AIDS VACCINE TRIAL

Publicity stunt or genuine attempt at progress?

On September 25th, a group of biomedical researchers, physicians and FDA representatives met at the National Institutes of Health to discuss the ethical, clinical and regulatory ramifications of testing an AIDS vaccine on human subjects. Under the proposed trial, scheduled for the year 2000 and organized by Charles Farthing (medical director of AIDS Healthcare Foundation, Los Angeles), a live-attenuated HIV vaccine will be administered to around 20 healthy individuals. If the outcome of this safety trial is favorable, Farthing hopes to carry out an efficacy trial in a high-risk group two years later.

The meeting was precipitated by the successful recruitment of volunteers — a factor that has hitherto been a major obstacle to advancing the AIDS vaccine movement. Farthing appealed for volunteers through a new organization called the International Association of Physicians in AIDS Care (IAPAC), because he thinks it is "scandalous" that vaccine development is not progressing simply because regulators think that no one will step forward for the trial. To the surprise of a great many people, almost 60 volunteers have registered since the appeal was made in August, and Farthing hopes that this figure will more than double before he announces details of the trial at IAPAC's first meeting on 10th November in Washington, D.C.

But is this just a publicity stunt, or does Farthing believe that he will get FDA approval for such a trial?

In an interview held prior to the September meeting, Farthing told *Nature Medicine* that he sees no other way to succeed in getting approval than by applying "moral pressure" from physicians who are personally prepared to suffer the consequences. Farthing is himself a volunteer and likens the commitment to the pioneering self-experimentation work of Louis Pasteur and Walter Reed.

If volunteers have been the first hurdle to a vaccine trial, then safety will be the second. FDA approval is certain to rest heavily on this issue, and therein lies the caveat. Attenuated vaccines are more potent at inducing an immune response than other types of vaccine because although they have had some of their disease-causing genes deleted, they present virtually intact virus to the immune system — virus that can replicate and cause infection. Although the mechanism by which the vaccine affords protection is unknown, it has been suggested that infection with the attenuated strain blocks subsequent infection by the wild-type, i.e. the immune system is not able to become "super-infected."

It is planned to use a multiply deleted HIV vaccine, lacking the *nef*, *vpr*, *vpu* and a portion of the *lpr* genes, for the trial. The concept is based on the primate work of Ronald Desrosiers of the New England Primate Treatment Center, Southborough, Massachusetts, who has shown *nef*-deleted SIV to be the most successful vaccine in rhesus monkeys.

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Once volunteers have been injected, viral load and CD4 count will be monitored as prognostic markers of disease status. "If the vaccine is given to 100 people and none of them establish a viremia of 5000 copies/ml or more within a few weeks, then the vaccine should be deemed to be safe," says Farthing. He admits, however, that this does not rule out the possibility of 20 percent of volunteers developing AIDS years later — a concern raised by National Institute of Allergy and Infectious Diseases director Anthony Fauci — but says it is impractical to wait a lifetime before proceeding.

Desrosiers believes the question of safety is really an issue of risk/benefit ratio. Data from monkey studies show that attenuated viruses can occasionally cause high viral load and disease, but he adds that no live-attenuated vaccine — even those currently in use — is 100 percent safe. "If your target group has a 20 percent lifetime chance of HIV-1 infection, then you have to weigh this against the vaccine," says Desrosiers.

Adventitious clinical evidence in support of the vaccine does exist. Desrosiers himself reported a case of a US male infected with a *nef*-deleted form of HIV in 1983 who continues to maintain low virus loads and normal CD-4 counts to this day. A similar case has been recorded in Australia involving a donor who gave infected blood to eight people. Seven remain healthy, and one has died from an unrelated cause.

Meanwhile, some high-profile AIDS researchers have voiced their opinion of the trial.

David Baltimore, who recently announced that he has found past

HIV vaccine development strategies to be "flawed," told *Nature Medicine* that he was ambivalent about the issue. While he "recognizes the dangers of moving ahead with human testing," he has "seen how slowly other concepts are proceeding." He acknowledges that the "live-attenuated virus has shown the greatest efficacy of any vaccine concept in monkeys," but is troubled by its potential effects in older and immunosuppressed people.

Luc Montagnier, who together with Robert Gallo is credited with discovering the role of HIV in AIDS, is not in favor of the trial or the future use of a live-attenuated HIV vaccine. He believes that subunit vaccines offer a safer approach and says that "no one can predict the long-term impact of exogenous retrovirus in a human population." He, personally, would not volunteer for such a trial.

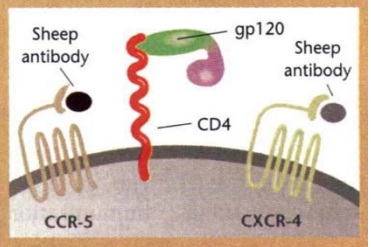
Gordon Nary, executive director of IAPAC, and a volunteer, thinks that, if approved, financial backing for the clinical element of the trial may come from the company currently developing a prototype of the Desrosiers vaccine — Therion Biologics — or even from the NIH.

The greatest expense, however, will be volunteer insurance, warns Nary. The trial cannot proceed without the guarantee of lifetime coverage — both medical and financial — for all volunteers in the event of any adverse reactions. However, Nary maintains that the cost of liability protection should be offset against the economic consequences of delaying its development. "What can we save in the long run by investing the money now in human trials of a vaccine?" asks Nary.

Thus, IAPAC's call for volunteers has brought the organization some publicity, but more importantly, it has forced a debate that could be a turning point for AIDS vaccine development.

KAREN BIRMINGHAM

Montagnier collaborates to develop HIV co-receptor antibodies



Luc Montagnier has given his support to an alternative immunotherapeutic strategy to tackle HIV. He is to collaborate with a UK-based drug development company to develop high-affinity, humanized-sheep antibodies that target the HIV co-receptors, CXCR-4 and CCR-5.

For an antibody to displace binding of HIV to its co-receptors, it requires a binding affinity greater than 10^{10} L/moL. Sheep-derived antibodies have this capacity, according to the managing director of KS-Biomedix Holdings, Kim Tan.

While Tan's company is looking to generate therapeutic agents from the venture, Montagnier told *Nature Medicine* that the agreement is intended to "foster development of new reagents for HIV research only" and not for any clinical applications. K.B.

From human rights to the human genome — stopping biopiracy

Genetic research by academic institutions and biotechnology companies around the globe is yielding long-sought-after clues to mutations that could help cure a wide range of diseases. This research is being increasingly conducted on tissue samples from native populations known to have increased frequencies of certain diseases, such as the Tristan de Cunha islanders who have a high propensity for asthma.

To address the rights of indigenous populations and the ethics involved in such research, this summer UNESCO published a draft of "A Universal Declaration on the Human Genome and Human Rights," which is the latest in a series of international treaties and declarations dealing with this issue. The document, which will pass before the UN General Assembly in November, serves more an "exhortatory than legal function for nations," according to Bartha Knoppers, professor at the Université de Montréal and member of the International Bioethics Committee of UNESCO.

It sets out guidelines that are intended to give indigenous peoples more negotiating power with biotechnology companies and universities, and will hopefully discourage what has been called "bleed and run" research — taking blood samples without returning any benefit to the subjects. Moreover, Knoppers believes that the declaration will encourage the exchange of appropriate "gifts" — such as helping a community build infrastructure, rather than encouraging the "commodification" of human life through the exchange of money for blood or DNA.

Knoppers compared the document to the 1948 Universal Declaration of Human Rights, and the Nuremberg Code, noting "the new declaration takes the next step, from human rights to the human genome." She acknowledged that, like these two international codes of law, it will take some time for the document guidelines to become known and adopted, but is optimistic that, over time, acceptance of its principles will occur.

Not waiting for international treaties to protect its people from genetic exploitation and "biopiracy," the Icelandic parliament may pass a law this autumn to prevent the export of human tissue. Companies wanting to do research on samples from the Icelandic population would need to maintain a presence in the country.

A supporter of the proposed legislation is Kari Stefansson, founder and CEO of DeCODE Genetics, a biotechnology company based in Reykjavik. "Ours is a powerful population for genetics research," says Stefansson. "A relatively small, homogeneous population, Icelanders don't have a lot of advantages, but we do possess a unique genetic heritage," he says.

Stefansson wants to ensure that any research done with the Icelandic population will also benefit them. To prevent what he calls "helicopter science" — samples being sent abroad for analysis — DeCODE has established a network of Icelandic physicians whose biomedical research it funds. However, some would say there is a conflict of interest because the company has access to samples from patients of physicians in its network, whereas researchers from abroad may not if the bill is passed.

The company, which is barely a year old, recently mapped the familial essential tremor gene, *FET1* (*Nature Genet.* 17, 84; 1997), and is pursuing targets such as multiple sclerosis, psoriasis, schizophrenia and manic depression. Stefansson says that he is prepared to publish data more rapidly than most researchers in order to benefit Icelandic patients sooner.

VICKI BROWER
New York