POWERED BY genOway's PRECLINICAL MODELS

Featuring the genO-BRGSF-HIS (scan or click)

genOway ULTIMATE PREDICTABILITY

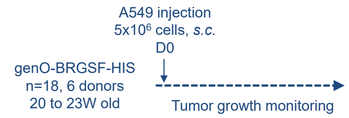
NK cell recruitment into A549 TME in genO-BRGSF-HIS mice

Siham HEDIR, Florent CREUSAT, Amélie MARGUIER, Julie GORRY, Yacine CHERIFI, Fabiane SÔNEGO, Gaelle MARTIN, Kader THIAM
genOway, Lyon, 69007, France

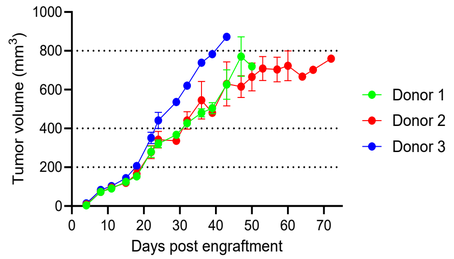
SITC 2025
Abstract #812

Background: Natural killer (NK) cells are key components of the innate system, and their high cytotoxicity has been associated to a more favorable prognosis of cancer. Therefore, strategies focusing on enhancing the effector function of NK cells are being investigated. Assessment of NK-targeting therapies in humanized mice is often challenging, as human NK cell levels are low, requiring supplementation with human IL-15 to enhance their development. Here we describe the recruitment of NK cells in the tumor microenvironment (TME) of A549 lung cancer tumor model in genO-BRGSF-HIS mice (BALB/c Rag2$^{-/-}$, IL2Rγ$^{-/-}$, SIRPα^{NOD} and Flt3$^{-/-}$ immunodeficient mice reconstituted with human cord blood CD34^{+} cells), without the need of supplementation with human IL-15 (1).

1. Permissiveness of genO-BRGSF-HIS mice to A549 xenograft engraftment



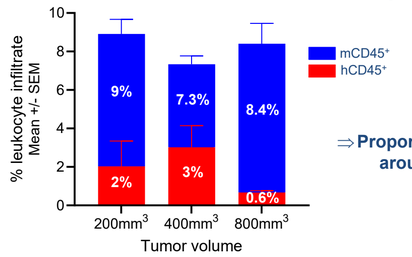
genO-BRGSF-HIS mice were inoculated with A549 cells and tumor growth was analyzed.



⇒ A549 cell line shows 100% take rate
⇒ A549 tumor growth is CD34^{+} donor-independent

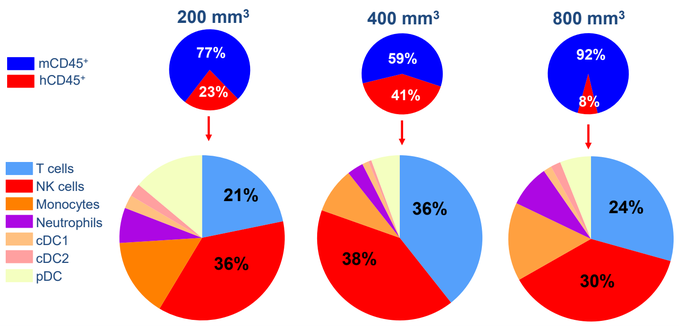
2. TME of A549 is highly infiltrated with NK cells

genO-BRGSF-HIS mice were inoculated (5x10^{6} cells) with the human lung adenocarcinoma A549 cell line and TME was analyzed over time.



⇒ **Proportion of leukocyte infiltration in the tumor is around 10% and remains constant over time**

Among immune infiltrate



⇒ TME of A549 engrafted mice is mainly composed of NK cells (40%) and T cells (20-30%)

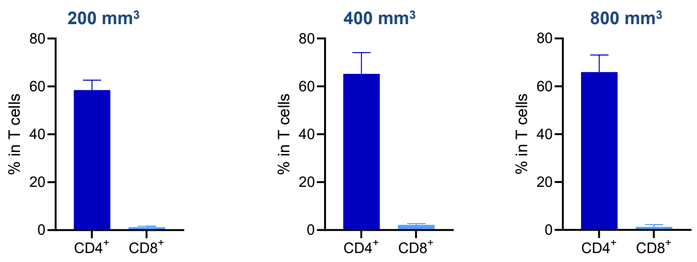
Among NK cell infiltrate

- NK1: Cytotoxic CD56^{dim} cells
- NK2: CD56^{bright} cells, with immature chemokine secreting profile
- NK3: Adaptive mature NK, responsible for ADCC

⇒ NK cells develop and polarize *in vivo* without IL-15 supplementation in A549-bearing genO-BRGSF-HIS
⇒ Clusterization confirms the presence of 3 NK cells subpopulations as described in human tumors(2)
⇒ Cytotoxic NK1 and chemokine-secreting NK2 population decrease upon tumor growth while adaptive NK3 cells increase

3. TME of A549 is also infiltrated with T cells

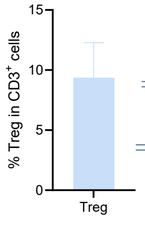
Among T cell infiltrate



⇒ Most of infiltrated T cells are total CD4^{+}
⇒ Proportion of each T cell subset remains constant along tumor growth

Termination – TV= 800 mm³

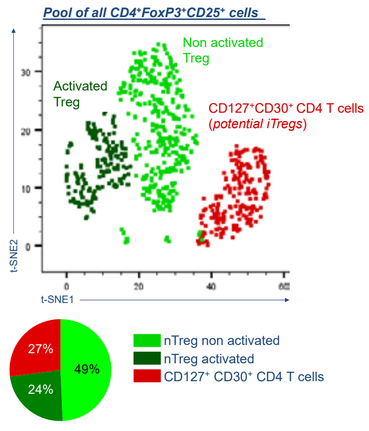
Treg gated on:
CD4^{+} CD25^{+} FoxP3^{+} CD127^{-}

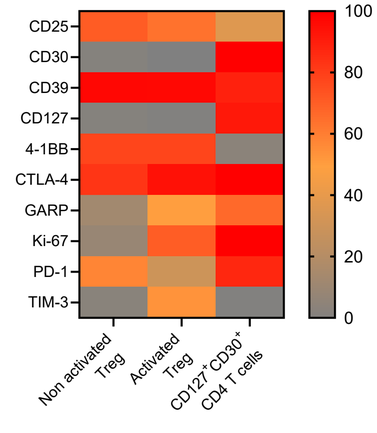


⇒ Treg are detected and account for 5-10% of T cells in the tumor infiltrate at termination

⇒ Proportion of Treg is highly variable between mice, independently of the donor

Treg cell subsets at termination – TV= 800 mm³





⇒ Treg subsets develop in A549-bearing genO-BRGSF-HIS at termination (TV= 800mm³):
- 2 subsets corresponding to activated and non-activated Treg based on the expression of GARP, Ki-97 and TIM-3 markers
- A third subset expressing CD127, CD30, CD39 and high levels of activating markers are potential induced Tregs

Conclusion: Overall, NK cells respond to environmental stimulus and are recruited into the TME of A549-bearing genO-BRGSF-HIS mice, without the supplementation with human IL-15. NK cells functionality remains to be investigated in future studies and would make genO-BRGSF-HIS mouse model a valuable tool to assess NK-targeting immunotherapies.
The A549 TME is also highly infiltrated in T cells. Among T cells, Treg are present and found at different activation status at termination, suggesting that the model could also be used for assessment of therapies targeting Treg.

References:
(1): Martin *et al.*, Front. Immunol., 2025
(2): Rebuffet *et al.*, Nat. Immunol., 2024

Download as PDF

genO-BRGSF-HIS

www.genOway.com