Vaccinal effect of HIV-1 antibody therapy

Mar Naranjo-Gomez, Mireia Pelegrin

Vaccinal effect of HIV-1 antibody therapy

Mar Naranjo-Gomez[1,2] and Mireia Pelegrin[1] *

Address:

[1] Institut de Génétique Moléculaire de Montpellier, Université de Montpellier, CNRS, Montpellier, France

[2] Current address: IRMB, INSERM, University of Montpellier, Montpellier, France

***Corresponding author:**

Mireia Pelegrin

Institute of Molecular Genetics of Montpellier

1919, route de Mende

34293 Montpellier Cedex 5

France

mireia.pelegrin-zurilla@umontpellier.fr

ABSTRACT

Purpose of the review:

This review recalls recent findings regarding the induction of vaccinal effects by HIV-1 broadly neutralizing antibodies (bNAbs) and highlights potential therapeutic strategies to exploit such immunomodulatory properties.

Recent findings:

Studies in different animal models have shown that monoclonal antibodies can generate long-lasting protective immunity. Induction of this vaccinal effect by HIV-1 bNAbs has also been more recently reported in animal models of HIV-1 infection. Notably, bNAbs treatment of macaques infected with the SHIV chimeric virus improved both humoral and cellular adaptive immune responses that contributed to disease control. Importantly, this concept has been extended to HIV-1 infected patients as enhancement of humoral responses was recently reported in HIV-1 patients treated with bNAbs. Studies aiming at elucidating the mechanisms underlying these immunomodulatory properties of bNAbs have identified a role for immune complexes in shaping immune responses against HIV-1. They also highlight different Fc effector functions that might be required for the enhancement of HIV-1 immune responses upon bNAbs treatment.

Summary:

HIV-1 bNAbs can elicit protective adaptive immune responses through mechanisms involving multiple cellular and molecular actors of the immune system. Harnessing these mechanisms will be crucial to achieve protective immunity against HIV-1 infection by bNAbs.

Key-words:

mAb-based immunotherapy, vaccinal effect, immunomodulation, adaptive immunity, immune complexes

Introduction

Monoclonal antibodies (mAbs) offer new therapeutic opportunities for the treatment of viral infections [1]. Recent clinical data have demonstrated the efficacy of several broadly neutralizing antibodies (bNAbs) to control viremia in HIV-infected patients, supporting the idea that bNAbs could broaden the therapeutic arsenal against HIV-1 infection [2–5].

Beyond their neutralization capacity through the binding of their Fab fragment to viral antigens, the biological activity of mAbs is also mediated by the Fc moiety upon interaction with the complement system and Fcγ receptors (FcγRs) expressed by many of the immune system's cells. Much attention has been paid to the potential of bNAbs to clear free virions from the blood as well as to guide host immune effector cells to kill HIV-1 infected cells by several Fc-mediated mechanisms (i.e. complement-dependent cytotoxicity, antibody-dependent cellular phagocytosis, antibody-dependent cell-mediated cytotoxicity,…) [6,7]. However, the opsonization of viral particles and/or infected cells by antiviral mAbs generates immune complexes (ICs) that can bind complement receptors (CRs) and FcγRs expressed on antigen-presenting cells which in turn modulate the antiviral adaptive immune response [8–10]. There is now accumulating evidence that mAbs can enhance antiviral immune responses by recruiting the endogenous immune system of infected individuals. Studies in murine models of retroviral infection have reported the generation of long-lasting protective immunity following mAb-based immunotherapies [11–14], revealing the potential of antiviral mAbs to elicit vaccinal effects. Such studies in mice have since been extended to different preclinical models of viral infections (reviewed in [15]) and more recently in HIV-1 infected patients [16**]. These observations have led to a change in the paradigm on the therapeutic effect of bNAbs as this concept of vaccinal effect induction by antiviral antibodies is now being considered by the scientific and medical communities.

This review summarizes the studies supporting the notion of the vaccinal effects of HIV-1 antibody therapy. It also focuses on the main mechanisms involved in such immunomodulatory properties and discusses the major issues at stake in the elaboration of efficient treatment of HIV-1 infected patients by bNAbs to enhance host immune responses.

HIV-1 bNAbs elicit antiviral host immune responses

Antiviral immune responses induced by antibody-based immunotherapies have been observed in several models of HIV-1 infection in NHP (i.e. infection of macaques by different strains of simian immunodeficiency virus (SIV) or the chimeric virus SHIV) [17]. Treatment of SIV-infected adult macaques with neutralizing polyclonal IgG (SIVIG) effectively controlled viremia and accelerated B cell responses resulting in reduced pathogenesis [18]. SIVIG-treatment of infected macaques was also shown to drive enhanced $CD4^+$ and $CD8^+$ T-cell responses allowing a T cell-based SIV control for up to 2 years [19–21]. Similarly, early treatment of SHIV-infected infant macaques with polyclonal HIV-neutralizing IgG accelerated a *de novo* neutralizing antibody production that was associated with disease protection [22,23]. These observations might have important therapeutic implications if transferable to humans. Supporting this possibility, enhancement of humoral responses by bNAbs has been recently reported in HIV-1 infected patients [16**]. Thus, the administration of the 3BNC117 bNAb to HIV-1 infected individuals elicited host humoral responses in both viremic and virally suppressed subjects on antiretroviral therapy (ART). Significantly, viremic patients showed stronger levels of endogenous anti-HIV-1 antibodies suggesting, as previously reported, that viremia might contribute to the development of antibody responses [24*,25].

HIV bNAbs have also been shown to enhance adaptive cellular responses in SHIV-infected macaques, both in terms of magnitude (by inducing Gag-specific $CD4^+$ and $CD8^+$ T-cells proliferative responses) [26] and quality (by decreased expression of the exhaustion marker PD-1 on Gag-specific $CD4^+$ and $CD8^+$ T-lymphocytes) [27]. Improved T-cell function was observed upon bNAbs treatment 9 months after SHIV infection and was associated with a moderate increase in neutralizing antibody titers. Moreover, long-term viral control in the absence of further bNAbs infusions was achieved in a subset of animals. Importantly, these data show that bNAbs might induce vaccinal effects when administered after establishment of chronic infection. Recently, bNAbs-mediated induction of a protective virus-specific $CD8^+$ T-cell response has been reported after administration of two bNAbs (3BNC117 and 10-1074) to SHIV-infected macaques [28*]. In this study $CD8^+$ T cells depletion led to viral rebound suggesting an essential role of this T-cell subset in controlling viral infection. However, neither the

polyfunctionality of $CD8^+$ T cells nor the distribution of $CD8^+$ T-cell memory subsets differed in controllers *versus* non-controllers. Importantly, very recent exciting results in clinical trials suggest that enhancement of virus-specific T-cell responses might also occur in bNAbs-treated, HIV-1-infected patients. Notably, two out of nine patients treated with a combination of two bNAbs (3BNC117 and 10-1074) during analytical treatment interruption [2] showed long-term HIV-1 control that was associated with improved HIV-1-specific $CD4^+$ and $CD8^+$ T-cell responses (unpublished observation, [29]).

These results highlight the potential of HIV-1 bNAbs in boosting adaptive immune responses. However, the elucidation of the mechanism involved and whether such enhanced immune responses might lead to long-term protection in HIV-1 infected patients still needs further investigations.

Mechanisms involved in the enhancement of adaptive immune responses by antiviral mAbs

Evidence shows that the immunomodulatory action of therapeutic mAbs depends on Fc-FcγR interactions [13,14,30]. Several studies point to a role for ICs in enhancing antigen uptake and presentation by dendritic cells (DCs) *via* FcγRs binding. DCs are in turn strongly activated and drive enhanced immune responses [9,10]. In agreement with this, DCs activated *in vitro* with antibody-opsonized SIV virions improved antiviral T-cell responses. IC-mediated DC stimulation resulted in increased virus-specific $CD4^+$ T-cell responses [19] and enhanced cross-presentation of viral proteins in an Fc-dependent manner [31] (Figure 1). In contrast, DCs activated *in vitro* with polyclonal IgG-opsonized HIV-1 virions showed a decreased capacity to stimulate HIV-specific cytotoxic T lymphocytes (CTL) [32]. However, the nature of the antibody (neutralization capacity, isotype, …) as well as that of the antigen (viral proteins, virions, infected cells) used for the generation of ICs are important parameters affecting the immune response outcome [9]. Taking this into consideration, the question whether ICs generated with HIV-1 bNAbs and different viral determinants might improve T-cell responses deserves further investigations.

Vaccine approaches also support a role for ICs in shaping antibody responses against HIV-1 [33–35]. Immunization of mice with ICs formed with different recombinant HIV-1 envelope gp120 proteins (*r*gp120) and a panel of anti-gp120 antibodies directed against different sites of vulnerability led to enhanced serum levels of HIV-1-specific antibodies. Interestingly, IC-mediated modulation of humoral responses led to a marked skewing to the V1V2 or V3 regions of the HIV-1 viral envelope which was dependent on the gp120 strain and the specificity of the mAb used to form the ICs [36*]. Additional mice immunization studies showed that ICs formed with *r*gp120 proteins and polyclonal antibodies from HIV-neutralizers induced higher HIV-specific antibody titers, higher-avidity antibodies and expanded germinal centers (GC) B-cell reactions as compared to mice vaccinated with ICs from non-neutralizers [37**]. These enhanced humoral responses occurred *via* the acceleration of antigen deposition within B-cell follicles and were dependent on ICs interaction with CRs (Figure 1). These observations are consistent with the role of the complement system in modulating humoral immunity *via* IC-mediated antigen deposition on follicular dendritic cells (FDC) [38]. Importantly, the glycosylation pattern of the antibodies used to generate the ICs was determinant to modulate humoral responses: notably sialylated ICs drove enhanced antigen deposition on B cells and FDC within the GC in a complement-dependent manner [37**] as compared to non-sialylated ICs.

IC-based immunization studies, while informative, do not reflect the viral and immunological environment associated with HIV-1 infection (i.e. viral replication, immune cells activation, immunosuppression, …). In this regard, it is worth mentioning that virus-driven inflammation has been associated with bNAbs development in spontaneous controllers of HIV-1 [24*]. Moreover, ICs used for vaccination studies were mostly generated with *r*gp120. However, in an ongoing infection bNAbs can also opsonize viral particles and infected cells. This different composition of ICs associated with the lysis of opsonized viral determinants by immune effector cells might generate a broader spectrum of danger signals able to modulate the host immune response. Supporting this notion, HIV-1 infected cells are stronger inducers of innate immunity than cell-free virions [39]. Thus, an important issue is to elucidate the immunological mechanisms that drive protective adaptive immune responses in a context of antibody therapy in HIV-1 ongoing infection. Addressing this issue

may be challenging because it requires relevant *in vivo* experimental settings that permit an in-depth study of host immune responses but ethical, technical and cost reasons still limit this type of investigations in humans and NHP. However, *in vivo* studies in retrovirus-infected mice allowed to characterize and conceptualize several molecular and cellular mechanisms involved in the induction of protective humoral and cellular responses by antiviral mAbs [15] (Figue 1). First, ICs formed with infected cells, rather than virions, lead to antiviral CTL responses through FcγR-mediated binding to DCs [13]. This is due to the fact that CTL immunodominant epitopes expressed on infected cells are poorly incorporated into virions [40]. Second, antiviral mAb treatment counteracts the induction of immunosuppressive responses by preventing the expansion of regulatory T cells (Tregs) *via* an Fc-dependent mechanism [41]. Importantly, Tregs depletion leads to improved humoral and cellular antiviral responses [41–43]. Third, mAb-mediated induction of high levels of virus-specific antibodies contribute to the long-term maintenance of $CD8^+$ T-cell responses and is crucial to achieve long-term protection [13,44*]. Forth, neutrophils are essential innate cells for the induction of protective immunity *via* the acquisition of B-cell helper functions that lead to strong primary and memory humoral responses [44*]. These recent findings show a hitherto overlooked immunomodulatory role of neutrophils in mAb-based therapies. They are consistent with previous studies reporting B-cell helper functions of neutrophils in other experimental settings [45,46] and with recent works describing the role of neutrophil-mediated phagocytosis in the protective effect of antiviral mAbs [47–49]. Taken together, these mouse studies highlight the importance of boosting both T-cell and B-cell responses to achieve long-term protective immunity. They also identify several immune actors that come into play. A key question now is to assess whether these mechanisms of antibody-mediated immunomodulation also apply to HIV-1 bNAbs-based immunotherapies.

How can the vaccinal effect be improved?

A fine dissection of the immune actors at play in the boosting of adaptive immune response by bNAbs will be required to translate this concept of vaccinal effect into efficient HIV-1 treatment. However, the immunological mechanism involved in this process already identified in preclinical studies might

help the design of improved immunotherapies. Two distinct but complementary approaches might be considered: the improvement of bNAbs properties [50] and appropriate host-directed therapies (HDT) [51] (Figure 2). Both approaches might be guided by immune correlates of protection (identified either from vaccine strategies [52–54*] or from analysis of cohorts of HIV-1-infected subjects with or without disease progression [55,56*]) that point to a key role of the quality of antibody responses (i.e. polyfunctionality, glycoforms, ….) rather than the quantity.

Improvement of bNAbs properties might be achieved by exploiting optimal Fc-FcγRs/CRs interactions. This will require the identification of Fc-dependent effector functions needed for the induction of vaccinal effects together with the identification of the main immune cells and molecular effectors involved. In keepin with this, defined Fc effector functions involving both FcγRs and CRs might predict the development of HIV-1-neutralizing antibody responses [56*,57*]. Antibody subclass selection together with Fc-glycoengineering may represent a major asset to induce vaccinal effects, as both isotype and Fc-glycosylation pattern regulate antibody activity. Due to its enhanced affinity for FcγRs, most HIV-1 bNAbs tested in clinical trials are of the IgG1 isotype. Reflecting the antiviral efficiency of this antibody subclass, IgG1 responses against HIV-1 antigens have been shown to be the best predictor of HIV-1 neutralization breadth in plasma of chronically-infected patients [58]. However, highly-functional HIV-1-specific IgG3 have been shown to correlate with vaccine efficacy [59] and to contribute to disease control in spontaneous HIV-1 controllers [60]. This suggests that bNAbs of IgG3 isotype might also be considered, alone or in combination with IgG1, to exploit multiple Fc effector functions [55].

Fc-engineering to enhance neonatal Fc receptor (FcRn) binding might represent another interesting approach. This Fc modification leads to increased bNAbs half-life *in vivo* [61**] and improved protection against SHIV infection in macaques [62]. It could also potentially promote the induction of vaccinal effects due to the role of FcRn in the regulation of immune responses [63]. Fc-glycoengineering might also be exploited to enhance protective immune responses by bNAbs as antibody glycosylation alters the affinity of antibodies for Fc receptors and has immunomodulatory

properties (reviewed in [64]). Supporting this notion, as above-mentioned, sialylated HIV-1 bNAbs used in IC-based immunization studies enhanced humoral responses [37**]. A refined understanding of Fc glycosylation profiles linked to the associated Fc effector functions and FcRs/CRs interactions will guide the engineering of therapeutic antibodies with enhanced immunomodulatory properties.

The combination of improved bNAbs with HDT might also be rewarding to enhance host immune responses. However, prior to treatment it would be necessary to take into consideration the viral and immunological status of HIV-1-infected patients because virus-driven inflammation, immune cells-activation, function and counts as well as immunosuppression mechanisms differ between acute *versus* chronic infection. Host intrinsic factors such as gender, genetic landscape and gut microbiome might also be considered [65–67].

One approach might rely on counteracting immunosuppressive immune responses already established in infected subjects. To this end, inhibition of Tregs-mediated immunosuppression has been attempted by several therapeutic approaches aiming at their modulation and/or depletion [68–71]. It is noteworthy that treatment intensification (5-drug ART) in HIV-1-infected patients has been recently associated with reduced frequencies of Tregs and broad HIV-1-specific $CD8^+$ T cell responses [72]. Release of immunosuppression might be also achieved by targeting 'immune checkpoints' molecules that play a critical role in the exhaustion/dysfunction of immune responses (i.e. PD-1, CTLA4, TIM-3, CD160, … reviewed in [73,74]). Inhibiting the PD-1–PD-1L interaction has been shown to enhance virus-specific cellular responses in animal models of HIV-1 infection [75] and in HIV-1-infected patients [76]. Notably, a drastic and sustained decrease of the HIV-1 reservoir was associated with an increase in HIV-1-specific $CD8^+$ T cells in a HIV-positive lung cancer patient under anti-PD1 therapy. Interestingly, PD-1 blockade has also been shown to improve HIV-specific $CD4^+$ T cells [77] and NK cells function [78**] as well as to enhance HIV-1-specific immunoglobulin production [79]. Finally, the simultaneous blocking of PD-1 and the immune checkpoints BTLA and TIM-3 enhanced proliferation of HIV-1-specific T cells and cytokine production in response to Gag and Nef peptides [80].

Combo therapies with bNAbs and immunostimulatory agents might also be considered to induce vaccinal effects. Targeting T-cell co-stimulatory receptors such as CD40, OX40, GITR, and CD137 [73,81] has been shown to improve antiviral immune responses in different infection settings [82–84] and to synergize with PD-1 blockade [73]. An alternative approach would reside in the use of agonists of Toll-like receptors (TLRs) as their activation is essential for the development of antiviral responses. Supporting this idea, the administration of the PGT121 bNAb together with the TLR7 agonist vesatolimod (GS-9620) during ART delayed viral rebound following discontinuation of ART in SHIV-infected monkeys [85**]. GS-9620 administration resulted in the activation of $CD4^+$ T cells, NK cells and monocytes as well as increased plasma levels of proinflammatory cytokines. TLR7 agonists also induced transient viremia and reduced the viral reservoir in SIV-infected macaques on ART [86**]. Interestingly, TLR7 agonists not only activated multiple innate and adaptive immune cell populations (i.e. $CD4^+$T-cells, $CD8^+$ T-cells, NK cells and B cells) but also induced expression of SIV RNA, suggesting that TLR7 agonists may facilitate reduction of viral reservoirs. Comparable effects on HIV-1 reservoirs reactivation and immune activation were reported by the TLR3 agonist poly (I:C) [87*]. Overall, these data point to the potential of bNAbs administration together with innate immune stimulation as a possible strategy for both targeting the viral reservoir and enhancing antiviral host responses. Similarly, combining bNAbs therapy with latency-reversing agents, other than TLR agonists, might lead to the release of viral antigens that should favor the formation of ICs and, thereby, the stimulation of anti-HIV-1 immunity [88,89]. Along with this, the contribution of PD-1 to the establishment and maintenance of HIV latency has recently been shown [90], suggesting that this immune checkpoint might be also explored as a target to reverse latency.

While the above-mentioned immunomodulation strategies seem promising, the achievement of protective immune responses allowing a HIV functional cure will certainly need combinatorial interventions involving multiple HDT and bNAbs with improved properties.

Conclusion

Evidence shows that bNAbs can elicit protective adaptive immune responses. This highlights the need to revisit the concept of bNAbs as only "passive" immunotherapies. However, converting bNAbs into "active" immunotherapies will require the rethinking of the design of antiviral bNAbs-based immunotherapies. A major challenge ahead of us is to elucidate the molecular and cellular mechanisms driving vaccinal effects by bNAbs, such as they might be harnessed and efficiently exploited in therapeutic applications to achieve protective immunity against HIV-1 infection.

To achieve this aim, it is likely that the induction of protective immune responses by HIV bNAbs will require not only the development of new generations of bNAbs with enhanced efficacy, but also the improvement of their use, alone or in combination therapies.

Key points:

- bNAbs can elicit protective adaptive immune responses
- bNAbs shape immune response through the formation of immune complexes that bind to Fc receptors expressed by different immune cells
- bNAbs-induced vaccinal effects might be potentiated by therapeutic interventions including engineering of bNAbs with improved properties combined with host-directed therapies
- A refined understanding of the multiple mechanisms involved in the boosting of immune responses by bNAbs is required to optimally exploit their immunomodulatory properties

Acknowledgements

We are grateful to Helen Phillips Bevis (Traductions Stratégiques) for English editing services and to Dr. Gilles Uzé for critical reading of the manuscript.

Financial support and sponsorship

This work was supported by grants from Sidaction, ANRS and the Fondation pour la Recherche Médicale. M. Naranjo-Gomez and M. Pelegrin are members of the "MabImprove Labex", a public grant overseen by the French National Research Agency (ANR) as part of the "Investments for the future" program (reference: ANR-10-LABX -53-01) that also supported this work.

Conflict of interest

None.

Figure legends

Figure 1. Mechanisms involved in the enhancement of adaptive immune responses by antiviral mAbs. Antiviral mAbs can opsonize both virus and infected cells. The resulting ICs can be recognized by different Fc receptors (FcγRs/CRs) expressed on multiple immune system's cells and regulate immune responses : (i) ICs recognition by DCs through FcγRs binding leads to enhanced antigen uptake and presentation, allowing the induction of stronger cellular antiviral immune responses, (ii) ICs can also drive enhanced antigen deposition on B cells and FDC in a complement-dependent manner resulting in improved humoral responses, (iii) upon mAb treatment of infected individuals, splenic neutrophils can acquire B-cell helper functions in a FcγR-dependent manner leading to improved humoral responses, and (iv) mAb treatment of infected individuals prevents the expansion of Tregs in a Fc-dependent manner *via* mechanisms still to be elucidated. Tregs depletion allows the restoration of both cellular and humoral responses. The potential role of other innate immune cells (i.e. NK cells, monocytes, …) in the induction of vaccinal effects by antiviral mAbs, by either direct or indirect mechanisms [90,91] , needs to be further investigated.

Figure 2. Potential therapeutic interventions to improve the vaccinal effect of HIV-1 antibody therapy.

The elucidation of the immunological mechanism that drive the induction of vaccinal effects by bNAbs will guide the design of efficient therapeutic interventions. Two distinct but complementary approaches might be considered: the improvement of bNAbs properties combined with adapted HDT. Improvement of bNAbs properties might rely on isotype selection as well as on Fc-engineering to enhance Fc receptors-specific binding. Regarding HDT, prior to any therapeutic intervention, the viral and immunological status of infected patients as well as host intrinsic factors will have to be taken into consideration. HDT might rely on counteracting immunosuppressive responses and/or promoting potent antiviral immune response through the use of different immunostimulatory molecules and latency-reversing agents.

References and recommended reading

Papers of particular interest, published within the annual period of the review, have been highlighted as:

* of special interest

** of outsatnding interest

1. Salazar G, Zhang N, Fu T-M, An Z. Antibody therapies for the prevention and treatment of viral infections. *NPJ Vaccines* 2017, 2:19.

2. Mendoza P, Gruell H, Nogueira L, *et al*. Combination therapy with anti-HIV-1 antibodies maintains viral suppression. *Nature* 2018, 561:479–484.

3. Bar-On Y, Gruell H, Schoofs T, *et al*. Safety and antiviral activity of combination HIV-1 broadly neutralizing antibodies in viremic individuals. *Nat Med* 2018, 24:1701–1707.

4. Carrillo J, Clotet B, Blanco J. Antibodies and Antibody Derivatives: New Partners in HIV Eradication Strategies. *Front Immunol* 2018, 9:2429.

5. Gruell H, Klein F: Antibody-mediated prevention and treatment of HIV-1 infection. *Retrovirology* 2018, 15:73.

6. Lu LL, Suscovich TJ, Fortune SM, Alter G. Beyond binding: antibody effector functions in infectious diseases. *Nat Rev Immunol* 2018, 18:46–61.

7. Bournazos S, Ravetch JV. Anti-retroviral antibody FcγR-mediated effector functions. *Immunol Rev* 2017, 275:285–295.

8. Nimmerjahn F, Ravetch JV. Antibody-mediated modulation of immune responses. *Immunol Rev* 2010, Jul, 236:265–75.

9. Lambour J, Naranjo-Gomez M, Piechaczyk M, Pelegrin M. Converting monoclonal antibody-based immunotherapies from passive to active: bringing immune complexes into play. *Emerg Microbes Infect* 2016, 5:e92.

10. Wang X-Y, Wang B, Wen Y-M. From therapeutic antibodies to immune complex vaccines. *NPJ Vaccines* 2019, 4:2.

11. Gros L, Dreja H, Fiser AL, *et al*. Induction of long-term protective antiviral endogenous immune response by short neutralizing monoclonal antibody treatment. *J Virol* 2005, 79:6272–80.

12. Gros L, Pelegrin M, Michaud HA, *et al*. Endogenous cytotoxic T-cell response contributes to the long-term antiretroviral protection induced by a short period of antibody-based immunotherapy of neonatally infected mice. *J Virol* 2008, 82:1339–49.

13. Michaud HA, Gomard T, Gros L, T *et al*. A crucial role for infected-cell/antibody immune complexes in the enhancement of endogenous antiviral immunity by short passive immunotherapy. *PLoS Pathog* 2010, 6:e1000948.

14. Nasser R, Pelegrin M, Michaud H. A, *et al*. Long-lasting protective antiviral immunity induced by passive immunotherapies requires both neutralizing and effector functions of the administered monoclonal antibody. *J Virol* 2010, 84:10169–81.

15. Pelegrin M, Naranjo-Gomez M, Piechaczyk M. Antiviral Monoclonal Antibodies: Can They Be More Than Simple Neutralizing Agents? *Trends Microbiol* 2015, 23:653–65.

16. Schoofs T, Klein F, Braunschweig M, *et al*. HIV-1 therapy with monoclonal antibody 3BNC117 elicits host immune responses against HIV-1. *Science* 2016, 352:997–1001.

** This is the first and only study reporting the elicitation of antiviral immune responses by bNAbs in HIV-1 infected patients.

17. Hessell AJ, Haigwood NL. Animal models in HIV-1 protection and therapy. *Curr Opin HIV AIDS* 2015, 10:170–176.

18. Haigwood NL, Montefiori DC, Sutton WF, *et al*. Passive immunotherapy in simian immunodeficiency virus-infected macaques accelerates the development of neutralizing antibodies. *J Virol* 2004, 78:5983–95.

19. Yamamoto H, Kawada M, Takeda A, *et al*. Post-infection immunodeficiency virus control by neutralizing antibodies. *PLoS One* 2007, 2:e540.

20. Yamamoto T, Iwamoto N, Yamamoto H, T *et al*. Polyfunctional CD4+ T-cell induction in neutralizing antibody-triggered control of simian immunodeficiency virus infection. *J Virol* 2009, 83:5514–24.

21. Iseda S, Takahashi N, Poplimont H, *et al*. Biphasic CD8+ T-Cell Defense in Simian Immunodeficiency Virus Control by Acute-Phase Passive Neutralizing Antibody Immunization. *J Virol* 2016, 90:6276–6290.

22. Ng CT, Jaworski JP, Jayaraman P, *et al*. Passive neutralizing antibody controls SHIV viremia and enhances B cell responses in infant macaques. *Nat Med* 2010, 16:1117–9.

23. Jaworski JP, Kobie J, Brower Z, *et al*. Neutralizing polyclonal IgG present during acute infection prevents rapid disease onset in simian-human immunodeficiency virus SHIVSF162P3-infected infant rhesus macaques. *J Virol* 2013, 87:10447–59.

24. Dugast A-S, Arnold K, Lofano G, *et al*. Virus-driven Inflammation Is Associated With the Development of bNAbs in Spontaneous Controllers of HIV. *Clin Infect Dis* 2017, 64:1098–1104.

*This study reports that antigen persistence is associated with a unique inflammatory profile that might be linked to the development of neutralizing antibodies.

25. Mikell I, Sather DN, Kalams SA, *et al*. Characteristics of the earliest cross-neutralizing antibody response to HIV-1. *PLoS Pathog* 2011, 7:e1001251.

26. Watkins JD, Siddappa NB, Lakhashe SK, *et al*. An anti-HIV-1 V3 loop antibody fully protects cross-clade and elicits T-cell immunity in macaques mucosally challenged with an R5 clade C SHIV. *PLoS One* 2011, 6:e18207.

27. Barouch DH, Whitney JB, Moldt B, *et al*. Therapeutic efficacy of potent neutralizing HIV-1-specific monoclonal antibodies in SHIV-infected rhesus monkeys. *Nature* 2013, 503:224–8.

28. Nishimura Y, Gautam R, Chun T-W, *et al*. Early antibody therapy can induce long-lasting immunity to SHIV. *Nature* 2017, 543:559–563.

** This study reports that passive immunotherapy by bNAbs during acute SHIV infection facilitates the emergence of potent and durable $CD8^+$ T-cell immunity.

29. Nussenzweig MC: Discovery and development of HIV broadly neutralizing antibodies*, 26th Conference on Retroviruses and Opportunistic Infections,* Seattle, Washington, CROI Foundation/IAS-USA (2019).

30. DiLillo DJ, Ravetch JV. Differential Fc-Receptor Engagement Drives an Anti-tumor Vaccinal Effect. *Cell* 2015, 161:1035–45.

31. Villinger F, Mayne AE, Bostik P, *et al*. Evidence for antibody-mediated enhancement of simian immunodeficiency virus (SIV) Gag antigen processing and cross presentation in SIV-infected rhesus macaques. *J Virol* 2003, 77:10–24.

32. Posch W, Cardinaud S, Hamimi C, *et al*. Antibodies attenuate the capacity of dendritic cells to stimulate HIV-specific cytotoxic T lymphocytes. *J Allergy Clin Immunol* 2012, 130:1368–74 e2.

33. Hioe CE, Visciano ML, Kumar R, *et al*. The use of immune complex vaccines to enhance antibody responses against neutralizing epitopes on HIV-1 envelope gp120. *Vaccine* 2009, 28:352–60.

34. Kumar R, Tuen M, Li H, *et al*. Improving immunogenicity of HIV-1 envelope gp120 by glycan removal and immune complex formation. *Vaccine* 2011, 29:9064–74.

35. Kumar R, Tuen M, Liu J, *et al*. Elicitation of broadly reactive antibodies against glycan-modulated neutralizing V3 epitopes of HIV-1 by immune complex vaccines. *Vaccine* 2013, 31:5413–21.

36. Hioe CE, Kumar R, Upadhyay C, J *et al*. Modulation of Antibody Responses to the V1V2 and V3 Regions of HIV-1 Envelope by Immune Complex Vaccines. *Front Immunol* 2018, 9:2441.

* This study reports that allosteric and antigenic changes can be detected on immune complexes involving anti-HIV-1 antibodies and HIV-1 envelope gp120. These changes can modify the immunogenic properties of the target antigen and can shape antibody responses towards defined HIV-1 envelope sites of interest.

37. Lofano G, Gorman MJ, Yousif AS, *et al*. Antigen-specific antibody Fc glycosylation enhances humoral immunity via the recruitment of complement. *Sci Immunol* 2018, 3.

** This study reports that antibody Fc glycosylation is crucial to enhance humoral immune responses by immune complexes *via* the recruitment of the complement receptors.

38. Carroll MC, Isenman DE. Regulation of humoral immunity by complement. *Immunity* 2012, 37:199–207.

39. Lepelley A, Louis S, Sourisseau M, *et al*. Innate sensing of HIV-infected cells. *PLoS Pathog* 2011, 7:e1001284.

40. Chen W, Qin H, Chesebro B, Cheever MA. Identification of a gag-encoded cytotoxic T-lymphocyte epitope from FBL-3 leukemia shared by Friend, Moloney, and Rauscher murine leukemia virus-induced tumors. *J Virol* 1996, 70:7773–82.

41. Nasser R, Pelegrin M, Plays M, *et al*. Control of regulatory T cells is necessary for vaccine-like effects of antiviral immunotherapy by monoclonal antibodies. *Blood* 2013, 121:1102–11.

42. Dietze KK, Zelinskyy G, Liu J, *et al*. Combining regulatory T cell depletion and inhibitory receptor blockade improves reactivation of exhausted virus-specific CD8+ T cells and efficiently reduces chronic retroviral loads. *PLoS Pathog* 2013, 9:e1003798.

43. Moore TC, Messer RJ, Gonzaga LM, *et al*. Effects of Friend Virus Infection and Regulatory T Cells on the Antigen Presentation Function of B Cells. *MBio* 2019, 10.

44. Naranjo-Gomez M, Lambour J, Piechaczyk M, Pelegrin M. Neutrophils are essential for induction of vaccine-like effects by antiviral monoclonal antibody immunotherapies. *JCI Insight* 2018, 3.

* This study reports for the first time the essential immunomodulatory role of neutrophils in the induction of protective immunity by antiviral mAbs.

45. Puga I, Cols M, Barra CM, *et al*. B cell-helper neutrophils stimulate the diversification and production of immunoglobulin in the marginal zone of the spleen. *Nat Immunol* 2011, 13:170–80.

46. Parsa R, Lund H, Georgoudaki AM, *et al*. BAFF-secreting neutrophils drive plasma cell responses during emergency granulopoiesis. *J Exp Med* 2016, 213:1537–53.

47. Ackerman ME, Dugast AS, McAndrew EG, *et al*. Enhanced phagocytic activity of HIV-specific antibodies correlates with natural production of immunoglobulins with skewed affinity for FcgammaR2a and FcgammaR2b. *J Virol* 2013, 87:5468–76.

48. Sips M, Krykbaeva M, Diefenbach TJ, *et al*. Fc receptor-mediated phagocytosis in tissues as a potent mechanism for preventive and therapeutic HIV vaccine strategies. *Mucosal Immunol* 2016, 9:1584–1595.

49. Gunn BM, Yu W-H, Karim MM, *et al*. A Role for Fc Function in Therapeutic Monoclonal Antibody-Mediated Protection against Ebola Virus. *Cell Host Microbe* 2018, 24:221-233.e5.

50. Sun M, Li Y, Zheng H, Shao Y. Recent Progress toward Engineering HIV-1-Specific Neutralizing Monoclonal Antibodies. *Front Immunol* 2016, 7:391.

51. Kaufmann SHE, Dorhoi A, Hotchkiss RS, Bartenschlager R. Host-directed therapies for bacterial and viral infections. *Nat Rev Drug Discov* 2018, 17:35–56.

52. Yates NL, Liao HX, Fong Y, *et al. V*accine-induced Env V1-V2 IgG3 correlates with lower HIV-1 infection risk and declines soon after vaccination. Sci Transl Med. 19 mars 2014;6:228ra39.

53. Alter G, Barouch D; Immune Correlate-Guided HIV Vaccine Design. *Cell Host Microbe* 2018, 24:25–33.

54. Pauthner MG, Nkolola JP, Havenar-Daughton C, *et al*. Vaccine-Induced Protection from Homologous Tier 2 SHIV Challenge in Nonhuman Primates Depends on Serum-Neutralizing Antibody Titers. *Immunity* 2019, 50:241-252.e6.

* This study reports that neutralizing antibody titers induced by HIV envelope trimer immunization correlate with the protection of macaques against SHIV challenge. It also highlights that neither T-cells nor antibody-dependent cellular cytotoxicity correlate with protection.

55. Ackerman ME, Mikhailova A, Brown EP, *et al*. Polyfunctional HIV-Specific Antibody Responses Are Associated with Spontaneous HIV Control. *PLoS Pathog* 2016, 12:e1005315.

56. Alter G, Dowell KG, Brown EP, *et al*. High-resolution definition of humoral immune response correlates of effective immunity against HIV. *Mol Syst Biol* 2018, 14:e7881.

***** This study computationally analyzes and modelizes humoral immune responses (IgG Fab properties, Fc characteristics and effector functions) in a cohort of HIV-infected subjects with varying viral control to identify humoral correlates of potent antiviral antibody-directed effector activity and effective viral suppression.

57. Richardson SI, Chung AW, Natarajan H, *et al*. HIV-specific Fc effector function early in infection predicts the development of broadly neutralizing antibodies. *PLoS Pathog* 2018, 14:e1006987.

* This study investigates Fc effector functionality of HIV-specific IgG plasma antibodies in HIV-infected patients with or without development of neutralizing antibody responses. It highlights that the Fc effector function profile might predict the development of neutralization breadth.

58. Kadelka C, Liechti T, Ebner H, *et al*. Distinct, IgG1-driven antibody response landscapes demarcate individuals with broadly HIV-1 neutralizing activity. *J Exp Med* 2018, 215:1589–1608.

59. Chung AW, Ghebremichael M, Robinson H, *et al*. Polyfunctional Fc-effector profiles mediated by IgG subclass selection distinguish RV144 and VAX003 vaccines. *Sci Transl Med* 2014, 6:228ra38.

60. Sadanand S, Das J, Chung AW, *et al*. Temporal variation in HIV-specific IgG subclass antibodies during acute infection differentiates spontaneous controllers from chronic progressors. *AIDS* 2018, 32:443–450.

61. Gautam R, Nishimura Y, Gaughan N, *et al*. A single injection of crystallizable fragment domain-modified antibodies elicits durable protection from SHIV infection. *Nat Med* 2018, 24:610–616.

** This study reports that the introduction of the LS mutation to the Fc-fragment of HIV-1 bNAbs increases the bNAbs half-life and extends the protection period in SHIV-infected macaques.

62. Ko SY, Pegu A, Rudicell RS, *et al*. Enhanced neonatal Fc receptor function improves protection against primate SHIV infection. *Nature* 2014, 514:642–5.

63. Rath T, Baker K, Pyzik M; Blumberg RS: Regulation of immune responses by the neonatal fc receptor and its therapeutic implications. *Front Immunol* 2015, 5:664.

64. Jennewein MF, Alter G; The Immunoregulatory Roles of Antibody Glycosylation. *Trends Immunol* 2017, 38:358–372.

65. Fischinger S, Boudreau CM, Butler AL, *et al*. Sex differences in vaccine-induced humoral immunity. *Semin Immunopathol* 2018, doi:10.1007/s00281-018-0726-5.

66. Subbaraman H, Schanz M, Trkola A; Broadly neutralizing antibodies: What is needed to move from a rare event in HIV-1 infection to vaccine efficacy? *Retrovirology* 2018, 15:52.

67. Koay WLA, Siems LV, Persaud D; The microbiome and HIV persistence: implications for viral remission and cure. *Curr Opin HIV AIDS* 2018, 13:61–68.

68. Younas M, Hue S, Lacabaratz C, *et al*. IL-7 modulates in vitro and in vivo human memory T regulatory cell functions through the CD39/ATP axis. *J Immunol* 2013, 191:3161–3168.

69. Brezar V, Hani L, Surenaud M, *et al*. Negative modulation of suppressive HIV-specific regulatory T cells by IL-2 adjuvanted therapeutic vaccine. *PLoS Pathog* 2017, 13:e1006489.

70. Nishikawa H, Sakaguchi S. Regulatory T cells in cancer immunotherapy. *Curr Opin Immunol* 2014, 27:1–7.

71. Huijts CM, Lougheed SM, Bodalal Z, v *et al*. The effect of everolimus and low-dose cyclophosphamide on immune cell subsets in patients with metastatic renal cell carcinoma: results from a phase I clinical trial. *Cancer Immunol Immunother* 2019, doi:10.1007/s00262-018-2288-8.

72. Grützner EM, Hoffmann T, Wolf E, *et al*. Treatment Intensification in HIV-Infected Patients Is Associated With Reduced Frequencies of Regulatory T Cells. *Front Immunol* 2018, 9:811.

73. Attanasio J, Wherry EJ. Costimulatory and Coinhibitory Receptor Pathways in Infectious Disease. *Immunity* 2016, 44:1052–1068.

74. Seddiki N, Lévy Y. Therapeutic HIV-1 vaccine: time for immunomodulation and combinatorial strategies. *Curr Opin HIV AIDS* 2018, 13:119–127.

75. Velu V, Titanji K, Zhu B, *et al*. Enhancing SIV-specific immunity in vivo by PD-1 blockade. *Nature* 2009, 458:206–10.

76. Guihot A, Marcelin A-G, Massiani M-A, *et al*. Drastic decrease of the HIV reservoir in a patient treated with nivolumab for lung cancer. *Ann Oncol* 2018, 29:517–518.

77. Porichis F, Kwon DS, Zupkosky J, *et al*. Responsiveness of HIV-specific CD4 T cells to PD-1 blockade. *Blood* 2011, 118:965–974.

78. Porichis F, Hart MG, Massa A, *et al*. Immune Checkpoint Blockade Restores HIV-Specific CD4 T Cell Help for NK Cells. *J Immunol* 2018, 201:971–981.

** This study demonstrates the relationship between $CD4^+$ T cell impairment and NK cells exhaustion in HIV-1 infection and reports that PD-1 blockade enhances cytokine secretion of NK cells *via* restored HIV-specific $CD4^+$ T-cell function.

79. Cubas RA, Mudd JC, Savoye A-L, *et al*. Inadequate T follicular cell help impairs B cell immunity during HIV infection. *Nat Med* 2013, 19:494–499.

80. Grabmeier-Pfistershammer K, Stecher C, Zettl M, *et al*. Antibodies targeting BTLA or TIM-3 enhance HIV-1 specific T cell responses in combination with PD-1 blockade. *Clin Immunol* 2017, 183:167–173.

81. Mayes PA, Hance KW, Hoos A. The promise and challenges of immune agonist antibody development in cancer. *Nat Rev Drug Discov* 2018, 17:509–527.

82. Goulding J, Tahiliani V, Salek-Ardakani S. OX40:OX40L axis: emerging targets for improving poxvirus-based CD8(+) T-cell vaccines against respiratory viruses. *Immunol Rev* 2012, 244:149–68.

83. Lee S, Mittler RS, Moore ML. Targeting CD137 enhances vaccine-elicited anti-respiratory syncytial virus CD8+ T cell responses in aged mice. *J Immunol* 2014, 192:293–9.

84. Vezys V, Penaloza-MacMaster P, Barber DL, *et al*. 4-1BB signaling synergizes with programmed death ligand 1 blockade to augment CD8 T cell responses during chronic viral infection. *J Immunol* 2011, 187:1634–42.

85. Borducchi EN, Liu J, Nkolola JP, *et al*. Antibody and TLR7 agonist delay viral rebound in SHIV-infected monkeys. Nature 2018, 563:360–364.

** This study reports the potential of bNAbs administration combined with innate immune stimulation (TLR7 agonists) as possible strategy for enhancing antiviral immunity and targeting the viral reservoir.

86. Lim S-Y, Osuna CE, Hraber PT, *et al*. TLR7 agonists induce transient viremia and reduce the viral reservoir in SIV-infected rhesus macaques on antiretroviral therapy. *Sci Transl Med* 2018, 10.

**This study reports that TLR7 agonists induce transient viremia and reduce the viral reservoir in SIV-infected rhesus macaques on antiretroviral therapy

87. Cheng L, Wang Q, Li G, Banga R, *et al*. TLR3 agonist and CD40-targeting vaccination induces immune responses and reduces HIV-1 reservoirs. *J Clin Invest* 2018, 128:4387–4396.

*This study reports that TLR3 agonist in combination with a CD40-targeting vaccination induces HIV-1-specific human $CD8^+$ and $CD4^+$ T-cell responses and reduces HIV-1 reservoirs in humanized mice with HIV-1 persistent infection.

88. Perdigão P, Gaj T, Santa-Marta M, *et al*. Reactivation of Latent HIV-1 Expression by Engineered TALE Transcription Factors. *PLoS ONE* 2016, 11:e0150037.

89. Cary DC, Peterlin BM. Targeting the latent reservoir to achieve functional HIV cure. *F1000Res* 2016, 5.

90. Evans VA, van der Sluis RM, Solomon A, *et al*. Programmed cell death-1 contributes to the establishment and maintenance of HIV-1 latency. *AIDS* 2018, 32:1491–1497.

91. Bradley T, Peppa D, Pedroza-Pacheco I, *et al.* RAB11FIP5 Expression and Altered Natural KillerCell Function Are Associated with Induction of HIV Broadly Neutralizing Antibody Responses. Cell. 4 oct 2018;175(2):387-399.e17.

92. Kramski M, Parsons MS, Stratov I, Kent SJ. HIV-specific antibody immunity mediated through NK cells and monocytes. Curr HIV Res. juill 2013;11(5):388-406.

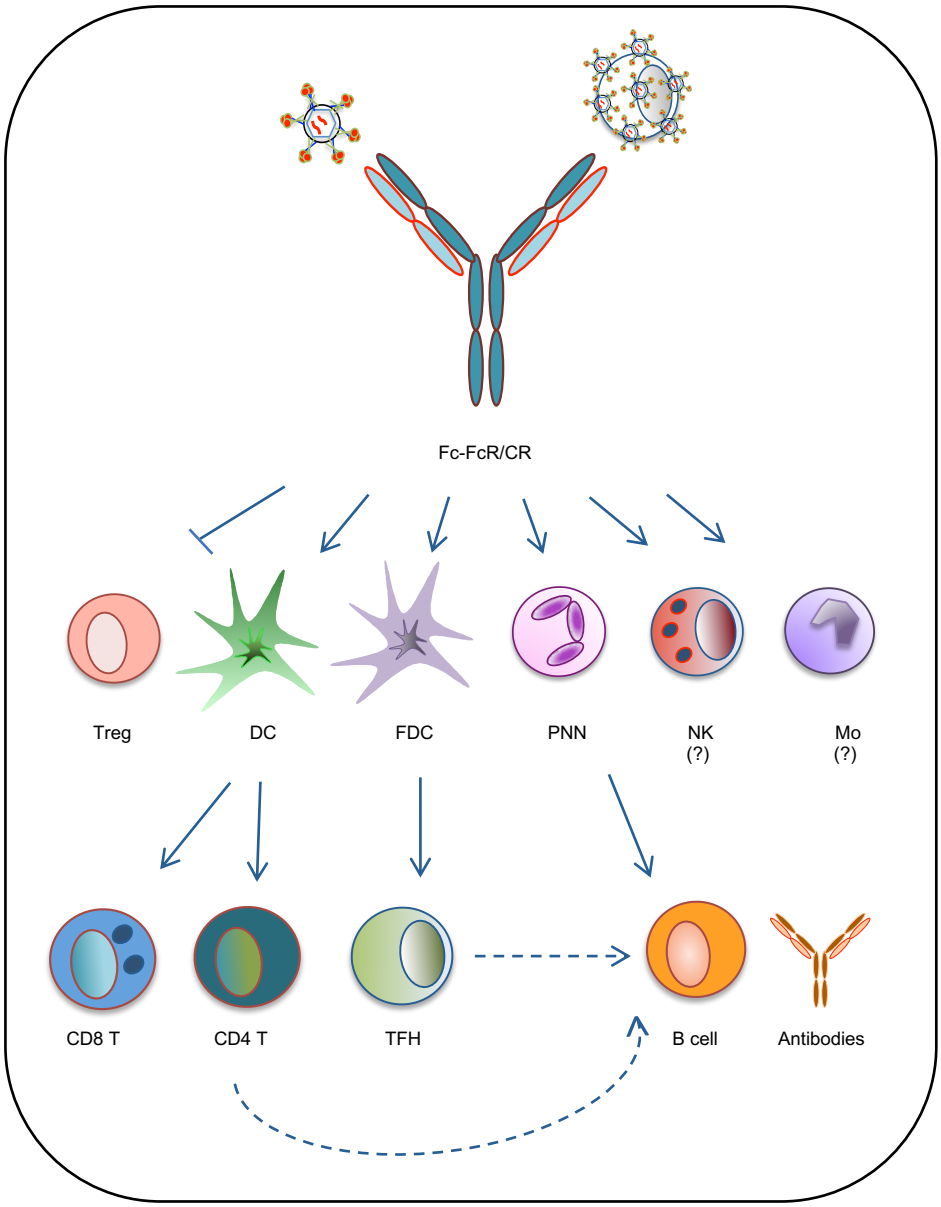

Figure 1

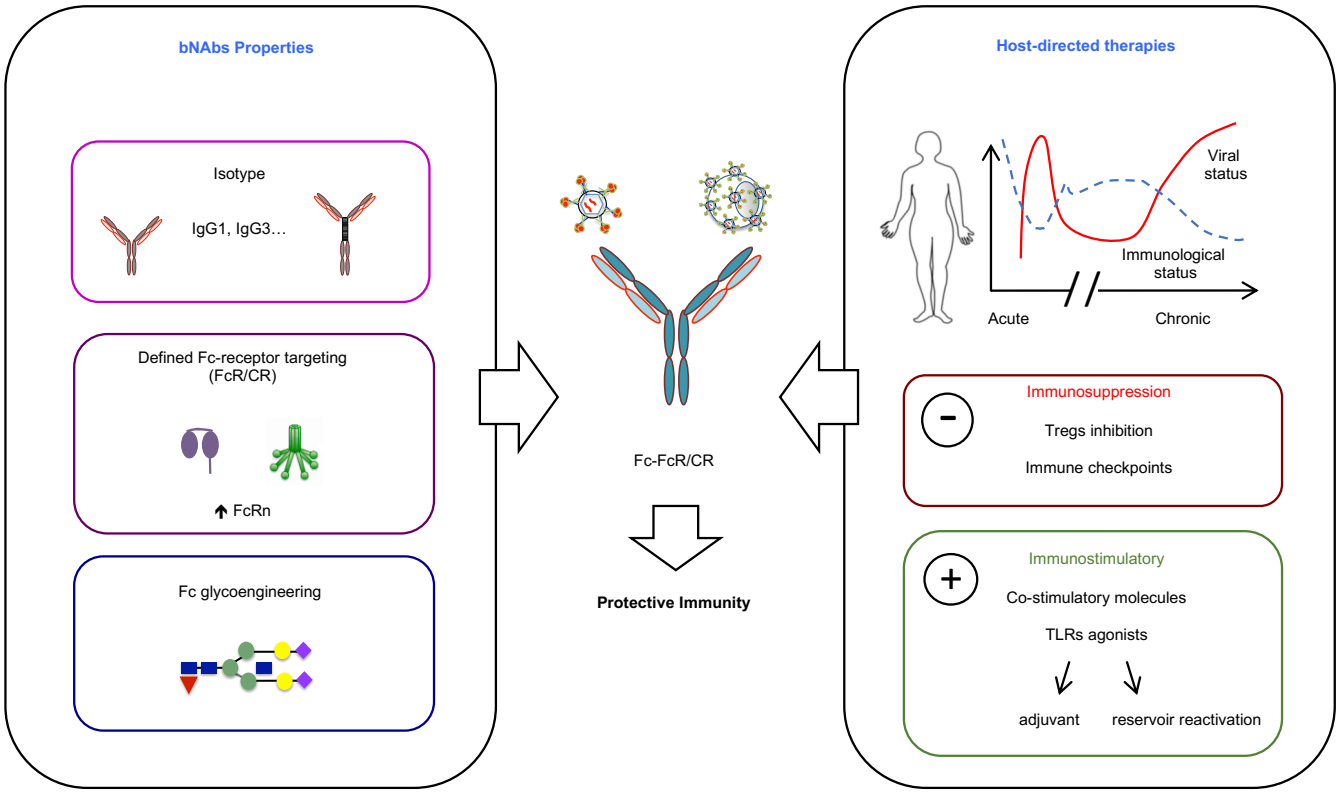
bNAbs Properties
Isotype
IgG1, IgG3…
Defined Fc-receptor targeting
(FcR/CR)
FcRn
Fc glycoengineering
Fc-FcR/CR
Protective Immunity
Host-directed therapies
Viral
status
Immunological
status
Acute
Chronic
Immunosuppression
Tregs inhibition
Immune checkpoints
Immunostimulatory
Co-stimulatory molecules
TLRs agonists
adjuvant
reservoir reactivation

Figure 2