HIV-1 Vaccines

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More than thirty years of laboratory and clinical research has proven developing a vaccine against HIV is one of the most challenging tasks that the field of medicine has been encountered. In early years, no one realized that HIV is more complex than any other viral diseases for which effective vaccines have been developed. Either live-attenuated or whole-inactivated viruses could not be used in HIV vaccine development due to the danger associated with integration of the proviral DNA in the host chromosome[1]; therefore, other approaches have been taken to develop a vaccine for controlling HIV.

First "wave" of HIV vaccine: Induction of neutralizing antibody

In last thirty years, the advances in molecular biology and recombinant DNA technologies provided the essential tools to identify the major HIV structural proteins, and sequence its genome. In 1985, neutralizing antibodies were described for the first time[2]. Despite of lack of evidence for their protective efficiency, the envelope glycoproteins (mainly gp120 and gp160, i.e., the main target for the neutralizing antibodies) were genetically engineered and cloned into vectors, such as poxvirus vectors, to elicit the neutralizing antibody responses[1]. Vaccinia vector, expressing gp160, was the first HIV vaccine to be tested in a human clinical trial. However, this trial was terminated due to ethical issues[1]. In 1987, another vaccine, which was developed by expressing gp160 in a baculovirus-insect cell system, was tested in a clinical trial. Although this vaccine showed to be safe, the induction of the neutralizing antibodies was not significant[3]. Many more vaccines and clinical trial were conducted between 1988 and 2003, and the results showed to be safe and immunogenic. However, all HIV vaccines tested in 1980s and early 1990s showed to induce the neutralizing antibodies response to lab strains of HIV but not to the clinically isolated viruses[1].

Second "wave" of HIV vaccine: induction of CTL responses

Following the recognition of the crucial importance of CD8+ T-cell responses in controlling HIV infection, induction of CTL responses became the main focus in HIV vaccine development. The animal studies provided a strong evidence for the importance of CLTs in controlling the HIV replication in infected people; however, they do not eliminate the virus completely. This discovery led to development of live recombinant viral vectors, especially poxvirus and adenovirus vectors, as well as DNA vaccines. DNA vaccine showed to be less immunogenic in humans than in small animals[2]. By 2004 a candidate vaccine, i.e., adenovirus 5 (Ad5) vector expressing the HIV gag, pol and nef genes, was tested in two clinical trials. However, both trials were terminated as the reviewing one of the trials revealed that this vaccine was not protective, and in fact it was associated with an increase risk of HIV acquisition in vaccinated volunteers who have pre-existing immunity to Ad5[4].

"Waves" of HIV vaccine	Vaccine Components	Efficacy
1. Induction of humoral immune response		
e.g.,		
- Vax004	- Recombinant gp120	- No
- Vax003	- Recombinant gp120	- No
2. Induction of immune response		
e.g.,		
- STEP	- Ad5 (gag, pol, nef)	- No
3. Immune responses combination		
e.g.,		
- RV144	- Canarypox (gag, pol, env) & recombinant gp120	- Yes (31.2%)
- HVTN50	- DNA (gag, pol, nef) & Ad (gag, pol) & Ad5 (env)	- No
- P5	- Canarypox (gag, pol, env) & recombinant gp120	- No

Table 1. Summary of HIV-1 vaccine development "waves"

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Third "wave" of HIV vaccines: Combinations of immune responses

Due to the unsuccessful outcomes of HIV vaccine clinical trials, the field shifted towards exploring combination of the two adaptive immune responses: humoral and cellular. More and more evidences are suggesting that humoral immune response is the critical force to prevent acquisition of HIV infection, whereas CTL is the crucial response in controlling the replication of the virus in vaccinated individual who become subsequently infected. In 2009, RV144 trial showed some promising results. This vaccine was combination of two vaccines: a canarypox-HIV recombinant vector followed by a recombinant gp120 protein. The results of this trial showed a 31.2% efficacy in prevention of HIV infection. A high level of envelope specific IgA antibodies was detected in individuals, developing immunity. However, no neutralizing antibodies were observed, resulting in turning the attention to the antibody-dependent cell-mediate cytotoxicity (ADCC)[1]. In recent years, the field is focusing on induction of the broadly neutralizing antibodies (bnAb), the "Holy Grail" of HIV vaccine research. These antibodies can potentially develop protection against a large number of different strains of HIV. More researches are focusing on identifying the target epitopes of bnAbs. These antibodies can potentially be applied both in prevention and treatment of HIV infection; however, more investigations are required.

References

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