Vaccine 34 (2016) 3557–3561

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Conference report

Report of the Cent Gardes HIV Vaccines Conference. Part 1: The antibody response; Fondation Mérieux Conference Center, Veyrier-du-Lac, France, 25–27 October 2015☆

ARTICLE INFO

Keywords:
HIV
Neutralizing antibodies
B cell lineage
Passive immunization
ADCC
Mucosal immunity

ABSTRACT

The 2015 Cent Gardes Conference on HIV vaccines took place on October 25–27 at the Merieux Foundation Conference Center in Veyrier du Lac, near Annecy, France. The meeting reviewed progress in the development of HIV vaccines and identified new directions of future research. The field has advanced incrementally over the past year but major progress will require additional information from new clinical trials. In this article, we review the presentations on humoral immune responses to HIV, and highlight the difficulty of eliciting broadly neutralizing antibodies by vaccination. Advances in cellular immunity for HIV prevention will be reviewed separately, in a following article.

1. Introduction

Antibody (Ab) responses to the HIV-1 envelope glycoproteins can be classified into three groups [4]: (1) binding, but non-neutralizing Abs, that nevertheless display anti-viral activity through Fc-mediated killing by NK cells or macrophages, e.g. by Ab-dependent cellular cytotoxicity (ADCC) or Ab-dependent cellular virus inhibition (ADCVI); (2) strain-specific neutralizing Abs that target the hypervariable structures of gp120, especially the variable loops V1–V5 and the α2-helix in C3: such Abs neutralize only the infecting or immunizing strain of HIV-1 and a few of its close relatives; and (3) broadly neutralizing Abs (bNAbs) that neutralize 50% or more of primary HIV strains in a cross-clade manner. These Abs usually take years to evolve a high level of breadth and potency, perhaps because they all show one or more unusual features such as a high level of somatic mutations, poly- or autoreactivity, frequent insertions or deletions, and long heavy-chain third complementarity determining regions (HCDR3) [15]. These bNAbs can neutralize up to 90% of circulating HIV-1 strains and represent the type of antibody that an effective HIV vaccine should elicit. However, despite 30 years of research and many immunogen designs, bNAbs have never been elicited through vaccination. Developing a strategy to induce them would represent a major breakthrough in the search for a protective HIV vaccine.

2. The broadly neutralizing antibody response

In his opening Keynote lecture, Dr Barton Haynes (Duke University Human Vaccine Institute, Durham, NC) discussed the mechanisms of bNAb induction and the evolution of lineages that give rise to bNAbs. In one individual who developed the CH505 bNAb that targets the Env CD4-binding site, two B cell lineages were found that were initiated by the transmitter/founder (T/F) virus, a bNAb lineage and a second, autologous neutralizing Ab lineage. Both lineages bound to the CD4-binding site, the autologous neutralizing Ab lineage helping to drive the bNAb lineage by selecting virus escape mutants, giving rise to CH505. The same process was found in another HIV-1-infected individual who developed V3-glycan-specific bNAbs. Thus, cooperating B cell lineages are hypothesized to be a general mechanism of bNAb induction. This has obvious practical implications for the design of vaccine immunogens able to simultaneously drive both helper and broadly neutralizing B cell lineages [10], as well as for directing the choice of sequential Envs for induction of bNAbs [16].

Individuals who make bNAbs show common traits such as high viral loads, low $CD4^+$ T cell counts [14], high frequency of plasma autoantibodies [13], and high levels of memory PD-1^+CXCR3^-CXCR5^+ Tfh cells [21]. Altogether, this raises the hypothesis that perturbation of the immune system following HIV infection is required to generate bNAbs. In an attempt at eliciting bNAbs such as 2F5, whose ELDKWAS epitope was identified long ago in the membrane-proximal external region (MPER) of gp41, a MPER peptide-liposomal formulation was used as an immunogen in human Ig knock-in mice [9]: the immunogen was able to initiate the bNAb lineages and drive them to proliferate, but the process did not generate fully mature bNAb, likely because of immune tolerance. Tolerance controls of 2F5-like gp41 bNAbs were similarly observed in outbred rhesus macaques, the monkeys making an alternative neutralizing lineage which progressed to near bNAb status, but negative selection of antibodies with long hydrophobic HCDR3 regions did not support sufficient affinity maturation to generate bNAbs.

The epitope specificity of the various identified bNAb groups, together with their potency and breadth, was reviewed by Dr Dennis Burton (The Scripps Research Institute, La Jolla, CA), who divided

☆ Webcasts and slides from several of the presentations at the meeting can be viewed on the Fondation Mérieux website: <http://www.globe-network.org/en/cent-gardes-conference-hiv-vaccines-2015/background>.

http://dx.doi.org/10.1016/j.vaccine.2016.05.024
0264-410X/

them into three groups: those with very broad neutralization, such as the PGT121 group, which neutralize 90–95% of all known HIV-1 strains; those with an intermediate range (the PG9, PGT143 and VRC01 group), which are able to neutralize more than 60% of known isolates; and those with a low neutralization range (less than 60%), such as PGT151. Surprisingly, it was observed that some bNAbs do not completely neutralize susceptible HIV-1 strains. This was well documented with the MPER-targeted bNAb 10E8 [18]. Similarly, bNAb PG9 typically neutralized only about 80% of SHIV BalP4 infectivity when measured in the TZM-bl assay, although it fully protected macaques against $SHIV_{BalP4}$ challenge when administered passively to the animals. Thus, the level of neutralization *in vitro* does not equal level of protection *in vivo* [26].

Highly potent bNAbs that target the V2 loop, such as members of the PG9-16 family, the PGT141-145 family, or the CAP256 series, have a typically long (more than 24 amino acid-long) CDRH3 sequence with sulfated tyrosine residues, and bind both the glycan residues at positions N156 and N160 and the lysine-rich protein sequence at the apex of the V2 loop (K169) in the Env trimer [22]. The germline version of these monoclonal Abs neutralizes among others the circulating recombinant form CRF02_AG_250. A SOSIP mimic of the CRF02 Env trimer was found to bind neutralizing but not non-neutralizing Abs, and could therefore be a good immunogen for priming the immune system response to make V2 apex-targeting bNAbs. Such priming, however, would require boosting with appropriate trimers to increase the breadth of the antibody and hopefully achieve a bNAb gene maturation, but which trimer variants to use remains a question.

Dr Peter Kwong (Vaccine Research Center, NIAID, NIH, Bethesda, MD) noted that B cell lineages from different donors generally develop different Ab responses to the same antigen, whereas in the case of HIV-1 bNAbs, a similar B cell lineage ontogeny is found in various donors [35], but the process requires extensive maturation over years [9,10,17]. This finding was initially observed for the VRC01 lineage but, similarly, all the V1/V2-specific bNAbs share a common ontogeny [8,25]. In addition, virus and antibody gene sequencing often reveals concomitant virus evolution and antibody maturation [27], as was observed in the case of bNAb CH103, which targets the CD4-binding site [20].

Dr Pamela Bjorkman (California Institute of Technology, CA, USA) described bNAb 8ANC195, whose epitopes span the gp120 and gp41 Env subunits: the antibody molecule inserts itself into a gap in the glycan shield to interact with gp120 and gp41 glycans and protein residues. Interestingly, 8ANC195 can bind different Env conformations, a potential advantage for eventual therapeutic applications.

Dr Lynn Morris (National Institute for Communicable Diseases, Johannesburg, South Africa) highlighted that the development of bNAbs is not restricted by the germline immunoglobulin, as could be observed in studying the germline repertoire of 28 individuals in the CAPRISA cohort [29]. Actually, the human immune system is capable of generating multiple bNAbs in response to a constantly evolving viral population [24,34], but all individuals appear to have the same potential to develop bNAbs: there is no difference in the germline repertoire of those who do and those who do not develop bNAbs. The key event that drove neutralization breadth in an individual from the CAPRISA cohort who developed V1V2-specific bNAbs, was the superinfection of the host by a second virus strain, eventually followed by the constant evolution of its Env sequence due to viral escape and resulting in the appearance of multiple immunotypes [3]. This study provides insight into how co-evolution of HIV-1 Env and a unique B cell lineage can enable the development of a bNAb lineage [7,31]. As discussed by Dr Alexandra Trkola (University of Zurich, Switzerland), appearance of bNAbs is favored by higher viral loads and longer time of infection. The role of ethnicity has also been suspected, as Africans and Afro-Americans seem to have a greater chance of developing bNAbs than Europeans, but this hypothesis has not yet been validated.

Dr George Shaw (University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA) made the interesting observation that 3 of 3 rhesus macaques infected with a SHIV bearing the subtype C CH505T/F Env exhibited the same early neutralizing antibody and virus coevolution patterns as that exhibited by the human subject CH505 who was infected by HIV-1 bearing the same T/F Env and who developed bNAbs [20]. These data will help determine the viral and antibody co-evolutions which lead to induction of a HIV-1 bNAb and they hopefully may provide insights into strategies to elicit bNAbs by vaccination.

Finally, Dr Julie Overbaugh (Fred Hutchinson Cancer Res Center, Washington University, Seattle, WA, USA) reported that an 11 month-old, HIV-1 clade A-infected infant was found within a cohort of breastfeeding infants in Nairobi, who had developed a bNAb (K12) able to neutralize Tier-2 viruses from multiple clades. This bNAb targeted the V3-glycan epitope in gp120, was moderately potent and not as broad as VRC01, and showed a lower degree of somatic hypermutation than adult bNAbs. Several infants who were 20 months of age had developed bNAbs able to neutralize more than 90% of a 23 Tier-2 virus library. This study shows that infected infants can develop bNAbs with relatively rapid kinetics.

3. Passive immunization with bNAbs

The history of passive immunization with antiviral or antibacterial antibodies to prevent or treat infectious diseases goes back to the beginnings of immunology [12]. As reviewed at the meeting by Dr John Mascola (Vaccine Research Center, NIH, Bethesda, MD), passive immunization with potent HIV-1 bNAbs has been shown to protect humanized BLT mice as well as non-human primates from infection [28,32]. The new very potent bNAbs recently uncovered by single cell-based antibody cloning methods, such as PGT121, VRC01 or 3BCN117, can protect rhesus macaques against SHIV infection at the dose of less than 1 mg/kg. Dr Hugo Mouquet (Institut Pasteur, Paris) showed that in addition to their virus neutralization capacities, many bNAbs also drive Antibody-Dependent Cellular Cytotoxicity (ADCC), as can be demonstrated *in vitro* in the presence of NK cells. They seem, however, unable to block virus transcytosis through a monolayer epithelium *in vitro*, even when transformed into IgA1 and IgA2, but the virus transcytosed in their presence appears to be completely inactivated. The mechanism involved in this unexpected finding is under study.

Phase I clinical trials of passive immunization with several bNAbs have now been performed in both HIV-uninfected and HIV-infected volunteers, as reviewed by Dr John Mascola and Barney Graham (VRC, NIH, Bethesda, MD), and by Dr Michel Nussenzweig (The Rockefeller Institute, New-York). No serious adverse event or dose-limiting toxicity was observed in any of these studies using VRC01 or 3BNC117, even after repeated infusions of the bNAb. In the VRC01 study, six of eight ART-untreated HIV-infected subjects who received a dose of 20 mg/kg had a 1.1–1.8 log reduction in viral load. In the 3BNC117 study, which included 49 HIV-infected subjects, infusion of a dose of 30 mg/kg resulted in up to 2.5 log decrease in viral loads that lasted for more than 28 days [5]. The next step in the development of passive immunization, Phase II/IIb efficacy trials, is in preparation. Trials are planned to begin in 2016 using VRC01, or, perhaps, VRC07, on cohorts in North and South America and in Sub-Saharan Africa.

In four of the passively immunized subjects in the VRC01 study, infusion of the bNAb was followed by the emergence of resistant virus, emphasizing the need to use in the future combinations of several bNAbs to prevent the emergence of resistant viral mutants [19]. Another approach might be to use bi-specific Abs, as discussed

by Dr Gary Nabel (Sanofi, Cambridge, MA). Bispecific bNAbs that recognize two different epitopes, such as the VRC07/PG9 combination, can cover 97% of virus isolates. Efforts are also made to try to improve immunotherapy in HIV-infected persons by using bispecific bNAbs able to direct $CD8^+$ T cells to virally infected cells, by combining for example anti-CD3 specificity in one Fab arm with the VRC07 specificity in the other arm. Knowing that HIV-1 replicates mostly in $PD1^+$ $CD4^+$ T cells, Dr Giuseppe Pantaleo (CHUV, Lausanne, Switzerland) developed a bispecific bNAb that bears anti-PD1 specificity in one Fab arm and broad neutralizing specificity in the other arm. In addition, the Fc arm was conjugated to a toxin. This Ab seems able to completely suppress virus replication.

A very different way of preventing HIV infection by immunoglobulin derivatives was reported by Dr Michael Farzan (The Scripps Res Institute, La Jolla, CA, USA). The immunoadhesin form of CD4, CD4-Ig, was fused with a 15-amino acid tyrosine-sulfated mimetics of the CCR5 coreceptor, CCR5mim1, to form a single molecule, eCD4-Ig. The resulting molecule was found to neutralize a wide panel of HIV-1 isolates, with a geometric mean IC50 of less than 0.05 μg/mL, about 3–4 times lower than those of bNAbs VRC01, NIH45-46 or 3BNC117 [11]. Moreover, eCD4-Ig efficiently neutralized 100% of a diverse panel of neutralization-resistant HIV-1, HIV-2 and SIV isolates, including isolates resistant to VRC01, NIH45-46 and 3BNC117. Rhesus macaques inoculated with an AAV vector stably expressing a rhesus eCD4-Ig were protected from repeated challenges with $SHIV_{-AD8}$. These data suggest that AAV-delivered eCD4-Ig could function like an effective HIV-1 vaccine.

4. Non-neutralizing antibodies

Dr Galit Alter (Ragon Institute, MGH, MIT and Harvard, Cambridge, MA) showed that non-neutralizing Abs which drive antibody-dependent cellular cytotoxicity (ADCC) through their Fc arm play an important role in containing HIV infection, as was reported from the study of correlates of protection in the RV144 clinical trial. These Abs are rapidly generated and primarily target and kill HIV-infected cells. As reported by Dr Margie Ackerman (Thayer School of Engineering, Dartmouth College, USA), they are readily found in elite controllers (EC) who are characterized by their ability to persistently suppress viremia due to their remarkable HIV-specific polyfunctional humoral immune responses. HIV control in ECs is associated with high IgG1 and IgG3 responses, whereas HIV-specific IgG2 and IgG4 responses are prevalent among viremic subjects [1]. The high glycosylation of the IgG molecule (especially the IgG3 molecule) is another notable characteristics of potent anti-HIV Abs.

Dr Julie Overbaugh using an HIV VLP-based sorting strategy identified in a HIV-1 clade A–infected Kenyan woman several specific memory B cells encoding Abs that mediated potent ADCC as well as ADCVI. Two of the ADCC-mediating Abs targeted a CD4-induced epitope, and showed strong cross-clade activity against clades A, B, C, A/D and C/D envelopes. A third Ab targeted the Env V3 loop and showed more limited breadth. Protection of infants by breastfeeding appears to be mostly mediated by maternal IgG1s with broad ADCC activity.

Dr Stephen Kent (Peter Doherty Institute, Melbourne, Australia) showed that semen can interfere with ADCC and inhibit the effectiveness of non-neutralizing anti-HIV Abs. Indeed, seminal plasma seems to contain multiple factors that actively inhibit the ability of NK cells to mediate HIV-specific ADCC as well as the ability of CD8+ T cells to become activated. This raises concerns for mucosal protection against vaginal infection. The question is being studied in the macaque model using cell-associated $SHIV_{162P3}$ challenges.

As reported by Dr Ruth Ruprecht (Texas Biomedical Research Institute/Southwest National Primate Research Center, San-Antonio, TX) passive mucosal immunization studies have provided proof-of-principle that dimeric IgA1s (dIgA1s), but to a lesser extent dIgA2s, can block SHIV acquisition in rhesus macaques challenged by the mucosal route [33]. Thus, passive intrarectal administration of dIgA1 derived from NAb HGN194 [6] protected 5 out of 6 macaques against intrarectal challenge with R5 clade C $SHIV_{1157ipEL-p}$, whereas passive immunization with dIgA2s derived from the same monoclonal NAb protected only 1 out of 6 macaques, in spite of the fact that the two dIgA preparations showed the same virus neutralization potency *in vitro*. The obvious conclusion is that protection against mucosal challenge does not depend on neutralizing potency but probably correlates with virion capture efficacy and with inhibition of virus transcytosis, both of which are definitely higher for dIgA1s than dIgA2s.

Whereas these results demonstrate protective efficacy of mucosal IgAs, the RV144 clinical trial had identified plasma IgA responses to HIV Env as a risk factor for increased HIV acquisition. In an experiment in which rhesus macaques received both an intrarectal infusion of dIgA2 and a non-protective i.v. injection of IgG1, all the animals turned out to be fully protected against an Intrarectal challenge with $SHIV_{1157ipEL-p}$ whereas none of the control animals which received only IgG1 i.v. was protected. This strongly suggests that, to be effective, a HIV vaccine will need to generate both mucosal IgA and systemic IgG responses, a double-edged strategy which the authors like to compare to the military concept of "defense-in-depth" [30]. Infecting HIV will first be countered by the IgAs at the mucosal surface and if some virus particles escape and enter the tissues underneath, they will be arrested by the IgGs.

Dr Julie McElrath (Fred Hutchinson Cancer Res Center, USA) reminded the audience that the risk of mucosal AIDS transmission has been estimated to be 138 per 10,000 receptive anal exposures, 8 per 10,000 vaginal or penile exposures, and 11 per 10,000 insertive anal exposures. Working with mucosal explant models from human foreskin, rectal or vaginal tissue, she was able to show that non-neutralizing Abs, but not bNAbs such as b12, were unable to protect mucosal target cells. The role of Fc-mediated effector functions thus seems surprisingly limited in this model.

A quite different category of non-neutralizing Abs that appears efficient at controlling infection, is the anti-α4β7 Abs [2]. The gut-associated lymphoid tissue (GALT) is a major site of HIV replication, whether infection occurs *via* the sexual (mucosal) route or the i.v. route. It leads to mucosal tissue dysfunction which promotes bacterial translocation and chronic immune activation. The α4β7 integrin heterodimer expressed by lymphoid cells plays a major role in the migration of T cells, NK cells and plasmacytoid dendritic cells to the gut. The same α4β7 can also serve as a receptor and signaling molecule for HIV and SIV. Thus, GALT resident, α4β7-expressing $CD4^+$ T cells with a resting memory phenotype are the primary target of SIV replication during acute infection. The administration of an anti-α4β7 mAb to rhesus macaques just prior to and at 28 days after vaginal or rectal SIV infection delayed the kinetics of infection, greatly reduced the viral load peaks and set points, and preserved the $CD4^+$ T cell count [2]. Most importantly, as outlined by Dr James Arthos (NIAID, NIH, Bethesda, MD, USA), all the anti-α4β7 Ab treated monkeys were still alive at 6 or7 years after infection, whereas all the control animals had died within less than 2 years. PET/CT scan analysis of the surviving infected animals by administration of a labeled anti-SIV Env MAb showed that replication of the virus occurred in many tissues but spared the large intestine. Thus, inhibiting the trafficking of gut-homing $CD4^+$ T cells, NK cells and pDCs allowed to lower gut pathology and to control the evolution of the disease. Protecting the GALT

represents a promising approach to limit the progression of disease in HIV-infected patients.

5. Concluding remarks

The world badly needs an AIDS vaccine: adding an AIDS vaccine to existing prevention measures would dramatically reduce the global spread of HIV, which today affects more than 35 million people worldwide and leads to more than 1.2 million deaths each year. The field of bNAbs, which are able to neutralize a broad array of primary HIV isolates in a cross-clade manner, has opened new horizons for the development of an efficacious preventive AIDS vaccine. BNAbs will likely be a key component of an effective HIV vaccine. However, even though great progress has been made in understanding the ontogeny of the B cell lineages which lead to bNAbs production, it has still not yet been possible to design an immunogen nor a vaccine regimen that induces the full evolution of the B cell lineage toward the production of bNAbs. Numerous studies are exploring rational immunogen modifications that might promote the activation of naïve B cells toward the production of bNAbs and reproduce the lengthy process of affinity maturation and the accumulation of extensive somatic mutations needed to obtain increasingly effective bNAbs [23].

In view of these challenges, several attempts have been made to use passive immunization with bNAbs to prevent HIV or SHIV infection. This approach has been successful in animal models and on-going clinical trials seem to confirm the efficiency of the process in human volunteers. Among innovative techniques is the delivery of the bNAb by vector immunoprophylaxis using an AAV vector. AAV-delivery of eCD4-Ig, which seems so efficient at protecting rhesus macaques against infection with a variety of SHIV or SIV isolates, could also provide a potent and long-lasting protection against HIV-1 and HIV-2 in humans.

The role of non-neutralizing HIV-specific IgG should not be forgotten and may also play an important role in protection against viral infection, as suggested in the RV144 trial by the inverse correlation between the risk for HIV acquisition and the elicitation of IgGs directed against the V2 loop of HIV Env. Finally, mucosal administration of non-neutralizing anti-HIV-1 Abs in the form of dIgA1s represents a potential means to temporarily protect against vaginal or rectal infection for pre-exposure prophylaxis (PrEP).

References

[1] Ackerman ME, Mikhailova A, Brown EP, Dowell KG, Walter BD, Bailey-Keller C, et al. Polyfunctional HIV-specific antibody responses are associated with spontaneous HIV control. PLoS Pathog 2016;12(1):e1005315.

[2] Ansari AA, Reimann KA, Mayne AE, Takahashi Y, Stephenson ST, Wang R, et al. Blocking of α4β7 gut-homing integrin during acute infection leads to decreased plasma and gastro-intestinal tissue viral loads in simian immunodeficiency virus-infected rhesus macaques. J Immunol 2011;186:1044–59.

[3] Bhiman JN, Anthoby C, Doria-Rose NA, Karimanzira O, Schramm CA, Khoza T, et al. Viral variants that initiate and drive maturation of V1V2-directed HIV-1 broadly neutralizing antibodies. Nat Med 2015;21:1332–6.

[4] Burton DR, Mascola JR. Antibody responses to envelope glycoproteins in HIV-1 infection. Nat Immunol 2015;16:571–6.

[5] Caskey M, Klein F, Lorenzi JC, Seaman MS, West Jr AP, Buckley N, et al. Viraemia suppressed in HIV-1-infected humans by broadly neutralizing antibody 3BNC117. Nature 2015;522:487–91.

[6] Corti D, Langedijk JP, Hinz A, Seaman MS, Vanzetta F, Fernandez-Rodriguez RM, et al. Analysis of memory B cell responses and isolation of novel monoclonal antibodies with neutralizing breadth from HIV-1-infected individuals. PLoS ONE 2010;5:e8805.

[7] Derdeyn CA, Moore PL, Morris L. Development of broadly neutralizing antibodies from autologous neutralizing antibody responses in HIV infection. Curr Opin HIV AIDS 2014;9:210–6.

[8] Doria-Rose NA, Schramm CA, Gorman J, Moore PL, Bhiman JN, DeKosky BJ, et al. Developmental pathway for potent V1V2-directed HIV-neutralizing antibodies. Nature 2014;509:55–62.

[9] Dosenovic P, von Boehmer L, Escolano A, Jardine J, Freund NT, Gitlin AD, et al. Immunization for HIV-1 broadly neutralizing antibodies in human Ig knockin mice. Cell 2015;161:1505–15.

[10] Gao F, Bonsignori M, Liao HX, Kumar A, Xia SM, Lu X, et al. Cooperation of B cell lineages in induction of HIV-1-broadly neutralizing antibodies. Cell 2014;158:481–91.

[11] Gardner MR, Kattenhorn LM, Kondur HR, von Schaewen M, Dorfman T, Chiang JJ, et al. AAV-expressed eCD4-Ig provides durable protection from multiple SHIV challenges. Nature 2015;519:87–91.

[12] Graham BS, Ambrosino DM. History of passive antibody administration for prevention and treatment of infectious diseases. Curr Opin HIV AIDS 2015;10:129–34.

[13] Gray ES, Madiga MC, Moore PL, Mlisana K, Abdool Karim SS, Binley JM, et al. Broad neutralization of human immunodeficiency virus type 1 mediated by plasma antibodies against the gp41 membrane-proximal external region. J Virol 2009;83:11265–74.

[14] Gray ES, Madiga MC, Hermanus T, Moore PL, Wibmer CK, Tumba NL, et al. The neutralization breadth of HIV-1 develops incrementally over four years and is associated with CD4+ T cell decline and high viral load during acute infection. J Virol 2011;85:4828–40.

[15] Haynes BF. New approaches to HIV vaccine development. Curr Opin Immunol 2015;35:39–47.

[16] Haynes BF, Kelsoe G, Harrison SC, Kepler TB. B-cell-lineage immunogen design in vaccine development with HIV-1 as a case study. Nat Biotechnol 2012;30:423–33.

[17] Jardine JG, Ota T, Sok D, Pauthner M, Kulp DW, Kalyuzhniy O, et al. HIV VACCINES. Priming a broadly neutralizing antibody response to HIV-1 using a germline-targeting immunogen. Science 2015;349:156–61.

[18] Kim EY, Lorenzo-Redondo R, Little SJ, Chung YS, Phalora PK, Maljkovic Berry I, et al. Human APOBEC3-induced mutation of human immunodeficiency virus type 1 contributes to adaptation and evolution of natural infection. PLoS Pathog 2014;10:e1004281, http://dx.doi.org/10.1371/journal.ppat.1004281.

[19] Klein F, Halper-Stromberg A, Horwitz JA, Gruell H, Scheid JF, Bournazos S, et al. HIV therapy by a combination of broadly neutralizing antibodies in humanized mice. Nature 2012;492:118–22.

[20] Liao HX, Lynch R, Zhou T, Gao F, Alam SM, Boyd SD, et al. Co-evolution of a broadly neutralizing HIV-1 antibody and founder virus. Nature 2013;496:469–76.

[21] Locci M, Havenar-Daughton C, Landais E, Wu J, Kroenke MA, Arlehamn CL, et al. Human circulating PD-1+CXCR3-CXCR5+ memory Tfh cells are highly functional and correlate with broadly neutralizing HIV antibody responses. Immunity 2013;39:758–69.

[22] McLellan JS, Pancera M, Carrico C, Gorman J, Julien JP, Khayat R, et al. Structure of HIV-1 gp120 V1/V2 domain with the broadly neutralizing antibody PG9. Nature 2011;480:336–43.

[23] McGuire AT, Dreyer AM, Carbonetti S, Lippy A, Glenn J, Scheid JF, et al. Antigen modification regulates competition of broad and narrow neutralizing HIV antibodies. Science 2014;346:1380–3.

[24] Moore PL, Williamson C, Morris L. Virological features associated with the development of broadly neutralizing antibodies to HIV-1. Trends Microbiol 2015;23:204–11.

[25] Pancera M, Shahzad-ul-Hussan S, Doria-Rose NA, McLellan JS, Bailer RT, Dai K, et al. Structural basis for diverse N-glycan recognition by HIV-1-neutralizing V1-V2-directed antibody PG16. Nat Struct Mol Biol 2013;20:804–13.

[26] Pegu A, Yang ZY, Bovington JC, Wu L, Ko SY, Schmidt SD, et al. Neutralizing antibodies to HIV-1 envelope protect more effectively in vivo than those to the CD4 receptor. Sci Transl Med 2014;6:243ra88, http://dx.doi.org/10.1126/scitranslmed.3008992.

[27] Sather DN, Carbonetti S, Malherbe DC, Pissani F, Stuart AB, Hessell AJ, et al. Emergence of broadly neutralizing antibodies and viral coevolution in two subjects during the early stages of infection with human immunodeficiency virus type 1. J Virol 2014;88:12968–81.

[28] Saunders KO, Wang L, Joyce MG, Yang ZY, Balazs AB, Cheng C, et al. Broadly neutralizing human immunodeficiency virus type 1 antibody gene transfer protects non-human primates from mucosal simian-human immunodeficiency virus infection. J Virol 2015;89:8334–45.

[29] Scheepers C, Shrestha RK, Lambson BE, Jackson KJH, Wright IA, Naicker D, et al. Ability to develop broadly neutralizing HIV-1 antibodies is not restricted by the germline Ig gene repertoire. J Immunol 2015;194:4371–8.

[30] Sholukh AM, Watkins JD, Vyas HK, Gupta S, Lakhashe SK, Thorat S, et al. Defense-in-depth by mucosally administered anti HIV dimeric IgA2 and systemic IgG1 mAbs: complete protection of rhesus monkeys from mucosal challenge. Vaccine 2015;33:2086–95.

[31] Smith SA, Derdeyn CA. A pathway to HIV-1 neutralization breadth. Nat Med 2015;21:1246–7.

[32] Stoddard CA, Galkina SA, Joshi P, Kosikova G, Long BR, Maidji E, et al. Efficacy of broadly neutralizing monoclonal antibody PG16 in HIV-infected humanized mice. Virology 2014;462–463:115–25.

[33] Watkins JD, Sholukh AM, Mukhtar MM, Sidappa NB, Lakhashe SK, Kim M, et al. Anti-HIV IgA isotypes: differential virion capture and inhibition of transcytosis are linked to prevention of mucosal R5 SHIV transmission. AIDS 2013;27:F13–20.

[34] Wibmer CK, Bhiman JN, Gray ES, Tumba N, Abdool-Karim SS, Williamson C, Morris L, Moore PL. Viral escape from HIV-1 neutralizing antibodies drives increased plasma neutralization breadth through sequential recognition of multiple epitopes and immunotypes. PLoS Pathog 2013;9(10):e1003738.

[35] Zhou T, Zhu J, Wu X, Moquin S, Zhang B, Acharya P, et al. Multidonor analysis reveals structural elements, genetic determinants, and maturation pathway for HIV-neutralization by VRC01-class antibodies. Immunity 2013;30:245–58.

Marc P. Girard*
French National Academy of Medicine, 16 rue Bonaparte, 75006 Paris, France

Roger Le-Grand
Atomic Energy Commission (CEA) INSERM, Paris Sud University, UMR 1184, IDMIT Infrastructures, 92265 Fontenay aux Roses Cedex, France

Valentina Picot
Christophe Longuet
Fondation Mérieux, 17 rue Bourgelat, 69002 Lyon, France

Gary J. Nabel
Sanofi, 640 Memorial Drive, Cambridge, MA 031 39, USA

* Corresponding author. Tel.: +33 680 237 682.
E-mail addresses: Marc.girard36@wanadoo.fr (M.P. Girard), Roger.le-grand@cea.fr (R. Le-Grand), Valentina.picot@fondation-merieux.org (V. Picot), Christophe.longuet@fondation-merieux.org (C. Longuet), Gary.nabel@sanofi.com (G.J. Nabel).

5 February 2016
Available online 20 May 2016