VACCINE WATCH

Mapping the future of HIV vaccines

Gary J. Nabel

Efforts to develop an HIV vaccine have been slower than expected, but significant progress has been made in recent years. Gary Nabel provides an update on this progress, and describes how the field is now poised to begin translating scientific understanding into improved vaccine candidates.

More than 59 vaccines have been licensed in the United States for 24 infectious diseases worldwide[1], saving tens of millions of lives each year. When the AIDS virus HIV was discovered more than 25 years ago, it seemed a simple proposition to develop a vaccine that would be similarly effective. Few viruses had resisted concerted vaccine development efforts, and it seemed that the discovery of the virus, as well as the development of methods to propagate and detect viral infection, would facilitate these efforts, rapidly leading to a human vaccine.

HIV has been studied in great detail, producing insights into viral immunopathogenesis that initially provided encouragement for rapid development of a vaccine. However, efforts to develop a vaccine have been significantly slower than expected, thanks to several surprises that lay in store during the growth of the AIDS pandemic. First, the extraordinary genetic diversity of the virus, not appreciated in the early years, became evident. Factors such as the high mutation rate, RNA recombination and immune selection combined to produce viral strains with considerable genetic heterogeneity, making it necessary to develop a vaccine that could protect against not just a single virus, but millions of variants that had evolved around the world (for a review, see REF. 2). Second, as the virus spread throughout the population, it began to develop mechanisms for evasion of the host immune response[3]. Thus, there were no highly conserved elements for recognition by T or B cells. In fact, despite more than 60 million infections worldwide, there have been no documented cases of long-term immunity to HIV infection based on a cellular or humoral immune response that eradicates the virus.

Traditionally, vaccines have been developed by identifying examples of immunity to infection in nature and generating vaccines that elicit the most crucial aspects of the protective immune response. In the case of HIV/AIDS, there are no examples of immunity from nature and no immune correlates of protection, and hence no well-charted path to an effective vaccine.

For these reasons, the early optimism about the prospects for an HIV vaccine faded. It has typically taken several decades to develop effective vaccines for various viral infections, such as measles, mumps, rubella and chickenpox. In the case of HIV/AIDS, it could take even longer. In the absence of natural immunity that defines the correlates of protection, vaccine development for HIV must rely on rational vaccine design, including the use of the latest advances in viral and host molecular genetics, structural biology, immunology and modern vaccine production technologies[4]. This effort requires the generation of vaccine candidates that advance into human trials and provide guidance through the definition of immune correlates in natural settings. Such trials must take place in areas of high HIV/AIDS incidence, and they are likely to last for several years. In this context, it is important to plan for the next phase of research and to predict the most promising future directions, even before new data are available.

In recent years, significant progress has been made. Newer and more promising human vaccine candidates are now progressing into clinical efficacy studies. Such trials now define not only safety issues and the immune response in humans but also the potential for vaccine efficacy. Within the next few years, several clinical trials will reveal whether T-cell-based vaccines have the potential to prevent or contain viral infection. As this effort proceeds, it

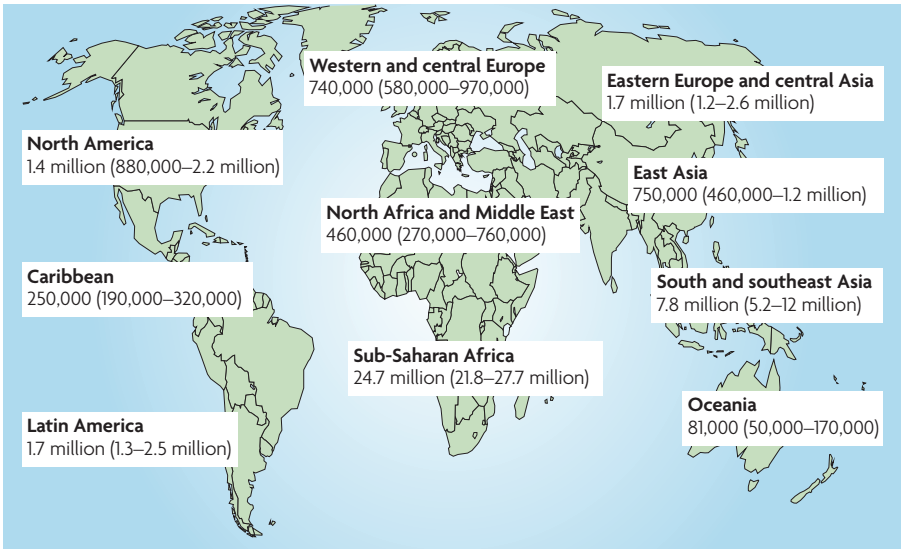

Figure 1 | **The global distribution of HIV infection.** Data from REF. 5.

Table 1 | **HIV vaccine candidates in advanced clinical trials**

Delivery	Immunogen*	Immune basis	Sponsor
Canarypox ± protein	Env (E), Gag/Pol (B) and Env (B and E)	Cellular ± humoral	Sanofi/Vaxgen
rAd5	Gag (B), Pol (B) and Nef (B)	Cellular	Merck
DNA/rAd5	Gag (B), Pol (B), Nef (B) and Env (A, B and C)	Cellular	VRC, NIAID/ NIH

* The letter(s) in parentheses indicates clade of origin. Env, envelope; Gag, group-specific antigen protein; Nef, negative regulatory factor; NIAID, National Institutes of Allergy and Infectious Diseases; NIH, National Institutes of Health; Pol, polymerase; rAd5, recombinant adenovirus 5; VRC, Vaccine Research Center.

will be crucial to focus on the elusive goals of inducing broadly neutralizing antibodies, developing improved vaccine vectors, defining the immune correlates of protection and harnessing mucosal and innate immunity. Although a licensed vaccine could still be a decade or more away, researchers are now ideally positioned to translate scientific understanding into improved vaccine candidates.

Global distribution and disease burden

Although unrecognized as a disease entity 30 years ago, HIV has now infected more than 60 million individuals worldwide and has led to over 20 million deaths[5]. Most HIV-infected individuals live in the developing world and do not have access to facilities that can rapidly diagnose and treat the complications of this infection. It is estimated that 11,000 individuals worldwide become infected with HIV every day. The largest burden of infection is in southern (sub-Saharan) Africa, with almost 30 million infected individuals in this locale (FIG. 1). Regions of south and southeast Asia, particularly India, have borne the next highest burden of disease, with an estimated 5–10 million infections. In the United States, 40,000 people were newly diagnosed with the infection last year[5]. As the pandemic has spread, the incidence of disease in women has dramatically increased, particularly in South Africa and the Caribbean.

Although efforts have been made to improve the availability of treatment in the developing world, current treatments do not eradicate the disease, and they require lifelong administration, often with debilitating side effects that limit long-term use. Early in the pandemic, transmission was associated with intravenous drug use and homosexual activity. Although these factors do result in increased risk, the rates of heterosexual transmission have increased significantly, particularly in the developing world. Given the limitations of drug therapy and the challenges associated with the long-term delivery of these medicines, the preferred strategy for containing the disease is to prevent infection entirely. Vaccination has traditionally been the most effective method of preventing devastating outbreaks of viral diseases, and it has been the cornerstone of public health efforts. At the same time, given the limited success of HIV vaccines to date, alternative prevention strategies remain under intensive development, including behavioural interventions, public health measures and the development of microbicides. Although it will be necessary to use various approaches to contain HIV transmission, a highly effective vaccine, if it can be found, would provide perhaps the most powerful tool to protect individuals from the risk of this infection, particularly in the developing world.

Vaccine concepts and clinical trials

The effort to develop an effective HIV vaccine dates back to the 1980s, and more recently it has expanded to include multiple clinical trials supported by governmental and non-governmental agencies. More than 95 clinical trials of different HIV vaccine candidates have been completed, involving more than 26,000 healthy volunteers. Two efficacy studies are currently in progress: the 16,000-person trial in Thailand of a canarypox and recombinant envelope (Env) glycoprotein in combination, and an adenovirus vector encoding Gag, Pol and Nef proteins from HIV clade B in the Americas and Australia (TABLE 1). Results of the trials will begin to emerge in early 2009.

The recognition of three scientific facts has facilitated efforts to improve each new generation of HIV vaccines. First, analysis of the genetics of HIV has led to the realization that a vaccine must protect against a diverse array of viruses. Recognition of linear peptide epitopes is mediated by the cellular immune system, and there is much evidence, from humans and non-human primates, that T-cell immunity can help to contain infection and prolong survival[6]. Thus, T-cell vaccines have become a central focus of current vaccine efforts. Implicit in this strategy is the idea that the vaccine should include components that are representative of diverse naturally circulating viruses and preferably critically conserved protein sequences.

Many licensed vaccines elicit antibodies to viral spike proteins. Env, which is required for attachment and entry into host cells, is conformationally flexible and highly variable, which confounds efforts to develop broadly neutralizing antibodies[3]. A Phase III trial designed to test the efficacy of non-neutralizing antibodies demonstrated their inability to protect against infection[7], so significant efforts have been made to develop improved Env immunogens. So far, no promising candidates of this type have emerged; however, considerable progress has been made in understanding the structural basis of Env sensitivity. Recently, the atomic level structure of HIV Env complexed to a broadly neutralizing monoclonal antibody has revealed the molecular details of these interactions and the ability of this antibody to bind to a critical region of CD4 docking, thus preventing infection[8]. Such structures might provide the basis for the development of improved Env immunogens in the future.

These studies reveal the second feature of the virus that has made the development of a vaccine so difficult: not only is the virus diverse with respect to its genetic sequence, but its envelope is variable and the critical components for viral entry are not exposed until it is too late for antibodies to neutralize the virus[9]. The ability to raise antibodies that can neutralize the virus is one of the most effective forms of protection that has been exploited in vaccines so far. Such antibodies have formed the bases for the poliovirus and influenza virus vaccines, and the major childhood vaccines that have been licensed for use in the United States and elsewhere in the world. It has been particularly challenging to develop antibodies that neutralize the diverse strains of HIV, so-called broadly neutralizing antibodies, and this scientific obstacle remains the holy grail of HIV vaccine research. In the face of these obstacles, what can be done? Among other things, it is possible to use structural biology to generate artificial scaffolds or sub-structures that can elicit antibody responses. Efforts of this kind might catalyse the breakthrough that will allow for the generation of a highly effective HIV vaccine.

The third fact important for progress in HIV vaccine research is the recognition that immune control can be gained through an effective T-cell response. Depletion of cytotoxic T cells or killer T cells in the setting of infection exacerbates disease, and highly effective $CD8^+$ T-cell responses are associated with containment of symptoms[10–12]. Our ability to elicit consistent and potent cellular immune responses with new-generation vaccine vectors, including plasmid DNA and replication-defective adenovirus, is a technological breakthrough. It will allow the testing of a first-generation T-cell vaccine that has been developed at the National Institutes of Health, at the Vaccine Research Center in the National Institutes of Allergy and Infectious Diseases (NIAID).

This prototype T-cell vaccine contains components from multiple genes of the virus — the genes encoding the Gag, Pol, Nef and Env proteins — and is representative of diverse virus clades throughout the world. It will be tested in partnership with the Division of AIDS in NIAID and three clinical trial networks in different regions of the world. Phase II studies have begun at most of these sites and, barring unforeseen hurdles, proof-of-concept efficacy studies will begin next year. The results from recent non-human primate studies with a comparable vaccine are encouraging. When this analogous virus was used in the aggressive SIVmac239 challenge model, an increase in survival was noted in vaccinated animals[13]. More importantly, an immune correlate of survival, the memory $CD4^+$ T-cell population, was defined. Should this marker hold true in human studies, it could provide a surrogate for vaccine efficacy that would greatly accelerate future human clinical trials.

Outlook

What does the future hold for HIV vaccine research? An HIV vaccine might not prevent infection, but could prevent the occurrence of symptoms. In the absence of a vaccine, it is likely that the pandemic will continue to spread although, with the help of other prevention and intervention strategies, the rate of increase of new infections could be reduced. If the levels of virus in the blood can be lowered sufficiently by a vaccine, we could have an opportunity to reduce transmission and eventually eliminate the disease. With a highly effective preventive vaccine, we can begin to confer protection to individuals, and rapidly bring extinction to the ever-expanding pandemic.

There are scientific questions that must be solved in order to make progress towards an effective HIV vaccine. Can we develop the types of potent immune responses at the sites of mucosal entry that are necessary to prevent the spread of the virus? Are there natural innate immune mechanisms that can contain the virus before it spreads? Are there molecular structures that we can identify and use to elicit broadly neutralizing antibodies and penetrate the shield of carbohydrate and moving structures that the virus presents to evade the immune system?

The solution will come from innovative and creative science, perhaps even from approaches not yet imagined that are fostered by groundbreaking research and progress in basic science. It is vital that the full range of intellectual resources and biomedical infrastructure be brought to bear on this problem. The collective energy and creativity of aspiring scientists will be needed to achieve the goal of a practical, cost-effective vaccine to contain and control emerging outbreaks so that AIDS becomes a disease of our past rather than our future.

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VACCINE WATCH

Tuberculosis vaccines — an update

Peter Andersen

The current tuberculosis (TB) vaccine *Mycobacterium bovis* bacillus Calmette-Guérin (BCG) is the most widely used vaccine worldwide, but it does not prevent the establishment of latent TB or reactivation of pulmonary disease in adults. Peter Andersen looks at the progress of the candidates to improve or replace BCG.

Tuberculosis (TB), a disease which is both curable and preventable, still kills 2–3 million people every year. After decades of neglect, the immense public health impact of TB is now widely recognized, and the development of new tools to combat and control the epidemic has become an international priority. The current strategy for TB control is based on reducing the spread of infection through effective treatment of individuals with active disease and vaccination of children. The WHO has initiated the directly observed therapy (DOTS) campaign in many regions, but so far this programme has not been able to control the global TB epidemic or prevent the increase in multidrug resistant (MDR) strains of *Mycobacterium tuberculosis*[1].

The current TB vaccine *Mycobacterium bovis* bacillus Calmette–Guérin (BCG) is the most widely used vaccine worldwide. BCG provides efficient protection against TB in newborns, but does not prevent the establishment of latent TB or reactivation of pulmonary disease in adults. Being a viable organism, the activity of BCG depends on its initial replication, and it therefore cannot be used as a booster in an adult population that is already sensitized by prior BCG vaccination, exposure to environmental mycobacteria or latent TB[2]. A novel, effective vaccination strategy against adult pulmonary TB is therefore a crucial goal and an active field of research, development and clinical evaluation.

Global distribution and disease burden

In 2004, approximately 9 million people developed active TB. Although this places TB as one of the most important global health problems, active disease represents only the tip of the iceberg, as it has been estimated that one-third of the world's population is latently infected with *M. tuberculosis*. Globally, the incidence of TB is growing, mainly owing to the spread of HIV in

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