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Review

Focus on the therapeutic efficacy of 3BNC117 against HIV-1: *In vitro* studies, *in vivo* studies, clinical trials and challenges

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ABSTRACT

3BNC117, which was discovered in 2011, is a broadly neutralizing antibody (bNAb) and specifically neutralizes the human immunodeficiency virus type-1 (HIV-1) by targeting the CD4-binding site. This is the first comprehensive review that focuses on the role of 3BNC117 in the prevention of HIV-1 and acquired immune deficiency syndrome (AIDS). Briefly, 3BNC117 neutralizes many HIV/SHIV strains *in vitro*, blocks HIV-1 acquisition in animal models *via* a pre-exposure prophylaxis, alleviates HIV-1-associated viremia *via* a post-exposure therapeutic effect, prevents the establishment of latent HIV-1 reservoirs, and induces both humoral and cellular anti-HIV immune responses *in vivo*. The outcomes of Phase I and Phase IIa clinical trials in 2015 and 2016 showed the safety, tolerability, and therapeutic efficacy of 3BNC117 in HIV-1-infected human individuals. Nevertheless, anti-3BNC117 antibodies and HIV-1 strains resistant to 3BNC117 pose clinical challenges to immunotherapy with 3BNC117, so potential strategies for optimizing the potency of 3BNC117 are suggested here. Predictably, HIV-1 prevention and AIDS treatment will benefit from combinational immunotherapies with 3BNC117 and other pharmaceuticals (bNAbs, antiretroviral medicines, viral inducers, *etc.*) in the near future.

1. Introduction

Human immunodeficiency virus type-1 (HIV-1) and acquired immune deficiency syndrome (AIDS) threaten human health throughout the world [1–3]. Over the past few years, the pathogenic mechanisms of HIV-1 have been comprehensively studied, and the life quality of HIV-1-infected individuals has been improved significantly [4–8]. However, novel anti-HIV pharmaceuticals are still emergently needed in order to prevent HIV-1 infection and AIDS development more efficiently.

Previously, one traditional anti-HIV strategy was to inhibit key molecules that play a crucial role in the life cycle of HIV-1 [9–12]. In recent years, immunotherapy with specific antibodies has attracted more and more scientific attention [13–15], and novel broadly neutralizing antibodies (bNAbs) have contributed to a lot of anti-HIV strategies [16–21]. Particularly, 3BNC117 is a bNAb that targets the CD4 binding site of HIV-1, and it neutralizes HIV-1 potently both *in vitro* and *in vivo* without causing obvious side effects [22–25]. In recent two years, many noteworthy advancements (as shown in Table 1) in the anti-HIV effects of 3BNC117 have been revealed, which brings a new hope for the treatment of HIV-1 infection.

In brief, this work summarizes the multiple anti-HIV roles of 3BNC117 in cells, mice, rhesus monkeys and human volunteers, highlights the therapeutic potential of 3BNC117 to clear HIV-1, elucidates the major clinical challenges to 3BNC117-based immunotherapy, and predicts optimization of 3BNC117 potency in the future.

2. Advancements in the anti-HIV role of 3BNC117 since its discovery in 2011

Due to technical advancements in single-B-cell-based production of monoclonal antibody, several bNAbs that specifically neutralize HIV-1 strains were found recently [22,23,26–28]. As reported by *Science* in 2011, Scheid et al. identified 576 antibodies from four HIV-infected individuals who produce bNAbs against the CD4-binding site of HIV-1 [22]. Among, 3BNC117, which was derived from the B-cell clone RU01, showed a high affinity to the YU2-gp140 trimer and had the most potent HIV-neutralizing activity [22]. In the following five years, more studies investigated the anti-HIV activity of 3BNC117 step by step, and the most important findings were briefly summarized in Table 1. As a matter of fact, these ground-breaking advancements strengthen the

Abbreviations: HIV-1, human immunodeficiency virus type-1; SHIV, simian-human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; bNAb, broadly neutralizing antibody; Env, envelope; AAV, adeno-associated virus; IC50, the half-maximum inhibitory concentration; ART, antiretroviral therapy; FcγR, Fc gamma receptor; ADCC, antibody-dependent cell-mediated cytotoxicity; IFN, interferon; CDR, complementarity determining region; FWR, framework region; CAR, chimeric antigen receptor

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Table 1
A succinct overview of 3BNC117-related anti-HIV studies since its discovery in 2011.

Year	Authors	Journal	Targets or models	Major findings	References
2011	Scheid et al.	*Science*	HIV-strain panel	3BNC117 was firstly discovered and showed the best HIV-neutralizing potency among 576 new antibodies isolated from four HIV-1-infected individuals.	[22]
2012	Pietzsch et al.	*PNAS*	HIV-LUC_{AdV} mice	Key pharmacological properties of 3BNC117 were determined in the newly-constructed humanized HIV-LUC_{AdV} mice, including high serum levels, long half-life, IC50, *etc*.	[24]
2013	Barouch et al.	*Nature*	Rhesus monkeys	The infusion of 3BNC117 and PGT121 rapidly reduced the plasma concentration of SHIV-SF162P3 in rhesus monkeys, and a further inhibitory effect was confirmed after the second-time infusion.	[29]
2013	Gruell et al.	*J Virol*	HIV-Luc_{TG} mice	The administration of 3BNC117 prior to the cervicovaginal infection with the YU2-Cre strain elicited a pre-exposure protection against HIV-1 entry in the newly-generated HIV-Luc_{TG} mice.	[30]
2013	Horwitz et al.	*PNAS*	Humanized mice	3BNC117 suppressed viral RNA in plasma as well as cell-associated DNA in humanized mice, and protected the mice from viral rebound for a long period of time.	[31]
2013	Klein et al.	*Cell*	HIV strains	Somatic mutations in the framework regions may enhance the breadth and potency of bNAbs, which puts forward possible methods to improve the therapeutic potential of 3BNC117 in future.	[32]
2013	Shingai et al.	*Nature*	Macaques	Inhibitory IC50 of SHIV-AD8 by 3BNC117 was as low as 0.14 mg/mL as determined by TZM-bl cell assay, and 3BNC117 blocked SHIV acquisition and attenuated viremia in macaques.	[33]
2014	Halper-Stromberg et al.	*Cell*	Humanized mice	3BNC117, 10-1074, PG16, and viral inducers cooperatively prevented the establishment of latent reservoirs and viral rebound in humanized mice infected with HIV-1_{YU2}, giving rise to an effective post-exposure prophylaxis.	[34]
2015	Caskey et al.	*Nature*	Human	The Phase I clinical trial indicated that 3BNC117 is safe and well tolerated in HIV-1-infected human individuals and that 3BNC117 reduces the concentration of HIV-1 in blood for over 28 days.	[23]
2015	Derking et al.	*Plos Pathog*	HIV Env trimer	When 3BNC117 and other bNAbs bind to the HIV Env trimer simultaneously, the cross-competition between them was studied, and the results emphasized that synergistical, but not competitive, combination of bNAbs should be designed to enhance their anti-HIV potency.	[35]
2015	Gardner et al.	*Nature*	HIV-1 strains	Some HIV strains resistant to 3BNC117 were listed, but they could be neutralized effectively by eCD4-Ig.	[36]
2016	Ali et al.	*J Virol*	HIV-1 strains	The 3BNC117-based chimeric antigen receptor induced potent, reproducible, antiviral activity against five HIV-1 strains.	[37]
2016	Gautam et al.	*Nature*	Rhesus macaques	3BNC117 exhibited a long-term protective effect against weekly-repeated low-dose SHIV challenges, delaying SHIV-AD8 acquisition for > 10 weeks compared with control monkeys.	[38]
2016	Bournazos et al.	*Cell*	Humanized mice	An IgG3C-hinge-modified bispecific 3BNC117/10-1074 antibody showed enhanced HIV-neutralizing breadth and potency.	[39]
2016	Huang et al.	*Cell*	HIV-1 pseudoviruses	Bispecific antibodies 3BNC117-ibalizumab and 3BNC117-P140, generated by CrossMAb technology, exhibited enhanced suppression on 118 kinds of tier-2 HIV-1 Env pseudoviruses.	[40]
2016	Martinez-Navio et al.	*Mol Ther*	Rhesus monkeys	Persisting anti-antibody response against 3BNC117 was detected in SHIV-AD8-infected rhesus monkeys from the 4th week to at least the 50th week after the treatment with AAV1-delivered 3BNC117.	[41]
2016	Scheid et al.	*Nature*	Human	The Phase IIa clinical trial reconfirmed the safety and tolerability of 3BNC117-based immunotherapy and indicated that 3BNC117 attenuated viral rebound during the interruptions of antiretroviral therapy compared with historical control individuals.	[25]
2016	Lu et al.	*Science*	Cellular immunity	3BNC117 recognized the HIV-1 Env glycoprotein expressed on the surface of CD4 + T cells and stimulated host cellular immunity to clear these HIV-1-associated cells.	[42]
2016	Schoofs et al.	*Science*	Humoral immunity	3BNC117 stimulated host humoral immunity and promoted HIV-1-infected individuals to produce multi-functional antibodies against autologous HIV-1 variants.	[43]
2016	Pham et al.	*Scientific Reports*	HIV-infected T cells	3BNC117 mediated ADCC to eliminate latent HIV-1-infected T cells, which can be down-regulated by BST2 but up-regulated by IFNα.	[44]
2017	Nishimura et al.	*Nature*	Rhesus monkeys	Three-time weekly infused 3BNC117 plus 10-1074 at the earliest possible time (the third day) after SHIV infection facilitated potent stimulation of CD8 + T cells and significantly protected 10 of 13 rhesus monkeys for up to 177 days.	[45]