

MILESTONES UPDATE

Last year's AVAC report, "*How do you fight a disease of mass destruction?*," documented the inability of trial sponsors to move AIDS vaccine candidates into human clinical trials as rapidly as they had projected in their milestone goals.

This year, we can report substantive progress in overcoming many of the obstacles noted last year:

- The AlphaVax VEE-vectored vaccine, which was originally to have moved into Phase 1 trials in 2000, finally did so in 2003. The vaccine, made with the *gag* gene from the clade C virus that predominates in southern Africa, is being tested in South Africa and the United States. It was the first clade C vaccine to enter human trials. Three more clade C-based vaccines—made by other groups—also began human trials later in the year.
- Three of six vaccines originally scheduled for the clinic in 2002 made it into Phase 1 studies by 2003. These were Chiron's clade B DNA+novel envelope vaccine; DNA+fowlpox clade B vaccine of the University of South Wales; and Wyeth's clade B peptide vaccine. Investigational New Drug (IND) filings have been submitted for the other three products, which are expected to enter Phase 1 trials by July 2004.
- Five of seven vaccines, which had fallen behind plans for Phase 1 testing, have now entered small human studies. These include DNA+IL2; DNA from clades A, B and C; and the DNA portion of a DNA+adenovirus vector expressing genes from clades A, B and C. All three vaccines have been developed by the US government's Vaccine Research Center (VRC). The DNA portion of Wyeth's DNA+IL12 also advanced into a Phase 1 trial in recent months.

Altogether, thirteen vaccine candidates moved into Phase 1 trials in the twelve months since the last AVAC report was issued in June 2003. Even though many entered human trials later than originally projected in the milestone goals, that's still more Phase 1 trials initiated in a single year than in any year since scientists began the quest for an AIDS vaccine.

Six of the Phase 1 trials of new products were launched as part of the US government's HIV Vaccine Trials Network (HVTN). Both the network and the Division of AIDS (DAIDS) deserve credit for overcoming the delays noted by AVAC last year. In addition, HVTN expanded its Phase 1 testing of Merck's clade B adenovirus- vectored vaccine (*Ad5 gag*) to sites in Peru, Thailand and the United States in trials that are expected to enroll 435 volunteers.

Merck also launched the first Phase 1 trial of the multigene version of its *Ad5* vaccine, which expresses the *gag*, *pol* and *nef* genes of clade B. A trial to test the multigene approach—which the company views

as its lead candidate—began last May and has now enrolled more than 188 volunteers in the United States toward a goal of 273 by June.

The International AIDS Vaccine Initiative (IAVI) also stepped up the pace compared to last year. It deserves credit for putting two new vaccines into Phase 1 trials over the past twelve months, and for adding South Africa to the countries where its DNA+MVA vaccine is being tested.



One of IAVI's new products makes use of adeno-associated virus (AAV) as a recombinant vector to deliver the *gag* gene from Clade C. The product, developed in collaboration with Columbus Children's Research Institute and Targeted Genetics Corp., is being tested in small safety trials in Belgium and Germany. Another new product, developed by AIDS researcher David Ho and colleagues at the Aaron Diamond AIDS Research Center and Vical, Inc., is a DNA plasmid multigene clade C vaccine being tested among 45 volunteers in the United States.

During the past 12 months, IAVI also extended human testing of its clade A DNA+MVA vaccine to South Africa. The vaccine was already in human trials in the United Kingdom, Kenya and Uganda.

Despite the inability of the AIDSVAX gp120 vaccine to demonstrate overall protection from infection in two Phase 3 trials last year, the US Army—whose AIDS vaccine program is now part of the National Institute of Allergy and Infectious Disease (NIAID)—and the Thai government successfully launched the world's largest Phase 3 trial in Thailand last October. The trial, which is to enroll 16,000 people, is testing Aventis Pasteur's canarypox-vectored vaccine as a prime, followed by VaxGen's clade E AIDSVAX as a boost. Scientists hope that the two vaccines in combination will have a protective effect even though AIDSVAX alone did not.

Still, AVAC notes that not much headway has been made in solving some of the key problems described in last year's report. In particular, manufacturing snafus continue to rain on the parade to the clinic, with two vaccines using modified vaccinia Ankara (MVA) posing hard-to-solve problems.



The problems were so frustrating that last year the VRC abandoned a 2002 milestone to test its MVA vaccine candidate. Another MVA vaccine—developed by Bernard Moss and colleagues at NIAID—is still delayed by manufacturing difficulties. Also a 2000 milestone, the vaccine was to enter human trials in the first quarter of 2001.

Likewise, batch-release problems have delayed another 2002 milestone, Chiron's clade C DNA+envelope boost. A Phase 1 trial was to begin the first quarter of 2005, but manufacturing problems have now delayed the start date.

Similarly, a Phase 1 trial of the GlobeImmune yeast-vectored vaccine, a 2003 milestone, has been delayed by the need to remanufacture the product to meet good manufacturing practices (GMP) standards.

To solve manufacturing problems, the AIDS vaccine field will have to diagnose problems earlier, pool talent to address the challenges, and come up with sufficient funds to support whatever improvements are necessary.

Key to the effort will be a commitment to share information. One vehicle could be the US government's new Partnership in AIDS Vaccine Evaluation (PAVE), set up last fall. PAVE aims to bring together US government agencies, and government-funded organizations involved in AIDS vaccine research and development, to forge coordinated planning efforts.



PAVE has already made notable progress toward the development of common assays for use in AIDS vaccine evaluation. It has also set up a new laboratory to look at the stability of vectors to deliver the genes used to make AIDS vaccines. Now PAVE needs to focus on additional manufacturing issues. For the consortium to achieve its full potential, all US agencies, as well as the International AIDS Vaccine Initiative, need to fully participate.

A broader initiative, the Global HIV Vaccine Enterprise established by the Bill & Melinda Gates Foundation (see page 43), can also provide a forum for evaluating manufacturing issues, along with myriad other questions involving both pre-clinical and clinical research.

Hopefully, both forums will not only ask the tough questions, but also serve as venues to develop creative solutions to problems.