

# On the trail of two trials

Development of an AIDS vaccine will not be helped by duplicative trials.

**John P. Moore**

The need to develop an effective vaccine against HIV-1 is now probably the world's greatest single public-health problem. The global AIDS pandemic — 40 million people are estimated to be infected at present — will only ever be controlled by the use of a vaccine that significantly curtails transmission of the virus. Because of the vast cost involved and the organizational framework required, the scientific resources of the US government are the most critical component of international efforts to develop a vaccine. For the past 15 years or so, such efforts have been dominated by the US National Institutes of Health (NIH) and the US Department of Defense (DOD).

The US government's involvement in vaccine-trial programmes is also necessary to ensure that trials are always conducted safely and ethically. The need to apply high standards should be obvious, yet some US scientists are believed to be planning to use private or charitable funds to test controversial vaccines in developing countries, without proper safety testing in higher animals or prior evaluation in humans in the United States.

Whatever some scientists' desire to cut corners, evade the scrutiny of the US Food and Drug Administration and 'save time', the development of an HIV-1 vaccine is not a race for glory. When corners are cut, crashes can occur that force the safe as well as the cavalier drivers into the ditch. Ensuring federal government oversight means that the road to an effective vaccine, although long, will be safe for all — especially for those participating in vaccine trials.

## Effective action?

But are the government's resources being applied in the most efficient and cost-effective manner? Unfortunately, the competitive mentality also applies to federal agencies — although without ever compromising ethical standards. It has long been known in the HIV-1 vaccine field that the NIH and the DOD regard each other as rivals, not collaborators. Both have conducted duplicate trials of many vaccine concepts: denatured gp160 virus proteins, monomeric gp120s, and live virus vectors have all been tested by both agencies, usually more-or-less simultaneously. It has seemed as if each agency has felt compelled to 'shadow' the other, to insure against the embarrassing outcome of a working vaccine candidate emerging that was sponsored by the other agency.

This situation has led to a massive waste



**Competitive approach:** the race to claim the prize of discovering a vaccine against AIDS stands a chance of disrupting, rather than helping, the overall research effort.

of money and other resources, and was made even worse by the advent of the International AIDS Vaccine Initiative (IAVI). Whatever is said in public, the rivalry between the NIH, the DOD and the IAVI is an open secret among scientists working on HIV-1 vaccine development — whether it is competition for clinical-trial sites or for funding of the more promising vaccine candidates or scientific programmes. Too often, rivalries have been fuelled by on- and off-the-record criticisms, usually unjustified, of the NIH in the media.

This state of affairs should not be allowed to continue. A coordinated effort could make so much more progress than one that is fractured by institutional rivalries. There will be more than enough credit to be shared out if an effective vaccine is eventually made.

## Duplicated effort

The fractured nature of US vaccine programmes is fully revealed by the provisional plans of the NIH and the DOD to conduct duplicate phase III efficacy trials of a second-generation HIV-1 vaccine. Details were disclosed by Jon Cohen a few months ago (*Science* 293, 1973; 2001) in an article that was, unfortunately, published on 14 September and consequently was overlooked given the horrific events of that week.

Both proposed trials will evaluate vaccines based on combining a recombinant canarypox/HIV-1 vaccine vector, made by

Avantis Pasteur, with a monomeric gp120 subunit protein, made by VaxGen, as a boosting antigen. There are some differences in the canarypox vectors involved, and in the particular gp120 protein to be used, but for all practical purposes, these trials are duplicative.

The NIH-sponsored trial will be conducted in the United States, the Caribbean and South America, involving 11,080 volunteers at a cost of between US\$60 million and \$80 million. Funding will come from the NIH's National Institute of Allergy and Infectious Diseases, through the Seattle-based HIV Vaccine Trials Network. The DOD's rival trial will be conducted in Thailand, using 15,800 volunteers at a cost of between US\$35 million and \$40 million, and will start this summer, at least six months before the NIH's trial can begin. A decision on whether to conduct the NIH trial will be made in the next few months, once the phase II trials have been fully evaluated.

Few independent scientists are optimistic that the canarypox/gp120 vaccine will succeed in preventing HIV-1 infection, or will have a sustained, beneficial impact on the course of disease in those individuals who become infected after vaccination. This vector only weakly induces cellular immunity — the current focus of the NIH-sponsored phase II trials is to find out if as few as 30% of the vaccine recipients can develop a measurable cellular immune

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response at any (not every) time point after vaccination. But even with the bar set so low for 'success' at the phase II level, the vaccine trials network may still not be able to find a way to lift the vaccine over it.

Moreover, the gp120 boosting-antigen does not induce a significant level of neutralizing antibodies against naturally circulating viruses. The limitations of gp120 proteins as immunogens have been well-known since 1993, yet they are still being used, solely because they are the only safety-tested HIV-1 proteins available in sufficient quantity. Monomeric gp120 proteins are now in phase III trials as solo antigens, both in North America and in Thailand, but a preliminary analysis last November revealed no evidence of efficacy. The probable failure of the gp120 concept cannot now be formally documented until November 2002, when the first of the two efficacy trials is unblinded. Unfortunately, this is several months after the decision about using these same gp120 proteins as boosting antigens in the canarypox vaccine trials.

It would surely be prudent to wait for the results of the gp120 efficacy trial before deciding whether to continue using these proteins in humans. Some argue that a boosting antigen is needed to enhance the effect of the canarypox vector. But, although there is some immunological basis for this view, why use a boosting antigen that is, for all practical purposes, inert? Why not use a Gag antigen that might more efficiently induce T-cell help and hence boost the immune system? Product availability must not dominate scientific rationale in decision-taking on this scale.

### A difficult challenge

Recent studies in macaque monkeys with the simian immunodeficiency virus (SIV) analogue of the canarypox/gp120 vaccine show that gp120, either alone or as a boosting antigen, has no effect on the outcome on the viral challenge (R. Pal *et al.* *J. Virol.* **76**, 292–302; 2002). Indeed, the gp120 component was so ineffective that the gp120 recipients were pooled with the true control animals to increase the statistical power of subsequent comparative analyses. In the study, all recipients of recombinant canarypox became infected on challenge, but there were modest, short-term reductions in post-infection viral load and a slightly better preservation of CD4 T-cells in the vaccinees over a several-month period.

Given that the combination of canarypox vectors with gp120 is not impressive in human or macaque trials, why is there still such enthusiasm for the two efficacy trials? The main reasons seem to be that the vaccine trial networks regard it as a 'practice run' for when a better vaccine comes along, and that 'we might learn something'. Unfortunately, just what might be learned, and how, in this

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large and very expensive rehearsal has not been clearly defined. The NIH, in particular, is always under pressure, sometimes unfairly, from various interest groups about the scale of its investment in HIV-1 vaccines; it may in this case be responding to the need to be seen to be doing something on a large and noticeable scale. Yet the NIH is, and always has been, the engine-room of HIV vaccine development globally, even if it does not often receive the credit it deserves.

### Once is enough

The animal studies mentioned above provide some support for further evaluation of the recombinant canarypox immunogen in humans, although not for the inclusion of the gp120-boosting component. It might be possible to learn whether a properly quantifiable cellular immune response could slow the rate of disease progression in infected vaccinees, at least in the short term. Any beneficial effect is likely to be marginal, however.

But why do the trial twice? Although duplication can mean rapid confirmation, surely there is a better way to make progress, given the resources required for two independent trials? The DOD's trial is likely to start earlier than that of the NIH, and it is the cheaper, so logically the NIH could support the DOD and abandon its own effort. Informal soundings suggest that DOD scientists would welcome the NIH's involvement. Some scientists in the NIH's trial network seem to believe that the DOD trial is under-funded, to the extent that the results will be under-analysed and a determination of 'correlates of protection' perhaps impossible. If so, all the more reason for the NIH network to provide resources to assist the DOD in the execution and analysis of a single, collaborative trial.

The recent announcement of a strategic link-up between the Merck HIV-1 vaccine-development programme and the NIH's vaccine trial network has major long-term significance. Many in the HIV-1 vaccine field believe that the Merck vaccine (DNA prime plus adenovirus vector boost) is an enormously more potent inducer of cellular immunity than the canarypox vector. Perhaps the NIH's vaccine trial network should now focus on this approach, leaving the DOD to study the earlier-generation canarypox vaccine, by analogy with the IAVT's extensive and wise investment in trials

of an MVA (modified vaccinia Ankara) vaccine, a more potent immunogen than canarypox, in the United Kingdom and Kenya. Alternatively, the DOD could leave HIV-1 vaccine development to the NIH and concentrate on bioterrorism defence instead.

The NIH's and DOD's leaders will no doubt be criticized whatever they do (see, for example, events recorded by Jon Cohen in his recent book *Shots in the Dark* — W. W. Norton, 2001). But they can now, if they choose, provide wise, statesmanlike guidance to the HIV-1 vaccine field if they place their programmes' narrow interests second to the need to save both volunteer cohorts and increasingly precious research dollars from being wasted in a turf war. To quote John Marburger, the White House's scientific adviser to the president (*Science* **294**, 1645; 2001): "If there are two agencies trying to do the same thing, I get them together and we work it out... There is nothing like OMB (the White House Office of Management and Budget) to help straighten out turf issues between agencies." If this particular turf war cannot be resolved by the agencies involved, perhaps the White House should take action. There are several possible options, but duplication is the least palatable.

### Tragic price

Although there is increasing pressure on the AIDS research budget nowadays, even more important is the need to minimize the number of human volunteers used for testing vaccines that are highly unlikely to work in the traditional sense of preventing HIV-1 transmission. Two efficacy trials of the VaxGen gp120 product are now in progress, so conducting two more canarypox/gp120 trials would mean four consecutive, probably failing, efficacy trials, all conducted in the glare of extensive publicity.

The fear of failure should never dominate decision-taking, but when failure is probable, it is prudent to examine the likely consequences. The price of the failure of four trials in succession will be high — the erosion of public confidence in science's ability ever to deliver an effective HIV-1 vaccine. This is especially the case in developing countries, in which public-health officials have all too often been told that the present generation of vaccines will help their populations when, in all probability, they will not. If multiple vaccine-efficacy trials all fail, the consequent loss of confidence in the West's ability to stem the AIDS pandemic could have tragic consequences for the developing world. ■

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