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New directions for HIV vaccine development from animal models

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Abstract

Purpose—The development of a preventive HIV vaccine remains an unresolved challenge. Animal models that can predict the results of HIV vaccine efficacy trials and identify the immune mechanisms responsible for vaccine protection would be most useful for HIV vaccine development. The purpose of the current review is to critique recent developments in the use of animal models of HIV infection in preclinical studies of AIDS vaccines and to describe how the use of improved animal models can inform the development of an HIV vaccine.

Recent findings—The results of preclinical experiments with candidate HIV vaccines can vary with the SIV challenge virus used. It is now known that there is considerable variability in the neutralization sensitivity and that the level of viral sequence diversity within the challenge stocks varies. This has allowed more realistic preclinical vaccine studies with heterologous vaccine antigens and challenge viruses. Further, the dose of challenge virus and the route of virus challenge can modify the efficacy of candidate vaccines in preclinical studies.

Summary—Recent experiments demonstrate that NHP models of AIDS can reproduce the complex biology of HIV transmission, recapitulate the results of HIV vaccine efficacy trials in humans and be used to identify correlates of protection.

Keywords

HIV vaccine; animal model; nonhuman primate (NHP); mucosal transmission

Introduction

The development of a preventive HIV vaccine remains an unresolved challenge [1]. This effort began in 1985 after the isolation and characterization of the virus and there have been clinical efficacy trials of 3 candidate HIV vaccines; Vaxgen's gp120, Merck's Ad5-HIV *gag/pol/nef* and the RV144 trial of a vaccine consisting of priming with Sanofi's ALVAC-HIV *gag/pol/env* and boosting with Vaxgen's gp120 [1]. The results of these efficacy trials were disappointing. The Vaxgen vaccine provided no protection from HIV acquisition in high-risk people. In homosexual men, the Merck Ad5-based vaccine provided no benefit and may have enhanced HIV acquisition in a subset of recipients participating in the Step trial.

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Finally, the initial analysis of the results of the RV144 trial of the ALVAC prime/ gp120 boost vaccine concluded that the vaccine provided modest protection from HIV acquisition in-low risk heterosexuals [1] and a virologic analysis suggested that specific HIV-1 variants were blocked from establishing HIV-1 infection or that viral sequences evolved as part of a post-infection sieve effect [2]. However a more recent statistical analysis of the RV144 trial data concluded that vaccination had low-level efficacy "with≥22% chance remaining for no efficacy under a range of prior assumptions" [3]; thus, there is greater uncertainty about the results of this trial than is generally acknowledged.

Recently another HIV vaccine trial, HVTN 505, was halted due to lack of efficacy (http://www.niaid.nih.gov/news/newsreleases/2013/Pages/HVTN505April2013.aspx). The vaccine consisted of 3 immunizations with DNA that encoded *gag*, *pol*, *nef* from clade B HIV-1 and *env* from HIV clades A, B and C ollowed by boosting with a recombinant Ad5vector that contained *gag*/*pol* from HIV clade B and *env* from HIV clades A, B and C. Despite the exclusion of risk factors from the earlier STEP trial (see discussion below), the inclusion of envelope immunogens and the use DNA priming, the vaccine was not effective at preventing HIV acquisition or reducing viral load post-infection. In fact, as with the Step trial, more HIV infections (n=41) occurred in the vaccinees than in placebo vaccine recipients (n=30). These 4 clinical trials consumed vast amounts of human and financial resources and may not have provided a commensurate level of insight into the means to produce an effective HIV vaccine [1], as the type, quality and magnitude of the immune responses that correlate with protection against HIV infection in humans cannot be determined until a vaccine demonstrates robust protection in a clinical trial.

Although the current approach to HIV-1 vaccine testing assumes that vaccine immunogenicity is a surrogate measure of vaccine efficacy, the validity of this assumption is unknown [4]. In fact, many HIV-1 vaccine candidates that are immunogenic in mice and nonhuman primates (NHP) have elicited only weak and/or transient immune responses in humans [4]. Because immunogenicity in NHP has been a poor predictor of human immune responses, it is generally accepted that a rigorous preclinical approach to judging the potential efficacy of an HIV vaccine candidate is to determine if it can protect the NHP from the uncontrolled replication of a virulent challenge virus that recapitulates the pathogenic effects of HIV-1 in humans [4]. Although the vaccine candidates discussed above were tested for efficacy against SIV or SHIV viral challenges in NHP models, the approaches employed did not alert the field to the potential weaknesses of these candidate vaccines. The purpose of the current review is to critique recent developments in the use of animal models of HIV infection and to describe how the improved use of animal models can inform the development of an HIV vaccine. There are 2 primary uses of animal models in the current exploratory phase of HIV vaccine development: 1) testing candidate vaccine effectiveness (ability to prevent viral infection or blunt viral replication) and, 2) identifying immune correlates of protection that can be followed in subsequent clinical trails to determine if they are also correlates of protection from HIV acquisition or infection in humans.

HIV is transmitted primarily by sexual contact, and the genital tract and rectum are the major anatomic sites of virus transmission [5]. Thus it may be important for candidate HIV vaccines to elicit immune responses in these mucosal tissues. Preclinical studies to test the

ability of an HIV vaccine to prevent mucosal virus transmission are becoming more common (reviewed in [6]) as SIV and SHIV can be experimentally transmitted to rhesus macaques by rectal, vaginal and penile inoculation resulting in systemic infection with a single or a few SIV *env* variants [7–9, 10**]. NHP models have been critical for understanding how a AIDS viruses enter these mucosal tissues, infect target cells and disseminate from mucosal surfaces [11, 12]. After mucosal inoculation, HIV and SIV rapidly penetrate the mucus covering the epithelial surface and infect intraepithelial dendritic cells and $CD4^+$ T cells in the epithelium and lamina propria [13]. These infected cells enter draining lymphatics and can be found in the proximal lymph nodes 18–24 hours after virus exposure [13]. However, there is a little detectable viral replication in tissues until 5–7 days after infection, when there are simultaneous and dramatic increases in viral replication and innate immune responses in all tissues [11, 14]. It was reported that plasmacytoid dendritic cells (pDC) accumulate in the reproductive tract mucosa soon after vaginal SIV exposure [15],leading to the conclusion that the viral inoculum initiates an "outside-in" signaling pathway that recruits pDC and T cells to the cervix and this putative influx of target cells supports the expansion of the nascent viral infection in the new host [16]. This interpretation of early events has recently been called into question as the number of pDC in the endocervix of normal rhesus macaques is highly variable and pDC can be found below and within the columnar epithelium of the cervix of monkeys never exposed to virus [17*].

As with sexual HIV transmission [7, 16, 18–21], SIV or SHIV infections are established by a very limited number (1 or 2) of viral *env* variants after mucosal inoculation [8, 9, 22]. This is a critical feature for preclinical vaccine testing; vaccine-induced immune responses may only need to prevent infection or replication of a small number of genetically homogenous virions transmitted during an exposure to HIV. Finally, intra venous inoculation of rhesus macaques with plasma from SIV-infected animals demonstrated that acute-phase plasma virions are more infectious than chronic-phase virions [23]. Similarly, it was recently reported that transmitted/founder HIV virions are more infectious *in vitro* than chronic-phase viruses [24*]. These recent insights and advances demonstrate that the virology of mucosal transmission in NHP faithfully models the biology of HIV sexual transmission.

Animal Models

The strengths and weaknesses of NHP and human/mouse chimeric models used for AIDS research have been recently reviewed [25*] and will not be discussed in detail here. As most HIV vaccine testing has been done in NHP models, this will be the focus of review. Cellular anti-viral restriction factors in Asian macaques can block replication of some SIV strains, a situation that requires that SIV challenge strains be matched with the NHP species used [25*].

Challenge viruses

It is important to note that the results of SIV vaccine experiments can vary with the SIV challenge virus used. Thus a DNA/Ad5 vaccine that afforded partial protection against acquisition of SIVsmE660, afforded no protection against SIVmac251 [26*]. A large number of monkeys were vaccinated with a plasmid DNA prime/recombinant adenovirus

serotype 5 (rAd5) boost vaccine regimen and then they were challenged intrarectally with either SIVmac251 or SIVsmE660 every week for 12 weeks. The vaccine had no impact on acquisition of the neutralization-resistant SIVmac251, but provided a 50% reduction in infection with the neutralization-sensitive SIVsmE660. Low levels of neutralizing antibodies and a CD4+ T cell response against Env correlated with the protection. Critically however, protection against SIVsmE660 only occurred in monkeys that had two *TRIM5* alleles that restrict SIV replication in host cells, whereas monkeys expressing one *TRIM5* allele that is permissive for SIV replication were not protected [26*]. As restricting *TRIM5* alleles have no effect on SIVmac251 acquisition or replication in NHP vaccine studies [27] and restricting *TRIM5* alleles can block acquisition of SIVsmE660 in unvaccinated animals [26*], the simplest interpretation of the above study is that this vaccine regimen was protective only in a host expressing restricting *TRIM5* alleles and challenged with a virus that is susceptible to *TRIM5* restriction. Although there are viral strain-specific differences in the sensitivity of HIV-1 to human TRIM5α alleles *in vitro* [28], there is no evidence that TRIM5α alleles reduce susceptibility to HIV infection or decrease virus replication in humans

The SIV stocks used in NHP experiments are generated by transfection of viral genomes and/or by *in vitro* expansion of virus isolates in T cells and the details of virus production may affect *in vivo* infectivity, mucosal transmissibility, and early infection events. A recent analysis of nine SIV challenge virus stocks demonstrated that all stocks had similar particle-to-infectivity ratios but the level of viral sequence diversity within the infection-derived SIVmac251 stocks varied, with evidence of selection and expansion of unique viral lineages in different 251 stocks [29*]. Although an HIV vaccine must protect against highly divergent virus strains [30*, 31], most preclinical vaccine studies in NHP models have used challenge viruses that match the immunogens in the vaccine. This is not a realistic approach to assessing the potential for vaccine efficacy against a highly variable pathogen, and more recent studies have used vaccine antigens and challenge viruses that are mismatched in the envelope gene sequence by up to 20% [32, 33**]. While these heterologous challenge models are more realistic, future studies that incorporate a pool of viruses with a range of sensitivity to antibody neutralization or that contain CTL escape mutant epitopes into a virus challenge may yield even more information regarding the potential of a vaccine to be effective against antigenically divergent HIV strains.

Route and dose of virus challenge

Vaccine-induced immune responses that correlate with protection from virus infection may be broadly distributed and capable of providing protection from many routes of challenge, or they may be narrowly focused on a specific site of transmission [17*]. Further, the extent to which a mucosal surface serves as a barrier to transmission varies by anatomic site. Thus, rectal SIV transmission is more efficient than vaginal transmission which is more efficient than penile transmission [10**].

Accurately modeling the different mucosal routes of HIV exposure that will occur among human trial participants in preclinical NHP testing of a candidate vaccine is likely to be necessary to predict the potential effectiveness of the vaccine in people. The Phase IIb Step

trial of the Ad5 HIV-1 subtype B vaccine was halted due to futility [34, 35] and it was subsequently found that there were an increased number of HIV-1 infections in Ad5-seropositive male vaccine recipients with an intact foreskin [34]. In preclinical NHP experiments, the Ad5 vector-based vaccines were highly effective against intravenous challenge with SHIV89.6P [36–38]. The inability of SHIV challenge to predict the results of the Step trial led to the conclusion that NHP models using SHIV are not adequate for preclinical evaluation of candidate HIV vaccines [4]. Indeed, subsequent NHP studies showed that Ad5-SIV vaccines are ineffective at preventing infection after intra rectal SIV challenge [39]; and that an Ad5-SIV vaccine enhanced SIV transmission after low-dose penile virus challenge [40**]. The above results demonstrate that NHP models using challenge viruses that recapitulate HIV pathogenesis and routes of exposure that mimic the complexity of HIV sexual transmission can reflect the results of a human vaccine trial.

In an NHP study designed to model the RV144 trial, NHP were immunized with a prime of ALVAC-SIV and boosted with gp120 in a vaccine regimen similar to the RV144 trial. After the immunized animals were challenged intrarectally with a low dose of SIV, 3 of the 11 vaccinated macaques were protected from SIV infection, but this rate of transmission was not significantly different than in the unimmunized control animals [41*] and was much less than the 60% level of protection seen in the RV144 trial early after the final immunization (1). The inability to achieve similar levels of protection in humans and NHP with the RV144 vaccine may be due to the fact that the clinical trial enrolled low-risk heterosexual humans that were presumably not exposed to HIV rectally, while the NHP were challenged intra rectally with SIV. Thus, the route of challenge in NHP studies should mirror the route of HIV transmission that is most important within the human population that is participating in the clinical trial.

In addition to route of challenge, it is clear that the results of preclinical NHP vaccine studies are also affected by the dose of challenge virus used. A recent vaccine study found that immunized NHP challenged rectally with a single high dose of SIV were not protected from infection while 3 of 12 animals challenged twice with a 10-foldlower virus dose were protected [42*]. In another NHP study, an Ad5-SIV vaccine enhanced SIVmac239 transmission after repeated penile low-dose SIV challenge but had no effect on SIV acquisition upon challenge with higher SIV doses [40**]. Thus, the dose of challenge virus can greatly influence vaccine efficacy in preclinical NHP studies. Using a repeated challenge model with escalation of the virus challenge dose from sub-infectious to high dose over the course of 21 weeks [40**], the potential for vaccine-enhanced transmission at a sub-infectious viral challenge dose and the limits of vaccine-induced protection in the face of higher doses were revealed.

Conclusions

NHP studies of HIV-1 vaccine candidates have begun to elucidate immunologic correlates of protection against neutralization-sensitive viruses [26, 43] and homologous, neutralization-resistant viruses [17*], but only recently has an SIV vaccine mediated protection against acquisition of heterologous, neutralization-resistant virus challenge [33**], allowing immunologic correlates to be tested in a setting that more realistically

models HIV infection. Ultimately animal models that can predict the results of HIV vaccine efficacy trials and identify the immune mechanisms responsible for vaccine protection would be most useful for HIV vaccine development. NHP models of HIV transmission have proved their value as the results of a large NHP study [26*] predicted the lack of efficacy in the HVTN 505 trial as the candidate vaccine provided no protection against rectal challenge with SIVmac251. Further, another recent relative large NHP study demonstrated that Ad5 vector vaccine-elicited SIV-specific immune responses, but not Ad5 specific immunity, were associated with an increased risk of HIV acquisition after penile inoculation with very low doses of SIVmac251 (29). Thus, the combined results of the NHP Step study and the HVTN505 trial demonstrate that Ad5 specific immunity did not alter HIV susceptibility in vaccinees, and strongly suggest that HIV-specific T cell responses elicited by vaccination enhanced HIV acquisition in the Step and HVTN505 trials.

While preclinical animal models may not be appropriate as a gatekeeper for entry of candidate HIV vaccines into human trials, they can and should be used to understand how a candidate vaccine actually work to either enhance or decrease HIV transmission, so that clinical trials can be designed to measure the immune responses that matter [44*]. The recent developments reviewed above demonstrate that NHP models of AIDS can reproduce the complex biology of HIV transmission and that these models can recapitulate the results of HIV vaccine efficacy trials in humans.

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Key Points

- The HIV pandemic presents a formidable challenge to contemporary vaccine research. Realistic and rigorous animal models are needed to advance the development of a successful prophylactic HIV vaccine.
- We now know that a number of critical experimental variables can influence the results of preclinical vaccine experiments including:
  - the NHP species used
  - the virus isolate and specific virus stock used for challenge
  - the route of virus exposure used for challenge
  - the dose of virus
- NHP models of AIDS can reproduce the complex biology of HIV transmission and these models can recapitulate the results of HIV vaccine efficacy trials in humans.