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Don't stop me now

Despite pessimism in the media surrounding the recent failure of the Merck HIV vaccine, researchers should applaud their achievements and step up to the challenges ahead.

Twenty-five years ago, Luc Montagnier's research team published the first evidence linking AIDS to a retrovirus. A year later, Robert Gallo's group showed this retrovirus caused AIDS. Now called human immunodeficiency virus (HIV), this retrovirus has infected over 60 million people, killed nearly half that number and has become the new scourge of humanity due to the very nature of how the virus is transmitted. To commemorate these landmark discoveries, Simon Wain-Hobson brought together many of the leaders in HIV research at the Institut Pasteur to discuss the progress and setbacks of HIV research in the past quarter century (see the Meeting Report by Amitage, McMichael and Drakesmith, p 823).

After HIV was isolated, the US Secretary of Health and Human Services, Margaret Heckler, famously declared that a preventative vaccine could be expected within 2–3 years. Now, 25 years later, the news (at least according to the mass media) is not good. In September 2007, Merck halted a large-scale clinical trial of the most promising HIV vaccine so far. This vaccine, designed to induce specific T cell responses, not only failed to protect against infection or contain virus replication in those infected but seemed to increase susceptibility to HIV infection in people seropositive for antibodies recognizing the adenovirus serotype 5 vector used to deliver the HIV antigens.

The reasons for the failure of this latest vaccine initiative are still not clear and await further analysis. Yet it is totally unwarranted to "pull the plug on vaccine research," as advocated by Michael Weinstein, president of the AIDS Healthcare Foundation. It is very short-sighted to think that despite the expenditure of billions of dollars on HIV research, no effective vaccine will ever be generated. In fact, 25 years can be considered young in vaccine research; it took 105 years to develop a vaccine for typhoid, 47 years for a polio vaccine and 42 years for a measles vaccine. It is also not unusual to change course during vaccine research, as the history of the development of the polio vaccine will attest.

HIV vaccine researchers nevertheless have a formidable task on their hands. First, there is in fact little direct evidence of how human vaccines work. Second, HIV is unique on several levels in terms of vaccine development. Perhaps foremost, the propensity for HIV to replicate and mutate rapidly creates obvious obstacles, especially given that the sequence diversity in HIV even in one person can be greater than that generated in an influenza virus pandemic. The ability of HIV to evade the immune system by many mechanisms, to attack the immune system itself causing loss of $CD4^+$ T cells, and to establish a latent reservoir through integration into the host's genome also hinder the development of an effective vaccine. Nonetheless, this is not the time to simply give up.

Yet in the face of such challenges, it should not be forgotten that enormous progress has been achieved since 1983. A test to screen blood for HIV was rapidly developed soon after the virus was isolated, and the ability to measure HIV viral loads helped disease management. The advent of antiretroviral therapy extended patients' lives and, in mother-to-infant transmission, such therapy can often prevent infection. Lesser known is the development of sperm washing, which has allowed HIV-discordant couples to have children. More recently, a large randomized trial in Africa showed that adult circumcision could significantly decrease male HIV infection via heterosexual intercourse.

In terms of understanding HIV pathogenesis, much remains to be learned, but also much has been learned. Back in 1984, the CD4 molecule was identified as the main receptor for HIV. By the mid-1990s, the identity of HIV's coreceptors, CXCR4 and CCR5, explained how the different strains of HIV-1, X4 and X5, could bind and enter cells. The importance of CCR5 was soon demonstrated by the finding that people homozygous for a deletion of 32 base pairs in the gene encoding CCR5 are highly resistant to HIV infection. It soon became apparent that lymphoid tissue is the main target and reservoir of HIV infection. Characterization of the immune response to HIV, such as neutralizing antibodies, cytotoxic T lymphocytes and T helper responses, has aided the understanding of HIV pathogenesis. The identity of host restriction factors, such as APOBEC3G, may offer new inroads for therapeutic intervention. The ability of HIV to severely impair the immune system within weeks of infection by causing massive loss of $CD4^+$ memory T cells in gut-associated lymphoid tissue is a more recent example of a substantial advance in the understanding of HIV pathogenesis.

In retrospect, given what is now known, it was naive to imagine that an HIV vaccine could be generated in a matter of a few years. However, the identification of exposed yet uninfected people and 'elite HIV-infected controllers' should provide optimism that a vaccine solution can be found. Indeed, long-term vaccine-mediated protection against simian immunodeficiency virus has been achieved with live attenuated virus, and high doses of neutralizing antibodies can achieve sterilizing immunity in a virus mucosal challenge animal model. Clearly, now is not the time to decrease HIV vaccine funding. Equally important, more basic research into HIV pathogenesis is required. Young researchers must not be deterred but instead must be encouraged to enter this field.

In the quest for an HIV vaccine, many challenging issues still must be resolved. How to harness the power of neutralizing antibodies and definition of the immune responses in elite controllers are but two avenues of fertile research. With recent advances in molecular and structural biology, and with more collaboration across diverse scientific fields, it would not be unthinkable to believe that a protective HIV vaccine can be attained. As Helen Keller once wrote, "Optimism is the faith that leads to achievement. Nothing can be done without hope and confidence."