EHVA at the STEPS HIV Cure Workshop

A cure for HIV would almost inevitably have to involve a vaccine to improve the body's natural ability to control HIV, a seminar on European HIV cure research heard last October. The STEPS seminar, held by the European AIDS Treatment Group (EATG) ahead of the 16th European AIDS Conference in Milan, also presented about the European HIV Vaccine Alliance. Dr Felipe Garcia of the University of Barcelona Hospital, one of the collaborating researchers in the EHVA project, told the seminar: "The problem with HIV vaccines is that what protects is not able to control and what controls is not able to protect."

What he meant was that on the one hand, so-called broadly neutralising antibodies and vaccines that generate them – B-cell vaccines – may be able to completely block onward infection of cells by HIV, but tend to lose efficacy quickly as HIV is usually able to mutate enough to develop resistance to them, though one, PRO 140, has produced sustained viral load suppression for over a year. Experiments with combinations of ready-made broadly neutralising antibodies, including ones of novel design, showed more efficacy in human and monkey studies, but these were still passively introduced antibodies, used like drugs: the challenge was to produce a vaccine that could induce the body to make them.

Vaccines that stimulate the cellular immune response of cells to HIV – T-cell vaccines – could potentially generate a much longer-lasting immune response to HIV, but so far that response has been too weak and too narrow to produce more than slight reductions in viral load, of the order of a threefold to tenfold (0.5 to one log) reduction in the level of virus in peripheral blood. A trial in monkeys produced much more sustained viral load reductions to the extent of producing an apparent cure in about half of them, but this vaccine may be tricky to adapt to humans.

Challenges in HIV vaccine research

Garcia quoted one mathematical model that suggested that an immune response would have to produce an ongoing tenthousand-fold drop in infected cells (4 logs) in order to produce lifelong remission.

He added that a more fundamental problem in vaccine trial design was that we still had no real correlates of immunity. Assays that have predicted efficacy in other vaccines in the past – such as the amount of interferon-gamma cells produce – do not in HIV vaccines. "After an immune response is validated by a trial," said Garcia, "*then* I can tell you it's a surrogate."

Correlates of efficacy or immunity emerged *from* large-scale clinical trials, he said. But the problem in vaccines was that trials were very expensive – the RV144 trial, the only phase III study to find efficacy so far, had involved 16,000 participants and had cost €100 million. Multiple trials were needed to find an effective HIV vaccine, and it is estimated that over 35,000 volunteers will be required per year for phase I–III HIV vaccine trials worldwide to achieve this goal. In addition, the recruitment of volunteers in these trials could be an issue. In a previous preventive vaccine clinical trial in which he had been involved, RISVAC02, 356 volunteers had been screened to find 41 eligible candidates of whom 30 had eventually been enrolled.

There needed to be a better way to select novel vaccine candidates for development, he said, and therapeutic vaccinations offered a way as trials of them did not need too many people.

Finally, because of the lack of surrogates, at present vaccine trials must assay and analyse a vast array of different proteins in case one of them turns out to be the crucial surrogate of efficacy. In a dendritic-cell vaccine trial Garcia was principal investigator for, the activity of over 50,000 molecules are being evaluated.

Combining approaches

This all added up to a formidable task for vaccine researchers. However, by combining approaches, the chances of generating a 'hit' when it came to a truly effective immune response were increased.

Strategies recently had included the following:

- **Latency-reversing agents** such as PD-1 antagonists that prolonged the natural immune response to HIV and stopped the body 'locking away' HIV into the cellular reservoir;
- **HIV Conserv vaccines** that focused on generating immune responses to the particular parts of the virus it could least afford to change and discarded less-relevant responses;
- **Combining vaccines with cytokines:** these are specific cell-signalling molecules such as IL-15 and CXCR5 which are able to ferry vaccines and drugs into 'sanctuary sites' such as the lymph node follicles where HIV is normally able to replicate in cells that are shielded form immune-system surveillance;
- **Dendritic-cell vaccines.**

Garcia had taken a particular interest in the latter. He explained: "Dendritic cells are the first line of defence in infection. They capture foreign molecules and present them to immune system cells as antigens. You need to target dendritic cells because if these cells don't say to the body 'you are infected', the body doesn't know it.

"The problem with HIV is that it has developed a loop in its membrane that allows whole live viruses to attach to the dendritic cells which then ferries them to the lymph nodes as a 'Trojan Horse'. But this does mean that if we develop a vaccine that attaches to dendritic cells, it could generate a strong cellular immune response in the lymph nodes, which is where it needs to be."

The European HIV Vaccine Alliance is a consortium of 39 partners from eleven countries in Europe plus four in sub-Saharan Africa and the US. It is pursuing a number of different vaccine strategies including improved viral vectors, modified versions of HIV envelope proteins and dendritic-cell vaccines.