Humanized Mice for Studies of HIV-1 Persistence

Subjects: Infectious Diseases | Transplantation

Contributor: Chen Zhang , Lubaba A. Zaman , Larisa Y. Poluektova , Santhi Gorantla , Howard E. Gendelman , Prasanta K. Dash

A major roadblock to achieving a cure for human immunodeficiency virus type one (HIV-1) is the persistence of latent viral infections in the cells and tissue compartments of an infected human host. Latent HIV-1 proviral DNA persists in resting memory CD4+ T cells and mononuclear phagocytes (MPs; macrophages, microglia, and dendritic cells). Tissue viral reservoirs of both cell types reside in the gut, lymph nodes, bone marrow, spleen, liver, kidney, skin, adipose tissue, reproductive organs, and brain.

HIV-1 latency experimental cell systems animal models humanized mice

1. Introduction

Despite advances in antiretroviral therapy (ART) toward improving the quality and longevity of life for people infected with human immunodeficiency virus (HIV) (PLWH), the medicines must be taken for life. Adherence is fraught with personal, social, behavioral, drug resistance, and pharmacologic limitations [1][2]. While ART can prevent viral transmission and suppress viral transmission [1][3], it is not a cure. The virus persists as a latent infection in multiple cell and tissue compartments. This includes populations of resting memory CD4+ T and myeloid cells [4]. Indeed, immediately after infection, a stable integration of the viral genome into the genomic DNA of the host cell occurs with limited changes in viral gene expression [5]. A reservoir of latent virus is quickly established. This occurs within a few days after viral infection and even before the virus is detectable in systemic circulation [6][7]. Current ART regimens cannot affect latent viral infection, resulting in viral rebound once therapy is discontinued. While early ART administration can lower the number of infected cells via viral suppression and limiting spread, it cannot eliminate the persistent, latent HIV-1 proviral DNA. Studies of HIV latency necessitate a multifaceted approach, integrating the disciplines of virology, immunology, and cell biology. Studies of HIV latency are of immediate importance as viral elimination cannot be achieved without a thorough understanding of the mechanisms of viral persistence.

2. Pitfalls for Studies of Latent HIV Infection

Studies on HIV-1 latency are hindered by the difficulty of performing in vivo studies as the cells that carry proviral DNA are low in abundance. The resting CD4+ T cell reservoir with integrated provirus accounts for less than 0.05% of the entire resting cell population. This suggests that productively infected cells have higher rates of turnover.

This may be partly due to apoptotic and pyroptic death caused by direct viral cytopathicity. Alternatively, host cytotoxic T-lymphocytes (CTLs) eliminate productively infected cells. Hence, most of the cells containing integrated provirus rarely persist to switch into a memory state [8]. It is also difficult to distinguish latently infected from uninfected cells without activation [9]. There is a lack of definitive biomarkers that differentiate latently infected from uninfected resting CD4+ T cells.

3. Model Systems for Studies of HIV Reservoirs

3.1. Cell-Based Model Systems

The selection of an appropriate model system is necessary when studying HIV latency and reactivation. Given the human host specificity of HIV-1, there are few animal models that can replicate long-term HIV infection and latency [10]. Consequently, in vitro models with primary and transformed cell lines are used to address the multifaceted challenges of virus–cell interactions. The HIV latencies observed in patients are affected by cell–tissue locations and environment and remain poorly understood [10]. Primary CD4+ T and myeloid cells recovered from peripheral blood mononuclear cells or lymphoid tissues [11][12] are the most commonly studied cell types when addressing latency [13]. A primary CD4+ T cell model was developed from PLWH memory CD4+ T cells that was subjected to two rounds of activation. Despite having similar reactivation patterns to latency-reversing agents (LRAs), CD4+ T cells can only survive for up to eight weeks [14]. Several groups have also attempted to mimic infection in activated CD4+ T cells by collecting and isolating CD4+ T cells from people without HIV (PWoH) and activating the cells [15] [16]. The first reported model isolated CD4+ T cells from PWoH with combinations of a CD3 antibody and interleukin-2 (IL-2). The cells were then infected with replication-competent virus, and the infection progressed to quiescence (latency) [15]. Another study employed similar methods for the activation of CD4+ T cells, followed by their infection with HIV-1NL4-3 and HIV-1 NLENG1-IRES [16]. The system allowed the latent infection to be studied for up to two months. These approaches have also been used to investigate HIV vectors lacking multiple HIV genes—tat, env, gag, and vif—that are needed to infect activated cells [17][18]. An ex vivo primary cell system can mimic in vivo latency. Cells were transduced using a B cell lymphoma gene (*Bcl2)* to increase their lifespan [19]. Other studies demonstrated that ex vivo CD4+ T cells obtained from PLWH could be reactivated by various classes of LRAs; however, CD4+ T cells infected in vitro could be activated by protein kinase C (PKC) agonists [12]. HIV-1-specific CD8+ T cells fail to eliminate CD4+ T cells; however, they are able to eliminate CD4+ T cells infected with outgrown virus from the same individual [20]. Cell procurement from PLWH poses challenges [21] as the longevity of primary cells in culture is limited [19] and another hurdle is the necessity if manipulation of these replicate cells using transfection or electroporation to introduce the exogenous genes, proteins, or HIV-specific therapeutic agents into them. Primary cells can contain non-replication-competent viruses and have different integration sites [22] that could affect active viral transcription and large numbers of biological replicates are required to perform mechanistic studies and to reach statistical significance [10].

To generate meaningful data sets, researchers have employed immortalized cell lines that include CD4+ T cells (Jurkat, CEM, MOLT4, THP1, and SupT1) and the promonocytic U1 cell lines to study viral latency [23][24]. The advantage of using in vitro model systems is that large numbers of infected cells are used to evaluate gene

expression and cell phenotype. Notably, the levels of involvement of transcription machinery in studying latency, specifically positive-transcription-elongation-factor-b-mediated pathways, are significantly elevated in the tested cell lines when compared to the primary resting CD4+ T cells and macrophages. Components of cellular transcription machinery are unique between cells, which can result in different experimental results when studies are performed to evaluate multiple stages of HIV transcription [25][26]. Also, resting primary CD4+ T cells carry latent HIV-1 in the G0 stage of the cell cycle [27][28][29]. Taking this into consideration, a major drawback of using transformed cell lines to study viral latency is that they may not accurately reflect what occurs in CD4+ T cells that carry latent HIV-1 in vivo.

Yet another complexity in assessing the latent viral reservoir are the inherent differences between CD4+ T and myeloid cells in their carrying capacities and transcriptional machineries that support infections. Both cell types are known reservoirs of HIV. Indeed, tissue macrophages and microglia, along with circulating monocytes, can play roles in bearing latent HIV. These cells can have longer lifespans and resist virus-induced cytopathology [30] and are resistant to CTL cell elimination [31]. Additionally, myeloid cell reservoirs in the brain and lymphoid organs may show differential responses to antiretroviral drugs [32][33]. The previous notion that macrophages lack the capacity for self-renewal has been challenged by recent findings that demonstrate a more prominent role of macrophages as HIV reservoirs [34][35][36]. Additionally, the lack of immune-mediated viral clearance of infected macrophages may make the replication-competent carriage of latent virus and ultimate viral rebound in these cells more likely during therapy interruption [35][36][37]. Additional studies on viral activation in tissue macrophages that include the broader use of newly minted viral outgrowth assays are needed [38]. This need is supported by recent studies that show monocyte-derived macrophages (MDMs) as sources of rebound virus [39][40][41]. Future studies must account for the tissue and cellular environments. This can affect, for example, macrophage polarization and ultimately, HIV reactivation [38]. Moreover, LRAs known to be effective in reversing HIV latency in CD4+ T cells have different effects in macrophages. These factors all require further attention.

Astrocytes, which represent some of the most abundant cell types in the brain, can harbor HIV [42][43]. The cells are involved in the secretion cellular and viral neurotoxic factors, including Tat [44]. They may affect the clinical signs and symptoms of HIV-associated neurocognitive disorders (HANDs) [45][46][47][48]. Despite prior studies demonstrating HIV infection in astrocytes [49][50][51], their role as viral reservoirs remains incompletely defined [52][53][54][55][56]. The presence of HIV-1p24 in astrocytes remains uncertain beyond 60 days after exposure to the virus [57][58]. Studies of HIV-1 infection in astrocytes were performed in cells with differential outcomes following viral exposures [59][60], or in cells isolated and differentiated from human fetal tissues [61]. The findings have not reliably allowed such virus-exposed cells to be used as accurate platforms for studies of HIV-1 latency. Newer approaches to studying viral latency in astrocytic cells have become available through HNSC-100, a human neural stem cell line. These cells may mimic the non-dividing nature of mature astrocytes in the adult human brain and are being used to analyze LRAs and inhibitors of latency reactivators [62]. However, suitable cell models remain in demand for studying HIV latency in CNS tissue compartments.

3.2. Nonhuman Primates (NHPs)

Over the last two decades, SIV/SHIV-infected NHP models of HIV-1 have been instrumental in studies of viral latency and cure research. This is based on the similarity at the cellular and molecular levels of the infection life cycle, disease progression, and immune responses observed [63][64][65][66]. In addition, when using NHPs, researchers can employ analytical treatment interruption to address questions relevant to HIV latency, persistent viral reservoirs, and cures which are risky and unethical to conduct in PLWH [67][68][69][70].

NHP models have allowed for the evaluation of novel therapeutic strategies that include immune regulators and boosters [71][72][73][74], LRAs [70][75][76], broad neutralizing antibodies (bnAbs) [67][68][77][78], HIV-specific chimeric antigen receptor T cell (CAR T) therapy [69][79][79][80], and CRISPR-based gene editing [81]. Prior studies tested antiviral efficacy against SIV/SHIV infection by measuring viral load, host antiretroviral immunity, and disease protection. However, few studies achieved control of SIV/SHIV latency [67][77][81][82]. Prior works have, nonetheless, demonstrated undetectable plasma SHIV after the administration of the bnAb PGT121. Here, a significant reduction in proviral DNA was demonstrated in the peripheral blood, gastrointestinal mucosa, and lymph nodes within weeks of treatment [82]. A delay in viral rebound after the antibody infusion was observed. Although the bnAb was not able to eliminate the virus from latent reservoir sites, it was able to reduce the reservoir size [82]. Similarly, in SHIV-infected macaques treated with five bnAbs, strong viral suppression was observed with a delay in viral rebound in less than five weeks compared with viral rebound seven days after single-bnAb infusions. The data indicate that combinations of bnAbs showed clearer advantages over single-bnAb therapy [77]. Regarding viral elimination studies in macaques, thus far, a single study reported a functional cure in a subset of macaques receiving a combination of a TLR agonist and antibody therapy [67]. Five out of eleven macaques in a dual-treated group had no viral rebound at 200 days after ART discontinuation, while the virus rebounded in most (10/11 and 9/11) macaques belonging to the single-treatment groups. AAV-mediated CRISPR-Cas9 targeting SIV LTR-Gag with daily ART in macaques was used to excise the latent provirus [81]. The authors reported an excision of SIV proviral DNA from the circulatory lymphocytes, spleen, lung, and lymph nodes of the treated animals at 6.5 months post infection, with differential efficiency among the animals. Interestingly, a substantial reduction (38–95%) in viral DNA was detected in the lymph nodes of all treated animals, suggesting the potential efficacy of CRISPR-mediated treatments.

Though NHP models have contributed to the characterization of latent reservoirs and the discovery/evaluation of novel therapeutic strategies, the dissimilarities in the structural and virological signatures of SIV and HIV-1 are major limitations to using SIV-infected macaque models in a translational approach [64][83]. For this reason, SIV-infected NHPs are presumed to respond differently to antiretroviral agents such as different classes of ART regimens, LRAs, and HIV-1-envelope-specific bnAbs. Though chimeric SHIV overcomes this barrier with the insertion of the HIV-1 envelope gene [84][85], several researchers have argued that the SHIV lacks naturally occurring broad viral diversity [86] and is thus less reflective of natural reservoir establishment in which a versatile founder virus is engaged. In fact, recent work revealed the existence of altered, persistent viral reservoirs between SIV, SHIV, and HIV1/2 infections following ART-mediated viral suppression. These results highlight the mechanistic complexity of strain-specific viral treatment responses [87].

In addition, the higher cost of animal maintenance, longer study period, and high laboratory and personnel requirements compared to rodent models are other practical limitations for latency and cure studies using NHP models. In summary, NHP viral latency studies have uncovered novel therapeutic pathways for viral suppression. However, there remains an immediate need for alternatives. These include small animal model systems that can accurately mimic natural HIV infection and disease progression while providing insights into established viral reservoirs. Such models can be employed to facilitate targeted therapeutic studies designed to improve viral suppression and elimination.

4. Rodent Animal Models

Rodents are the preferred small animal model systems for use in infectious disease research [88][89] because they mirror the human system in many ways and have well-characterized immune systems. However, due to the human host specificity of the HIV virus, it is very difficult to find an ideal mouse model for studying HIV latent reservoirs and the cure strategies targeting them. One earlier model, the EcoHIV infection model, in which parts of HIV-1 gp120 were replaced with gp80 from the ecotropic murine leukemia virus, allowed for permissive HIV infection in conventional mice [90]. Recent studies by different research groups have shown neurocognitive impairment in an EcoHIV model without any significant CD4+ cell depletion [91]. This model is also being used by researchers to investigate the roles of infected macrophages and monocytes to understand how the persistence of HIV affects cognitive function despite ART, using molecular and behavior tests [92]. However, the lack of a proper HIV disease progression pattern is a major limitation of this model for latency and cure studies. In addition, the considerable differences between murine and human immune systems in terms of immune cell profiles, innate and adaptive immune responses, and the production of HIV-1-associated antiviral cytokines make this model less ideal for studying long-term HIV latency and assessing therapeutic efficacy [93]. Thus, humanized mice that can recapitulate a functional human immune system and mimic a natural HIV infection process remain preferred for HIV persistence studies [94].

Currently, several humanized mouse models are being used by researchers for HIV-related studies and are mostly developed from severe immunodeficient backgrounds in which the mice are engrafted with human immune cells or tissues. The journey of the development and generation of humanized mice began with the discovery of an autosomal recessive mutation in a DNA-dependent protein kinase, Prkdc*scid* (severe combined immunodeficiency, SCID), on the CB17 mouse strain background [95]. SCID mice have severely impaired lymphopoiesis and differentiation; thus, they lack their own functional T and B lymphocytes [95]. In 1988, McCune et al reported the co-transplantation of human fetal liver hematopoietic cells (fetal thymus and lymph nodes) into SCID mice for the first time. Though this pioneering study showed reconstituted mature human T and B cells in mouse peripheral circulation 6–7 weeks post transplantation [96], the human T cell population and human IgG were found to be transiently present because of graft-versus-host disease (GVHD), and the model lacked a sustained hematopoietic supportive environment [96][97]. Shortly thereafter, Namikawa et al. found that the co-transplantation of human fetal thymus and intact fetal liver fragments into SCID mice could support human hematopoiesis for up to 11 months, marking their model as the first humanized mouse model for HIV studies [98].

In addition to SCID, further mutations targeting the common cytokine receptor gamma chain (*yc* or CD132) resulted in the generation of more immunodeficient mice strains: the NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Wjl} (NSG), NODShi.Cg*Prkdc*^{scid} *Il2rg*^{tm1Sug} (NOG), and BALB/c-*Rag2*^{null} *IL2rg*^{null} mice (BRG) strains [99][100][101][102], which took humanized mouse research progress one step forward. Since the common cytokine receptor gamma chain is shared by a family of cytokines, including IL-2, 4, 7, 9, 15, and 21, and is crucial for the development and survival of NK cells and lymphocytes, the knockout or truncated version of *yc* further reduced the risks of GVHD generation and enhanced the survival of the human cell engraftment in mice [103]. More advances have been made recently by knocking-in cytokine-encoding genes, for example, M-CSFh/h IL-3/GM-CSFh/h SIRPah/h TPOh/h RAG2−/− IL2Rg−/−, which led to support for the establishment of human cells in (MISTRG) mice [104]. Another mouse model with chimeric human–mouse class II transgenes, the NOD.Cg-*Rag1tm1Mom Il2rgtm1Wjl* Tg (DRAG) mouse, allowed for the engraftment of enhanced HLA-DR-matched hematopoietic stem cells (HSCs), which subsequently supported better human T and B cell development [105]. These most recent advances made in humanized mouse models further boost the planning and execution of infectious disease studies.

In spite of the advantages of rodent models, a few limitations do exist, including the shorter lifespan of human cell persistence in vivo, which limits long-term efficacy studies. Most of the humanized mouse models used for HIV latency and cure studies are developed on either well-characterized NSG, NOG-SCID, or BRG genetic backgrounds [106][107][108][109][110]. Depending on the different humanization methods, the three main mouse models are deployed to assess either short-term or long-term HIV persistence, virus–host interactions, and therapeutic developmental investigations that serve to best target the viral reservoirs (**Figure 1**).

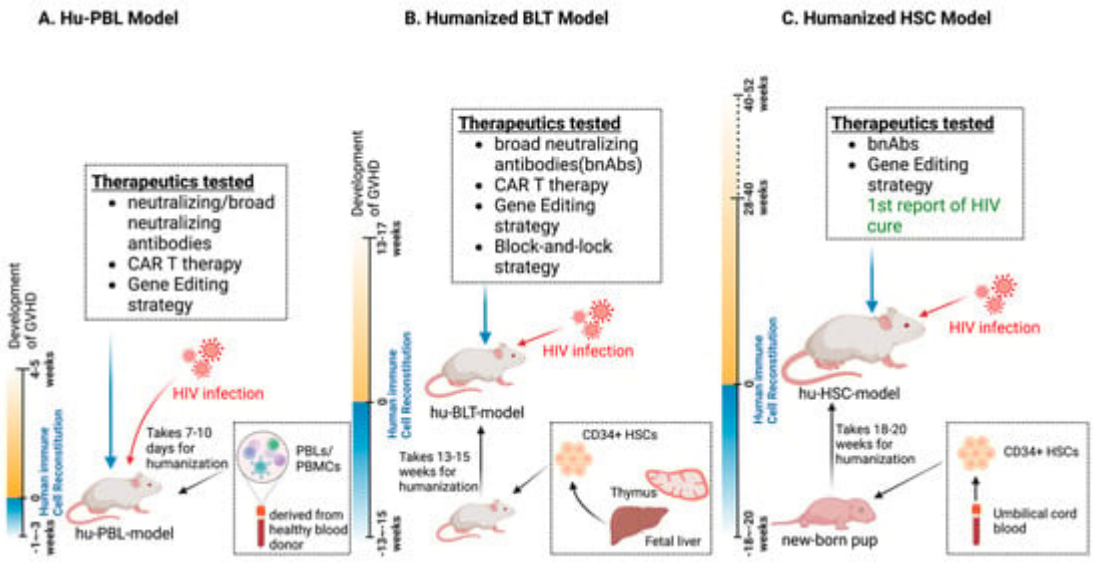


Figure 1. Humanized mouse models for preclinical HIV therapeutics. (**A**) The hu-PBL model employs peripheral blood mononuclear cells (PBMC/PBLs) from human donors that are injected into immunocompromised mice. This model typically reaches functional maturity within 1–2 weeks but is highly susceptible to graft-versus-host disease (GVHD) within 4–5 weeks of cell implantation. The hu-PBL model is commonly used for drug discovery and quick screening of antiretroviral drug combinations as well as novel antiretroviral therapies. (**B**) The hu-BLT model involves the transplantation of human HSCs and fetal liver and thymus tissues into immunocompromised mice to

generate a more complete human immune system. This model requires 13–15 weeks for human immune cells to reach full functional maturity, and it has been extensively used as a chronic HIV infection model for HIV latency and cure studies, enabling therapy testing for more than 10 weeks. (**C**) The hu-HSC model utilizes umbilical-cord-blood-isolated CD34+ hematopoietic stem cells (HSCs) that are transplanted into newborn pups to generate functional human immune systems. It necessitates 18–20 weeks for full maturation and allows for long-term testing of HIV reservoir establishment and therapeutic targeting studies for up to one year. The first report of an HIV cure in a humanized mouse model used sequential long-acting ART and CRISPR-based gene editing treatments. This model has better clinical translational potential than the other models.

5. Perspectives

Given the successful application of hu-HSC mice in long-term HIV studies due to the presence of a functional human immune system that can last up to one year (recent observations), this model is considered by far the closest small animal translational model system for HIV latency and cure studies. However, limitations do exist. First, the human T cells are produced and educated in the mouse thymus, which is of some concern for their development status [101][111]. A recent study, however, revealed that human T cells were preferentially developed in NRG-hu-BLT mice with more predominant and well-educated T cell populations than NRG-hu-HSC mice [112]. The same study also suggested that there are no significant differences in responses between hu-BLT and hu-HSC mice when used to study HIV-1 replication, pathogenesis, and therapeutics [112]. The primary advantages of hu-BLT mice over hu-HSC mice are in studies involving human HLA class I and class II restricted T cell responses. The second limitation is the underdeveloped lymph nodes and lower level of human cell reconstitution in the gut and mucosal tissues of the hu-HSC mouse. However, no significant differences were observed in HIV long-term studies compared to other animal model systems. Third, hu-HSC mice harbor fewer cells of human origin (microglia, macrophages, and astrocytes) responsible for carrying latent virus in CNS compartments [113][114]. Encouraging recent studies have described the development and successful use of another hu-HSC model with human microglia [115]. Human interleukin-34, a key macrophage–microglial differentiation factor, was introduced into the NOG strain, which led to the successful reconstitution of human microglia-like cells in the mouse brain, thus allowing for the study of principal CNS viral reservoirs. Additionally, this model was able to recapitulate neuroHIV. This was evidenced via transcriptomic analyses of antiviral, inflammatory, and human-specific molecular signatures, which offer insights into viral persistence in the brain.

CD34 mouse models are used in a variety of platforms and are employed as mainstream small animal models to study HIV pathobiology, drug safety and efficacy, latency, and reservoir targeting and in studies that can modulate the immune system. The optimization of preclinical small animal models is the key to testing the up-to-date clinical advances in HIV therapeutic developments, which can ensure the improved translation of various preclinical results into interventions and can ultimately benefit patients. In summary the hu-HSC background represents an ideal long-term model for studying HIV-1 latency and cure, with diverse cell types reconstituted in immunologically active compartments and well-defined human cells that can last for more than six months to one year, as described in **Figure 2**. Its advantages include the simplicity of the mouse generation procedure, abundant sources of CD34+

HSCs from umbilical cord blood, and the greatly reduced incidence of GVHD (less than 5%), making it the leading mouse model for studying and validating HIV cure strategies prior to assessments in NHP models or clinical translation.

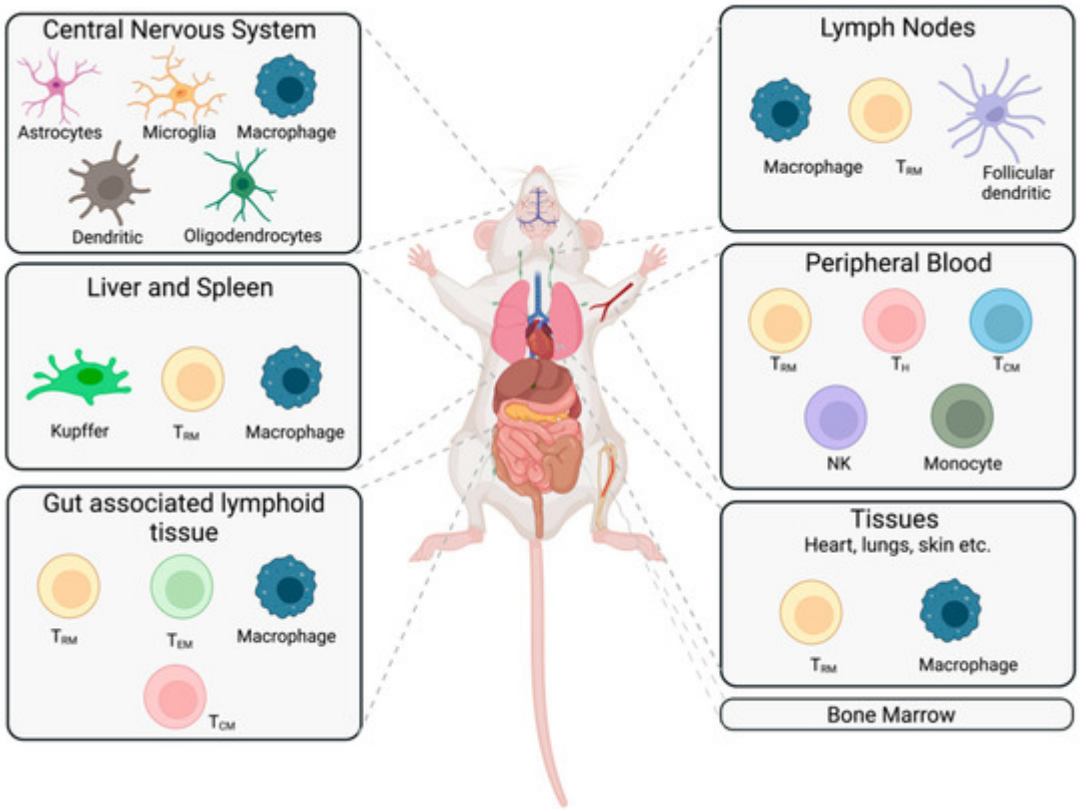


Figure 2. HIV reservoir target cells in a suitable small animal model system to study HIV latency. Cells demonstrated to harbor latent HIV in different tissues are shown. Researchers propose an ideal humanized rodent model system that depicts HIV reservoirs spread across various tissue types around the body. The majority of latent virus is found in CD4+ resting memory T cells (T_{RM}), along with other CD4+ T cell subsets (T_{EM}, T_{CM}, and T_H). MP reservoirs are in a range of tissue compartments. In addition to having a peripheral functional human immune system, the ideal humanized model system should have abundant cells of human origin which include T cells, B cells, dendritic cells, monocytes, and macrophages that can be maintained for a year for long-term HIV latency studies and subsequent targeting of those reservoirs for ultimate HIV elimination and for clinical translation. T_{EM} = T effector memory; T_{CM} = T central memory; T_H = T helper; NK = natural killer.

References

1. Chun, T.-W.; Davey, R.T., Jr.; Engel, D.; Lane, H.C.; Fauci, A.S. Re-emergence of HIV after stopping therapy. Nature 1999, 401, 874–875.
2. Davey, R.T.; Bhat, N.; Yoder, C.; Chun, T.-W.; Metcalf, J.A.; Dewar, R.; Natarajan, V.; Lempicki, R.A.; Adelsberger, J.W.; Miller, K.D.; et al. HIV-1 and T cell dynamics after interruption of highly

active antiretroviral therapy (HAART) in patients with a history of sustained viral suppression. Proc. Natl. Acad. Sci. USA 1999, 96, 15109–15114.

3. Finzi, D.; Blankson, J.; Siliciano, J.D.; Margolick, J.B.; Chadwick, K.; Pierson, T.; Smith, K.; Lisziewicz, J.; Lori, F.; Flexner, C.; et al. Latent infection of CD4+ T cells provides a mechanism for lifelong persistence of HIV-1, even in patients on effective combination therapy. Nat. Med. 1999, 5, 512–517.
4. Chun, T.-W.; Finzi, D.; Margolick, J.; Chadwick, K.; Schwartz, D.; Siliciano, R.F. In vivo fate of HIV-1-infected T cells: Quantitative analysis of the transition to stable latency. Nat. Med. 1995, 1, 1284–1290.
5. Siliciano, J.M.; Siliciano, R.F. The Remarkable Stability of the Latent Reservoir for HIV-1 in Resting Memory CD4+ T Cells. J. Infect. Dis. 2015, 212, 1345–1347. (accessed on 19 January 2023).
6. Cohen, M.S.; Shaw, G.M.; McMichael, A.J.; Haynes, B.F. Acute HIV-1 Infection. N. Engl. J. Med. 2011, 364, 1943–1954.
7. Vanhamel, J.; Bruggemans, A.; Debyser, Z. Establishment of latent HIV-1 reservoirs: What do we really know? J. Virus Erad. 2019, 5, 3–9.
8. Chun, T.-W.; Carruth, L.; Finzi, D.; Shen, X.; DiGiuseppe, J.A.; Taylor, H.; Hermankova, M.; Chadwick, K.; Margolick, J.; Quinn, T.C.; et al. Quantification of latent tissue reservoirs and total body viral load in HIV-1 infection. Nature 1997, 387, 183–188.
9. Brooks, D.G.; Zack, J.A. Effect of latent human immunodeficiency virus infection on cell surface phenotype. J. Virol. 2002, 76, 1673–1681.
10. Fujinaga, K.; Cary, D.C. Experimental Systems for Measuring HIV Latency and Reactivation. Viruses 2020, 12, 1279.
11. Doitsh, G.; Cavrois, M.; Lassen, K.G.; Zepeda, O.; Yang, Z.; Santiago, M.L.; Hebbeler, A.M.; Greene, W.C. Abortive HIV infection mediates CD4 T cell depletion and inflammation in human lymphoid tissue. Cell 2010, 143, 789–801.
12. Spina, C.A.; Anderson, J.; Archin, N.M.; Bosque, A.; Chan, J.; Famiglietti, M.; Greene, W.C.; Kashuba, A.; Lewin, S.R.; Margolis, D.M. An in-depth comparison of latent HIV-1 reactivation in multiple cell model systems and resting CD4+ T cells from aviremic patients. PLoS Pathog. 2013, 9, e1003834.
13. Archin, N.M.; Eron, J.J.; Palmer, S.; Hartmann-Duff, A.; Martinson, J.A.; Wiegand, A.; Bandarenko, N.; Schmitz, J.L.; Bosch, R.J.; Landay, A.L. Valproic acid without intensified antiviral therapy has limited impact on persistent HIV infection of resting CD4+ T cells. AIDS 2008, 22, 1131–1135.

14. Takata, H.; Kessing, C.; Sy, A.; Lima, N.; Sciumbata, J.; Mori, L.; Jones, R.B.; Chomont, N.; Michael, N.L.; Valente, S.; et al. Modeling HIV-1 Latency Using Primary CD4+ T Cells from Virally Suppressed HIV-1-Infected Individuals on Antiretroviral Therapy. J. Virol. 2019, 93, e02248-18.
15. Sahu, G.K.; Lee, K.; Ji, J.; Braciale, V.; Baron, S.; Cloyd, M.W. A novel in vitro system to generate and study latently HIV-infected long-lived normal CD4+ T-lymphocytes. Virology 2006, 355, 127–137.
16. Martins, L.J.; Bonczkowski, P.; Spivak, A.M.; De Spiegelaere, W.; Novis, C.L.; DePaula-Silva, A.B.; Malatinkova, E.; Trypsteen, W.; Bosque, A.; Vanderkerckhove, L.; et al. Modeling HIV-1 Latency in Primary T Cells Using a Replication-Competent Virus. AIDS Res. Hum. Retrovir. 2016, 32, 187–193.
17. Yang, H.-C.; Xing, S.; Shan, L.; O'Connell, K.; Dinoso, J.; Shen, A.; Zhou, Y.; Shrum, C.K.; Han, Y.; Liu, J.O. Small-molecule screening using a human primary cell model of HIV latency identifies compounds that reverse latency without cellular activation. J. Clin. Investig. 2009, 119, 3473–3486.
18. Tyagi, M.; Pearson, R.J.; Karn, J. Establishment of HIV latency in primary CD4+ cells is due to epigenetic transcriptional silencing and P-TEFb restriction. J. Virol. 2010, 84, 6425–6437.
19. Kim, M.; Hosmane, N.N.; Bullen, C.K.; Capoferri, A.; Yang, H.-C.; Siliciano, J.D.; Siliciano, R.F. A primary CD4+ T cell model of HIV-1 latency established after activation through the T cell receptor and subsequent return to quiescence. Nat. Protoc. 2014, 9, 2755–2770.
20. Huang, S.-H.; Ren, Y.; Thomas, A.S.; Chan, D.; Mueller, S.; Ward, A.R.; Patel, S.; Bollard, C.M.; Cruz, C.R.; Karandish, S. Latent HIV reservoirs exhibit inherent resistance to elimination by CD8+ T cells. J. Clin. Investig. 2018, 128, 876–889.
21. Khan, S.; Telwatte, S.; Trapecar, M.; Yukl, S.; Sanjabi, S. Differentiating immune cell targets in gut-associated lymphoid tissue for HIV cure. AIDS Res. Hum. Retrovir. 2017, 33, S-40–S-58.
22. Han, Y.; Wind-Rotolo, M.; Yang, H.-C.; Siliciano, J.D.; Siliciano, R.F. Experimental approaches to the study of HIV-1 latency. Nat. Rev. Microbiol. 2007, 5, 95–106.
23. Hakre, S.; Chavez, L.; Shirakawa, K.; Verdin, E. HIV latency: Experimental systems and molecular models. FEMS Microbiol. Rev. 2012, 36, 706–716.
24. Herold, N.; Anders-Össwei, M.; Glass, B.; Eckhardt, M.; Müller, B.; Kräusslich, H.G. HIV-1 entry in SupT1-R5, CEM-ss, and primary CD4+ T cells occurs at the plasma membrane and does not require endocytosis. J. Virol. 2014, 88, 13956–13970.
25. Cary, D.C.; Fujinaga, K.; Peterlin, B.M. Molecular mechanisms of HIV latency. J. Clin. Investig. 2016, 126, 448–454.

26. Rice, A.P. Roles of CDKs in RNA polymerase II transcription of the HIV-1 genome. Transcription 2019, 10, 111–117.
27. Han, Y.; Lassen, K.; Monie, D.; Sedaghat, A.R.; Shimoji, S.; Liu, X.; Pierson, T.C.; Margolick, J.B.; Siliciano, R.F.; Siliciano, J.D. Resting CD4+ T cells from human immunodeficiency virus type 1 (HIV-1)-infected individuals carry integrated HIV-1 genomes within actively transcribed host genes. J. Virol. 2004, 78, 6122–6133.
28. Liu, H.; Dow, E.C.; Arora, R.; Kimata, J.T.; Bull, L.M.; Arduino, R.C.; Rice, A.P. Integration of human immunodeficiency virus type 1 in untreated infection occurs preferentially within genes. J. Virol. 2006, 80, 7765–7768.
29. MacNeil, A.; Sankalé, J.-L.; Meloni, S.T.; Sarr, A.D.; Mboup, S.; Kanki, P. Genomic sites of human immunodeficiency virus type 2 (HIV-2) integration: Similarities to HIV-1 in vitro and possible differences in vivo. J. Virol. 2006, 80, 7316–7321.
30. Le Douce, V.; Herbein, G.; Rohr, O.; Schwartz, C. Molecular mechanisms of HIV-1 persistence in the monocyte-macrophage lineage. Retrovirology 2010, 7, 32.
31. Clayton, K.L.; Collins, D.R.; Lengieza, J.; Ghebremichael, M.; Dotiwala, F.; Lieberman, J.; Walker, B.D. Resistance of HIV-infected macrophages to CD8+ T lymphocyte–mediated killing drives activation of the immune system. Nat. Immunol. 2018, 19, 475–486.
32. Solas, C.; Lafeuillade, A.; Halfon, P.; Chadapaud, S.; Hittinger, G.; Lacarelle, B. Discrepancies between protease inhibitor concentrations and viral load in reservoirs and sanctuary sites in human immunodeficiency virus-infected patients. Antimicrob. Agents Chemother. 2003, 47, 238–243.
33. Cory, T.J.; Schacker, T.W.; Stevenson, M.; Fletcher, C.V. Overcoming pharmacologic sanctuaries. Curr. Opin. HIV AIDS 2013, 8, 190.
34. Llewellyn, N.; Zioni, R.; Zhu, H.; Andrus, T.; Xu, Y.; Corey, L.; Zhu, T. Continued evolution of HIV-1 circulating in blood monocytes with antiretroviral therapy: Genetic analysis of HIV-1 in monocytes and CD4+ T cells of patients with discontinued therapy. J. Leukoc. Biol. 2006, 80, 1118–1126.
35. Zalar, A.; Figueroa, M.I.; Ruibal-Ares, B.; Baré, P.; Cahn, P.; de Bracco, M.M.d.E.; Belmonte, L. Macrophage HIV-1 infection in duodenal tissue of patients on long term HAART. Antivir. Res. 2010, 87, 269–271.
36. Harrold, S.M.; Wang, G.; McMahon, D.K.; Riddler, S.A.; Mellors, J.W.; Becker, J.T.; Caldararo, R.; Reinhart, T.A.; Achim, C.L.; Wiley, C.A. Recovery of replication-competent HIV type 1-infected circulating monocytes from individuals receiving antiretroviral therapy. AIDS Res. Hum. Retrovir. 2002, 18, 427–434.
37. Wong, M.E.; Jaworowski, A.; Hearps, A.C. The HIV Reservoir in Monocytes and Macrophages. Front. Immunol. 2019, 10, 1435.

38. Wong, M.E.; Johnson, C.J.; Hearps, A.C.; Jaworowski, A. Development of a Novel In Vitro Primary Human Monocyte-Derived Macrophage Model to Study Reactivation of HIV-1 Transcription. J. Virol. 2021, 95, e0022721.
39. Graziano, F.; Aimola, G.; Forlani, G.; Turrini, F.; Accolla, R.S.; Vicenzi, E.; Poli, G. Reversible Human Immunodeficiency Virus Type-1 Latency in Primary Human Monocyte-Derived Macrophages Induced by Sustained M1 Polarization. Sci. Rep. 2018, 8, 14249.
40. Araínga, M.; Edagwa, B.; Mosley, R.L.; Poluektova, L.Y.; Gorantla, S.; Gendelman, H.E. A mature macrophage is a principal HIV-1 cellular reservoir in humanized mice after treatment with long acting antiretroviral therapy. Retrovirology 2017, 14, 17.
41. Campbell, G.R.; Bruckman, R.S.; Chu, Y.-L.; Spector, S.A. Autophagy induction by histone deacetylase inhibitors inhibits HIV type 1. J. Biol. Chem. 2015, 290, 5028–5040.
42. Churchill, M.J.; Gorry, P.R.; Cowley, D.; Lal, L.; Sonza, S.; Purcell, D.F.; Thompson, K.A.; Gabuzda, D.; McArthur, J.C.; Pardo, C.A. Use of laser capture microdissection to detect integrated HIV-1 DNA in macrophages and astrocytes from autopsy brain tissues. J. Neurovirol. 2006, 12, 146–152.
43. Takahashi, K.; Wesselingh, S.L.; Griffin, D.E.; McArthur, J.C.; Johnson, R.T.; Glass, J.D. Localization of HIV-1 in human brain using polymerase chain reaction/in situ hybridization and immunocytochemistry. Ann. Neurol. 1996, 39, 705–711.
44. Chauhan, A.; Turchan, J.; Pocernich, C.; Bruce-Keller, A.; Roth, S.; Butterfield, D.A.; Major, E.O.; Nath, A. Intracellular Human Immunodeficiency Virus Tat Expression in Astrocytes Promotes Astrocyte Survival but Induces Potent Neurotoxicity at Distant Sites via Axonal Transport*. J. Biol. Chem. 2003, 278, 13512–13519.
45. Chivero, E.T.; Guo, M.-L.; Periyasamy, P.; Liao, K.; Callen, S.E.; Buch, S. HIV-1 Tat primes and activates microglial NLRP3 inflammasome-mediated neuroinflammation. J. Neurosci. 2017, 37, 3599–3609.
46. Nookala, A.R.; Kumar, A. Molecular mechanisms involved in HIV-1 Tat-mediated induction of IL-6 and IL-8 in astrocytes. J. Neuroinflamm. 2014, 11, 214.
47. Kutsch, O.; Oh, J.-W.; Nath, A.; Benveniste, E. Induction of the chemokines interleukin-8 and IP-10 by human immunodeficiency virus type 1 tat in astrocytes. J. Virol. 2000, 74, 9214–9221.
48. El-Hage, N.; Gurwell, J.A.; Singh, I.N.; Knapp, P.E.; Nath, A.; Hauser, K.F. Synergistic increases in intracellular Ca2+, and the release of MCP-1, RANTES, and IL-6 by astrocytes treated with opiates and HIV-1 Tat. Glia 2005, 50, 91–106.
49. Thompson, K.A.; Churchill, M.J.; Gorry, P.R.; Sterjovski, J.; Oelrichs, R.B.; Wesselingh, S.L.; McLean, C.A. Astrocyte specific viral strains in HIV dementia. Ann. Neurol. Off. J. Am. Neurol. Assoc. Child Neurol. Soc. 2004, 56, 873–877.

50. Gyorkey, F.; Melnick, J.L.; Gyorkey, P. Human immunodeficiency virus in brain biopsies of patients with AIDS and progressive encephalopathy. J. Infect. Dis. 1987, 155, 870–876.
51. Saito, Y.; Sharer, L.; Epstein, L.; Michaels, J.; Mintz, M.; Louder, M.; Golding, K.; Cvetkovich, T.; Blumberg, B. Overexpression of nef as a marker for restricted HIV-1 infection of astrocytes in postmortem pediatric central nervous tissues. Neurology 1994, 44, 474.
52. Ko, A.; Kang, G.; Hattler, J.B.; Galadima, H.I.; Zhang, J.; Li, Q.; Kim, W.-K. Macrophages but not Astrocytes Harbor HIV DNA in the Brains of HIV-1-Infected Aviremic Individuals on Suppressive Antiretroviral Therapy. J. Neuroimmune Pharmacol. 2019, 14, 110–119.
53. Tso, F.Y.; Kang, G.; Kwon, E.H.; Julius, P.; Li, Q.; West, J.T.; Wood, C. Brain is a potential sanctuary for subtype C HIV-1 irrespective of ART treatment outcome. PLoS ONE 2018, 13, e0201325.
54. Gorry, P.R.; Ong, C.; Thorpe, J.; Bannwarth, S.; Thompson, K.A.; Gatignol, A.; Wesselingh, S.L.; Purcell, D.F. Astrocyte infection by HIV-1: Mechanisms of restricted virus replication, and role in the pathogenesis of HIV-1-associated dementia. Curr. HIV Res. 2003, 1, 463–473.
55. Lutgen, V.; Narasipura, S.D.; Barbian, H.J.; Richards, M.; Wallace, J.; Razmpour, R.; Buzhdygan, T.; Ramirez, S.H.; Prevedel, L.; Eugenin, E.A.; et al. HIV infects astrocytes in vivo and egresses from the brain to the periphery. PLoS Pathog. 2020, 16, e1008381.
56. Valdebenito, S.; Castellano, P.; Ajasin, D.; Eugenin, E.A. Astrocytes are HIV reservoirs in the brain: A cell type with poor HIV infectivity and replication but efficient cell-to-cell viral transfer. J. Neurochem. 2021, 158, 429–443.
57. Berman, J.W.; Carvallo, L.; Buckner, C.M.; Luers, A.; Prevedel, L.; Bennett, M.V.; Eugenin, E.A. HIV-tat alters Connexin43 expression and trafficking in human astrocytes: Role in NeuroAIDS. J. Neuroinflamm. 2016, 13, 54.
58. Eugenin, E.A.; Berman, J.W. Cytochrome C dysregulation induced by HIV infection of astrocytes results in bystander apoptosis of uninfected astrocytes by an IP3 and calcium-dependent mechanism. J. Neurochem. 2013, 127, 644–651.
59. Seth, P.; Major, E.O. Human brain derived cell culture models of HIV-1 infection. Neurotox. Res. 2005, 8, 83–89.
60. Brack-Werner, R. Astrocytes: HIV cellular reservoirs and important participants in neuropathogenesis. AIDS 1999, 13, 1–22.
61. Major, E.O.; Vacante, D.A. Human fetal astrocytes in culture support the growth of the neurotropic human polyomavirus, JCV. J. Neuropathol. Exp. Neurol. 1989, 48, 425–436.
62. Bauer, A.; Brack-Werner, R. Modeling HIV Latency in Astrocytes with the Human Neural Progenitor Cell Line HNSC.100. In HIV Reservoirs: Methods and Protocols; Poli, G., Vicenzi, E.,

Romerio, F., Eds.; Springer: New York, NY, USA, 2022; pp. 103–114.

63. North, T.W.; Higgins, J.; Deere, J.D.; Hayes, T.L.; Villalobos, A.; Adamson, L.; Shacklett, B.L.; Schinazi, R.F.; Luciw, P.A. Viral sanctuaries during highly active antiretroviral therapy in a nonhuman primate model for AIDS. J. Virol. 2010, 84, 2913–2922.
64. Veazey, R.S.; DeMaria, M.; Chalifoux, L.V.; Shvetz, D.E.; Pauley, D.R.; Knight, H.L.; Rosenzweig, M.; Johnson, R.P.; Desrosiers, R.C.; Lackner, A.A. Gastrointestinal tract as a major site of CD4+ T cell depletion and viral replication in SIV infection. Science 1998, 280, 427–431.
65. Lackner, A.A.; Veazey, R.S. Current concepts in AIDS pathogenesis: Insights from the SIV/macaque model. Annu. Rev. Med. 2007, 58, 461–476.
66. Dinoso, J.B.; Rabi, S.A.; Blankson, J.N.; Gama, L.; Mankowski, J.L.; Siliciano, R.F.; Zink, M.C.; Clements, J.E. A simian immunodeficiency virus-infected macaque model to study viral reservoirs that persist during highly active antiretroviral therapy. J. Virol. 2009, 83, 9247–9257.
67. Borducchi, E.N.; Liu, J.; Nkolola, J.P.; Cadena, A.M.; Yu, W.H.; Fischinger, S.; Broge, T.; Abbink, P.; Mercado, N.B.; Chandrashekar, A.; et al. Antibody and TLR7 agonist delay viral rebound in SHIV-infected monkeys. Nature 2018, 563, 360–364.
68. Wu, Y.; Xue, J.; Wang, C.; Li, W.; Wang, L.; Chen, W.; Prabakaran, P.; Kong, D.; Jin, Y.; Hu, D.; et al. Rapid Elimination of Broadly Neutralizing Antibodies Correlates with Treatment Failure in the Acute Phase of Simian-Human Immunodeficiency Virus Infection. J. Virol. 2019, 93, e01077-19.
69. Barber-Axthelm, I.M.; Barber-Axthelm, V.; Sze, K.Y.; Zhen, A.; Suryawanshi, G.W.; Chen, I.S.; Zack, J.A.; Kitchen, S.G.; Kiem, H.P.; Peterson, C.W. Stem cell-derived CAR T cells traffic to HIV reservoirs in macaques. JCI Insight 2021, 6, e141502.
70. McBrien, J.B.; Mavigner, M.; Franchitti, L.; Smith, S.A.; White, E.; Tharp, G.K.; Walum, H.; Busman-Sahay, K.; Aguilera-Sandoval, C.R.; Thayer, W.O.; et al. Robust and persistent reactivation of SIV and HIV by N-803 and depletion of CD8+ cells. Nature 2020, 578, 154–159.
71. Borducchi, E.N.; Cabral, C.; Stephenson, K.E.; Liu, J.; Abbink, P.; Ng'ang'a, D.; Nkolola, J.P.; Brinkman, A.L.; Peter, L.; Lee, B.C.; et al. Ad26/MVA therapeutic vaccination with TLR7 stimulation in SIV-infected rhesus monkeys. Nature 2016, 540, 284–287.
72. Huot, N.; Jacquelin, B.; Garcia-Tellez, T.; Rascle, P.; Ploquin, M.J.; Madec, Y.; Reeves, R.K.; Derreudre-Bosquet, N.; Müller-Trutwin, M. Natural killer cells migrate into and control simian immunodeficiency virus replication in lymph node follicles in African green monkeys. Nat. Med. 2017, 23, 1277–1286.
73. Lim, S.Y.; Osuna, C.E.; Hraber, P.T.; Hesselgesser, J.; Gerold, J.M.; Barnes, T.L.; Sanisetty, S.; Seaman, M.S.; Lewis, M.G.; Geleziunas, R.; et al. TLR7 agonists induce transient viremia and reduce the viral reservoir in SIV-infected rhesus macaques on antiretroviral therapy. Sci. Transl. Med. 2018, 10, eaao4521.

74. Del Prete, G.Q.; Alvord, W.G.; Li, Y.; Deleage, C.; Nag, M.; Oswald, K.; Thomas, J.A.; Pyle, C.; Bosche, W.J.; Coalter, V.; et al. TLR7 agonist administration to SIV-infected macaques receiving early initiated cART does not induce plasma viremia. JCI Insight 2019, 4, e127717.

75. Gama, L.; Abreu, C.M.; Shirk, E.N.; Price, S.L.; Li, M.; Laird, G.M.; Pate, K.A.; Wietgrefe, S.W.; O'Connor, S.L.; Pianowski, L.; et al. Reactivation of simian immunodeficiency virus reservoirs in the brain of virally suppressed macaques. AIDS 2017, 31, 5–14.

76. Nixon, C.C.; Mavigner, M.; Sampey, G.C.; Brooks, A.D.; Spagnuolo, R.A.; Irlbeck, D.M.; Mattingly, C.; Ho, P.T.; Schoof, N.; Cammon, C.G.; et al. Systemic HIV and SIV latency reversal via non-canonical NF-κB signalling in vivo. Nature 2020, 578, 160–165.

77. Shingai, M.; Nishimura, Y.; Klein, F.; Mouquet, H.; Donau, O.K.; Plishka, R.; Buckler-White, A.; Seaman, M.; Piatak, M., Jr.; Lifson, J.D.; et al. Antibody-mediated immunotherapy of macaques chronically infected with SHIV suppresses viraemia. Nature 2013, 503, 277–280.

78. Julg, B.; Liu, P.T.; Wagh, K.; Fischer, W.M.; Abbink, P.; Mercado, N.B.; Whitney, J.B.; Nkolola, J.P.; McMahan, K.; Tartaglia, L.J.; et al. Protection against a mixed SHIV challenge by a broadly neutralizing antibody cocktail. Sci. Transl. Med. 2017, 9, eaao4235.

79. Zhen, A.; Peterson, C.W.; Carrillo, M.A.; Reddy, S.S.; Youn, C.S.; Lam, B.B.; Chang, N.Y.; Martin, H.A.; Rick, J.W.; Kim, J.; et al. Long-term persistence and function of hematopoietic stem cell-derived chimeric antigen receptor T cells in a nonhuman primate model of HIV/AIDS. PLoS Pathog. 2017, 13, e1006753.

80. Iwamoto, N.; Patel, B.; Song, K.; Mason, R.; Bolivar-Wagers, S.; Bergamaschi, C.; Pavlakis, G.N.; Berger, E.; Roederer, M. Evaluation of chimeric antigen receptor T cell therapy in non-human primates infected with SHIV or SIV. PLoS ONE 2021, 16, e0248973.

81. Mancuso, P.; Chen, C.; Kaminski, R.; Gordon, J.; Liao, S.; Robinson, J.A.; Smith, M.D.; Liu, H.; Sariyer, I.K.; Sariyer, R.; et al. CRISPR based editing of SIV proviral DNA in ART treated non-human primates. Nat. Commun. 2020, 11, 6065.

82. Barouch, D.H.; Whitney, J.B.; Moldt, B.; Klein, F.; Oliveira, T.Y.; Liu, J.; Stephenson, K.E.; Chang, H.W.; Shekhar, K.; Gupta, S.; et al. Therapeutic efficacy of potent neutralizing HIV-1-specific monoclonal antibodies in SHIV-infected rhesus monkeys. Nature 2013, 503, 224–228.

83. Chahroudi, A.; Bosinger, S.E.; Vanderford, T.H.; Paiardini, M.; Silvestri, G. Natural SIV hosts: Showing AIDS the door. Science 2012, 335, 1188–1193.

84. Shibata, R.; Kawamura, M.; Sakai, H.; Hayami, M.; Ishimoto, A.; Adachi, A. Generation of a chimeric human and simian immunodeficiency virus infectious to monkey peripheral blood mononuclear cells. J. Virol. 1991, 65, 3514–3520.

85. Thippeshappa, R.; Ruan, H.; Kimata, J.T. Breaking Barriers to an AIDS Model with Macaque-Tropic HIV-1 Derivatives. Biol. (Basel) 2012, 1, 134–164.

86. Del Prete, G.Q.; Lifson, J.D.; Keele, B.F. Nonhuman primate models for the evaluation of HIV-1 preventive vaccine strategies: Model parameter considerations and consequences. Curr. Opin. HIV AIDS 2016, 11, 546–554.
87. Bender, A.M.; Simonetti, F.R.; Kumar, M.R.; Fray, E.J.; Bruner, K.M.; Timmons, A.E.; Tai, K.Y.; Jenike, K.M.; Antar, A.A.R.; Liu, P.T.; et al. The Landscape of Persistent Viral Genomes in ART-Treated SIV, SHIV, and HIV-2 Infections. Cell Host Microbe 2019, 26, 73–85.e74.
88. Brehm, M.A.; Wiles, M.V.; Greiner, D.L.; Shultz, L.D. Generation of improved humanized mouse models for human infectious diseases. J. Immunol. Methods 2014, 410, 3–17.
89. Dash, P.K.; Gorantla, S.; Poluektova, L.; Hasan, M.; Waight, E.; Zhang, C.; Markovic, M.; Edagwa, B.; Machhi, J.; Olson, K.E.; et al. Humanized Mice for Infectious and Neurodegenerative disorders. Retrovirology 2021, 18, 13.
90. Potash, M.J.; Chao, W.; Bentsman, G.; Paris, N.; Saini, M.; Nitkiewicz, J.; Belem, P.; Sharer, L.; Brooks, A.I.; Volsky, D.J. A mouse model for study of systemic HIV-1 infection, antiviral immune responses, and neuroinvasiveness. Proc. Natl. Acad. Sci. USA 2005, 102, 3760–3765.
91. Gu, C.-J.; Borjabad, A.; Hadas, E.; Kelschenbach, J.; Kim, B.-H.; Chao, W.; Arancio, O.; Suh, J.; Polsky, B.; McMillan, J.; et al. EcoHIV infection of mice establishes latent viral reservoirs in T cells and active viral reservoirs in macrophages that are sufficient for induction of neurocognitive impairment. PLoS Pathog. 2018, 14, e1007061.
92. Kim, B.-H.; Hadas, E.; Kelschenbach, J.; Chao, W.; Gu, C.-J.; Potash, M.J.; Volsky, D.J. CCL2 is required for initiation but not persistence of HIV infection mediated neurocognitive disease in mice. Sci. Rep. 2023, 13, 6577.
93. Mestas, J.; Hughes, C.C. Of mice and not men: Differences between mouse and human immunology. J. Immunol. 2004, 172, 2731–2738.
94. Victor Garcia, J. Humanized mice for HIV and AIDS research. Curr. Opin. Virol. 2016, 19, 56–64.
95. Bosma, G.C.; Custer, R.P.; Bosma, M.J. A severe combined immunodeficiency mutation in the mouse. Nature 1983, 301, 527–530.
96. McCune, J.M.; Namikawa, R.; Kaneshima, H.; Shultz, L.D.; Lieberman, M.; Weissman, I.L. The SCID-hu mouse: Murine model for the analysis of human hematolymphoid differentiation and function. Science 1988, 241, 1632–1639.
97. McCune, J.; Kaneshima, H.; Krowka, J.; Namikawa, R.; Outzen, H.; Peault, B.; Rabin, L.; Shih, C.C.; Yee, E.; Lieberman, M.; et al. The SCID-hu mouse: A small animal model for HIV infection and pathogenesis. Annu. Rev. Immunol. 1991, 9, 399–429.
98. Namikawa, R.; Weilbaecher, K.N.; Kaneshima, H.; Yee, E.J.; McCune, J.M. Long-term human hematopoiesis in the SCID-hu mouse. J. Exp. Med. 1990, 172, 1055–1063.

99. Shultz, L.D.; Brehm, M.A.; Garcia-Martinez, J.V.; Greiner, D.L. Humanized mice for immune system investigation: Progress, promise and challenges. Nat. Rev. Immunol. 2012, 12, 786–798.
100. Theocharides, A.P.; Rongvaux, A.; Fritsch, K.; Flavell, R.A.; Manz, M.G. Humanized hemato-lymphoid system mice. Haematologica 2016, 101, 5–19.
101. Shultz, L.D.; Lyons, B.L.; Burzenski, L.M.; Gott, B.; Chen, X.; Chaleff, S.; Kotb, M.; Gillies, S.D.; King, M.; Mangada, J.; et al. Human lymphoid and myeloid cell development in NOD/LtSz-scid IL2R gamma null mice engrafted with mobilized human hemopoietic stem cells. J. Immunol. 2005, 174, 6477–6489.
102. Baenziger, S.; Tussiwand, R.; Schlaepfer, E.; Mazzucchelli, L.; Heikenwalder, M.; Kurrer, M.O.; Behnke, S.; Frey, J.; Oxenius, A.; Joller, H.; et al. Disseminated and sustained HIV infection in CD34+ cord blood cell-transplanted Rag2−/−gamma c−/− mice. Proc. Natl. Acad. Sci. USA 2006, 103, 15951–15956.
103. Meazza, R.; Azzarone, B.; Orengo, A.M.; Ferrini, S. Role of common-gamma chain cytokines in NK cell development and function: Perspectives for immunotherapy. J. Biomed. Biotechnol. 2011, 2011, 861920.
104. Rongvaux, A.; Willinger, T.; Martinek, J.; Strowig, T.; Gearty, S.V.; Teichmann, L.L.; Saito, Y.; Marches, F.; Halene, S.; Palucka, A.K.; et al. Development and function of human innate immune cells in a humanized mouse model. Nat. Biotechnol. 2014, 32, 364–372.
105. Danner, R.; Chaudhari, S.N.; Rosenberger, J.; Surls, J.; Richie, T.L.; Brumeanu, T.D.; Casares, S. Expression of HLA class II molecules in humanized NOD.Rag1KO.IL2RgcKO mice is critical for development and function of human T and B cells. PLoS ONE 2011, 6, e19826.
106. Mosier, D.E.; Gulizia, R.J.; Baird, S.M.; Wilson, D.B. Transfer of a functional human immune system to mice with severe combined immunodeficiency. Nature 1988, 335, 256–259.
107. Kamel-Reid, S.; Dick, J.E. Engraftment of immune-deficient mice with human hematopoietic stem cells. Science 1988, 242, 1706–1709.
108. Péault, B.; Weissman, I.L.; Baum, C.; McCune, J.M.; Tsukamoto, A. Lymphoid reconstitution of the human fetal thymus in SCID mice with CD34+ precursor cells. J. Exp. Med. 1991, 174, 1283–1286.
109. Lan, P.; Tonomura, N.; Shimizu, A.; Wang, S.; Yang, Y.G. Reconstitution of a functional human immune system in immunodeficient mice through combined human fetal thymus/liver and CD34+ cell transplantation. Blood 2006, 108, 487–492.
110. Lavender, K.J.; Pang, W.W.; Messer, R.J.; Duley, A.K.; Race, B.; Phillips, K.; Scott, D.; Peterson, K.E.; Chan, C.K.; Dittmer, U.; et al. BLT-humanized C57BL/6 Rag2−/−γc−/−CD47−/− mice are resistant to GVHD and develop B- and T-cell immunity to HIV infection. Blood 2013, 122, 4013–4020.

111. Ishikawa, F.; Yasukawa, M.; Lyons, B.; Yoshida, S.; Miyamoto, T.; Yoshimoto, G.; Watanabe, T.; Akashi, K.; Shultz, L.D.; Harada, M. Development of functional human blood and immune systems in NOD/SCID/IL2 receptor (Akkina et al.) chain(null) mice. Blood 2005, 106, 1565–1573.
112. Cheng, L.; Ma, J.; Li, G.; Su, L. Humanized Mice Engrafted with Human HSC Only or HSC and Thymus Support Comparable HIV-1 Replication, Immunopathology, and Responses to ART and Immune Therapy. Front. Immunol. 2018, 9, 817.
113. Waight, E.; Zhang, C.; Mathews, S.; Kevadiya, B.D.; Lloyd, K.C.K.; Gendelman, H.E.; Gorantla, S.; Poluektova, L.Y.; Dash, P.K. Animal models for studies of HIV-1 brain reservoirs. J. Leukoc. Biol. 2022, 112, 1285–1295.
114. Honeycutt, J.B.; Garcia, J.V. Humanized mice: Models for evaluating NeuroHIV and cure strategies. J. Neurovirol. 2018, 24, 185–191.
115. Mathews, S.; Branch Woods, A.; Katano, I.; Makarov, E.; Thomas, M.B.; Gendelman, H.E.; Poluektova, L.Y.; Ito, M.; Gorantla, S. Human Interleukin-34 facilitates microglia-like cell differentiation and persistent HIV-1 infection in humanized mice. Mol. Neurodegener. 2019, 14, 12.

Retrieved from https://encyclopedia.pub/entry/history/show/105834