nature medicine

Back to basics

Basic HIV research has, over the past two decades, brought about enormous advances that have transformed a fatal disease into a manageable illness. HIV vaccine research has suffered more setbacks than successes, but a renewed focus on fundamental questions about HIV pathogenesis will provide new glimmers of hope.

Later this year, the results of the world's largest phase 3 trial of an HIV-1 vaccine candidate are expected to be released. More than 16,000 individuals in the Thai provinces of Chon Buri and Rayong have participated in the so-called RV144 trial to discover whether a prime-boost combination of Aventis Pasteur's canarypox vector, ALVAC-HIV, together with VaxGen's recombinant gp120 can either prevent HIV-1 infection or reduce viral load after infection.

Given the controversy that raged at the time of the trial's initiation at the end of 2003, it would seem that hopes are not high. The gp120 part of the vaccine, intended to induce neutralizing antibodies to the HIV envelope protein, had been tested in an earlier phase 3 trial and failed. The canarypox component, designed to induce protective T cell responses against the virus, has been criticized for being poorly immunogenic. We will soon find out whether the critics are right, or whether the trial can teach us something new about what is required for a protective immune response to HIV-1.

At least one thing seems relatively certain: the RV144 vaccine must be safe. Since the trial's initiation in 2003, an independent Data and Safety Monitoring Board has met eight times, and the trial has not been prematurely halted. Unfortunately, this was not the case with a phase 2b trial of a candidate that was widely perceived as the most promising product in the pipeline. Merck's adenovirus type 5–based candidate did not protect vaccine recipients from infection in the so-called STEP trial; on the contrary, it seemingly increased HIV-1 acquisition in uncircumcised individuals who had preexisting antibodies to the adenovirus vector. The mechanisms underlying this effect are unclear: two Brief Communications on pages 873–875 and 876–878 of this issue investigate the hypothesis that preexisting neutralizing antibodies to the adenovirus vector acted as surrogates for increased numbers of antivector $CD4^+$ T cells—target cells for HIV-1 infection.

On page 855 of this issue, we also present the result of a project that we undertook at *Nature Medicine* to identify some of the key roadblocks to translational research in the HIV field. We asked a group of HIV experts (not restricted to vaccine researchers) to tell us what they believe are the most important obstacles that their field faces. Their answers revealed that the roadblocks are not just scientific in nature. Nevertheless, for translational research in the HIV field to progress, it is clear that many fundamental scientific questions about the biology of virus infection and pathogenesis need to be addressed.

Although vaccine research—and, to some extent, microbicide research—has suffered disappointing setbacks, translational HIV research in other areas has been enormously fruitful. Basic investigation into the mechanisms of HIV replication has led to the development of an array of drugs that target various steps in the virus life cycle. Studies of long-term nonprogressors have led to the identification of a co-receptor for HIV, which, in turn has led to drugs that can block virus entry. Together, these drugs have transformed the prognosis for HIV-infected individuals, who can now hope for a normal life span (provided, of course, that they have access to the drugs).

Although nobody is ready to give up on the prospect of an HIV vaccine, it is possible that other strategies for HIV prevention may be effective. We know that circumcision greatly reduces the chances of men becoming infected with HIV. Ongoing trials of preexposure prophylaxis will reveal whether antiviral drugs can reduce HIV-1 acquisition in affected populations. Microbicides incorporating antiviral drugs may be effective. And 'out-of-the-box' approaches to prevention might also work. On page 901 of this issue, Philip Johnson and his colleagues show that gene transfer may be a viable alternative to vaccination.

The challenges that HIV poses are enormous, but the scientists working in this field are resilient, committed and purposeful. With the renewed focus on answering basic scientific questions, it would seem that these challenges may not be insurmountable, although overcoming them will certainly take time. But, as illustrated in our analysis of the roadblocks in HIV research, the pace of progress will not depend solely on scientific advances. Solving nonscientific challenges, such as finding ways to support high-risk, innovative research and ensuring that new developments in related disciplines, such as basic immunology, are harnessed as quickly as possible by the HIV community, will help set the future trajectory of HIV research.