Analysis of Challenges and Progress AIDS Vaccine Research

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Abstract. Since the first report of AIDS (acquired immunodeficiency syndrome) caused by human immunodeficiency virus (HIV) in 1981, this disease has become a serious social and public health problem worldwide. Scientists have always been committed to developing an efficient AIDS vaccine. This article discusses the research of AIDS vaccine and the difficulties encountered in its development. First of all, there is no ideal animal experimental model for AIDS vaccine research. Given that HIV is a virus specific to humans, there is currently no animal model that can fully simulate the process of human HIV infection, which poses challenges for vaccine development and testing. Furthermore, the envelope protein of HIV-1 does not inherently possess the ability to induce broad-spectrum neutralizing antibodies. The envelope protein of HIV is considered one of the key targets of vaccine research, but most existing antibodies induced by HIV-1 envelope protein can only neutralize some virus strains, so they cannot provide comprehensive protection. However, the latest scientific research suggests that the stable epitopes of HIV-1 envelope proteins contribute to the maturation and evolution of widely neutralizing antibodies. This new discovery has opened up a new direction and clue for the research and development of HIV vaccine. Targeted activation or enhancement of immune response to these conservative epitopes will help to generate antibodies with extensive neutralizing activity, thus creating the possibility of developing an effective AIDS vaccine.

Keywords: AIDS; Vaccine research; Challenge; Progress.

1 Introduction

AIDS is the abbreviation of "acquired immunodeficiency syndrome", which originates from the English abbreviation. AIDS(Acquired Immune Deficiency Syndrome), It is infected with the human immunodeficiency virus(Human Immunodeficiency

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Virus, HIV)A chronic, progressive, and fatal disease caused later on. The structure is shown in Figure 1.

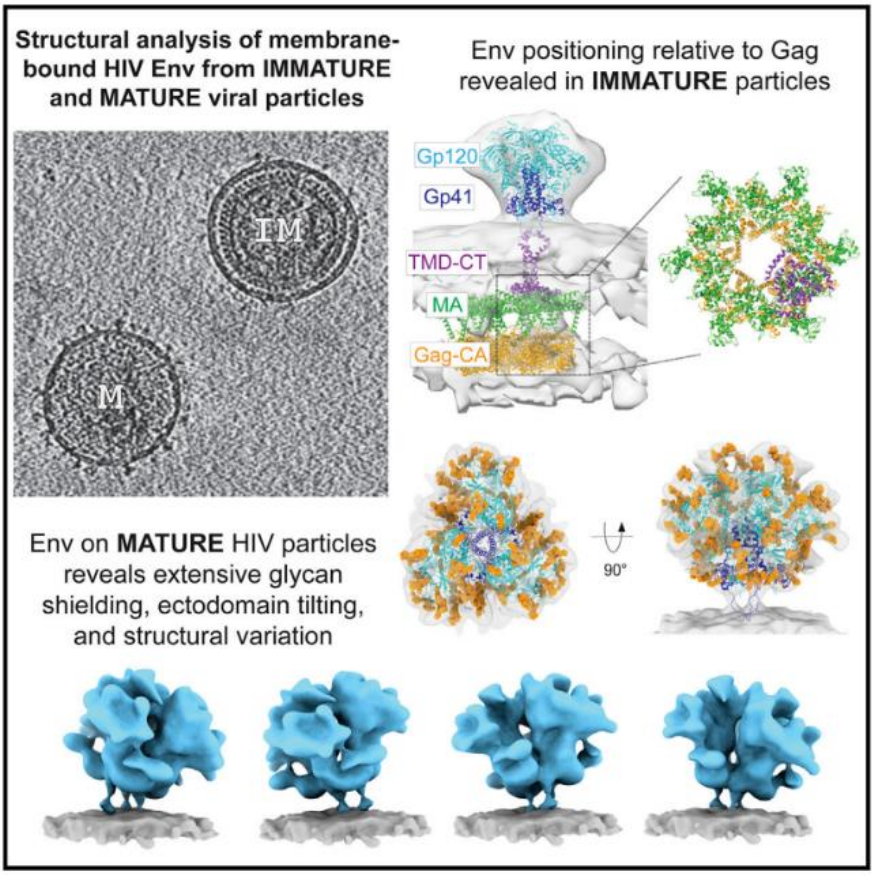

Fig. 1. Human Immunodeficiency Virus

Since the human immunodeficiency virus (HIV) and the AIDS caused by it were identified in the 1980s, it has been a huge test of global public health. Although the technical progress of antiretroviral therapy (ART) has significantly improved the quality of life and life expectancy of infected people, the development of AIDS vaccine is still an unresolved issue, which is crucial to control the spread of the epidemic and ultimately eliminate AIDS. This article will discuss the core challenges faced by the current AIDS vaccine research, and discuss the latest scientific research progress in depth.

The first problem is the lack of a perfect animal experimental model, which has become the main obstacle to the development of AIDS vaccine. Given that HIV is a virus specific to humans, current animal experimental models cannot fully simulate the entire process of human HIV infection, which limits the detection and evaluation of potential vaccines in the early clinical stage. Therefore, in order to accelerate the

development of vaccines, it is particularly crucial to develop new animal experimental models or optimize existing models to make them more closely related to human infection and immune response. Furthermore, relying solely on the envelope protein of HIV-1 is not sufficient to induce a broad-spectrum neutralizing antibody. The envelope protein is not only the core protein in the particle structure of HIV virus, but also regarded as the main focus of vaccine research. Despite the high variability of HIV, which allows the virus to evade immune system surveillance, vaccine induced antibodies often only neutralize some strains of the virus and cannot provide comprehensive protection. Faced with this challenge, scientists need to have a deeper understanding of how HIV evades the immune system, and develop vaccine programs that can stimulate more neutralizing antibodies. Despite facing numerous challenges, the latest scientific research has revealed that HIV-1 envelope proteins have conserved epitope characteristics, which may contribute to the maturation and evolution of broad-spectrum neutralizing antibodies. In different virus strains, these conserved epitope differences are not significant, which makes them a potential preferred target for vaccine development. Researchers expect to generate antibodies with wide neutralizing effect through specific trigger mechanisms or enhanced immune response to these conservative epitopes, creating conditions for the development of efficient AIDS vaccine.

The research of AIDS vaccine can be divided into three stages: vaccine to induce humeral immunity; Vaccines that induce T cell immunity; A vaccine that simultaneously induces antibodies and cellular immunity. We can compare these stages to the three major campaigns launched by adults against AIDS virus. The specific situation is shown in Table 1.After these three battles, although mankind has not yet been liberated from the evil AIDS disease, it has found the direction to continue to move forward and fight, and has seen the dawn of victory.

Table 1. Three milestone battles in the development process of HIV vaccines

Stage	Test ID	Immune strategy	Candidate vaccine	Number of people	Results
First Phase	VAX 003 / VAX 004	Classic vaccine strategy	AIDSVAX B / E	7900	Unprotected
Second Phase	HVTN 502, 503 / Merck Step	A New Strategy for Recombinant Viruses	MRKAd5 HIV-1gag/pol/nef ALVAC-HIV	6000	Unprotected Experimental termination
Third Phase	RV 144	Balanced immune strategy	vCP1521 / AIDSVAX gp120 B/E	16403	Partial protection

2 Lack of Ideal Animal Models

In the process of vaccine research, preclinical animal model evaluation is considered one of the most critical steps. At present, the HIV-1 virus cannot replicate in animals,

so we have not yet found a perfect animal model to evaluate the potential vaccine for HIV-1[1-4]. Monkey immunodeficiency virus (SIV) has many similarities with HIV-1 virus in terms of infection, transmission, and incubation period. Researchers have successfully created a new virus called Chimeric Virus (Ape/Human Immunodeficiency Virus SHIV) by replacing the corresponding with HIV-1 in the SIV genome. Researchers have successfully replaced the HIV-1 membrane protein gene (env) with a specific env from the SIV genome in non-human primates (NHP), thus constructing an animal model of primate/human immunodeficiency virus (SHIV) infection[5-8]. This model has been used by many researchers to evaluate the protective effect of HIV-1 vaccine, induce the production of bnAb and study its evolution process. However, factors such as the mode of infection, dosage, and duration of administration of SHIV may have a significant impact on vaccine evaluation[9-10].

HIV-1 is mainly transmitted naturally through contact with mucous membranes. However, the blood contains a large number of infectious virus particles, which makes viruses transmitted through the blood more infectious. In preclinical studies of animals, there are mainly two methods: mucosal injection and intravenous injection, with mucosal injection being the most commonly used method. In early studies, single high-dose injection (SHD) was widely used, but it has obvious shortcomings. Although the infection rate of SHD is close to 100%, the immune protection effect of the vaccine is weakened due to the high concentration of the virus, which leads to a serious underestimation of the actual protective effect of the candidate vaccine[11-12]. In addition, there is a significant difference in the normal infection process between SHD and HIV-1. Under normal circumstances, the HIV-1 infection rate among sexual contacts is very low. The semen of positive male patients contains an average of approximately 11000 virus copies per milliliter. However, in animal models, even at very low doses of the virus (TCID50<250), the number of virus copies per milliliter exceeds one million, which far exceeds the viral titer during normal infection processes[13-14]. Therefore, SHD cannot accurately simulate the normal transmission mechanism of HIV-1 virus. By repeating low-dose infection (RLD), we can more accurately simulate the natural infection process of HIV-1 virus, making it a standard research method for preclinical animal experiments. RLD has the ability to more accurately simulate the process and characteristics of human HIV-1 mucosal infection. Therefore, in a limited number of animal samples, the RLD model is considered a sensitive evaluation method for vaccine protection effectiveness.

The simulation experiment results show that using the RLD model can achieve sufficient statistical analysis ability, and only 50 monkeys (25 in each group) can demonstrate a 50% protective effect, greatly increasing the possibility of successful subsequent clinical trials[15]. When evaluating the RLD model, the viral infection titer and frequency are considered as core elements. There are significant differences in the viral infection titers used by different research teams, and the effective TCID50 values may differ by more than ten times. This is mainly due to the impact of different passage times and in vitro amplification techniques on the infectivity of the virus[14, 16]. Therefore, accurately determining the viral infection titer before testing is crucial to ensuring successful testing. In numerous studies, we typically use weekly infection frequency to construct infection models. For non immune monkeys, the initial infec-

tion rate is usually between 20% and 40%, which helps to more accurately evaluate the potential protective effect of vaccines. According to research, SIV infection typically occurs within 5-14 days after receiving a single dose of vaccine[17]. If monkeys are infected every two weeks and serum conversion measurements are taken on days 6, 10, and 14, then after these 10 days, 74% of positive conversions will occur[17]. This batch of experimental data shows that the number of infections per week may lead to an overestimation of the immune protection effect, while infection frequency and more frequent indicator testing every two weeks may provide us with a more accurate evaluation of the effect. Although the RLD model performs better in evaluating the protective effect of vaccines, it still has inherent limitations, making it difficult to fully demonstrate its evaluation results in human clinical trials:

(1)In this model, the SHIV used cannot fully simulate the infection process of HIV-1;(2)Due to significant differences in infection and pathogenicity among different SHIV strains, selecting the appropriate SHIV strain may have a profound impact on vaccine evaluation;(3)In this model, the initial infection rate is significantly higher than the natural infection rate of HIV-1, and the low-dose viral titers used for vaccination far exceed the viral amount in the vaginal secretions or semen of infected individuals. However, further vaccination to reduce infection rates is unrealistic. However, further reducing the titer of the virus to reduce infection rates may lead to longer research cycles and increased costs. Given the diversity and uncertainty of influencing factors, it is necessary to increase the number of animal samples in order to obtain significantly different statistical data and more accurately evaluate the protective effect of vaccines.

3 HIV-1 the Envelope Protein Itself is Insufficient to Induce Broad-Spectrum Neutralizing Antibodies

The genetic sequence of HIV-1 has high diversity, therefore preventive vaccines are needed to provide extensive immune protection. About 10% of people who have been infected with HIV-1 for a long time will naturally develop bnAb within 2-4 years after infection, but there are also a few who appear within one year after infection in children[18-19]. The latest research evidence also suggests that in order to achieve widespread and neutralizing activity, neutralizing antibodies in infected individuals need to undergo long-term accumulation through somatic hypermutation (SHM). Through in-depth analysis of antibody sequences during the evolutionary process, we found that the neutralizing ability and range of antibodies are positively correlated with the accumulation of somatic hypermutations. This means that obtaining broad-spectrum neutralizing HIV-1 antibodies requires a long accumulation of somatic hypermutations[20-21]. Due to the inherent weak immunogenicity of HIV-1 envelope protein (Env) and limitations in antibody development, previous immune strategies were unable to induce the production of bnAb targeting HIV-1.

HIV-1 Env is composed of two parts: gp120 and gp41. The surface envelope protein of the virus is composed of three independent monomers, which combine in a non covalent manner to form a trimeric structure; Gp120 is located outside the virus

membrane and its main function is to bind to cell receptors, while gp41 ensures that the entire membrane structure is firmly attached to the virus membrane and facilitates the fusion process of virus cells. The previous Env trimeric immunogen did not trigger a neutralizing antibody reaction, mainly due to its relatively weak immunogenicity, which cannot trigger a high degree of antibody neutralization reaction. Under similar environmental conditions, after immunization with HIV-1 gp120 and rabies virus G protein, the levels of IgG and IgA induced by HIV-1 gp120 were significantly lower than those of G protein[22]. Compared to the surface antigen vaccine for hepatitis B, the antibody response induced by gp120 in baboons is more intense, but its antibody concentration decreases significantly faster than that of hepatitis B antigen, which may be due to the relatively small number of long-acting plasma cells induced by gp120[23]. The data mentioned above shows that compared to other viral antigens, gp120 has weaker immunogenicity and therefore does not lead to sustained antibody reactions. With the continuous progress in the field of structural biology.

The in-depth analysis of the high-resolution spatial Env structure has driven further optimization of the HIV-1 immunogen structure. Through structural adjustments, we observed more stable trimers similar to natural Env, such as SOSIP and UFO [24-25]. Through observation under a cryoelectron microscope, we found that SOSIP.664 shares significant spatial similarities with the virus particle Env, making it a key structural precursor for developing HIV-1 immunogens. SOSIP.664 exhibits superior immunogenicity because it enhances the stability of trimers and the expression of antigens in vivo. The trimeric structure of SOSIP.664 triggered neutralization reactions against homologous secondary viruses for the first time in animal models such as rabbits, guinea pigs, and monkeys. However, neutralization reactions against heterologous viruses are relatively rare[24,26-27].

The specific reason for the weak immunogenicity of HIV-1 Env is not yet clear. Numerous pieces of evidence indicate that the strong glycosylation modification experienced by Env is one of the key influencing factors. By comparison, the hemagglutinin monomer in influenza viruses contains approximately 3 polysaccharide molecules, the respiratory syncytial virus fusion protein contains 5 to 6 polysaccharide molecules, and the HIV-1 Env monomer contains nearly 30 polysaccharide molecules, which far exceeds many other membrane proteins that may cause diseases[28]. Given that polysaccharides cannot be accurately recognized and exhibit immune tolerance characteristics in the immune system, severely glycosylated Env cannot effectively trigger immune responses. The maturation and evolution of neutralizing antibodies depend on the accumulation of high-frequency mutations in the antibody gene hypervariable region (V), which helps to generate various B cell clones, and this process relies on T helper cell Th2 to activate humoral immune responses. T helper cells can recognize T helper cell epitopes (THCE) on antigen-presenting cells through specific receptors, thereby promoting the activation of Th1 or Th2. At the same time, sugar molecules located near the antigen hydrolysis site can form a spatial barrier that prevents protease hydrolysis, thereby affecting the release of antigen epitopes and ultimately inhibiting the activation of humoral immunity[29-30]. Numerous sugar binding proteins are widely present within cells. Research has shown that mannose binding lectins have a high affinity for the polysaccharide epitopes of SOSIP membrane

proteins, which helps to reduce Env's immune response and inhibit the generation of neutralizing antibodies[31].

The immune evasion mechanism mediated by the HIV-1 membrane protein molecule gp120 can also affect the immunogenicity of Env, and the high-frequency variation of the gp120 gene helps to evade the pressure of the immune system. Although changes in amino acids do not significantly interfere with the physiological function of gp120, it can indeed accelerate the escape process of HIV-1 under the influence of neutralizing antibodies[32]. In order to enhance adaptive immune protection, the mechanism activates its natural immune mechanism, and vaccine adjuvants play a significant role in enhancing the efficacy of this mechanism. In plasma dendritic cells, TLR9 receptors can recognize oligodeoxynucleotide CpG, which helps promote the generation of type I interferon and pro-inflammatory factors, thereby further activating B cells. During this process, gp120 binds to the mannose lectin receptor on the surface of CD4 and dendritic cells, thereby reducing the expression of related pro-inflammatory factors and inhibiting the activation of B cells. This may affect the use of TLR9 agonist adjuvants in HIV-1 vaccines[33]. It is particularly noteworthy that in the early stages of immunization, when the concentration of gp120 at the vaccination site is relatively high, the interaction with CD4 receptors will be enhanced, which helps to further inhibit the activity of B cells. Research has found that when the affinity between gp120 and CD4 receptors is inhibited, the immunogenicity of DS-SOS-IP.4mut antigen is enhanced[34]. The W427S mutant of gp120 successfully inhibited the binding between gp120 and CD4 receptors. By using wild-type or wild-type immunogens, high levels of non-specific follicular T helper cells, plasma cells, and serum IgG antibodies can be induced. The principle of mutant immunity can trigger higher levels of specific humoral and cellular immune responses[35].

Improving the immunogenicity of antigens can trigger stronger antibody responses. We fused T cell epitopes from the tetanus vaccine into virus like particles containing HIV-1Env immunogen and conducted immune experiments on mice. The experimental results show that virus like particles containing THCE can stimulate stronger T cell responses and significantly increase the expression level of IgG1 antibodies against Env[36]. Given the widespread use of tetanus vaccines in the public, memory T cells associated with them can further enhance their immune response to this viral particle. Through the multivalent binding of nanoparticles, the efficiency of antigen presentation in the body can be significantly improved, thereby triggering stronger B cell reactions, which makes this material widely used in the field of vaccines[37-39]. Due to the nano antigen of respiratory syncytial virus, the number of neutralizing antibodies has increased by more than 10 times[37]. By integrating the HA receptor binding sites of different influenza virus strains, the embedded vaccine significantly enhances the neutralization range of antibodies[38]. However, nanoparticles made from HIV-1Env can only increase the titer of neutralizing antibodies by three times, which is far from the effectiveness of other viruses. This may be due to the site blocking effect of Env sugar molecules and their extensive binding with lectins[39].

Although vaccine adjuvants can significantly enhance the immunogenicity of vaccines, the most commonly used aluminum adjuvant may disrupt the structural integrity of HIV-1Env, which may be one of the main reasons why it cannot induce

bnAb[40]. However, in the model of SHIV infected monkeys, a novel liposome aluminum adjuvant called ALFA showed a 90% protective effect, but the control group of aluminum adjuvant did not show this effect[41]. Currently, we are conducting in-depth clinical studies on various combinations of aluminum adjuvants and HIV-1 vaccines. In addition, there are other adjuvants, such as mutated antipyretic Escherichia coli toxin, AS01b, and ALF43[42-43]. During the research on AIDS vaccine, the slow release of immunogen, as an attractive immunization strategy, is gradually gaining more attention[44]. Compared to traditional intermittent immunization methods, this method can better simulate the antigen display process in natural infections, stimulate stronger immune responses, and enhance the immunogenicity of antigens. Researchers conducted a continuous and slow antigen release experiment on mice using a non mechanical osmotic pump for two weeks, and conducted three repeated experiments. The research results indicate that compared with intermittent injection methods, sustained-release immunity significantly increases the number of follicular T helper cells TFH and reproductive center B cells, while the number of IgG antibodies also increases by 15 times[45].

The same research team used two different sustained-release models in the monkey experimental model to verify the enhancing effect of this immune mode[46]. The experimental model is shown in Figure 2. Similar to the mouse experimental model, slow release of antigens significantly optimized the response dynamics of TFH and B cells in the reproductive center, and the number of neutralizing antibodies against homologous Tier2 virus increased by more than 20 times. More importantly, the sequencing results of the second generation Env specific B cells showed that the sustained release effect led to more diverse forms of Env specific B cells, which in turn triggered the diversity of neutralizing antibodies. Surprisingly, in both scenarios, the performance of somatic SHM was very similar to that of the reference group. By applying antigen tracing technology, we observed that sustained release significantly increased the residence time of antigens in the lymphatic system, which means that the neutralizing epitopes of antigens are better displayed, thereby improving the diversity of neutralizing antibodies[46].

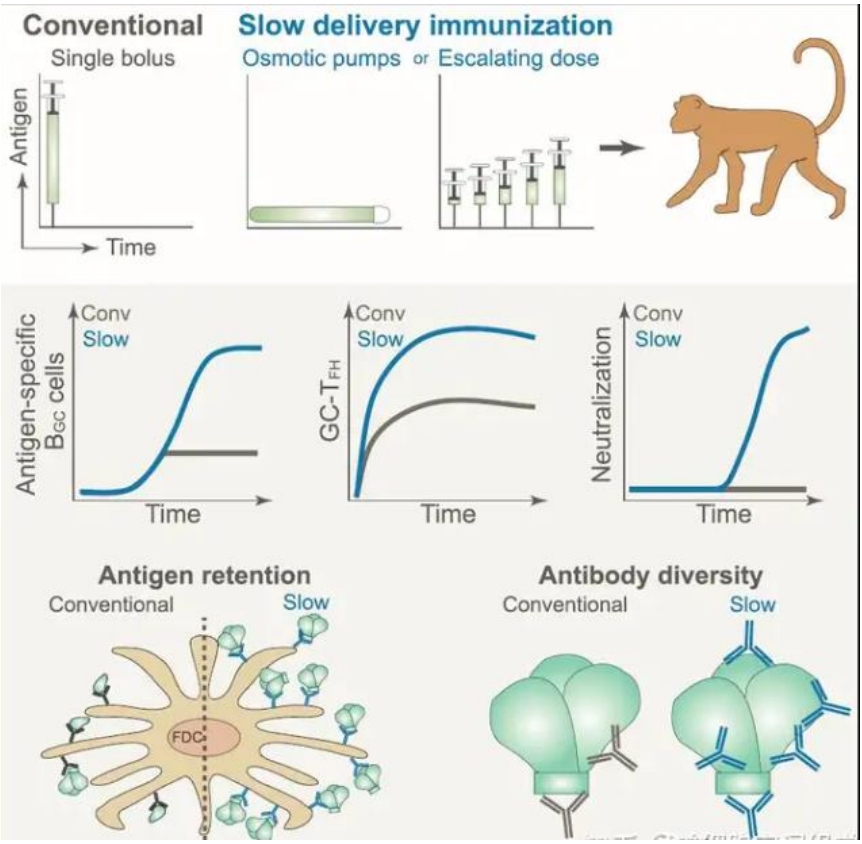

Fig. 2. Monkey experimental model

Image from Cell, 2019, doi:10.1016/j.cell.2019.04.012

4 HIV-1Conservative Epitopes of Envelope Proteins can Promote the Evolutionary Maturation of Broad-Spectrum Neutralizing Antibodies

Due to the diversity of HIV-1 virus sequences, vaccines need to have a wide range of immune protection. In recent years, researchers have extracted several bnAbs from infected individuals and identified conserved epitopes of antigens that interact with them. These epitopes include the CD4 binding site (CD4bs), the proximal outer membrane region of V1V2, V3C3, gp41, and the gp41 binding site of gp120[47]. The research team used recombinant gp120 antigen RSC3 from HIV-1 and single B cell sorting technology to conduct in-depth research on the monoclonal antibody VRC01 of gp120 CD4bs, and found that this antibody has a broad-spectrum neutralization effect of up to 91% on HIV-1 patients[48]. The high isolation frequency of CD4bs

targeting bnAb may be due to the virus's need for sufficient contact with conserved CD4bs to promote binding to target cells, effectively transferring epitopes and triggering the production of specific bnAb. Through the comparative analysis of 16 CD4bs specific bnAbs provided by 14 AIDS patients, we found that although there were significant differences in the base sequence of these antibodies, their spatial structures were very similar[49], This also provides an explanation for their ability to specifically recognize CD4bs epitopes. Although antibodies have significant differences in sequence, their functional similarity indicates that they have acquired the ability to bind to CD4bs epitopes through their respective evolutionary pathways and ultimately neutralize most broad-spectrum virus species.

Recently, scientists have observed that the formation of anti HIV-1-bnAb requires a long evolutionary and mature stage. The advancement of bio-informatics and single-cell sequencing technology provides us with a valuable opportunity to study their evolution and maturation processes. By sequencing and comparing the serum B cells of AIDS patients in different time periods, it was found that to obtain broad-spectrum neutralizing antibodies, a large amount of SHM needs to be accumulated. When B cells encounter antigens, they can significantly increase the diversity of B cell types through SHM. In theory, B cells can have 1012 different types, and this vast B cell pool ensures accurate recognition of TFH and screening of bnAb clones. CH103 has accumulated 17% of SHM over a period of 2.5 years, thus possessing the ability to neutralize 55% of the virus[20]; In the past 6 years, CH235 has accumulated 25.6% of SHM[21]. In the past 6 years, CH235 has accumulated 25.6% of SHM and successfully neutralized 90% of the virus[21]. Therefore, the accumulation of SHM plays a crucial role in the production of bnAb.

Considering that the formation of SHM is an uncertain event, how do neutralizing antibodies gradually enhance their role on certain conserved epitopes? The HIV-1 virus in the patient's body has acquired the ability to evade immune pressure through continuous mutation. The extracted bnAb from the patient's body cannot effectively neutralize the virus that was present in the patient's body at the time, nor can it reduce the titer of the virus and slow down the progression of the patient's disease. This fact indicates that the mutation of bnAb is not intended to enhance the broad-spectrum nature of neutralizing antibodies[50], But rather, the diversity caused by virus mutations plays a crucial role in promoting the broad-spectrum neutralizing antibodies[20, 51, 52]. Further research confirms that viral diversity and recombination caused by superinfections can significantly enhance the neutralization range of antibodies[53-54]. In order to achieve a wide range of neutralizing effects, neutralizing antibodies need to specifically target the conserved epitopes in Env's structure. For other non conserved epitope antibodies, although they may evolve, they cannot obtain broad neutralizing ability, which also explains why the possibility of obtaining bnAb from patient isolates is very low. The eutectic structures of CH235 and Env at different stages indicate that the early evolved CH235 can recognize the core and peripheral regions of CD4. However, as antibodies evolve, the recognized membrane protein epitopes gradually shrink. Ultimately, the evolved CH235 can only recognize highly conserved CD4bs shared by all HIV-1 strains, without being affected by the edge region of CD4bs mutations, thus being able to bind and neutralize other non conserved

epitopes. This technology can only identify highly conserved CD4bs regions without interference from CD4bs edge mutation regions, allowing it to bind to most viruses and achieve widespread neutralization of HIV-1[21]. The virus further releases CD4bs by removing the V2 region of the 160th polysaccharide modification site, which helps to neutralize the maturation process of CD4bs and antibodies[55]. In addition, the longer the antigen stays in the lymphatic system, the higher its efficiency in expressing conserved epitopes, which ultimately leads to an increase in neutralizing antibody diversity[46]. The data mentioned above indicates that complete exposure to antigenic epitopes is crucial for the production of bnAb. However, further scientific research is needed on how the immune system archives the collected epitope information and how to further enhance the molecular level mechanisms of these epitope information, such as whether these archived information will increase the binding affinity between TFH and specific B cells. Overall, although viral mutations and B-cell SHM exhibit certain randomness, highly conserved epitopes on envelope proteins may trigger the maturation and evolution of broad-spectrum neutralizing antibodies under specific environmental conditions. Although a large amount of bnAb has been isolated from HIV-1 infected individuals, not all existing immunogens can induce the production of bnAb in animal models and humans. This is the evolutionary mechanism of the four broad-spectrum neutralizing antibodies and their impact on the design of new vaccines. In order to gain a deeper understanding of the evolutionary mechanisms that lead to the generation of bnAb, researchers have successfully obtained a large number of antibody gene sequences generated during the maturation process of bnAb using single-cell and high-throughput sequencing techniques. Based on these data, they plotted the evolutionary lineage of antibodies and derived the evolution and maturation process of bnAb from it. We successfully extracted CD4bs target, bnAb (CH103), from individuals infected with the African HIV-1C subtype founding virus (CH505). Through the study of neutralizing antibody profiles, we have explored for the first time the co evolution and maturation process between the founding virus and bnAb. In subsequent studies, we further revealed the synergistic effects between different strains of B cells, as well as the evolution and maturation process of embryonic antibodies. The cooperative mechanism of B cells between different lineages and the maturation process of antibodies from lineage evolution to bnAb[20, 21, 52]. The mature mechanism of evolution for identifying bnAbs with the same or different epitopes has been explained in detail, which further confirms and expands the co evolutionary path between viruses and bnAbs[51, 56]. B cells are responsible for secreting broad-spectrum neutralizing HIV-1 antibodies in the body, completing the recombination of antibody genes, and forming an unmodified common ancestor (UCA). In order to complete this lengthy process of evolution and maturation, the reproductive center of B cells needs to accumulate a large amount of SHM. Based on in-depth research on the evolution and maturation mechanism of bnAb, we propose an immunogen development strategy based on B cell lines: Firstly, extract efficient bnAb from memory B cells; Next, we need to draw their evolutionary maps to determine the common origin between the lineage and intermediate antibodies (IA) in evolution; Finally, based on UCA and different IA and their corresponding viral envelopes, we chose UCA and IA as the common origins of this strain. Finally, based on the affinity and neutralizing ability of

UCA and its corresponding viral envelope proteins in evolving mutants, we successfully developed a continuous immunogen and gradually induced the generation of bnAb.

Based on the above research methods, scientists have successfully induced bnAb with the ability to neutralize grade 2 strains in humanized mice[57]. The sequential immune strategy is similar to natural infection and has the potential to control the growth and maturation of bnAb, while reducing the formation cycle of bnAb. However, this method has not been empirically demonstrated in experimental models of non-human primates. Significant progress has been made in the target design for lineage B cell antigens, with the core objective of activating target bnAb precursor B cells through optimization of immunogen design. VRC01 type bnAb has the ability to specifically bind to CD4bs targets, however, UCA antibodies specifically designed for this type of bnAb cannot bind to Env of heterologous viruses. Therefore, the Env of the heterologous virus cannot trigger the activation of UCA antibodies against this type of bnAb in the corresponding strain B cells, resulting in the inability of the Env of the heterologous virus to activate the corresponding strain B cells. The research team successfully studied and identified the optimized eOD-GT6 immunogen by designing protein-protein interactions, screening libraries, and optimizing multiple targets. Compared to the wild-type env, the number of mutation sites in eOD-GT6 increased by eight. There is a very high affinity between eOD-GT6 and VRC01, UCA, and IA, which may lead to the generation of SHM by corresponding B cells towards mature VRC01. Experimental data shows that eOD-GT6 nanoparticles can effectively activate B cell lines expressing VRC01 and its precursors[58]. Recently, the N332-GT2 immunogen developed by the same research team has successfully induced a relatively wide range of binding antibodies in mice[59]. Until now, this strategy still needs further improvement, as broad-spectrum antibodies with neutralizing effects have not been successfully induced in this group of humanized mice.

5 Conclusions

The research and development of AIDS vaccine is a long-term and arduous task, facing many challenges. From the lack of ideal animal models to the insufficient ability of HIV-1 envelope proteins themselves to induce broad-spectrum neutralizing antibodies, every step is full of difficulties and uncertainties. However, despite numerous challenges, the efforts and persistence of scientists have never stopped, and new discoveries and advancements continue to bring new hope for vaccine development. Firstly, although there is currently a lack of ideal animal models, scientists are continuously exploring and attempting through genetic engineering techniques, primate research, and other means, in order to find animal models that are closer to the human HIV infection process and provide stronger support for vaccine development. Secondly, although the HIV-1 envelope protein itself is not sufficient to induce broad-spectrum neutralizing antibodies, scientists have discovered conserved epitopes of the HIV-1 envelope protein, which can promote the evolutionary maturation of broad-spectrum neutralizing antibodies. This discovery provides a new direction for vaccine

design, allowing us to potentially induce antibodies with broad neutralizing ability by targeting these conserved epitopes. Although challenges still exist, the development of science is endless. With the continuous progress of science and technology, our understanding of HIV is also deepening, and new research methods and technologies are constantly emerging. These new methods and technologies, such as structural biology, immunology, gene editing, etc., provide new possibilities for the development of AIDS vaccines. In general, although there are many difficulties in the research and development of AIDS vaccine, the persistence and efforts of scientists, as well as new scientific discoveries and technological progress, have brought us new hope. We have reason to believe that as long as we continue to work hard, the research and development of AIDS vaccine will eventually make a breakthrough and provide a powerful weapon for the global fight against AIDS.

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