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EDITORIAL: Spectrum of HIV Antibodies in Vaccine and Disease

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Remarkable progress has been made regarding the different types of antibodies that have potential to block HIV-1 acquisition and therefore all of these different antibodies are of great interest for HIV-1 vaccine development. In addition to important new information on the epitopes and requirements for broadly neutralizing antibody (bnAb) responses, there is a growing interest in the antiviral effector functions of non-neutralizing antibodies and the possible role these played in the modest protection seen against HIV-1 acquisition in the RV144 Thai trial [1]. This edition of Current Opinion in HIV and AIDS presents a collection of articles that reflect a recent shift in the field toward a more balanced focus on multiple types of antibodies that are desirable to elicit with vaccines. Two papers, one coauthored by Cynthia Derdeyn and Lynn Morris, and another contributed by Quentin Sattentau describe four conserved regions on the HIV-1 envelope glycoprotein spike known to be vulnerable to bnAbs. Detailed studies of a plethora of new bnAbs and how these bnAbs arise in HIV-1-infected individuals are providing new insights for vaccine design. The reviews by Derdeyn, Morris and Sattentau agree that one essential weakness of current vaccine immunogens is their inability to engage appropriate germline receptors on naïve B cells and subsequent intermediates as essential steps in the maturation of these B cells to high affinity bnAb secreting cells. This offers a partial explanation for why current Env vaccine immunogens, although possessing epitopes for some highly matured bnAbs, have failed to re-elicite these types of antibodies. The authors discuss critical gaps in knowledge that need to be addressed to help overcome this roadblock.

Certainly, adequate binding to the appropriate B cell receptors alone will not be sufficient to drive the maturation and survival of B cells that make potent bnAbs. B cells must also receive appropriate stimulatory signals and overcome multiple tolerance checkpoints. In regard to the latter, Laurent Verkoczy and Marilyn Diaz describe how immune tolerance mechanisms are invoked by the self-reactivity of some conserved bnAb epitopes, especially those in the MPER of gp41, and explain why this represents a formidable roadblock to bnAb

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Conflicts of interest

None.

induction. They also describe an innovative immunoglobulin gene knock-in mouse model that is being used to delineate these tolerance mechanisms and to learn how to overcome them. This murine model has already provided a number of interesting insights that could prove useful. In terms of stimulatory signals, Constantinos Petrovas and Richard Koup describe what is currently known about the role of T follicular helper (Tfh) cells in the development of HIV/SIV-specific B cell responses. They suggest that an improved understanding of how these cells are regulated may lead to insights into how manipulate them in germinal centers to facilitate somatic hypermutation and the selection of high affinity memory and plasma B cells.

Additional opportunities to elicit antibodies with desired titers and properties may be afforded by adjuvants. Anthony Moody reviews what is known about the adjuvants tested with HIV-1 Env immunogens delivered as either purified proteins or in recombinant DNA and viral vaccine vectors. Although many adjuvants have been tested and shown to have benefits that include increased titers and dose sparing effects, no clearly superior adjuvant regimen has been identified and none have succeeded at generating bnAbs. More work is needed to explore new adjuvants and to perform standardized comparisons using the same immunogens, doses, routes and inoculation schedules. These comparisons should involve a broader range of immunologic measurements that encompass both neutralizing and non-neutralizing antibodies and include the RV144 correlates.

An approach that aims to circumvent the many obstacles encountered with adaptive immunity is the use vector mediated antibody gene transfer to directly express bnAbs in vivo. This technology is gaining traction as a result of the new generation of bnAbs that exhibit extraordinary potency and breadth of activity. Bruce Schnepp and Philip Johnson describe recent progress and success with adeno-associated virus (AAV) vectors designed to express protective levels of bnAbs in animal models for both the prevention and treatment of HIV-1 infection. These and similar vectors hold much promise but are not without potential pitfalls, including an uncertain level of immunogenicity of the expressed bnAb. The first human trial of AAV delivery of a potent bnAb (PG9) is slated to begin this year and should provide important information about safety and the magnitude and duration of neutralization capacity.

The recent advancements mentioned above have contributed to heightened efforts to develop an effective nAb-based vaccine for HIV-1. However, other antibodies are gaining increased attention because of the modest 31.2% efficacy that was seen in the RV144 Thai trial [1] of a vaccine that elicited relatively weak plasma nAb responses [2] and predominantly CD4+ T cells responses with little or no virus-specific CD8+ T cell responses [3,4]. Results of subsequent immunologic studies found that plasma antibodies to epitopes in the V2 and V3 loops of gp120 correlated with a reduced risk of infection in RV144 [3,5–7]. These findings, together with results of a genetic sieve analysis showing increased vaccine efficacy against viruses containing K169 in V2 [8], and a study by Liao *et al.* [5] showing V2 mAbs from RV144 target K169, raise the hypothesis that anti-V2 antibodies could have been directly involved in protection in RV144. How they might have protected is an area of intense interest, especially since these antibodies have no detectable bnAb activity. In this regard, multiple antibody effector functions were induced in RV144, with evidence for Fc receptor

(FcR) function [3,9,10] and infectious virion capture [11]. Moreover, an extended follow-up study of HIV-1 infected and vaccinated participants from RV144 [12] found lower viral loads in mucosal fluids in vaccinated participants, raising the hypothesis that as yet undefined immunological responses may contribute to reduced mucosal viral loads.

The final four papers in this issue address immune responses that involve FcR-mediated antiviral activities as well as the role of complement. Sarah Cocklin and Joern Schmitz review recent evidence supporting a role for FcRs in HIV-1 pathogenesis and in either the prevention or enhancement of HIV-1 transmission, depending on the type and allelic form of FcR utilized by particular antibodies. They also comment on the highly polymorphic nature of FcRs in nonhuman primates and how this might confound studies of antibody effector functions in simian models of AIDS virus infection as they relate to humans. One mechanism by which FcRs can mediate an antiviral effect is through antibody-dependent cellular cytotoxicity (ADCC). George Lewis and colleagues discuss recent evidence, pro and con, that non-neutralizing antibodies which mediate ADCC of infected cells can block HIV-1 acquisition. They make a distinction between epitopes that are exposed during viral entry and viral release from target cells and propose that entry epitopes are predominant targets for ADCC antibodies that can block acquisition of infection. These epitopes include the CD4-inducible A32 epitope in a highly conserved region of gp120 at the gp120-gp41 interface that was shown to be a target for ADCC-mediating monoclonal antibodies from RV144 [10].

Another mechanism by which non-neutralizing antibodies might block HIV-1 acquisition is through phagocytosis as mediated by either FcRs or complement. Ann Carias and Thomas Hope describe how these mechanisms operate and their potential to block HIV-1 at mucosal surfaces. Although few studies have addressed the role of these mechanisms in protection against AIDS viruses *in vivo*, recent findings suggest that detailed investigations are warranted, and that a new high throughput assay for phagocytosis may facilitate such studies. Finally, Michael Frank gives an overview of the complement system with a special focus on how HIV-1 activates and survives complement and the role complement plays in adaptive humoral immunity. He describes some of his recent findings using recombinant gp120 and gp140 proteins to study complement activation and how this activation might be modulated for improved antibody responses. This line of investigation led him to explore the fate of gp120 *in vivo* and to discover that the glycoprotein is rapidly degraded, possibly in the liver, after injection into mice and guinea pigs. Possible consequences of this rapid degradation for vaccines are discussed.

One consistent theme throughout all of these papers is the need for more research before the promise of bnAbs and non-neutralizing antibodies can be successfully translated into an effective HIV-1 vaccine. That said, the current pace of progress is remarkable and if sustained is reason for optimism that a solution to the development of an effective HIV-1 vaccine is much closer than it has ever been before.

References

1. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *N Engl J Med*. 2009; 361:2209–2220. [PubMed: 19843557]

2. Montefiori DC, Karnasuta C, Huang Y, et al. Magnitude and breadth of the neutralizing antibody response in the RV144 and Vax003 HIV-1 vaccine efficacy trials. *J Infect Dis.* 2012; 206:431–441. [PubMed: 22634875]
3. Haynes BF, Gilbert PB, McElrath MJ, et al. Immune-correlates analysis of an HIV-1 vaccine efficacy trial. *N Engl J Med.* 2012; 366:1275–86. [PubMed: 22475592]
4. de Souza MS, Ratto-Kim S, Chuenarom W, et al. The Thai phase III trial (RV144) vaccine regimen induces T cell responses that preferentially target epitopes within the V2 region of HIV-1 envelope. *J Immunol.* 2012; 188:5166–5176. [PubMed: 22529301]
5. Liao H, Bonsignori M, Alam SM, et al. Vaccine induction of antibodies against a structurally heterogeneous site of immune pressure within HIV-1 envelope protein variable regions 1 and 2. *Immunity.* 2013; 38:176–186. [PubMed: 23313589]
6. Zolla-Pazner S, deCamp A, Gilbert PB, et al. Vaccine-induced IgG antibodies to V1V2 regions of multiple HIV-1 subtypes correlate with decreased risk of HIV-1 infection. *PLoS One.* 2014 in press.
7. Gottardo R, Bailer RT, Korber BT, et al. Plasma IgG to linear epitopes in the V2 and V3 regions of HIV-1 gp120 correlate with a reduced risk of infection in the RV144 vaccine efficacy trial. *PLoS One.* 2013; 8(9):e75665. [PubMed: 24086607]
8. Rolland M, Edlefsen PT, Larsen BB, et al. Increased HIV-1 vaccine efficacy against viruses with genetic signatures in Env V2. *Nature.* 2012; 490:417–420. [PubMed: 22960785]
9. Tomaras G, Ferrari G, Shen X, et al. Vaccine induced plasma IgA specific for the C1-region of the HIV-1 envelope blocks binding and effector function of IgG. *Proc Natl Acad Sci USA.* 2013; 110:9019–9024. [PubMed: 23661056]
10. Bonsignori M, Pollara J, Moody MA, et al. ADCC-mediating antibodies from an HIV-1 vaccine efficacy trial target multiple epitopes and preferentially use the VH1 gene family. *J Virol.* 2012; 86:11521–11532. [PubMed: 22896626]
11. Liu P, Yates NL, Shen X, et al. Infectious virion capture by HIV-1 gp120 specific IgG from RV144 vaccinees. *J Virol.* 2013; 87:7828–36. [PubMed: 23658446]
12. Rerks-Ngarm S, Paris RM, Chunsutthiwat S, et al. Extended evaluation of the virologic, immunologic, and clinical course of volunteers who acquired HIV-1 infection in a Phase III vaccine trial of ALVAC-HIV and AIDSVAX B/E. *J Infect Dis.* 2013; 207:1195–1205. [PubMed: 22837492]