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## HIV Envelope-Specific Antibody and Vaccine Efficacy

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### 1. Introduction

Following transmission, the human immunodeficiency virus (HIV) initiates persistent infection by integrating into the genome of host cells. To date it has not been possible to clear these cells by anti-viral or immune therapy, during either active or latent infection. This makes design of an efficacious HIV vaccine exceedingly difficult, since complete prevention of infection, or “sterilizing immunity”, is required. As cellular immunity targets already infected cells, humoral immune responses which can prevent initial infection by means of anti-envelope neutralizing antibodies have been a prime focus of vaccine development. In proof of concept studies, passive administration of potent neutralizing antibodies has prevented infection of non-human primates by intravenous and mucosal routes (Mascola et al., 1999; Baba et al., 2000; Mascola et al., 2000; Parren et al., 2001), validating the research focus on neutralizing antibody induction. However, the task of designing an envelope vaccine is complicated by the extreme variability among HIV isolates, the propensity for neutralization escape resulting from immune pressure exerted by induced antibodies, conformational features of the HIV envelope which make immunogen design difficult, and additional envelope characteristics which effectively hide areas of vulnerability which might ordinarily be antibody targets. There are several excellent recent reviews covering the issue of broadly neutralizing antibodies (Mascola & Montefiori, 2010; Walker & Burton, 2010; Zolla-Pazner & Cardozo, 2010; McElrath & Haynes, 2010) and it is not the intent of this review to reproduce that information. Rather, we will briefly summarize some of the salient issues and approaches, and then discuss more extensively non-neutralizing anti-envelope antibodies.

Broadly neutralizing antibodies are difficult to elicit by vaccination. But the HIV envelope protein is quite immunogenic, and an array of non-neutralizing antibodies is induced by both natural infection and vaccination. Through use of sensitive new methods, these antibodies have exhibited several functional activities associated with protection. In serum these include antibody-dependent cellular cytotoxicity (ADCC) (Weinhold, 1990) and antibody-dependent cell mediated viral inhibition (ADCVI) (Forthal et al., 2006). Secretory antibodies have also been associated with protection via mechanisms such as transcytosis inhibition (Bomsel et al., 1998). Augmented by high avidity and recall memory responses which improve their efficacy, these antibody activities can contribute in varying degrees to vaccine-induced protective efficacy. The main thrust of this review will be to examine these

non-neutralizing antibody responses in HIV and SIV infection and following vaccination, to describe how they may contribute to protection, and to summarize their potential utility amidst the array of additional immune protective mechanisms available to the host, including innate, cellular, and mucosal immunity.

## 2. Neutralizing antibodies

The variability of the HIV envelope is notorious. The envelope exhibits a 30% difference in amino acid sequence between the 9 clades designated A – K, omitting E and I (Korber et al., 2001). Envelope diversity within clades can be as high as 20% (Mascola & Montefiori, 2010). Therefore the goal of eliciting anti-envelope antibodies able to broadly recognize and protect against this spectrum of isolates is daunting. In fact it is difficult to induce broadly neutralizing antibodies by vaccination. Most that arise are relatively weak and only able to neutralize the most sensitive or easy to neutralize “Tier I” isolates (Mascola et al., 2005; Seaman et al., 2010). Yet recent publications document development of cross-reactive neutralizing antibodies during HIV infection (Sather et al., 2009) with 20 to 34% of HIV-infected individuals possessing significant breadth (Simek et al., 2009; Doria-Rose et al., 2010). That vaccine induction of broadly neutralizing antibodies is a realistic goal is also illustrated by the isolation of a handful of naturally elicited antibodies that recognize a wide spectrum of HIV isolates. These include b12, a monoclonal antibody selected by random reassortment of a phage library which recognizes the CD4 binding site of the HIV envelope (Burton et al., 1994); 2G12, a monoclonal antibody that recognizes carbohydrate moieties (Trkola et al., 1996) on the silent face of the envelope; and monoclonal antibodies 2F5 and 4E10 that target the membrane-proximal external region (MPER) of the viral envelope transmembrane protein (Muster et al., 1993; Zwick et al., 2001). Additionally, the V3 region of the external envelope protein gp120, originally believed to elicit only type-specific neutralizing antibodies, has been shown to elicit broader responses. A panel of V3 monoclonal antibodies including 447-52D was recently reported to exhibit significant cross-clade neutralizing activity (Hioe et al., 2010). The basis for this breadth may be the conserved structural elements in the V3 loop which provide for its essential function as part of the binding region to chemokine co-receptors and which outweigh the inherent variability of the amino acid sequence in importance (Almond et al., 2010; Jiang et al., 2010). Portions of the V3 and V2 loops comprise a novel quaternary epitope, recognized only as part of the native trimer. Monoclonal antibody 2909, the first such described human antibody, is potent but relatively strain specific (Gorny et al., 2005). In contrast, the recently identified monoclonals PG9 and PG16 (Walker et al., 2009) also recognize quaternary epitopes, but differ by exhibiting great neutralization breadth, attributed to dependence on an asparagine-linked carbohydrate moiety at residue 160 in the V2 loop. The 2909 antibody recognizes a lysine at this position (Zolla-Pazner & Cardozo, 2010). New methods of high-throughput monoclonal antibody cloning and screening have facilitated isolation of several additional broadly neutralizing antibodies (Scheid et al., 2009; Corti et al., 2010). To date VRC01, a CD4 binding site antibody, has shown the greatest breadth, neutralizing 91% of tested HIV isolates, representative of all major HIV clades (Wu et al., 2010). Structural knowledge of the HIV envelope, computer-assisted protein design, and state-of-the-art methods for memory B cell sorting and single cell PCR facilitated its isolation. It is hoped that similar new methodologies can lead to design of an appropriate vaccine component able to elicit neutralizing antibody breadth.

### **2.1 Development of neutralizing antibodies in natural infection**

While a significant percentage of HIV-infected individuals with chronic disease have a degree of neutralizing antibody breadth, a much smaller percentage are able to neutralize across all HIV clades (Simek et al., 2009). Long-term non-progressors have rather poor neutralizing antibody responses. Rather potent neutralizing activity seems to require a lengthy time period of sustained viremia and development of strong binding avidity, suggesting that antigen persistence and antibody maturation are needed for development of a broad response (Sather et al., 2009). Neutralizing antibodies develop very slowly in HIV-infected individuals. Antibodies with specificity for gp41 appear first at around 13 days post-infection and anti-gp120 antibodies at around day 28 (Tomaras et al., 2008). However, neutralizing antibodies appear later, usually months after infection, and thus do not appear to control viremia (Aasa-Chapman et al., 2004; Gray et al., 2007). This slow development reflects, at least in part, the same obstacles facing vaccine-induction of a neutralizing antibody response: conformational and carbohydrate masking of critical epitopes; homology of some epitopes with self proteins, leading to polyreactive antibodies that are subject to immune tolerance; and envelope variability leading to immune selective pressure and viral escape (McElrath and Haynes, 2010). Later in the course of disease, loss of CD4 help and B cell dysfunction exacerbates the poor neutralizing antibody development (Alter and Moody, 2010).

### **2.2 Improved envelope immunogen design**

In addition to improved envelope design based on increasing knowledge of the structure of the HIV envelope, other approaches have attempted to better expose critical conserved epitopes on envelope immunogens. These have included deletion of variable loops to expose otherwise hidden regions of the envelope; alteration of glycosylation patterns to prevent masking; preparation of trimeric forms of the envelope to mimic the natural structure on the surface of the virion, and introduction of critical epitopes on other scaffolds for better presentation to the immune system (Hu and Stamatatos, 2007). These alterations have had varying degrees of success, although none has induced the breadth and potency of neutralizing antibody response needed for a highly effective vaccine. It is hoped that continued improvements in envelope immunogens fostered by greater knowledge of envelope structure and understanding of the natural process of broadly neutralizing antibody induction will achieve the desired goal.

## **3. Non-neutralizing antibodies**

The RV144 phase III trial in Thailand which assessed an ALVAC-recombinant prime/Env protein boost regimen, showed only modest efficacy, protecting 31% of vaccinated individuals in the intent-to-treat group (Rerks-Ngarm et al., 2009). Nevertheless, this outcome provided the first evidence that development of a safe and effective preventive HIV vaccine is possible. This study also highlighted the need to better understand immune correlates of protection associated with decreased HIV acquisition. The RV144 vaccine components have induced a broad constellation of immune responses, including T-cell-line adapted neutralizing antibody (Nitayaphan et al., 2004), antibody-dependent cell-mediated cytotoxicity (Karnasuta et al., 2005), and CD4<sup>+</sup> and CD8<sup>+</sup> T cell responses, but clear immune correlates have not been defined. Currently in order to combat the extensive genomic diversity of HIV both strong cellular and humoral immune responses are believed necessary

for a successful vaccine (Amanna & Slifka, 2010; Benmira et al., 2010). However, as strong cellular immunity was not elicited in the majority of RV144 vaccinees, humoral immunity is believed to have contributed to the protection against HIV acquisition. As the vaccine regimen did not elicit antibodies able to neutralize primary HIV isolates, the focus of research has shifted to the potential for non-neutralizing antibodies to mediate protection. Neutralizing antibodies are able to prevent infection of susceptible cells; however, once a cell is infected it is difficult to imagine a role for neutralizing antibodies (Battle-Miller et al., 2002). Other antibody functions such as ADCC and ADCVI working together with innate effector cells provide a means to target and kill virus infected cells (Fig. 1A). Such mechanisms could control or possibly eradicate the small foci of infected cells that form in the lamina propria after viral transmission and prior to systemic spread of the virus (Fig. 1B; Haase, 2005).

### 3.1 ADCC

ADCC bridges innate and adaptive immunity. It involves effector cells able to mediate cell lysis, target cells expressing cell surface antigen, and specific antibody that recognizes the cell surface antigen and activates effector cells via interaction with Fc receptors. The interaction between the Fc domain of the antibody and the corresponding receptor on effector cells triggers a series of events that lead to the destruction of the infected cell via cytotoxic granules (perforin, granzyme) or a death-receptor-dependent pathway (Fas/Fas ligand; TNF/TNFR) (de Saint Basile et al., 2010; Chavez-Galan et al., 2009).

Most ADCC responses described in the literature are directed against the envelope protein (Env) (Ahmad & Menezes, 1996; Baum et al., 1996; Alsmadi & Tilley, 1998), although Nef (Yamada et al., 2004) and Tat (Florese et al., 2009) have also been shown to be ADCC targets. Additionally, a recent study in chronically infected subjects reported that Pol is an ADCC target, but this Pol-specific ADCC activity did not correlate with delayed HIV progression (Isitman et al., 2010). Moreover, the *pol* gene encodes internal proteins, so it is possible that the Pol-specific ADCC activity observed was targeting by-stander cells that had scavenged dead-cell debris. Despite the potential efficacy of ADCC, little is known about specific epitopes recognized by antibodies able to mediate ADCC. Epitopes recognized by both anti-Env and anti-Nef antibodies that mediate ADCC have been described (Alsmadi et al., 1997; Yamada et al., 2004; Los Alamos National Laboratory Molecular Immunology Database). As discussed below, anti-Env antibodies that mediate ADCC have been associated with protection, however, whether anti-Nef or anti-Tat antibodies have an impact on natural infection is not known.

Effector cells that mediate ADCC are not major histocompatibility complex restricted, and multiple subpopulations of peripheral blood mononuclear cells (PBMCs) are involved in mediating ADCC function. NK cells,  $\gamma\delta$  T cells, neutrophils, monocytes, and macrophages all express the Fc receptor that can engage antibodies (Forthal & Moog, 2009). A large number of these cells are always present in peripheral tissues, in contrast to memory B and T cells in lymphoid tissue which require activation for neutralizing antibody or T cell functions. Since HIV infection rapidly spreads during the first 2 weeks after transmission, the significant time advantage provided, for example, by pre-existing vaccine-elicited antibody and Fc receptor-bearing cells, may facilitate better control of viremia. IgG1 and IgG3 are the most common IgG isotypes to mediate ADCC via strong interaction with the Fc-binding receptor CD16/Fc $\gamma$ RIII expressed mainly on NK cells (Niwa et al., 2005).



Traditionally, ADCC killing was assessed using assays in which target cells were labeled with radioactive isotopes such as  $^{51}\text{Chromium}$ . Disadvantages of this method include difficulty labeling certain cell types, low assay sensitivity and high spontaneous chromium release resulting in high background values (Volgmann et al., 1989). Several flow cytometry-based alternatives have recently circumvented the problems associated with radioactive labeling of target cells in cytotoxicity assays (Wilkinson et al., 2001; Gomez-Roman et al., 2006a; Stratov et al., 2008; Chung et al., 2009). These assays have provided greater ease of use and importantly greater sensitivity, facilitating investigation of the role of ADCC activity in natural infection and vaccine-induced protection.

### 3.1.1 HIV-specific ADCC responses in natural infection

Over the past 20 years, the dogma that T cells and neutralizing antibodies are protective immune correlates for many vaccines led to lack of interest in the ADCC mechanism. However the gradual accumulation of evidence from natural infection and vaccine studies supporting a protective role for ADCC has stimulated studies of this immune response. A number of early studies documented the induction of ADCC antibodies during HIV infection (Lyerly et al., 1987; Rook et al., 1987; Ojo-amaize et al., 1987). A potential role for ADCC in modulating the course of HIV infection was eventually suggested based on studies showing an inverse association between ADCC antibody levels and clinical stage of the disease. Baum et al. (1996) presented strong evidence that higher titers of antibodies mediating ADCC correlated with a successful host defense against HIV-1, and Forthal et al. (2001a) reported an inverse association between ADCC activity and plasma viremia. Higher ADCC activity has also been correlated with slower disease progression in children (Ljunggren et al., 1990; Broliden et al., 1993). More recently, ADCC activity has been demonstrated in cervical lavage fluids of HIV-infected women (Battle-Miller et al., 2002), and associated with lower genital HIV RNA loads (Nag et al., 2004). Elite controllers also have higher ADCC antibody titers than viremic individuals, whereas neutralizing antibody activity tends to be higher in viremic individuals (Lambotte et al., 2009). Nevertheless, not all studies have concluded that ADCC plays a role in protective efficacy (Dalglish et al., 1990; Lifson et al., 1991; Chuenchitra et al., 2003). The conflicting results reflect the complexity of the virus-host interaction and elements that contribute to the ADCC response, including the integrity of the host immune system, extent of viremia, level and affinity of antibodies induced, and functionality of effector cells.

### 3.1.2 ADCC responses in non-human primate models

Non-human primate studies have stimulated interest in the ADCC mechanism and its role in protective efficacy. ADCC activity has been correlated with delayed disease progression in SIV infected macaques (Banks et al., 2002). Additional convincing evidence has come from pre-clinical vaccine studies. A replicating adenovirus type 5 host range mutant (Ad5hr)-SIV recombinant prime/SIV gp120 protein boost regimen was shown to elicit potent protection against an intrarectal SIV<sub>mac251</sub> challenge (Patterson et al., 2004). The vaccine did not induce antibodies able to neutralize primary SIV<sub>mac251</sub>, however, the reduced acute viremia was significantly correlated with anti-envelope binding antibodies that mediated ADCC against SIV<sub>mac251</sub>-infected cells (Gomez-Roman et al., 2005). Subsequent studies, one involving a comparison of Ad5hr-SIV recombinant priming via the upper respiratory tract versus the oral route followed by SIV gp120 boosting and SIV<sub>mac251</sub>

challenge, and another involving a comparison of Ad5hr-recombinant priming with and without subsequent envelope protein boosting followed by challenge with the chimeric virus SHIV<sub>89.6P</sub>, again showed significant correlations of ADCC activity with reduced acute viremia (Hidajat et al., 2009; Xiao et al., 2010). The latter study also revealed a correlation of ADCC activity with reduced chronic viremia. The importance of antibody maturation in induction of the functional antibody responses was indicated by the significant correlation of ADCC-mediating antibodies with binding antibody avidity.

The non-human primate model provides a good mimic for exploration of vaccine strategies and immune mechanisms. For example, passive antibody transfer studies can directly explore the ability of antibodies to mediate protection. Binley et al. (2000) observed that passive infusion of IgG to rapid and normal progressor SIV<sub>mac251</sub> infected animals caused small and transient reductions in plasma viremia by a mechanism that was inconsistent with virus neutralization but which could have been effector cell mediated, implicating ADCC. In contrast, infusion of IgG possessing high titers of anti-Env antibodies able to mediate ADCC had no effect on viral loads following two sequential oral challenges of neonatal macaques with SIV<sub>mac251</sub> (Florese et al., 2006). In both these studies, high viral loads may have contributed to negligible protective effects. Further, the neonatal macaque study may have been compromised by low levels and poorly functioning effector cells in the baby animals. An improved experimental design using repetitive low dose challenge might yield more significant results.

Passive transfer of monoclonal antibodies has proven more informative in elucidating mechanisms of antibody-mediated protection. An elegant study by Hessel et al. (2007) using the neutralizing b12 monoclonal antibody and a mutant unable to bind the Fc receptor and complement, showed that protection from a SHIV<sub>SF162P3</sub> challenge mediated by the b12 antibody was in part due to Fc-mediated effects. A follow-on study using low-titered b12, mutant antibody, and low-dose repeated SHIV<sub>SF162P3</sub> challenge, supported a contribution of effector function to the delayed acquisition observed (Hessel et al., 2009).

As illustrated by the b12 monoclonal, neutralizing antibodies may also mediate ADCC activity via their Fc domain. However, all ADCC mediating antibodies do not necessarily possess neutralizing activity. A neutralizing antibody must target a specific region of the viral envelope, whereas antibodies that mediate ADCC are required only to recognize an exposed target epitope on the surface of the infected cell. Antibodies elicited in chimpanzees to an HIV clade B immunization regimen were able to mediate ADCC killing of clade A, B, C, and AE env-expressing target cells (Gomez-Roman et al., 2006). Therefore, in addition to the ability to rapidly respond, the ADCC effector mechanism can provide the breadth of antibody recognition believed necessary for protective efficacy.

The extent to which the ADCC mechanism contributes to vaccine-induced protection is not yet clarified. A definitive conclusion will perhaps come from immune correlates identified in human clinical vaccine trials. To date only a few such trials have evaluated ADCC activity. Goepfert et al. (2007) reported that Env-specific ADCC activity, correlated with binding antibodies, was detected in most individuals that received a candidate AIDS vaccine containing gp120. Further, as mentioned above, a phase II human trial in Thailand has shown induction of ADCC mediating antibodies (Karnasuta et al., 2005). The role of these antibodies in the protection against HIV acquisition seen in the RV144 trial which used similar immunogens is currently being actively explored.

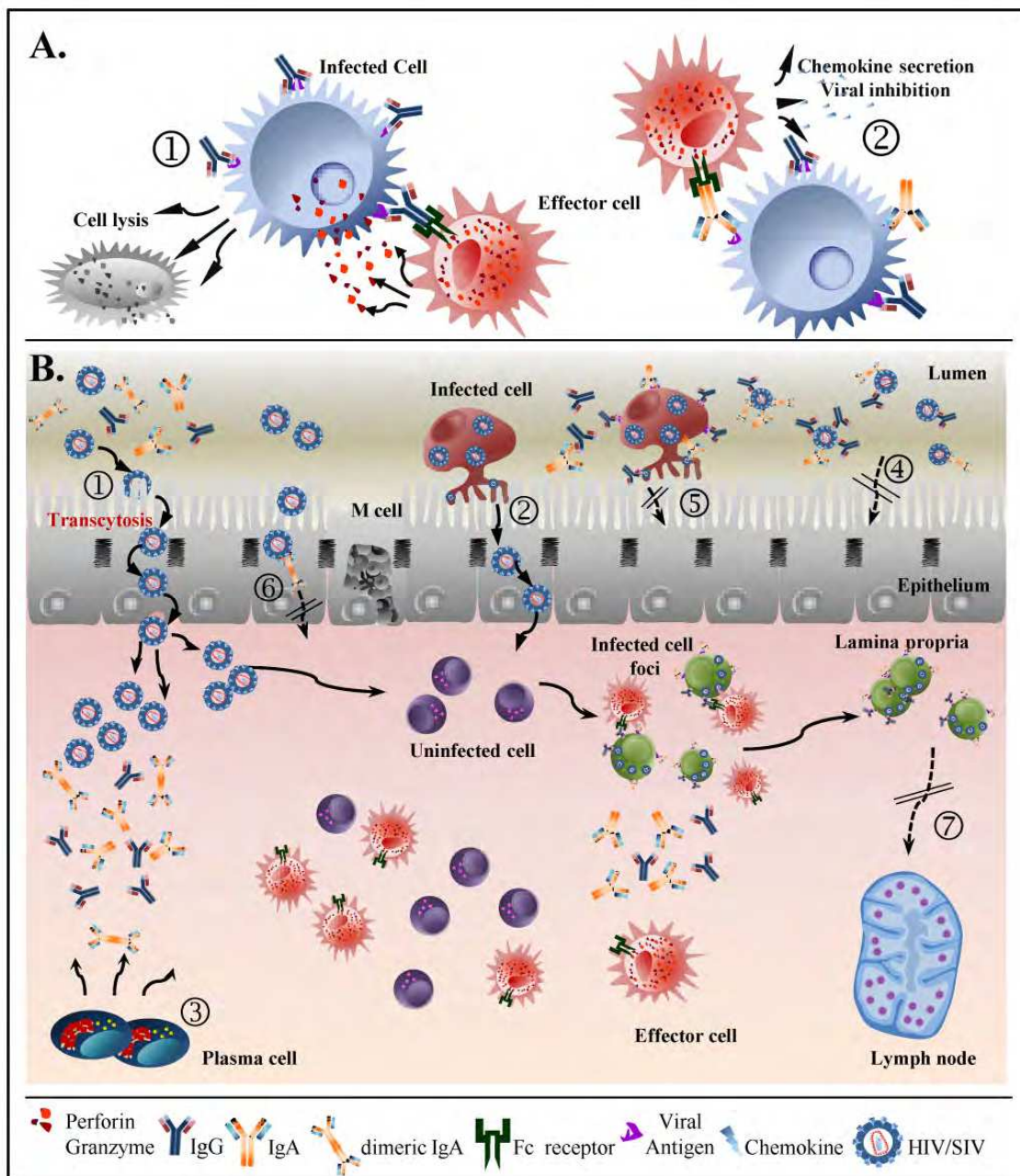


Fig. 1. **Control of viral infection by non-neutralizing antibodies.** **A. ADCC and ADCVI.** (1) Fc receptors on effector cells recognize the Fc domain of antibody bound to antigen on infected cells, inducing release of cytotoxic granules and cell lysis via ADCC. (2) Activation of effector cells may lead to production of chemokines and cytokines and viral inhibition by ADCVI. **B. A mucosal surface with a single layer of columnar epithelium.** Viral transmission may occur by transcytosis of cell-free (1) or cell-associated virus (2). T cells, effector cells (macrophages, monocytes, NK cells,  $\gamma\delta$  T-cells, neutrophils) and plasma cells are present in the lamina propria. Mucosal antibodies, secreted by plasma cells (3), may block infection by neutralizing virus (4), or by blocking transcytosis of cell-associated (5) or cell-free virus (6). Antibodies can mediate ADCC and ADCVI to eradicate or control infected cell foci, blocking dissemination of virus to lymph nodes (7).



### 3.2 ADCVI

Like ADCC, ADCVI requires antibody that forms a bridge between an infected target cell and an FcγR-bearing effector cell (Forthal et al., 2001). However, ADCVI is a broader activity not restricted to target cell lysis, as with ADCC. Rather it encompasses several mechanisms by which viral replication following target cell infection is inhibited. These may include ADCC activity, but also noncytolytic mechanisms of virus control, such as secretion of inhibitory chemokines (Fig. 1A), or FcγR-mediated phagocytosis of immune complexes. The readout in ADCVI assays is the percentage of virus inhibition due to effector cells together with a test antibody relative to a negative control antibody. This biological endpoint allows assessment of ADCVI against any lentiviral strain able to infect cells. As the ADCVI assay uses heat-inactivated serum, complement activities do not play a role (Forthal & Landucci, 1998). Overall, ADCVI is a measure of the combined ability of antibody and effector cells to inhibit the spread of virus infection (Forthal et al., 2001; Forthal & Moog, 2009). Both polyclonal and monoclonal antibodies can mediate ADCVI. Intact IgG, not just the F(ab')<sub>2</sub> portion is required (Forthal et al., 2006), emphasizing the importance of Fc-Fc receptor interactions in mediating the functional activity.

#### 3.2.1 ADCVI during HIV infection

ADCVI has been associated with reduction in viremia during HIV infection. In HIV-infected individuals, systemic non-neutralizing antibodies appear early during acute infection, generally before a neutralizing antibody response (Sawyer et al., 1990). Not surprisingly, in individuals with acute HIV infection, non-neutralizing ADCVI antibodies appeared as early as the first week after onset of symptoms or the first month after HIV exposure (Forthal et al., 2001). ADCVI activity became more potent as the viral load fell (in the absence of antiretroviral therapy), resulting in an inverse relationship between ADCVI activity and acute plasma viremia, suggesting a protective effect. Importantly, ADCVI antibodies appeared to be broadly reactive with different HIV strains. The demonstration of an association between non-neutralizing but functional antibodies able to mediate ADCVI activities and protection is noteworthy and timely, in view of the recent outcome of the RV144 phase IIb vaccine trial in Thailand as discussed above. A previous study of serum samples from the Vax004 trial which evaluated gp120 vaccines similar to those used for boosting in RV144 revealed an inverse correlation between the HIV infection rate of vaccinated individuals and vaccine-elicited ADCVI antibody activity (Forthal et al., 2007). Although this trial did not result in protection, the results support the hypothesis that similar functional antibody activities may have contributed to protection in the RV144 trial. Taken together, these observations have renewed interest in defining the mechanisms of FcγR-mediated protection by ADCC and ADCVI.

#### 3.2.2 ADCVI in rhesus macaque models

In support of a protective role for ADCVI, significant correlations between ADCVI activity mediated by vaccine-induced antibodies and decreased acute viremia have been reported in both SIV and SHIV rhesus macaque models (Florese et al., 2009; Hidajat et al., 2009; Xiao et al., 2010). Further, passive infusion of anti-SIV immune serum with strong ADCVI activity to newborn rhesus macaques prevented infection from an oral SIV<sub>mac251</sub> challenge (Forthal et al., 2006). A recent study showed that vaccine-elicited antibody mediated ADCVI activity that was recalled 4 weeks post-challenge. This post-challenge activity was correlated with

reduced chronic phase viremia (Xiao et al., 2010) suggesting a broader role for ADCVI in controlling viral replication over the course of disease rather than impacting only early post-transmission viral spread. In this same study, a negative correlation between ADCVI activity 4 weeks post-challenge and neutralizing antibody titer 8 weeks post challenge was observed which became progressively weaker over time, and disappeared by 24 weeks post-challenge. The ADCVI assay evaluates viral inhibition in the presence of serum plus effector cells, and subtracts inhibition observed with serum in the absence of effector cells. This latter inhibition is attributed to neutralizing antibody. Therefore, the inverse correlation between the two activities might indicate that both neutralizing and non-neutralizing antibodies were mediating ADCVI. Neutralizing monoclonal antibodies are known to mediate ADCVI activity (Hessell et al., 2007). Development of *de novo* neutralizing antibody depends on the presence of sufficient viral antigen to drive the antibody response. The inverse relationship between ADCVI and the more slowly developing neutralizing antibody may reflect control of viremia by ADCVI and/or other immune mechanisms at the expense of strong neutralizing antibody induction due to a reduced viral burden. The complexity of the *in vivo* situation makes the relationships between functional antibody activities and viral burden difficult to resolve.

#### 4. Secretory antibody

Mucosal surfaces are the major site for HIV entry. Therefore, an effective HIV vaccine may require the presence of antibodies able to prevent infection at mucosal sites. IgA antibodies are the most prevalent at mucosal surfaces, and might contribute to protection by one or more mechanisms including classical neutralization, but also non-neutralizing activities such as immune exclusion involving mucus entrapment and clearance, ADCC discussed above, and inhibition of HIV transcytosis across the epithelial cell barrier (Fig. 1B; Kozlowski and Neutra, 2003). Study of HIV-exposed but uninfected individuals (so called highly-exposed, seronegative; or HEPS), has shown the presence of functional HIV-specific IgA at mucosal surfaces of these individuals (Miyazawa et al., 2009; Lopalco, 2004), implicating the antibody in resistance to HIV infection.

Several vaccine approaches have been evaluated in non-human primates for the ability to elicit viral-specific IgA antibodies at genital/rectal sites. These have included tonsillar immunizations with replication-defective SIV (Vagenas et al., 2009), administration of DNA vaccines intranasally or rectally, followed by boosting with MVA recombinants (Bertley et al., 2004; Wang et al., 2004), intradermal or intramuscular administrations of DNA vaccines together with GM-CSF DNA or CCL27 DNA as adjuvants (Lai et al., 2007; Kraynyak et al., 2010) vaginal delivery of trimeric HIV envelope together with Carbopol gel (Cranage et al., 2011), upper respiratory track immunization with replication-competent Ad-recombinants followed by intramuscular boosting with envelope protein (Florese et al., 2009; Hidajat et al., 2009; Xiao et al., 2010), and intramuscular plus intranasal immunization with a gp41 subunit vaccine delivered on virosomes (Bomsel et al., 2011). These have had varying degrees of success in consistently eliciting mucosal IgA antibodies. Only a few studies, however, have investigated functionality of vaccine-elicited IgA as discussed below. Immune exclusion is difficult to assess *in vitro* due to the necessity for a mucus barrier, but neutralizing, ADCC, and ADCVI activities can be evaluated. Transcytosis inhibition seems especially relevant for mucosal protection.

#### 4.1 Transcytosis inhibition

HIV-1 transmission mainly occurs through exposure of mucosal surfaces to HIV-infected fluids, such as semen, cervicovaginal fluid, saliva, colostrum, and breast milk (Pope and Haase, 2003). A key entry event is translocation of virus across the epithelium. In rectal, intestinal, colonic, and endocervical mucosa, the epithelium is made up of a single layer of polarized, columnar epithelial cells with tight junctions separating the cells into the apical domain, which faces the lumen, and the basolateral domain, which faces the serosal side and the internal milieu (Bomsel, 1997). In contrast, ectocervical and vaginal epithelium is composed of pluristratified epithelial cells that lack a polarized plasma membrane and tight junctions, allowing intraepithelial dendritic cells and Langerhans cells to diffuse into the epithelium (Bomsel and Alfsen, 2003). Depending on the site of infection, several mechanisms for HIV-1 transmission across mucosal epithelia have been proposed, including columnar epithelial cell transcytosis, direct infection of epithelial cells, and dendritic/Langerhans cell transport (Bomsel & David, 2002; Shattock et al., 2000).

The major type of HIV transcytosis is cell-associated (Bomsel & Alfsen, 2003), generated by cell-cell contact of virally-infected cells with apical epithelial cell surfaces. It is a rapid, efficient, and nondegradative process in which virus is transported from the apical to the basolateral surface of polarized epithelial cells. Cell-free virus transcytosis is also possible but inefficient (Bobardt et al., 2007; Bomsel, 1997). Rather than fusion and infection, interactions between viral components, including gp41 (Alfsen et al., 2001), gp120 (Bobardt et al., 2007), and gp160 (Hocini et al., 1997), and host epithelial cell surface molecules, such as glycosphingolipid galactosyl-ceramide (GalCer) (Alfsen & Bomsel, 2002; Meng et al., 2002), an important component of endocytotic “raft” membrane microdomains, the coreceptor CCR5 (Bomsel et al., 2007), and the heparin sulfate proteoglycan attachment receptor, agrin (Alfsen et al., 2005), lead to transcytosis of the virus across the epithelial barrier and its trapping by submucosal dendritic cells which disseminate it to target CD4<sup>+</sup> T cells.

Immunoglobulin A (IgA) and immunoglobulin G (IgG) anti-HIV antibodies have been detected in nearly all external secretions. Although mucosal IgG may interfere with viral infection in tissues underlying mucosal epithelia and secondary lymphoid tissues, mucosal IgA is thought to best protect mucosal surfaces (Pope and Haase, 2003). HIV-1 entry via transcytosis *in vitro* can be inhibited by dimeric IgA (dIgA) isolated from HIV-1-infected subjects (Bomsel et al., 1998), secretory IgA specific for gp41 (Alfsen et al., 2001), and mucosal and serum IgA from HIV-1-exposed seronegative individuals (Devito et al., 2000). Recently, transcytosis inhibition of both SIV and SHIV by vaccine-elicited mucosal antibodies has been evaluated in pre-clinical studies in non-human primates. In rhesus macaques, mucosal priming with replication-competent Ad-HIV or SIV recombinants followed by intramuscular boosting with envelope protein elicited antibodies in rectal secretions able to inhibit SIV and SHIV transcytosis *in vitro* (Hidajat et al., 2009; Xiao et al., 2010). Importantly, a significant correlation between transcytosis inhibition and reduced chronic viremia was seen in the study by Xiao et al. (2010) suggesting that mucosal IgA present in the submucosa may play a role in viremia control during the course of infection. However, the strongest evidence to date for a contribution of transcytosis inhibition to vaccine-elicited protection was recently reported by Bomsel et al. (2011). Following intramuscular plus intranasal immunization with gp41 subunit immunogens on virosomes, 4 out of 5 rhesus macaques were protected from SHIV<sub>SF162P3</sub> acquisition following repetitive low-dose challenge, whereas all controls became infected. The protected macaques had

gp41-specific vaginal IgA that mediated transcytosis inhibition, and vaginal IgG that had neutralizing and/or ADCC activity. Both the transcytosis inhibition and ADCC activity were significantly inversely correlated with acute viremia. Of particular interest, sera from these macaques lacked anti-HIV activity in neutralization, ADCC, and transcytosis inhibition assays, suggesting that the IgG with protective activity was locally produced. A similar suggestion was reported in the study of Xiao et al. (2010).

## 5. Antibody avidity

In addition to functionality, the overall quality of an antibody response largely determines its effectiveness. Antibody avidity, a measure of the strength of the binding interaction between an antigen with multiple antigenic determinants and multivalent antibodies (Siegrist et al., 2004), is one characteristic which contributes to efficacy. It develops in germinal centers following somatic hypermutation of immunoglobulin genes and selection of B cells for high affinity binding to antigen (Berek et al., 1991; French et al., 1989; Griffiths et al., 1984). Thus, this antibody maturation process is dependent on both time and antigen exposure. The importance of antibody avidity has been shown in studies associating low antibody avidity with poor protective efficacy of an RSV vaccine (Delgado et al., 2009). In contrast, high-avidity neutralizing (Barnett et al., 2010) and non-neutralizing (Zhao et al., 2009; Xiao et al., 2010) HIV-1 Env-specific antibodies have been inversely correlated with reduced SHIV viremia following challenge. Importantly, in the Xiao et al. (2010) study, significant correlations were seen between antibody avidity and both functional antibody activities: ADCC and ADCVI, both also correlated with reduced viremia. The results overall suggest that antibody maturation following vaccination is associated with better functional antibody activity.

## 6. The role of memory B cells in vaccine-mediated immunity

A critical feature of protective humoral immunity is memory. The success of vaccination depends on the differentiation of naïve B cells into plasma cells and memory B cells. Plasma cells are terminally differentiated and continuously secrete antibody without requiring further antigenic stimulation. In contrast, memory B cells represent an important second line of immune defense that is initiated if pre-existing antibody levels are too low to prevent infection or if an invading pathogen is able to circumvent the pre-existing antibody response. Memory B cells do not actively secrete antibody but instead maintain their immunoglobulin in the membrane-bound form, which together with Ig $\alpha$  and Ig $\beta$  form the antigen-specific B cell receptor. Following exposure to the initial antigen these cells become fully activated, proliferate, and differentiate into antibody secreting cells (ASC) (Ahmed & Gray, 1996; McHeyzer-Williams & McHeyzer-Williams, 2005; Pierce & Liu, 2010). Little is understood about the regulation of vaccine-induced humoral immunity. Differentiation of memory B cells into short-lived plasma cells is dependent on the presence of antigen (Dorner & Radbruch, 2007; Cagigi, et al., 2008). In contrast, long-lived antibody responses generated by viral infections or vaccinations are not dependent on the continuous presence of memory B cells but are rather produced by long-lived plasma cells that reside in the bone marrow and do not require antigen for continued production of antibody (Dorner & Radbruch, 2007; Radbruch et al., 2006). In fact, vaccine-induced B cell memory is maintained for more than 50 years after smallpox vaccination (Crotty et al., 2003), whereas antibody



responses to tetanus toxoid and diphtheria vaccines have half-lives of 11 and 19 years, respectively (Amanna et al., 2007).

Memory B cell and serum antibody levels do not always correlate. This lack of correlation implies that the serum antibody level is maintained by long-lived plasma cells in the bone marrow and not by memory B cells circulating in the blood. However, in one of the first studies to examine the frequency of specific memory B cells in humans (Bonsignori et al., 2009), plasma antibody and memory B cell responses to HIV-1 envelope were compared in a group of chronic HIV-1 infected individuals and in volunteers vaccinated in the VAX004 clinical trial (Gilbert et al., 2005). A significant correlation between blood anti-Env memory B cells levels and plasma anti-Env antibody titers was found in both chronic HIV-1 infection and after vaccination with rgp120, suggesting that plasma antibody was maintained predominantly by short-lived memory B cells. Additionally, the half-life of anti-Env antibodies was shorter than those for influenza and tetanus toxoid, demonstrating that the HIV-1 envelope does not elicit long-lived B cell memory to the degree of other antigens. This outcome is not surprising for the HIV-infected cohort, as B-cell dysfunction, including loss of memory B cell subsets has been well-documented in HIV and SIV infection (Cagigi et al., 2008; Kuhrt et al., 2010a; Shen & Tomaras, 2011). However, the reasons for impaired memory induction in vaccinees is not well understood, and may include immune suppression due to binding of gp120 to CD4 or binding of carbohydrates to mannose receptors on dendritic cells and B cells (Bonsignori et al., 2009).

SIV and SHIV non-human primate models have been very valuable in HIV vaccine development. Human memory B cells have been extensively studied (Bonsignori et al., 2009; Crotty et al., 2004; Bernasconi et al., 2002), but only recently have rhesus macaque memory B cell studies been undertaken (Douagi et al., 2010; Kuhrt et al., 2010). We have recently shown induction of SIV and HIV Env-specific IgG and IgA ASC in rhesus macaques following priming with replicating Ad-SIV or HIV recombinants and boosting with SIV or HIV envelope protein (Brocca-Cofano et al., 2011). Env-specific IgG and IgA specific activities were correlated with several antibody activities, including ADCC, ADCVI, and/or transcytosis inhibition, indicating that maturation of antibody responses is critical for improved functionality. Further, IgG and IgA memory B cells post challenge were inversely correlated with chronic viremia indicating that vaccine-induced memory B cells were recalled and influenced disease outcome. That memory B cells should exhibit a protective role is not surprising in view of the reported association between loss of memory B cells and rapid disease progression in both HIV and SIV infection (Titanji et al., 2006; Titanji et al., 2010). Our induction of strong anti-envelope memory B cell responses by vaccination (Brocca-Cofano et al., 2011) may reflect use of a replicating vector to prime immune responses followed by envelope boosting. The combined approach may have provided both the antigen persistence and time necessary to allow antibody maturation.

## 7. Conclusion

Antibodies are key to host defense and critical for HIV vaccine design. Antibodies that recognize conserved epitopes and broadly neutralize virus can prevent infection. Once infection has occurred, other antibodies that interact with viral antigens expressed on the infected cell surface are needed to eliminate initial foci, or control subsequent systemic spread of the virus. Fc receptor-bearing effector cells, such as NK cells, can mediate killing of infected cells by ADCC and/or ADCVI activities. The latter can also inhibit viral

replication. Mucosal antibodies that block viral entry through mechanisms such as transcytosis inhibition help control viral transmission and spread. As summarized here, maturation of vaccine-induced antibody responses is necessary for optimal function. Both antibody avidity and memory are directly associated with functional activity and control of viremia. An HIV/AIDS vaccine should be able to induce both cellular and humoral immunity. Regarding the latter, the success of a vaccine will depend on stimulating the production of mature high-titered antibodies with sufficiently broad reactivity to protect against HIV and SIV encounters. The path to induction of protective anti-envelope antibodies will come from understanding the B cell regulatory pathway of specific antibody production and from design of optimal immunogens. Coordination between human vaccine clinical trials and nonhuman primate vaccine challenge studies is essential to advance new vaccine concepts and accelerate the pace of HIV-1 vaccine efficacy trials.

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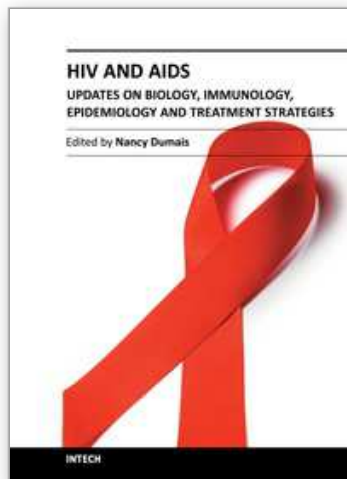


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The continuing AIDS pandemic reminds us that despite the unrelenting quest for knowledge since the early 1980s, we have much to learn about HIV and AIDS. This terrible syndrome represents one of the greatest challenges for science and medicine. The purpose of this book is to aid clinicians, provide a source of inspiration for researchers, and serve as a guide for graduate students in their continued search for a cure of HIV. The first part of this book, “From the laboratory to the clinic,” and the second part, “From the clinic to the patients,” represent the unique but intertwined mission of this work: to provide basic and clinical knowledge on HIV/AIDS.

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