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Humanized mice for HIV and AIDS research

J Victor Garcia

HIV has a very limited species tropism that prevents the use of most conventional small animal models for AIDS research. The *in vivo* analysis of HIV/AIDS has benefited extensively from novel chimeric animal models that accurately recapitulate key aspects of the human condition. Specifically, immunodeficient mice that are systemically repopulated with human hematolymphoid cells offer a viable alternative for the study of a multitude of highly relevant aspects of HIV replication, pathogenesis, therapy, transmission, prevention, and eradication. This article summarizes some of the multiple contributions that humanized mouse models of HIV infection have made to the field of AIDS research. These models have proven to be highly informative and hold great potential for accelerating multiple aspects of HIV research in the future.

Address
Division of Infectious Diseases, UNC Center for AIDS Research, University of North Carolina School of Medicine, Genetic Medicine Building, Rm. 2043, Chapel Hill, NC 27599-7042, United States

Corresponding author: Victor Garcia, J (Victor_garcia@med.unc.edu)

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HIV tropism

HIV is a human-specific pathogen that does not cause disease in other species, although it can replicate in chimpanzees [1–5]. HIV cannot infect mice, rats, rabbits, or macaques [6–10]. The species-specificity of HIV is not limited to its interactions with its receptor CD4 and co-receptors CXCR4 or CCR5 on host cells. Mouse and rat cells that have been engineered to express human CD4 and either CCR5 or CXCR4 on their cell surface do not support HIV replication [7,10]. Additional viral restriction factors like TRIM5α and APOBEC3 limit the ability of HIV to replicate in cells from other species [11–17]. The multiple barriers to HIV replication found in other species limit the availability of adequate animal models to study fundamental aspects of HIV biology and its interactions with the host.

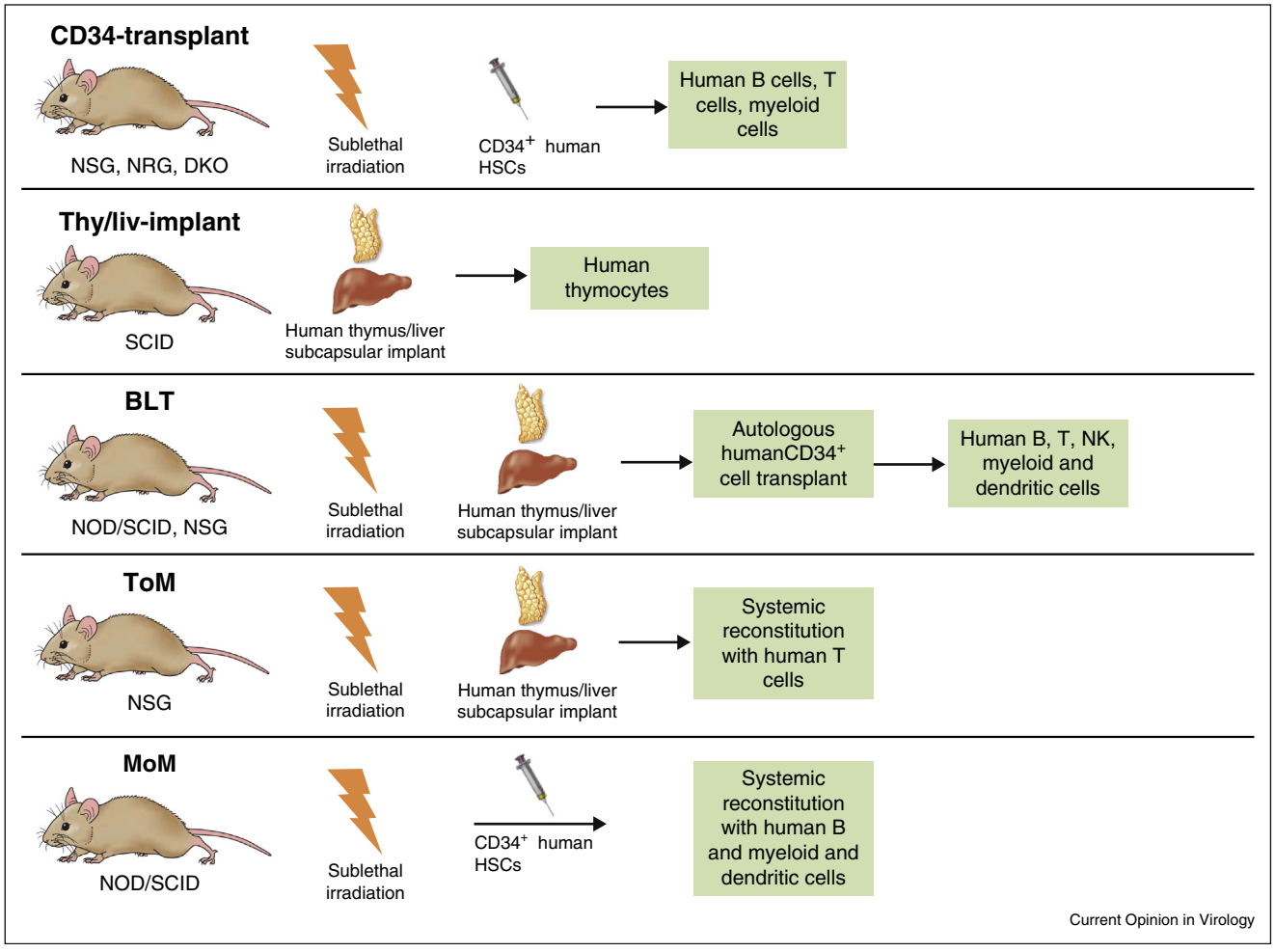
Human-mice chimeras

Human hematopoietic stem cells have the unique capacity of engrafting, greatly expanding, and repopulating immunodeficient mice with virtually all different types of human immune cells [18–27]. Humanized mouse models are produced *via* transplantation of CD34+ stem cells and/or implantation of human tissue into immunodeficient mice [27]. Depending on whether tissue or CD34+ cells are used and the strain of mouse, this results in systemic or local reconstitution with human hematopoietic cells. Different humanized mouse models are repopulated with different human immune cell populations that can include B cells, monocytes/macrophages, dendritic cells, NK cells and T cells. The types of human cells present in each model depend on the strain of immunodeficient mouse used. However, all animals generated with CD34+ cells first generate human myeloid and B cells. Only certain mouse strains human T cells are generated. These T cells are produced in the mouse thymus and presumed to be educated in the context of mouse major histocompatibility complex (MHC) [28–30]. In order to generate human T cells that are educated in the context of bona-fide human MHC (HLA molecules), human thymus tissue is implanted under the kidney capsule. Over time, the thymic tissue involutes and disappears. Co-implantation of thymus with a piece of autologous human liver results in the creation of a functional human thymus that persists for the life of the animal and continuously produces human thymocytes (SCID-hu thy/liv mice, T cell-only mice (ToM), and bone marrow/liver/thymus (BLT) mice). In this unique circumstance, T cells can develop in the presence of human thymic epithelium, resulting in HLA class I and II restriction [31,32]. BLT mice differ from SCID-hu thy/liv mice and ToM in that they also receive an autologous human bone marrow transplant after the implantation of human liver and thymus tissue, from which T cell progenitors and other human hematopoietic cells are derived. As a result, BLT mice are systemically reconstitution with virtually all other types of human hematopoietic cells [33,34]. Several new strains of immunodeficient mice have been recently used to generate humanized mice that have been extensively employed to study relevant aspects of HIV *in vivo* [35].

Current humanized mouse models

Humanized mouse models currently available (Figure 1) are capable of replicating both HIV-1 and 2 exclusively in human immune cells that are present both in the periphery and in tissues. Human immune cells present in these different types of humanized mice are capable of inducing innate and adaptive immune responses, albeit with

Figure 1



Humanized mice for HIV research. Illustrated are five different humanized mouse models that have been extensively used for the study of HIV *in vivo*. Note that each model has a different type and/or distribution of cells. For example ToM have systemic repopulation with human T cells whereas MoM do not have any T cells but have a full complement of antigen presenting cells. BLT mice have both all different types of T cells in addition of a full complement of antigen presenting cells.

different efficiency [27,34,36–39]. The systemic distribution of human immune cells in all tissues examined, render humanized mice susceptible to HIV infection by the same natural routes in which humans acquire HIV. Specifically, humanized mice can be infected with HIV after a parenteral, rectal, vaginal, or oral HIV exposure. Infection can be readily monitored in peripheral blood plasma using conventional viral load assays and it results in progressive CD4+ T cell depletion in peripheral blood and tissues. Similar to what occurs in humans, early after infection, there is a dramatic and rapid depletion of CD4+ T cells in mucosal tissues like the gastrointestinal (GI) tract of humanized mice that is not reflected in peripheral blood. One important attribute of humanized mice is that HIV infection can be treated with the same antiretroviral drugs that are used in humans [40–46]. Also like in humans, treatment of HIV infection in humanized mice results in systemic recovery of CD4 T cells.

As with any animal model, there are limitations to the use of humanized mice in HIV research. These include the relatively small volume of peripheral blood plasma that can be obtained longitudinally from the same animal for viral load analysis, the limited number of peripheral blood cells that can be used for *ex vivo* functional analysis, and their relatively short life-span. Therefore, humanized mice are an accelerated model to evaluate relevant aspects of HIV infection. Because of the fact that humanized mice are xenographs between humans and mice, the structure of their secondary lymphoid tissues do not always fully replicate what is observed in humans. In addition, wasting disease can develop over time in highly