PUBLIC HEALTH

Toward an HIV vaccine: A scientific journey

Different strategies are coming together to provide insights for an effective HIV vaccine

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In the face of a global pandemic, the search for an effective vaccine against the human immunodeficiency virus (HIV) remains an urgent priority. From the first HIV vaccine trials in the 1980s to the present, a tension has existed between the desire to move quickly to clinical trials to stem the spread of the epidemic and the view that research into HIV pathogenesis and host immunity were necessary predicates to and informative of vaccine design. Those advocating the first strategy—an empirical (or inductive) approach—argued that in vitro and animal studies were poorly predictive of the human response to HIV infection and that the only way to gauge vaccine efficacy was to test candidates in humans. Those advocating the second strategy—a theoretical (or deductive) approach—hoped to establish an understanding of the immune response to natural infection and to find ways to recapitulate and enhance that response through vaccination. Today, these approaches are coalescing into concomitant paths toward a safe and effective HIV vaccine.

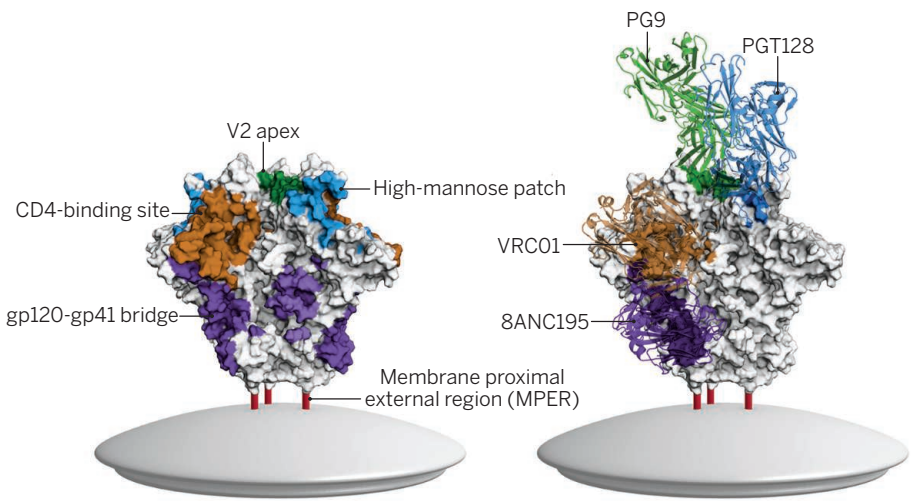
POLICY

When HIV was identified in 1983 and proven to be the causative agent of AIDS in 1984, the field of vaccinology was experiencing dramatic successes. Traditional vaccine approaches using whole pathogens, either attenuated or killed, to induce immunity paid substantial dividends in reducing the global burden of polio, measles, mumps, and other important diseases. Smallpox was eradicated, by using a relative of *Variola major* to induce protection. New technologies, such as subunit vaccines were producing impressive efficacy against hepatitis B virus. Against this backdrop, a vaccine against a novel virus such as HIV seemed to be readily attainable; now, in retrospect, this is seen as a somewhat naïve perspective.

However, even in the 1980s, many virologists deemed a vaccine using inactivated whole virus unsafe because of the possibility that poorly inactivated HIV could integrate into the host genome or revert to a pathogenic wild-type phenotype (as had been seen with an inactivated polio vaccine) (*1*). Moreover, unlike smallpox and measles, HIV invariably produced a chronic, progressive illness that was not ultimately cleared by the host immune response. Thus, the host response to natural infection did not provide a clear blueprint on which to base vaccine design. Additional challenges emerged. For example, HIV superinfection is regularly observed, which demonstrates that constant in vivo immune stimulation by replicating autologous virus fails to protect against subsequent challenges with heterologous viruses. Furthermore, the propensity of HIV for mutation is quite high among human viruses (*2*).

The first U.S. government-sponsored phase I trial of an HIV vaccine, a gp160 subunit candidate, was launched in 1987. Many similar constructs entered safety trials over the next few years, with disappointing results. Although the investigational vaccines often yielded robust antibody titers, most of the antibodies failed to neutralize in vitro. Moreover, the neutralization that was seen was against laboratory-adapted virus, not primary isolates (*3*).

This inability to induce an adequate antibody response was perplexing. Furthermore, contemporaneous studies of passive infusion of HIV-specific immune globulin into nonhuman primates (NHPs) failed to protect against HIV or related viruses (*4*). Thus, broadly neutralizing antibodies were difficult to induce, and HIV-specific antibodies in general were apparently ineffective. Famed vaccinologist Maurice Hilleman voiced the frustration best, stating: "I don't know of anything like this. This is the first time in vaccine development that neutralizing antibodies don't seem to amount to much" (*5*).



HIV trimer with neutralizing epitopes and selected bNAbs. Crystal structure of the HIV-1 trimer in its closed state, labeled with binding sites for broadly-neutralizing antibodies (left), and with antigen-binding fragments of selected bNAbs (right). Crystal structures of membrane-proximal external region (MPER) antibodies have not been determined in the trimer context, and therefore are not pictured.

Despite such challenges, the growing HIV pandemic created intense pressure to expedite vaccine development. Some prominent scientists advocated large-scale empiric trials (*6*). Advocates for basic research studies questioned the utility of clinical trials when fundamental questions remained unanswered. This debate came to a head in 1994, when a panel convened by the National Institute of Allergy and Infectious Diseases (NIAID) considered the merits of phase III trials for two vaccine candidates based on a recombinant HIV envelope protein platform (*6*). Citing limited immune responses in early-stage trials, concerns about recruitment for larger future studies, and cost, the panel recommended against government sponsorship of such trials. Nonetheless, trials of one candidate moved forward with industry support: VaxGen's AIDSVAX

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gp120. Unfortunately, two phase III studies that used the envelope from different clades of HIV in men who have sex with men and injection drug users, respectively, failed to demonstrate protection (*7*, *8*).

Given the disappointment associated with B cell–targeted vaccines (designed to induce antibodies), many HIV vaccinologists turned to the induction of T cell responses against HIV. These vaccines were not intended to prevent acquisition of virus; rather, they were designed to lower the viral set point (or the level of plasma virus at which HIV settles after acute infection in the absence of therapy), which would mitigate, somewhat, the deleterious effects of the virus. Given favorable immunogenicity in animal studies and early-stage human trials, adenovirus type 5–vectored (Ad5) candidates garnered interest. Unfortunately, two phase IIb trials (STEP and Phambili) testing a candidate that expressed HIV *gag, pol*, and *nef* were halted after interim Data and Safety Monitoring Board reviews revealed poor efficacy (*9*). In fact, the trials demonstrated evidence of increased risk of viral acquisition among vaccine recipients as compared with placebo. A scientific symposium reviewing those data concluded that vaccine-related immune activation might have led to increased susceptibility to infection (*10*).

Although certain investigators pursued Ad5 vectors, others proposed combining a pox virus–vectored gp120 *env* prime with a gp120 protein boost, two candidates that alone did not induce potentially protective immunity. The RV144 trial stirred controversy in the scientific field, once again pitting empirical approaches against theoretical approaches. In the end, advocates of empiricism pushed ahead and the trial proceeded. To the surprise of many, the trial demonstrated a 31% reduction in HIV acquisition (*11*). Investigators now seek to improve on RV144, hoping to increase the durability, potency, and breadth of responses. A range of trials under the auspices of the Pox-Protein Public-Private Partnership (P5) are examining the impact of alternate priming and dosing schedules, as well as various vectors and adjuvants (*12*). Several teams are also studying the immune responses of RV144 participants, looking for markers predictive of efficacy. In this regard, attention has centered on an immunoglobulin G response against the V_1V_2 loop of the HIV envelope, which appeared particularly prominent as a correlate of decreased HIV transmission risk in RV144 (*13*).

Concomitantly, those pursuing a theoretical approach made a series of discoveries related to broadly neutralizing antibodies (bNAbs). Investigators found that ~20% of infected individuals develop antibodies capable of neutralizing a wide range of viral isolates; however, development of this breadth of response typically occurred only with continuous viremia after 2 to 4 years of infection. The time lapse is largely explained by the evolutionary hurdles that bNAbs must surmount. Some are autoreactive and clonally deleted to prevent the development of autoimmunity; some have specialized structures, such as long complementarity-determining regions that are rare among germline B cells; and others require a high degree of somatic hypermutation (the process by which B cell receptors adapt to produce higher-affinity antibodies) (*14*). With careful study of existing cohorts, a range of bNAbs has been characterized (see the figure).

"...human in vivo studies have shown decreased levels of circulating virus after administration of bNAbs."

Although bNAbs provide an intriguing model for vaccine development, their efficacy in preventing infection is as yet unproven in humans. Passive transfer studies using bNAbs in NHPs, have demonstrated prevention of viral acquisition among uninfected animals (*15*) and suppression of viremia among infected animals (*16*, *17*). Ex vivo studies have shown marked suppression of expression of virus from HIV viral reservoirs by bNAbs (as measured by in vitro replication of reservoir virus in $CD4^+$ T cells obtained from infected individuals receiving antiretroviral therapy) (*18*). In addition, human in vivo studies have shown decreased levels of circulating virus after administration of bNAbs (*19*). Other approaches to the utilization of preformed bNAbs are increasing the half-life of the antibodies and vector-based delivery. Primary prevention studies in humans are imminent.

Although passive transfer studies are instructive, ultimately a pragmatic vaccine approach will likely require induction of bNAbs by active immunization. Several recent findings have advanced the field. First, the epitopes to which the bNAbs bind have been characterized in detail; in fact, the envelope trimer itself has been stabilized in a soluble form and might be a suitable immunogen (see the figure) (*20*–*24*). In addition, B cell lineages for bNAbs have been defined and the cellular evolutionary process necessary to create such antibodies has been characterized. Some of these lineages show minimal mutation, although these antibodies display modest breadth of neutralization. Combinations of modestly mutated antibodies, however, could offer an alternative means to achieve breadth. In addition, combinations of antibodies targeting different binding sites (neutralizing epitopes) could impede development of resistance.

Even with these approaches, however, B cells will likely require sequential stimulation by different immunogens in order to drive the B cell lineage to express broadly neutralizing antibodies (*25*).

Alternative approaches are also being pursued. One promising method uses live rhesus cytomegalovirus vectors encoding simian immunodeficiency virus (SIV) genes *gag*, *pol*, *rev*, *nef*, *tat*, and *env*. The strategy does not prevent initial infection but provides a powerful stimulation of SIV-specific $CD8^+$ T lymphocytes that control and eliminate virus in 50% of animals (*26*).

These bNAb and $CD8^+$ T cell–based approaches remain at early stages, as they move from theory toward regimen design. Simultaneously, research stemming from the RV144 trial could improve upon the modest efficacy already seen. Ultimately, the theoretical and empirical approaches will coalesce, converging upon the effective vaccine so critically needed to end HIV transmission worldwide. ■

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