

Forum in immunology

Criteria for selection of HIV vaccine candidates—general principles

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Available online 15 September 2005

Abstract

The generation of a vaccine against HIV/AIDS is extremely challenging, as evidenced by more than 20 years of attempts. Here are highlighted the strategies adopted within the AIDS Vaccine Integrated project (AVIP) to speed up the clinical evaluation of novel vaccine candidates and to increase the chances to get an effective preventive and/or therapeutic vaccine.

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Keywords: HIV vaccine candidates; Antibody; Selection criteria

1. Introduction

The design of protective HIV vaccines within the AIDS Vaccine Integrated Project (AVIP) program is currently based on two general ideas. One is a “minimalistic” approach using only two HIV proteins (a regulatory and a structural protein). The other approach aims at “imitating” a live attenuated vaccine using as many HIV genes as necessary (“maximalistic” approach). In both general approaches different technical ways will be tested to achieve a protective immune response. “Protective immunity” is primarily defined as protection against “infection” but also as protection against “disease development” in case of failure of protection against infection. Thus, both protective mechanisms should be evaluated with the proposed vaccines.

The “minimalistic” approach is based on the fact that the primary target cells for HIV in mucosal tissues, the Langerhans cells as well as other dendritic cell types, need further contact with specific T cells in order to initiate a full infection cycle (Sugaya et al., *J. Immunol.*, 2004). Like other cell types characterized by low HIV replication capacity, these cells seem to be also predominantly expressing early regulatory proteins like Tat and Nef. Tat and Nef, on the one hand, induce the expression of cytokines and chemokines in the infected cells, activating further gene expression, and on the other hand are, as extracellular proteins, chemoattractants for

HIV target cells, which they activate in order to facilitate and increase virus infection. These extracellular proteins are also efficiently taken up by target cells where they activate and/or facilitate directly or indirectly virus replication. Thus, to interfere with this local process in the mucosa, the following immune responses are necessary:

- strong cytotoxic T lymphocyte responses against early proteins like Tat and/or Nef to eliminate the first infected cells;
- specific neutralizing antibodies (Ab) against the activities of extracellular Tat and/or Nef to prevent their role in facilitating further virus transmission and replication in new HIV target cells;
- broadly neutralizing Ab against HIV to block the transfer of the virus from the first to the next generation of infected cells.

The aim of the “minimalistic” approach is, therefore, to design a vaccine that elicits T cell responses and neutralizing Ab against Tat or Nef, as well as neutralizing Ab against Env. The Tat/Env vaccine will be administered as a protein/protein vaccine regimen with adjuvant, whereas the Nef/Env vaccine will be based on a modified vaccinia virus Ankara vector/protein approach.

The “maximalistic” approach aims at a vaccine that can provide the same protection mechanism as that inherent to a “live attenuated vaccine”. Technically, this will be achieved by the use of multiple HIV genes, rather than live virus. Since it is not completely understood as yet how protection is provided by a live attenuated virus, the inclusion in the vaccine of all possible HIV genes known to be antigenic and to induce both broad T-cell responses, as well as Ab responses, will be necessary. The two technical approaches are to provide either

Abbreviations: Ab, antibody.

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the vaccine in a “flexible” way as a mixture of single DNAs together with immunostimulatory genes, or as a single DNA vector containing all the necessary genes/epitopes.

Based on the results of preclinical evaluation in mice and monkeys, candidates will be advanced to the phase I clinical trials described herein. The selection will be based primarily on immunogenicity criteria; efficacy data from the mouse and monkey models will be generated in parallel with the phase I activities and will provide further (secondary) information for ranking the candidates. Go/No Go decisions for advancement to phase II will be made after the completion of the phase I trials. In general, candidate vaccines that induce relevant immune responses in more than 50% of the trial participants (preferably, at multiple timepoints) will be considered for phase II trials.

In particular, the key elements for selection of a use in prophylactic vaccine in adults at risk of infection will be: a) the ability to induce cross-reactive cellular immune responses and/or cross-reactive neutralizing Ab against circulating strains in the country where the phase II trial will be conducted; b) the ability to induce CD4+ T helper cell activity and memory functions for HIV-specific cytotoxic CD8+ T cells, providing a potential barrier that will limit the initial spread of virus or virus-infected cells.

For vaccines to be used in HIV-positive individuals the selection criteria include the induction of CD4+ and CD8+ T cell immunity (expansion of the epitope repertoire or favorable changes in the antigen-specific T cell phenotypes) against HIV-specific antigens (Gag, Nef, Tat, RT and Env) recognized during infection.

Vaccines that show responses in fewer than 50% of the participants may be considered for inclusion in prime-boost regimens with other vaccine antigens/candidates. In some cases, more stringent or additional criteria may also be applied to further select amongst the field of vaccine candidates. The clinical and laboratory methods will be performed by standard operational procedures to permit the ranking, common evaluation and comparison of these criteria.

For all vaccine candidates ranking for phase II evaluation, selection will also include results from mice/monkeys pre-clinical efficacy testing.

It is anticipated that prime-boost regimens with the different candidates will be considered where feasible and according to the results obtained.

2. Vaccine 1—Tat + ΔV2 Env

The rationale for this vaccine concept is to combine the Tat early regulatory viral antigen with the surface glycoprotein Env. The trimeric ΔV2 Env immunogen was designed to expose cryptic conserved sites for neutralization, and Tat protein will serve as both an antigen and an immunoactivator. Expected immune responses are specific Ab production, induction of CD4+ helper activity and CD8+ cytotoxic activity. Immune responses to these two antigens have the poten-

tial to act synergistically to prevent or to reduce virus entry via anti-Env responses, and virus spread via anti-Tat or anti-Env responses. In addition to safety and feasibility, the criteria for advancement beyond phase I of this approach will be the observation that the combined Tat plus ΔV2 Env vaccine shows an increase in the potency and/or breadth of the immune responses as compared to the single vaccine alone. Minimum criteria for Env-specific responses will be the measurement of neutralizing Ab against the vaccine strain and Env-specific CD4+ T cell responses in at least 50% of the trial participants. Minimum criteria for Tat will be specific Ab production, induction of CD4+ and CD8+ responses in at least 50% of the trial participants. Potency and breadth of virus neutralization will be measured against a well-characterized panel of subtype B strains. Potency and breadth of Tat Ab and T cell responses will be measured by ELISA, Elispot, and peptide epitope mapping, respectively, using standardized procedures.

3. Vaccine 2—Nef + ΔV2 Env

The major scientific rationale for this vaccine concept is to combine the early regulatory gene *nef*, in order to induce primarily anti-Nef cellular immunity, with the structural protein Env to elicit humoral immunity. The ΔV2 Env exposes cryptic sites for Ab neutralization. This approach also seeks to achieve immunity against both early and late phases of the virus replication cycle. In addition to safety and feasibility, the criteria for advancement of this approach beyond phase I will be the observation that the combined Nef plus Env vaccine shows an increase in the potency and/or breadth of the immune responses, as compared to the single antigens. Minimum criteria for Env-specific responses will be the induction of neutralizing Ab against the vaccine strain in at least 50% of the trial participants. Potency and breadth of virus neutralization will be measured against a panel of subtype B primary strains. Minimum criteria for Nef will be CD4+ and CD8+ T cell responses in at least 50% of the trial participants as well as Nef chemotaxis-neutralizing Ab.

4. Vaccine 3—multi-HIV antigens/epitopes

This DNA-based vaccine is a combination of full length genes encoding the regulatory proteins Nef, Tat and Rev, genes encoding the Gag products p17 and p24, and DNA encoding for more than 20 T helper and cytotoxic epitopes from Pol, Protease and Env (A,B,C and FGH clade) antigens. It is aimed at inducing CD4+ help, CD8+ cytotoxicity, while the inclusion of the GM-CSF adjuvant will warrant high neutralizing Ab titers. Delivery by Biojector will increase the efficacy of dendritic cell targeting. Minimum criteria for advancement will be the induction of CD4+ and CD8+ T cell responses to more than one viral antigen and the presence of neutralizing Ab in at least 50% of the trial participants.

5. Vaccine 4—HIV multigene

The vaccine includes in a DNA plasmid the regulatory antigens *nef*, *tat* and *rev*, the structural antigen *gag* and 20 predicted epitopes for *env* and *rt*. The plasmid localizes in the nucleus for increased transcription and has a prolonged half-life. It will induce cytotoxic T lympho-

cytes against the encoded HIV antigens, and delivery devices (i.e. gene gun or alike) aimed at reducing the dose of DNA will be used. Minimum criteria for advancement will be the induction of CD4+ and CD8+ T cell responses to more than one viral antigen and the presence of neutralizing Ab in at least 50% of the trial participants.