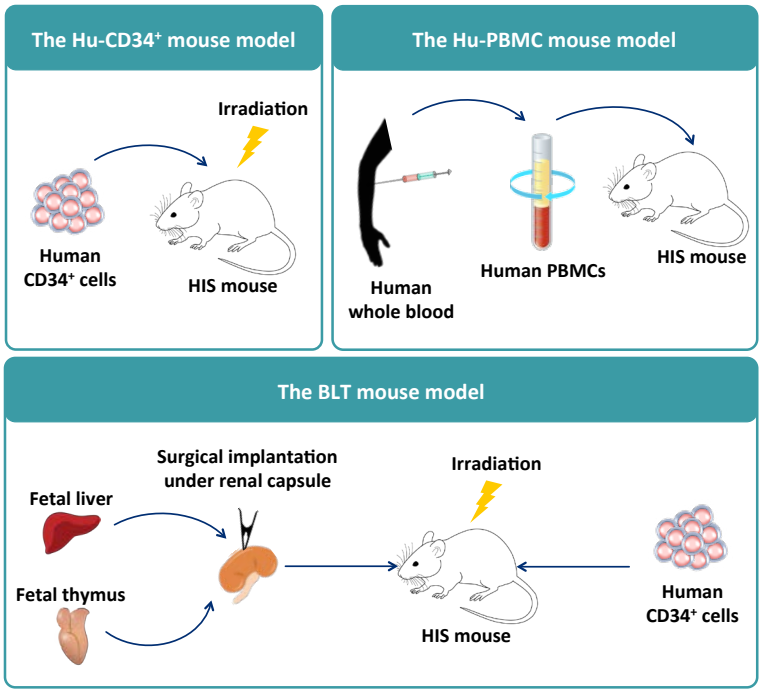
# Part Three: BRGSF-HIS, a New Human Immune System Mouse Model for Immuno-Oncology Studies

*Commentary by Alessia Armezzani, PhD* 21/04/2020

As discussed in our first commentary, the most relevant and widely used models in preclinical cancer research are (i) xenograft mouse models engrafted with human tumor cells, (ii) genetically engineered mouse models (GEMMs), (iii) patient-derived xenografts (PDXs), and (iv) human immune system (HIS) mice. The first three models present one major drawback for immunotherapies investigations, which is that they still possess a murine immune system, which does not always recapitulate human immune responses. HIS mice, on the other hand, are humanized for cellular and molecular components of the immune system and, as such, represent ideal tools to study and modulate the immune components and, more particularly, the interactions with tumors of human origin.[1]

HIS mice are generated by injecting human immune cells into immunodeficient host mice. Two major sources of human immune cells are currently used for this purpose: human peripheral blood mononuclear cells (PBMCs), and human CD34⁺ hematopoietic stem cells (HSCs).[2]

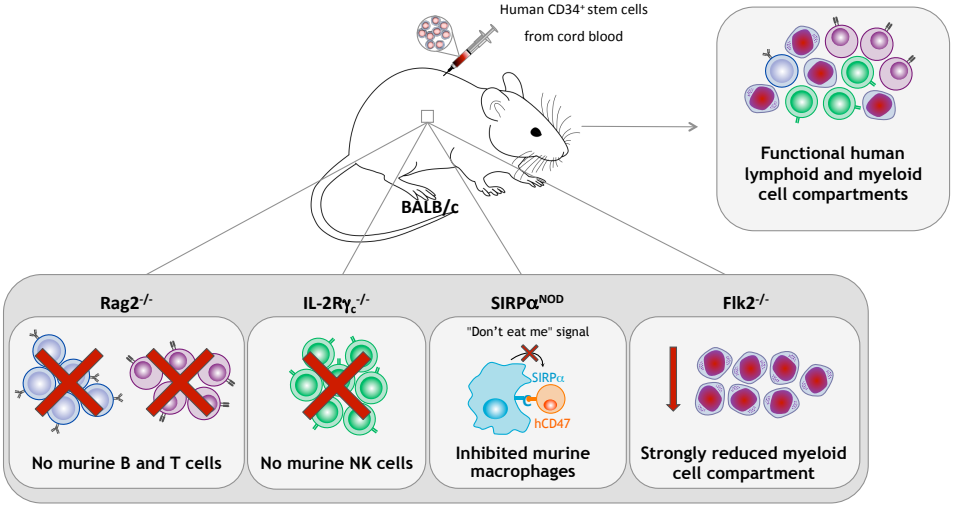
The injection of human PBMCs into immunodeficient adult mice provides the basis of the human peripheral blood lymphocyte (Hu-PBL) mouse model, characterized by low levels of human B and myeloid cells, and a prevalence of functional T cells.[3] For this reason, the Hu-PBL model is suitable for studying human immune cell function – more specifically, T cell function – *in vivo*. However, the injected human lymphocytes preserve their education from the donor and, thus, each time they encounter murine cells, they become active and react against the latter, ultimately leading to the development of graft-versus-host disease (GvHD). While the Hu-PBL model enables, therefore, preclinical investigations of immunosuppressive drugs, its relatively short survival prevents long-term studies (2–3 weeks maximum).[4]




Another strategy to generate HIS mice consists of injecting CD34⁺ HSCs into newborn or young adult immunodeficient mice. This approach results in the development of Hu-CD34⁺ mice, the most widely used models in immuno-oncology preclinical research. Indeed, these animals repopulate with a human functional immune system, and enable, therefore, long-term studies of immune responses to checkpoint inhibitors and other immunotherapies.[4] Prior to injection, these mice are conditioned with sublethal whole-body irradiation, which causes myeloablation and thereby facilitates the circulation and colonization of human immune cells.[5]

These mice can also be engrafted with human fetal liver and thymus fragments under the renal capsule, resulting in the bone marrow, liver, thymus (BLT) humanized model. These animals possess functional and educated human lymphoid and myeloid cell compartments and, accordingly, can sustain long-term human cells and tissues engraftment.[6,7] However, although the transplanted human fetal liver and thymus support the development of human T cells, those with affinity for mouse major histocompatibility complex (MHC) are not eliminated, with the consequence of a higher incidence of GvHD than seen in the Hu-CD34$^{+}$ mouse model.[4]

HIS mice are generated from highly immunodeficient background strains – the more immunodeficient the mice, the better the engraftment and reconstitution of the human immune system. The BRGSF (BALB/c Rag2$^{tm1Fwa}$ Il2rγ$^{tm1Cgn}$ Sirpα$^{NOD}$ Flt3$^{tm1Irl}$) model is in a BALB/c genetic background and carries mutations in the IL2 receptor common γ-chain (IL2rγ) and Rag2; as a result, this mouse does not exhibit murine B, T, or NK cell leakage, contrary to what is reported for SCID based immune-compromised mice.[8] Moreover, the BRGSF displays a high degree of human xenotransplantation due to the expression of the NOD-specific polymorphic Sirpα*, and a strongly reduced myeloid compartment caused by its deficiency in the fetal liver kinase-2 (Flk2), making this model and its derivative strains (e.g., BRGSF-A2-HIS**) highly immunodeficient and better suited to the engraftment and maturation of the human immune system than SCID mice.[10,11]




Furthermore, BRGSF-HIS mice can be specifically boosted for the human dendritic cell compartment when treated with exogenous human Flt3-ligand, resulting in increased and more specific human immune cell responses.[12] Of note, BRGSF-HIS mice show also reactivity upon vaccination and against tumor cells, thereby representing ideal models to assess vaccine development, bi-specifics, and CAR-T cell therapies, and to study the pathophysiology of infectious and inflammatory diseases.[13–15]

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* Upon interaction with CD47, Sirpα negatively regulates host cell phagocytosis (i.e., "don't eat me" signal).[9]

** Studies conducted in 55-week-old BRGSF-A2-HIS mice demonstrated the presence of a preserved human T cell chimerism.[10]

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