINGTON, D.C.—The world's premier annual AIDS vaccine meeting used to have an entire session devoted to the results of initial human tests of candidate vaccines. But not this year. Organizers of the 8th Annual Conference on Advances in AIDS Vaccine Development, put on by the National Institute of Allergy and Infectious Diseases (NIAID),* deemed that only one early vaccine strategy had produced clinical results sufficiently promising to merit an oral presentation. "There's not a great deal out there, and that's a concern," says Patricia Fast, who heads NIAID's AIDS vaccine division. Dani Bolognesi, an AIDS vaccine researcher at Duke University, is similarly worried. "The pipeline [of new AIDS vaccines] is almost shut down," says Bolognesi.

Although several researchers welcomed the meeting's focus on basic science rather than clinical results—"there's less hype and more science," says epidemiologist William Blattner of the University of Maryland—the dearth of promising candidate vaccines provided a subtext for much of the discussion. Indeed, one of the most notable—and controversial—presentations at the 5-day meeting was the unveiling of an ambitious new plan that aims to forge stronger ties between NIAID and vaccine developers to try to encourage companies to remain in the field. "The importance of industrial partners cannot be overemphasized," said NIAID Director Anthony Fauci when he described the new "development plans."

NIAID

Strong medicine? NIAID's Patricia Fast and Anthony Fauci plan a booster shot for vaccine makers.

Many attribute the loss of momentum in AIDS vaccine development to NIAID's 1994 decision not to stage large-scale, real-world tests of two vaccines containing genetically engineered versions of HIV's surface protein gp120. NIAID and its outside advisers concluded that early results with the vaccines were too lackluster to warrant spending millions of dollars on efficacy trials in the United States. But although there may have been a strong scientific rationale for not going ahead, the decision "had an impact on the pipeline," as Margaret Johnston, who recently left the number two job at NIAID's Division of AIDS, said at the conference.

The vaccine developers, Genentech and Biocine, were outraged, contending that NIAID did a last-minute about-face and that the move made it an unreliable business partner for future vaccine development (*Science*, 24 June 1994, p. 1839). Indeed, Genentech has all but left the AIDS vaccine field; its preparation has now been taken over by a spin-off company called Genenvax (see p. 1237). Many other companies also cut their AIDS vaccine programs or scaled them back as a result, says Johnston, who now heads the Rockefeller Foundation's International AIDS Vaccine Initiative—a new attempt to stimulate the field. To revive the companies' interest, she added, "we need to devise some nontraditional partnerships."

One such nontraditional partnership appears in the new plan spelled out by Fauci. For the first time, NIAID is attempting to act like a true business partner and is thus negotiating with companies specific criteria that a vaccine must meet before it moves from a small human trial to a medium-sized one to a large efficacy test. The idea is that if the companies know what they have to do to get NIAID funding for an efficacy trial, they are more likely to remain in the business. "It's essential that we don't have a moving target," concludes Fauci, who says he took "considerable heat" for not staging the gp120 efficacy trials.

* The conference was held from 11 to 15 February in Bethesda, Maryland.

... While Gore Tries a Bully Pulpit

Although AIDS researchers agree that the primary obstacles to developing better ways to prevent and treat the disease are scientific, there is growing concern that another major barrier is industry's apparent waning interest in developing these products. Now Vice President Al Gore is putting his brainpower into figuring out why this might be, and he's using his bully pulpit to try to keep industry fully engaged in the battle.

On 20 February, Gore gathered representatives from 11 pharmaceutical and biotechnology companies at the White House to meet with him and government AIDS officials to discuss how they might work together to speed the searches for effective AIDS vaccines, therapeutics, and the anti-HIV chemical barriers known as microbicides.

Industry and government attendees alike judge the meeting—which ran more than twice as long as scheduled—a success. "I was impressed," says Dan Hoth, the chief operating officer at California's Cell Genesys Inc. "This guy didn't have to hold a two-and-a-half hour meeting and ask persistent, dogged questions." Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases, also thought it was worth his while. "The impression I was left with is the Vice President wants to continue the dialogue," says Fauci. "It looked like it wasn't one of those perfunctory things."

Although the meeting did not lead to any concrete plans, several ideas surfaced that attendees believe might have a chance of making a difference if they have the clout of the vice president's office behind them. One proposal is to have the Clinton Administration approach international funding agencies such as the World Bank about spending more money on AIDS vaccine development.

It remains to be seen whether Gore can make any more impact on AIDS than the numerous task forces, blue ribbon panels, and summits that have tackled the problem in the past (*Science*, 26 January, p. 438). But Hoth says the closed-door nature of this meeting made it much franker and more efficient than similar meetings held in the open by the Clinton Administration's now-defunct National Task Force on AIDS Drug Development, of which he was a member. "There was a huge difference," says Hoth. "I had the sense that if the same group could get together a couple of times, they could really get down to the issues." White House staff members say Gore intends to hold more such meetings soon.

–J.C.

Fauci said such a contract is now being drafted between NIAID and the two companies involved in the only human tests whose results were presented at the meeting. The trial combines two separate vaccines in hopes of delivering a one-two punch against the AIDS virus. This strategy "primes" the immune system with a vaccine made by Pasteur Mérieux-Connaught that contains one or more HIV genes stitched into a canarypox virus that is harmless to humans. When injected into a human, the canarypox enters cells and manufactures the given HIV protein or proteins. When displayed on the infected cells, these "endogenously" made HIV proteins should activate cytotoxic T lymphocytes (CTLs), immune cells that can specifically obliterate HIV-infected cells. A "boost" with the Biocine vaccine, which contains gp120, is then supposed to stimulate production of antibodies that can neutralize HIV floating freely in the bloodstream.

As Fauci explained, NIAID is now funding "phase one" trials of this prime-boost strategy that involve a total of about 100 people. Preliminary results presented at the meeting show that the vaccines easily stimulate production of antibodies and trigger CTLs in anywhere from 12% to 44% of the people vaccinated. Before these vaccines can move on to the next phase, the companies and NIAID have agreed that at least 90% of the people who receive both vaccines must produce neutralizing antibodies and at least 30% must produce CTLs. If the vaccines meet those milestones and are shown to work in a nonhuman primate study, they could move into efficacy trials by the middle of 1998.

Already, some leading researchers are questioning how NIAID officials arrived at such specific criteria, as well as how they'll be used. "It concerns a number of people that we don't know what's going on," says the University of Minnesota's Ashley Haase, who headed NIAID's AIDS vaccine working group until it disbanded in 1994. "They're essentially setting up numbers arbitrarily."

Fauci concedes that these criteria are "semiarbitrary" and were based on the results already seen. But however they are set, some criteria are necessary, Fauci maintains. He says one of the main criticisms of the earlier gp120 trials is that they hardly elicited any CTLs, and NIAID came up with these criteria after the working group Haase headed said it was "impossible" for them to do so. Fauci also stresses that these are "minimal criteria" and are subject to change if new scientific information surfaces. "I made the leadership decision we want to deal in good faith," says Fauci. "Either we're going to have a vaccine program or not."

Fauci will not explicitly say that if these minimal criteria are met, NIAID will definitely move the vaccines forward. Both Haase and Duke's Bolognesi have strong reservations about NIAID making any such commitment. Then again, Bolognesi thinks it makes sense to set minimal criteria, so that "a floor" is set and companies don't feel jilted if NIAID decides to stop testing their vaccines. "It's a good thing to do right now with the industrial partners that are left in the world," says Bolognesi. That's a sober response to NIAID's earnest new development plans—and it speaks volumes about the state of the AIDS vaccine search in 1996.

–Jon Cohen

REGULATORY AGENCIES

FDA Reform Starts Down the Track

Congressional efforts to reform the Food and Drug Administration moved into the spotlight last week as a Senate panel devoted 2 days to a Republican proposal that would prod FDA into processing new drug applications more quickly. The bill has won support from academics and drug company officials, who see timely reviews as an important factor in getting products to market. Although the bill's prospects in the Senate appear good, its ultimate fate may rest with House colleagues, some of whom want to remove FDA's authority to conduct in-house reviews of new drugs and devices.

Last week's hearing before the Senate Labor and Human Resources Committee focused on a bill introduced by its chair, Senator Nancy Kassebaum (R–KS). The bill would press FDA to meet its current requirement to review new drug applications within 6 months—a standard that it now falls far short of. It would also force FDA to approve within 120 days drugs to treat life-threatening illnesses or those for which no other treatment exists. If the FDA failed to meet these goals by mid-1998, it would be required to contract out new applications. In addition, products that had passed review in the United Kingdom or the European Union would be allowed on the market unless FDA could show the product was unsafe or ineffective.

Testifying at the hearing, FDA Commissioner David Kessler said a 1992 user fee program has helped the agency meet, 3 years ahead of schedule, a goal to process most drug applications within 12 months. But he's troubled by the strict timetables. "If you rush too much," he said, "you're either going to do something potentially dangerous or turn down applications and take longer in the end." An overemphasis on speed, he added, would also force FDA to divert scarce resources from helping companies prepare for clinical trials. Kessler is also concerned about the agency's ability to protect confidentiality and avoid conflict of interest if reviews are contracted out, although he said the agency is testing the idea on a small scale.

"If you rush too much, you're either going to do something potentially dangerous or turn down applications and take longer in the end."

—David Kessler

Louis Lasagna, dean of the Sackler School of Graduate Biomedical Sciences at Tufts University and an FDA critic, sympathizes with Kessler on one point: FDA could be "tempted to cut corners" to meet tight deadlines on reviews, he told *Science*. But he said Kessler's fears about outside reviews are unwarranted, noting that a contractor used several years ago in a pilot project "did a good job quickly and inexpensively."

Drug companies see the bill as a good start toward needed reforms. The Pharmaceutical Research and Manufacturers of America have praised the bill, noting that the deadline and contracting provisions could speed reviews. However, the group would like to add a provision to eliminate FDA requirements for raw patient data and make other changes.

Although Kassebaum hopes to mark up her bill this month, it may face tough going when measured against proposals, some more radical than hers, being drafted in the House. In particular, Kassebaum's counterpart, Representative Thomas Bliley (R–VA), chair of the House Commerce Committee, is said to favor a bill that would turn over the entire review process to outside review groups and mandate other fundamental changes in how the FDA operates (*Science*, 25 August 1995, p. 1038).

The ongoing budget morass and a limited legislative calendar during an election year could also derail plans for significant reform. As a result, some observers doubt that anything more than a bill affecting exports or medical devices is likely to pass this year. "I am skeptical [that a major reform bill will pass]," says Washington attorney William Vodra, a former FDA associate chief counsel for drugs. But Kassebaum has a major incentive to wrap up a reform bill this year: She is retiring from the Senate this fall after 18 years, and reforming FDA is a priority item on her political to-do list.

–Jocelyn Kaiser