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New Approaches to HIV Vaccine Development

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Abstract

Development of a safe and effective vaccine for HIV is a major global priority. However, to date, efforts to design an HIV vaccine with methods used for development of other successful viral vaccines have not succeeded due to HIV diversity, HIV integration into the host genome, and ability of HIV to consistently evade anti-viral immune responses. Recent success in isolation of potent broadly neutralizing antibodies (bnAbs), discovery of mechanisms of bnAb induction, and in discovery of atypical mechanisms of CD8 T cell killing of HIV-infected cells, have opened new avenues for strategies for HIV vaccine design.

Introduction

T cell protective immunity to HIV

The overall immune correlates of protection from HIV are poorly understood. Moreover, unlike successful vaccines for non-integrating viruses such as measles, a successful HIV vaccine must either completely prevent infection, or eliminate the first round of infected CD4 T cells before the latent pool of HIV-infected cells is established (1). Thus, an effective HIV vaccine requires high levels of protective immunity at the time of virus contact with the host, and cannot rely on memory immune responses to occur (1). CD8 T cells can effectively kill HIV-infected T cells, but in most cases of acute HIV infection, the virus rapidly escapes (2). Rare elite controllers of HIV viral load are frequently HLA B57 or B27 and control viral load levels by CD8 cytolytic T lymphocytes (CTL) responses (3). Recently Hansen et al. have reported that vaccination of rhesus macaques with an attenuated rhesus cytomegalovirus (rhCMV) containing simian immunodeficiency virus (SIV) genes resulted in eradication of infection in ~50% of rhCMV-vaccinated SIV-challenged rhesus macaques (4, 5). The rhCMV-SIV gene vector induced recognition of more CTL epitopes than conventional vectors, and remarkably, induced atypical CD8 T cell killing that either recognized HIV antigens in the context of MHC class II molecules, or in the context of HLA E molecules (4). That 50% of macaques are protected with attenuated CMV vaccination, yet the CMV vaccine had no effect on viral load control in the 50% that are not protected, is

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perplexing. An all or none pattern of protection is usual for CD8 T cell mediated antiviral immunity, and possibly suggests genetic or other host factors in regulating protection. Nonetheless, the hypothesis is that in 50% of macaques, attenuated rhCMV vector induced atypical CD8 T cell responses from which SIV was not able to escape. Thus, as an immune correlate, anti-HIV CD8 CTL activity is capable of eliminating virus-infected T cells in the setting of vaccination with attenuated rhCMV (2), but in the setting of acute HIV infection, the transmitted/founder virus usually escapes from CD8 T cell control (1).

B cell protective immunity to HIV

The RV144 ALVAC/AIDSVAX B/E® vaccine trial induced an estimated 31% vaccine efficacy (6). An immune correlates analysis demonstrated that antibodies to the second variable (V2) loop of gp120 correlated with decreased transmission risk (7), and a viral molecular sieve analysis demonstrated a key site of immune pressure was at gp120 V2 amino acid K169 (8). While the RV144 vaccine induced no neutralization of HIV primary isolates, the vaccine did induce V2 antibodies that bound to the surface of primary isolate-infected CD4 T cells and mediated antibody dependent cellular cytotoxicity (ADCC) of HIV-infected T cells (9, 10). Thus, one current hypothesis is that the correlate of protection in the RV144 vaccine trial was ADCC-mediated decrease in HIV transmission (7, 11, 12).

A major question in HIV vaccinology is why does vaccination with HIV envelope not induce bnAbs? A recent study has demonstrated that up to 50% of HIV-infected individuals will make cross-reactive antibodies that neutralize 50% of HIV primary strains (13). However, when bnAbs do develop in HIV infection, they only occur after 2–4 years of infection (14, 15). In contrast, no vaccine immunizations to date have induced high levels of bnAbs. BnAbs are targeted to one of 5 conserved sites on the HIV Env trimer: the CD4 binding site, the membrane proximal gp41 region, the V3-glycan site, the V1V2-glycan site and gp41-gp120 bridging regions (Figure 1) (16, 17). Each of these sites is protected by surrounding glycans, and each one of these sites is restricted in access, such that relatively few antibody variable heavy (V_HDJ_H) and variable light (VL) combinations may be used to bind these Env sites. Examples of restricted V_HDJ_H/VL usage is the use of VH1-2 paired with a 5 aa VL complementarity determining region 3 (LCDR3) for the VRC01-type of CD4 binding site bnAb (18), and the use of VH1-69, V_K3-20 for 4E10-like gp41 bnAbs (19, 20). Moreover, all bnAbs have one or more unusual traits, including high levels of somatic mutations, poly- or autoreactivity, and long HCDR3 regions—all traits that can result in immune tolerance control of production of bnAbs (16, 21–27). Studies in bnAb V_HDJ_H knock-in mice have confirmed immune tolerance control for bnAbs or their unmutated common ancestors that are polyreactive (24–27). Thus, for many reasons, production of bnAbs is disfavored, and when bnAbs do develop, they are still subdominant antibody responses, with the dominant non- or restricted-neutralizing antibody responses to Env targeted to Env non-bnAb epitopes (16). However, in the simian-human immunodeficiency virus (SHIV) rhesus macaque challenge model, passive infusion of the new bnAbs can potentially protect against SHIV challenge (28). Thus, the hypothesis is that if bnAbs could be induced by a vaccine and be present at inhibitory concentrations at the time of contact with HIV, the vaccine would be broadly protective and overcome HIV diversity.

New vaccine strategies

New strategies for induction of protective CD8 T cell responses

The recent HVTN 505 DNA prime, recombinant Adenovirus Type 5 vaccine trial failed to show vaccine efficacy, and induced CD8 T cell responses in only 64% of vaccinees (29). Thus, any new T cell vaccines will need to show a greater response rate than that seen in the HVTN 505 trial. To date, among the most immunogenic vaccines for inducing HIV CD8 T cell responses in humans have been adenovirus vector prime, pox vector boost vaccines (30–33).

Efforts have been ongoing for several years to overcome HIV diversity for T cell epitope recognition by the *in silico* design of centralized consensus or mosaic HIV gene inserts based on optimizing the coverage of T cell epitopes in HIV strains in the Los Alamos HIV Sequence Database (<http://www.hiv.lanl.gov/content/sequence/HIV/mainpage.html>) (30, 34–36), or based on conserved epitopes in the vaccine (37–39). Recently, Borthwick et al. (31) have demonstrated considerable breadth and depth of CD8 T cell epitope recognition induced in a human clinical trial, using a conserved epitope vaccine in a chimpanzee adenovirus vector prime, modified vaccinia Ankara (MVA) boost regimen. As mentioned above, an attenuated rhCMV vector has induced the broadest CD8 T cell response in rhesus macaques with both typical CD8-MHC class I-restricted specificities as well as atypical CD8-MHC class II and HLA-E-restricted T cell responses (4, 5, 33). While there is concern that an attenuated CMV vector may be problematic in humans, such a human attenuated vaccine vector is under development. HLA E anti-pathogen responses also have been induced by mycobacteria (40), and it will be important to search for alternative vectors that can induce either CD8 MHC class II or HLA E anti-HIV CTL responses. It will also be of interest to determine if inclusion of the next generation of mosaic or conserved vaccines in attenuated CMV vectors can further improve the breadth of induced CD8 responses.

Follow-up of the RV144 vaccine trial

The ADCC-mediating antibodies that are the putative protective antibodies in the RV144 ALVAC/AIDSVAX B/E® vaccine trial are commonly induced, dominant antibodies, some of which are targeted against the envelope V2 loop (9–12). Thus, to improve on the 31% efficacy of the RV144 trial, a new trial for South Africa has been designed with a bivalent clade C Env gp120 vaccine with new adjuvants in combination with either ALVAC, other pox vectors, DNAs, or recombinant Adenovirus 26.

Mechanisms of induction of bnAbs

Recently, a number of very potent and broad neutralizing antibodies have been isolated from HIV-infected individuals using recombinant monoclonal antibody technology (16, 17). Locci et al. (40) have demonstrated that HIV-infected individuals that make bnAbs have a higher frequency of T follicular helper cell-phenotype CD4 T cells in blood than those who do not make bnAbs. Before the era of anti-retroviral treatment, it was noted that approximately 50% of individuals with chronic HIV infection make autoantibodies (41,42). Thus, it is reasonable to propose that one reason that bnAbs arise in ~ 50% of HIV- infected individuals but not in HIV envelope vaccinees, is due to HIV perturbation of the immune

system in infection, leading to release of immune regulatory T cell controls that normally limit bnAb production.

Over the past 20 years, a myriad of immunization studies in animals and five vaccine efficacy trials in humans using HIV envelope as an immunogen have failed to induce bnAbs (Table 1) (43). New strategies for the induction of bnAbs have come from the isolation of new bnAbs from HIV-infected individuals, from elucidation of mechanism of bnAb development, and from the realization that bnAbs are disfavored due to host immune tolerance controls (16, 17, 44). In 2012, we proposed the need for immunogens that directly targeted bnAb B cell lineages, whereby Envs that were optimized for binding to bnAb unmuted common ancestors (UCAs) and intermediate antibodies, as a strategy for providing a survival advantage to disfavored subdominant bnAb lineages (45). This strategy is termed B cell lineage immunogen design (45). Liao et al. described the co-evolution of a transmitted-founder virus with bnAb lineage development in the African CH505 individual, and demonstrated the association of virus diversification with the development of CD4 binding site bnAbs (46). In the CH505 individual, the CD4 binding site bnAb lineage first neutralized the autologous transmitted/Founder virus, and then evolved to broad neutralizing breadth (46). Although most HIV-infected individuals make autologous neutralizing antibodies, why some go on to bnAb activity and most do not is not well understood. A second co-evolution study mapping V1V2 bnAb evolution from the time of transmission to bnAb development has been reported, and demonstrated similar requirement of viral diversification for bnAb development (47). Moore et al. demonstrated the evolution of virus mutations and plasma antibodies in the generation of V3-glycan antibodies and other bnAbs (48, 49). Gao et al. (50) showed in the CH505 bnAb-producing individual the mechanism of CD4 bs bnAb induction whereby one B cell lineage (the cooperating lineage) selected viral escape mutants that were resistant to the cooperating B cell lineage antibodies, but were highly sensitive to the bnAb B cell lineage antibodies. From these antibody-virus co-evolution studies have come a series of envelope immunogens that have been selected for their ability to induce bnAb development during infection *in vivo*, and now are being developed as vaccine immunogens for use in the setting of vaccination (46, 50).

Envelope trimer immunogen designs

A major advance in the past two years in HIV research has been progress made in the characterization and structural analysis of the HIV trimer envelope glycoprotein (51–55). The most well-studied trimeric Env is from the HIV isolate envelope BG505 in a stable disulfide linked, cleaved form, called the BG505 SOSIP Env (51, 52, 55). Both cryo-electron microscopic and crystallization trimer structures have been generated, with the highest resolution at 3.5 Angstroms (Figure 1). The goal of HIV Env trimer design and stabilization is to obtain an Env immunogen that mimics the native trimer in expression of bnAb epitopes, while at the same time minimizing the expression of dominant structures that are not exposed on the surface of transmitted/founder virus Env (56). A perfect Env trimer immunogen would induce only bnAbs, and not induce non- or restricted neutralizing antibodies that cannot target transmitted/founder primary isolate virions. While a number of new trimer designs are now being tested as immunogens, several well-folded trimers have been tested, that to date, have not induced bnAbs (57–59). Thus, it is possible that

simultaneous immunizations with an optimal immunogen with a formulation of the Env in an adjuvant or other drugs that can transiently modify host tolerance controls of bnAb production may be required for induction of full bnAb maturation.

Epitope-based immunogen designs

Epitope-based immunogen design to induce bnAb B cell lineages encompasses both the concepts of B cell lineage immunogen design of targeting bnAb UCAs (45), and design of Env epitope immunogens that reflect native Env epitopes on virions while minimizing expression of non- or restricted neutralizing antibody epitopes (56). For example, for triggering the VRC01 CD4 binding site type of B cell lineage (Figure 1), Env cores (60), deglycosylated Envs (61, 62), and autologous Envs (18), have all been proposed as immunogens that can all target the VRC01 UCA or germline antibody and potentially start bnAb B cell lineage maturation. For the V1V2-glycan bnAb epitope (Figure 1), Aussedat et al. have synthesized a mimic of the V1V2-glycan bnAb epitope that selectively binds well to the UCAs of V1V2 bnAbs CH01 and PG9, and binds poorly to the linear epitope non-bnAb CH58 UCA (63, 64). Finally, for the membrane proximal region neutralization epitopes, native deglycosylation of HIV JRFL Env gp140 exposes the gp41 bnAb epitopes for UCA binding (65). A peptide-liposome has been designed that binds to the UCAs of gp41 bnAbs 2F5 and 4E10 (66, 67), and triggers anergic peripheral bnAb-producing B cells leading to plasma bnAb in 2F5 mature bnAb V_HDJ_H/V_L knock-in mice (26).

Summary

Over the last two years, much progress has been made in the discovery of atypical CD8 responses that can eliminate HIV-infected CD4 T cells, design of centralized and conserved T cell vaccines, mapping the co-evolution of bnAbs and mutating virus to define the HIV-antibody “arms race”, discovery of B cell lineage cooperation as a mechanism of bnAb induction, elucidation of the structure of the HIV Env trimer, and design of epitope-based Env immunogens for bnAb induction (Table 2). The constraints placed on the induction of HIV bnAbs by host immune controls are necessitating new approaches to inducing protective antibodies that include targeting bnAb UCAs and lineage intermediates to drive bnAb lineages (45). Whether B cell lineage immunogen design coupled with detailed knowledge of bnAb maturation pathways and mechanisms of induction, as well as trimer structure, can induce high levels of sustained plasma bnAbs remains unclear. Nonetheless, the progress that has been made have provided definitive proof of concept that bnAbs can be made in the setting of HIV infection, and provided novel insights into mechanisms of bnAb induction.

For building on the 31% efficacy seen with the ALVAC/AIDSVAX® RV144 vaccine, new gp120 immunogens and adjuvants have been designed to expand the coverage of ADCC-mediating antibodies to test the hypothesis that increase in vaccine immunogenicity can increase the vaccine efficacy seen with the initial RV144 efficacy trial. For induction of T cell control of HIV, the discovery of the 50% efficacy of the attenuated rhCMV vaccine, coupled with the development of conserved and mosaic immunogen vaccine inserts, now provides a goal of development of practical immunogens that can induce sufficient CD8 T cell immunity to clear virus-infected cells in the setting of acute infection. For induction of

antibody prevention of HIV infection, immunogen design progress utilizing new Env structures, coupled with insight into bnAb mutation mechanisms and pathways of bnAb development will undoubtedly teach immunologists an enormous amount about host-pathogen interactions in general, and hopefully will lead HIV vaccinologists to immunization regimens that will induce bnAbs. Finally, the ultimate and most protective HIV vaccine will in all likelihood require the combination of T cell-inducing and antibody-inducing vaccine candidates with appropriate adjuvant formulations, since the innate and adaptive arms of the immune system work in exquisite coordination for virus neutralization and pathogen-infected cell elimination.

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Highlights

1. New progress has been made in understanding effective protective mechanisms of anti-HIV CD8 cytolytic T lymphocytes
2. New progress has been made in understanding the mechanisms of induction of broadly reactive neutralizing antibodies.
3. New progress has been made in elucidation of the structure of the HIV envelope trimer.
4. New strategies have been developed for induction of protective T and B cell responses to HIV infection.

Figure 1. Sites of vulnerability on the HIV glycoprotein spike

The structure of a HIV pre-fusion trimer is displayed with gp120 and gp41 protomers colored in dark and light gray, respectively. The five common specificities of isolated bnAbs are: V1/V2 loop (green), the base of the V3 loop (blue), the CD4-binding site (magenta), gp120-gp41 bridging region (red), and the membrane proximal external region (orange). The MPER near the base of the Env trimer near the viral membrane has only limited structural information and is highlighted for reference (orange lines). Below each bnAb site are listed prototype antibodies that can bind at each site. Adapted with permission from Pancera et al. Nature, 2014; PDB: 4TVP.

TABLE 1**HIV VACCINE EFFICACY TRIALS**

Trial	Vaccine	Location	Result
VAX004	Bivalent Clade B gp120 in Alum	U.S., Europe	No efficacy
VAX003	Bivalent CRF_01AE/B gp120 in Alum	Thailand	No efficacy
HVTN 502 (step)	Adenovirus type 5 Clade B gag/pol/nef	U.S.	No efficacy; increased Infection in vaccinees
HVTN 503 (Phambili)	Adenovirus type 5 Clade B gag/pol/nef	South Africa	No efficacy; increased Infection in male vaccinees
RV144	ALVAC with gag/pro/Env; Bivalent CRF_01AE/B gp120s in Alum	Thailand	Estimated 31.2% vaccine efficacy at 42 months; 12 month efficacy, 60%
HVTN 505	DNAs with Clade B gag/pol/nef And DNAs with Clade A, B, C Envs Adenovirus type 5 with gag/pol and Clades A, B, and C Envs	U.S.	No efficacy

TABLE 2**Recent Advances in HIV Vaccine Development**

	Breakthrough	Impact
T Cell Vaccines		
	Attenuated CMV vector inducing CD8– MHC Class II and CD8-HLA-E HIV Cytotoxic T cells	Brings new effector mechanisms to bear for eliminating virus-infected CD4 T cells in acute HIV infection
	Conserved, Centralized (consensus, mosaic) HIV gene inserts	Provides optimal T cell immunogens for induction of both CD4 and CD8 T cell responses
Antibody-Inducing Vaccines		
	Antibody-virus evolution; Mapping of transmitted/founder virus and bnAb evolution	Provides insight into Env mutations required for bnAb development
	Concept of cooperating B cell Lineages for bnAb induction	Allows for identification of specific Envs involved in bnAb induction
	Immune tolerance controls of bnAb induction	Provides insight into both adjuvant and immunogen designs that may be needed for conferring survival advantage to bnAb B cell lineages in germinal centers
	Cryo-electron microscopy and crystal structures of the HIV trimer	Provides structural insight into bnAb epitopes and informs both trimer and epitope-base Immunogen design