GENETICALLY ENGINEERED MODELS (GEM)

NATURAL IMMUNO-DEFICIENT

WILD TYPE

NATURAL MUTANTS

MICE
Mutant inbred

# BRGS TSLP-HIS Mouse

**Strain name:** C-*Rag2*$^{tm1}$-*Il2rg*$^{tm1}$-*Sirpa*$^{NOD}$-Tg(*Tslp*)/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

**Grafted human cells:** CD34 from blood cord

**Treatment:** Irradiation

## Presentation of the model

Humanized CD34+ mice are the epitome of mice models in terms of surrogate models for humans. Application field ranges from immunology, oncology, infectious diseases and more. This innovative approach bridges the gap between in vitro studies and clinical trials, providing a platform for more accurate and translational investigations in immunology and regenerative medicine.

In that frame, BRGS TSLP-HIS mice provides additional features in comparison to standard models by displaying a complete development of secondary lymphoid tissues (SLT) as well as consisting in the best model up to date for atopic dermatitis.

### The BRGS TSLP mouse model:

The BRGS TSLP strain is a highly immunodeficient inbred model characterized by two knockout mutations in the *Il2rg* and *Rag2* genes, resulting in a lack of T, B, and NK cells. The *Rag2* knockout hinders VDJ gene recombination necessary for B and T cell receptor formation, while the *Il2rg* knockout affects the gamma c chain, essential for immune cell differentiation and function. This strain also carries the NOD variant of the *Sirpa* gene, reducing phagocytosis of transplanted human cells. Compared to the NXG strain, it replaces the *Prkdc*$^{scid}$ mutation with *Rag2* knockout, making it more resistant to various stressors and improving its stability for xenograft purposes. Additionally, it overexpresses murine thymic-stromal-cell-derived lymphopoietin (*Tslp*).

### The humanization process:

The process of humanization involves injecting cord blood-derived human CD34+ cells into mice after inducing myeloablation. This technique allows for the development of a functional and multi-lineage human immune system within the murine host. The use of cord blood as a source of hematopoietic stem cells offers advantages such as accessibility, ethical considerations, and the potential for diverse immune cell populations.

The overexpression of the *Tslp* gene leads to the formation of a complete range of lymph nodes (LNs) containing segregated human B and T cells. In comparison to other immune system humanized mice, BRGST-HIS mice exhibit a larger thymus, increased presence of mature B cells, and a higher number of IL-21-producing follicular helper T ($T_{FH}$) cells, resulting in augmented antigen-specific responses. In essence, BRGST-HIS mice accurately represent the impact of SLT development on human immune responses and offer a valuable model for studying and manipulating immune regulation.
Proper engraftment of the immune system engraftment is assessed between weeks 12-14 by ensuring that over 20% of human CD45+ cells are present in the peripheral blood.

### A model for human atopic dermatitis:

Atopic dermatitis is a chronic inflammatory skin condition characterized by dry, itchy, and inflamed patches of skin. It commonly affects individuals with a family history of allergies, asthma, or eczema, and can flare up due to triggers such as allergens, irritants, or stress. It is a prevalent condition, affecting approximately 15-20% of children and 1-3% of adults worldwide. This disease places not only heavy financial costs on patients and society, but also tremendous negative impact on the quality of life for patients and their family.

While non humanized BRGS TLSP do not show signs of AD development, BRGS TSLP-HIS mice universally demonstrate clinical, histological, immunological and skin commensal changes resembling human AD. Multiple human hematopoietic lineages associated with human AD were identified in BRGS TSLP-HIS mice, such as skin infiltrating Th2 and Th22 cells, IgE secreting B cells and hFcεRIα expressing mast cells and basophils. Similar to clinical findings, AD progression and skin homing chemokine receptor expression on CD4 T cells were highly correlated.

Together, BRGS TSLP-HIS constitutes a novel humanized model, showcasing enhanced immune system development that mirrors the impact of SLT development on human immune responses. This model offers a platform for visualizing and investigating immune regulatory mechanisms.

Moreover, these mice serve as the inaugural spontaneous human AD model and represent an optimal preclinical model for evaluating novel therapeutic interventions.

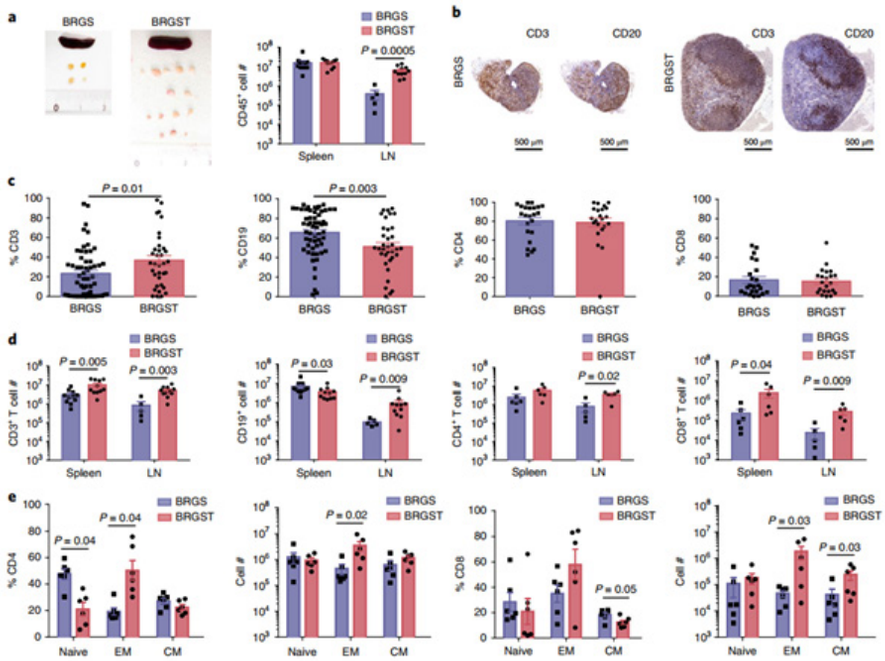
### Services:

The scientific team at Janvier Labs is always available to assist you in optimizing the utilization of our BRGS-HIS mice. Reach out to us to explore how we can contribute to the success of your experiments.

- Typically, our mice, along with a comprehensive report on human system engraftment and sanitary status, are shipped to customers around week 16 post-engraftment. But we can offer to liberate the animals sooner to accommodate your needs.
- Engraftment of CD34+ cells carrying a specific HLA from a donor can be a valuable tool for your research. We can routinely offer engraftment with HLA-A*02:01 donors but can accommodate additional requests.
- If specific percentages of the lymphoid and myeloid compartments are desired to tailor the use of NRG-HIS mice to your research needs, we can selectively choose animals that best suit your requirements.

JANVIER LABS

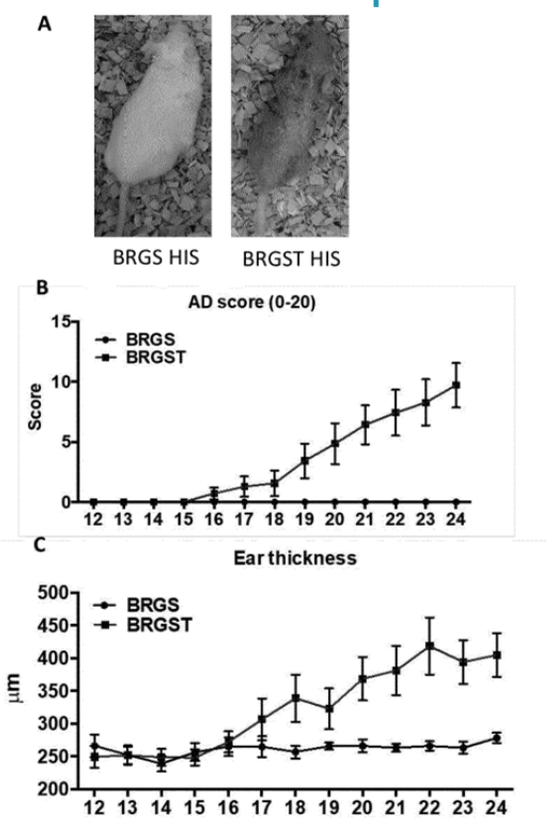
# Characterization of human immune cell reconstitution in BRGS TSLP-HIS mice




a, Representative organs (left; scale bars in centimeters) and absolute numbers of human CD45+ cells (right) in the spleens and LNs of BRGS and BRGS TSLP HIS mice (n = 11 mice per group). All visible LNs in BRGS or BRGS TSLP-HIS mice were pooled.
b, Representative immunohistochemistry images of LN sections from BRGS (left) and BRGS TSLP (right) HIS mice. Scale bars, 500 µm.
c, Percentages of human T cells and B cells (n = 60 (BRGS) or 35 (BRGS TSLP) mice) and CD4+ and CD8+ T cells (n = 23 (BRGS) or 22 (BRGS TSLP) mice) among human hematopoietic cells (hCD45+mCD45– (h, human; m, mouse)) in the blood of the indicated mice. d, Absolute numbers of human T and B cells (n = 11 mice per group) and CD4+ and CD8+ T cells (n = 6 mice per group) in the spleen and LNs of the indicated groups of mice. All visible LNs in BRGS or BRGS TSLP-HIS mice were pooled. e, Percentages and absolute numbers of human naive and memory cell subsets, identified by expression of CCR7 and CD45RA among hCD45+CD3+CD4+ cells and hCD45+CD3+CD8+ cells in the spleen of the indicated groups (n = 6 mice per group). EM, effector memory; CM, central memory. a,c–e, Data are shown as mean ± s.e.m.; P values determined by two-tailed Mann–Whitney U test. Each black square or circle represents an individual mouse.



# Characterization the development of AD in BRGST TSLP-HIS mice




a, Representative photographs of BRGS and BRGS TSLP HIS mice 25 weeks post CD34+ cells engraftment.
b, AD scores evolution post CD34+ cells engraftment. The scoring system based on a system scoring the hair density and coverage, the presence of erosions, crusts and scales from 4 regions of the body on a scale of 0 to 4.
c, Ear thickness evolution post CD34+ cells engraftment.



Quality control allows to measure the relative humanization rate of humanized mice in the peripheral blood. The standardization of quality control is performed by flow cytometry of the different human populations: hematopoietic, lymphoid and myeloid.
Each BRGS TSLP-HIS is tested and analyzed before sending and use. BRGS TSLP-HIS mice are produced with SOPF status. Each batch provided is supplied with a list showing the animal repartition according to the different CD34+ donors.

contact@janvier-labs.com
Tel +33 (0)2 43 02 11 91
**www.janvier-labs.com**