Special Article

Progress and Challenges Toward an AIDS Vaccine: Brother, Can You Spare a Paradigm?

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The development of a safe and effective vaccine for prevention of AIDS has thus far proven to be exceedingly difficult due to the complexities associated with HIV pathogenesis including but not limited to antigenic hypervariability, multiple routes and modes of transmission, a lack of defined correlates of protective immunity, and a tropism for infection of immunoregulatory cells which are essential for orchestrating an effective host immune response. Recent observations, including the identification of significant differences between primary isolates of HIV circulating in the population and laboratory-adapted isolates, animal model protection studies demonstrating prevention of AIDS-like disease progression in nonhuman primates in the absence of sterilizing immunity, and epidemiologic studies which question the current dogma surrounding HIV variation and control, have led to the development of novel approaches for antigen presentation and adjuvant development targeted at AIDS vaccine development. The goal of developing a safe and effective AIDS vaccine will likely occur when continued advances in understanding the immunopathogenesis of HIV is balanced with a healthy dose of empirical testing of innovative candidate AIDS vaccines.

KEY WORDS: AIDS vaccine; human immunodeficiency virus (HIV) variation; correlates of immunity.

INTRODUCTION

The identification in 1983 of human immunodeficiency virus (HIV)4 as the etiologic agent responsible for acquired immunodeficiency syndrome (AIDS) led to tremendous optimism that advances from biotechnology and molecular immunology would rapidly translate into the successful development of a safe and effective AIDS vaccine (1,2). During the subsequent decade, significant strides were made in molecularly dissecting the HIV genome (3,4), identifying the principal humoral and cellular immunologic epitopes (5,6), characterizing the cellular receptor through which HIV initiates its pathogenic process (7), and developing animal models for both HIV and its simian (SIV) counterpart (8,9). These advances led to the development of a first generation of candidate AIDS vaccines (10) which focused predominantly on mimicking the successful approach taken for hepatitis B vaccines, by targeting induction of antiviral neutralizing antibody to the major viral surface antigen (11). Ten years and approximately 1700 immunized volunteers later, these candidate vaccines appear to be safe and capable of stimulating modest levels of neutralizing antibodies against a narrow spectrum of laboratory-adapted HIV isolates (10). The inability of these candidate vaccines to achieve the level and breadth of HIV-specific immune responses commonly observed in HIV-infected individuals, coupled with the fact that virtually 100% of infected individuals eventually succumb to AIDS despite raising vigorous anti-HIV immune responses, raised serious doubts as to the potential efficacy of the candidate vaccines. These observations, combined with the formidable obstacles which HIV presents to vaccine design including antigenic hypervariability, multiple routes and modes of transmission, lack accounts for more than 90% of HIV infections, with HIV-2 accounting for the remaining 10%.

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4 For purposes of notation, HIV refers to human immunodeficiency virus type 1 (HIV-1), the principal cause of AIDS. HIV-1 presently accounts for more than 90% of HIV infections, with HIV-2 accounting for the remaining 10%.
of defined correlates of protective immunity, and a
tropism for immunoregulatory cells, failed to stimulate
sufficient interest for further clinical development of
these products (12,13). As a result, several companies
either scaled back or canceled AIDS vaccine develop-
ment programs, and scientists and policymakers called
for a reevaluation of the worldwide AIDS vaccine
development effort (14,15).

This article does not attempt to review comprehen-
sively the history and current status of AIDS vaccine
development (for review, see Ref. 16) but, rather, fo-
cuses on a small group of recent observations which, in
our opinion, are shifting the emphasis of AIDS vaccine
research toward the development of a new generation of
AIDS vaccines with a significantly greater likelihood of
success. These observations include (a) differences be-
tween "primary" or clinical isolates of HIV circulating in
the population and laboratory-adapted isolates; (b) ani-
mal model protection data demonstrating that new vac-
cine approaches may effectively impede or completely
block disease progression in the absence of sterilizing
immunity; (c) epidemiologic data which alter current
paradigms on HIV variation and control and the potential
for consideration of live vaccines; and (d) novel devel-
lopments in antigen presentation, adjuvant formulation,
and cytokine modulation which facilitate new ap-
proaches to vaccine development.

THE PRIMARY ISOLATE DILEMMA

Sera obtained from individuals immunized with the
first generation of envelope-based HIV vaccines are
capable of neutralizing HIV clade B isolates which had
been laboratory adapted (e.g., HIV-MN) to grow effect-
vively on cell lines, but generally fail to neutralize primary
isolates of HIV grown on peripheral blood
mononuclear cells (PBMC) (17). In contrast, sera from
HIV-infected individuals are capable of neutralizing both
laboratory and primary isolates of HIV (18), although
significantly higher concentrations of sera from HIV-
infected subjects are usually required for effective neu-
tralization of the primary isolates. Since volunteers
immunized with candidate HIV vaccines generally in-
duce 10- to 100-fold less HIV-specific neutralizing
antibody than HIV-infected individuals (17,19), attempts
were made to pool and concentrate vaccinee sera, with
the aim of determining whether the inability to neutralize
primary HIV isolates was due simply to the quantity of
antibody produced falling below the threshold required
for neutralization. These studies clearly demonstrated
that even when concentrated to neutralization titers
higher than 1:500,000 vs laboratory strains, such sera
were still incapable of neutralizing the primary HIV
isolates grown on PBMC (20).

These observations led several groups to pursue the
strategy that the principal neutralizing domain (PND) of
primary HIV isolates differed from the well-character-
ized third variable loop (V3) of the envelope glycopro-
tein gp120, which is well characterized as the PND of
laboratory-adapted HIV isolates. Monoclonal antibodies,
developed by groups led by Dennis Burton (21) and
Herman Katinger (22), demonstrated not only that anti-
bodies could be generated that neutralized primary iso-
lates, but also that these antibodies could neutralize
across diverse geographic clades of HIV, thereby estab-
lishing new targets for vaccine development (23). These
findings are particularly relevant since it has now been
documented that several heterogeneous subtypes of HIV
are circulating concomitantly in different regions of the
world (12,24), reinforcing the importance of developing
vaccines which would be effective against multiple and
variable HIV subtypes. Preliminary efforts to map the
neutralization domains of HIV primary isolates by site-
directed mutagenesis studies are now under way, with
the goal of further elucidating these additional targets for
vaccine development (25).

In summary, these findings suggest that the presenta-
tion of the HIV surface antigen envelope glycoproteins,
gp120 and gp41, to the immune system during natural
infection differs quite significantly from the presenta-
tion of HIV envelope glycoproteins produced by standard
recombinant DNA expression systems. In an effort to
resolve this problem, some vaccine developers have
reverted to the classical methods of live attenuation and
whole-killed vaccines to maintain the glycoproteins in
their natural conformation, while others have utilized
novel biotechnological strategies such as production of
pseudovirions, oligomerization of proteins, and develop-
ment of experimental DNA vaccines to mimic and/or
improve upon the immune response conferred during
natural infection. To date, however, no candidate vaccine
has reproducibly stimulated antibodies capable of neu-
tralizing the broad range of primary HIV isolates cir-
culating in the general population (26).

ANIMAL PROTECTION STUDIES

Until recently, the dogma for an effective AIDS
vaccine suggested that complete prevention of HIV
infection would be required if there were to be any hope
of preventing AIDS, since establishment of a persistent
infection and associated integration of the virus into the
host genome led to the inexcusable development and
progression of AIDS. However, a new paradigm has