360° MODEL RANGE

NRG mouse

- **Strain name:** NOD-*Rag2-IL2rg^{Tm1}*/Rj
- **Type:** Inbred mutant mouse, GMO
- **Origin:** JANVIER LABS, in 2021
- **Colour and related genotype:** Albino mouse

PRESENTATION OF THE MODEL

The NRG or NOD Rag2 γc strain is a severely immunodeficient inbred strain model (NOD background) with 2 Knock Out (KO) genetic mutations: the γc KO gene (Interleukin 2 receptor gamma chain, *IL2rg^{Tm1}*) and the Rag2 KO gene (recombinase 2 activation gene).

The *Rag2^{Tm1}* mutation, commonly known as Rag2, is a KO mutation of the gene coding for the recombinase 2 enzyme, which plays a key role in the generation of receptors in lymphocytes T and B. This absence blocks the development of T and B lymphocytes and induces an immune deficiency. Mice homozygous for this mutation have a complete absence of T and B lymphocytes in the periphery.

The *IL2rg^{Tm1}* mutation called γc is a KO mutation in the gene encoding the gamma c chain common (in particular) to interleukins (IL-2, IL-4, IL-7, IL-9 and IL-15). This gene is required for the differentiation and function of many hematopoietic cells with a complete impact on Natural Killer (NK) cell development.

The combination of these two mutations *Rag2^{Tm1} -IL2rg^{Tm1}*, induces severe immunodeficiency with absence of T, B and NK lymphocyte compartments.

The NRG strain was also tested for the Sirpα gene polymorphism. The expression of the Sirpα protein (NOD background alleles) on the surface of bone marrow macrophages, allows a binding of high affinity with CD47 markers of human hematopoietic cells.

This binding induces a "don't eat me" signal that blocks murine macrophages and prevents phagocytosis of transplanted human cells.

This is a notable feature of the NOD background that gives it an advantage in human transplantation and xenografting in general. The NRG strain differs from the NXG strain (NOD-*Prkdc^{scid}-IL2rg^{Tm1}*/ Rj) by the absence of the *Prkdc^{scid}*, mutation, commonly known as"SCID" for "Severe Combined Immunodeficiency". The NRG strain is thus more resistant to irradiation, injection of genotoxic products and stress, conferring a more stable and durable use to xenograft in general.

JANVIER LABS obtained the B6 Rag2γc (C57BL/6N-*Rag2^{Tm1}-IL2rg^{Tm1}*/Rj) strain by homologous recombination (mouse ES cellsB6N), developed at the Center for Immunophenomics (Ciphe, Marseille,France) in 2019.

The NRG congenic model was then obtained by high speed backcross (N=6) on NOD background in 2021.
The animals are bred to maintain both the genetic background and the mutations of interest in their homozygous forms. The NRG strain is bred in inbreeding mode and the phenotype is controlled according to the JANVIER LABS GENETIC POLICY®.

Main application and research fields

⋊ **Oncology**
- Tumor implantation studies
- Studies on gene therapy
- Studies of cancer therapies
- Study on hematopoietic cancer cells
- Studies focused on breast cancer
- Humanized model for the evaluation of anticancer gene therapy

⋊ **Immunology and immunotherapy**

⋊ **Human cell implantation in a murine model**

⋊ **Implantation of hematopoietic cells of human origin in a murine model**
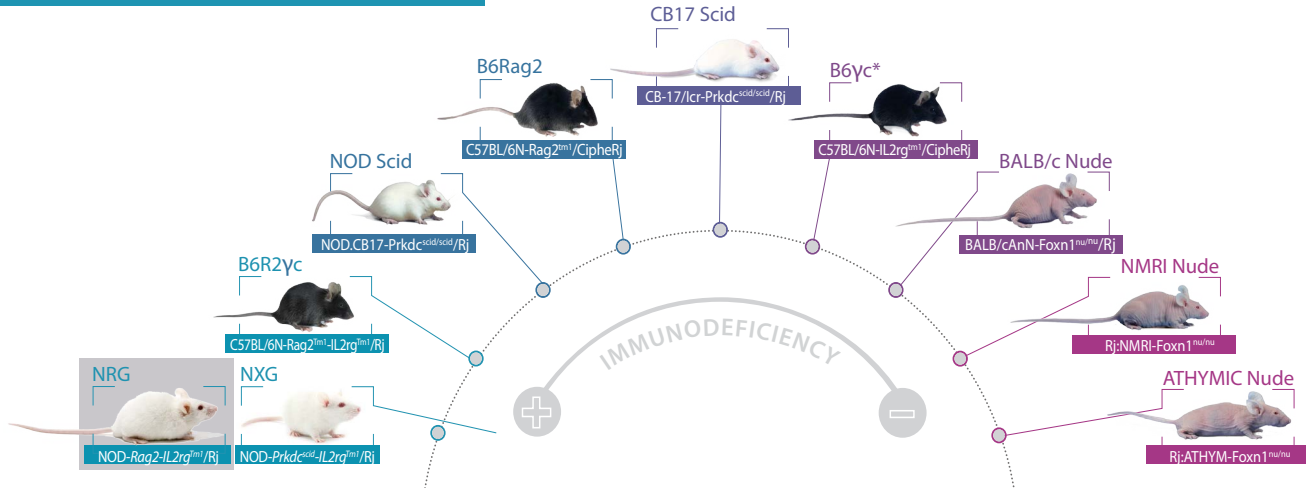
⋊ **Transplants and grafts**
- Human primary tumor xenografts of pulmonary origin
- A platform for the study of stem cells of epithelial origin
- Study the rejection of allograft after a pancreatic transplant against for type 1 diabetes

⋊ **Infectious Diseases**
- Humanized models for the study of humanspecific infectious diseases such

JANVIER LABS
Expertise in Rodent
Research Models

360° MODEL RANGE

NRG AND THE IMMUNODEFICIENT RANGE

CB17 Scid
CB-17/Icr-Prkdc$^{scid/scid}$/Rj

B6Rag2
C57BL/6N-Rag2^{tm1}/CipheRj

B6γc*
C57BL/6N-IL2rg^{tm1}/CipheRj

NOD Scid
NOD.CB17-Prkdc$^{scid/scid}$/Rj

BALB/c Nude
BALB/cAnN-Foxn1$^{nu/nu}$/Rj

NMRI Nude
Rj:NMRI-Foxn1$^{nu/nu}$

B6R2γc
C57BL/6N-Rag2^{Tm1}-IL2rg^{Tm1}/Rj

ATHYMIC Nude
Rj:ATHYM-Foxn1$^{nu/nu}$

NRG
NOD-*Rag2-IL2rg^{Tm1}*/Rj

NXG
NOD-*Prkdc^{scid}-IL2rg^{Tm1}*/Rj

IMMUNODEFICIENCY

+   −

BIOLOGICAL AND HAEMATOLOGICAL PARAMETERS

■ Biochemistry profile

	Amount	Units
Glucose	1550	mg/L
Urea (BUN)	498	mg/L
AST (GOT)	176,5	U/l
ALT (GPT)	40	U/l
Cholesterol	1160	mg/L
Triglycerides	2895	mg/L
Creatinine	1,2	mg/L
LDH	530,8	U/l
a-amylase	2944,3	U/l

■ Haemogram profile

	Amount	Units
Leukocytes	2,4	10^9/l
Erythrocytes	11,5	10^{12}/l
Haemoglobin concentration	17,6	g/dl
Packed cell volume (PCV)	0,59	L/L
MCV	52	fl
MCH	15	pg
MCHC	30	g/dl
Thrombocytes	819	g/l

■ Differential blood count

	Amount	Units
Basophils (absolute)	0	10^9/l
Eosinophils (absolute)	0,096	10^9/l
Band neutrophils (absolute)	0	10^9/l
Segmented neutrophils (abs)	1,392	10^9/l
Lymphocytes (absolute)	0,816	10^9/l
Monocytes (absolute)	0,096	10^9/l
Atypical cells	0	%

PHENOTYPIC CHARACTERISATION

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

Background	Breeding	Coat
NOD	Inbred	Albino
T Lymphocytes	**B Lymphocytes**	**Leakiness**
Absent	Absent	-
NK cells	**Dendritic cells**	**Macrophages**
Absent	Dysfunctional	Dysfunctional
Complement	**Irradiation tolerance**	**Life span**
-	High	89 week
Humoral immunity	**Lymphoma outcome**	**Genes of interest**
Absent	Indefinite	Rag2 et IL2rg

FLOW CYTOMETRY ANALYSIS, SPLEEN

Tc

DC and Bc

NKc
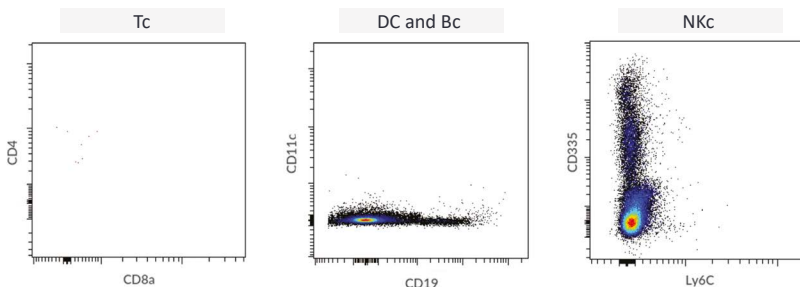
All lymphoid organs of our models were analysed.

ARTICLES OF INTEREST

■ Differential effect of HLA class-I versus class-II transgenes on human T and B cell reconstitution and function in NRG mice
Sai Majji et al
Scientific Reports volume 6, Article number: 28093 (2016)
Cite this article
https://www.nature.com/articles/srep28093

■ Comparative utility of NRG and NRGS mice for the study of normal hematopoiesis, leukemogenesis, and therapeutic response
Aditya Barve et al
Experimental Hematology Volume 67, November 2018, Pages 18-31
https://www.sciencedirect.com/science/article/pii/S0301472X18307513