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Tumor cell line-derived xenograft subtype shapes tumor microenvironment composition in genO-BRGSF-HIS mice

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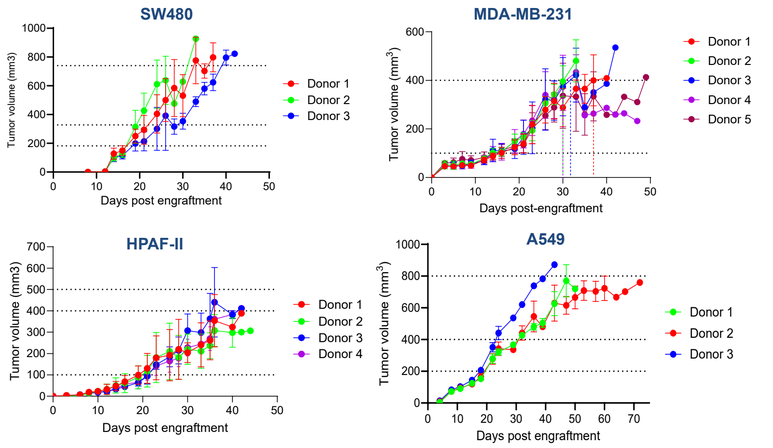
Background: The relevance of preclinical models has vastly improved with mice bearing a human immune system, especially in the context of immunotherapy. genO-BRGSF (BALB/c Rag2$^{-/-}$ IL2Rγ$^{-/-}$, SIRPα^{NOD} and Flt3$^{-/-}$) is a highly immunodeficient mouse featuring reduced murine myeloid cells. genO-BRGSF mice reconstituted with human cord blood CD34^{+} cells (genO-BRGSF-HIS) develop functional lymphoid and myeloid compartments. This engraftment is stable over a year(1) and mice do not develop GvHD. Additionally, the myeloid compartment can be transiently boosted with exogenous human Flt3L injections. In contrast to other models which overexpress human cytokines to develop human myeloid cells, Flt3L-treated genO-BRGSF-HIS mice do not show side effects. genO-BRGSF-HIS mice are permissive to mouse and human cancer cell line engraftment and represent a valuable preclinical model to study cancer development and evaluate novel therapeutics.

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

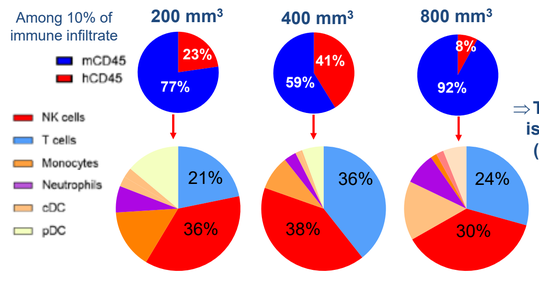
genO-BRGSF-HIS mice were boosted with Flt3L and inoculated with SW480, MDA-MB-231, HPAF-II or A549 cells and tumor growth was analyzed.



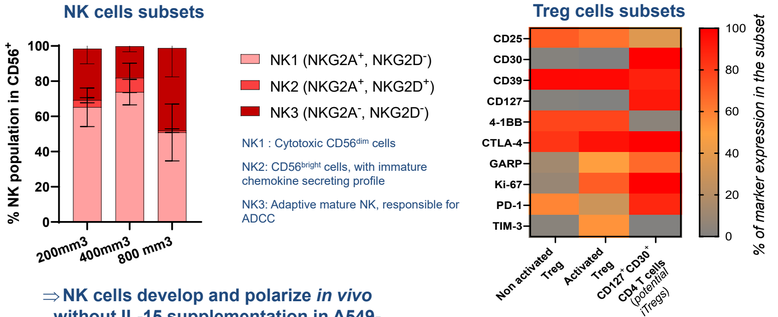
⇒ **Tumor cell lines tested show 100% of take rate**
⇒ **Tumor growth is CD34^{+} donor-independent**

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.



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



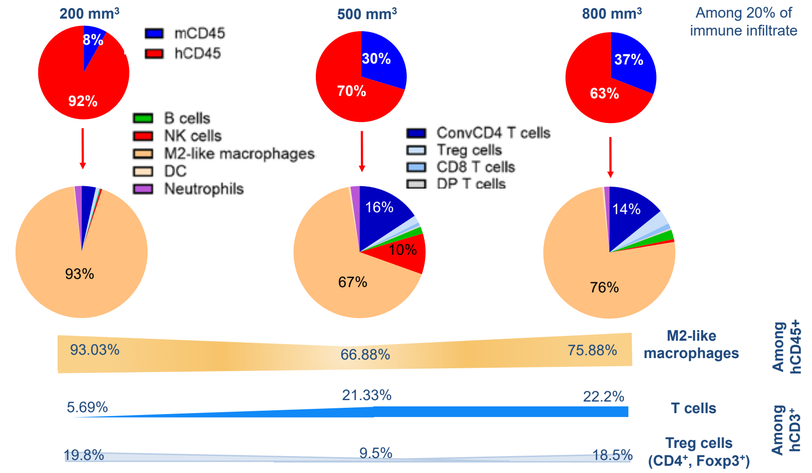
⇒ **NK cells develop and polarize *in vivo* without IL-15 supplementation in A549-bearing genO-BRGSF-HIS**

⇒ **Treg subsets develop in A549-bearing genO-BRGSF-HIS**

3. TME of MDA-MB-231 is highly infiltrated with myeloid cells

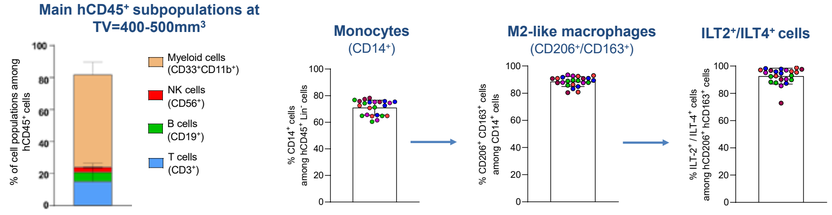
genO-BRGSF-HIS mice were boosted with Flt3L and inoculated (5x10^{6} cells) with the triple negative breast cancer cell line MDA-MB-231 and TME was analyzed over time (among the 20% immune cell infiltrate)

3.1. TME composition of MDA-MB-231 is shaped by tumor burden

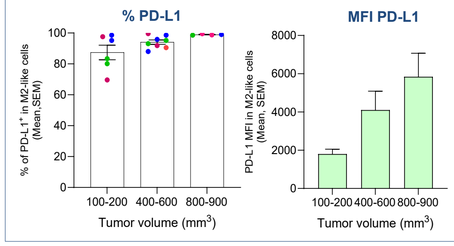


⇒ **TME composition evolves with tumor burden: myeloid cell recruitment reduces in large tumors while T cell recruitment increases**

3.2. Myeloid cell activation status in TME of MDA-MB-231



PD-L1 expression on M2-like macrophages in the TME



⇒ **TME of MDA-MB-231 bearing genO-BRGSF-HIS mice is enriched in myeloid cells, mostly CD206^{+}/CD163^{+} M2-like macrophages and they express both ILT2 and ILT4**

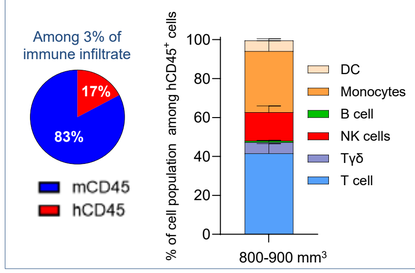
⇒ **PD-L1 MFI increases with tumor burden indicating myeloid cells activation**

Conclusion: genO-BRGSF-HIS mouse model is a valuable tool to investigate immune cell infiltration in the TME, enabling a translatable assessment of mechanism of action of immunotherapies.

Reference: (1) Labarthe et al., J. Leukoc. Biol., 2019

4. TME of SW480 is infiltrated with T-cell and γδT cells

genO-BRGSF-HIS mice were boosted with Flt3L and inoculated (5x10^{6} cells) with the human colon adenocarcinoma SW480 cell line and TME was analyzed at TV= 800-900mm^{3}

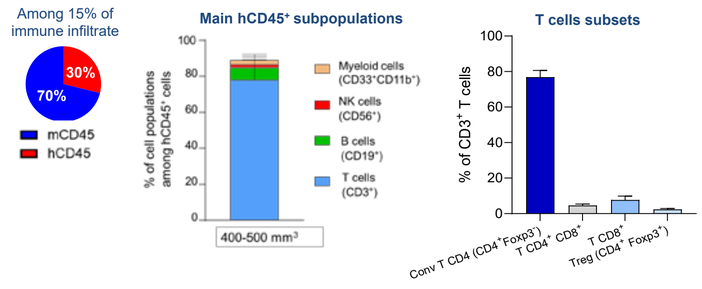


⇒ **TME of SW480 engrafted mice is mainly composed of T cells (40%) and monocytes (30%)**

⇒ **Presence of γδT cells (5-6%)**

5. TME of HPAF-II is highly infiltrated with T cells

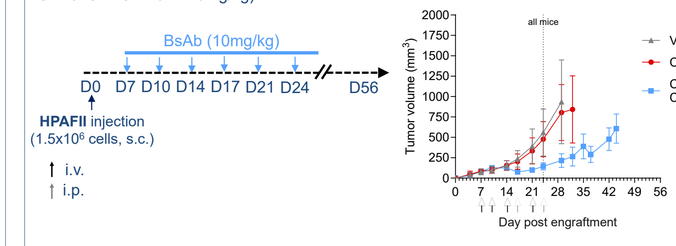
genO-BRGSF-HIS mice were boosted with Flt3L and inoculated (1.5x10^{6} cells) with the human pancreatic adenocarcinoma HPAF-II cell line and TME was analyzed at TV= 400-500mm^{3}



⇒ **TME of HPAFII engrafted mice is mainly composed of T cells**

6. Response to T-Cell Engagers

genO-BRGSF-HIS mice were injected with the human pancreatic adenocarcinoma HPAFII and treated 6 times from D7 to D24 with bispecific antibodies (CD3xCEACAM5 and CD3xCEACAM5 + CD28xCEACAM5 at 10mg/kg)



⇒ **Treatment with TCE combo therapy efficiently reduces tumor growth *in vivo***

⇒ **These results corroborate data reported by Majocchi *et al.*, Cancer Immunol. Res., 2024 using CEA/CD3 and CD28/PD-L1 T-cell engagers combination**

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