Review article
https://doi.org/10.36233/0372-9311-307

Anatomical and physiological aspects of the HIV infection pathogenesis in animal models

Aleksey M. Nagornykh✉, Marina A. Tyumentseva, Aleksandr I. Tyumentsev, Vasily G. Akimkin

Central Research Institute for Epidemiology, Moscow, Russia

Abstract

Understanding the entire pathogenesis of HIV infection, from penetration at the gates of infection to the induction of severe immunodeficiency, is an essential tool for the development of new treatment methods. Less than 40 years of research into the mechanisms of HIV infection that lead to the development of acquired immunodeficiency syndrome have accumulated a huge amount of information, but HIV's own unique variability identifies new whitespaces.

Despite the constant improvement of the protocols of antiretroviral therapy and the success of its use, it has not yet been possible to stop the spread of HIV infection. The development of new protocols and the testing of new groups of antiretroviral drugs is possible, first of all, due to the improvement of animal models of the HIV infection pathogenesis. Their relevance, undoubtedly increases, but still depends on specific research tasks, since none of the *in vivo* models can comprehensively simulate the mechanism of the infection pathology in humans which leads to multi-organ damage.

The aim of the review was to provide up-to-date information on known animal models of HIV infection, focusing on the method of their infection and anatomical, physiological and pathological features.

Keywords: *HIV infection, pathogenesis, animal models of HIV infection, review*

Funding source. This work is supported by the Ministry of Science and Higher Education of the Russian Federation within the framework of a grant in the form of a subsidy for the creation and development of the «World-class Genomic Research Center for Ensuring Biological Safety and Technological Independence under the Federal Scientific and Technical Program for the Development of Genetic Technologies», agreement No. 075-15-2019-1666.

Conflict of interest. The authors declare no apparent or potential conflicts of interest related to the publication of this article.

For citation: Nagornykh A.M., Tyumentseva M.A.,Tyumentsev A.I., Akimkin V.G. Anatomical and physiological aspects of the HIV infection pathogenesis in animal models. *Journal of microbiology, epidemiology and immunobiology = Zhurnal mikrobiologii, èpidemiologii i immunobiologii.* 2022;99(5):587–604.
DOI: https://doi.org/10.36233/0372-9311-307

Научный обзор
https://doi.org/10.36233/0372-9311-307

Анатомо-физиологические аспекты патогенеза ВИЧ-инфекции у животных моделей

Нагорных А.М.✉, Тюменцева М.А., Тюменцев А.И., Акимкин В.Г.

Центральный научно-исследовательский институт эпидемиологии Роспотребнадзора, Москва, Россия

Аннотация

Понимание всего патогенеза ВИЧ-инфекции — от проникновения инфекции до индукции тяжёлого иммунодефицита — важно для разработки новых методов лечения. Неполные 40 лет исследований механизмов ВИЧ-инфекции, приводящих к развитию синдрома приобретённого иммунодефицита (СПИДа), собрали колоссальное количество информации, однако собственная уникальная изменчивость ВИЧ выявляет все новые пробелы.

Несмотря на постоянное усовершенствование протоколов антиретровирусной терапии и успехи её применения, остановить распространение ВИЧ-инфекции пока не удаётся. Развитие новых протоколов и испытание новых групп антиретровирусных препаратов возможно, в первую очередь, благодаря совершенствованию животных моделей патогенеза ВИЧ-инфекции. Их релевантность, несомненно, повышается, но в то же время зависит от конкретных исследовательских задач, т.к. ни одна из моделей *in vivo* не может всесторонне имитировать механизм инфекционной патологии человека, приводящей к мультиорганному поражению.

Цель работы — представить актуальную информацию по известным животным моделям ВИЧ-инфекции, акцентируя внимание на способе их инфицирования и анатомо-физиологических и патологических особенностях.

Ключевые слова: *ВИЧ-инфекция, патогенез, животные модели ВИЧ-инфекции, обзор*

Источник финансирования. Данная работа выполнена при финансовой поддержке Министерства науки и высшего образования РФ в рамках гранта в форме субсидии на создание и развитие «Центра геномных исследований мирового уровня по обеспечению биологической безопасности и технологической независимости в рамках Федеральной научно-технической программы развития генетических технологий», соглашение № 075-15-2019-1666.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Для цитирования: Нагорных А.М., Тюменцева М.А., Тюменцев А.И., Акимкин В.Г. Анатомо-физиологические аспекты патогенеза ВИЧ-инфекции у животных моделей. *Журнал микробиологии, эпидемиологии и иммунобиологии.* 2022;99(5):587–604.
DOI: https://doi.org/10.36233/0372-9311-307

Introduction

HIV is a human-specific pathogen, the infection with which leads to depletion and death of mature peripheral $CD4^+$ T cells ($hCD4^+$) and immature hematopoietic progenitor cells in the organs and tissues responsible for their production, including bone marrow (BM), thymus, brain and lymph nodes (LNs) [1].

HIV-1 is transmitted by percutaneous, perinatal, and sexual routes, while 80% of adult infection cases become infected through the exposure of mucosal surfaces to the virus [2]. Recent studies have demonstrated the ability of HIV to infect not only cells of the immune system, but also tissues of many organs, including the brain, the intestine, kidneys, and the prostate [3, 4].

CCR5-utilizing (non-syncytium-inducing, CCR5-tropic, or R5 isolates) HIV-1 strains are macrophage-tropic [5, 6] and are detected in blood during early or acute infection [7]. They are characterized by high rates of replication, producing large numbers of viral progeny. Some studies suggest that the initial infecting R5 virus often evolves into a dual-tropic R5/X4 virus [8]. The subsequent development of AIDS accompanied by depletion of CXCR4-expressing memory $hCD4^+$ T cells in LNs, spleen, Peyer's patches, nasal-associated lymphoid tissue, adenoids, tonsils, bronchus-associated lymphoid tissue, cryptopatches (CP), and isolated lymphoid follicles [6, 9–11] leads to emergence of a more cytopathic virus [8] utilizing the CXCR4 chemokine receptor (syncytium-inducing, CXCR4-tropic, or X4 isolate).

CCR5 is expressed at low levels on $hCD4^+$ and $hCD8^+$ thymocytes and on a subset of circulating memory or activated $CD4^+$ T cells. Given this differential characteristic, X4 isolates, as opposed to R5 isolates, rapidly infect and destroy both immature and mature T cells, resulting in immune system collapse [12]. Nevertheless, R5 isolates are detected in approximately 50% of AIDS cases [13].

As mucosae contain higher levels of $hCD4^+$ T cells with initially high activation and expression of CCR5 as compared to blood [3, 4, 14], they become the main reservoir of HIV-1 target cells in the contact route of transmission [15]. In addition, the induction of chemokines during early stages of infection initiates migration of HIV target cells to infection and inflammation sites, prompting rather than preventing the spread of the virus through its antiviral activity [16].

Regardless of the transmission route, the gastrointestinal tract (GIT) is a major site of HIV-1 replication and $hCD4^+$ T cell depletion [17]. Therefore, the main consequence of acute HIV infection is massive destruction of $hCD4^+$ T cells in the GIT mucosa-associated lymphoid tissue [18]. Furthermore, the disruption of the GIT epithelium integrity leads to translocation of bacteria to the blood stream and, consequently, becomes the cause of inflammation and activation contributing to the loss of $hCD4^+$ cells [19].

If mucosae remain intact, HIV can penetrate the epithelium by transcytosis and translocation of virus particles across epithelial cells [20, 21]; recent studies have demonstrated that Langerhans cells are capable of endocytic internalization of HIV-1 virions, which is followed by replication of virus particles in the cytoplasm and potential infectivity for the neighboring $hCD4^+$ T cells [14]. In addition, the mucosal epithelium of the female reproductive tract (FRT) is a substantial barrier against infection; therefore, not all HIV-1 exposures result in productive infection [20].

Although $hCD4^+$ T cells, brain macrophages and microglia are the main targets for HIV-1, lymphoid tissues are the main reservoir for HIV, compromising primarily latently infected, resting $hCD4^+$ T cells carrying an integrated, replication-competent HIV form even in patients receiving antiretroviral therapy (ART). Biomarkers of macrophage activation and neuronal damage in the cerebrospinal fluid of HIV-infected patients with viral suppression demonstrate the induction of neurocognitive disorders through chronic inflammation of the central nervous system (CNS) tissues, presenting CNS tissues as a latent reservoir of the replication-competent virus [22]. Although resting $hCD4^+$ lymphocytes are characterized by low levels of productive viral infection due to inhibition of the early reverse transcription of incoming viral genomes, the viral production, which results in formation of the fully infectious HIV particle, starts immediately after the latently infected, resting $hCD4^+$ T cells have been activated [23].

Although HIV can replicate in chimpanzees (*Pan troglodytes*), it cannot infect mice, rats, rabbits, or macaques [24, 25]. The species-specificity of HIV is not limited to its interactions with CXCR4 or CCR5 on the surface of $hCD4^+$ T cells. Multiple barriers to HIV replication, which have been found in mammals, limit the availability of adequate animal models to study fundamental aspects of HIV biology and its interactions with the host [16]. For example, rat or mouse cells that have been developed to express hCD4 and CCR5 or CXCR4 on their surface do not support HIV replication due to the absence of additional viral restriction factors such as TRIM5α and APOBEC3. The Vif protein interacts directly with APOBEC3, disrupting its activity and preventing its incorporation into viral particles [26, 27]. In its turn, TRIM5α regulates the ability of some retroviruses to infect human cells and the ability of HIV to infect primate cells. This protein interacts with the viral capsid and by blocking the process prevents its integrity disruption during the reverse transcription [28].

Chronic immune activation is a hallmark of the HIV pathogenesis [29]. Hyperimmune responses with the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) exhibiting cytotoxic properties [30] and HIV proteins [23] can increase the HIV replication rate and $hCD4^+$ and $hCD8^+$ T cell apoptosis [31]. In most cases, apoptosis is the result of

DOI: https://doi.org/10.36233/0372-9311-307

direct viral infection or an indirect effect of immune activation. The direct cytopathic effect of HIV is caused by disturbance of metabolic processes and disruption of integrity of cell membranes of $hCD4^+$ T lymphocytes and precursors, leading to apoptosis. Autophagy is pointed out as a possible cause of accidental death of $hCD4^+$ cells [30, 32]. Another causative factor can be the activity of cytotoxic $hCD8^+$ T cells against normal $hCD4^+$ cells [20, 33]. The reduction of peripheral blood $hCD4^+$ lymphocytes over time is caused by destruction of BM, lymphoid tissue, and by inhibition of cell reproduction, for example, in the thymus [30, 34].

Model organisms keeping natural anatomical and physiological characteristics

Great apes

Previous genetic studies have shown that HIV-1 groups M and N evolved from the simian immunodeficiency virus (SIV) infecting chimpanzees (SIVcpz), while groups O and P originated from SIV of gorillas (SIVgor) circulating in the gorilla population (*Gorilla gorilla* spp.) [2, 35]. SIVgor resulted from the SIVcpz transmission 100–200 years ago [36]. The analysis of highly conserved regions of the viral genome, which changed when the human species barrier has been crossed by monkey precursors of HIV-1, detected one site in the Gag-30 viral matrix protein, which encoded methionine and switched to arginine in the assumed ancestors of HIV-1 groups M, N, and O, thus resulting in arginine or lysine presence as a basic amino acid in most of the HIV-1 strains with than the isogenic virus with lysine at the same position, while the opposite process is observed in human cells [37]. The reversibility of the process is confirmed by experimental infection of chimpanzees with HIV-1 [38], which resulted in reversion of the basic residue from Gag-30 to methionine [39]. The progressive loss of $CD4^+$ T cells, severe thrombocytopenia, and AIDS-specific signs result in fatal outcome in SIVcpz-infected chimpanzees [40].

Ethical issues significantly limit studies involving great apes. Although the kinetics of SIVcpz replication *in vitro* in $hCD4^+$ T cells is similar to that of HIV, cell cultures fail to capture all the conditions of virus replication and transmission *in vivo* [41].

Non-human primates

It has been found that HIV-2 groups A through H originated from SIV of sooty mangabeys (*Cercocebus atys*) after it was transmitted to humans [2, 35, 42]. In the meantime, mangabeys, even when infected with SIV of sooty mangabeys, do not tend to develop AIDS [43], demonstrating their relevance as a natural model of HIV pathogenesis in "elite controllers" having low viremia levels due to the absent chronic immune activation [44, 45]. In its turn, HIV-1 infecting humans does not replicate in most of the non-human primates; therefore, related monkey viruses with their inherent limitations are used to model HIV infection [46].

Early *in vivo* studies of HIV infection pathogenesis in macrophages were conducted by infecting southern pig-tailed macaques (*Macaca nemestrina*) with SIV [47]. However, the replication of HIV and SIV in macrophages was difficult to study at that time; therefore, the presence of viral nucleic acids in these cells was attributed to the phagocytosis of infected T cells and cell debris [48].

SIV infection of southern pig-tailed macaques triggers virus production after activation of latently infected, resting $CD4^+$ T cells in tissues and peripheral blood [23]. Although SIV was absent in peripheral blood of 85.7% of the animals undergoing ART, latently infected macrophages containing the replication-competent virus were detected in basal ganglia and parietal cortex *ex vivo*. However, this model employs viruses having tropism both for $CD4^+$ lymphocytes and for macrophages; therefore, this study cannot be directly compared with studies of other phenotypically limited animal models or HIV-infected patients [22]. Infection of the related species, Sundaland pig-tailed macaques (*Macaca leonina*), with chimeric HIV demonstrates the relationship between higher intracellular APOBEC3 expression and lower virus replication rates during the acute stage [49, 50].

The inability to infect rhesus macaque (*Macaca mulatta*) cells with HIV-1 *in vitro* is in part due to the HIV-1 capsids being blocked by the TRIM5α host cell restriction factor and the failure of Vif to bind and induce APOBEC3 degradation. To bypass these limitations, sequences of the capsid and Vif of SIV of macaques (SIVmac) are incorporated in HIV-1 molecular clones. After its *in vitro* passage in human CEMx174 cells, the chimeric virus acquires 88% of the HIV-1 genome, including the capability of replicating steadily and inducing massive cytopathic effects. Thus, the accidental or adaptive bypass of capsid and Vif-associated limitations can guarantee the cross-species transmission of primate lentiviruses [46].

The HIV tropism for $hCCR5^+/hCD4^+$ lymphocytes in the intestinal lamina propria (LP) [51, 52] positively correlates with the data obtained from the $SIVmac_{251}$ infected animals [53–55], when the virus affects 30–60% of all $CD4^+$ T cells during the acute stage. On the 3rd day after they were infected intravenously (i/v), almost all the animals demonstrate an increase in the number of $CD4^+$ T cells, which reaches the peak on the 10th day to be followed by a sharp decrease in their number in blood and LNs, and a few days later – in the intestinal LP having highest levels of $CD4^+$ lymphocytes. However, after having disappeared from blood, $CCR5^+/CD8^+$ T cells continue to be detected in other tissues [56].

Within two days of the intravaginal (i/vag) inoculation of SIV, rhesus macaques developed infection of

the cervix. The virus spreads further through migration of $CD4^+$ and dendritic cells to regional LNs and then to the blood stream. The infection is propagated not only in activated and proliferating T cells corresponding to the short-lived population that produces the bulk of HIV-1 virions in humans, but also in resting T cells [57].

To imitate *in vivo* development of CNS disorders associated with AIDS, rhesus macaques infected with $SIVmac_{251}$ received i/v injections of CD8 antibodies to promote migration and deposition of monocytes and macrophages to brain tissues, thus resulting in development of SIV-induced encephalopathy [58]. In its turn, the preliminary depletion of $CD4^+$ lymphocytes by recombinant antibodies causes persistent infection of macrophages and the CD4-independent membrane developed by the virus to promote its entry to the CCR5-expressing cells in the absence of CD4 [59].

Ethical issues limiting *in vivo* studies using human hematopoietic stem cells (HSCs) in primates [60] prompted further studies of HIV infection in small animal models that partially have a human immune system.

Table 1 summarizes the data on model organisms having natural anatomical and physiological characteristics.

Chimeric model organisms

The hu-Thy/Liv model

The chimeric SCID-hu Thy/Liv model constructed by transplanting human fetal thymus and liver tissues under the kidney capsule to homozygous $C.B\text{-}17_{scid/scid}$ mice with severe combined immunodeficiency (SCID) [61, 62] has a reduced graft-versus-host disease (GVHD) and can support functions of grafts for up to 15 months [63]. The transplanted thymus tissues demonstrate morphological and functional similarity to tissues of the human normal fetal thymus by the composition of thymocyte subpopulations and expression of hCXCR4 and hCCR5 [12].

In contrast to identical kinetics of HIV infection during progression to AIDS, which is observed both in R5-isolate carriers and in X4-isolate carries, R5 isolates go through a two-stage infection cycle in the SCID-hu Thy/Liv model, first slowly replicating in medullary

Table 1. Models maintaining natural anatomical and physiological features

Model	Method of infection; pathogen	Pathophysiological features
Chimpanzee	Natural; SIV of schimpanzee	$CD4^+$ T-cell depletion, severe thrombocytopenia, and signs of AIDS leading to death [40]
	Intravenously (i/v); HIV-1	Mild thrombocytopenia and leukopenia [38]
Sooty mangabey	I/v; SIV of sooty mangabey-infected homologous plasma	Absence of chronic immune activation that preclude high levels of viremia [44]
Rhesus macaque	I/v; HIV-1 chimeric strain	Possibility of interspecific transmission between primates [46]
	I/v; SIV_{mac251}	30–60% of all $CD4^+$ T cells are affected. Almost complete loss of all $CCR5^+/CD4^+$ T cells in the jejunum [53–56]. The spread of the virus through the migration of dendritic and $CD4^+$ T cells, including dormant ones, into the regional LN and bloodstream [57]. Acceleration of migration and deposition of monocytes and macrophages in brain tissues stimulate the development of SIV-induced disorders in the central nervous system against the background of AIDS [58].Persistent infection of macrophages and the appearance of CD4-independent envelope in the virus after the previous infection depletion of $CD4^+$ cells [59]
Northern pig-tailed macaque	I/v; HIV-1-infected peripheral blood autologous mononuclear cells	Stable replication of HIV-1 in a non-target organism [50]
Sundaland pig-tailed macaque	I/v; macrophage-tropic SIV	Virus replication after activation of only latently infected resting $CD4^+$ T cells [23]
	I/v; immunosuppressive and neurovirulent SIV	Persistent infection of macrophages [47]
	I/v; SIV	Retention of latently infected macrophages in the basal ganglia and parietal cortex in the absence of SIV after antiretroviral therapy [22]

DOI: https://doi.org/10.36233/0372-9311-307

stromal cells, without causing any apparent pathology, and then infecting cortical $CD4^+/CD8^+$ thymocytes, thus subsequently causing their moderate depletion [6, 12]. The absolute levels of replication X4 isolates in cortical thymocytes, which are observed after 17 days of the infection [6, 12], decrease after 20 days of the infection due to HIV-1-mediated depletion of these thymocytes, resulting in their complete loss during the next 15–20 days [61]. At the same time, the p24 levels in mice infected with X4 isolates are 14 times as high as those in mice infected with R5 isolates due to the effect of Nef on replication and enhancement of the cytopathic component of the pathogenesis of X4 isolates during infection *in vivo* [64]. At the same time, X4 isolates can acquire an R5-like phenotype and infect medullary stromal thymocytes that poorly express CCR5, slowly replicating in them and occasionally causing their depletion [1].

In the SCID-hu Thy/Liv model, transplanted thymocytes can be infected only by the mode different from natural routes of pathogen transmission. The absence of systemic viremia prevents the analysis of viral replication and its effect on thymocytes, requiring surgical removal of the tissue fragment or animal euthanasia [62]. This explains the need for the animal model that can be infected through the routes similar to those in humans, for example, through mucosae, as HIV-infected cells can transmit the virus both to cells of the immune system and to cells of mucous membranes [65, 66].

BM of NOD/SCID/γc−/− (NSG)-hu Thy/Liv mice that have only T cells (also known as T-cell only mice or ToM) does not produce human myeloid cells and B cells [67, 68], and as the model is *γc* deficient, it does not manifest GVHD signs for 14 months. After the i/v or intraperitoneal infection with R5 isolate, which does not replicate *in vivo* in tissue macrophages and which is tropic exclusively for human T cells, the presence of viral RNA (vRNA) and $p24^+$ cells is observed across the entire brain, including cerebellum, medulla oblongata and cerebral cortex [67]. High levels of viral replication maintained in peripheral blood result in moderate reduction on the population of $hCD4^+$ lymphocytes; however, daily administration of combined ART can significantly decrease the viral load to undetectable levels in plasma, while preserving latently infected, resting $CD4^+$ T cells [68]. Thus, the NSG-hu Thy/Liv model demonstrates the competence of T cells in establishment and support of productive HIV infection of the brain and the absent need for myeloid cells for transportation of the virus from the periphery to the brain [67].

The hu-BLT model

The possibility of rectal and ivag infection of chimeric mice with HIV depends on the presence of human cells in FRT and rectum; however, the reconstitution of these cells depends directly on the mouse strain and the humanization protocol. The lower activity of endogenous natural killer cells in NOD/SCID and NSG mice compared to SCID mice contributes to longer and more reliable reconstitution of cells involved in the human innate and adaptive immune response. In addition, T cells of these mice, similar to human T cells, demonstrate quite a versatile repertoire of Vβ T-cell receptors [17]. These mice are humanized by the mode similar to that used for the hu-Thy/Liv model: the transplantation of the human fetal thymus-liver-thymus graft sandwich under the kidney capsule and its engraftment are followed by inoculation of fetal $CD34^+$ HSCs. The model is referred to as bone marrow-liver-thymus (BLT). In NOD/SCID-hu BLT mice, the transplanted thymus tissue is developed into a human thymus-like thymic organoid, in which progenitor cells of human T lymphocytes, which are limited by the human leukocyte antigen (HLA), can migrate and develop into fully functional peripheral T cells within the autologous epithelium of human thymus [69].

The analysis of tissue distribution of populations of human immune cells in NOD/SCID-hu BLT mice revealed the respective distribution of human lymphoid and myeloid cells in BM, spleen, LNs, liver, lungs, and GIT [17]. Mucosae of the vagina, exocervix, endocervix, uterus, and intestine were characterized by intensive reconstitution of $hCD4^+$ T cells, monocytes/macrophages, and dendritic cells. T cells are located directly inside the epithelial layer, forming a streak on the borderline between the epithelium and LP, along the basal membrane and along the lamina propria, while macrophages and dendritic cells are located in the lamina propria along the entire FRT of mice [69]. These morphological characteristics correlate with location of T cells in humans, providing the NOD/SCID-hu BLT model with susceptibility to effective vaginal transmission of R5 isolates [69, 70] and rectal transmission of X4 and R5 isolates [71, 72].

Non-traumatic i/vag inoculation of a single cell-free dose of the primary R5 isolate of HIV-1 to NOD/SCID-hu BLT mice results in establishment of systemic infection in 88% of mice, which is demonstrated by the presence of p24 antigen and/or vRNA in plasma 2 weeks after the infection and by progressive reduction in the population of $hCD4^+$ T cells in peripheral blood, being similar to the acute stage of HIV-1 infection in humans. Disseminated infection is observed along the entire GIT: Infected cells are detected in LP and small intestine epithelium, causing a sharp loss of tissue $hCD4^+$ lymphocytes and effector memory cells [69].

Most of the $hCD4^+$ T cells, which are present in FRT of NOD/SCID-hu BLT and NSG-hu BLT mice, express simultaneously CCR7 and CCR5, being potential target cells for HIV, similar to the human cervical tissue. As stromal cells are a major source of CCL19 and CCL21 as well as CCR7 mouse ligands, humani-

zed mice express them at higher levels than human ligands in the cervicovaginal tract and iliac LNs. 6-10 days after the infection, the number of $p24^+$ $hCD4^+$ T cells increases in the cervicovaginal tract compared to their number in cervical LNs, and 14 days later, infected cells and vRNA are detected in the intestine, plasma, and spleen, while vDNA is detected in mesenteric LNs. This kinetics of processes demonstrates the absence of critical significance of CCR7-dependent migration of leukocytes for HIV spread [73].

Structures similar to the gut-associated lymphoid tissue (GALT), which are present in humans, brought up a question regarding the ability of mouse CP to initiate the genesis of human GALT. Transmission of IL-7R signals is essential for the GALT genesis; therefore, GALT cannot develop normally in mice with disturbed transmission of IL-7R signals, including NSG mice, which do not have the common γ-chain. For this reason, rectal transmission of HIV-1 is studied in NOD/SCID-hu BLT mice that have CP and can accurately reproduce depletion of $hCD4^+$ T cells in GALT structures. The reconstitution of $hCD4^+$ and $hCD8^+$ T cells, myeloid cells and single naive T cells along the entire epithelium and LP of small and large intestine makes the NOD/SCID-hu BLT model susceptible to rectal transmission of HIV-1 [17]. In addition, in NOD/SCID-hu BLT mice, plasmatic cells secreting hIgA dominate over cells secreting hIgG, thus correlating positively with the IgA secretion in intestinal LP of humans. Furthermore, the intestine of NSG hu-BLT mice contains small numbers of plasmatic cells with high levels of hIgA and hIgG secretion [74].

Rectal infection results in a significant increase in the number of perforin-positive cells in GALT structures in NOD/SCID-hu BLT mice, in production of $p24^+$ cells and in decreased numbers of $hCD4^+$ lymphocytes across the entire GIT [17], thus demonstrating the consistency with depletion of $hCD4^+$ T cells in intestinal LP and intraepithelial compartments during HIV infection in humans. No differences in levels of $hCD8^+$ T cells in HIV-positive and HIV-negative animals have been observed [74]. The human thymic stroma, which is present in NOD/SCID-hu BLT mice, is essential for production of human thymocytes within the entire human major histocompatibility complex (MHC), thus making the model quite promising for assessment of specific immune responses to potential vaccines against HIV [75].

Unfortunately, adoptive transfer of activated Vδ2 cells, which demonstrates relative therapeutic effectiveness in treatment of some infectious diseases, does not help control HIV infection in NSG-hu BLT mice; on the contrary, it aggravates viremia, thus suggesting a possible role of Vδ2 cells as early HIV targets in promotion of virus spread [76].

Interstitial $hCD4^+$ lymphocytes in lungs, which express both hCCR5 and hCXCR4 [77], unlike $hCD4^+$ lymphocytes of the alveolar space or circulating blood, tend to deplete during early stages of HIV-1 infection *ex vivo* in the human lung tissue and *in vivo* in NOD/SCID-hu BLT and NSG-hu BLT mice, demonstrating the highest levels of their infection [78]. The hu-BLT mice that are i/vag infected with the R5 isolate provide the possibility to observe *in vivo* depletion of $hCD4^+$ T cells in the interstitial lung tissue [73] during acute and early chronic HIV-1 infection [79, 80]. The viral load in the common lung tissue and sorted $hCD4^+$ T cells of the lung tissue as well as the $p24^+/hCD4^+$ cell ratio were higher compared to those in the spleen tissue, while the numbers of $hCD4^+$ T cells in the interstitial lung tissue and bronchoalveolar lavage fluid showed a gradual decrease during 7 weeks. The total number of $hCD4^+$ and $hCD8^+$ T cells correlates with the number in the bronchoalveolar lavage fluid, though not in the interstitial lung tissue, suggesting that T lymphocytes are recruited to the alveolar space. Thus, the early and severe depletion of $hCD4^+$ T cells in the lungs of these models correlates with the depletion observed in the intestine [78].

Considering that microglia evolved from early progenitor cells that developed in the yolk sac, it was doubtful that human microglial cells could be reproduced by modern models of humanized mice [67]. However, NSG-hu BLT and IL34-Tg/NOG-hu BLT mouse models demonstrate effective reconstitution of human microglia and the ability to support replication of HIV in the brain [67, 81].

NSG mice being hypersensitive to ionizing radiation demonstrate lower total numbers of human HSCs, myeloid cells and B cells in the brain after preconditioned irradiation at high dose rates. In addition, the brain of female NSG-hu BLT mice shows higher levels of reconstituted human B cells than the brain of male mice, though the number of T cells and the $hCD4^+/hCD8^+$ ratio do not depend on the gender or the dose rate. The presence of HIV target cells in the entire brain of NSG-hu BLT mice is confirmed by migration of HSCs $hCD45^+$, $hCD3^+$ T cells and $hCD68^+$ macrophages from the olfactory bulb through brainstem base to the medulla oblongata. Subsets of $hCD4^+$ and $hCD8^+$ lymphocytes are present across the brain, including the olfactory bulb, cortex, caudate nucleus, thalamus, midbrain, pons, and cerebellum; the latter contains significantly larger numbers of $hCD68^+$ macrophages than in the other compartments of the brain. The infection of NSG-hu BLT mice with R5 and X4 isolates through mucous membranes and parenterally results in detection of cell-associated vDNA and vRNA in 85.1% and 92.9% of the brain, respectively, regardless of the infection mode. As the infection is progressing, the increased vDNA levels in the brain entail rapid and steady reduction in the total number of human T cells and $hCD4^+$ T cells as well as reduction in the $hCD4^+/hCD8^+$ ratio in the brain, which is similar to the loss of $hCD4^+$ T cells in FRT and GIT mucosal tissues during early stages of

DOI: https://doi.org/10.36233/0372-9311-307

infection. p24$^+$ cells are detected in the cortex, cerebellum, thalamus, medulla oblongata, and midbrain. There is a direct relationship between the levels of cell-associated vRNA in the brain and the viral load in plasma as well as between the duration of infection and the number of myeloid cells [67]. In addition, the significance of atypical cell subsets in HIV persistence is demonstrated by reactivation of the persisting virus in perivascular macrophages, astrocytes, and microglia of the brain in infected mice [82].

While in NSG-hu BLT mice, human T cells develop in the human thymus epithelium and are limited by human MHC [70, 83], in NOD-Rag2−/−γc−/− (NRG)-hu BLT mice, human T cells are produced in the thymus with the mouse MHC [84–86]. In the same way, in the above model, HIV-1 infection induces activation and depletion of T cells [87–89].

Humanization of the BLT model of TKO mice lacking *Rag2*, *Il2rg,* and *CD47* genes is accompanied by stable reconstitution of all major cell subsets in BM, spleen, and mesenteric LNs, including hCD4$^+$ and hCD8$^+$ T lymphocytes, hCD19$^+$ B cells, hCD14$^+$ monocytes, myeloid and plasmacytoid dendritic cells. In addition, the areas organized into follicles in the white pulp of the spleen are reconstituted with primarily mature hCD3$^+$ T cells and hCD20$^+$ B cells, and in GALT of the large and small intestine – with subsets of activated hCD4$^+$ and hCD8$^+$ lymphocytes as well as with myeloid cells and plasmacytoid dendritic cells. Rectal and intraperitoneal [90] infection of TKO-hu BLT mice with the R5 isolate of HIV-1 induces production of gp120-specific antibodies and reduction in the number of hCD4$^+$ T cells along with the increasing number of activated hCD8$^+$ T cells. Thus, the TKO-hu BLT model demonstrates classical immunological signs of acute HIV-1 infection in humans [91].

Depending on the selected mouse strain, hu-BLT models can reconstitute the human functional immune system [92, 93] and become infected with HIV-1 through routes similar to those of humans [94], bringing the model to the level of the gold standard for *in vivo* studies of HIV-1 [95, 96].

The hu-HSC model

NOD (non-obese diabetic) models based on Rag1$^{-/-}$Il2rg$^{-/-}$ and Rag2$^{-/-}$Il2rg$^{-/-}$ deficient mice (lacking two genes, double knockout, DKO) that are engrafted with human hCD34$^+$ HSCs demonstrate susceptibility to infection with R5 and X4 isolates of HIV-1 through the mucous membrane, resulting in chronic infection [97, 98].

Transplantation of BM cells or hCD34$^+$ umbilical cord blood cells to NSG mice results in successful differentiation among various populations of cells, including human T and B cells as well as natural killer cells, monocytes/macrophages, and dendritic cells. In addition, hCD4$^+$ T cells of this model are highly susceptible to R5 and X4 isolates inducing a high viral load in the plasma [99–101] for more than 40 days [101].

BRG mice were used to create the model with consistent reconstitution and development of LNs eliminating downsides of development of the secondary lymphoid tissue. The BRGST-hu HSC model based on Balb/c *Rag2*$^{-/-}$*Il2rg*$^{-/-}$*Sirpa*^{NOD} (BRGS) mice expresses transgenic thymic stromal lymphopoietin, which does not depend on *IL2rg* and is similar to *IL7* by its structure and function; the model has stable cellular and humoral human responses due to stimulation of B and T-cell responses [102]. Thus, BRGST-hu HSC mice demonstrate enhanced immunoglobulin isotype switching, development of central memory and effector memory T cells and follicular T-helper cells in secondary lymphoid tissues with pronounced B-cell zones [103].

Humanized mice devoid of human T cells (myeloid-only mice, MoM) are one of the versions of the hu-HSC model; they are characterized by stable levels of viremia accompanied by the increased number of human macrophages in the brain. Replication of macrophage-tropic R5 isolates of HIV-1 and HIV-2 takes place only in reconstituted macrophages and myeloid cells within 15 weeks. In their turn, T cell-tropic R5 isolates of HIV-1 or HIV-2 do not replicate as T cells are absent. In infected NOD/SCID-hu Mo mice, hCD68+ macrophages and p24+ cells are detected across the brain, including the cerebellum, putamen, cortex, ventral striatum, and brainstem [104]. In this model, the long-term infection supported by tissue macrophages in the absence of T cells implies that they become vulnerable as true targets and latent reservoirs of HIV infection in humans. In addition, these mice can transmit *de novo* the pathogen, which replicates effectively in the new host in the presence or in the absence of human T cells [104].

The results obtained in the NRG-hu Thy/HSC model, which was created by transplantation of a fetal thymus fragment beneath the kidney capsule and i/v injection of human HSCs to sublethally irradiated NRG mice, demonstrate the activation, functionality loss, and T cell depletion similar to those observed in NRG-hu HSC mice after the infection with HIV-1 as well as the similar level of CD38 and HLA expression on hCD8$^+$ lymphocytes. The hCD4$^+$/hCD8$^+$ T cell ratio was insignificantly higher in these mice, while the percentage content of human natural killer cells, plasmacytoid dendritic cells, and monocytes was lower than in the NRG-hu HSC mice. In addition, NRG-hu Thy/HSC mice can express *PD-1* – the marker of T-cell functionality loss [105].

Despite the absence of mature B cells capable of isotype switching [106], productive infection of FRT mucous membranes in NRG-hu HSC mice provides the best model of the contact route of HIV-1 transmission and offers the possibility to study changes in the micro-

Table 2. Chimeric models

Mouse model	Method of infection; pathogen	Anatomical and physiological features	Pathophysiological features
SCID-hu Thy/Liv	HIV-1 inoculation into graft tissue	Grafts' thymocytes subpopulations composition and hCXCR4 and hCCR5 expression are similar to the normal human fetal thymus tissues, the functionality is kept for 6 to 15 months [6, 12, 61–63]	MHC-limited T cells infection and depletion, up to their complete disappearance [6, 12, 61–63]
NSG-hu Thy/Liv	I/v and intraperitoneally; T-cell-tropic R5 HIV-1 isolate	System reconstitution of human T-cells [68]	Productive infection of all brain divisions. Myeloid cells are not required to transport HIV from the periphery to the brain [67]. Maintaining high levels of virus replication in peripheral blood, leading to a moderate decrease in the $hCD4^+$ T cell population. Administration of combined antiretroviral therapy leads to a significant suppression of virus replication up to undetectable in plasma with the preservation of latently infected resting $hCD4^+$ T cells [68]
NOD/SCID-hu BLT	Intravaginally (i/vag) [17, 69] or rectally [70, 71, 74]; HIV-1	HLA-limited intensive reconstitution, corresponding distribution and functionality of human lymphoid and myeloid cells in the tissues of the thymic organoid [69], BM, spleen, LN, liver, lungs, FRT [17, 69], gastrointestinal tract [17, 70, 71, 74] and thymic organoid [69] in the context of human MHC [65]. T cells demonstrate a diverse repertoire of Vß TCR receptors [17, 69]. The predominance of hIgA-secreting plasma cells over hIgM-secreting cells [74]	System infection and progressive depletion of $hCD4^+$ T cells [17, 71] including interstitial lung tissue [74]. The number of human perforin-positive cells was significantly increased [74]
NSG-hu BLT	I/v [76, 88, 89, 104], i/vag, rectally or orally [94]; HIV-1	The genesis of GALT is impossible [74]. $hCD34^+$ HSCs differentiate to mature forms capable of HIV infection [76]. Effective reconstitution of human microglia due to migration of $hCD45^+$ cells, $hCD3^+$ T cells and $hCD68^+$ macrophages from the olfactory bulb through the base of the brainstem to the medulla oblongata [67]. There are a large number of human B cells in the brain of females than in males [67]. The presence of $hCD4^+$ and $hCD8^+$ T cells in the entire brain, while the cerebellum contains a significantly larger number of $hCD68^+$ cells than in the brain. A small number of plasmocytes with a high level of hIgA and hIgG secretion [74]	Activation and depletion of $hCD4^+$ T cells [74, 88, 89]. Maintenance of HIV replication in bone marrow $hCD68^+$ macrophages [67, 104], regardless of the method of infection [67]. There is a direct relationship between the viral load in plasma and the levels of cell-associated RNA in the brain, and between the number of myeloid cells and the duration of infection [67]. Adoptively transferred activated Vδ2 cells promote the spread of the virus as early HIV targets [76]
NRG-hu BLT	I/v; HIV-1	Reconstitution of all major leukocyte subgroups $hCD45^+$, including in the thymus in the context of mouse MHC [84–86, 105]	Activation and depletion of T cells [87–89]. Persistent HIV-1 infection leads to stable and systemic induction of IFN-I [87]

DOI: https://doi.org/10.36233/0372-9311-307

End of the Table 2

Mouse model	Method of infection; pathogen	Anatomical and physiological features	Pathophysiological features
DKO-hu HSC	I/vag; HIV-1	Reconstitution of T-, B-, myeloid cells and natural killers in central and peripheral lymphoid organs [97, 98]	Susceptibility to mucosal viral transmission. $hCD4^+$ T-cells depletion [97, 98]
NRG-hu HSC	I/v; HIV-1	Human hemopoiesis reconstitution, including T-, B-, myeloid and plasmocytoid dendritic cells, natural killers and HSCs [84, 86]. The percentage of $hCD45^+$ cells engraftment in the bone marrow is 6-fold higher than in NOD/SCID mice [86]	Depletion, activation and exhaustion of T cells [87–89]. Expression of the PD-1 T-cell depletion marker [105]
NRG-hu HSC	I/vag; HIV-1		System infection and progressive depletion of $hCD4^+$ T-cells in the gastrointestinal tract and FRT [107]
NRG-hu Thy/HSC	I/v; HIV-1	The ratio of $hCD4^+/hCD8^+$ T cells is slightly higher, and the percentage of natural killer cells, plasmacytoid dendritic cells and monocytes is lower compared to NRG-hu HSC mice [86, 105]	Depletion, activation and exhaustion of T cells, CD38 and HLA expression on hCD8 T cells, expression of PD-1 T cell depletion marker [105]
NOD/SCID-hu Mo	I/v; macrophage-tropic R5 HIV-1 and HIV-2 isolates [104]	Reconstitution of $hCD68^+$ macrophages throughout the brain [104]	HIV replication occurs only in myeloid cells and $hCD68^+$ macrophages, increasing the number of the latter. The absence of a significant decrease in the level of viremia after reaching the peak. The possibility of de novo transmission of infection and effective replication in the new host in the presence or complete absence of human T-cells [104]
NSG-hu PBMC	I/v; $HIV\text{-}1_{DH\ 12}$	Recovery of $hCD45^+$ cells in peripheral blood, lymph nodes, spleen and liver. $hCD19^+$ cells are detected only in the lymph nodes and spleen. T cells are actively regenerated in lymph nodes containing single mouse T cells [110]	Depletion and complete disappearance of $hCD4^+$ T-cells in peripheral blood [110]
IL34–Tg/NOG-hu BLT		Effective reconstitution of human microglia [81]	Maintenance of HIV replication in the brain [81]
BRGST-hu HSC		Reconstitution of central and effector memory T cells and follicular T helper cells providing stable human cellular and humoral reactions [118] in secondary lymphoid tissues with pronounced B-cell zones [119]. The presence of HLA class I and II transgenes improve the development and functionality of T and B cells, including switching of Ig isotype classes and antigen-specific responses [103]	–
CD4C/HIV^{WT} Tg		HIV-1 expression in mouse cells corresponding to cells of HIV-positive humans [114]	Low viability of mice, a significant decrease in monocyte-macrophage-lymphocyte cell populations in the presence of concomitant lung and kidney lesions [114]
GT-tg		Tat protein expression in the central nervous system [116]	

biota [107], local pre-exposure prevention [108, 109], and vaccine therapy [106].

The hu-PBMC model

The hu-PBMC model offers the simplest method for mouse humanization; however, the heterogeneity of transplanted cell populations increases the risk of early development of GVHD and requires animals with high levels of immunodeficiency. Reconstituted $hCD45^+$ cells are detected in peripheral blood, LNs, spleen, and liver of the mice approximately 4 weeks after human peripheral blood mononuclear cells have been injected intraperitoneally into NSG mice, while $hCD19^+$ cells are detected only in LNs and the spleen. $hCD3^+$ T cells are detected in LNs, the spleen and liver, while $hCD4^+$ and $hCD8^+$ subpopulations have extensive localization. Most of the $hCD3^+$ T cells in the red pulp are $hCD8^+$ T cells, while the white pulp contains mainly $hCD4^+$ T cells. $hCD8^+$ lymphocytes are also detected around periportal regions of the liver, while $hCD4^+$ T cells are distributed across tissues more diffusively. $hCD4^+$ and $hCD8^+$ T cells reconstitute actively in LNs containing single mouse T cells. The normal $hCD4^+/hCD8^+$ ratio was detected only in the donor; it was twice as high in recipient mice and remained unchanged for 10 weeks. The intravenous infection with the dual-tropic HIV-1_{DH12} strain resulted in depletion of $hCD4^+$ T cells in peripheral blood 3 weeks after the infection, and in their complete loss in another 2 weeks. In the mice infected with X4 isolate, depletion of $hCD4^+$ T cells is observed 4 weeks after the infection, demonstrating the relationship between the kinetics of $hCD4^+$ lymphocyte depletion and the tropism of the infectious agent [110].

Although NSG mice do not have mature endogenous T and B cells and natural killer cells, the NSG-hu PBMC model developed GVHD signs within 4–16 weeks after the humanization [110, 111]. For this reason, the use of the model contravenes the animal-involving research policy adopted by most research institutions [112].

TKO mice are the most suitable animals for creating the hu-PBMC model [112], as the lack of *CD47* and subsequent tolerance to transplanted human cells delay the GVHD development and body weight loss on average by 24 days compared to the NSG-hu PBMC model [112]. The TKO-hu PBMC mice demonstrate the capability of massive repopulation of multiple tissues and organs by $hCD3^+$, $hCD4^+$, and $hCD8^+$ cells, including the spleen, mesenteric LNs, BM, liver, large intestine, rectum, and brain, while $hCD14^+/hCD163^+$ macrophages and $hCD20^+$ B cells reconstitute in LNs and spleen. Intraperitoneal infection with the R5 isolate causes steady viremia 2 weeks later; the viremia is accompanied by reduction in the number of $hCD4^+$ lymphocytes; note that the viral load in the plasma increases while the number of circulating $hCD4^+$ T cells decreases proportionally, accurately mimicking HIV-1 infection in humans. Rectal and i/vag modes of infection demonstrate similar results, though with some delay in development of infection signs. The p24 antigen is detected in mesenteric LNs, BM, spleen, and rectum; however, although the model is able to reconstitute $hCD4^+$ T cells in the brain, the p24 indication results are not convincing [112]. With the humanization technique, which does not require special skills, and sufficiently safe infection methods used by the operator to infect animals, this new model stands a good chance to gain recognition from the scientific community.

Transgenic animals

Resources of human tissue for creating humanized mice are limited, the transplantation procedure for successful engraftment requires profound technical skills of the personnel, and additional animal models are required due to the impossibility of AIDS pathogenesis assessment. As it turned out, activation of cell signaling pathways, inhibition of mouse MHC, increased pathogenicity of virus particles and Nef-mediated enhancement of viral replication and pathogenesis by inhibition of hCD4, which were observed during some *in vitro* studies, are not the most important characteristics for the Nef phenotype *in vivo* [113]. For example, the mice expressing the whole HIV-1 genome containing a modified long terminal repeat and the mice capable of expressing Nef, Gag, or protease in lens fibers develop depletion and eye disorders. The expression of a 3' half-HIV-1 genome causes severe nephropathy in mice, while the expression of Nef or Tat causes epidermal hyperplasia. In their turn, mice, whose T cells express $CD4^+$, and $CD4C/HIV^{WT}$ Tg mice, which have cells expressing the whole HIV-1 genome, are characterized by low viability due to reduced monocyte-macrophage-lymphocyte cell populations, if they have concomitant kidney and lung disorders phenotypically close to those in humans with AIDS [114]. The similarity between this model and AIDS manifestations in children points at the critical role of Nef in AIDS progression in humans, regardless of its role in virus replication [115]. The expression of Tat protein in CNS of GT-tg mice helps assess behavioral disorders associated with HIV-1 Tat effect [116].

Some models expressing myeloid hSCF, hGM-CSF, and hIL-3 cytokines (NSGS mice) [117, 118] as well as MITRG and MISTR models [119] turned out to be non-viable, demonstrating short life span of 10–20 weeks after the humanization.

Finally, it has been reported about creation of transgenic rabbits carrying the HIV-1hCD4/hCCR5 entry receptor complex through combined microinjection of both constructs. The developers of this model are planning to use primary cell cultures obtained from these animals for HIV adaptation and, subsequently, for changes in the virus [23].

DOI: https://doi.org/10.36233/0372-9311-307

Table 2 presents the summarized data on chimeric model organisms.

Conclusion

SIV shares only 50% identity with HIV; there are significant differences in the composition of the γδ-lymphocyte subset in the monkey and human phenotype [76]; however, SIV-infected non-human primates are used as the main animal model for *in vivo* assessment of the effectiveness of potential vaccines and microbicides [120, 121]. Although in vaccines, epitopes must be compatible with the infection-inducing virus, for a long time SIV of rhesus macaques has been used most frequently for preclinical assessment of vaccines against HIV [75].

When using humanized mice in ART studies, close attention should be given to preparation and provision of viral epitopes in the context of human rather than mouse MHC. For example, immunodominant epitopes presented by mouse MHC for human T-cell receptors may not be directly relevant to human immunodominant epitopes presented by MHC, let alone to human T-cell receptors; therefore, the process of development of T cells in humanized mice in the absence of human stroma should be thoroughly studied [75].

Compared to NSG-hu HSC, NSG-hu Thy/Liv, and NRG-hu HSC mice, NSG-hu BLT mice have better reconstitution of the functional human immune system, including mucosal immune system [92, 93], and can be infected with HIV-1 through intravaginal, rectal, and oral routes [94]. For this reason, hu-BLT mice are currently considered the gold standard for HIV-1 research in murine models [95, 96].

In humans, the transition of T cell-tropic CNS viruses to a macrophage-tropic phenotype generally corresponds with a longer timer of infection and extensive replication leading to viral evolution. However, the overall lifespan of mice is relatively short compared with that of humans; therefore, there is no possibility to follow the animal models over several years after their infection [67], and the problem of the relevant animal model for HIV infection remains unsolved.

REFERENCES

1. Berkowitz R., Alexander S., McCune J. Short communication: causal relationships between HIV-1 coreceptor utilization, tropism, and pathogenesis in human thymus. *AIDS Res. Hum. Retroviruses*. 2000; 16(11): 1039–45. https://doi.org/10.1089/08892220050075291
2. Sharp P., Hahn B. Origins of HIV and the AIDS pandemic. *Cold Spring Harb. Perspect. Med*. 2011; 1(1): a006841. https://doi.org/10.1101/cshperspect.a006841
3. Wong J., Yukl S. Tissue reservoirs of HIV. *Curr. Opin. HIV AIDS*. 2016; 11(4): 362–70. https://doi.org/10.1097/coh.0000000000000293
4. Heyns C., Groeneveld A., Sigarroa N. Urologic complications of HIV and AIDS. *Nat. Clin. Pract. Urol*. 2009; 6(1): 32–43. https://doi.org/10.1038/ncpuro1273
5. Berger E., Murphy P., Farber J. Chemokine receptors as HIV-1 coreceptors: Roles in viral entry, tropism, and disease. *Annu Rev Immunol*. 1999; 17(1): 657–700. https://doi.org/10.1146/annurev.immunol.17.1.657
6. Meissner E., Duus K., Loomis R., D'Agostin R., Su L. HIV-1 replication and pathogenesis in the human thymus. *Curr. HIV Res*. 2003; 1(3): 275–85. https://doi.org/10.2174/1570162033485258
7. Moore J., Kitchen S., Pugach P., Zack J. The CCR5 and CXCR4 coreceptors — central to understanding the transmission and pathogenesis of human immunodeficiency virus type 1 infection. *AIDS Res. Hum. Retroviruses*. 2004; 20(1): 111–26. https://doi.org/10.1089/088922204322749567
8. Singh A., Collman R. Heterogeneous spectrum of coreceptor usage among variants within a dualtropic human immunodeficiency virus type 1 primary-isolate quasispecies. *J. Virol*. 2000; 74(21): 10229–35. https://doi.org/10.1128/jvi.74.21.10229-10235.2000
9. Doitsh G., Galloway N., Geng X., Yang Z., Monroe K.M., Zepeda O., et al. Cell death by pyroptosis drives CD4 T-cell depletion in HIV-1 infection. *Nature*. 2014; 505(7484): 509–14. https://doi.org/10.1038/nature12940
10. Ruddle N.H., Akirav E.M. Secondary lymphoid organs: responding to genetic and environmental cues in ontogeny and the immune response. *J. Immunol*. 2009; 183(4): 2205–12. https://doi.org/10.4049/jimmunol.0804324
11. Buettner M., Lochner M. Development and function of secondary and tertiary lymphoid organs in the small intestine and the colon. *Front. Immunol*. 2016; 7: 342. https://doi.org/10.3389/fimmu.2016.00342
12. Berkowitz R., van't Wout A., Kootstra N., Moreno M.E., Linquist-Stepps V.D., Bare C., et al. R5 strains of human immunodeficiency virus type 1 from rapid progressors lacking X4 strains do not possess X4-type pathogenicity in human thymus. *J Virol*. 1999; 73(9): 7817–22. https://doi.org/10.1128/jvi.73.9.7817-7822.1999
13. Kwa D., Vingerhoed J., Boeser B., Schuitemaker H. Increased in vitro cytopathicity of CC chemokine receptor 5-restricted human immunodeficiency virus type 1 primary isolates correlates with a progressive clinical course of infection. *J Infect Dis*. 2003; 187(9): 1397–403. https://doi.org/10.1086/374650
14. Hladik F., Sakchalathorn P., Ballweber L., Lentz G., Fialkow M., Eschenbach D., et al. Initial events in establishing vaginal entry and infection by human immunodeficiency virus type-1. *Immunity*. 2007; 26(2): 257–70. https://doi.org/10.1016/j.immuni.2007.01.007
15. Ma T., Luo X., George A., Mukherjee G., Sen N., Spitzer T.L., et al. HIV efficiently infects T cells from the endometrium and remodels them to promote systemic viral spread. *Elife*. 2020; 9: e55487. https://doi.org/10.7554/elife.55487
16. Greco G., Fujimura S., Mourich D., Levy J. Differential effects of human immunodeficiency virus isolates on β-chemokine and gamma interferon production and on cell proliferation. *J. Virol*. 1999; 73(2): 1528–34. https://doi.org/10.1128/jvi.73.2.1528-1534.1999
17. Olesen R., Wahl A., Denton P., Victor Garcia J. Immune reconstitution of the female reproductive tract of humanized BLT mice and their susceptibility to human immunodeficiency virus infection. *J. Reprod. Immunol*. 2011; 88(2): 195–203. https://doi.org/10.1016/j.jri.2010.11.005
18. Guadalupe M., Reay E., Sankaran S., Prindiville T., Flamm J., McNeil A., et al. Severe $CD4^+$ T-cell depletion in gut lymphoid tissue during primary human immunodeficiency virus type 1 infection and substantial delay in restoration following highly active antiretroviral therapy. *J. Virol*. 2003; 77(21): 11708–17. https://doi.org/10.1128/jvi.77.21.11708-11717.2003
19. Brenchley J., Price D., Schacker T., Asher T.E., Silvestri G., Rao S., et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nat. Med*. 2006; 12(12): 1365–71. https://doi.org/10.1038/nm1511
20. Bobardt M., Chatterji U., Selvarajah S., Van der Schueren B., David G., Kahn B., et al. Cell-free human immunodeficiency virus type 1 transcytosis through primary genital epithelial cells. *J. Virol*. 2007; 81(1): 395–405. https://doi.org/10.1128/jvi.01303-06
21. Nazli A., Chan O., Dobson-Belaire W., Ouellet M., Tremblay M.J., Gray-Owen S.D., et al. Exposure to HIV-1 directly impairs mucosal epithelial barrier integrity allowing microbial translocation. *PLoS Pathog*. 2010; 6(4): e1000852. https://doi.org/10.1371/journal.ppat.1000852
22. Avalos C., Abreu C., Queen S., Li M., Price S., Shirk E.N., et al. Brain macrophages in simian immunodeficiency virus-infected, antiretroviral-suppressed macaques: a functional latent reservoir. *mBio*. 2017;8(4): e01186-17. https://doi.org/10.1128/mbio.01186-17
23. Electronic Theses of LMU Munich. Baldauf H. Rabbits as a model to study HIV-1 infection and the search for new innate immunity players in resting CD4 T cells. Available at: https://edoc.ub.uni-muenchen.de/24163/
24. Baumann J., Unutmaz D., Miller M., Breun S.K., Grill S.M., Mirro J., et al. Murine T cells potently restrict human immunodeficiency virus infection. *J. Virol*. 2004; 78(22): 12537–47. https://doi.org/10.1128/jvi.78.22.12537-12547.2004
25. Tervo H., Keppler O. High natural permissivity of primary rabbit cells for HIV-1, with a virion infectivity defect in macrophages as the final replication barrier. *J. Virol*. 2010; 84(23): 12300–14. https://doi.org/10.1128/jvi.01607-10
26. Sheehy A., Gaddis N., Choi J., Malim M. Isolation of a human gene that inhibits HIV-1 infection and is suppressed by the viral Vif protein. *Nature*. 2002; 418(6898): 646–50. https://doi.org/10.1038/nature00939
27. Sheehy A., Gaddis N., Malim M. The antiretroviral enzyme APOBEC3G is degraded by the proteasome in response to HIV-1 Vif. *Nat. Med*. 2003; 9(11): 1404–7. https://doi.org/10.1038/nm945

28. Stremlau M., Owens C., Perron M., Kiessling M., Autissier P., Sodroski J. The cytoplasmic body component TRIM5α restricts HIV-1 infection in Old World monkeys. *Nature*. 2004; 427(6977): 848–53. https://doi.org/10.1038/nature02343
29. Grossman Z., Meier-Schellersheim M., Paul W., Picker L. Pathogenesis of HIV infection: what the virus spares is as important as what it destroys. *Nat. Med*. 2006; 12(3): 289–95. https://doi.org/10.1038/nm1380
30. Levy J. HIV pathogenesis: 25 years of progress and persistent challenges. *AIDS*. 2009; 23(2): 147–60. https://doi.org/10.1097/qad.0b013e3283217f9f
31. Ameisen J. Programmed cell death (apoptosis) and cell survival regulation: relevance to AIDS and cancer. *AIDS*. 1994; 8(9): 1197–213. https://doi.org/10.1097/00002030-199409000-00001
32. Espert L., Denizot M., Grimaldi M., Robert-Hebmann V., Gay B., Varbanov M., et al. Autophagy is involved in T cell death after binding of HIV-1 envelope proteins to CXCR4. *J. Clin. Invest*. 2006; 116(8): 2161–72. https://doi.org/10.1172/jci26185
33. Zinkernagel R., Hengartner H. T-cell-mediated immunopathology versus direct cytolysis by virus: implications for HIV and AIDS. *Immunol. Today*. 1994; 15(6): 262–8. https://doi.org/10.1016/0167-5699(94)90005-1
34. McCune J. The dynamics of CD4+ T-cell depletion in HIV disease. *Nature*. 2001; 410(6831): 974–9. https://doi.org/10.1038/35073648
35. Veazey R., Lackner A. Nonhuman primate models and understanding the pathogenesis of HIV infection and AIDS. *ILAR J*. 2017; 58(2): 160–71. https://doi.org/10.1093/ilar/ilx032
36. Takehisa J., Kraus M., Ayouba A., Bailes E., Van Heuverswyn F., Decker J.M., et al. Origin and biology of simian immunodeficiency virus in wild-living western gorillas. *J. Virol*. 2009; 83(4): 1635–48. https://doi.org/10.1128/jvi.02311-08
37. Wain L., Bailes E., Bibollet-Ruche F., Decker J.M., Keele B.F., Van Heuverswyn F., et al. Adaptation of HIV-1 to its human host. *Mol. Biol. Evol*. 2007; 24(8): 1853–60. https://doi.org/10.1093/molbev/msm110
38. Novembre F., Saucier M., Anderson D., Klumpp S.A., O'Neil S.P., Brown C.R. 2nd, et al. Development of AIDS in a chimpanzee infected with human immunodeficiency virus type 1. *J. Virol*. 1997; 71(5): 4086–91. https://doi.org/10.1128/jvi.71.5.4086-4091.1997
39. Mwaengo D., Novembre F. Molecular cloning and characterization of viruses isolated from chimpanzees with pathogenic human immunodeficiency virus type 1 infections. *J. Virol*. 1998; 72(11): 8976–87. https://doi.org/10.1128/jvi.72.11.8976-8987.1998
40. Etienne L., Nerrienet E., LeBreton M., Bibila G.T., Foupouapouognigni Y., Rousset D., et al. Characterization of a new simian immunodeficiency virus strain in a naturally infected Pan troglodytes troglodyteschimpanzee with AIDS related symptoms. *Retrovirology*. 2011; 8: 4. https://doi.org/10.1186/1742-4690-8-4
41. Takehisa J., Kraus M., Decker J., Li Y., Keele B.F., Bibollet-Ruche F., et al. Generation of infectious molecular clones of simian immunodeficiency virus from fecal consensus sequences of wild chimpanzees. *J. Virol*. 2007; 81(14): 7463–75. https://doi.org/10.1128/jvi.00551-07
42. Wall J. Great ape genomics. *ILAR J*. 2013; 54(2): 82–90. https://doi.org/10.1093/ilar/ilt048
43. Palesch D., Bosinger S., Tharp G., Vanderford T.H., Paiardini M., Chahroudi A., et al. Sooty mangabey genome sequence provides insight into AIDS resistance in a natural SIV host. *Nature*. 2018; 553(7686): 77–81. https://doi.org/10.1038/nature25140
44. Estes J., Gordon S., Zeng M., Chahroudi A.M., Dunham R.M., Staprans S.I., et al. Early resolution of acute immune activation and induction of PD-1 in SIV-infected sooty mangabeys distinguishes nonpathogenic from pathogenic infection in rhesus macaques. *J. Immunol*. 2008; 180(10): 6798–807. https://doi.org/10.4049/jimmunol.180.10.6798
45. Silvestri G., Paiardini M., Pandrea I., Lederman M., Sodora D. Understanding the benign nature of SIV infection in natural hosts. *J. Clin. Invest*. 2007; 117(11): 3148–54. https://doi.org/10.1172/jci33034
46. Hatziioannou T., Princiotta M., Piatak M. Jr., Yuan F., Zhang F., Lifson J.D., et al. Generation of simian-tropic HIV-1 by restriction factor evasion. *Science*. 2006; 314(5796): 95. https://doi.org/10.1126/science.1130994
47. Zaritsky L., Dery A., Leong W., Gama L., Clements J. Tissue-specific interferon alpha subtype response to SIV infection in brain, spleen, and lung. *J. Interferon Cytokine Res*. 2013; 33(1): 24–33. https://doi.org/10.1089/jir.2012.0018
48. Calantone N., Wu F., Klase Z., Deleage C., Perkins M., Matsuda K., et al. Tissue myeloid cells in SIV-infected primates acquire viral DNA through phagocytosis of infected T cells. *Immunity*. 2014; 41(3): 493–502. https://doi.org/10.1016/j.immuni.2014.08.014
49. Ulenga N., Sarr A., Thakore-Meloni S., Sankalé J., Eisen G., Kanki P. Relationship between human immunodeficiency type 1 infection and expression of human APOBEC3G and APOBEC3F. *J. Infect. Dis*. 2008; 198(4): 486–92. https://doi.org/10.1086/590212
50. Pang W., Song J., Lu Y., Zhang X.L., Zheng H.Y., Jiang J., et al. Host restriction factors APOBEC3G/3F and other interferon-related gene expressions affect early HIV-1 infection in northern pig-tailed macaque (Macaca leonina). *Front Immunol*. 2018; 9: 1965. https://doi.org/10.3389/fimmu.2018.01965
51. Brenchley J., Schacker T., Ruff L., Price D.A., Taylor J.H., Beilman G.J., et al. CD4+ T cell depletion during all stages of HIV disease occurs predominantly in the gastrointestinal tract. *J. Exp. Med*. 2004; 200(6): 749–59. https://doi.org/10.1084/jem.20040874
52. Mehandru S., Poles M., Tenner-Racz K., Horowitz A., Hurley A., Hogan C., et al. Primary HIV-1 infection is associated with preferential depletion of CD4+ T lymphocytes from effector sites in the gastrointestinal tract. *J. Exp. Med*. 2004; 200(6): 761–70. https://doi.org/10.1084/jem.20041196
53. Veazey R., DeMaria M., Chalifoux L., Shvetz D.E., Pauley D.R., Knight H.L., et al. Gastrointestinal tract as a major site of $CD4^+$ T Cell depletion and viral replication in SIV infection. *Science*. 1998; 280(5362): 427–31. https://doi.org/10.1126/science.280.5362.427
54. Veazey R., Mansfield K., Tham I., Carville A.C., Shvetz D.E., Forand A.E., et al. Dynamics of CCR5 expression by $CD4^+$ T cells in lymphoid tissues during simian immunodeficiency virus infection. *J. Virol*. 2000; 74(23): 11001–7. https://doi.org/10.1128/jvi.74.23.11001-11007.2000

55. Picker L., Hagen S., Lum R., Reed-Inderbitzin E.F., Daly L.M., Sylwester A.W., et al. Insufficient production and tissue delivery of CD4+ memory T cells in rapidly progressive simian immunodeficiency virus infection. *J. Exp. Med*. 2004; 200(10): 1299–314. https://doi.org/10.1084/jem.20041049
56. Mattapallil J., Douek D., Hill B., Nishimura Y., Martin M., Roederer M. Massive infection and loss of memory CD4+ T cells in multiple tissues during acute SIV infection. *Nature*. 2005; 434(7037): 1093–7. https://doi.org/10.1038/nature03501
57. Zhang Z., Schuler T., Zupancic M., Wietgrefe S., Staskus K.A., Reimann K.A., et al. Sexual transmission and propagation of SIV and HIV in resting and activated CD4$^+$ T cells. *Science*. 1999; 286(5443): 1353–7. https://doi.org/10.1126/science.286.5443.1353
58. Nowlin B., Burdo T., Midkiff C., Salemi M., Alvarez X., Williams K. SIV encephalitis lesions are composed of CD163+ macrophages present in the central nervous system during early SIV infection and SIV-positive macrophages recruited terminally with AIDS. *Am. J. Pathol*. 2015; 185(6): 1649–65. https://doi.org/10.1016/j.ajpath.2015.01.033
59. Micci L., Alvarez X., Iriele R., Ortiz A.M., Ryan E.S., McGary C.S., et al. CD4 depletion in SIV-infected macaques results in macrophage and microglia infection with rapid turnover of infected cells. *PLoS Pathog*. 2014; 10(10): e1004467. https://doi.org/10.1371/journal.ppat.1004467
60. Carvalho C., Gaspar A., Knight A., Vicente L. Ethical and scientific pitfalls concerning laboratory research with non-human primates, and possible solutions. *Animals (Basel)*. 2018; 9(1): 12. https://doi.org/10.3390/ani9010012
61. Rabin L., Hincenbergs M., Moreno M., Warren S., Linquist V., Datema R., et al. Use of standardized SCID-hu Thy/Liv mouse model for preclinical efficacy testing of anti-human immunodeficiency virus type 1 compounds. *Antimicrob. Agents Chemother*. 1996; 40(3): 755–62. https://doi.org/10.1128/aac.40.3.755
62. Camerini D., Su H., Gamez-Torre G., Johnson M., Zack J., Chen I. Human immunodeficiency virus type 1 pathogenesis in SCID-hu mice correlates with syncytium-inducing phenotype and viral replication. *J. Virol*. 2000; 74(7): 3196–204. https://doi.org/10.1128/jvi.74.7.3196-3204.2000
63. Namikawa R., Weilbaecher K., Kaneshima H., Yee E., McCune J. Long-term human hematopoiesis in the SCID-hu mouse. *J. Exp. Med*. 1990; 172(4): 1055–63. https://doi.org/10.1084/jem.172.4.1055
64. Stoddart C., Geleziunas R., Ferrell S., Linquist-Stepps V., Moreno M.E., Bare C., et al. Human immunodeficiency virus type 1 Nef-mediated downregulation of CD4 correlates with Nef enhancement of viral pathogenesis. *J. Virol*. 2003; 77(3): 2124–33. https://doi.org/10.1128/jvi.77.3.2124-2133.2003
65. Phillips D., Bourinbaiar A. Mechanism of HIV spread from lymphocytes to epithelia. *Virology*. 1992; 186(1): 261–73. https://doi.org/10.1016/0042-6822(92)90080-9
66. Kaizu M., Weiler A., Weisgrau K., Vielhuber K.A., May G., Piaskowski S.M., et al. Repeated intravaginal inoculation with cell-associated simian immunodeficiency virus results in persistent infection of nonhuman primates. *J. Infect. Dis*. 2006; 194(7): 912–6. https://doi.org/10.1086/507308
67. Honeycutt J., Liao B., Nixon C., Cleary R.A., Thayer W.O., Birath S.L., et al. T cells establish and maintain CNS viral infection in HIV-infected humanized mice. *J. Clin. Invest*. 2018; 128(7): 2862–76. https://doi.org/10.1172/jci98968
68. Honeycutt J., Wahl A., Archin N., Choudhary S., Margolis D., Garcia J. HIV-1 infection, response to treatment and establishment of viral latency in a novel humanized T cell-only mouse (TOM) model. *Retrovirology*. 2013; 10: 121. https://doi.org/10.1186/1742-4690-10-121
69. Denton P., Estes J., Sun Z., Othieno F.A., Wei B.L., Wege A.K., et al. Antiretroviral pre-exposure prophylaxis prevents vaginal transmission of HIV-1 in humanized BLT mice. *PLoS Med*. 2008; 5(1): e16. https://doi.org/10.1371/journal.pmed.0050016
70. Wege A., Melkus M., Denton P., Estes J., Garcia J. Functional and phenotypic characterization of the humanized BLT mouse model. *Curr. Top. Microbiol. Immunol*. 2008; 324: 149–65. https://doi.org/10.1007/978-3-540-75647-7_10
71. Sun Z., Denton P., Estes J., Othieno F.A., Wei B.L., Wege A.K., et al. Intrarectal transmission, systemic infection, and CD4+ T cell depletion in humanized mice infected with HIV-1. *J. Exp. Med*. 2007; 204(4): 705–14. https://doi.org/10.1084/jem.20062411
72. Denton P., Krisko J., Powell D., Mathias M., Kwak Y.T., Martinez-Torres F., et al. Systemic administration of antiretrovirals prior to exposure prevents rectal and intravenous HIV-1 transmission in humanized BLT mice. *PLoS One*. 2010; 5(1): e8829. https://doi.org/10.1371/journal.pone.0008829
73. Deruaz M., Murooka T., Ji S., Gavin M.A., Vrbanac V.D., Lieberman J., et al. Chemoattractant-mediated leukocyte trafficking enables HIV dissemination from the genital mucosa. *JCI Insight*. 2017; 2(7): e88533. https://doi.org/10.1172/jci.insight.88533
74. Nochi T., Denton P., Wahl A., Garcia J. Cryptopatches are essential for the development of human GALT. *Cell Rep*. 2013; 3(6): 1874–84. https://doi.org/10.1016/j.celrep.2013.05.037
75. Denton P., Garcia J. Novel humanized murine models for HIV research. *Curr. HIV/AIDS Rep*. 2009; 6(1): 13–9. https://doi.org/10.1007/s11904-009-0003-2
76. Biradar S., Agarwal Y., Lotze M., Rinaldo C., Bility M., Mailliard R. Adoptive transfer of allogeneic gamma delta T cells promotes HIV replication in a humanized mouse model. *bioRxiv*. 2021. Preprint. https://doi.org/10.1101/2021.02.08.430263
77. Purwar R., Campbell J., Murphy G., Richards W., Clark R., Kupper T. Resident memory T cells (TRM) are abundant in human lung: diversity, function, and antigen specificity. *PLoS One*. 2011; 6(1): e16245. https://doi.org/10.1371/journal.pone.0016245
78. Corleis B., Bucsan A., Deruaz M., Vrbanac V.D., Lisanti-Park A.C., Gates S.J., et al. HIV-1 and SIV infection are associated with early loss of lung interstitial CD4+ T cells and dissemination of pulmonary tuberculosis. *Cell Rep*. 2019; 26(6): 1409–18.e5. https://doi.org/10.1016/j.celrep.2019.01.021
79. Dudek T., Allen T. HIV-specific CD8+ T-cell immunity in humanized bone marrow–liver–thymus mice. *J. Infect. Dis*. 2013; 208(Suppl. 2): S150–4. https://doi.org/10.1093/infdis/jit320
80. Dudek T., No D., Seung E., Vrbanac V.D., Fadda L., Bhoumik P., et al. Rapid evolution of HIV-1 to functional CD8$^+$ T cell responses in humanized BLT mice. *Sci. Transl. Med*. 2012; 4(143): 143ra98. https://doi.org/10.1126/scitranslmed.3003984
81. Zhang J., Lohani S., Cheng Y., Wang T., Guo L., Kim W.K., et al. Human microglia extensively reconstitute in humanized-BLT mice with human interleukin-34 transgene and support

HIV-1 brain infection. *Front. Immunol*. 2021; 12: 672415. https://doi.org/10.3389/fimmu.2021.672415

82. Llewellyn G., Alvarez-Carbonell D., Chateau M., Karn J., Cannon P. HIV-1 infection of microglial cells in a reconstituted humanized mouse model and identification of compounds that selectively reverse HIV latency. *J. Neurovirol*. 2017; 24(2): 192–203. https://doi.org/10.1007/s13365-017-0604-2
83. Lan P., Tonomura N., Shimizu A., Wang S., Yang Y. Reconstitution of a functional human immune system in immunodeficient mice through combined human fetal thymus/liver and CD34+ cell transplantation. *Blood*. 2006; 108(2): 487–92. https://doi.org/10.1182/blood-2005-11-4388
84. Ishikawa F., Yasukawa M., Lyons B., Yoshida S., Miyamoto T., Yoshimoto G., et al. Development of functional human blood and immune systems in NOD/SCID/IL2 receptor γ chain^{null} mice. *Blood*. 2005; 106(5): 1565–73. https://doi.org/10.1182/blood-2005-02-0516
85. Zhang L., Kovalev G., Su L. HIV-1 infection and pathogenesis in a novel humanized mouse model. *Blood*. 2006; 109(7): 2978–81. https://doi.org/10.1182/blood-2006-07-033159
86. Shultz L., Lyons B., Burzenski L., Gott B., Chen X., Chaleff S., et al. Human lymphoid and myeloid cell development in NOD/LtSz-scid IL2Rγ^{null} mice engrafted with mobilized human hemopoietic stem cells. *J. Immunol*. 2005; 174(10): 6477–89. https://doi.org/10.4049/jimmunol.174.10.6477
87. Cheng L., Ma J., Li J., Li D., Li G., Li F., et al. Blocking type I interferon signaling enhances T cell recovery and reduces HIV-1 reservoirs. *J. Clin. Invest*. 2016; 127(1): 269–79. https://doi.org/10.1172/jci90745
88. Cheng L., Yu H., Li G., Li F., Ma J., Li J., et al. Type I interferons suppress viral replication but contribute to T cell depletion and dysfunction during chronic HIV-1 infection. *JCI Insight*. 2017; 2(12): e94366. https://doi.org/10.1172/jci.insight.94366
89. Zhen A., Rezek V., Youn C., Lam B., Chang N., Rick J., et al. Targeting type I interferon–mediated activation restores immune function in chronic HIV infection. *J. Clin. Invest*. 2016; 127(1): 260–8. https://doi.org/10.1172/jci89488
90. Sutter K., Lavender K.J., Messer R.J., Widera M., Williams K., Race B., et al. Concurrent administration of IFNA14 and CART in TKO-BLT mice enhances suppression of HIV-1 viremia but does not eliminate the Latent Reservoir. *Sci. Rep*. 2019; 9(1): 18089. https://doi.org/10.1038/s41598-019-54650-9
91. Lavender K.J., Pang W.W., Messer R.J., Duley A.K., Race B., Phillips K., 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(25): 4013–20. https://doi.org/10.1182/blood-2013-06-506949
92. Latinovic O.S., Medina Moreno S., Hippler L.M., Zapata J.C., Redfield R.R. Humanized NSG mouse models of HIV-1 infection and pathogenesis. *Hum. Virol. Retrovirol*. 2016; 3(2). https://doi.org/10.15406/jhvrv.2016.03.00088
93. Skelton J., Ortega-Prieto A., Dorner M. A Hitchhiker's guide to humanized mice: new pathways to studying viral infections. *Immunology*. 2018; 154(1): 50–61. https://doi.org/10.1111/imm.12906
94. Weichseldorfer M., Heredia A., Reitz M., Bryant J., Latinovic O. Use of humanized mouse models for studying HIV-1 infection, pathogenesis and persistence. *J. AIDS HIV Treat*. 2020; 2(1): 23–9. https://doi.org/10.33696/aids.2.003
95. Victor Garcia J. Humanized mice for HIV and AIDS research. *Curr. Opin. Virol*. 2016; 19: 56–64. https://doi.org/10.1016/j.coviro.2016.06.010
96. Karpel M., Boutwell C., Allen T. BLT humanized mice as a small animal model of HIV infection. *Curr. Opin. Virol*. 2015; 13: 75–80. https://doi.org/10.1016/j.coviro.2015.05.002
97. Choudhary S., Rezk N., Ince W., Cheema M., Zhang L., Su L., et al. Suppression of human immunodeficiency virus type 1 (HIV-1) viremia with reverse transcriptase and integrase inhibitors, CD4^{+} T-cell recovery, and viral rebound upon interruption of therapy in a new model for HIV treatment in the humanized Rag2$^{-/-}$γ$_c$ $^{-/-}$ mouse. *J Virol*. 2009; 83(16): 8254–8. https://doi.org/10.1128/jvi.00580-09
98. Neff C., Ndolo T., Tandon A., Habu Y., Akkina R. Oral pre-exposure prophylaxis by anti-retrovirals raltegravir and maraviroc protects against HIV-1 vaginal transmission in a humanized mouse model. *PLoS One*. 2010; 5(12): e15257. https://doi.org/10.1371/journal.pone.0015257
99. Ito M., Hiramatsu H., Kobayashi K., Suzue K., Kawahata M., Hioki K., et al. Nod/SCID/γcnull mouse: An excellent recipient mouse model for engraftment of human cells. *Blood*. 2002; 100(9): 3175–82. https://doi.org/10.1182/blood-2001-12-0207
100. Hiramatsu H., Nishikomori R., Heike T., Ito M., Kobayashi K., Katamura K., et al. Complete reconstitution of human lymphocytes from cord blood CD34+ cells using the nod/SCID/γcnull mice model. *Blood*. 2003; 102(3): 873–80. https://doi.org/10.1182/blood-2002-09-2755
101. Watanabe S., Terashima K., Ohta S., Horibata S., Yajima M., Shiozawa Y., et al. Hematopoietic stem cell–engrafted nod/SCID/IL2RΓNULL mice develop human lymphoid systems and induce long-lasting HIV-1 infection with specific humoral immune responses. *Blood*. 2006; 109(1): 212–8. https://doi.org/10.1182/blood-2006-04-017681
102. Gillgrass A., Wessels J., Yang J., Kaushic C. Advances in humanized mouse models to improve understanding of HIV-1 pathogenesis and immune responses. *Front. Immunol*. 2021; 11: 617516. https://doi.org/10.3389/fimmu.2020.617516
103. Li Y., Masse-Ranson G., Garcia Z., Bruel T., Kök A., Strick-Marchand H., et al. A human immune system mouse model with robust lymph node development. *Nat. Methods*. 2018; 15(8): 623–30. https://doi.org/10.1038/s41592-018-0071-6
104. Honeycutt J., Wahl A., Baker C., Spagnuolo R.A., Foster J., Zakharova O., et al. Macrophages sustain HIV replication in vivo independently of T cells. *J. Clin. Invest*. 2016; 126(4): 1353–66. https://doi.org/10.1172/jci84456
105. 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. https://doi.org/10.3389/fimmu.2018.00817
106. Godot V., Tcherakian C., Gil L., Cervera-Marzal I., Li G., Cheng L., et al. TLR-9 agonist and CD40-targeting vaccination induces HIV-1 envelope-specific B cells with a diversified immunoglobulin repertoire in humanized mice. *PLoS Pathog*. 2020; 16(11): e1009025. https://doi.org/10.1371/journal.ppat.1009025
107. Wessels J., Lajoie J., Cooper M., Omollo K., Felker A.M., Vitali D., et al. Medroxyprogesterone acetate alters the vaginal microbiota and microenvironment in a Kenyan sex worker cohort and is also associated with increased susceptibility to

HIV-1 in humanized mice. *Dis. Model. Mech*. 2019; 12(10): dmm039669. https://doi.org/10.1242/dmm.039669

108. Veselinovic M., Preston Neff C., Mulder L., Akkina R. Topical gel formulation of broadly neutralizing anti-HIV-1 monoclonal antibody VRC01 confers protection against HIV-1 vaginal challenge in a humanized mouse model. *Virology*. 2012; 432(2): 505–10. https://doi.org/10.1016/j.virol.2012.06.025
109. Veselinovic M., Yang K., LeCureux J., Sykes C., Remling-Mulder L., Kashuba A.D.M., et al. HIV pre-exposure prophylaxis: Mucosal tissue drug distribution of RT inhibitor Tenofovir and entry inhibitor Maraviroc in a humanized mouse model. *Virology*. 2014; 464-465: 253–63. https://doi.org/10.1016/j.virol.2014.07.008
110. Kim K.C., Choi B.S., Kim K.C., Park K.H., Lee H.J., Cho Y.K., et al. A simple mouse model for the Study of Human Immunodeficiency virus. *AIDS Res. Hum. Retroviruses*. 2016; 32(2): 194–202. https://doi.org/10.1089/aid.2015.0211
111. Walsh N.C., Kenney L.L., Jangalwe S., Aryee K.E., Greiner D.L., Brehm M.A., et al. Humanized mouse models of clinical disease. *Annu. Rev. Pathol*. 2017; 12: 187–215. https://doi.org/10.1146/annurev-pathol-052016-100332
112. Holguin L., Echavarria L., Burnett J.C. Novel humanized peripheral blood mononuclear cell mouse model with delayed onset of graft-versus-host disease for preclinical HIV research. *J. Virol*. 2022; 96(3): e0139421. https://doi.org/10.1128/jvi.01394-21
113. Foster J., Garcia J. Role of Nef in HIV-1 replication and pathogenesis. *Adv. Pharmacol*. 2007; 55: 389–409. https://doi.org/10.1016/s1054-3589(07)55011-8
114. Hanna Z., Kay D., Cool M., Jothy S., Rebai N., Jolicoeur P. Transgenic mice expressing human immunodeficiency virus type 1 in immune cells develop a severe AIDS-like disease. *J. Virol*. 1998; 72(1): 121–32. https://doi.org/10.1128/jvi.72.1.121-132.1998
115. Hanna Z., Kay D., Rebai N., Guimond A., Jothy S., Jolicoeur P. Nef harbors a major determinant of pathogenicity for an AIDS-like disease induced by HIV-1 in transgenic mice. *Cell*. 1998; 95(2): 163–75. https://doi.org/10.1016/s0092-8674(00)81748-1
116. Paris J., Singh H., Carey A., McLaughlin J. Exposure to HIV-1 Tat in brain impairs sensorimotor gating and activates microglia in limbic and extralimbic brain regions of male mice. *Behav. Brain Res*. 2015; 291: 209–18. https://doi.org/10.1016/j.bbr.2015.05.021
117. Wunderlich M., Chou F., Sexton C., Presicce P., Chougnet C.A., Aliberti J., et al. Improved multilineage human hematopoietic reconstitution and function in NSGS mice. *PLoS One*. 2018; 13(12): e0209034. https://doi.org/10.1371/journal.pone.0209034
118. Yoshihara S., Li Y., Xia J., Danzl N., Sykes M., Yang Y. Post-transplant hemophagocytic lymphohistiocytosis driven by myeloid cytokines and vicious cycles of T-Cell and macrophage activation in humanized mice. *Front. Immunol*. 2019; 10: 186. https://doi.org/10.3389/fimmu.2019.00186
119. Ivic S., Rochat M., Li D., Audigé A., Schlaepfer E., Münz C., et al. Differential dynamics of HIV infection in humanized MISTRG versus MITRG mice. *ImmunoHorizons*. 2017; 1(8): 162–75. https://doi.org/10.4049/immunohorizons.1700042
120. Van Rompay K. Evaluation of antiretrovirals in animal models of HIV infection. *Antiviral. Res*. 2010; 85(1): 159–75. https://doi.org/10.1016/j.antiviral.2009.07.008
121. Veazey R.S. Microbicide safety/efficacy studies in animals: macaques and small animal models. *Curr. Opin. HIV AIDS*. 2008; 3(5): 567–73. https://doi.org/10.1097/coh.0b013e32830891bb

DOI: https://doi.org/10.36233/0372-9311-307

Информация об авторах

Нагорных Алексей Михайлович✉ — к.вет.н., с.н.с. научной группы разработки экспериментальных моделей лаб. экспериментальной фармакологии отдела молекулярной диагностики и эпидемиологии ЦНИИ Эпидемиологии Роспотребнадзора, Москва, Россия, nagornih@cmd.su, https://orcid.org/0000-0002-8320-2999

Тюменцева Марина Алексеевна — к.б.н., зав. лаб. геномного редактирования отдела молекулярной диагностики и эпидемиологии ЦНИИ Эпидемиологии Роспотребнадзора, Москва, Россия, https://orcid.org/0000-0002-3145-3702

Тюменцев Александр Игоревич — к.б.н., зав. лаб. экспериментальной фармакологии отдела молекулярной диагностики и эпидемиологии ЦНИИ Эпидемиологии Роспотребнадзора, Москва, Россия, https://orcid.org/0000-0003-0537-2586

Акимкин Василий Геннадиевич — д.м.н., профессор, академик РАН, директор ЦНИИ Эпидемиологии Роспотребнадзора, Москва, Россия, https://orcid.org/0000-0003-4228-9044

Участие авторов. Все авторы внесли существенный вклад в проведение поисково-аналитической работы и подготовку статьи, прочли и одобрили финальную версию до публикации.

Статья поступила в редакцию 05.07.2022;
принята к публикации 04.10.2022;
опубликована 30.10.2022

Information about the authors

Aleksey M. Nagornykh✉ — Cand. Sci. (Vet.), senior researcher, Scientific group of experimental models' development, Laboratory of experimental pharmacology, Department of molecular diagnostics and epidemiology, Central Research Institute for Epidemiology, Moscow, Russia, nagornih@cmd.su, https://orcid.org/0000-0002-8320-2999

Marina A. Tyumentseva — Cand. Sci. (Biol.), Head, Laboratory of genome editing, Department of molecular diagnostics and epidemiology, Central Research Institute for Epidemiology, Moscow, Russia, https://orcid.org/0000-0002-3145-3702

Aleksandr I. Tyumentsev — Cand. Sci. (Biol.), Head, Laboratory of experimental pharmacology, Department of molecular diagnostics and epidemiology, Central Research Institute for Epidemiology, Moscow, Russia, https://orcid.org/0000-0003-0537-2586

Vasily G. Akimkin — D. Sci. (Med.), Professor, Full Member of the Russian Academy of Sciences, Director, Central Research Institute for Epidemiology, Moscow, Russia, https://orcid.org/0000-0003-4228-9044

Author contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published.

The article was submitted 05.07.2022;
accepted for publication 04.10.2022;
published 30.10.2022