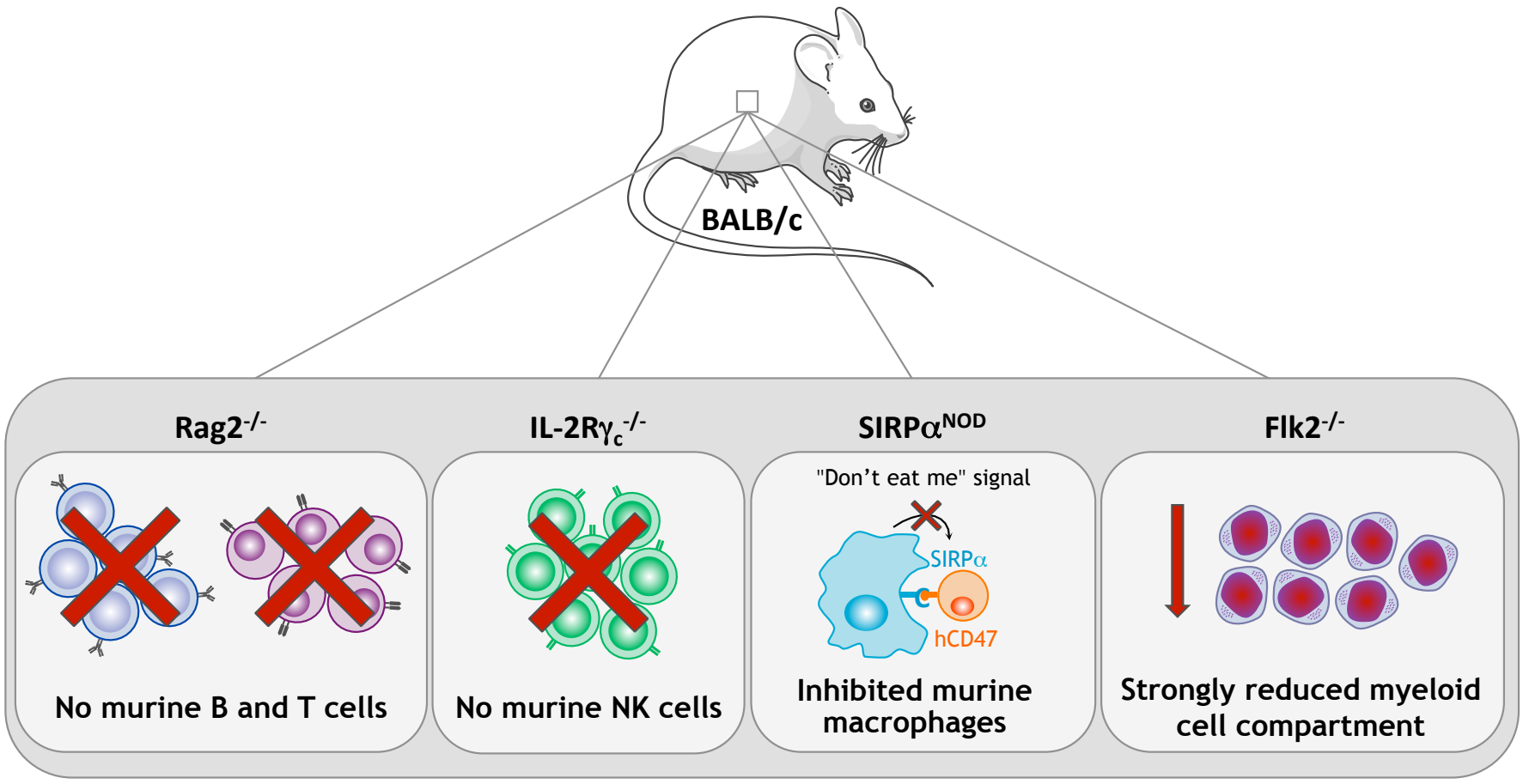
Frequently asked questions on BRGSF mice

1. What is the BRGSF mouse model?

The BRGSF is the most immunodeficient mouse model generated to date, with defects in both myeloid and lymphoid compartments ($Rag2^{-/-}$, IL $2R\gamma^{-/-}$, $Flk2^{-/-}$). Here is its genetic background:



2. What makes the BRGSF an immunodeficient mouse model?

The BRGSF carries multiple genetic defects, including mutations in:

- The recombination-activating gene 2 (RAG2). Together with RAG1, RAG2 initiates the VDJ recombination, a site-specific recombination process that ensures the generation of a large repertoire of unique antigen receptors on B and T lymphocytes. As such, mutations in RAG2 cause depletion in these immune cells.
- The gamma chain of the interleukin 2 receptor (IL-2Rγc). The gamma chain is an essential subunit of functional IL-2 receptors, as well as four other interleukins (IL-4, IL-7, IL-9, and IL-15). Mutations in this gene lead to X-linked severe combined immune deficiency (X-SCID), a combined cellular and humoral immunodeficiency characterized by a profound T- and NK-cell deficiency.
- The fetal liver kinase-2 (Flk2). This is a receptor tyrosine kinase that regulates the development of the myeloid compartment; as such, mutations in Flk2 lead to a strongly reduced myeloid cell compartment.

3. How would you make the most of the BRGSF?

The BRGSF mouse model represents a valuable tool for:

- Human hematopoietic cell engraftment
- Tumor engraftment
- Efficacy and safety of chimeric antigen receptor (CAR) T-cell therapy
- Myeloid compartment development studies

4. Which unique valuable features do BRGSF mice possess?

BALB/c genetic background

As such, these animals represent valuable tools to predict clinical response to certain anticancer drugs, and for long-term transplantation studies. Indeed, contrary to NOD and NOD-derived strains such as NSG and NOG, BRSGF mice do not carry the Prkdc mutation and, therefore, do not show the SCID side effect of high sensitivity to radiation, T-cell leakage, and increased incidence of thymic lymphoma formation.

NOD-specific polymorphic SIRPα

This renders BRGSF mice highly permissive to human cell engraftment. SIRPα is a transmembrane glycoprotein expressed on early hematopoietic progenitors, on myeloid cells such as macrophages and granulocytes, and on dendritic cells and neurons. It binds CD47, an immunoglobulin that acts as a self-marker for macrophages. Importantly, several studies have shown that $Cd47^{-/-}$ mouse hematopoietic cells grafted into wild-type mice, and into mice lacking T, B and NK cells, are rapidly 'eaten' by macrophages, as are wild-type cells if the CD47–SIRPα binding is disrupted. Polymorphisms in SIRPα thereby represent a potent genetic determinant of human hematopoietic stem cell engraftment and host survival.

Fully functional complement cascade

Unlike NOG-based strains, where C5A is knockout, BRGSF mice possess a fully functional complement cascade.

5. How do BRGSF mice compare to other immunocompromised mice?

	BRG/BRGS/BRGSF	NRG	NSG/NOG
No mature B and T lymphocytes	$Rag2^{-/-}$ → no V(D)J recombination		*Prkdc*^{SCID} → Impaired DNA repair
Leakiness: IgG appearance with age	None		Yes (Bosma *et al.*, J Exp Med, 1988)
No NK cells	$IL\text{-}2rg^{-/-}$		
Spontaneous tumor	None		Thymic lymphomas (Monticello *et al.*, Vet Pathol, 1994)
Radiation	Normal (lethal dose 9 Gy)		Sensitive (lethal dose <3 Gy)
Drugs	Not known limitation		Drugs which damage DNA cannot be tested
Additional described phenotypes	• BALB/c → Functional complement cascade • $Flk2^{-/-}$ → Immature mouse myeloid cell compartment		• NOD → Absence of circulating complement → Macrophages and DC: immature and weak functional response