HHS Public Access

Author manuscript

Science. Author manuscript; available in PMC 2015 June 25.

Published in final edited form as:

Science. 2014 July 11; 345(6193): 167–168. doi:10.1126/science.1256526.

A critical question for HIV vaccine development: Which antibodies to induce?

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Abstract

A vaccine against HIV-1 must prevent infection against genetically diverse virus strains. Two approaches are currently being pursued to elicit antibody-mediated protection: vaccines that induce potent and broadly reactive neutralizing antibodies (bnAbs) or vaccines that induce "conventional antibodies," which are less potent and broadly neutralizing in comparison. Although bnAbs may provide the greatest level of protection, their structural and genetic characteristics make their elicitation through vaccination a major challenge. In contrast, conventional HIV-1 antibodies have been induced by vaccination and correlated with reduced HIV-1 infection in a phase III vaccine trial. Here, I present evidence that both approaches should be pursued with equal vigor.

A major goal of HIV vaccine design is to elicit a protective immune response mediated primarily by antibodies (Abs). This is particularly challenging in the case of HIV because the virus mutates rapidly, leading to many viral subgroups. A successful vaccine would therefore need to elicit Abs that are able to recognize a range of genetically diverse strains. Although HIV infection induces a vigorous Ab response in nearly all infected individuals, only ~1% produce Abs that can neutralize a wide range of HIV subtype Abs (1), and only ~10 to 25% of HIV-infected subjects produce cross-neutralizing Ab responses with moderate breadth and potency. The majority of infected individuals make "conventional Abs" that have limited breadth and potency in standard neutralization assays (2, 3). Many vaccine candidates tested to date produce these conventional Abs, but none have yet induced broadly reactive neutralizing antibodies (bnAbs). A comparison of some of the characteristics of conventional and bnAbs is shown in Table 1. A great deal of effort and funding currently supports the design of vaccine regimens that will elicit these exceptional bnAbs, because it is thought that such a vaccine would induce high levels of protection. However, extensive data suggest that vaccine-induced conventional Abs may provide a level of protection that could have a considerable impact on the epidemic.

Many factors contribute to the rarity of bnAbs in patients and the difficulty of inducing them by vaccination: (i) the epitopes they target are poorly immunogenic; (ii) bnAbs are characterized by extensive somatic hypermutation (4, 5); (iii) bnAbs are often polyreactive and/or autoreactive (6, 7); (iv) bnAbs display unusual structural characteristics in their antigen binding region (8–10); and (v) bnAbs take months to years to evolve in response to

virus evolution within the host (11–13). Since their discovery, a critical question for HIV vaccine development has been whether to design vaccines that stimulate these exceptional bnAbs. This approach would represent a departure from previous vaccine strategies that elicit conventional Abs—i.e., Abs that are normally induced by infection or vaccines that are not highly mutated from germline immunoglobulin genes and do not display unusual structural or genetic characteristics (14, 15). Therefore, the induction of exceptional bnAbs through vaccination is a new and major challenge. Although this approach has not been attempted previously, there is a general consensus that a set of immunogens will be needed to "guide" the immune system through the complex process of affinity maturation (16). This lineage-based approach to vaccine design is based on the hypothesis that it will be necessary to initiate immunization with an antigen that stimulates an appropriate germ-line immunoglobulin gene and then boost with a series of immunogens recapitulating the evolution of the virus as it escapes from Ab-mediated immune pressure, thus steering B cell differentiation through mutational steps that are required in vivo for the production of bnAbs. Targeting of more than one epitope will likely be needed, given the mutation rate of HIV. Notably, there are currently no data demonstrating that this approach is feasible.

Simultaneously, there is a growing literature describing rationally designed vaccines that induce protective conventional Abs. This approach depends on identification of the epitopes recognized by protective conventional monoclonal Abs (mAbs) and the subsequent use of structural, bioinformatics, and molecular methods to design immunogens that will induce polyclonal Abs similar to the originally identified protective mAbs. This approach has led to the design of vaccine candidates against several pathogens (17, 18), and epitope-scaffold immunogens have already been shown to successfully induce conventional crossclade neutralizing Abs against HIV (19–21). Initially, conventional Abs were shown to be protective against HIV by demonstrating that chimpanzees could be protected by infusing the challenged animals with immunoglobulin G (IgG) from an HIV-infected chimpanzee (22). Subsequently, human mAbs, representing conventional Abs made by most chronically infected individuals, were shown to neutralize multiple lab-adapted and/or primary isolates in vitro (23–29), and two of these mAbs, specific for the third variable region (V3) of the HIV gp120 envelope glycoprotein, provided protection against heterologous HIV strains in relevant animal models (30, 31). More than 90% of chronically infected HIV+ subjects make similar V3 Abs (32).

Unlike in many viral infections, HIV-infected individuals can become "superinfected" with a second HIV strain. This might suggest that Abs that develop in HIV patients are not protective. However, several studies suggest that Abs made in HIV-infected individuals do affect the rate of superinfection. For instance, superinfected individuals had lower levels of cross-protective and autologous neutralizing Abs than the nonsuperinfected case-controls (33, 34). Although some studies are contradictory to these (35, 36), and other data suggest that cytotoxic T lymphocytes are capable of imposing selective pressure on HIV (37), results from a recent adequately powered study demonstrated that a first HIV infection reduces the risk of a subsequent infection by ~50% in high-risk Kenyan women (38). Additional evidence for the protective role of Abs comes from studies of maternal-fetal transmission. Although not replicated universally, several studies showed lower transmission rates from

infected pregnant women with high Ab titers or with high-affinity/ avidity Abs to portions of the HIV-1 envelope glycoproteins (39).

These studies complement those showing that Abs commonly exert strong and rapid immune pressure on viruses in vivo. For instance, when serial plasma samples from patients with primary HIV infection were examined for neutralizing activity against autologous viruses, the plasma virus continually and rapidly evolved to escape neutralization (40, 41). Moreover, as early as 2 weeks after seroconversion, very low titers of neutralizing Abs select for escape viruses in acutely infected patients (42). These studies indicate that Abs produced in the majority of patients can eliminate viruses bearing cognate antigenic determinants. If a vaccine were to produce a similar conventional polyclonal Ab response in uninfected individuals, it may be possible that most or all of an incoming virus inoculum could be eliminated by these Abs.

Additional support for the role of Abs in protection comes from the RV144 clinical vaccine trial in which subjects received four doses of a recombinant HIV–avian pox virus and two doses of gp120 proteins from two different HIV subtypes. An estimated vaccine efficacy of 31% was noted at 3 years of follow-up (43) and 60% at 1 year after immunization (44). Higher levels of IgG Abs specific for epitopes in the second variable loop (V2) and V3 region of gp120—Abs commonly found in HIV-infected individuals (32, 45, 46)—were significantly associated with the reduced rate of infection (47–49). Several independent studies have confirmed that Abs to V2 and V3 correlated with the reduced rate of infection noted in RV144 vaccine recipients (48, 50–52).

There are, therefore, many lines of evidence that indicate that despite their reduced potency and breadth as compared to bnAbs, conventional Abs made by the majority of HIV-infected individuals may be able to prevent infection. Moreover, conventional Abs display additive and synergistic activity (53–56) that may explain the ability of polyclonal conventional Ab responses to reduce the risk of HIV-1 infection.

At this point, there are no definitive data demonstrating that either vaccine-induced conventional or exceptional Abs will result in protection from HIV infection in humans. The clearest indication comes from the data emanating from the RV144 vaccine trial (47, 48, 50–52), but, strong as these data are, there is as yet no absolute proof of the hypothesis that conventional Abs are protective in humans. Nor do such data exist for bnAbs. In addition, it is possible that vaccine-induced conventional Abs will need to be induced at higher titers than bnAbs and may not protect against as many strains. The data do suggest that conventional Abs may be more feasible to induce, whereas bnAbs may ultimately be more effective. Therefore, both approaches have their strengths and weaknesses, and both must be pursued with equal vigor.

Acknowledgments

This work was sponsored by funds from the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, and grants from the National Institutes of Health (P01 AI 100151 and R01 HL59725).

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Table 1

Comparison of conventional and exceptional broadly neutralizing antibodies.

Characteristics	Conventional antibodies	Exceptional broadly neutralizing antibodies
Neutralizing potency in vitro		
Tier 1 pseudoviruses	<0.02 to >50 ug/ml (57) <0.04 to 26 ug/ml (58)	≪1 ug/ml
Tier 2 pseudoviruses	0.6 to >50 ug/ml (57) 15 to >50 ug/ml (58)	0.02 to 27 ug/ml (62–64)
Percentage VH chain somatic hypermutation from germline	1 to 12% (59, 60)	17 to 48% (16, 62, 65)
Breadth of neutralization		
Tier 1 pseudoviruses	29 to 42% (57); 50 to 90% (26); 7 to 50% (58)	100%
Tier 2 pseudoviruses	1 to 4% (57) 0 to 9% (58)	72 to 100% (62, 65–67)
Vaccine strategy required	Prime (ALVAC) + Boost (gp120) (43) Prime (DNA or pox vector) + Boost (gp120 protein) or recombinant protein alone (61) Prime (DNA) + Boost (epitope-scaffold protein immunogen) (20)	Starting with a bnAb, infer the full antibody lineage, including the unmutated ancestor and early intermediates and use their sequences as templates for the design of HIV-1 immunogens with high-affinity binding to design sequential immunogens to guide the Ab response to produce bnAbs.
Prevalence in infection	Present in virtually all infected individuals	1 to 25% (1–3)
Time needed to evolve	Weeks to months (41, 42)	Months to years (11, 12)