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Chapter 9

Experimental Animal Models of HIV/AIDS for Vaccine Trials

Bartholomew Okechukwu Ibeh and Efejiro Ashano

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http://dx.doi.org/10.5772/intechopen.76698

Abstract

AIDS still persists as a relevant disease in public health and scientific research. There have been significant advances in HIV research, notably the development of an effective regimen in antiretroviral therapy. However, the emergence of drug resistance has facilitated continued research in administration of therapy and the development of new antiretroviral drugs. In spite of nearly three (3) decades of intensive research, there still is not an effective vaccine against HIV-1. Animal models have been a crucial tool in drug discovery process for invasive investigation of HIV disease mainly in preclinical evaluation of drugs and vaccines. This undoubtedly is an integral part of successes so far achieved in HIV/AIDS research. Advances in both non-human primate and murine model immunogenetics in response to recombinant viruses have greatly increased the options of animal models available for research. Understanding the pros and cons of these models is imperative for animal study design that could further the development of vaccines and antiretroviral therapies for HIV prevention and treatment of AIDS patients.

Keywords: HIV/AIDS, animal models, clinical trials, humanized mouse model, candidate vaccine testing, primates, HIV reserviour

1. Introduction

To understand the etiology, and mechanistic approach to eliminating disease processes and its attendant challenges, animal models have been indispensable in shortening the length of time, resources and complications inherent in disease prevention and drug discovery. Animal models, however, play a central role in the extensive research of HIV infection since the early 1980 [1].

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Numerous animal species could be infected with HIV, but hardly do they develop AIDS-like syndrome that approximates humans. Several reasons have been adduced to this including decreased viral infectivity factor, efficiency of HIV replication in the animal species and host immunologic response proteins thus referred to as host factors [2].

Evolutionarily, the Chimpanzee had been believed to be close to humans thus exploited in AIDS research. Scientists later understood that HIV does not infect the Chimps but SIV besides the high cost attached to its use in HIV diseases research. Maintaining a primate research facility tends to incur huge cost, and most centers are being shut down around the world. These animal models are used to study diseases and infections of lentiviruses specifically Feline Immunodeficiency Virus (FIV) in cats, and Simian Immunodeficiency Virus (SIV) in monkeys. However, these viruses are distinct from HIV and have the problem associated with extrapolating data from experimental studies [2]. Consequently, researchers resorted to intensive search for alternative experimental model for HIV infection. Mouse, being 90% genetically similar to humans poses as a 'go' option hence the intensive and successful development of mouse models for HIV research.

It is worth mentioning though that testing the effectiveness and toxicity of anti-HIV medications such as anti-proteases and HIV-1 Reverse Transcriptase inhibitors (AZT, and 3TC) are experimentally conducted using cell culture techniques derived from human white blood cells [3–5]. No such mechanistic model for HIV pathobiology has been created [6].

Murine experimental HIV models are putatively regarded as the most extensive approach appropriate for evaluating the safety, efficacy and salient aspects of novel drugs or vaccine candidates. These models, to a high degree, have achieved remarkable success thus bridging the gap between preclinical and clinical evaluations on humans. Similarly, they are effectively utilized in toxicological evaluations of drugs, testing of novel anti-HIV small and interfering molecules and pre clinical trials. Bearing that humans cannot be used experimentally, continued development of the animal subjects for use in research has seen tremendous improvement and modifications [2].

2. Initiation and progression of HIV infection

The so-called latent period after the infection by the virus does not mean the virus is inactive [7]. Apart from humans, HIV-1 naturally infects a small number of nonhuman primate species, notably chimpanzees, which have been known to host the virus. Development of AIDS from HIV progression only occurs in humans [8, 9].

To gain insights in the transmission, pathobiology and progression of HIV infection, development of an animal model of HIV-induced immunodeficiency becomes mandatory. Several approaches were adopted to circumvent species tropism, that is, finding a similar lentivirus specific to other species that can cause similar symptoms, that is, immune deficiencies as a results of affinities to CD4+ T-cells and macrophages [9].

2.1. In humans

HIV-1 mainly infects through the genital mucosa with persistence chronic infection even when the virus triggers a notably strong cellular and humoral (both innate and adaptive)

immunity. The reason for this action may stem from the virus genomic integration and subsequent cellular latent activity coupled with its extreme genetic variability, which provides a consistent immune specific escape. It is known that HIV-specific CD8+ lymphocytes are key players involved in initial decrease or suppression of viremia during acute HIV infection conversely this becomes highly dysfunctional and burdened under the strenous condition of chronic viral antigenic persistency [10, 11]. Viral neutralizing antibodies (Abs) are similarly triggered which also accompany immune escape. In some individuals, particularly elite HIV controllers or suppressors, they develop broad neutralizing Abs thereby have an effective control of the virus [12].

HIV infection is hallmarked by massive reduction of CD4+ T cells. During the primary HIV infection, the effector memory CD4+ T cells present in the gut mucosa are consistently and preferentially depleted [13]. The immunopathogenic presentations, in addtion to the systemic and chronic state of immune activation, are believed to contribute directly to HIV disease progression [14]. As a result, persistent antigenic stimulation presents a dysfunctional T-cell population with a loss of functional potential in cytokine production and cytotoxic activity, and the ability to proliferative in response to antigen stimulation. It is believed that this loss of immune balance between Th17 and regulatory T cells (Treg) during HIV disease progression may be the reason for the permeabilization of gut integrity and the pathogenesis of HIV.

Microbial translocation caused by gut permeability is thought to contribute to systemic immune stimulation seen in chronic HIV infection [15]. Additionally, hyper-responsiveness of plasmacytoid DCs during the cause of primary HIV infection, typically results in type-1 IFN excess production which contributes to systemic immune stimulation and HIV-1 disease progression [16].

Previous studies suggest a relationship between CD8+ T cells and the control of chronic HIV replication similar to that of simian immunodeficiency virus (SIV) viremia in non-human primates [17]. There are also rare individuals who control HIV-1 replication to levels which the virus cannot be detected also known as elite controllers with attendant characteristics [18]. This phenotype shows a strong association with certain MHC class I alleles with HIV-specific CD8+ T cells demonstrating superior cytotoxic capacity to kill any HIV-infected target.

Two examples of markers in HIV-1+ patients associated with T-cell exhaustion are Programmed Death-1 (PD-1) and T cell immunoglobulin and mucin domain 3 (Tim-3), which likely are caused by consistent antigenic stimulation [19]. These two molecules have been shown to participate in the downregulation of host immune responses, playing a key role in sustenance of T cell tolerance. It is obvious that Tim-3 is upregulated on virus-specific CD8+ T cells in subjects with chronic progressive HIV infection [19]. Similarly, another report stated the upregulation of Tim-3 on antigen-specific CD8+ T cells in subjects with active TB [20], buttressing similarity in the role played by the inhibitory receptor/ligand interactions with respect to modulation of host immunity to both HIV and M. tuberculosis infections in humans.

2.2. In primates

Several non-human primates are naturally infected with simian T lymphotropic virus (STLV) types I and III. The exogenous type C retrovirus isolated from macaque monkeys in captivity

reported in the USA with an immune deficiency syndrome otherwise known as simian AIDS has been termed STLV-III mac. It is worthy to note that STLV types I and III are similar and/or related to the human T lymphotropic viruses (HTLV-I and LAV/HTLV-III) the causative agent(s) for AIDS. The striking similarities include growth characteristics, similar size of viral structural proteins, morphology, T4 cell tropism and serological cross reactivity of viral proteins [21]. The residing proteins found in the simian virus also have similar molecular weight with respect to the gag and env encoded proteins of LAV/HTLV-III [22]. Both are recognized by reference LAV/HTLV-III human serum and monoclonal antibodies to the core protein, p24, of the human virus. These proteins are basic and have relevant information needed in the development of candidate vaccine, rapid diagnostics and elucidation of HIV virology [21]. Knowledge of the molecular structure and pathobiology of simian viruses yielded a wealth of information and was very useful in the study of the HIV and AIDS in humans [21].

2.3. In rodents

In addition to looking for other lentiviruses, rodents were genetically engineered so that their cells could express both the human version of the CD4 receptor as well as the chemokine co-receptors to which HIV-1 binds, notably the main route of entry to target cells [23]. The envelope glycoprotein 120 (gp120) domiciled on the surface of the HIV-1 virus fuses with the host target cell membrane specifically invoking a cascade of activity involving the CD4+ receptors and chemokines co-receptors thus initiates viral entry. In successfully developed transgenic mice, however, the gp120 will not successfully bind to CD4-expressing T cells thus preventing targeted cell infection. Replacement of the gp120 coding region of the HIV with gp80 region obtained from the murine leukemia virus results in altered virus thus overcoming the problem. This chimeric HIV-1 clone could infect conventional mice cells, but not human cells. Although this has been extensively adopted in research, these models could not produce some disease progression seen in humans, for example, neuro-HIV disease [9].

Humanized mice model also known as humice are mice carrying functioning human genes, cells, tissues, and/or organs engraftment mostly on genetically modified mouse background. They replicate the human HIV immune responses and are currently used to study mechanisms of immune activation, mucosal transmission and prevention, immune pathogenesis and anti-viral drug development.

2.4. Developmental perspectives of HIV animal models

The development of fitting animal models is seen as one of the most important challenges in studies of co-infection, since HIV does not cause disease in rodents and in non-human primates [24].

Lentiviruses specific to other species that also compromise the immune systems in ways similar to HIV-1 have been useful in providing information about the pathogenicity of the virus. In spite of the similarities to HIV, there are species-specific differences in their respective gene products as well as the pathogenesis of the disease fueling the drive for search of better models of HIV disease control.

3. Defining animal models

3.1. Macaques

SIV in macaques follow a disease course that is similar to HIV in humans. This is useful since it can be exploited for evaluation of drug/vaccine candidates closely related to that being developed for respective human HIV infection. The model thus provides leading and insightful results in and related to drug safety and efficacy of prospective candidates [1]. Certain animal models have been developed over the years through intensive research for insightful and revealing studies on HIV/AIDS and associated cancers. These include both specific rat and mouse models designed for HIV pathogenesis and candidate vaccine development. Scientists have albinitio created the SIV non-human primate(NHP) model (**Figure 1**), for example, the Indian-origin rhesus macaque (*Macaca mulatta*), *Cynomolgous* macaque (*M. fascicularis*), and pigtailed macaque (*M. nemestrina*), for same purposes including development of microbicides. These models are useful in elucidating the mechanism of AIDS pathogenesis as well as in preclinical testing of novel drugs directed at HIV infection and cancer [1, 25, 26].

SIV infection in macaques has been used as a model for AIDS since it was established that non-human primates are resistant to infection by HIV (**Table 1**). Simply put, SIV is a retrovirus causing immunodeficiency similar to AIDS in Asian macaques. More importantly, Macaques also develop TB that is very similar to that of humans, other notable similarities in viral activity and disease manifestation include cavitary lung disease and necrotic lession. The TB latency seems in contrast to humans to have only a small proportion of lately infected Macques develop reactivation [27] though it develops persistent Mycobacterium *bovis bacillus Calmette Guerin* (BCG) [28] and *M. tuberculosis* co-infection [29].

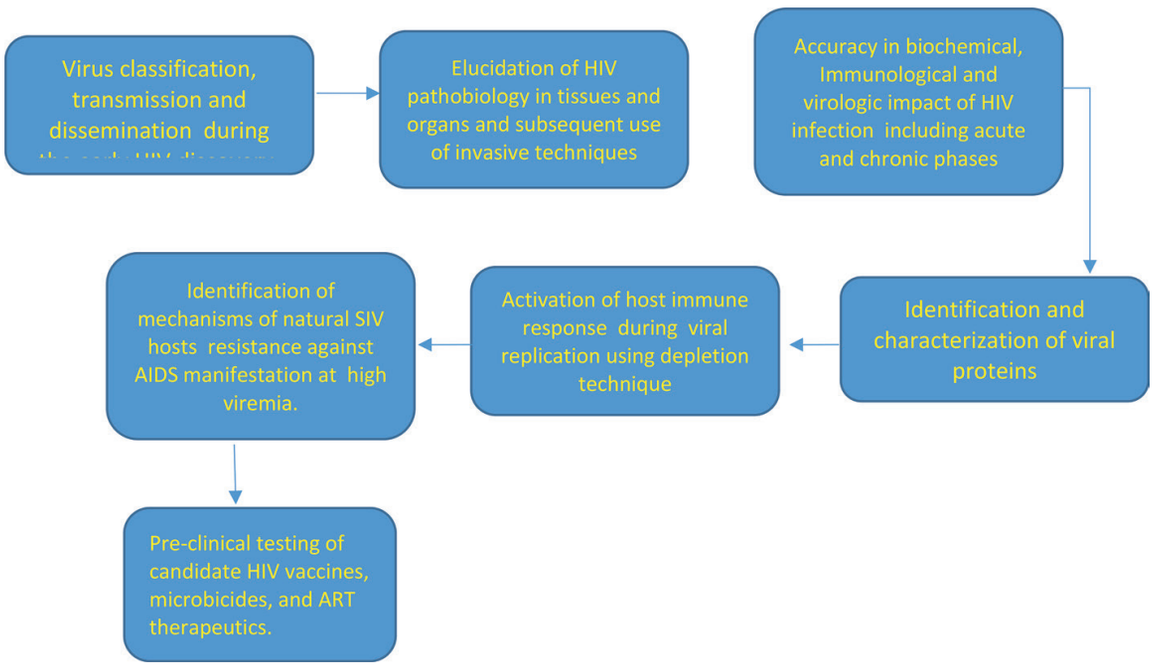


Figure 1. Historical trend and impact of HIV/AIDS research in NHPs.

Animal model	Species	Cons	Pros	Retroviral study sub-types
Macaques	Rhesus macaques (*Macaca mulatta*)	• Resistant to HIV. SIV shows discrepancies to HIV which Macaques are resistance to especially with respect to the association of TB reactivation and viral load. • Low turnaround of the model. • Availability of some rhesus macaques depends on domestic breeding capacity and skill. • Have poorly characterized MHC allelic profiles and may not be suitable for vaccine studies. • May not be appropriate for comparative menstrual cycle-related SIV/SHIV studies.	• Can be infected with SIV which compromises immunity • Ability to causes secondary complications similar to HIV in humans. • Intravenous, intrarectal, intravaginal and penile-exposure models are established • Studies of SIV/TB co-infection models. • Indian macaques have well characterized MHC allelic profiles thus suitable for as a model for vaccine candidates.	SIVmac239 SIVsmPBj6.9 SIVsmPBj6.6 SIVPBj14 SIVmac316 SIVsmE543–3 SIVsmE660 SIVmac251 RT-SHIV SHIV-SF162P3
	Pigtail macaques (*Macaca nemestrina*	• SIVmac infections typically does not refelct HIV-1 infection and is more aggressive. • Usually more expensive to maintain • Not an established model for evaluation of vaccine candidates	• In the female vaginal ecology, physiology and intravaginal virus challenge is similar to that of human. • SIV/SHIV and STI co-infection models can be studied.	SIVmac251 + SHIV/17E-Fr SIVmne SIVmneCl8 SIVmne170 SIVmne027
	Cynomologus macaques (*M. fascicularis*)	• Difficult in sample collection due to smaller size. • Exhibit low viral loads. • Its suitability for vaccine studies is low.	• Has smaller size therefore, easier to handle. • It is more readily available.	RT-SHIV SIVmac251
Baboons		• Limited HIV replication activity in monocytes or macrophages, CSF or brain • Not a good model for heterosexual transmission as shown in SHIV89.6P chimera model	• Supports HIV-2 replication but not HIV-1 • Baboon microglial cells can be infected by SHIV chimera with strong tropism for baboon PBMC but not for rhesus macaque PBMC.	

Animal model	Species	Cons	Pros	Retroviral study sub-types
Genetic comparison of non human primates in HIV research				
Cons		**Opportunities provided by the NHP models in studies of HIV eradication**	**Pros**	
• High cost, maintenance and availability. • Have limitated suitability for vaccine studies. • SIV differs from HIV in genetic organization especially the Vpx gene of SIV and Vpu of HIV • Simian AIDS generally develops within 6–12 months while the human AIDS develops after several years of infection with HIV		• Identity, dose, and route of virus challenge known. • Control for various clinical parameters that are virtually impossible to control in humans (time of infection, duration of ART etc). • Comprehensive cellular and anatomic characterization of both active and persistent reservoirs (including elective necropsy). • Pilot trials of *in vivo* eradication conducted in a timely and controlled fashion; treatment interruption is possible. • Testing of "risky" interventions (i.e., cell depletion experiments, stem cell-based interventions etc).	• Steady environmental conditions can be applied for long periods therefore enhancing the chances to detect genetic effects • Varying environmental settings can be imposed sequentially on NHP in order to characterize genotype-environment interactions; • Possibility of testing genetic hypotheses in a prospective selective mating • Important and needed invasive and terminal experiments can be conducted and validated	

Table 1. Advantages and disadvantages of non-human primate models used in HIV-1 research.

http://dx.doi.org/10.5772/intechopen.76698

In the model, co-infection with BCG and SIV hastened the progression to AIDS [30] and reveals severe diminution of CD4+ T cells, loss of BCG-specific T cell responses, and reactivation of the clinically latent BCG infection into a TB-like disease as reported by Shen et al. [31]. *M. tuberculosis* reactivation in SIV-infected macaques is linked with peripheral T-cell depletion instead of viral load [32].

3.2. Other primates

Chimpanzees support productive infection, but the disease does not occur for at least 10 years. Alter et al.'s [33] investigative study was designed to determine the possibility of using a transmissible agent in humans with capability to induce AIDS in non-humans thus established an animal model in which the pathogenesis, treatment regimen, and prevention of AIDS could be studied (**Table 1** and **Figure 1**). This early attempt pre-dates the virologic investigations that linked human AIDS to a type C retrovirus [33]. The NHP models have recorded tremendous successes, the limitations observed notwithstanding (**Table 2**).

Interestingly, Baboons can support replication of certain strains of HIV-2, but difficult with HIV-1 strains (**Table 1**). It has been shown that HIV infection replicates mainly in the T-cells, with limited or no activity in the monocytes or macropahges, CSF or brain of Baboons and macaque monkeys [34–36].

3.3. Mice

For better assessment of the HIV-linked clinical presentations, murine models have been developed and proved a better tool in elucidating the mechanism of disease progression. Equally giving lead to scientific direction as against non-human primates [37] geared toward the future of HIV drug and vaccine development [38]. Besides that, it is usually costly to work with the non-human primates (large animals), which further underscores the necessity for murine models [9].

Evaluation	Species	Study outcome	Drug
Efficacy and toxicology	Macaques	Long term-highdose HIV treatments had adverse effects not found using short term-high dose treatment	Tenofovir
Prophylactic treatment with anti-virals	Macaques	The effectiveness of prophylaxis in blocking HIV infection as seen in the treatment for occupational exposures.	Various
Mother-to-fetus transmission, and fetal prophylaxis	Macaques	Provided guidelines for antiviral treatment in HIV positive pregnant mothers	Tenofovir and AZT
Vaccine efficacy in SHIV 89.6p, a hybrid SIV, genetically engineered from HIV	Macaques	The Monkeys were not protected against infection with SHIV however, they did have lower viral	MRK-Ad5

Table 2. Successful clinical testing conducted in NHP models.

3.3.1. Murine AIDS

In many ways, murine AIDS (or MAIDS) and human AIDS are similar. Immunological analysis and genetic studies reveal resistant gene(s) in the H-2 complex of mice, an indication that genetic differences in mice could modify features of HIV disease. The defective murine leukemia virus is the major etiologic agent of MAIDS, which seems to be able to induce disease in the absence of virus replication. Target cell proliferation and oligoclonal expansion are induced by the virus, which suggests repressed immunity seen in mice thus referred to as paraneoplastic syndrome. This is further supported by the good response(s) of MAIDS mice to antineoplastic agents. This animal model is useful in demonstrating the emergence of novel hypotheses about AIDS, including the roles of defective HIV and HIV replication in the progression of the disease, and also the importance of identifying the HIV targeted cells *in vivo*.

Although MAIDS and AIDS are triggered by retroviruses of different classes, the availability of a model in small, accessible animal species with elaborated genetics is beneficial in understanding the pathogenesis of AIDS especially in cases where one or more of the affected cellular and molecular pathways are common in both diseases [39].

3.3.2. Genetic modifications/gene manipulations

Potash et al. [40] designed a model of HIV-1 infection of mice for the study of viral replication, its pathogenesis and control. The team substituted the coding region of gp120 in HIV-1/NL4–3 with gp80 from ecotropic murine leukemia virus, which infects only rodents, targeted at infecting rodents with HIV-1 in rodents. The EcoHIV was developed through the chimeric virus construct, which productively infected lymphocytes in mice, but failed to do the same in human lymphocyte culture. It was recorded that immunocompetent adult mice were easily prone to infection by a single dose EcoHIV inoculant as the demonstrated by viral detection in lymphocytes in the spleen, brain cells and peritoneal macrophages. The passage in culture, and induction of antibodies to HIV-1 Gag and Tat showed that the animal produced virus was indeed infectious and immunogenic, respectively.

3.3.3. Transgenic mice

Mice are not susceptible to HIV infection due to the virus specificity for the human cell. These would have otherwise been ideal models, however, owing to the large diverse tools and wide knowledge about the rodent immunity. To circumvent limitation in mice (**Table 3**), complementary mouse models have thus been developed over the years targeting specific genes (**Table 4**). Using these models, the more important features of HIV infections and *M. tuberculosis* can be replicated in mice (e.g. virus replication in splenic lymphocytes, peritoneal macrophages and brain tissue; typical TB granuloma formation; immune repression and/or chronic immune stimulation; and susceptibility to systemic, vaginal, and rectal infection by HIV) [24].

Mice modified genetically are often used for research and/or simply as an animal model of human diseases. The use of genetic engineering tools has greatly improved the ability to develop various mouse models important to preclinical research. With the recent developments in gene editing technologies, it is now possible to generate quickly highly adjustable

Animal Model	Parameters	HIV/SCID-hu	HIV/hu-HSC	HIV/BLT	Reference
Mice	• Sample size	Small	Small	Small	[41]
	• Anatomical comparison with humans	Different same	Different same	Different same	[42–44]
	• Similarity of infective agent to HIV	Similar	Similar	Similar	[45–48]
	• Infection manifestation in comparison with human/HIV	Yes	Yes	Yes	[46, 49]
	• Availability for experimental infection in controlled conditions vis-à-vis route and dose of virus inoculation, drug regimens etc.	Yes	Yes	Yes	[47, 50, 51]
	• Ability to deplete major immune components	Similar	Similar	Similar	
	• Reservoir comparison to human/HIV	Minimal	Minimal	Minimal	
	• Cost of maintenance compared to NHP	SCID mice implanted with fetal human thymus/live.	NOD/ NSG mice irradiated and injected with human HSCs	NOD/SCID mice irradiated & implanted with fetal human thymus/live plus injection with HSCs	
	• Methods mouse model development	5–7 months from time of birth	2–3 months	5–7 months	
	• Timeframe needed for mouse development	T cells	T & B cells, DCs	T & B cells, monocytes, macrophages, NK cells, DCs	
	• Cellular composition during reconstitution	Only thymus/live implant	Murine lymph organs and bone marrow	Murine lymph organs, rectum, vagina, gut, bone marrow	
	• Degree of colonization	Grafts last almost 12 months	6–7 months	Over 12 months	
	• Length infection sustained				

Table 3. Comparison of major mice chimeric models used in HIV-1 research.

mouse models tailored to research needs. Mouse is still putatively the preferred animal model used in drug discovery and therapeutic agent development [52]. Below are some specific examples of genetically modified mouse model backgrounds which resulted from targeted mutations of specific mouse genes as presented in **Table 4**.

3.3.3.1. NOD/SCID mice

Since the early 2000s, a series of immune-deficient mice suitable for developing humice have been successively designed through the introduction of IL-2Rγ^{null} gene (e.g. NOD/SCID/γc^{null} and Rag2$^{null}\gamma c^{null}$ mice) using various genomic approaches. Mouse backgrounds serve as the basic genetic modified rodent from which other disease models are generated mostly by further modification and/or by human tissue engraftment. These mice were generated by genetically introducing human cytokine genes into NOD/SCID/γc^{null} and Rag2$^{null}\gamma c^{nul}$l mouse backgrounds [52]. There are other models that rely on the transplantation of human tissues into the SCID mice, and they are referred to as the SCID-hu mouse model.

Gene name	**Characteristics**
B2m *beta-2 microglobulin*	This is required for normal expression of major histocompatibility class I proteins which displays viral and self-antigens to responsive T cells and secondly for CD8+ T cell maturation and NK cell development.
Foxn1 *forkhead box N1, formerly Hfh11*	*Foxn1*^{nu} mutation is generally known as nude mutation. Homozygote (*nu/nu)* type lack a thymus that is they are 'hypothymic'/'athymic' and thus are T cell deficient. Their responses to thymus-dependent antigens are poor. However, the allogenic and xenogenic grafts though may have NK activity show evidence of leakiness. → Greatly increased susceptibility to infection.
Il2rg *interleukin 2 receptor, gamma chain*	*The Il2rg* is required for IL2, IL4, IL7, IL9, IL15, and IL21 high-affinity binding and signaling. It is required in mediating susceptibility to thymic lymphomas in mice. Mostly observed is the *Il2rg* deficiency that blocks the development of NK cells and the resultant defects in innate immunity.
Myd88 *myeloid differentiation primary response gene 88*	Myd88 is critical adaptor protein utilized by all TLRs (except TLR 3) to activate transcription factor NF-κB in innate immunity signal transduction. Myd88 mutation leads to decreased *innate responsesespecially neutrophils, macrophages,* *hematopoietic, molecular signaling, and apoptotic abnormalities.*
Prf1 perforin 1	*Prf1* is a pore-forming protein that is an important component of the lytic pathway by which NK and CD8+ lymphocytes kill targeted cells.
Prkdc protein kinase, DNA-activated, catalytic polypeptide	The *scid* mutation in the *Prkdc* gene means severe combined immunodeficient. *Prkdc* plays a role in repairing double-stranded DNA breaks and in recombining the variable (V), diversity (D), and joining (J) segments of immunoglobulin and T-cell receptor genes. Homozygous (scid/scid) mutants have no mature T and B cells, cannot mount cell-mediated and humoral adaptive immune responses, do not reject allogeneic and xenogeneic grafts, and are useful cancer research models. The disadvantage is its leakiness as some functional B and T cells as they age, in non-SPF conditions. They cannot be as thoroughly irradiated as other immunodeficient models before being engrafted renders NOD mice diabetes-free.
Rag1 *recombination activating gene 1*	*Rag1* is essential for the V(D)J gene rearrangements that generate functional antigen receptors in T and B cells; homozygous *Rag1*^{tm1Mom} mutants have no mature, functional T and B cells. The *Rag1*^{tm1Mom} mutation on the NOD background renders NOD mice diabetes-free. However, aging NOD.129S7(B6)-*Rag1*^{tm1Mom}/J mice develop B cell lymphomas at a high frequency.
Ticam1 *Trif*	Toll-like receptor adaptor molecule 1. It is an adapter protein used by TLR 3 to activate transcription factor NF-κB in innate i immunity signal transduction. *Its mutation leads to decreased innate responses especially when combined with Myd88 mutation.*

Table 4. Common genetic mutations found in mouse models and their functions (source: Ibeh et al. [52]).

Earlier versions of humanized mice were developed mainly to study HIV-1 infection especially in modeling for immune-pathogenesis [53, 54], although the SCID-hu Thy/Liv model is still used to test for antiviral drugs [55]. In the improved humanized mice strains, several HIV-1 strains have been successfully used for HIV infection in the developed mouse model, and these include CCR5-tropic [56], CXCR4-tropic and dual-tropic (NL4-R3A) viruses [56]. Obviously, HIV-1 infection can be established in immune-deficient mouse models by inoculation through various routes of entry, namely intraperitoneal, intravenous and/or mucosal routes [57, 58]. Various research reports have established sustained viral replication and depletion of CD4+ T-cell using the routes of infection.

Evidently, Nie et al. have shown similar depletion of CD45RAþ naive and CD45RA + effector/memory CD4þT lymphocytes by CXCR4- tropic HIV-1 in humanized mouse as were observed in HIV-1 patients. Similarly, the preferential depletion of CD45RA + CD4þT lymphocytes by CCR5-tropic HIV-1 was also observed. Further reports on humanized mice have shown its usefulness as a tool for studying various aspects of HIV-1 infection namely the roles of regulatory T cells (Tregs) [57], dendritic cells (pDCs) revealing the pathophysiology of human DC subsets [59] and pDC instigator function during disease initiation [60], HIV-1 immuno-pathogenesis [54, 61, 62], development of new antiviral therapy [6, 63], mucosal transmission, microbicide development [64] and currently in studying latent HIV infections. Latent HIV infections can now be established in a mouse model in the presence of administered ARV [65, 66].

3.3.3.2. BLT mice

Consequently, latency has been successfully generated in humanized BLT mice [67, 68]. Available report has shown that poly lactic-co-glycolic acid (PLGA) nanoparticles with encapsulated rilpivirine (an anti-retoviral drug) coated reproductive tract offered significant protection to BLT humanized mouse model from a vaginal high-dose HIV-1 challenge [68]. Several improvements of humice models with an enhanced human immune cell reconstitution especially the female genital tract tissues create a potential mice, susceptible to intravaginal HIV infection. This type of mouse model will enable studies on mechanisms involved in HIV transmission *in vivo* and represent powerful tool for studying hematopoiesis, inflammatory disease and viral host-pathogen interactions. Several potent HIV vaccines have been put on trial and enjoyed a well-publicized but prematurely terminated results due to high frequency of seroconversions among vaccine recipients [69, 70]. Previously, the only known model for HIV testing is infection of rhesus macaques with simian immunodeficiency virus (SIV) which has provided an excellent non-human primate model for studying HIV pathogenesis [71]. This model, however, has three major disadvantages despite its application in transmitting HIV experimentally to rhesus macaques across the cervicovaginal or rectal mucosa. The established scenario makes it possible to test for microbicides and engages in laboratory study of mucosal HIV transmission. First, they are costly both in procurement and housing (limited number of primate facility globally) and is in high demand; secondly, SIV differs from HIV in genetic organization especially the Vpx gene of SIV and Vpu of HIV and lastly, while simian AIDS generally develops within 6–12 months of infection, the human AIDS develops after several years of infection with HIV (**Table 1**). However, these limitations serve as impediments in the search for an appropriate model of HIV drug testing and disease study, the transgenic mice model has overcome these feared problems associated with the SIV model. Mice have the utmost advantages of being inexpensive, have high reproductive capacity and may be housed in large numbers in a fairly small facility [72]. Furthermore, conduct of experimentation can be done in large numbers and in replicates. The severe combined immune deficiency mouse engrafted with human peripheral blood mononuclear cells (hu-PBL-SCID) could be co-engrafted with xenografts containing the dual of human fetal thymus and liver tissue (SCID-hu thy/liv)/(SCID-hu thy/liv), and this model is widely applied in preclinical evaluation of antiretroviral therapy [55, 58]. In another study, Denton et al. supported these findings and showed that the female reproductive tissues in BLT mice are adequately reconstituted with

HIV-susceptible human CD4þT cells, as well as other relevant populations [67]. Similarly, Dagur et al. in a current study demonstrated dual reconstitution in TK-NOG mouse model as a possible platform to investigate hepatocyte-related HIV-1 immunopathogenesis [73].

3.3.3.3. Other examples

The human hematopoietic progenitor cells (CD34+) from human cord blood are used to reconstitute the immune system of immune-deficient mice also known as humanized mouse [41]. An additional feature or rather advancement incorporates a fragment of the fetal human thymus engraftment, which performs functionally as a human thymus. The significance of this is to allow for a more proper positive/negative T-cell selection previously not obtainable from the original model [74]. Immunologi and virologic parameters such as CD4+ cell depletion, extent of viremia, and co-receptor-mediated tropism were all observed in HIV infection of humanized experimental mice [74, 75]. The humice demonstrated transplanted human cells in mucosal linings therefore, most possibly get infected by intravaginal and/or intrarectal routes [76]. This model is used to evaluate novel approaches in HIV prevention and treatment options including human-neutralizing antibodies, usage of prophylactic anti-retroviral therapies, and T cell-specific siRNA transfer [77]. The effect of M. tuberculosis infection on the induction of HIV gene expression has been studied with HIV transgenic mice integrating the entire viral genome [78]. In this model, viral gene expression was triggered by M. tuberculosis and suppressed after anti-mycobacterial chemotherapy [78].

4. Model suitable for vaccine trials

The question of whether or not there should be a standardized model is the basis on which the current controversies in HIV research rest on [26]. Differences in SIV and SHIV replication in the rhesus macaque, cynomolgous and pigtailed macaques' species have been observed and is favored in the design of experimental models depending on the question raised [40]. For vaccine research, the rhesus does present the ideal for pathogenesis research; however, demanding for its use as a standard does present problems the current wave is to base considerations on the transgenic mice models. Besides, vaccine testing in more than one species of macaques with similar vaccine modalities provides an opportunity to compare outcomes thus increasing confidence of research reproducibility [79].

Regulatory authorities require vaccine candidates to undergo preclinical evaluation in animal models before they enter the clinical trials in humans [80]. The overarching goal of a new vaccine is to stimulate the immune system to elicit an effective immune response against the pathogen it has been designed for, and currently no alternatives to live animal use currently exist for evaluation of this response despite advances in computational sciences for the search of an *in-silico* model [80].

Integral studies such as elucidation of immune protection mechanism, optimizing route and constitutions of vaccines; determining the onset and duration of immunity, as well as satisfying safety and efficacy requirements of the new vaccines, must be done in an integrated

living system [80]. As discussed earlier, a standardized animal model that provides all the information required for advancing a new vaccine through the preclinical stage has still not been met and even if it were, it is still bereft with problems bordering on bioethics. Current trend suggests that humanized mice (**Table 3**) more accurately predict vaccine outcomes that approximate humans.

5. HIV preclinical vaccine trials and predictive biomarker discovery in animal models

To accelerate effort in bridging the translational gap between preclinical evaluation and clinical trials, it is pertinent to make animal model testing more clinical trial like. It is important that clinical endpoints may not be easily established in animal models because of the use of questionnaires to derive the quality of life issues from end users and cannot be replicated in experimental animals; however, there are recent attempts to model pain questionnaires in animals [81]. Obviously, animal models could be designed to use other endpoints that relate or translate into the expected endpoints of clinical trials. The humanized NSG among all other models have been successfully used for multiple *in vivo* preclinical validation studies. Potentially tested areas of validation include: (1) activation of human NK cells with an IL-15 superagonist to inhibit acute HIV infection; (2) delivering anti-CCR5 and antiviral silencing RNAs (siRNA) direct delivery to T cells in order to control viral replication and prevent CD4+ T cell loss; (3) provision of prophylactic protection from HIV infection through induction of neutralizing anti-HIV monoclonal antibodies and (4) suppression of viral replication through introduced engineered HSCs that expresses an HIV-specific T cell receptor (TCR).

It is possible to design an integrated preclinical approach using PDX models organized with systems biology to enable the discovery and development of predictive biomarkers in order to classify clinical tumor responsiveness to a novel agent [82]. Peradventure the classifier achieved a high level of accuracy in the experiment, and biomarker-driven clinical trials could be developed based on the prevalent rate of the identified biomarkers and their link with efficacy.

6. Next generation models

The actual mechanism of sexual transmission is not precisely defined. What is known, however, is that HIV must be transmitted via the mucosal surfaces of the genital tract in both hetero- and homosexual cases [83]. The fact that some individuals remain uninfected despite multiple exposures, whereas others get infected after an exposure to HIV-infected semen further confounds the situation. An animal model adapted to mucosal transmission of the virus would aid elucidation of the mechanisms and dose of virus required for transmission and provide a system for testing pharmacologic and biologic cofactors that may affect HIV transmission.

Although intravenous inoculation of SIV into macaques is a near perfect model for studies of pathogenesis, this route is not appropriate for studying factors involved in the sexual transmission

of HIV. In one of the earliest experiments on the subject(macaques) [73], an animal model for the heterosexual transmission of HIV was developed by applying SIV onto the genital mucosa of both mature and immature male and female rhesus macaques. The study suggests that in the genital tract, the mucous membrane acts as a barricade to SIV infections as well as the non-involvement of spermatozoa and seminal plasma for genital HIV transmission.

Recent animal model research has focused on: (1) refinement of existing models and the development of new ones; (2) development of a model in response to latency especially HIV reservoir and immune perseverance and (3) evaluation of vaccine candidate that would elicit broadly neutralizing antibodies. As discussed in the chapter, a suitable and cost-effective animal model for HIV has been a goal spanning three decades with important milestones accomplished.

Author details

Bartholomew Okechukwu Ibeh[1]* and Efejiro Ashano[2]

*Address all correspondence to: barthokeyibeh@yahoo.com

1 Laboratory of Animal Models for Human Diseases, Medical Biotechnology Department, National Biotechnology Development Agency, Abuja, Nigeria

2 Immunovirology and Vaccine Development Laboratory (IVL), Medical Biotechnology Department, National Biotechnology Development Agency, Abuja, Nigeria

References

[1] Haigwood NL. Update on animal models for HIV research. European Journal of Immunology. 2009;**39**(8):1994-1999

[2] Sharma B. Exploring experimental animal models in HIV/AIDS research. Biochemistry and Analytical Biochemistry. 2013;**2**(129):1009-2161

[3] Sharma B. Anti-HIV-1 drug toxicity and management strategies. Neurobehavioural HIV Medicine. 2011;**3**:27-40

[4] Hartman TL, Buckheit RW. The continuing evolution of HIV-1 therapy: Identification and development of novel antiretroviral agents targeting viral and cellular targets. Molecular Biology International. 2012;**2012**:401965, 17 p

[5] Saayman S, Barichievy S, Capovilla A, Morris KV, Arbuthnot P, Weinberg MS. The efficacy of generating three independent anti-HIV-1 siRNAs from a single U6 RNA pol III-expressed long hairpin RNA. PLoS One. 2008;**3**(7):e2602

[6] Hatziioannou T, Evans DT. Animal models for HIV/AIDS research. Nature Reviews Microbiology. 2012;**10**(12):852-867

[7] Langford SE, Ananworanich J, Cooper DA. Predictors of disease progression in HIV infection: A review. AIDS Research and Therapy. 2007;**4**(1):11

[8] Gao F, Bailes E, Robertson DL, Chen Y, Rodenburg CM, Michael SF, Cummins LB, Arthur LO, Peeters M, Shaw GM, Sharp PM, Hahn BH. Origin of HIV-1 in the chimpanzee pan troglodytes troglodytes. Nature. 1999;**397**(6718):436-441

[9] Vigorito M, Connaghan KP, Chang SL. The HIV-1 transgenic rat model of neuroHIV. Brain, Behavior, and Immunity. 2015;**48**:336-349

[10] Streeck H, Brumme ZL, Anastario M, Cohen KW, Jolin JS, Meier A, Brumme CJ, Rosenberg ES, Alter G, Allen TM, Walker BD, Altfeld M. Antigen load and viral sequence diversification determine the functional profile of HIV-1–specific CD8+ T cells. PLoS Medicine. 2008;**5**(5):e100

[11] Hess C, Altfeld M, Thomas SY, Addo MM, Rosenberg ES, Allen TM, Draenert R, Eldrige RL, van Lunzen J, Stellbrink HJ. HIV-1 specific CD8+ T cells with an effector phenotype and control of viral replication. The Lancet. 2004;**363**(9412):863-866

[12] Euler Z, van Gils MJ, Bunnik EM, Phung P, Schweighardt B, Wrin T, Schuitemaker H. Cross-reactive neutralizing humoral immunity does not protect from HIV type 1 disease progression. Journal of Infectious Diseases. 2010;**201**(7):1045-1053

[13] Brenchley JM, Price DA, Schacker TW, Asher TE, Silvestri G, Rao S, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nature Medicine. 2006;**12**(12):1365-1371

[14] Moir S, Chun TW, Fauci AS. Pathogenic mechanisms of HIV disease. Annual Review of Pathology: Mechanisms of Disease. 2011;**6**:223-248

[15] Brenchley JM, Douek DC. HIV infection and the gastrointestinal immune system. Mucosal Immunology. 2008;**1**(1):23-30

[16] Fitzgerald-Bocarsly P, Jacobs ES. Plasmacytoid dendritic cells in HIV infection: Striking a delicate balance. Journal of Leukocyte Biology. 2010;**87**(4):609-620

[17] Schmitz JE, Kuroda MJ, Santra S, Sasseville VG, Simon MA, Lifton MA, Racz P, Tenner-Racz K, Dalesandro M, Scallon BJ, Ghrayeb J, Forman MA, Montefiori DC, Rieber EP, Letvin NL, Reimann KA. Science. 1999;**283**(5403):857-860

[18] Ibeh BO. Oxidative stress, redox regulation and elite controllers of HIV infection; towards a functional cure, Chapter 7. In: Dr. Ibeh B, editor. "Trends in Basic and Therapeutic Options in HIV Infection—Towards a Functional Cure". Croatia: INTECH publishers; 2015. p. 183-207. ISBN: 978-953-51-2157-2

[19] Jones RB, Ndhlovu LC, Barbour JD, Sheth PM, Jha AR, Long BR, Wong JC, Satkunarajah M, Schweneker M, Chapman JM, Gyenes G, Vali B, Hyrcza MD, Yue FY, Kovacs C, Sassi A, Loutfy M, Halpenny R, Persad D, Spotts G, Hecht FM, Chun TW, McCune JM, Kaul R, Rini JM, Nixon DF, Ostrowski MA. Tim-3 expression defines a novel population of dysfunctional t cells with highly elevated frequencies in progressive hiv-1 infection. The Journal of Experimental Medicine. 2008;**205**:2763-2779

[20] Wang X, Cao Z, Jiang J, Li Y, Dong M, Ostrowski M, Cheng X. Elevated expression of Tim-3 on CD8 T cells correlates with disease severity of pulmonary tuberculosis. Journal of Infection. 2011;**62**(4):292-300

[21] Zuckerman AJ. AIDS in primates. British Medical Journal (Clinical research ed.). 1986; **292**(6514):155-220

[22] Barin F, Denis F, Allan JS, M'Boup S, Kanki P, Lee TH, Essex M. Serological evidence for virus related to simian T-lymphotropic retrovirus III in residents of West Africa. The Lancet. 1985;**326**(8469-8470):1387-1389

[23] Nischang M, Sutmuller R, Gers-Huber G, Audigé A, Li D, Rochat MA, et al. Humanized mice recapitulate key features of HIV-1 infection: A novel concept using long-acting anti-retroviral drugs for treating HIV-1. PLoS One. 2012;**7**(6):e38853

[24] Pawlowski A, Jansson M, Sköld M, Rottenberg ME, Källenius G. Tuberculosis and HIV co-infection. PLoS Pathogens. 2012;**8**(2):e1002464

[25] Veazey RS. Animal models for microbicide safety and efficacy testing. Current Opinion in HIV and AIDS. 2013;**8**(4):295

[26] Jayaraman P, Haigwood NL. Animal models for perinatal transmission of HIV-1. Frontiers in Bioscience: a Journal and Virtual Library. 2005;**11**:2828-2844

[27] Diedrich CR, Flynn JL. HIV-1/mycobacterium tuberculosis coinfection immunology: How does HIV-1 exacerbate tuberculosis? Infection and Immunity. 2011;**79**(4):1407-1417

[28] Shen Y, Zhou D, Chalifoux L, Shen L, Simon M, Zeng X, et al. Induction of an AIDS virus-related tuberculosis-like disease in macaques: A model of simian immunodeficiency virus-mycobacterium coinfection. Infection and Immunity. 2002;**70**(2):869-877

[29] Safi H, Gormus BJ, Didier PJ, Blanchard JL, Lakey DL, Martin LN, et al. Spectrum of manifestations of Mycobacterium tuberculosis infection in primates infected with SIV. AIDS Research and Human Retroviruses. 2003;**19**(7):585-595

[30] Zhou D, Shen Y, Chalifoux L, Lee-Parritz D, Simon M, Sehgal PK. Mycobacterium bovis bacille Calmette-Guerin enhances pathogenicity of simian immunodeficiency virus infection and accelerates progression to AIDS in macaques: A role of persistent T cell activation in AIDS pathogenesis. The Journal of Immunology. 1999;**162**(4):2204-2216

[31] Shen Y, Shen L, Sehgal P, Huang D, Qiu L, Du G, et al. Clinical latency and reactivation of AIDS-related mycobacterial infections. Journal of Virology. 2004;**78**(24):14023-14032

[32] de Noronha AL, Bafica A, Nogueira L, Barral A, Barral-Netto M. Lung granulomas from Mycobacterium tuberculosis/HIV-1 co-infected patients display decreased in situ TNF production. Pathology-Research and Practice. 2008;**204**(3):155-161

[33] Alter HJ, Eichberg J, Masur H, Saxinger WC, Gallo RC, Macher AM. Transmission of HTLV-III infection from human plasma to chimpanzees: An animal model for AIDS. Science. 1984;**226**:549-553

[34] Pandrea I, Silvestri G, Apetrei C. AIDS in African nonhuman primate hosts of SIVs: A new paradigm of SIV infection. Current HIV Research. 2009;**7**(1):57-72

[35] Pandrea I, Apetrei C. Where the wild things are: Pathogenesis of SIV infection in African nonhuman primate hosts. Current HIV/AIDS Reports. 2010;**7**(1):28-36

[36] Gardner MB, Luciw PA. Macaque models of human infectious disease. ILAR Journal. 2008;**49**(2):220-255

[37] Denton PW, Søgaard OS, Tolstrup M. Using animal models to overcome temporal, spatial and combinatorial challenges in HIV persistence research. Journal of Translational Medicine. 2016;**14**(1):44

[38] VandeWoude S, Apetrei C. Going wild: Lessons from naturally occurring T-lymphotropic lentiviruses. Clinical Microbiology Reviews. 2006;**19**(4):728-762

[39] Jolicoeur P. Murine acquired immunodeficiency syndrome (MAIDS): An animal model to study the AIDS pathogenesis. The FASEB Journal. 1991;**5**(10):2398-2405

[40] Potash MJ, Chao W, Bentsman G, Paris N, Saini M, Nitkiewicz J, et al. A mouse model for study of systemic HIV-1 infection, antiviral immune responses, and neuroinvasiveness. Proceedings of the National Academy of Sciences of the United States of America. 2005;**102**(10):3760-3765

[41] Traggiai E, Chicha L, Mazzucchelli L, Bronz L, Piffaretti JC, Lanzavecchia A, Manz MG. Development of a human adaptive immune system in cord blood cell-transplanted mice. Science. 2004;**304**(5667):104-107

[42] Pettoello-Mantovani M, Kollmann TR, Raker C, Kim A, Yurasov S, Tudor R, et al. Saquinavir-mediated inhibition of human immunodeficiency virus (HIV) infection in SCID mice implanted with human fetal thymus and liver tissue: An in vivo model for evaluating the effect of drug therapy on HIV infection in lymphoid tissues. Antimicrobial Agents and Chemotherapy. 1997;**41**(9):1880-1887

[43] McCune JM, Namikawa R, Shih CC, Rabin L, Kaneshima H. Suppression of HIV infection in AZT-treated SCID-hu mice. Science. 1990;**247**(4942):564-566

[44] McCune JM, Namikawa R, Kaneshima H, Shultz LD, Lieberman M, Weissman IL. The SCID-Hu mouse: Murine model for the analysis of human hematolymphoid differentiation and function. Science. 1988;**241**(4873):1632-1639

[45] Berges BK, Rowan MR. The utility of the new generation of humanized mice to study HIV-1 infection: Transmission, prevention, pathogenesis, and treatment. Retrovirology. 2011;**8**(1):65

[46] Brainard DM, Seung E, Frahm N, Cariappa A, Bailey CC, Hart WK, et al. Induction of robust cellular and humoral virus-specific adaptive immune responses in human immunodeficiency virus-infected humanized BLT mice. Journal of Virology. 2009; **83**(14):7305-7321

[47] Bonyhadl ML, Kaneshima H. The SCID-hu mouse: An in vivo model for HIV-1 infection in humans. Molecular Medicine Today. 1997;**3**(6):246-253

[48] Dagur RS, Wang W, Cheng Y, Makarov E, Ganesan M, Suemizu H, Gebhart CL, Gorantla S, Osna N, Poluektova LY. Human hepatocytes depletion in the presence of HIV-1 infection in dual constituted humanized mice. Biology Open. 2018;**7**(2):bio029785. DOI:10.1242/bio.029785,LicenseCC BY 4

[49] Baenziger S, Heikenwalder M, Johansen P, Schlaepfer E, Hofer U, Miller RC, et al. Triggering TLR7 in mice induces immune activation and lymphoid system disruption, resembling HIV-mediated pathology. Blood. 2009;**113**(2):377-388

[50] Nischang M, Gers-Huber G, Audigé A, Akkina R, Speck RF. Modeling HIV infection and therapies in humanized mice. Swiss Medical Weekly. 2012;**142**:w13618

[51] Berges BK, Akkina SR, Remling L, Akkina R. Humanized Rag2−/− γc−/− (RAG-Hu) mice can sustain long-term chronic HIV-1 infection lasting more than a year. Virology. 2010; **397**(1):100-103

[52] Ibeh BO, Furuta Y, Habu JB, Ogbadu L. Humanized mouse as an appropriate model for accelerated global HIV research and vaccine development: Current trend. Immunopharmacology and Immunotoxicology. 2016;**38**(6):395-407

[53] Liu L, Wen M, Zhu Q, Kimata JT, Zhou P. Glycosyl phosphatidylinositol-anchored C34 peptide derived from human immunodeficiency virus type 1 Gp41 is a potent entry inhibitor. Journal of Neuroimmune Pharmacology. 2016;**11**(3):601-610

[54] Zhang L, Su L. HIV-1 immunopathogenesis in humanized mouse models. Cellular & Molecular Immunology. 2012;**9**(3):237-244

[55] Stoddart CA, Bales CA, Bar JC, Chkhenkeli G, Galkina SA, Kinkade AN. Validation of the SCID-hu thy/liv mouse model with four classes of licensed antiretrovirals. PLoS One. 2007;**2**(8):e655

[56] Shultz LD, Brehm MA, Garcia-Martinez JV, Greiner DL. Humanized mice for immune system investigation: Progress, promise and challenges. Nature Reviews Immunology. 2012;**12**(11):786-798

[57] Sun Z, Denton PW, Estes JD, Othieno FA, Wei BL, Wege AK, et al. Intrarectal transmission, systemic infection, and CD4+ T cell depletion in humanized mice infected with HIV-1. Journal of Experimental Medicine. 2007;**204**(4):705-714

[58] Namikawa R, Kaneshima H, Lieberman M, Weissman IL, McCune JM. Infection of the SCID-hu mouse by HIV-1. Science. 1988;**242**(4886):1684

[59] Palucka AK, Gatlin J, Blanck JP, Melkus MW, Clayton S, Ueno H, et al. Human dendritic cell subsets in NOD/SCID mice engrafted with CD34+ hematopoietic progenitors. Blood. 2003;**102**(9):3302-3310

[60] Glitzner E, Korosec A, Brunner PM, Drobits B, Amberg N, Schonthaler HB, et al. Specific roles for dendritic cell subsets during initiation and progression of psoriasis. EMBO Molecular Medicine. 2014;**6**(10):1312-1327

[61] Ince WL, Zhang L, Jiang Q, Arrildt K, Su L, Swanstrom R. Evolution of the HIV-1 env gene in the Rag2−/− γC−/− humanized mouse model. Journal of Virology. 2010;**84**(6):2740-2752

[62] Sato K, Izumi T, Misawa N, Kobayashi T, Yamashita Y, Ohmichi M. Remarkable lethal G-to-a mutations in vif-proficient HIV-1 provirus by individual APOBEC3 proteins in humanized mice. Journal of Virology. 2010;**84**(18):9546-9556

[63] Gruell H, Bournazos S, Ravetch JV, Ploss A, Nussenzweig MC, Pietzsch J. Antibody and antiretroviral preexposure prophylaxis prevent cervicovaginal HIV-1 infection in a transgenic mouse model. Journal of Virology. 2013;**87**(15):8535-8544

[64] Moench TR, Mumper RJ, Hoen TE, Sun M, Cone RA. Microbicide excipients can greatly increase susceptibility to genital herpes transmission in the mouse. BMC Infectious Diseases. 2010;**10**(1):331

[65] Sato K, Nie C, Misawa N, Tanaka Y, Ito M, Koyanagi Y. Dynamics of memory and naive CD8+ T lymphocytes in humanized NOD/SCID/IL-2Rγ null mice infected with CCR5-tropic HIV-1. Vaccine. 2010;**28**:B32-B37

[66] Choudhary SK, Archin NM, Cheema M, Dahl NP, Garcia JV, Margolis DM. Latent HIV-1 infection of resting CD4+ T cells in the humanized Rag2−/− γc−/− mouse. Journal of Virology. 2012;**86**(1):114-120

[67] Denton PW, Olesen R, Choudhary SK, Archin NM, Wahl A, Swanson MD, et al. Generation of HIV latency in BLT humanized mice. Journal of Virology. 2011;**86**(1):630-634

[68] Marsden MD, Kovochich M, Suree N, Shimizu S, Mehta R, Cortado R. HIV latency in the humanized BLT mouse. Journal of Virology. 2012;**86**(1):339-347

[69] Cohen J. Did Merck's failed HIV vaccine cause harm? Science. 2007;**318**(5853):1048-1049

[70] Sekaly RP. The failed HIV Merck vaccine study: A step back or a launching point for future vaccine development? Journal of Experimental Medicine. 2005;**205**(1):7-12

[71] Lackner AA, Veazey RS. Current concepts in AIDS pathogenesis: Insights from the SIV/macaque model. Annual Review of Medicine. 2007;**58**:461-476

[72] Shacklett BL. Can the new humanized mouse model give HIV research a boost? PLoS Medicine. 2008;**5**(1):e13

[73] Miller CJ, Alexander NJ, Sutjipto S, Lackner AA, Gettie A, Hendrickx AG. Genital mucosal transmission of simian immunodeficiency virus: Animal model for heterosexual transmission of human immunodeficiency virus. Journal of Virology. 1989;**63**(10):4277-4284

[74] Gorantla S, Makarov E, Finke-Dwyer J, Gebhart CL, Domm W, Dewhurst S, et al. CD8+ cell depletion accelerates HIV-1 immunopathology in humanized mice. The Journal of Immunology. 2010;**184**(12):7082-7091

[75] Zhang L, Kovalev GI, Su L. HIV-1 infection and pathogenesis in a novel humanized mouse model. Blood. 2007;**109**(7):2978-2981

[76] Joseph A, Zheng JH, Chen K, Dutta M, Chen C, Stiegler G, et al. Inhibition of in vivo HIV infection in humanized mice by gene therapy of human hematopoietic stem cells with a lentiviral vector encoding a broadly neutralizing anti-HIV antibody. Journal of Virology. 2010;**84**(13):6645-6653

[77] Kumar P, Ban HS, Kim SS, Wu H, Pearson T, Greiner DL, et al. T cell-specific siRNA delivery suppresses HIV-1 infection in humanized mice. Cell. 2008;**134**(4):577-586

[78] Scanga CA, Bafica A, Sher A. Viral gene expression in HIV transgenic mice is activated by Mycobacterium tuberculosis and suppressed after antimycobacterial chemotherapy. Journal of Infectious Diseases. 2007;**195**(2):246-254

[79] Haigwood NL. Predictive value of primate models for AIDS. AIDS Reviews. 2004; **6**(4):187-198

[80] Gerdts V, Wilson HL, Meurens F· van Drunen Littel-van den Hurk S, Wilson D, Walker S, et al. Large animal models for vaccine development and testing. ILAR Journal. 2015;**56**(1):53-62

[81] Brown DC, Boston R, Coyne JC, Farrar JT. A novel approach to the use of animals in studies of pain: Validation of the canine brief pain inventory in canine bone cancer. Pain Medicine. 2009;**10**(1):133-142

[82] Tentler JJ, Tan AC, Weekes CD, Jimeno A, Leong S, Pitts TM, Arcaroli JJ, Messersmith WA, Eckhardt SG. Patient-derived tumour xenografts as models for oncology drug developmentNat. Nature Reviews Clinical Oncology. 2012;**9**(6):338-350

[83] Kim HC, Raska K, Clemow L, Eisele J, Matts L, Saidi P. Human immunodeficiency virus infection in sexually active wives of infected hemophilic men. The American Journal of Medicine. 1988;**85**(4):472-476

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