

# Humanized mice: are we there yet?

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**Animal models have been instrumental in increasing the understanding of human physiology, particularly immunity. However, these animal models have been limited by practical considerations and genetic diversity. The creation of humanized mice that carry partial or complete human physiological systems may help overcome these obstacles. The National Institute of Allergy and Infectious Diseases convened a workshop on humanized mouse models for immunity in Bethesda, MD, on June 13–14, 2005, during which researchers discussed the benefits and limitations of existing animal models and offered insights into the development of future humanized mouse models.**

## Introduction

Experimental therapy in humans is limited by technical and ethical considerations, and studies in closely related nonhuman primates are constrained by high cost, limited availability, paucity of genetic models for human diseases, and lack of genetically inbred strains suitable for stem cell or tissue transplantation. In contrast, studies in mice have provided proof of principle for stem cell transplantation and other therapies. But rodents are not humans, and thus experiments performed solely in mice may not accurately predict outcomes in humans. This limitation creates a critical need for effective small animal models in which human hematolymphoid cells and tissues can be transplanted and studied. The development of these humanized mouse models, their use in various areas of research, and limitations of the currently available models are discussed below.

## Historical perspective

The ability to transplant human tissues into experimental animals benefited

from early studies with fetal sheep (1) and genetically athymic nude mice. In fetal sheep, human hematopoietic stem cells (HSCs) successfully colonized the bone marrow, persisted for many years, and retained the ability to differentiate into multiple cell lineages. But the utility of this model is hampered by cost and time constraints. Early studies with T cell-deficient nude mice were discouraging, as these mice failed to support the growth of transferred human hematopoietic cells (2). A few years later, however, the ability to study human hematopoiesis in experimental animal models was facilitated by the discovery of the severe combined immunodeficiency (*Prkd<sup>scid</sup>*), or SCID mutation, which results in a lack of both T and B cells (3). Transplantation of human hematolymphoid cells into SCID mice proved more successful, although the number of human cells that successfully engrafted in the mice was very low (4). The limited engraftment was due in part to the rejection of the cells by the host innate immune response. The SCID mutation occurred on the CB17 strain, which has high levels of innate immunity, most notably natural killer (NK) cells, which eliminated a majority of the transferred foreign cells. To circumvent this problem, researchers crossed the SCID mutation onto various strains of inbred mice with known defects in innate immunity. As described below, the transfer of the SCID mutation onto the nonobese diabetic (NOD) and other strains has led to better engraftment of

transferred human cells and has facilitated studies of HSC development, autoimmunity, and infectious diseases in these humanized mouse models.

## Immune system reconstitution

The study of human hematopoiesis and the development of a functional human immune system following HSC engraftment has benefited from recent advances in the SCID and other profoundly immunodeficient mouse models. These models include mice with targeted mutations in the recombination activating gene-1 (*Rag1*) or 2 (*Rag2*),  $\beta$ 2 microglobulin (*B2m*), and perforin (*Prf1*) genes. The *Rag1<sup>null</sup>* and *Rag2<sup>null</sup>* mutations prevent development of mature lymphocytes, and the *B2m<sup>null</sup>* and *Prf1<sup>null</sup>* mutations prevent development and functional activity of mouse NK cells, respectively. In NOD-*scid* *B2m<sup>null</sup>* and NOD-*Rag1<sup>null</sup>* mice, human HSCs engraft at moderate levels and differentiate into multiple myeloid lineages. However, lymphoid reconstitution in these mice is limited to immature B cells because residual NK activity appears to constrain development and survival of mature T and B cells (5–7). The NOD-*scid* *B2m<sup>null</sup>* and NOD-*Rag1<sup>null</sup>* *Prf1<sup>null</sup>* mice are also problematic as lymphomas limit their lifespan. The hurdles of NK activity and accelerated lymphomagenesis were recently overcome in three new strains: NOD/Shi-*scid* *IL2r $\gamma$ <sup>null</sup>* (8, 9), NOD-*scid* *IL2r $\gamma$ <sup>null</sup>* (10, 11), and BALB/c-*Rag2<sup>null</sup>* *IL2r $\gamma$ <sup>null</sup>* (12), which all lack the IL-2 family common cytokine receptor  $\gamma$  chain gene (*IL2rg*). The absence of functional receptors for IL-2, IL-7, and other cytokines may prevent the expansion of NK cells and early lymphoma cells in NOD-*scid* *IL2r $\gamma$ <sup>null</sup>* mice, resulting in better engraftment of transferred cells and longer lifespans of the mice. The characteristics of these and other recently developed

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immunodeficient mouse models are summarized in Table I.

During the meeting, Leonard Shultz (10) (Bar Harbor, ME), Fumihiko Ishikawa (11) (Fukuoka, Japan) and Markus Manz (12) (Bellinzona, Switzerland) reported that human HSCs and progenitor cells engraft successfully in these mice and produce all human myeloid and lymphoid lineages. They showed that T and B cells migrate into lymphoid organs and intestinal tissues where typical lymphoid structures are created, mount HLA-dependent allogeneic responses, and generate antibodies against T cell-dependent antigens such as ovalbumin and tetanus toxoid. Ishikawa and Manz also reported that newborn NOD-*scid* IL2 $\gamma$ <sup>null</sup> and BALB/c-*Rag2*<sup>null</sup> IL2 $\gamma$ <sup>null</sup> mice have some advantages over adult recipients, including no requirement for exogenous human IL-7 to sustain thymopoiesis, better HSC bone marrow chimerism (50–80% versus ~30% in adults), and the ability to support long-term hematopoiesis with a self-renewing population that engrafts in secondary recipients.

Takeshi Watanabe (Yokohama, Japan) suggested that these mice could be engrafted with artificial lymph nodes, because of their capacity to develop all the components of the human immune system. These artificial lymph nodes, which consist of biocompatible scaffolds containing human stromal cells (13), could provide insights into human secondary lymphoid organ development and the induction of adaptive immune responses.

### Infection and vaccine development

Humanized mice might be instrumental in developing vaccines and therapeutics for human pathogens. The reconstitution of a functional human immune system in mice would provide an experimental system in which natural and vaccine-induced immune responses could be evaluated. The transplanted human immune system could be tested for its ability to protect against infection by pathogens following immunization. Immune responses to a variety of viral

and bacterial infections in humanized mice are currently being studied, and progress in some of these infectious models was reported at the meeting.

Dengue virus is a mosquito-borne pathogen that infects over 50 million people annually and causes a lethal hemorrhagic fever syndrome in as many as half a million. Dengue virus has been problematic to model, as it does not infect adult mice. Thus, murine models of Dengue virus infection require the engraftment of human HSCs, dendritic cells, peripheral blood monocytes, or liver cell lines, which can support virus infection and growth. Joseph Blaney (Bethesda, MD) reported a large scale screening of attenuated Dengue virus serotypes in SCID mice engrafted with human hepatoma cells (14). Blaney identified several attenuated strains that are now in clinical trials as vaccine candidates. NOD-*scid* mice engrafted with human HSCs can also provide a useful model for Dengue infection, as infected mice develop erythremia and thrombocytopenia, both characteristic symptoms of human Dengue fever (Garcia, J.V., and R. Rico-Hesse, personal communication). This model might thus allow studies of the pathogenesis of Dengue virus infection and the testing of anti-Dengue therapeutics.

Influenza vaccine development might also be aided by research in humanized mouse models. Due to rapid antigenic drift, influenza has eluded attempts to create a vaccine that provides long-term protection. Discovery of invariable influenza T cell epitopes by large-scale screening of vaccine candidates might now be feasible in NOD-*scid* (15) and NOD-*scid* B2m<sup>null</sup> mice reconstituted with human HSCs and autologous T cells, as described by Karolina Palucka (Dallas, TX). Palucka showed that all subtypes of human dendritic cells, which orchestrate the adaptive immune response, develop in these mice, with appropriate tissue distribution and function. Deep lung viremia and production of inflammatory cytokines result after inhalation of influenza virus, making this system a promising model for human pathogenesis.

Humanized mice have also been used to study Epstein-Barr virus (EBV), which infects most people as a lifelong asymptomatic infection. Although only a low percentage of healthy carriers develop EBV-associated non-Hodgkin and Burkitt's lymphomas, the tumor incidence is much higher in HIV<sup>+</sup> individuals. J. Victor Garcia showed that NOD-*scid* mice reconstituted with human HSCs are proving useful for study of EBV infection and tumor promotion, as these mice develop lymphoproliferative tumors, such as large B cell lymphomas, within a few weeks of infection with EBV (16).

Diarrheal illness caused by enteric bacteria and protozoa results in significant morbidity and mortality worldwide. Samuel Stanley (St. Louis, MO) and Kim Barrett (San Diego, CA) reported on SCID mice transplanted with human fetal intestinal xenografts to study *Entamoeba histolytica*, *Shigella flexneri*, *Cryptosporidium parvum*, and *Salmonella typhimurium*. Their work indicates that the host innate immune response contributes to the inflammatory colitis and diarrhea that is associated with these infections in humans (17, 18). Finally, Chella David presented studies on toxic shock, which is caused by interaction of HLA class II molecules with staphylococcal enterotoxins, in mice transgenic for human HLA class II genes. In this model, inhaled toxins cause full-blown toxic shock syndrome (19), thus providing a new model to study mechanisms of bacterial toxin pathogenesis in the lung, skin, and gastrointestinal system. HLA-transgenic mice have also been used to identify epitopes of infectious agents for vaccine development (20).

### Autoimmunity

HLA-transgenic mice are particularly useful in modeling human autoimmune diseases that are associated with specific HLA alleles. HLA-transgenic mouse models have been established for rheumatoid arthritis, relapsing polychondritis, experimental autoimmune encephalomyelitis, celiac disease, and Type 1 diabetes (21). These mice offer

**Table I.** Recently developed immunodeficient mouse models

| Host mouse strain  | Human component  | Characteristics   | Applications   | References                                  |
|--|--|---|--|---|
| NOD/Shi- <i>scid</i><br><i>IL2r<math>\gamma</math><sup>null</sup></i><br>(adult)                 | Cord blood HSCs  | B cell, T cell and NK cell development; structured thymus, spleen, lymph nodes; functional lymphocytes  | Hematopoietic reconstitution; microbial infection; vaccine development         | (8, 9)                                      |
| NOD- <i>scid</i> <i>IL2r<math>\gamma</math><sup>null</sup></i><br>(adult)                        | Mobilized HSCs   | B cell, T cell and DC development; structured spleen follicles, proliferative responses to mitogens; need for exogenous human IL-7 for sustained thymopoiesis | Hematopoietic reconstitution; microbial infection; vaccine development         | (10)  |
| NOD- <i>scid</i> <i>IL2r<math>\gamma</math><sup>null</sup></i><br>(newborn)                      | Cord blood HSCs  | B cell, T cell and DC development; structured thymus, spleen; functional immune responses   | Hematopoietic reconstitution; microbial infection; vaccine development         | (11)  |
| BALB/c- <i>Rag2<sup>null</sup></i><br><i>IL2r<math>\gamma</math><sup>null</sup></i><br>(newborn) | Cord blood HSCs  | B cell, T cell and DC development; structured thymus, spleen, lymph nodes; functional immune responses  | Hematopoietic reconstitution; microbial infection; vaccine development         | (12)  |
| NOD- <i>scid</i><br>and NOD- <i>scid</i><br><i><math>\beta</math>2m<sup>null</sup></i>           | Cord blood or mobilized peripheral blood HSCs; autologous T cells          | B cell development; reconstitution of functional DC subsets; no T cell development from HSCs; limited influenza-specific serum IgG                            | Influenza infection; vaccine development; tumor therapeutics                   | (15; Palucka, A.K., personal communication) |
| NOD- <i>scid</i>   | Cord blood HSCs  | B cell development; reconstitution of functional DC subsets; no T cell development from HSCs  | Acute response to LPS  | (25)  |
| NOD- <i>scid</i>   | Cord blood HSCs  | Key features of human Dengue infection; high levels of viremia; viral replication in the spleen, liver, and skin  | Dengue pathogenesis  | Bente, D. (personal communication)          |
| NOD- <i>scid</i>   | Cord blood HSCs  | Fulminating lymphoproliferative tumors as observed in EBV-infected AIDS patients  | EBV-related lymphomagenesis  | (16)  |
| C.B.17- <i>scid</i>  | HuH-7 hepatoma cells   | Dengue viremia approximates human pathology   | Dengue virus vaccine candidate screening                                       | (14)  |
| C.B.17- <i>scid</i>  | Fetal intestine  | Intact human intestinal tissue formation  | Enteric microbial pathogenesis; anti-diarrheal and anti-inflammatory therapies | (17)  |
| C.B.17 <i>scid/bg</i>  | Vascularized skin; artery segments; synthetic vascular beds; T cells       | Tissue engraftment and vascularization; induction of tissue injury and rejection  | Immune-mediated vascular tissue injury and transplant rejection                | (24)  |
| NOD- <i>Rag1<sup>null</sup>Prf1<sup>null</sup></i>   | Pancreatic islet $\beta$ cells from HLA-A2 transgenic mice and humans; PBL | Allograft rejection by allogeneic human PBLs  | Transplantation tolerance  | (23)  |
| BALB/c- <i>scid</i> and<br>BALB/c- <i>scid/bg</i>  | Skin; T cells  | Key features of human psoriasis   | Anti-psoriatic therapeutics  | (22)  |
| Various immunocompetent backgrounds  | Class II HLA transgenes  | Key features of autoimmune pathologies  | Autoimmune diseases  | (21)  |
| Various immunocompetent backgrounds  | Class II HLA transgenes  | Key features of human toxic shock syndrome  | Toxic shock syndrome   | (19)  |
| Various immunocompetent backgrounds  | Class I and II HLA transgenes  | Expression of human HLA molecules   | Vaccine epitope screening  | (20)  |

advantages over many other experimental models as they more closely reflect human pathologies. For example, HLA-DQ8 transgenic mice have rheumatoid factor, an antibody typically expressed only in rheumatoid arthritis patients, whereas this marker is absent in other animal models of this disease. And the NOD.HLA-DQ8 model of celiac disease is unique in presenting with dermatitis herpetiformis, a chronic and extremely itchy rash which is a predominant pathological feature of the human disease.

The classical mouse models of autoimmune skin diseases are inadequate because of their complex pathophysiology and the marked differences between human and mouse skin-associated immunity, a major limitation being that experimental mouse skin reactions are primarily acute, whereas the human diseases are mostly chronic. Thomas Zollner (Richmond, CA) presented data showing that psoriasis could be induced by injection of bacterial superantigens or autologous T cells into nonlesional skin grafts taken from psoriasis patients and grafted onto SCID mice or onto SCID mice that are also homozygous for the beige (*Lyst<sup>bg</sup>* or *bg*) mutation (*scid/bg* mice) (22), which results in lowered NK cell activity. The ensuing dermatitis resembled human psoriasis in key features such as excessive skin growth, and thickening and scaling of the skin accompanied by T cell expansion, keratinocyte hyperproliferation, and focal ICAM-1 expression. Furthermore, all antipsoriatic compounds currently used to treat humans were effective in treating dermatitis in *scid/bg* mice. Efficacy testing in this model should allow selection of the best new drug candidates for clinical studies.

### Transplantation

It has been recently reported that pancreatic islets transplanted from HLA-A2 transgenic NOD-*scid* mice can reverse chemically induced diabetes in NOD-*Rag1<sup>null</sup> Ppf1<sup>null</sup>* recipients engrafted with PBLs from an HLA-A2 donor, but such islets are rejected if the

PBLs are derived from an HLA-disparate donor (as are HLA-disparate engrafted human islets) (23). It has also been shown that allogeneic human PBLs transferred into *scid/bg* mice engrafted with human vascularized skin, artery segments, or synthetic vascular beds quickly reject these grafts, mimicking human immune-mediated vascular tissue injury (24). Treatment of the grafts with a variety of agents allowed dissection of the molecular events responsible for lymphocyte-mediated vascular tissue remodeling, dysfunction, and destruction, thus providing new therapeutic targets for the reduction of immunological rejection.

### Limitations and possible solutions

Humanized mouse models have made tremendous progress since their inception nearly two decades ago. However, as highlighted by Ronald Gill (Aurora, CO), a number of practical limitations still prevent the current models from serving as fully faithful paradigms of human systems. One of these limitations is the lack of HLA class I and II expression in the mouse thymus, which is required to support the selection of T cells following human stem cell engraftment. To some extent, these issues are being addressed by expressing human HLA molecules as transgenes in mice engrafted with human HSCs, autologous marrow stroma, and thymic tissues. Addition of human endothelium, growth factors, and chemokines might also improve these models by promoting the appropriate trafficking and expansion of human cells.

However, the clinical translational capacity of even the most optimized models may be restricted by limited diversity in the human major and minor histocompatibility alleles that can be expressed in a mouse. As discussed by George Georges (Seattle, WA), humanized mice may not replace the need for large animal studies, but should help limit the number of studies that are required in large animals and humans. Furthermore, as these models acquire an increasing number of human physiological elements, they will

likely provide more straightforward assay systems for the study of the human hematolymphoid system and function. They will likely also provide for the rapid preclinical evaluation of novel vaccines and therapeutic agents.

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