Published in final edited form as:

Curr Opin HIV AIDS. 2015 May ; 10(3): 170–176. doi:10.1097/COH.0000000000000152.

Animal Models in HIV-1 Protection and Therapy

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Abstract

Purpose of the review—The purpose of this review is to highlight major advances in the development and use of animal models for HIV-1 research during the last year.

Recent findings—Animal model research during the last year has focused on the: (i) development and refinement of models; (ii) use of these models to explore key questions about HIV entry, immune control, and persistence; and (iii) key discoveries with these models testing therapeutic and vaccine concepts. Some of the greatest breakthroughs have been in understanding early events surrounding transmission, the effectiveness of broadly neutralizing human monoclonal antibodies as passive prophylaxis, and some new ideas in the area of eliminating the viral reservoir in established infection.

Summary—Despite the lack of a flawless HIV-1 infection and pathogenesis model, the field has several models that have already made important contributions to our understanding of early events, immune control, and the potential for novel therapies.

Keywords

SIV; SHIV; HIV-1; nonhuman primate; humanized mice; animal models

Introduction

The HIV field is constrained by the absence of animal models that fully recapitulate all aspects of infection and pathogenesis of HIV in humans. Despite this limitation, existing models have provided valuable insights that complemented findings from clinical studies. We have highlighted many of the major developments during the past year that have contributed to a better understanding of limitations, or a further advancement of the animal models currently in use for HIV research. To summarize, we have outlined briefly some examples of the major contributions of these models to understanding mechanisms of pathogenesis and in identifying and testing strategies to prevent infection and ameliorate disease pathogenesis.

Conflicts of interest: none

Model refinements and use of animal models to illuminate mechanisms of infection and pathogenesis

Models that utilize SIV infection of rhesus macaques continue to hold prominence in the literature. Several studies shed significant new light on the development or avoidance of pathogenic consequences in SIV-infected macaques. In the first of these, Chahroudi et al showed that the rates of mother to infant transmission (MTIT) in nonpathogenic versus pathogenic models for SIV may depend on an evolutionary adaptation to reduce the CD4⁺ T cell population in infants [1]. In an excellent and timely review, this group recaps three key aspects of natural nonhuman primate lentiviral infection that should provide a focus for future research to gain a complete understanding of the mechanisms of protection in natural SIV hosts [2]. Robert Siliciano and colleagues used humanized mice to explore the question of HIV control in elite suppressors. They isolated virus from elite suppressors and from HIV-1-infected patients who have the usual progressive disease course and compared how well the isolates from the two groups of patients replicated in culture and in humanized mice [3]. Their findings support the concept that elite suppressors possess unique host factors and are not typically infected with defective virus.

An investigation of the role of inflammation in HIV infection, in particular the impact of type I interferons (IFN-I) was conducted by Sandler et al in SIV-infected rhesus macaques. They found that the timing of IFN-induced innate responses in acute SIV infection significantly affects overall disease course outweighing any detrimental consequences of increased immune activation caused by increasing the numbers of target cells [4]. Another group studying the differences in pathogenic versus nonpathogenic models of infection characterized a recently identified subset of memory T cells with stem cell-like properties (T(SCM)) in rhesus macaques and in sooty mangabeys [5]. They concluded that increased proliferation and infection of CD4(+) T(SCM) may contribute to the pathogenesis of SIV infection in rhesus macaques. The dynamics of germinal center (GC) formation in lymphoid tissues following acute SIV infection was found to be an important predictor of disease in rhesus macaques. Hong, et al showed that local production of IL-21 in lymphoid tissue GCs was an indicator of better control of viral replication and slower disease progression [6]. Thus, limiting dysregulated lymphoid function may be a critical target for new therapeutics. Roederer et al identified one strategy by which both SIV and HIV escape host immune pressures. They found a two-amino-acid signature that alters antigenicity and confers neutralization resistance [7]*. This discovery, revealing selective pressure against neutralization sensitive Envs, implies a shared mechanism of immune escape by SIV and HIV against a protective antibody response.

Repeated low-dose viral exposure does not prime macaques

In a retrospective study involving cohorts of male Indian rhesus (n=40) and female pigtail (n=46) macaques enrolled in repeat low-dose rectal or vaginal SHIV_{SF162P3} challenge studies, Henning et al showed that infections in these models occur independently of exposure history [8]*. These data provide assurance that neither inoculation route nor number of exposures required for infection correlates with post-infection viremia and support the concept that vaginal and rectal repeated low-dose exposure models in macaques provide a reasonable surrogate system for mucosal exposure with HIV-1.

Relevance of cell-associated virus transmission

The complexity of natural sexual transmission of HIV-1 is not fully recapitulated in nonhuman primate challenge studies and may fall short of an accurate representation of human exposure to infection *via* body fluids. A new review by Bernard-Stoecklin et al outlines the importance of increasing efforts to ensure the nonhuman primate model accurately represents the mechanism of virus seeding by infected leukocytes present in seminal plasma [9]. The importance of understanding virus interactions in real-time at mucosal portals of entry has recently been elucidated by Hope and colleagues with stunning visual images of individual virions trafficking into mucosal tissues. Using both human explants and *in vivo* exposure to female rhesus macaques, their work shows that virus rapidly enters the female reproductive tract (FRT) and infiltrates the intact epithelial barriers by simple diffusion in the vagina to depths where the virus can encounter potential target cells [10]**. The study provides detailed descriptions of early infection events in the FRT with critical insights for the role of mucus as an impediment to virus motility, and extrapolates the number of penetrating virions per coital act based on the highest levels of acute and chronic levels of infection. This work adds important guidelines for the development of new prevention strategies for women.

New discoveries for SHIV/macaque models

Pre-clinical models of HIV-1 infection are critical to achieving a successful vaccine or development of effective immunotherapy strategies. Chimeric SIV/HIV (SHIV) infection of macaques has been the primary platform to model HIV-1 transmission and pathogenesis in humans, and the models are commonly used to evaluate protection efficacy of bNmAbs in the context of mucosal transmission and CCR5-using viruses. However, SHIVs have been criticized for lack of sustained robust viremia and variable CD4+ T cell loss in adult macaques. The most clinically relevant HIV-1 envelopes may be transmitted/founder (T/F) variants that are established upon mucosal exposure during human sexual transmission, but the CCR5 SHIVs most commonly used were isolated during chronic stages of HIV-1 infection after extended exposure to host immune pressures. Moreover, most SHIVs have been generated by amplification in cell culture followed by serial passage in macaques resulting in divergent SHIV envelopes with sequence variations not representative of most circulating HIV-1 isolates responsible for mucosal transmission in humans. Very recently, two different groups have focused their efforts on developing new SHIVs derived from T/F HIV-1 envelopes. Hatzioannou and colleagues [11]* generated and tested 37 new clade B SHIV constructs expressing Env proteins from newly transmitted HIV-1 strains. Macaques were inoculated with cocktails of multiple SHIV variants thus allowing natural *in vivo* competition to select Env sequences that were most replication competent in macaques and that caused AIDS-like disease without requiring animal-to-animal passage. A similar approach using clade C SHIVs expressing Env proteins from T/F viruses resulted in three new SHIVs that replicated moderately in naïve rhesus monkeys [12]*. The SHIVs are mucosally transmitted and were neutralized by sCD4 and several HIV-1 broadly neutralizing antibodies. Together, these new approaches of SHIV development provide additional improvements to the SHIV/macaque models of HIV-1.

The advancement of NHP models for HIV-1 infection and pathogenesis has been deterred by the lack of sustained replication of most SHIVs, especially those bearing recently transmitted Envs. Several host restriction factors are known to prevent robust replication, and in an earlier study [13] a macaque species-specific amino acid difference in the macaque CD4 receptor was identified that causes a reduction in infectivity of HIV in rhesus or pig-tailed macaques compared to the human CD4 receptor. Now, a new study [14]** has identified two substitutions in HIV-1 Env that enhance entry using the macaque CD4 receptor, A204E and G312V. However, these mutations resulted in conformational changes that expose variable domain epitopes and disrupt quaternary epitopes in the native Env trimer. These revelations sound a cautionary note for the use of SHIVs in vaccine and antibody testing, if the altered Envs are not representative of more native closed structures. More work is needed to determine how these findings affect our interpretation and future experimental design of SHIV challenge studies.

Antibody-mediated effector functions in HIV prevention and pathogenesis

The degree to which antibody Fc receptor-mediated anti-viral functions may contribute to protection remains an open topic of debate and this has been re-examined recently in detail in excellent reviews[15-17]. Also, the role of anti-HIV antibody-dependent cellular cytotoxicity (ADCC) antibodies in the prevention and control of HIV infection has still not yet been fully determined. The RV144 HIV-1 vaccine trial induced anti-HIV ADCC antibodies that may have played a role in the partial protection observed encouraging continued efforts to show similar efficacy in the macaque model. Although passive transfer studies in macaques support a role for the Fc region of antibodies in assisting in the prevention of SHIV infection [18], a study this year using passively transferred polyclonal antibodies enriched for ADCC activity failed to protect macaques from mucosal challenge [19]. The disappointing results strongly suggests that evidence derived from *in vitro* assays may not accurately reflect the complexity of human Fc γ R structure and function and highlights the difficulty in recapitulating similar responses in macaques. Additional reports from at least two groups experimentally re-addressed the issue with studies that parsed protection outcomes based on Fc-mediated inhibitory activity. The topical application of non-neutralizing mAbs characterized for inhibitory activities, including ADCC, by Moog et al failed to protect macaques against vaginal SHIV challenge but showed modest evidence of tempering viremia[20]. Ko et al engineered an enhanced FcRn-binding variant of bNmAb VRC01 with a three-fold longer serum half-life. The variant, VRC01-LS, showed increased gut mucosal tissue localization and persisted in the rectal mucosa when it was no longer detectable in serum and mediated improved protection against SHIV challenge compared to VRC01[21].

Using *in vivo* infection in the luciferase reporter mouse model, Pietzsch et al [22] provided convincing evidence for improved efficacy associated with Fc effector function of bNAbs. They correlated the protective ability of bNAbs with engagement of activating Fc γ Rs, but not with *in vivo* neutralization activity [23]*. This study is extremely important for HIV antibody immunotherapy and vaccine strategies designed to elicit protective immunity. While these and similar outcomes justify the curiosity to determine the contribution of Fc-

mediated functions in protection, the abundance of evidence still weighs heavily for neutralization activity as the most predictive metric of protective efficacy *in vivo* [24].

Animal models have been used extensively to study the interaction between Fc γ receptors and IgG. Despite an overall similarity between human and mouse Fc γ receptors, species diversification has resulted in the evolution of a much more complex system in humans, making predictions of biological effect based on extrapolations from mice data a challenging endeavor. Recently, progress in the field of mouse engineering has resulted in the development of a fully humanized Fc γ receptor mouse expressing hFc γ RI, hFc γ RIIA, hFc γ RIIB, hFc γ RIIIA, and hFc γ RIIIB [25, 26]. The closer similarity between humans and macaques compared to humans and mice should make the nonhuman primate model much more attractive. Unfortunately, little is known about the Fc γ receptors in nonhuman primates. In addition to Fc γ R sequences variations, not all macaque Fc γ R structure and function characteristics are the same as human. For example, the inhibitory macaque Fc γ RIIB uses an alternative regulatory strategy that could lead to unpredicted complications and misinterpretations of outcomes when testing various human immunoglobulin isotypes in macaques [27].

Characterizing immunity: B cell studies in rhesus macaques

In order to gain a better understanding of mucosal and systemic B cell dynamics in rhesus macaques, Demberg et al characterized rhesus macaque memory B cell populations at three mucosal sites [28]. Their results confirm that rectal biopsies adequately report B cell dynamics in the gut mucosa of macaques and provide new information on the development of B cell responses associated with protection from infection and control of pathogenesis. A separate report found that rectal explants could be used instead of duodenal tissue for culturing mucosal IgA from macaques [29]. This awareness can be useful for evaluation of mucosal vaccines.

Nonhuman primate models for protection

NABs raised in macaques following vaccination have been shown to be protective against homologous SHIV challenge[30, 31], and polyclonal preparations of NABs derived from infected macaques can block infection and ameliorate disease progression[32, 33]. Even more than a decade ago, several notable studies established convincing evidence that passive transfer of broadly neutralizing human monoclonal antibodies (bNmAbs) could prevent infection in macaques against SHIV challenge[18, 34-38]. However, the neutralization titers in plasma[39] that were needed to confer protection by the few known bNABs at the time were high and not believed to be a reasonable goal attainable by vaccination. Fortunately, the tide may be turning with the present generation of bNmAbs that target multiple linear and conformational epitopes that are extremely broad and potent *in vitro*, reviewed in[40, 41] and can prevent mucosal transmission of SHIV in macaques at much lower doses[42]. In fact this year, a notable study using five different potent bNmAbs and a cohort of sixty macaques challenged with two different SHIVs, demonstrated that a relatively modest plasma neutralization titer ($\sim$ 1:100) which is potentially achievable by vaccination, prevented infection[43]**. An interesting caveat to this study was the discovery that *in vitro* virus neutralization may not be absolutely predictive of *in vivo* protection. Authors found

that an *in vitro* engineered CD4bs mAb neutralized with very high potency in the TZM-bl cell assay, but it showed no *in vivo* protection. Pegu et al also demonstrated a dissimilar protective efficacy between bNmAbs targeting highly conserved epitopes on HIV-1 Env versus a high-affinity anti-CD4bs-directed mAb that had been clearly shown to block HIV-1 entry *in vitro*[44]. Thus, ongoing vaccine efforts designed to elicit antibodies targeted to specific regions of Env remains a critically important goal. It was also demonstrated this year that the *in vitro* and *in vivo* anti-viral activities of bNmAbs can be improved further using structure-guided modifications. VRC07-523, an engineered version of VRC01, was enhanced by five to eight fold in neutralization potency and breadth and protected SHIV-challenged macaques at a five-fold lower concentration[45]. This pioneering study shows innovation for engineering next-generation antibodies for improved therapeutic potential.

Use of animal models for HIV therapies

The new generation of extremely potent bNmAbs has brought a renewed sense of potential in their use not only as pre-exposure blocking agents (as discussed above), but also as immunotherapeutics in established infection. In the therapeutic mode, a cocktail containing five of the new potent bNmAbs reduced HIV-1 replication for sixty days in humanized mice [46]. This year, the therapeutic potential of cocktails and a single bNmAb (PGT121) was examined in macaques chronically infected with SHIV_{SF162P3}. Infusion of PGT121 resulted in rapid control of viremia and reduced proviral DNA in peripheral blood and gastrointestinal mucosa [47]**. Viral rebound occurred in all animals correlating with decay of the transferred bNmAbs. Detectable provirus DNA in tissues confirmed that virus was not eradicated. Nevertheless, the study is a landmark for pre-clinical proof-of-principle. In another study, 2 potent bNmAbs (3BNC117 and 10-1074) were tested for their ability to block infection and control SHIV-AD8 infection in macaques. Either antibody alone could block virus acquisition and when given together plasma viremia could be transiently suppressed. Virus rebound could also be controlled after a second cycle of therapy [48]**.

In the humanized mouse model, Halper-Stromberg et al showed that combinations of viral transcript inducers and bNmAbs can synergize to decrease viral reservoirs in established infection and prevent viral rebound. Moreover, bNmAbs alone were shown to interfere with establishing viral reservoirs by Fc-FcR mechanisms[49]. Baltimore and colleagues recently demonstrated the ability of vectored immunoprophylaxis (VIP) expressing bNmAbs to prevent transmission to humanized mice *via* intravenous and repeated vaginal exposure [50]. Moreover, animals receiving VIP that expresses a modified VRC07 antibody were completely resistant to repetitive intravaginal challenge by a heterosexually T/F HIV strain, suggesting that VIP may be effective in preventing vaginal transmission of HIV between humans. Both animal models strongly suggest a role for antibody immunotherapy alone or in combination with antiretroviral drugs as treatment for chronic infection.

With strict adherence to pre-exposure use, topically applied vaginal microbicide gels have been shown to be a safe and effective intervention to limit HIV transmission [51]. This year a microbicide gel based on clinically approved integrase inhibitors was tested in pig tailed macaques that can be applied up to three hours after SHIV exposure [52]*. The study

addresses the challenge of developing intervention strategies that will enhance user compliance and thereby increase the potential for infection prevention.

An investigation of the contribution of host autologous antibody responses in suppressing host immune escape brings new hope for the potential benefits of monoclonal immunotherapy [53]*. Using HIV-1_{YU2}-infected humanized mice and panels of isolated antibodies from macaques and humans, Klein et al showed that antibodies produced during infection that fail to control viremia can synergize with passively administered bNmAbs to prevent the emergence of escape variants.

Finally, in some of the most promising news in many years, a vaccine based on rhesus CMV that generates very strong and persistent T effector memory partially controlled infection and had the unprecedented outcome of eliminating viral reservoirs in SIV-infected macaques that had been vaccinated with this recombinant virus [54]**. These data suggest that some lentiviral reservoirs may be susceptible to the continuous effector memory T cell-mediated immune surveillance elicited by CMV vectors. This research underscores the importance of using animal models to test concepts that cannot be as easily broached in the clinic.

Conclusion

A tractable and affordable animal model for HIV has been a goal for at least 30 years, and important milestones have been accomplished. The past year has heralded the introduction of new animal models and new ways of optimizing established models. NHPs are favored for pre-clinical protection and therapeutic studies and vaccines, but the recent development of sophisticated mouse models engineered with engrafted parts of the human immune system has added strength to the field. The field is driven by both technology and innovative research, both of which will continue to shape the discoveries of tomorrow.

Acknowledgments

Acknowledgements: none

Financial support and sponsorship: This work was supported by National Institutes of Health research grants P51 OD011092, P01 AI078064, R21 AI104392, and by a 55T research grant from amfAR.

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** of outstanding interest

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Key points

- Both macaque and murine animal models continue to be refined and to add to our understanding of immune control of HIV
- Powerful human neutralizing monoclonal antibodies are very effective in blocking infection and potentially in controlling post-acute viremia
- SHIV isolates based on transmitted/founder HIV-1 isolate Envs are now available for testing
- Reduction of viral reservoirs in established infection may be a tractable approach with powerful antibodies or effector T cells.