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Vaccinal effect of HIV-1 antibody therapy: dream or reality?

Mar Naranjo-Gomez¹ and Mireia Pelegrin¹ *

Address:

¹IRMB, Univ Montpellier, INSERM, CNRS, Montpellier, France

***Corresponding author:**

Mireia Pelegrin

Institute of Regenerative Medicine and Biotherapy of Montpellier, UMR1183

80, Avenue Agustin Fliche

34293 Montpellier Cedex 5

France

Phone number: + 33 4 67 33 52 67

mireia.pelegrin@inserm.fr

ABSTRACT

Purpose of the review:

This review summarizes recent studies reporting the induction of vaccinal effects by HIV-1 antibody therapy. It also puts into perspective preclinical studies that have identified mechanisms involved in the immunomodulatory properties of antiviral antibodies. Finally, it discusses potential therapeutic interventions to enhance host adaptive immune responses in HIV-1 infected patients treated with broadly neutralizing antibodies (bNAbs).

Recent findings:

Recent studies in promising clinical trials have shown that, in addition to controlling viremia, anti-HIV-1 bNAbs are able to enhance the host's humoral and cellular immune response. Such vaccinal effects, in particular the induction of HIV-1-specific CD8⁺ T-cell responses, have been observed upon treatment with two potent bNAbs (3BNC117 and 10-1074) alone or in combination with latency-reversing agents (LRA). While these studies reinforce the idea that bNAbs can induce protective immunity, the induction of vaccinal effects is not systematic and might depend on both the virological status of the patient as well as the therapeutic strategy chosen.

Summary:

HIV-1 bNAbs can enhance adaptive host immune responses in HIV-1 infected patients. The challenge now is to exploit these immunomodulatory properties to design optimized therapeutic interventions to promote and enhance the induction of protective immunity against HIV-1 infection during bNAbs therapy.

Key-words: OK

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

Introduction

Monoclonal antibodies (mAbs) have become therapeutic tools of choice to combat serious human diseases, such as severe viral infections [1–6]. Today, there are as many as 100 mAbs approved for human use and several hundred in development. Potent broadly neutralizing antibodies (bNAbs) against HIV-1 have been developed over the past decade and several have demonstrated efficacy in controlling viremia in HIV-infected patients, suggesting that bNAbs may become viable therapeutic agents for combating HIV-1 infection (reviewed in [7–11]).

The therapeutic efficiency of mAbs is driven by their multiple mechanisms of action that go well beyond their neutralization capacity. In addition to the neutralization of free virions by their Fab fragment, the antiviral effect of mAbs is also achieved via the Fc fragment through interactions with Fc receptors (FcRs) expressed by many cells of the immune system [12–14]. Importantly, Fc-Fc γ R interactions are a very versatile system for shaping immune responses [13,15,16]. On one hand, there are multiple Fc γ Rs, either activating or inhibitory, with different affinities for different IgG isotypes. On the other hand, Fc γ Rs are differentially expressed in multiple immune cells, each with specific functions. This diversity enables a myriad of immune functions essential for combating invading pathogens through direct elimination of viruses and infected cells, as well as modulating host immune responses in an Fc-dependent manner.

Fc-Fc γ R interactions can lead to viral clearance through different functional mechanisms [12–14]. The Fc domain allows antibody-opsonized virions to bind to Fc γ Rs and induce their phagocytosis by cells of the innate immune system. Infected cells can also be eliminated by antibody-dependent cellular phagocytosis (ADCP), antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC). Fc-Fc γ R interactions can also directly affect viral propagation through other mechanisms, such as antibody-dependent cellular viral inhibition (ADCVI). In addition, upon opsonization of viral targets and formation of immune complexes (ICs), engagement of Fc γ Rs by antiviral mAbs has been shown to have immunomodulatory effects leading to the induction of protective immunity ("vaccinal effect") (reviewed in [17,18]). These immunomodulatory effects have been reported in several preclinical models of viral infections. While much attention has been paid to the potential of HIV-1 bNAbs to control viral spread, either by neutralizing virions or eliminating infected cells through Fc-mediated effector functions, their immunomodulatory functions have been much less studied to date. However, recent data from HIV-1 infected patients showing that bNAbs can enhance adaptive immune responses, have reinforced the concept that vaccinal effects can be induced under certain conditions and contribute to protection against the disease.

Vaccinal effect of antiviral mAbs: from preclinical models of viral infection to HIV-1 infected patients

The first evidence of induction of vaccinal effects by antiviral antibodies was reported in the early 2000s. They were reported in preclinical models of retroviral infection in mice [19] and in non-human primates (NHPs) [20] (**Figure 1**). Both studies reported improved long-term humoral responses after treatment with antiviral antibodies (administration of mAbs or polyclonal antibodies, respectively). Similar observations were later on reported in other preclinical NHP models of henipavirus- and HIV-1 infection [21–24]. Notably, treatment of SHIV-infected infant macaques with polyclonal HIV-1 neutralizing IgG led to neutralizing antibody production that contributed to disease protection [23,24]. Enhanced T-cell responses were subsequently reported in various experimental settings, including in NHP models of HIV-1 infection (**Figure 1**) [25–30]. Worthy of note, administration of bNAbs induced Gag-specific CD4⁺ and CD8⁺ T cells that showed reduced expression of the exhaustion marker PD-1. This antibody-mediated induction of the HIV-specific CD8⁺ T-cell response was essential to protect infected macaques, as CD8⁺ T-cell depletion resulted in viral rebound [29]. These observations were the basis for studying the induction of vaccinal effects in bNAb-treated HIV-1 infected patients.

The vaccinal effect of anti-HIV bNAbs was first described in HIV-1 infected patients by Schoofs *et al* [31] (**Figure 1**). This study showed that the administration of the bNAb 3BNC117 to HIV-1 infected individuals elicited host humoral responses in viremic and virally suppressed subjects on antiretroviral therapy (ART). Later, Niessl *et al.* [32] showed that anti-HIV-1 antibody therapy was associated with increased virus-specific T-cell immunity. HIV-1-infected individuals on ART received an infusion of a combination of two anti-HIV-1 bNAbs (3BNC117 and 10-1074) at 0, 3, and 6 weeks, followed by an interruption of antiretroviral therapy (analytical treatment interruption; ATI) 2 days after the first antibody infusion. HIV-1-infected individuals on ART without antibody treatment had stable or decreasing levels of HIV-1-specific CD8⁺ and CD4⁺ T-cell responses over time. In contrast, patients treated with bNAbs in the ATI setting had improved virus-specific CD8⁺ T-cell responses as well as improved CD4⁺ T-cell responses, which were associated with viral suppression for at least 15 weeks after ATI. More recently, two other studies have also reported the effect of anti-HIV-1 bNAbs on the stimulation of T-cell immunity. Rosas-Umbert *et al.* [33 **] showed that administration of HIV-1 bNAbs at the initiation of ART maintained long-term CD8⁺ T-cell immunity. They observed that the frequency of Pol- and Gag-specific CD8⁺ T cells, as well as Gag-induced interferon- γ (IFN- γ) responses, were significantly higher in patients who received adjuvant 3BNC117 therapy than in those who received ART alone. The observed changes in cellular immunity were correlated with the pre-treatment sensitivity to 3BNC117. Notably, increased HIV-1-specific immunity was associated with partial or complete virologic control without ART during treatment interruption for up to 4 years.

These results suggest that treatment with bNAbs at the time of ART initiation maintains the HIV-1-specific CD8⁺ T-cell responses that are associated with virologic control without ART.

Another clinical trial (phase 1b/2a) in newly diagnosed HIV-1-infected individuals showed that early intervention with the 3BNC117 bNAb, with or without romidepsin (a latency reversal agent, LRA), at ART initiation enhanced plasma HIV-1 RNA decay rates and accelerated the clearance of infected cells compared to ART only [34 **]. Interestingly, early administration of the 3BNC117 bNAb in combination with romidepsin was associated with (i) increased Gag-specific CD8⁺ T-cell immunity compared with ART alone [34] and (ii) sustained ART-free virologic control among persons with 3BNC117-sensitive virus. On the contrary, in an open-label, phase 2a trial including virological suppressed adults infected with HIV-1 and on ART for at least 18 months (NCT02850016), the combination of 3BNC117 bNAb and romidepsin neither significantly affected the latent HIV-1 reservoir nor induced virus-specific CD8⁺ T-cells responses [35]. This treatment regime resulted in an unmodified delay in viral rebound during ATI in individuals on long-term ART. These findings support early interventions administered at the time of ART initiation as a strategy to limit long-term HIV-1 persistence. However, a two-component clinical trial involving either participants who initiated ART during the acute/early phase of HIV-1 infection (first component) or individuals with viremic control who were naive to ART (second component) reported that bNAb treatment did not alter cellular immune responses. Both groups showed unchanged frequencies of TIGIT⁺, PD-1⁺, CD38⁺HLA-DR⁺ and subsets of CD8⁺ T cells (assessed in peripheral blood mononuclear cells of study participants). Similarly, the level of poly-functional (IFN γ ⁺TNF⁺MIP-1 β ⁺) HIV-Gag-specific CD8⁺ T cells remained unchanged despite the early intervention [36]. Thus, whether and how early treatment is a key parameter to induce vaccinal effects still needs further investigation.

Overall, these observations highlight the potential of HIV-1 bNAbs to stimulate adaptive immune responses under certain treatment regimens. The elucidation of the mechanism involved as well as the identification of immunological, virological and pharmacological factors required to achieve bNAb-mediated protective immunity are now key questions with important therapeutic consequences.

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

Ethical, technical and economic reasons limit the study of the main mechanisms underlying the vaccine effects of mAbs in humans. Thus, this type of research therefore requires relevant experimental models. Although NHPs are extremely useful to assess the protective effects of anti-HIV mAbs [37,38], their use in the study of host immunity is limited by technical and cost considerations. In contrast, infection systems in mice offer many immunological tools and have allowed the dissection of several molecular and cellular mechanisms involved in the enhancement of host immune responses

by antiviral mAbs (reviewed [17,18]). Using a mouse model of retroviral infection, Pelegrin and colleagues demonstrated that neutralizing antiviral mAbs act as immunomodulatory agents capable of stimulating protective immunity that persists long after the end of treatment (more than 1 year). These studies highlighted the key role for ICs in enhancing humoral and cellular antiviral response by dendritic cells (DCs) [26,39], neutrophils [40], monocytes [41] and natural killer (NK) cells [42] in an FcγRs-dependent manner (**Figure 2**). They also underline that multiple FcγR-expressing cells are involved and cooperate in the induction of vaccinal effects by mAbs.

More recently, monocytes and DCs have been shown to play a key role in enhancing CD8⁺ T cell responses in animal models of acute respiratory viral infections such as SARS-CoV2 and influenza, respectively [43,44]. As in the retroviral infection model, this immunomodulatory effect was Fc-dependent. During HIV immunotherapy, it has been suggested that the stimulation of the host adaptive immunity is mediated by DC-IC interactions that enhance CD8⁺ T cell responses, as has been reported in other infectious contexts [26,45]. However, this hypothesis has not been formally demonstrated and the molecular and cellular mechanisms involved have not been identified. Nevertheless, in support for this hypothesis, several *in vitro* studies with antibody-opsonized SIV virions have shown that ICs activate DCs leading to increased virus-specific CD4⁺ T-cell responses [46] and enhanced cross-presentation of viral proteins [47]. In sharp contrast, *in vitro* activation of DCs by HIV-1 virions opsonized with polyclonal IgG showed a decreased capacity to stimulate HIV-1-specific cytotoxic T lymphocytes than free virions [48]. However, it is important to note that the polyclonal nature of the IgG used in this study, whose neutralizing capacity was not characterized, may have had an impact on the results observed. Thus, whether and how DC-IC interactions drive T-cell responses upon bNAb-treatment remains an open question.

The role of ICs in shaping antibody responses against HIV-1 has been described in vaccine approaches based on immunization of mice with ICs formed with recombinant HIV-1 envelope gp120 proteins and anti-gp120 mAbs or polyclonal antibodies from HIV-1-neutralizers. These immunization methods increased serum levels of HIV-1-specific antibodies [49–53]. Mechanistically, modulation of humoral responses occurred *via* the antigen deposition within B-cell follicles in germinal centers and was dependent on the interaction of ICs with complement receptors (CR), suggesting a role for the complement system in modulating humoral immunity *via* IC-mediated antigen deposition on follicular dendritic cells (FDC).

Taken together, these mouse studies highlight several mechanisms involved in antibody-mediated boosting of both T-cell and B-cell responses. They also highlight the complexity of immune players potentially involved, including several Fc-mediated mechanisms and multiple cells expressing FcγRs

and CRs. Whether these mechanisms are also involved in immunotherapies based on HIV-1 bNAbs deserves further investigation.

How can the vaccinal effect be improved?

Different clinical trials have now shown the immune-enhancing effect of bNAbs, through the potentiation of the humoral [31] and cellular immune response [32–34]. However, the induction of vaccinal effects is not systematic, as it has not been observed in other clinical trials performed with the same bNAbs [35,36]. A better understanding of the immunological, virological and pharmacological factors leading to their induction is thus essential to potentiate them in a wider number of patients. Bearing in mind the Fc-dependent nature of the induction of vaccinal effects and the potential involvement of multiple immune cells, the potentiation of host adaptive immune responses might be achieved by Fc-engineered, gain-of-function bNAbs in combination with personalized host-directed therapies (HDT).

Exploiting Fc-Fc γ R interactions offers the possibility to improve direct viral propagation control and to enhance vaccinal effects. This could be achieved in several ways. First, Fc-mutations leading to increased affinity for Fc γ Rs expressed in key immune cells are a suitable approach (reviewed in [16,54,55]). Notably, Fc-mutated mAbs against influenza virus showed an improved therapeutic effect that was associated with increased activation of DCs and development of protective CD8⁺ T-cell responses [43]. These Fc-optimized mAbs included mutations allowing an increased binding to the activating Fc γ Rs, Fc γ RIIa and Fc γ RIIIa. Worthy of note, the same mutations included in anti-SARS-CoV2 mAbs were found to have increased binding to both Fc γ RIIIa alleles (F158 and V158), in contrast to the unmutated Fc variants that display reduced affinity for the F158 allele [56]. These mAbs are currently being tested in clinical trials (NCT04746183). Second, isotype choice and Fc-glycoengineering of bNAbs can also alter Fc γ R and CR binding. In keeping with this, a-fucosylated mAbs have been shown to enhance effector functions [55,57] although whether they modulate anti-HIV-1 immune responses has not been addressed to date. In addition, sialylated anti-HIV-1 antibodies used in immunization studies have been shown to enhance humoral responses [53] through CR-dependent, IC-mediated antigen deposition on FDC. Third, consideration of Fc γ R polymorphisms in patients to be treated may represent an asset for improving mAb-based therapies. This is an important issue because several Fc γ R polymorphisms have been associated with HIV-1 disease progression and vaccine protection [58]. Thus, Fc γ R polymorphisms can therefore be used as a predictive factor. In addition, Fc-engineering might also help to overcome decreased binding of bNAbs to specific Fc γ R alleles, as above mentioned [56].

Combinatorial approaches involving improved bNAbs and HDT may also represent a major asset for inducing vaccinal effects. Given the development of suppressive immune responses and immune dysfunctions associated with HIV-1 infection, combination therapies will most likely need to target different immune players in order to not only potentiate immune responses but also to counteract the immunosuppressive mechanisms associated with HIV-1 infection. It is now a question of identifying the most effective combination, which will certainly depend on the virological and immunological status of the patients as well as on the treatment regime (i.e. time of ART initiation, ATI, ...). One of the approaches currently being evaluated is the use of LRA. Vaccinal effects have been observed in HIV-1 infected patients in clinical trial based on early intervention with bNAbs combined with the LRA romidepsin (a pan-HDACi, histone deacetylase inhibitor) [34]. However, the same combination treatment in chronic patients did not improve CD8⁺ T-cell responses [35]. To further exploit this combinatorial approach, it may be necessary to take into account the effect of pan-HDACi on immune cells. For example, pan-HDACi have been described to reduce NK cell function, which is not the case with selective HDACi, such as Entinostat [59 *]. Interestingly, the use of pan-HDACi in combination with IL-15 reversed the negative effects of the former [59]. In addition, the combination of HDACi with distinct LRA might also be of interest, as they have been shown to variably affect HIV reactivation and susceptibility to NK cell-mediated killing of T cells that exit viral latency [60]. Furthermore, HDACi have also been shown to affect the basic physiologic features of other effector cells such as macrophage, including their phagocytosis capacity [61]. These observations could help to “re-think” the use of these LRA. Toll-like receptors (TLR) agonists are also being used as LRA in combination with bNAbs [62]. The use of TLR agonists offers the advantage of activating lymphoid and myeloid cell subsets (i.e. CD4⁺ T cells, NK cells and monocytes). Three different studies investigated the effect in viral rebound of two different TLR7 agonists (GS-9620 or GS-986) in combination with bNAbs (PGT121 alone or administered together with the N6 bNAb) after ATI in acute or chronically SHIV-infected monkeys [63–65]. All studies reported either a delay or a partial prevention of viral rebound, including in monkeys chronically infected with SHIV [65 *]. Interestingly, the induction of SHIV-specific responses was observed in some animals after GS-986 administration. Notably, after ATI, the frequency of IFN γ ⁺ Gag-specific CD4⁺ and CD8⁺ T cells was significantly higher than in control individuals [64], suggesting that the dual combination of GS-986 and bNAbs might represent a suitable approach to enhance SHIV-specific T-cell responses. In keeping with this, TLR9 agonists have also been tested for their antiviral effects in HIV-1 infected patients [66] and are currently being tested in combination with bNAbs in a trial (NCT03837756). Further investigations are needed to determine whether and how this dual treatment induce vaccinal effects.

An alternative approach involving immunostimulatory agents would be to use therapeutic combinations with bNAbs and antibodies targeting regulatory receptors on immune cell. This could be based on the use of agonistic antibodies targeting co-stimulatory receptors (i.e. CD40, OX40, GITR,

and CD137) [67,68] and/or the administration of immune checkpoint blocking antibodies (ICB) directed against receptors involved in T-cell exhaustion (i.e. PD1, CTLA4, LAG-3, TIM-3 and TIGIT) (reviewed in [69 *]). Several studies have shown the effect of inhibiting the PD-1–PD-1L interaction in enhancing HIV-1-specific CD4⁺ T and CD8⁺ cells responses in NHP- models of HIV-1 infection [70] and in HIV-1-infected patients [71,72]. Furthermore, PD-1 blockade has also been shown to enhance HIV-1-specific CD4⁺ T-cell responses [73] as well as HIV-1-specific immunoglobulin production [74]. This underlines the effect of PD-1-directed immunotherapy on the enhancement of humoral immune responses, as has also been recently described in the context of influenza infection [75]. Similarly, CTLA-4 blocking agents also augment HIV-1 antibody responses, either alone or in combination with OX40 agonistic antibodies [76]. PD1 and TIGIT blockade have also been shown to enhance NK cell function [77,78]. Finally, the combination of different ICB (i.e. CTLA4, LAG-3 and TIGIT) might also be beneficial in improving anti-HIV immune response [79], although potential adverse effects of such a combination cannot be ruled out. These observations suggest that combinatorial approaches may need to not only "step on the gas" but also "take off the brake" to achieve protective immunity. With this in mind, it will be important to determine the effect of therapeutic approaches combining bNAbs and antibodies targeting immune cell regulatory receptors in the enhancement of adaptive immune responses in HIV-1 infected patients.

Overall, different therapeutic interventions seem promising for enhancing adaptive immune responses in HIV-1 infected patients. Due to the multiples HDT available with distinct modes of action, a myriad of potential combinatorial approaches could be considered for this purpose. A key issue will be thus to identify the most appropriate combination, which will most likely need to be tailored according to the patient's virological and immunological status. This will allow the right medicine to be given to the right patient at the right time.

Conclusion

Several clinical trials have now demonstrated that anti-HIV-1 bNAbs can induce vaccinal effects, reinforcing this concept previously described in preclinical models of HIV-1 infections. These recent studies provide insight into potential factors that may be involved in eliciting protective adaptive immune responses in HIV-1 infected patients. In particular, the virological and immunological status of patients seems to be a key issue, as well as the treatment regimen. In this sense, early treatment could be a key parameter to enhance vaccinal effects. Importantly, current clinical trials now include the study of the modulation of innate and adaptive immune responses [11]. There is no doubt that the results of these ongoing studies will shed light on the mechanisms involved in enhancing host immune responses and will guide the development of improved immunotherapies. These will certainly be based on Fc-modified mAbs with improved functions and on combinatorial therapeutic approaches.

The challenge now is to identify and exploit the key mechanisms underlying the vaccine effects of bNAbs, which will be essential to design optimal therapeutic interventions.

Key points: 3-5

- bNAbs can elicit humoral and cellular adaptive immune responses
- Immunological, virological, and pharmacological factors are involved in the induction of adaptive immune responses by bNAbs
- Identification of mechanisms involved in immune-enhancing effects of bNAbs will allow the design optimal therapeutic interventions.
- Improvement of immune-enhancing effects of bnAbs will likely rely on the design of Fc-optimized bNAbs in combinatorial therapeutic approaches involving tailored host-directed therapies

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Conflict of interest

None.

Figure legends

Figure 1. Timeline of discovery of vaccinal effects by antiviral mAbs.

Figure 2: Mechanisms involved in the induction of vaccinal effects. Short treatment of retrovirus-infected mice with a mAb induces a long-term protective humoral and cellular immune response. The enhancement of adaptive immunity is associated with the inhibition of immunosuppressive responses. The mechanisms underlying the induction of protective immunity involve multiple FcγR-expressing cells (i.e. DC, monocytes, neutrophils and NK cells) each with specific functions and mechanisms of action. Reprinted from “Mechanisms Involved in the Induction of Vaccinal Effects”, created by "M.Pelegrin, M. Naranjo-Gomez and S. Marsile-Medun" using BioRender.com (2023). Retrieved from <https://app.biorender.com/biorender-templates>".

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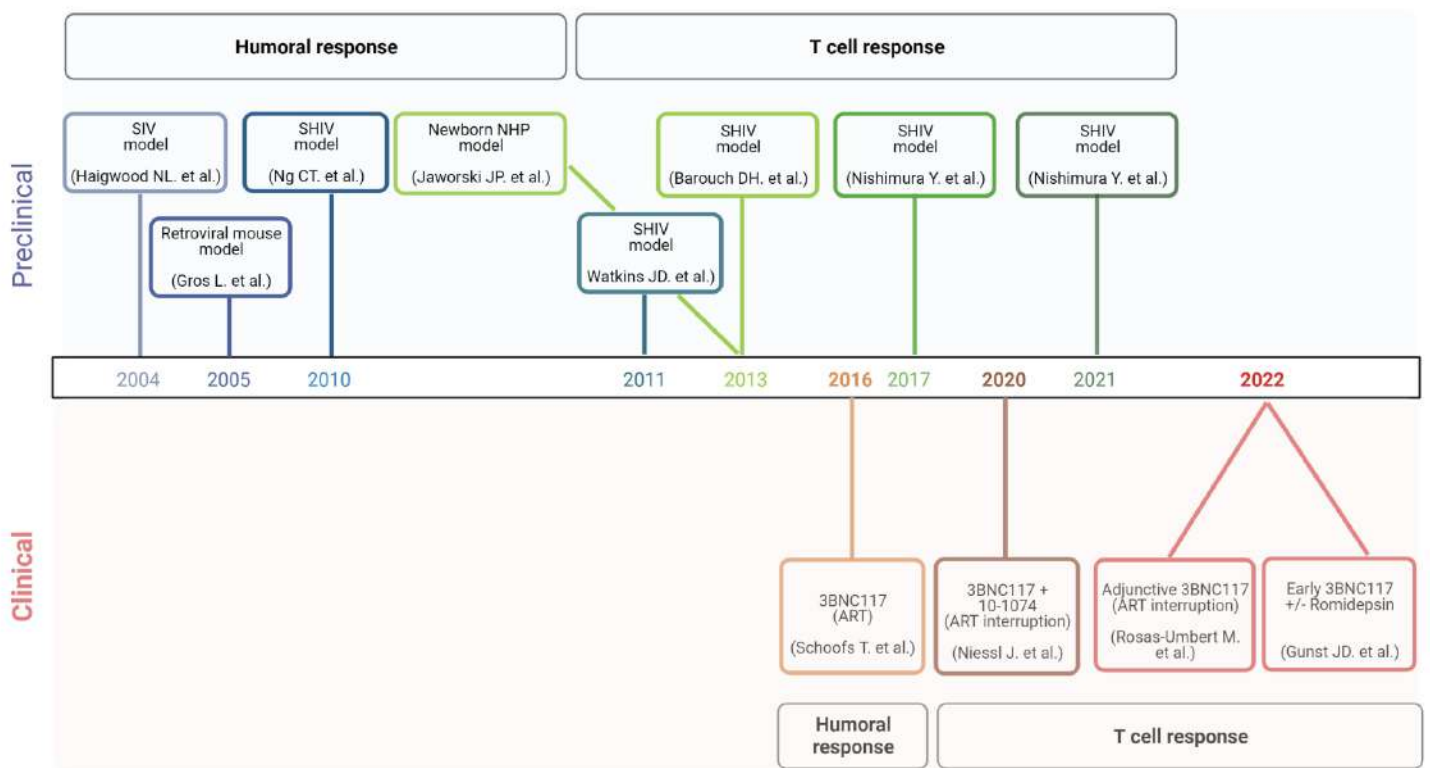


Figure 1

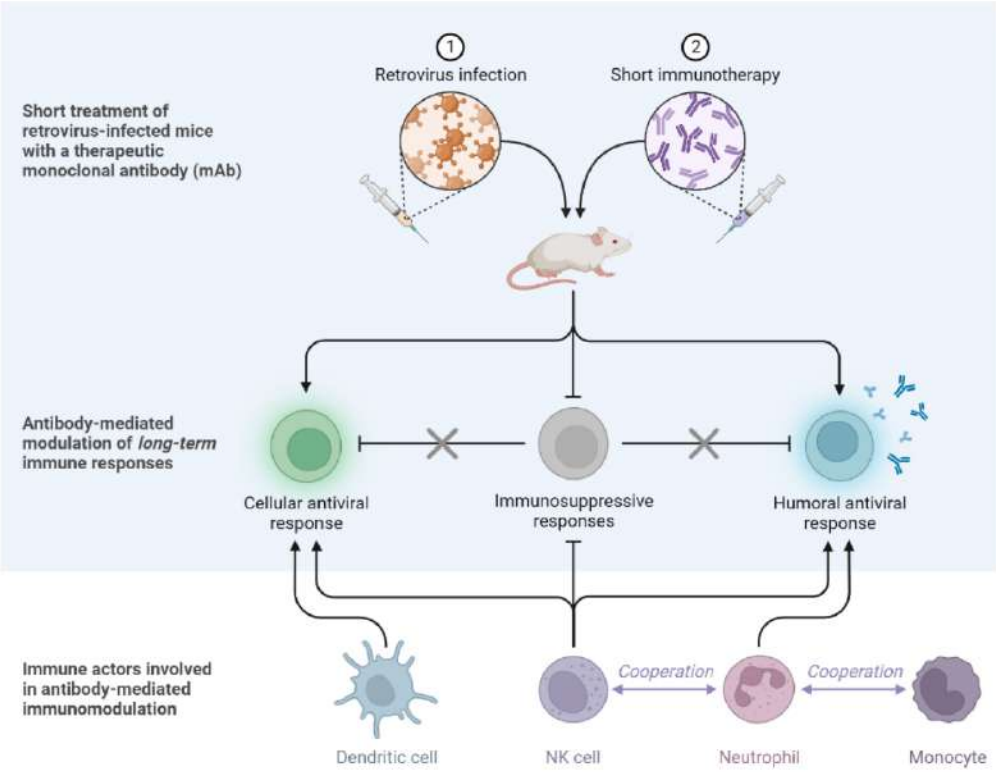


Figure 2