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Is developing an HIV-1 vaccine possible?

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Abstract

Purpose of review—This review discusses select recent data that suggest that indeed it is possible to make a clinically useful preventive vaccine for HIV-1 and outlines some of the remaining obstacles that stand in the way of success.

Recent findings—Passive protection studies, with broad neutralizing antibodies for mucosal simian-HIV challenges, in nonhuman primates have suggested that lower doses of neutralizing antibodies than previously thought may be effective in preventing HIV-1 infection. The use of recombinant antibody technology coupled with the ability to culture single memory B cells has yielded new broad neutralizing antibodies and new targets for vaccine design. The success of the RV144 Thai HIV-1 efficacy trials with a replication-defective recombinant canarypox vector (ALVAC)/gp120 prime, clade B/E recombinant gp120 protein boost showing 31% efficacy has given hope that indeed a protective HIV-1 vaccine can be made.

Summary—Recent data in the last year have provided new hope that a clinically useful preventive HIV-1 vaccine can potentially be made. The path forward will require development of improved immunogens, understanding the correlates of protection to HIV-1, and development of immunogens to induce antibodies that can prevent the initial stages of HIV-1 infection at mucosal sites, in order to improve on the RV144 trial results.

Keywords

antibodies; trials; vaccine

Introduction

Although the RV144 Thai trial represents a new hope for the field that a preventive HIV-1 vaccine can be made, 31% vaccine efficacy is not sufficient for widespread deployment of the current RV144 immunogen, nor did the protective effect last sufficiently long to be optimally useful. Moreover, many questions remain regarding the path for follow up of the

RV144 trial. We review recent progress in the AIDS vaccine field that bear on the prospects and feasibility of ultimately developing a clinically useful vaccine to prevent HIV-1 infection.

Overview

The failure of the first two antibody-based vaccines of clade B gp120 s (VAX004) [1] and clades B and E gp120 s (VAX003) [2], coupled with the failure of the T-cell vaccine based on the recombinant type 5 adenovirus vector (Step) trial [3] induced a degree of skepticism in the HIV-1 vaccine development field that a vaccine could be made. With the outcome of the Step trial in which there not only was no efficacy, but also a trend toward vaccine-induced acquisition of HIV-1, the field reassessed the state of research once again and redoubled the commitment to basic research [4]. Studies of the earliest viral and immunologic events following HIV-1 transmission have demonstrated that for a preventive vaccine to be successful, protective immunity will need to be present before infection [reviewed in [5]].

Now that the recent results of the RV144 Thai efficacy trial [canarypox (ALVAC) prime with an AE_01 recombinant gp120 membrane anchored insert followed by AIDSVAX gp120 B/E boost] resulted in 31% efficacy in the RV144 trial in heterosexual individuals [6•], the field is hopeful that the RV144 results signify a proof of concept that indeed a vaccine for HIV-1 is possible. The gp120 B/E boost proteins are the same immunogen that showed no efficacy in high-risk intravenous drug users in Thailand [2], raising the question of whether it was the ALVAC prime that made the difference or the heterosexual (presumed lower-risk) population which the RV144 trial utilized [7]. Because CD8 T cells responses were low in phase II trials utilizing the RV144 vaccine [8] and there was no impact on viral load, and the protective efficacy declined over time, the notion is that the correlate of protection in RV144 vaccines will either be traditional neutralizing antibodies or virus inhibitory antibodies capable of blocking HIV-1 transmission.

Even if the results of the Thai trial can be recapitulated and the correlate found to be an easy-to-elicited antibody response, the durability of this anti-HIV antibody response and variability of antibody response among individuals is still an issue. Thus, T cell help and engaging the full arsenal of innate, cellular and humoral responses to provide a durable humoral response to block transmission as well as a robust cellular response to limit virus replication for those that do become infected will be critical. Because the level of donor plasma viral load correlates with risk of HIV-1 transmission, reducing virus replication after transmission will yield fewer transmission events at the population level, with the overall effect of decreasing the number of new HIV-1 infections. Cellular immunity is important both for direct antiviral functions to decrease virus replication and also for providing help for a durable and effective humoral response. Thus, it is critical for the field to consider all components of adaptive and innate immune responses as synergistic immune responses that should be harnessed for an optimally effective vaccine. Moreover, detailed studies of how each of these immune responses are induced and maintained at mucosal surfaces so that they can be preexisting to prevent or extinguish transmitted/founder virus infection are needed.

Protection trials with neutralizing antibodies and in-vitro mucosal protection assays

With high dose intravenous challenges of simian-HIVs (SHIVs), the levels of neutralizing antibody needed have been high, but recent studies with mucosal SHIV challenges have shown that rather modest levels of neutralizing activity can protect. Hessel *et al.* [9] demonstrated that a serum titer of 1 : 1 in macaques after infusion of the broad neutralizing

antibody 2G12 was able to protect from intravaginal SHIV challenge. The same group had shown that high dose SHIV vaginal challenge required relatively high levels of serum neutralizing antibody titers to protect following infusion of the broad neutralizing antibody, 1b12, and that Fc receptor interactions were important for 1b12 protection [10]. They have now gone on to show that ~10 fold less serum titers of neutralizing antibodies after 1b12 infusion can protect against a low-dose SHIV vaginal challenge [11••]. Recently, Hessel *et al.* [12] have also shown that clinically relevant levels of the broad neutralizing antibodies 2F5 and 4E10 could also protect against intrarectal challenge with SHIV. The level of 90% neutralization at low serum dilutions is a benchmark for levels to be attained by new vaccine candidates [13,14]. The VAX003 and VAX004 failed efficacy trials did not achieve these neutralizing antibody levels [14]. Thus, one set of good news from the last year is that broad neutralizing antibodies, if able to be induced, can protect against SHIV challenge at levels that are clinically relevant.

Candidates for protective mucosal antibodies could be traditional neutralizing antibodies that neutralize HIV-1 in peripheral blood mononuclear cell infection assays or neutralize HIV-1 pseudotyped viruses in reporter cell-based assays. Alternatively, protective antibodies could be antibodies that mediate antibody dependent cellular cytotoxicity (ADCC) or antibody dependent cell-mediated virus inhibition (ADCVI) [15,16]. Protective antibodies could also be multimeric immunoglobulin A (IgA) or immunoglobulin M (IgM) antibodies that could block virus traversing mucosal surfaces. Presently it is not clear whether mucosal induction of dimeric IgA anti-HIV-1 antibodies will be needed for protection, nor is it known if the RV144 trial immunogens induced mucosal dimeric IgA anti-gp120. In this regard, Tudor *et al.* [17] constructed HIV-1 gp41 membrane proximal external region IgA antibodies from phage displayed libraries of exposed and uninfected individuals and demonstrated their ability to block HIV-1 epithelial cell transcytosis *in vitro*. Shen *et al.* [18] used CCR5-expressing epithelial cells *in vitro* as a model of free virus transcytosing across colonic epithelium and showed both a neutralizing gp41 monoclonal antibody (mAb) (2F5) as well as a gp41 immunodominant region nonneutralizing mAb (7B2) blocked cell-free HIV-1 transcytosis through rectal mucosal cells.

A number of vaccine studies have reported degrees of antibody-mediated protection via mucosal immunizations in either SHIV or simian immunodeficiency virus (SIV) challenge [reviewed in [19,20]]. One example reported antibody mediated complete protection against homologous mucosal SHIV challenge of macaques immunized with alphavirus replicon particles and boosted with trimeric envelope (Env) glycoprotein [21]. A significant association was found between the titer of neutralizing and binding antibodies induced as well as antibody avidity with protection from infection. Another example showed that intranasal/oral immunization with replication competent rAd5 partially protected against homologous SIV challenge and induced mucosal IgA anti-Env responses that blocked virus transcytosis across epithelial cells [22].

New broadly neutralizing antibodies and new envelope vaccine targets

Recent progress in mAb technology and the application of recombinant human antibody generation to the problem of why broadly neutralizing antibodies are not routinely made have provided new reagents, new Env targets and new enthusiasm for the prospects of learning how to induce broad neutralizing antibodies to HIV-1 by a vaccine. Although previously thought to be quite rare, recent surveys have suggested the prevalence of broad neutralizing antibodies to range between 5 and 20% depending on the criteria for breadth [23]. However, it has become clear that when breadth does develop, it takes a considerable period of time after transmission for broadly neutralizing antibodies to develop [23-25]. The reason for this delay in onset of production of broadly neutralizing antibodies is not clear,

but perhaps may involved genetic predispositions to make broadly neutralizing antibodies coupled with gradual onset of perturbations of immune tolerance that occurs with progressive HIV-1 infection [[24], reviewed in [26,27]].

The CD4-binding site of the HIV gp120 component of Env is one of the more conserved Env regions. Recent structural studies of crystals of poorly neutralizing CD4-binding site antibodies versus the potent neutralizing antibody, 1b12, revealed the structural basis of immune evasion of HIV at the site of gp120 binding to CD4, and demonstrated the need for precise targeting of this region by potent neutralizing antibodies [28].

In a recent study, recombinant human antibody technology was used to probe the repertoire of individuals with broad neutralizing antibodies by sorting, with gp140 oligomers, and found no single specificity of neutralizing antibodies [29••]. Rather, the notion was put forth that a composite of different species of anti-Env antibodies contributed to neutralization breadth [29••].

For neutralization, antibodies must bind the native trimer on the virion or virus-infected cells. It has long been known that the monomeric gp120 tended to give rise to either type-specific or isolate-specific neutralizing antibodies or to nonneutralizing antibodies. Quarternary Env epitopes or those epitopes that are only expressed on the Env trimer would be candidates for inducing neutralization breadth, although the initial mAbs that bound to quaternary Env epitopes were quite narrow in neutralization activity [30]. In contrast to the study above sorting B cells with gp140 oligomers, Walker *et al.* [31•] used single cell cultures of memory B cells and high-through-put neutralization screens to find two new human mAbs, PG9 and PG16, with striking neutralizing breadth that bind to a quaternary epitope involving the V2 and V3 loops of gp120. In addition, Wu *et al.* [32•] have now used a rationally designed mimic of the Env CD4-binding site to identify new mAbs (VRC01 and VRC02) that also have striking breadth of neutralization for multiple HIV-1 clades. Thus, these studies show that very broad neutralizing antibodies can be made, but as with the first generation of human broad neutralizing antibodies, these latter new specificities are not routinely induced in HIV-1 infection or by current vaccine candidates.

Mechanisms of prevention of induction of broad neutralizing antibodies

HIV-1 has evolved a myriad of ways to evade immune responses, and in particular, how to protect conserved Env regions [reviewed in [33]]. Many of the broad neutralizing antibodies have long HCDR3 regions, are polyreactive for non-HIV antigens, and the hypothesis has been raised that some broad neutralizing antibodies may be controlled or limited by tolerance mechanisms [34,35]. Direct evidence has been published for immunoregulatory and/or tolerance control for antibodies that bind to gp41 neutralizing epitopes near the virion membrane. First, several groups found that mutations in the portion of the HCDR3 of the 2F5 [36] and 4E10 [36-38] broad neutralizing antibodies were able to abrogate neutralization, but did not interfere with antibody binding to gp41, demonstrating the need for virion (self) lipid binding for the mAbs to neutralize HIV. Verkoczy *et al.* [39] have produced 2F5 variable heavy (VH) homologous recombinant mice and demonstrated that the 2F5VH is sufficiently autoreactive to invoke both clonal deletional and other peripheral tolerance mechanisms in the 2F5 VH knock-in mice. Thus, for some broad neutralizing antibodies, probing peripheral tolerance mechanisms as well as design of immunogens may be instructive for vaccine design. The newer broad neutralizing antibodies, PG9, PG16 and VRC01, while heavily somatically mutated, are not polyreactive ([31•,32•], Haynes BF and Mascola JR, unpublished), yet these antibodies are not commonly made. Studies into the structural basis of lack of responsiveness as well as deciphering pathways of affinity maturation will likely be important to unraveling how these antibodies can be induced and

whether they can be induced in the general population. In particular, definition of the B cells of origin and reconstruction of the B cell clonal lineage pathways that eventuate in neutralization breadth in individuals that make broad neutralizing antibodies is important. All these caveats notwithstanding, this last year has seen considerable progress in understanding why some types of antibodies are not made and in discovery of new targets of broad neutralizing antibodies.

The RV144 Thai trial

Clearly the defining event of the last year in the HIV-1 vaccine field was the announcement of the positive results of the RV144 Thai HIV-1 vaccine trial [6•]. This ALVAC prime, B/E Env gp120 boost provided 31% efficacy, but with several caveats. First, although not powered for evaluation at the 6-month period just after the last vaccine dose, there was a trend to higher efficacy early on that decreased after 6 months. Second, there was no effect on postinfection viral load in those that received the vaccine. Third, there was a trend to more protection in individuals categorized as lower risk than in those in the higher risk group [7], with the proviso that the incidences of infection were not high – 0.227/100 person years in the lowest risk group and 0.364/100 person years in the highest risk group. Thus, the characteristics of protection have suggested that the correlate of protection may be some type of a short-lived antibody response and the search is now on to define the antibodies that might be present in protected vaccines, but not in those vaccines that became infected. Such antibodies could be one or a combination of traditional neutralizing antibodies, antibodies that mediate ADCC or ADCVI [15,16], antibodies that mediate other Fc receptor mediated antiviral activities such as induction of β -chemokines [40], or IgM or IgA antibodies that inhibit virus movement across mucosal barriers. Commonly made antibodies such as CD4 inducible (CD4i) as well as other types of binding antibodies are being considered [41].

Other considerations for correlates of protective immunity in RV144 are CD8 T-cell responses (though these responses were infrequent in phase I/II trials and in the initial immunogenicity data from RV144) and CD4 T-cell responses that undoubtedly are critical for robust antibody responses. With recent reports of natural killer (NK) cell memory induced by certain infections [42] and the potential for β -chemokine inhibition of HIV-1 [40], innate mechanisms are being studied as well. Genetic studies are being evaluated to follow up on observations of the role of Fc receptor polymorphisms and other genetic factors that might play a role in salutary immune responses [43,44]. Finally, antibodies capable of inhibiting HIV-1 envelope interactions with integrin alpha 4 beta 7 on mucosal CD4 T cells are being considered [45,46].

The way forward

Considerable discussion is ongoing regarding the next steps in HIV-1 vaccine development in the wake of the RV144 Thai trial. Clearly the first step is to determine if study of RV144 trial clinical samples can provide insights into what induced immune responses contributed to protection. Because the population in the RV144 trial was at risk primarily by mucosal transmission routes, yet there are no mucosal samples from the trial, new studies are underway to obtain mucosal samples from individuals immunized with ALVAC prime, B/E gp120 boost vaccine. New immunogen design for overcoming T-cell diversity and improving the anti-HIV-1 potency of induced antibodies is important, and thus the search has intensified for better T cell and B cell immunogens. For overcoming T-cell diversity, a number of strategies show promise including the mosaic immunogen design [47-49], as well as vaccines that focus on conserved T-cell epitopes [50,51]. The ability to harness innate NK cell memory is a tantalizing notion, but requires more basic research on the phenomenon in

the context of induced responses to retroviral antigens before practical translation to vaccine studies can be considered.

B-cell immunogen designs will follow closely on the work to define correlates of immunity in the RV144 trial. If a commonly made type of antibody is found that can interdict HIV-1 infection at an early stage of the transmission event, then that will be critical information that will drive immunogen design. To find those types of antibodies and design immunogens to induce them, it is important to use those assays that are capable of measuring virus movement across mucosal barriers and antibody role in blocking transmission. If protective antibody candidates are found, it will be key to use recombinant human antibody technologies such as have been used to isolate new broad neutralizing antibodies to isolate human mAbs reflective of protection in in-vitro assays, and to test these candidate mAbs in passive protection trials *in vivo*. The development of pathogenic R5 SHIVs for these studies is important. Future challenge studies of vaccine-immunized animals should use SHIVs or SIVs that are heterologous to the vaccine being tested. The rarer broadly neutralizing antibodies will be more difficult to induce, whether because of interfering immuno-regulatory and tolerance controls, because of the rarity of complex and extensive somatic mutations, or because of structural constraints of Env immunogens. Nonetheless, continued research into the structural nature of B cell recognition of Env and the maturational pathways of responding B cells and their immunoregulatory control is key to pursue.

Conclusion

This has been an important and exciting year in HIV-1 vaccine development. The field has made remarkable progress in working together in collaborative teams and sharing of data. The positive results of the RV144 trial coupled with multiple insights into new avenues of T, B and NK cell biology as they pertain to HIV-1, all have energized the field. Focus now should be on the earliest events involved in HIV-1 and SIV transmission at mucosal sites, and on the types of mucosal innate, T and B cell responses that can be present before the transmission event or can arise within hours of transmission and prevent or extinguish the HIV-1 transmitted/founder virus. Although formidable roadblocks and tasks remain, the prospects for successful development of a well tolerated and effective HIV-1 vaccine are promising. What is needed is continued intense and coordinated basic, and translational clinical research with iterative testing of promising concepts in both nonhuman primates and human trials.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 453–454).

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