OPINION

Accelerating HIV vaccine development

Translational-research programmes supported by flexible, long-term, large-scale grants are needed to turn advances in basic science into successful vaccines to halt the AIDS epidemic, says **Wayne C. Koff**.

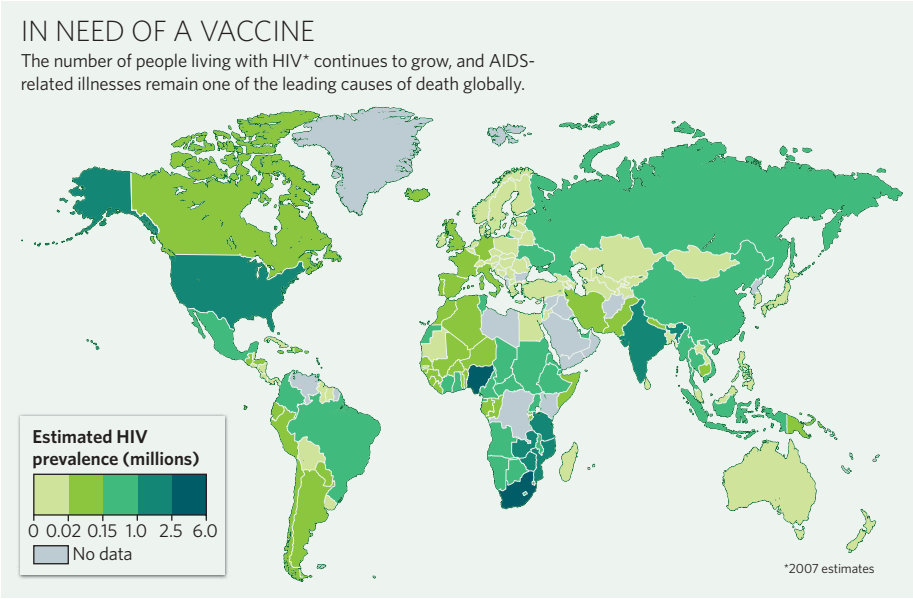
The world needs a vaccine as soon as possible to help halt the inexorable spread of HIV. But vaccine development has not kept pace with breakthroughs in basic science. However, during the past year, advances in vaccine research and development (R&D) have generated great excitement. These include the first, partial protection in humans by an HIV vaccine[1]; identification of a new target for broadly neutralizing antibodies on HIV's surface[2]; and evidence for significant vaccine-induced control of simian immunodeficiency virus (SIV) in non-human primates[3].

New leads for vaccine discovery should come from linking HIV vaccine research with the broader field of viral immunology, and understanding the early events in HIV pathogenesis — as recommended elsewhere in this issue of *Nature*[4,5]. Translational-research programmes need to be expanded to connect this basic science with existing vaccine-development tools, including hypothesis-driven clinical trials to assess novel immunogen designs. This will probably require solutions to two problems that have remained unsolved for more than 20 years: the design of immunogens to elicit broadly neutralizing antibodies to prevent HIV infection, and the design of immunogens to elicit robust cellular immune responses to control HIV infection.

Most importantly, the field should launch flexible, large-scale, long-term funding mechanisms ideally by the beginning of 2011 that invest in multidisciplinary teams rather than in projects. Such mechanisms would foster greater innovation and shorten the timeline to a safe and effective HIV vaccine.

The neutralizing-antibody problem

Licensed viral vaccines protect against disease by priming the immune system before pathogen exposure. This generates antibody responses that can prevent infection, and cellular responses that target and eliminate virus-infected cells. Virus-specific neutralizing antibodies bind to proteins on the surface of viral particles and stop them from infecting host cells. Neutralizing antibodies can also bring about the destruction of virus-infected cells, via cellular effector mechanisms. Where natural virus infection elicits robust neutralizing-antibody responses, vaccines have been developed by using attenuated versions of the live virus (such as for measles, mumps and rubella); inactivation (for polio); and virus surface protein subunits or virus-like particles (for hepatitis B and human papilloma virus).



There are, however, three formidable obstacles for vaccine developers attempting to raise HIV-specific neutralizing antibodies. First, the virus is hypervariable so a vaccine must elicit broadly neutralizing antibodies to counter myriad circulating isolates of HIV. Second, the target for broadly neutralizing antibodies, the envelope spike, is very unstable and so is difficult to recreate in a form that can act as a vaccine[6]. Lastly, most highly conserved targets for HIV-neutralizing antibodies are hard to access on the virus spikes[7]. However, broad and potent neutralizing antibodies against HIV have been identified from HIV-infected subjects[8], demonstrating the feasibility of inducing such antibodies. Unfortunately, experimental attempts to elicit such antibodies have to date universally failed.

Recent technological advances — in structural biology, cryoelectron tomography, computational biology, B-cell immunobiology, and high-throughput robotic micro-neutralization screening assays — have been brought together to try to 'reverse engineer' a solution to this problem[9]. These studies may inform the rational design of vaccines against other highly variable viruses such as influenza and hepatitis C. This approach identifies infected subjects with broadly neutralizing serum antibody responses, isolates the corresponding broadly neutralizing monoclonal antibodies (bnMAbs), characterizes the interaction of these bnMAbs with the virus envelope, and then engineers immunogens based on this information.

However, in an era of global economic uncertainty, the multidisciplinary centres and consortia likely to be required to adequately address this problem are currently too few and in jeopardy of not achieving critical mass or long-term commitment. This is due in large part to increasingly restrictive funding mechanisms such as milestone based, short-term, project-specific funding.

The cellular immune-response problem

Several lines of evidence, from human HIV natural history and simian immunodeficiency virus (SIV) studies, suggest that cell-mediated immune responses are required to control HIV by keeping the viral load very low or undetectable. Because control of infection is required to prevent disease, and as the best licensed vaccines against other pathogens do not necessarily completely prevent infection, a successful HIV vaccine will probably also need to elicit cell-mediated immune (CMI) responses capable of controlling HIV infection. This is difficult because the virus

becomes persistently established in host-cell reservoirs within days of exposure, allowing only a small window of opportunity for CMI-based control.

Three HIV vaccine concepts have now advanced through efficacy trials and none controlled HIV infection as measured by viral load in the blood. In contrast, a small subset of HIV-infected people can control HIV infection to nearly undetectable levels without antiretroviral therapy[10], and some SIV vaccines can control pathogenic SIV infections to similarly low viral loads[11]. To solve this problem, three key issues need to be addressed. First, elucidating the mechanisms of CMI-based control of HIV infection in humans and of SIV in SIV-immunized monkeys would provide important leads. Second, improving functional assays of CMI responses would enhance preclinical and clinical prioritization of candidate vaccines. Third, researchers need to design and screen immunogens capable of outwitting HIV's ability to mutate rapidly and evade CMI responses.

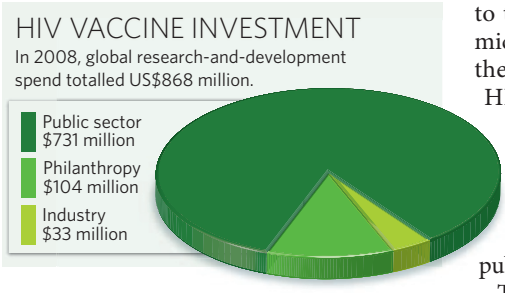
Again, such complex challenges require multidisciplinary teams, and a different approach to funding translational research.

Enhancing translational research

Total global investment for HIV vaccine R&D for 2008 was US$868 million (see chart), a 10% decrease from 2007 (ref. 12). However, only 5–10% was focused directly on trying to solve the two major vaccine-design problems detailed above. Moreover, funding for translational research has generally been limited to 3–5 year programmes that primarily support small academic consortia, and lack many of the industrial-style disciplines needed for vaccine discovery and development. Collectively, such projects have a very low probability of success. In addition, academic scientists must split their time between research, getting grants, teaching and fulfilling administrative and managerial responsibilities, limiting their time focused on the scientific problems.

The funding mechanisms from national public-sector research agencies have been effective in fostering basic research, primarily through investigator-initiated programmes. These should continue. However, these mechanisms are not optimal for attracting new talent to HIV vaccine research, fostering innovation in vaccine discovery, establishing links with industry or providing long-term multidisciplinary commitment. It is unfortunate then that philanthropic foundations and other donors aiming to fill the translational science gap have increasingly tilted towards the public-sector model.

There are examples of successful integration of basic and translational research practices that should be learned from and expanded



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on. These include the Neutralizing Antibody Consortium (NAC) set up by the International AIDS Vaccine Initiative (IAVI); the US National Institute of Allergy and Infectious Diseases (NIAID) intramural Vaccine Research Center; and the recently established Ragon Institute in Boston, Massachusetts. Teams associated with these three institutions have been responsible for many of the most promising recent advances[2,7,10,13–15].

These institutions have established practices that emphasize long-term (eight years or more) institutional commitment. They reward proven scientific leadership and track records rather than project-specific proposals; they try to link researchers with those from outside HIV vaccine R&D; and they limit major project reporting and reviews of laboratories to multi-year cycles, increasing time for HIV vaccine design.

Building on these successes, three new translational-research funding mechanisms should be instituted.

Young investigator awards should be set up by major stakeholders of the Global HIV Vaccine Enterprise (www.hivvaccineenterprise.org) for scientists under age 35. These awards would attract the best new scientists to the challenges of HIV vaccine R&D by offering 5–7 years of salary and flexible funding. Investigators would be free, within broadly defined research programmes, to redirect their funds as new data emerge, in exchange for expending at least 75% of their effort on the two major scientific problems noted above. Developing such grants will require stakeholders, including public-sector research agencies and non-profit foundations to invest in young scientists as components of multidisciplinary teams, rather than relying on traditional investments in specific projects.

Incentives for expanded biopharmaceutical investment need to be set up. Vaccines are made in industry, yet industrial involvement in HIV vaccine R&D is minimal because of the scientific challenges, market disincentives and opportunity costs. Support for industrial investment — from the Bill & Melinda Gates Foundation and IAVI — to Theraclone Sciences in Seattle, Washington, and Monogram Biosciences in San Francisco, California, led to the application of B-cell screening and micro-neutralization technologies central to the recent identification of a new target on HIV for broadly neutralizing antibodies[2].

Additional mechanisms to enhance biopharmaceutical investment, particularly in process development for vaccines, could include advanced market commitments, intellectual-property incentives, and direct public-sector support for vaccine R&D.

Translational-research teams must be established. The Howard Hughes Medical Institute (HHMI) successfully supports internationally recognized basic-research scientists with a salary plus a portion of laboratory costs for a minimum of five years, without restriction on their research direction. This attracts talented scientists and fosters innovation. Few HHMI-like mechanisms exist for teams focused on HIV vaccine translational research. Ten per cent of the annual investment in HIV vaccine R&D should be refocused to provide such a mechanism for HIV vaccine development.

In sum, major funders will bring a successful HIV vaccine closer by establishing long-term translational-research programmes, attracting scientific talent and technologies, providing greater incentives for industry participation and focusing on rational vaccine design. These initiatives should be formulated over the coming months, debated at the international AIDS Vaccine 2010 conference starting on 28 September in Atlanta, Georgia, and implemented by the beginning of next year. This effort will also provide a framework for the rational design of vaccines against other global infectious diseases. ■

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