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Review Article

Distinct advancements and challenges in HIV 1 vaccine development and cure—A review

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ABSTRACT

HIV vaccine development demands for two crucial needs to be successful; firstly, to identify immunologic vulnerabilities of HIV, and secondly, to develop a vaccine approach that safely and durably exploits such vulnerabilities. Rv144 vaccine trail has laid foundations for identification of HIV vulnerabilities and HIV broadly neutralizing monoclonal antibodies as an approach for the HIV vaccine development. Even though this trail failed, it provided a platform for the extensive research options and challenges faced in developing successful HIV 1 vaccine candidate. In this review, we are providing various research advancements and challenges faced. Recombinant Adenovirus serotype 26 HIV-1 Env vaccine (IPCAVD 001) has shown that broadly neutralizing monoclonal antibodies from this is capable of producing antibody-dependent cell-mediated phagocytosis, virus inhibition, and degranulation functional activity to a great extent. And many new distinct approaches like B cell aided HIV carbohydrate vaccine design strategies, enhancing strategies for mucosal immunity based vaccine development, new features in HIV 1 Env protein structural studies, and various computational studies are identified, and extensive research is being carried in developing successful vaccine candidate. Apart from research advancements, researchers are facing challenges like hyper variability of HIV, using relevant animal model and, translation of preclinical findings to a human system. This presentation will review the recent distinct challenges and opportunities for development of vaccine candidates capable of eliciting broadly neutralizing antibodies against HIV.

1. Introduction

The search for an effective HIV vaccine still continues. The discovery of wide range of HIV medications in to market has dramatically prolonged the lives of people infected with HIV. But with all the advances achieved through the use of medication combinations, complete prevention has been not yet achieved [1–4]. Prevention efforts can be successful but to win the battle against HIV we need to stop the spread of the epidemic, an effective HIV vaccine must be developed.

For successful vaccine development, there are two crucial needs; first, to find the immunologic vulnerabilities of HIV, which is considered to be not an easy task because of the fact that HIV and its simian immunodeficiency virus precursors have evolved to efficiently evade immunity and therefore cause chronic active infection and secondly, to develop a vaccine approach that safely and durably exploits such vulnerabilities [5–7]. The extensive research in HIV vaccine around the globe leads to the development of Rv144 vaccine and carried forward for clinical trials. Rv144 vaccine trail has laid foundations for identification of HIV vulnerabilities and HIV broadly neutralizing monoclonal antibodies as an approach for the HIV vaccine development. The RV144 HIV-1 trial of the canary pox vector (ALVAC-HIV) plus the gp120 AIDSVAX B/E vaccine demonstrated an estimated efficacy of 31% [3,8], which correlated directly with antibodies to HIV-1 envelope variable regions 1 and 2 (V1–V2). But even though this trail has failed, it has given a lot of hope and a platform for extensive research in developing successful vaccine candidate. In this review, we are providing the recent advancements and challenges faced in HIV 1 vaccine development.

2. Advancements in antibody based vaccine candidate

One of the challenges that we are facing in the development of an AIDS vaccine is eliciting antibody (Ab) capable of preventing the acquisition of HIV. Broadly neutralizing Ab (bNAb) that can prevent HIV infection has proven to be difficult to elicit. It is observed that broadly neutralizing antibodies PG9 and PG16 from an International AIDS Vaccine Initiative (IAVI) Protocol G subject show high potency and viral neutralizing capacity greater than 70% [9]. When viral sequence based immuno design started it showed a resistant to majority of envelope proteins. But, when Virus

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BG505.W6M.ENV.C2 (BG505) based gp120 expressed, it showed broad neutralizing activity along with PG9 and PG16. Further modification with point mutation at L111a and adjuvant formation on gp120 increased the antibody neutralization and showed BG505 as a stand-alone protein or as a component of a vaccine vector for future investigations [9]. At Center for Virology and Vaccine Research in Beth Israel Deaconess Medical Center, Boston, Adenovirus serotype 26 (Ad26) has been developed as a novel candidate vaccine vector for human immunodeficiency virus type 1 (HIV-1) and other pathogens [10]. It is observed that dose-dependent expansion of the magnitude, breadth, and epitopic diversity of Env-specific binding antibody showed strong responses elicited by this vaccine along with the antibody-dependent cell-mediated phagocytosis, virus inhibition, and degranulation functional activity. It also induced Env-specific cellular immune responses including multiple $CD8^+$ and $CD4^+$ T-lymphocyte memory subpopulations and cytokine secretion phenotypes, even though the cellular immune breadth was limited. These results indicate that Adenovirus serotype 26 (Ad26) has been considered as a novel and strong candidate for HIV 1 vaccine. From the previous studies it is observed that bNAb is not able to elicit strong responses inside body and they are very slow in entering into cells [11,12]. To face this challenge, experts consider that these challenges provide a window opportunity for protective non-neutralizing Ab (pnnAb) as potential methodology to provide the much needed Ab component for an HIV vaccine [13]. Such Ab acts by "tagging" virus or infected cells for destruction by the innate immune system. The advancements in eliciting the bNAb responses in preventing HIV infection have shown potential vector and vaccine candidates for successful vaccine development. It has been identified that protective non-neutralizing Ab (pnnAb) tagged with virus particles can also act against the HIV infection through destruction of tagged virus by innate immune system, which can replace the Broadly neutralizing Ab (bNAb) approach.

3. New features in HIV-1 Env structural studies

The trimeric envelope glycoprotein of HIV-1, composed of gp120 and gp41 subunits, remains a major target for vaccine development. The structures of the core regions of monomeric gp120 and gp41 have been determined previously by X-ray crystallography. New insights into the structure of trimeric HIV-1 envelope glycoproteins will help in understanding the gp160 in better and developing effective vaccine candidate [14].

Glycosylation patterns on gp120 are crucial for understanding the modulating biological and structural properties, which in return are important in developing the effective vaccine candidate. Recently it is observed that recombinant HIV-1 surface glycoprotein, gp120, derived from clade C transmitted/founder virus 1086.C expressed in Chinese hamster ovary (CHO) and human embryonic kidney containing T antigen (293T) cell lines shows different patterns of *N*-linked glycosylation, *O*-linked glycosylation and phosphorylated glycans at different regions on gp120 [15]. For *N*-linked glycosylation, two sites (N386 and N392) in the V4 region were populated with high mannose glycans in the CHO cell-derived 1086.C gp120, while these sites had a mixture of high mannose and processed glycans in the 293T cell-derived 1086.C gp120 [15]. Compositional analysis of *O*-linked glycans revealed that 293T cell-derived 1086.C gp120 consisted of core 1, 2, and 4 type *O*-linked glycans, while CHO cell-derived 1086.C exclusively consisted of core 1 type *O*-linked glycans. Site-specific glycopeptide analysis of 1086.C gp120 expressed in CHO cells revealed the presence of phosphorylated glycans, while 293T cell-produced 1086.C gp120 glycans were not phosphorylated. Irrespective of variations in these glycosylation profiles in various expression systems, these profiles may be important in finding the immunogenicity and functional capacities of recombinant envelope proteins produced based on the expression systems. The recent studies on kinetic properties of carbohydrate-binding agents (CBA's), antibody 2G12 and sCD4 binding to monomeric gp120 and trimeric gp140 indicate that monomeric gp120 is a good surrogate molecule for native HIV-1 Env trimer to investigate the binding affinities of Env-binding compounds that show that all three gp120 in Env trimer have similar binding patterns [16].

Even though HIV-1 carries a relatively low number of glycoproteins in its membrane, the mechanism of Env recruitment and virus incorporation is incompletely understood. A recent research study in Env recruitment has revealed that Env is recruited to HIV-1 assembly sites in a Cytoplasmic Tail (CT)-dependent manner. A study by employing dual-color super-resolution microscopy on Gag assembly sites and HIV-1 Env proteins in virus-producing and Env expressing cells has shown an interesting result in formation of Env clusters. The study states that "formation of Env clusters depended on the presence of other HIV-1 proteins and on the long cytoplasmic tail (CT) of Env. CT deletion or Env expression in the absence of other HIV-1 proteins led to much smaller Env clusters, which cannot be embellished at viral assembly sites. This indicates that Env is recruited to HIV-1 assembly sites in a CT-dependent manner [17]."

4. B cell: a potential tool for carbohydrate immunogen screening

The highly conserved regions of high-mannose glycans on HIV 1 envelope glycoprotein, gp120, are considered to be as a target for broadly neutralizing antibodies [18,19]. 2G12, a HIV-1 antiglycan neutralizing antibody, binds to these regions with an unusual domain-exchanged structure that creates a high-affinity multivalent binding surface [18,20].

It has become a challenge to design such type of vaccines that generate immunogens which can act to raise domain exchanged 2G12 like responses. It was observed that carbohydrate-based immunogens aimed at inducing 2G12-like antibodies may need to drive both di-mannose recognition and domain exchange through interactions with B cell receptors. To assess that information, a research study was carried out on different B cells such as domain-exchanged wild-type 2G12 (2G12 WT), a non-domain-exchanged Y-shaped variant (2G12 I19R), and germ line 2G12 (2G12 gl) [21]. The results show that only discrete clusters of high-mannose glycans, as on recombinant forms of the HIV-1 envelope trimer and oligodendrons, can activate 2G12 WT B cells and no immunogen tested activated 2G12 gl cells, which satisfies "in order to drive domain exchange of an anti-mannose antibody response, we need a immunogen displaying discrete clusters of high-mannose glycans that are not recognized by conventional Y-shaped antibodies". The results have inferred the broadly neutralizing antibody-expressing B cells as potentially useful tools in carbohydrate immunogen screening [21].

5. VRC01: a new vaccine candidate to HIV 1

Advanced research from last 10 years has provided many broadly neutralizing antibodies (bNABs), but still we are unable to develop a vaccine which can elicit bNABs in human body. A new broadly neutralizing antibody, VRC01 [22,23], is able to neutralize 90% of the viral strains considering HIV viral protein as an immunogen [22,23]. But, the problem is that envelope protein gp120 is not able to bind with detectable affinity to B cells to launch broadly neutralizing antibody responses. Scientists have investigated the VRC01 genes and expressed them in germ line B cells. These germ line B cells transformed to mature B cells, but they are unable to

bind to gp120 and elicit the responses. To overcome this challenge, the scientists have started up to design an immunogen using an artificial immunogen strategy that would be successful in hitting the target [22]. Using protein modeling software, libraries created by mutations allowed to find possible beneficial mutations to find the immunogen and these mutants are screened by yeast surface display and FACS. eOD-GT6, an engineered outer domain, optimized immunogen, is able to bind with high affinity to germ line VRC01 antibodies. And they found that this immunogen looks like a tiny viral particle, when 60 copies of eOD-GT6 was copied over some 60 obscure bacterial enzymes and it was able to activate B germ cell lines and mature B cells too. This study makes a hope that it could be one of the potential vaccine candidates for HIV 1. The next existing challenge before us is to check the ability of this immunogen, which is oriented in proper manner, to stimulate antibody response in vitro in the laboratory animals.

6. Challenges faced in HIV vaccine development

Recent distinct advancements in HIV vaccine development have made to a platform in search of safe and effective vaccine candidate. We are able to find the successful strategies in preventing the HIV infection, but we are unable to make a successful vaccine candidate which can be effective in stopping the spread of the epidemic. The road to an effective vaccine is made with so many hurdles and barriers, which made development HIV 1 vaccine a challenging task. Here, we provide some of our views and challenges that weigh in vaccine development.

7. Think about $CD4^+$ T cell responses

$CD4^+$ T cells can perform variety of tasks to shape an effective response against a pathogen. But, limited attention has been paid to the potential importance of functional $CD4^+$ T cell responses in the context of the development of next-generation vaccines, including HIV vaccines. Many $CD4^+$ T cell functions are newly appreciated and only partially understood [24]. For example, recently it is observed that a recombinant fusion protein (F4) consisting of HIV-1 p17, p24, reverse transcriptase (RT) and Nef, adjuvanted with AS01, induced strong and broad $CD4^+$ T-cell responses in healthy volunteers, which shows some interesting functional capabilities of $CD4^+$ cells in HIV 1 vaccine development [25]. It is very much important to work on $CD4^+$ T cell responses against HIV 1, which could aid to the development of successful vaccine [26].

8. Hyper variability of HIV

HIV virus is constantly evolving, with rapid replication in vivo that produces 1010 new virions/day which facilitate rapid generation of sequence variants, and a variety of new strains are on the rise, generating inter- and intra-subtype combination viruses. HIV has an error-prone reverse transcriptase that combined with a rapid replication rate, leads to such high mutation rate. It also has a high capacity for recombination. These lead to hypervariability of HIV and enables "immune escape". Hypervariability renders HIV a moving target – by the time a vaccine candidate has been designed and tested, the virus might well have mutated significantly. These challenges on hypervariability on HIV leads to questions as to whether there is a need to develop candidate vaccines for each subtype due to low neutralizing capacity to other antibodies [27].

To address this, current and future phase III clinical trials should take into consideration appropriate epidemiological characteristics when testing different vaccine concepts and/or a broadly neutralizing antibody needs to be developed [28]. This will also be crucial in order to ascertain whether other factors such as diversity in the routes of infection, genetic make-up, nutritional or health backgrounds of populations affect the efficacy of the HIV vaccine.

9. Lack of relevant animal model

We have a restricted ability to determine cause and effect of the vaccines by active in vivo intervention, which includes both therapeutic potential and acceptable safety profiles. It is also important to consider that every human infection is with a different virus and we have limited access to human tissues other than blood. Thus, it is important to develop an effective vaccine and cure strategies that will invariably involve use of a relevant animal model or develop an animal model which can be commonly used for different vaccine strategies [29,30]. Although many non-primate AIDS virus model exists, each is not equivalent to other and every model cannot answer every scientific question [31].

10. Market potential and financial support

The projected demand for an HIV vaccine as well as the general nature of the vaccine market suggests slim profit potential. The countries most in need of the vaccine are precisely those which have the least ability to pay: low- to middle-income nations. This has contributed to the delay in the vaccine development as most of the industrialists showed least interest toward the investment [28,32]. It is important to increase the market potential for the future HIV vaccine by convincing the industrialists to invest in the HIV Vaccine development, which is worth of investment even though the availability of scientific knowledge is limited.

11. Expenses in clinical trials

The context of increase in the expenses for clinical trials demands for the more financial support from the government organizations and other charitable units. Billions of dollars have already been invested on the development of vaccine, but still we are unable to find an effective one. Because of this, even if efficacious modalities rise it becomes difficult to carry them to clinical trials [34].

12. Translation of experimental data

Clinical investigators are facing a number of barriers in translating the preclinical experimental findings in to human system due to lack of clear knowledge about HIV transmission and persistence [29,33]. During therapy, it is important to know the transmission and persistence of HIV which require the study of mucosal and lymphoid tissues in depth. Due to limited groups accessing and processing those tissues it became difficult to get clear knowledge on transmission and persistence of HIV [34,35].

13. Conclusion

With recent advancements and strategies in developing a successful vaccine candidate, we can be optimistic for an effective and safe vaccine for HIV 1 in not more than a decade. Adenovirus serotype 26 (Ad26) and Virus BG505.W6M.ENV.C2 based strategies in eliciting the broadly neutralizing antibodies have shown promising results but they need more investigations to be carried out in making those strategies effective. eOD-GT6, an engineered immunogen, has shown rare nature of immune response by acting against many types of HIV. This has got the structure mimics viral like particle and was able to bind effectively to germ line VRC01 broadly neutralizing antibody. The next existing challenge before us is to check the ability of this immunogen, which is oriented in proper manner, to stimulate antibody response in vitro in the

Table 1
A brief descriptive tabulation of various advancements and their challenges.

	Advancements	Challenges	Year	Institution
Rv144 vaccine trail	HIV broadly neutralizing monoclonal antibodies [3,8]	Failure in Clinical Trails	2009, 2012	[3]. Department of Disease Control, Ministry of Public Health, Nonthaburi, Thailand [8]. Duke Human Vaccine Institute, Duke University Medical Center
Virus BG505.W6M.ENV.C2	As a stand-alone protein or as a component of a vaccine vector [9]	Needs further investigations for successful application	2013	Vaccine Design and Development Lab, International AIDS Vaccine Initiative, Brooklyn, New York, USA
Adenovirus serotype 26 (Ad26)	Strong vaccine candidate with more efficient broadly neutralizing antibodies [10]	Cellular immune breadth was limited	2013	Center for Virology and Vaccine Research, Beth Israel Deaconess Medical Center, Boston, MA, USA
The HIV 1 Env (gp160) structural studies	Glycosylation and phosphorylation profiles [15], mechanism of Env recruitment and virus incorporation [17]	The studies are incomplete for complete understanding	2013	[15]. Department of Chemistry, University of Kansas, Lawrence, Kansas, United States. Duke Human Vaccine Institute, Duke University Medical Center [17]. Department of Infectious Diseases, Virology, University Hospital Heidelberg, Heidelberg, Germany
VRC01	Able to neutralize 90 percent of the viral strains [19,20]	Unable to bind to immunogen (gp120) in B-cell germ lines	2010, 2013	[22]. Department of Immunology and Microbial Science, The Scripps Research Institute, La Jolla, CA 92037, USA [23]. Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH), Bethesda, MD 20892, USA
eOD-GT6, an engineered outer domain of gp120	Optimized immunogen and was able to bind to the bNABs of VRC01 [19]	To check the ability of this immunogen to stimulate antibody response in vitro in the laboratory animals	2013	[22]. Department of Immunology and Microbial Science, The Scripps Research Institute, La Jolla, CA 92037, USA

laboratory animals. New insights into the structure of trimeric HIV-1 envelope glycoproteins, *N linked* glycosylation, *O linked* glycosylation and phosphorylation profiles on variable and core regions and dependence of recruitment and incorporation of Env proteins on other viral proteins and cytoplasmic tail (CT), have provided better understanding of gp120 in vaccine development. But, it needs to have more understanding of HIV 1 structural & functional proteins and their role for successful vaccine development. In Table 1, a brief descriptive tabulation of various advancements and challenges faced by them is given. The other challenges faced in vaccine development include lack of relevant animal model, lack of financial support, demand in market, hyper-variability of HIV, difficulties in translation of preclinical experiments, increase in expenses of clinical trials, etc.

Conflict of interest

None declared.

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None declared.

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