GENETICALLY ENGINEERED MODELS (GEM)

NATURAL IMMUNO-DEFICIENT

WILD TYPE

NATURAL MUTANTS

MICE
Mutant inbred

BRGS A2DR2 Mouse

Strain name: C-*Rag2*^{tm1}-*Il2rg*^{tm1}-*Sirpa*^{NOD}-Tg(HLA-A*02-HHD)-Tg(HLA-DR2)/Rj

Type: Mutant inbred mouse,

Origin: Institut Pasteur, France, 2022

Colour and related genotype: Albino mouse

Use of this strain: Is restricted to private sector users

Presentation of the model

The BRGS A2DR2 strain is a highly immunodeficient inbred model with two knockout mutations in the *Il2rg* (*interleukin-2 receptor subunit gamma*) and *Rag2* (*recombination activating gene 2*) genes and carrying a NOD background gene.

The *Rag2*^{tm1} mutation is a knockout of one of the two genes controlling the expression of recombinase activity for VDJ genes, crucial for the formation of B and T cell receptors. This absence hinders the development of these cells, resulting in a total lack of T and B lymphocytes.

The *Il2rg*^{tm1} mutation is a knockout of the gene encoding the gamma c chain, shared by several interleukins (IL-2, IL-4, IL-7, IL-9, and IL-15). This gene is essential for the differentiation and proper functioning of many immune system cells, including natural killer (NK) cells.

The combination of these two mutations, *Rag2*^{tm1} and *Il2rg*^{tm1}, induces severe immunodeficiency, characterized by the absence of T, B, and NK cells. The BRGS A2DR2 strain also carries the NOD variant of the polymorphic *Sirpa* gene. This expression of the SIRPA protein on murine bone marrow macrophages allows cross-recognition with CD47 ligands on human cells, reducing phagocytosis of transplanted human cells.

Finally, this strain expresses two human transgenes: HLA-A*02 and HLA-DR2. The presence of these two transgenes allows for a more rapid emergence of T cells in the hosts' circulation, indicating a potentially more efficient development of human T cells in the mouse thymus following the engraftment of human CD34+ stem cells. The acceleration of CD4+ and CD8+ T cell development in BRGS A2DR2-HIS mice leads to a more balanced composition of B and T cell compartments in peripheral lymphoid organs. The presence of human HLA transgenes enhances both B- and T-cell functions, resulting in elevated levels of class-switched Ig, increased percentages of polyfunctional T cells, and clear indications of antigen-specific T-cell responses post-immunization.

JANVIER LABS has licensed the BRGS A2DR2 strain from the Institut Pasteur. The use of this strain is restricted to private sector users. The animals are bred to maintain both the genetic background and the mutations of interest in their homozygous forms. The BRGS A2DR2 strain is bred in inbred mode and the phenotype is controlled in accordance with the JANVIER LABS GENETIC POLICY®.

In summary, this strain combines a severe immunodeficiency resulting in the total absence of murine T, B, and NK cells, and the expression of class I and II HLA that enhance the differentiation, maturation, and specificity of human T cells after transplantation. It serves an ideal model for the development of T-cell focused therapies, particularly those based on the development of an HLA and epitope specific response such as vaccines.

Main application and research fields

XENOGRAFT
- Tumor xenograft (syngeneic, CDX, PDX...)
- Human CD34+ hematopoietic stem cells
- Human PBMCs
- Organs (pancreas...)

PRE-CLINICAL DEVELOPMENT
- Therapeutic antibodies
- Cell therapy (TCR-redirected T-cells, CAR...)
- Vaccines (DNA, mRNA, peptides...)
- Surgery
- Chemotherapy
- Radiotherapy

THERAPEUTIC AREAS
- Oncology
- Infectious diseases (HIV, EBV, malaria, dengue...)
- Auto-immune diseases (type I diabetes...)

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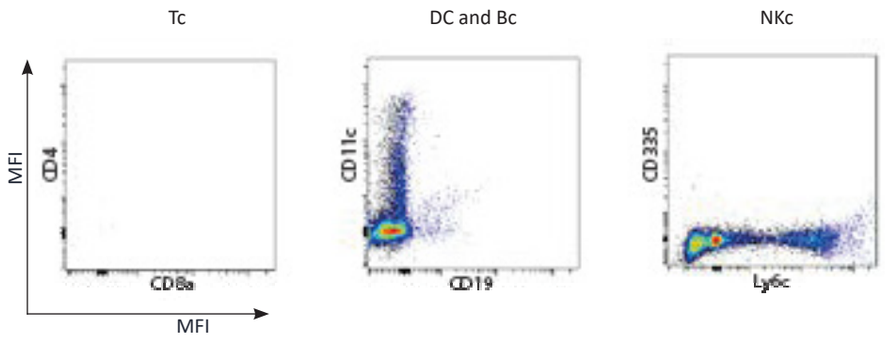
Flow cytometry analysis, spleen



Representative flow cytometry analysis confirming the absence of B cells (CD19), T cells (CD4 and CD8) and NK cells (CD335) in the peripheral blood of BRGS A2DR2 mice.

Characterisation phenotypic

This model has been entirely characterized. The immunological and hematological parameters were characterized by Center of Immunophenomics (Ciphe, Marseille, France).

Background	Breeding	Coat	T Lymphocytes	B Lymphocytes	Leakiness	NK cells	Dendritic cells
BALB/c	Inbred	Albino	Absent	Absent	-	Absent	Dysfonctional
Macrophages	**Complement**	**Irradiation tolerance**	**Life span**	**Humoral immunity**	**Phagocytic tolerance**	**Mutations of interest**	
Normal	Normal	High	89 Wk.	Absent	High	*Sirpa^{NOD} Rag2^{tm1} Il2rg^{tm1}*	

Phenotypical / Physiological observations

BRGS A2DR2 mice are viable, fertile, of normal size, and show no obvious physical or behavioral abnormalities. Histological examination of the lymphoid tissues reveals the absence of lymphoid cells and certain cystic structures in the thymus, an absence of follicles in the spleen, and markedly reduced cellularity of the lymph nodes. BRGS A2DR2 mice are deficient in mature lymphocytes, serum Ig is not detectable. These mice are resistant to the development of lymphomas even after treatment with sublethal radiation. These mutant mice have been shown to readily support the transplantation of human CD34+ hematopoietic stem cells and represent a superior long-lived model suitable for studies using xenotransplantation strategies.

Origin / creation

The BRGS A2DR2 strain carries the transgenes expressing the human HLA molecules A2 and DR2. HLA-A*02-HHD class I and HLA-DR2 class II transgenic mice (B6 background), have been backrossed (>10 generations) to the Balb/c Rag2 γc Sirpα strain (BRGS), to create the BRGS A2DR2 strain.

REFERENCE / PUBLICATION

Accelerated thymopoiesis and improved T-cell responses in HLAA2/-DR2 transgenic BRGS-based human immune system mice

Guillemette Masse-Ranson[1,2,3], Mathilde Duss'eaux[1,2], Oriane Fiquet[1,2], Sylvie Darche[1,2], Maud Boussand[1,2], Yan Li1[2], Silvia Lopez-Lastra[1,2], Nicolas Legrand[4], Erwan Corcuff[4], Antoine Toubert[5,6], Mireille Centlivre[3], Timothee Bruel[3,7,8], Hergen Spits[9], Olivier Schwartz[3,7,8], Yves L'evy[1,10,11], Helene Strick-Marchand[1,2] and James P. Di Santo[1,2]

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