SUPPLEMENT ARTICLE

Developing a Successful HIV Vaccine

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Human immunodeficiency virus (HIV) genome integration indicates that persistent sterilizing immunity will be needed for a successful vaccine candidate. This suggests a need for broad antibodies targeting the Env protein. Immunogens targeting gp120 have been developed that block infection in monkeys and mimic the modest success of the RV144 clinical trial in that protection is short-lived following a decline in antibody-depending cell-mediated cytotoxicity–like antibodies. Attempts to induce antibody persistence have been complicated by a loss of efficacy, presumably by increasing the number of HIV-target cells. The key seems to be achieving an immune balance.

Keywords. HIV; AIDS; vaccine; antibodies; T cells.

It would have been a good idea to place a reminder on the bathroom mirror that no one should work on a vaccine, especially one against a chronic persisting virus infection, if they are older than 30 years. More than 3 decades have past, and we still have no certainty about success, and the remarks of the late Albert Sabin, that a human immunodeficiency virus (HIV) vaccine would not be possible, sometimes ring in the ear. What then are these obstacles? What approaches do we need? What are the impediments to the approaches for achieving them? How can we overcome those impediments?

Limited to a Subunit Vaccine or Inactive Particles

Because of the hazard, a replicating attenuated vaccine is not acceptable, and for the same reason neither is an inactivated virus suitable. In addition, inactivation leads to alterations in the vaccine-critical envelope protein. However, subunit vaccines have sometimes been partly successful in nonhuman primates and in one clinical trial (RV144) by the US Army, so it is possible that this obstacle could be overcome.

Variation in Genomes

The extensive variation in HIV discovered at the onset of the field demands that the vaccine immunogen induce an immune response that will target conserved regions of HIV and those regions must be essential for HIV replication. Studies over the years have shown that this too is something we can overcome [1].

Rapid Establishment of Persistent Infection (Within 24 Hours) by Integration

The rapid integration of the HIV DNA provirus establishes permanent infection within 24 hours and leads to virus production after a few days and soon the development of HIV variants. These characteristics have suggested to us since the beginning of the field that sterilization immunity (complete prevention of any infection) may be required. This is a criterion that has not been needed previously with other viruses or microbes in general, as far as I know, and it suggests that the gp120 Env protein is a key, if not the sole, component of the immunogen vaccine, since this is the HIV component first seen by the cell. The goal is to induce antibodies (Abs) to Env (anti-Env) that block HIV entry (such as neutralizing Ab) and/or quickly kill HIV-target cells as they are being infected (such as Ab-dependent cell-mediated cytotoxicity [ADCC]–inducing Abs or ADCC-like Abs).

Problems in the use of conventional gp120 are its hypervariability, its movement into different forms, and the presence of a so-called glycan shield and protein folds that cover the conserved regions needed for its function. These characteristics of gp120 are likely responsible for the failure of the first clinical trial (VAX-GEN), which used conventional gp120 because it was expected that the major immune responses would not produce anti-Env with sufficient breadth.

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Because of that failure, some subsequent trials focused on inducing cell-mediated immunity— notably, by stimulating the emergence of cytotoxic T lymphocytes (CTLs). These trials predictably failed, likely because infection would have been established prior to development of the CTLs and because CTLs may not kill all infected cells, particularly if variants emerged.

Replication in the Immune System, Especially in Activated $CD4^+$ T Cells

Additional trials using adenovirus vectors either failed or actually increased the number of infected persons. It seems likely that this was due to adenovirus-associated activation of $CD4^+$ T cells to a level above the threshold necessary for T-cell–dependent Ab production, providing more-abundant targets for HIV infection.

One modestly successful trial (RV144) used a canarypox virus (ALVAC)–vectored gp120 (along with some other immunogens), and protection correlated with anti-Env Abs. The measured function of the Abs that correlated with protection was ADCC and not neutralization. It is notable that early after vaccination falling off with time as the Abs declined.

Continued studies in the field will help us determine whether the rapid establishment of persistent infection and replication in the immune system are obstacles that can be overcome.

METHODS, RESULTS AND DISCUSSION

Based on the considerations described above, we (George Lewis, Anthony DeVico, and I, of the Institute of Virology, in collaboration with Timothy Fouts, of Profectus Bioscience) developed a candidate vaccine immunogen we call the "full-length single chain" (FLSC). It consists of an HIV R strain gp120 (strain Ba-L) and the D1D2 domain of CD4 joined by a linker of 20 neutral amino acids so that CD4 binding to gp120 occurs. This interaction leads to major structural changes to gp120 that restrain its mobility and culminate in a configuration that exposes several previously hidden new sites of gp120. These include the sites that bind CCR5 to initiate HIV infection. Such sites provide several new epitopes for anti-Env Abs and are referred to as "CD4-induced epitopes," or "CD4i."

We have performed several studies in nonhuman primates with the FLSC, using various adjuvants with or without other HIV proteins. In all these experiments, the challenge virus was always heterologous so that the results could show the breadth of protection. The unpublished results show that we can obtain sterilizing immunity against multiple challenges with low-dose simian/human immunodeficiency virus or simian immunodeficiency virus and that, like the RV144 clinical trial, success is short-lived and correlates with ADCC. The loss of protection correlates with the decline in Ab persistence. Consequently, we think that inadequate persistence of anti-Env is a serious problem, as is true of all HIV anti-Env–based vaccines [2, 3].

When we attempted to solve this problem by using various potent adjuvants or other HIV proteins to produce more T-helper cells, especially T-follicular helper cells, no candidate vaccines were efficacious [2, 3]. It appears, then, that there must be an immune balance that leads to a proper level of T-follicular helper cells without an abundance of new HIV-target cells.

It seems to us that these problems can only be solved by basic immunological studies [2, 3].

Notes

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Potential conflict of interest. R. C. G. is a cofounder of Profectus Biosciences, which produces the FLSC-candidate vaccine.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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