The Quest Trial, a paradigm of HIV collaborative research

To the editor—A recent *News* story in your journal addressed the issue of whether there is a commitment to move forward with the development of preventive vaccines for principal infectious diseases, including human immunodeficiency virus (HIV)-1 infection, tuberculosis and malaria[1]. For HIV-1, although it is accepted that prophylactic vaccines are an urgent priority to prevent new infections, the plight of those already infected must also be considered. Consequently, there is a strong case for promoting the development of therapeutic vaccines in parallel with drug intervention.

Pharmaceutical companies have been criticized widely by advocacy groups and others, and in the aforementioned *News* article, for their failure to collaborate with the academic community at large in the development of new HIV therapies. Here we present an example of a clinical trial involving multi-party collaboration.

In 1998, GlaxoWellcome initiated an international study (QUEST) to assess whether highly active anti-retroviral therapy (HAART) consisting of amprenavir, abacavir and combivir administered for at least 2 years to patients acutely infected with HIV-1 would allow for the long-term control of viral replication when treatment was stopped. When new information emerged during the trial that virus in a latently infected reservoir may replenish infection, the trial was amended to incorporate a double blind randomized vaccination strategy to be compared with HAART alone before treatment interruption[2]. The intention was to explore whether therapeutic vaccination can expand the magnitude and breadth of HIV-specific immune responses over HAART alone[3], which would in turn restrain viral replication after treatment cessation.

Two vaccines were selected: one produced by Aventis Pasteur (ALVAC-HIV-vCP1452, a live recombinant avipox -vectored HIV-1 vaccine expressing envelope, core, pol and nef antigens), and the other produced by Immune Response Corporation (Remune, an envelope-depleted, inactivated HIV-1 vaccine). To date, the trial has included 150 patients, at present the largest prospectively enrolled cohort of such patients, with a median follow-up of 52 weeks. So far, the addition of vaccines to HAART regimens has not provided conclusive long-lasting benefits over HAART alone. Preliminary results from this trial are expected next year.

From the beginning of the trial, there was a commitment from the sponsor to offer these patients the most clinically advanced therapy available. The selection of vaccines from different manufacturers required an intense period of negotiation between investigators, vaccine manufacturers and the sponsor. Why would the main sponsor of the study (GlaxoWellcome), whose strength lies in the discovery and development of new antiviral drugs rather than vaccines, sponsor a trial with the ultimate goal of achieving viral replication control by the addition of vaccines from other commercial enterprises and the ultimate aim of stopping drug treatment? They did this for several reasons. Acute infection data from this study may have as-yet unforeseen consequences for the wider population of HIV-infected subjects. Although not associated with short-term commercial gain, the benefit for society in general will come from any progress made in medical care and the possibility that results from this trial may increase the value of new immunological markers in the design of future vaccination studies. In addition, with treatment interruption strategies being regarded increasingly by patients as a means of liberating themselves from continuous substantial drug regimens, there is a need to preserve future treatment options. Self-initiated, unguided drug 'holidays' may result in the emergence of resistance and negate future treatment options. By advocating a formal, planned strategic HAART cessation in this cohort after an optimal treatment period, new strategies for subsequent successful reintroduction of treatments are enhanced.

QUEST is a collaboration between clinicians and research scientists from both academia and the pharmaceutical industry, and the pursuit of the research objectives in this study have resulted in a synergistic network of expertise among all the collaborating parties. The foresight of a multilateral drug development approach should be encouraged and used as an example for the pharmaceutical industry as a whole.

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1. Birmingham, K. Industry outlines its perspective on new Third-World vaccine development. *Nature Med.* **6**, 723–724 (2000).
2. Finzi, D. *et al*. Latent infection of CD4+ T cells provides a mechanism for lifelong persistence of HIV-1 even in patients on effective combination therapy. *Nature Med.* **5**, 512–517 (1999).
3. Rosenberg, E. *et al*. Vigorous HIV-1 specific CD4+ T cell responses associated with control of viremia. *Science* **278**, 1447–1450 (1998).