

Exploring Experimental Animal Models in HIV/AIDS Research

Sharma B*

Department of Biochemistry, University of Allahabad, Allahabad-211002, UP, India

The animal experimental models for HIV/AIDS research are considered to be the most suitable way to evaluate salient aspects of new medicines or vaccine candidates, as they have to be tested for their safety and efficacy. These models, to certain extent, have been able to pave the gap between laboratory evaluation and clinical trials on humans. In addition, they are needed to make toxicological evaluations of drugs, to test new anti HIV small molecules, clinical trials, to determine the efficacy of an array of anti-HIV/AIDS drugs or vaccines. Moreover, due to socio-ethical issues and individual rights, human beings cannot be used as an experimental model. Therefore, the development of the animal subjects for use in research is essential in taking a discovery from laboratory to the clinic. This article presents an account of current information about the need to generate human like experimental animal models for HIV/AIDS research, for producing safe and effective tools to combat this pandemic, and also addresses the difficulties and possible solutions.

The use of animals as experimental models for human diseases has been indispensable in understanding the causes, biology and prevention of a disease. However, the animal models have been used extensively in the field of HIV/AIDS research, since the early 1980's [1]. Many animals have been infected with human immunodeficiency virus (HIV), but they do not develop the AIDS-like syndrome, as observed in humans. It could have been due to lack of viral infectivity, or efficient replication of HIV-1 in these subjects. The animal relative closest to humans, the chimpanzee, had been exploited extensively in AIDS research, but it was realized off late that even chimpanzees do not develop human AIDS-like symptoms [1]. Thereafter, the scientists started using animal models in AIDS research by infecting them with HIV-like viruses, such as FIV (feline immunodeficiency virus) in cats, and SIV (simian immunodeficiency virus) in macaques, etc., to generate useful information on above mentioned issues. However, these viruses differ markedly from HIV, and therefore, problems arise from extrapolating the data obtained from such studies. Alternatively, testing of the efficacy and toxicity of anti-AIDS medications like antiproteases and HIV-1 RT inhibitors (AZT, and 3TC), however, are being performed using cell culture techniques, using human white blood cells [2-4]. The prerequisite characteristics of an ideal animal model for HIV/AIDS research include: (i) It should be a close relative, or in a close host range (similar if not identical to host), tissue distribution, disease progression and similar route of infection, if not identical. (ii) Disease course should be relatively shorter in animals, in order to complete the efficacy test in reasonable time, permitting rapid transition to human clinical testing. (iii) Despite the differences in genetic make up of humans and animals, there should be sufficient immunological correlates for protection. (iv) Animal model should be easy to maintain, work with, easily available in adequate number, relatively inexpensive, and free of regulatory constraints. Unfortunately, no such models have been created [5]. The researchers are therefore, currently using a variety of animal models, involving infection by closely related lentiviruses to understand various aspects of HIV-1 infection, pathogenesis, disease progression, and nature of protective immunity. For example: EIAV: (Equine Infectious Anemia Virus) infects horses, mules, donkeys, and other equine species. The EIAV transmission takes place by biting insects, and by contaminated instruments and needles. The target cells

for EIAV include macrophages and erythroid precursors (but not CD4+ T-cells). EIAV possess similarity with HIV, as the protective immunity includes cellular immune responses responsible for clearance of EIAV and HIV-infected cells.

Another virus which is similar to HIV is the bovine immunodeficiency virus (BIV), which infects the cattle, goats, sheep and rabbits. The viral transmission takes place through lymphocytes as the target cells. The similarities in their characteristics include mother to child transmission (MTCT), persistent infection, genomic variations, etc. Recently, a chimera of BIV/HIV-1 (LTR sequences of HIV and gag-pol region of BIV) has been developed, and named as HBIV3753, to develop animal models responding more like humans [6]. Further, simian immunodeficiency virus (SIV), HIV and their chimera SHIV infections in non-human primate models, such as chimpanzees (*Pan troglodytes*), Baboons (*Papio cynocephalus*), and macaque monkeys, have been attempted. The chimera SHIV consists of tat, rev and env genes of HIV and gag, pol, vif, vpr and vpu genes of SIV with LTR sequences of SIV to develop AIDS like disease in nonhuman primates (NHP), as mentioned above. However, the Chimpanzees support productive infection, but disease does not occur for at least 10 years. Baboons can support replication of strains of HIV-2, but not HIV-1. It has been observed that HIV infection takes place only into T-cells, but not into monocytes or macrophages, CSF or brain of Baboons and macaque monkeys [7-9]. The macaque model is useful because SIV in macaques follows a disease course that is similar to HIV, and hence, they are used to evaluate vaccines that closely resemble the ones being developed for humans. This trial provides some clues to the safety and potential efficacy of prospective vaccine candidates [1]. Other lentiviruses such as maedi-visna virus (MVV) and caprine arthritis-encephalitis virus (CAEV), which infect sheep and goats, respectively, display similarities in the amino acid sequences with that of HIV-1 gp120 from their surface glycoproteins (SU) gp135 regions, interacting with the transmembrane glycoprotein [10]. Feline Immunodeficiency Virus (FIV), which infects kittens and cats is a lentivirus like HIV-1, and infects their host T-cells in a similar manner, because they are both retroviruses causing immunodeficiency in the subjects. These viral infections in their respective hosts are being attempted for testing different parameters of a prospective antiHIV drug or a vaccine candidate.

The Animal Models Division at the Institute of Human Virology has developed certain models for studying AIDS and AIDS-associated cancers, such as AIDS-NHL, HIV-1 transgenic rat model for studying

*Corresponding author: Sharma B, Department of Biochemistry, University of Allahabad, Allahabad-211002, UP, India, Tel: 91-9415715639; E-mail: sharmabi@yahoo.com

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HIV-1 pathogenesis, HIV-1 transgenic mouse model for studying HIV-1 pathogenesis, HIV-associated diseases, and for cancer studies, and for the development of HIV-1 vaccines. They have also developed the SIV non-human primate (NHP) models, such as the Indian-origin rhesus macaque (*Macaca mulatta*), Cynomolgous macaque (*M. fascicularis*), and pigtailed macaque (*M. nemestrina*), to carry out studies about viral pathogenesis, design and development of vaccines and microbicides. All of these models are playing crucial roles in not only understanding the pathogenesis of AIDS, but also in pre-clinical testing of new anti-HIV molecules and anti-cancer drugs [1,11-13].

In 2008, Bailey [14] reported that current and past research using chimpanzees to develop and test an AIDS vaccine had failed. The report illustrated as how the responses of AIDS vaccine in chimpanzees could not project the real responses as occur in humans. Keeping these intricacies in view, some scientists got involved in development of Lentiviral Vector Systems against both the (1) Primate (Human immunodeficiency virus (HIV)), and Simian immunodeficiency virus (SIV)), and (2) Non-human-primate (NHP) (Feline immunodeficiency virus (FIV), and Equine infectious anemia virus (EIAV)), systems as effective alternates of use of experimental animal models [15,16].

The recent reports indicate that the use of Rhesus macaque models of AIDS have revealed many key aspects of HIV-1 pathogenesis, such as virus transmission and early events of postinfection, the sites of viral replication and CD4+ T cell depletion, and virus and cell turnover [5,17,18]. The macaque models have also been useful for vaccine research, allowing the evaluation of increasingly potent DNA and vector immunogens, and the potential combinations of these [19]. Macaque models of pre-exposure prophylaxis (PrEP) have helped elucidate the ARV exposures, and the timing of exposure required to maximize protection from virus challenge with certain limitations [20]. Rhesus macaque/SIV model has not contributed much to the development and optimization of ARV therapy [21], because of their unsuitability. The problems associated to their use include (i) the emergence of natural resistance of SIVs against non-nucleoside reverse transcriptase inhibitors (NNRTIs) [22], (ii) major differences in ARV pharmacokinetics between humans and macaques [22,23], and (iii) divergent interactions of SIVmac and HIV-1 with host restriction factors [13,23]. Since HIV-1 subtypes do not replicate in monkey species, the use of simian counterparts derived from naturally infected sooty mangabeys, such as SIVmac/smm, could be a viable option [24]. The use of the RM/SIVmac models for antiretroviral testing, however, has been limited because of the differences of SIVsmm from HIV-1 in ARV susceptibility and pharmacokinetics [13,25]. The complete control of viral replication has not been achieved. These models are relatively resistant to the development of AIDS, and are highly expensive [26]. The limitations of using such animal model for AIDS research prompted the scientists to explore for other smaller animal models [20].

The studies on HIV infection and evaluation of HIV vaccine candidate(s) in small animal models are being tried extensively [26]. For example: the transgenic mice and rats may express various receptors, coreceptors, and other accessory molecules necessary for viral entry and infection, in range of tissues and cell types. The SCID (severe compromised immunodeficient) mice lack functional T-lymphocytes and B-lymphocytes. Since the rodents are inexpensive, reproduce quickly, and may be housed in large numbers in a small facility and the experiments may be carried out in many replicates to retrieve statistically significant results. The rodent cells are, however, nonpermissive for HIV infection. The attempts to produce transgenic rodents permissive for HIV replication and dissemination have not

been completely successful [20,26]. Rats stably expressing human CD4 and CCR5, the major receptor and coreceptor for HIV-1, respectively, are partially permissive [27]. The SCID-hu thy/liv model is extensively used for preclinical testing of antiretroviral drugs [28]. The transgenically altered rodents (e.g. nonobese diabetic/SCID mice), and infused with human components (e.g. autologous human fetal thymic and liver CD34+ stem cells), exhibited establishment and maintenance of human T and B cells, monocytes, and macrophages, but with some degree of limitations [1,20,29,30].

Still not much is known about SIV infection in nonhuman primates (NHP), about successful control of simian immunodeficiency virus (SIV) infection and production of AIDS like symptoms [1,13]. Finding an animal model for HIV has proven difficult. The virus exclusively infects and causes disease in humans, making it more difficult for scientists to evaluate potential AIDS vaccine candidates. Studies to assess mobilization and recombination with wild type HIV are difficult, because (i) HIV replicates, but is non-pathogenic in Chimpanzees, (ii) Macaque model is appropriate for SIV vector only, (iii) Murine model is limited due to blocks in HIV replication, and (iv) SCID mouse models can serve as “*in vivo* test tube”, but replication still limited to human cells [1,13,20]. Despite similarity to HIV, SIV and HIV differ in numerous ways *viz.* the genetic organization (for example, the *Vpx* gene is unique to SIV; *Vpu* is unique to HIV), and the course of disease. The simian AIDS develops within 6-12 months of infection with SIV, while it can take many years for human AIDS to develop after infection with HIV [20]. HIV and SIV need different hosts for infection. Unlike bHI-1, SIV is a close relative of HIV-2. Though HIV and SIV utilize the same cellular receptors (CD4) and co receptors (preferably CCR5), they are genetically and anti-genetically distinct [20]. Antibodies that neutralize HIV fail to neutralize SIV, and *vice versa*, due to subtle differences in their envelope protein. Furthermore, T-cell epitopes are not shared between the viruses [1,20]. Keeping these facts in view, some new humanized mouse models were developed and used, but they also exhibited certain limitations and hence, could not boost HIV research [20].

A careful look on available information regarding use of NHP and small animal models for research about various aspects of HIV/AIDS suggests that the attempts towards development and judicious application of suitable “nearly HIV” NHP model must be continued, to augment the quest for development of new and potential antiHIV-1 drugs and microbicides, reduction of viral reservoirs and testing antiHIV-1 vaccine(s). The reagents generated could be cost effective, with immense potential to save the lives of million who are infected, and several others likely to get new infections in future. In order to get useful information, the most viable approach could be to consider both the new humanized rodents and nonhuman primate models, as complementary systems.

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