



Broadly Neutralizing Antibodies: The Path towards Universal Vaccines

Authors

Dr Hrishikesh Kashyapa^{1*}, Dr Laxman Verma², Dr Rupali B. Jadhav³

^{1,2,3} Dept. of Pharmacology, Dr. V.M.G.M.C., Solapur-413003, Maharashtra, India

*Corresponding Author

Dr Hrishikesh Kashyapa

Flat no. 9, Mangal Residency phase-2, Asara chowk, Solapur, Maharashtra-413003

Email: hkashyapa@yahoo.co.in, Mobile No.: +919921449181

Abstract

Active and passive immunization to prevent Influenza virus and Human Immunodeficiency Virus-1 (HIV-1) infection has long been considered a potential treatment modality. Earlier efforts were largely unsuccessful as the antibodies studied neutralized only a narrow spectrum of viral strains. However, recent discovery of a large portfolio of human monoclonal antibodies that are broadly neutralizing across many HIV-1 subtypes and influenza strains has laid the foundation for such immunization strategies with universal vaccines being the ultimate aim. These antibodies target multiple different epitopes on the HIV envelope and influenza glycoprotein, thus neutralizing a broad range of viral variants. In this review, the role of broadly neutralizing antibodies (bNAbs) in HIV and Influenza infection will be discussed along with their potential for use in developing structure based universal vaccines.

Keywords: broadly neutralizing antibodies, structure based vaccine, universal vaccine.

Introduction

The ability to effectively prevent infection by viruses which harbor high levels of antigenic variability, such as Influenza virus and Human Immunodeficiency Virus-1 (HIV-1), has proven to be a difficult task.¹ Infection with either virus leads to the induction of abundant strain-specific antibodies that are easily evaded by subsequent 'escape variants'.² To date, much of the considerable challenge involved in using neutralizing antibodies or antiviral agents to block virus infection can be attributed to the rapid changes in the immunogenic head of the viral glycoproteins, hemagglutinin of influenza and Env of HIV-1. More recently, researchers have turned to the identification and utilization of

broadly neutralizing antibodies (bNAbs), which bind to highly conserved neutralization epitopes and thereby neutralize a broad range of viral variants. Not only can bNAbs be administered to patients as a form of passive immunotherapy, but they can also potentially be used for the rational design of universal vaccines.¹

Isolation of bNAbs and structure-based vaccine design

bNAbs can be isolated from vaccinated patients, as well as from individuals who have been suffering from virus infection over a prolonged period of time or long after the infection cycle is complete^{3,4,5} (Fig 1).

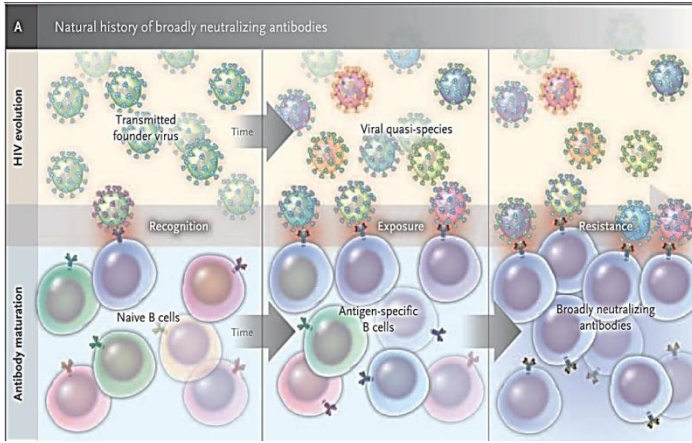


Fig 1: Early recognition of the transmitted virus by a naive B cell (in blue) leads to the selection, expansion, and diversification of the antigen-specific population, followed by exposure to a rapidly diversifying viral quasi-species and leading to the generation of bNAbs.²

Role of bNAbs in HIV infection

In the case of HIV-1, it is the envelope protein Env, which produces the surface glycoproteins gp120 and gp41 responsible for virus entry into host cells.¹ Though these glycoproteins tend to exhibit a high degree of sequence variability, they also possess conserved epitopes needed to maintain viral fitness. These epitopes are masked by sugar moieties (glycans) forging them into an evolving protective shield that prevents antibody binding.⁶ bNAbs can penetrate the glycan shield and bind to these conserved peptide sequences⁷ (Fig 2 & Table 1).

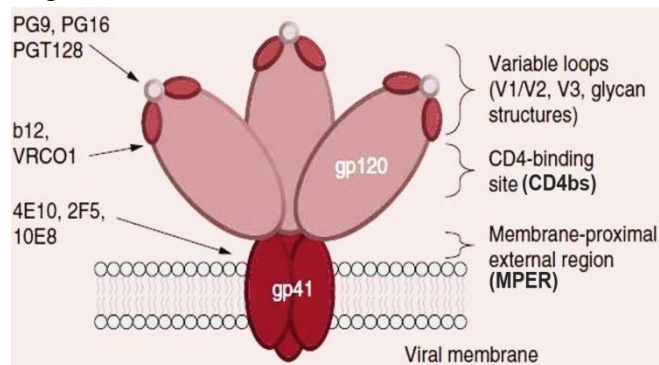


Fig 2: Currently, there are four broad classes of bNAbs against the HIV-1 trimeric spike: those that bind the gp41 MPER, gp120 V1/V2, V3 glycan and the gp120 CD4bs (prime target for the elicitation of bNAbs due to its high degree of conservation)

Table 1: Selected examples of bNAbs directed toward HIV-1.

BNAbs	Target site	HIV isolates neutralized
PG9, PG16	gp120 variable loops (V1/V2/V3)	70–80%
4E10, 2F5, 10E8*	gp41 MPER	98%
b12, VRCO1*	gp120 (CD4 binding site)	90%

*the most potent bNAb in the group, to which the percentage of neutralization corresponds.

Two to three years after infection, upto 25% of HIV-infected patients develop bNAbs which can neutralize 70-90% of all circulating HIV virus isolates. Co-crystallization of the bNAb with its epitope yields information regarding which exposed conserved regions or peptide sequences on the antigen can elicit an antibody response, and the epitope structure may help guide subsequent vaccine design containing a variety of epitope mimics⁷ (Fig 3 & 4).

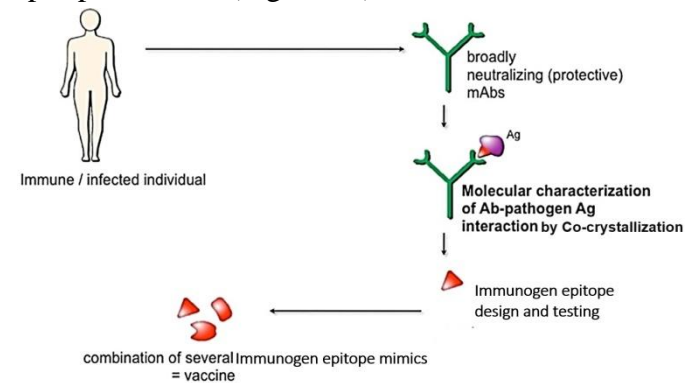


Fig 3: Structure based vaccine design for highly mutable pathogens

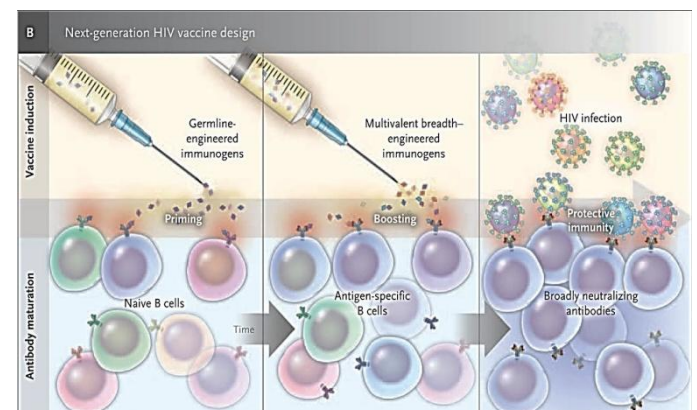


Fig 4: Immunogens could be designed to interact with naive B-cell receptors and coax B cells along specific maturation pathways. These B cells could then be boosted by designer envelope

immunogens engineered to mimic the rapid diversification of the viral population and thereby accelerate the pace of B-cell selection and mutation — all of which would drive the induction of bNAb responses in the vaccinated subject.²

Role of bNAbs in Influenza infection

In case of the influenza virus, the globular head of Hemagglutinin (HA) glycoprotein is subject to antigenic drift whereas the stem region is more conserved in structure. In most cases, neutralizing antibodies are targeted to the head domain and can result in the production of 'escape' mutants.^{6, 8, 9} bNAbs such as C179, 5A7, CR6261 and F10 target the conserved stem domain of the HA of influenza virus^{10, 11} (Fig 5). These bNAbs show an unprecedented breadth of cross reactivity enabling them to neutralize many different strains within a subtype, group or even between groups and different types of influenza virus.¹²

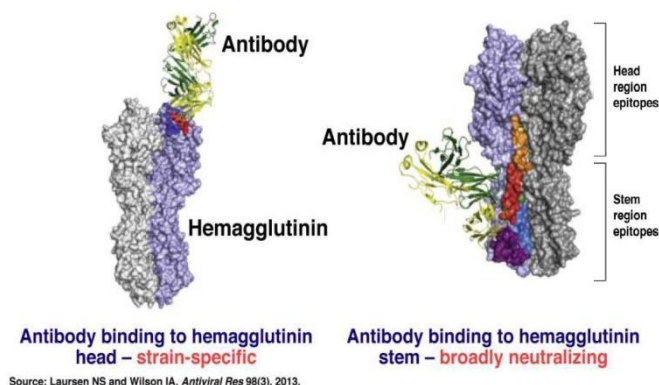


Fig 5: Binding of bNAb to HA stem.

Conclusion

It is clear from the steadily increasing number of bNAbs that have been identified and characterized, that the vision of universal vaccines is becoming increasingly realistic. After encouraging results in monkeys and mice in preventing HIV and influenza infections respectively, the next steps will involve human clinical trials, to fully demonstrate the potential of bNAbs as a substantial means to protect against all possible isolates of some the most difficult to control viruses known today.

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