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Assessment of γδ T-cell therapies in humanized mice

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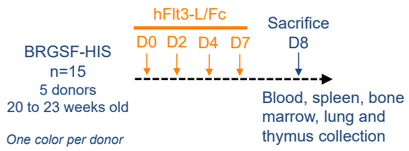
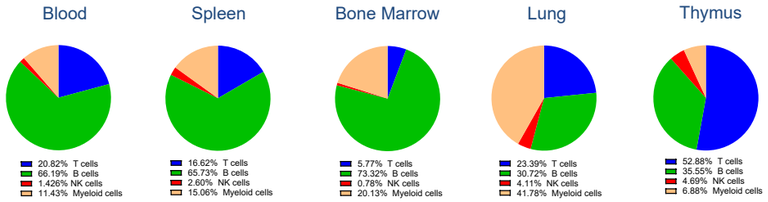
Abstract #877

Background: Current therapeutic approaches involving γδ T cells include adoptive cell transfer, *in vivo* stimulation and combined therapies. While preliminary results are promising, investigation of such therapies in preclinical models is challenging, because γδ T cells are not developed at satisfactory levels in most of the humanized mouse models. Here we describe the presence and functionality of γδ T cells in BRGSF (BALB/c Rag2$^{-/-}$ IL2Rγ$^{-/-}$, SIRPα^{NOD} and Flt3$^{-/-}$), a highly immunodeficient mouse featuring reduced murine myeloid cells. BRGSF mice reconstituted with human cord blood CD34$^+$ cells (BRGSF-HIS) develop functional lymphoid and myeloid compartments. This engraftment is stable over a year[1] and mice do not develop GvHD.

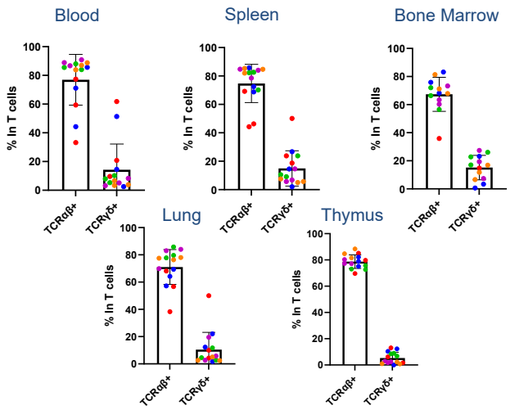
1. γδ T cells develop in BRGSF-HIS mice



- Human immune cell reconstitution in BRGSF-HIS animals (% in hCD45)

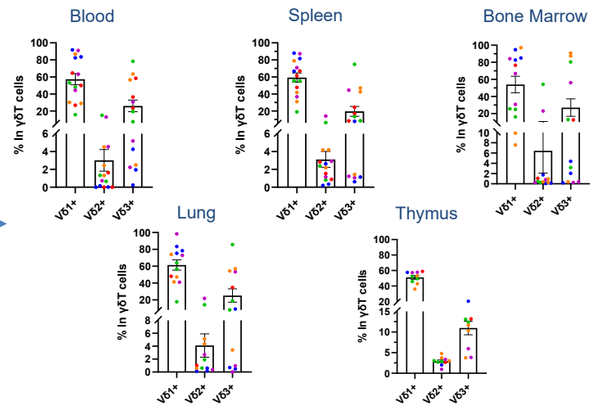


- Human T-cell subpopulations evaluated in T cells (CD3$^+$ CD56$^-$) in BRGSF-HIS



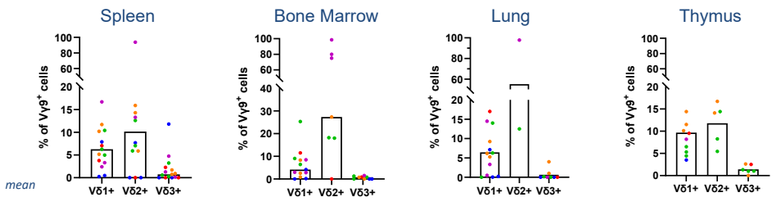
⇒ **Similar to human PBMC, the ratio of TCRαβ Vs. TCRγδ is approximately 80:20 in all tissues from BRGSF-HIS mice, except thymus**

- Characterization of human γδ T cells in BRGSF-HIS



⇒ **γδ T cells develop in BRGSF-HIS and express Vδ1, Vδ2 and Vδ3, although their ratio in BRGSF-HIS mice is different from the ratio in human PBMC**
⇒ **Frequency of γδ T cells is donor-dependent**

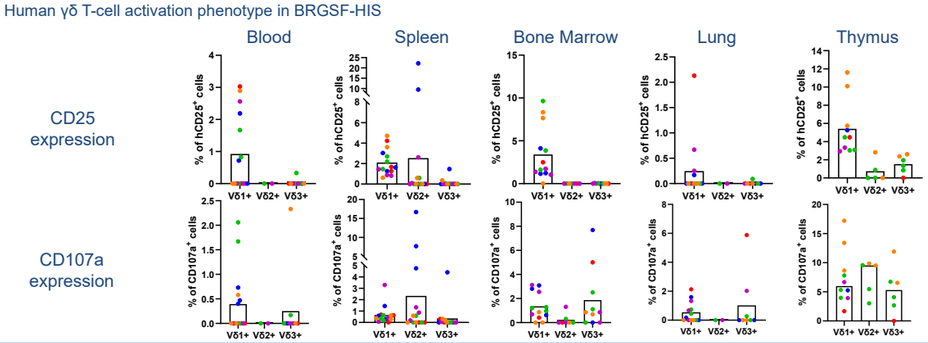
- Vγ9 expression on human γδ T cells in BRGSF-HIS



⇒ **Vγ9 is preferentially paired with Vδ2+ cells, as reported in human PBMC**

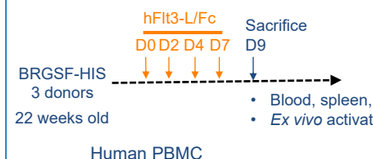
⇒ **Vγ9 is also expressed in ~5% of Vδ1$^+$ cells in all tested tissues and very low to no expression is observed in Vδ3$^+$ cells, as described in human physiology**

- Human γδ T-cell activation phenotype in BRGSF-HIS

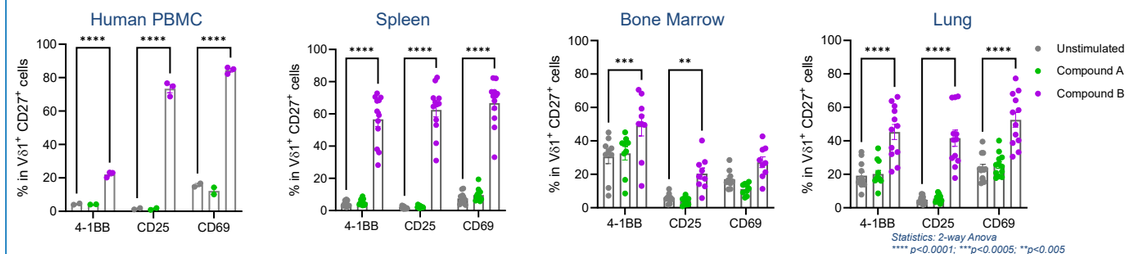


⇒ **Low/no CD25 and CD107a expression in γδ T-cell subpopulations, except in the thymus, as would be expected in naïve mice**

2. *Ex vivo* γδ T-cell activation in BRGSF-HIS mice

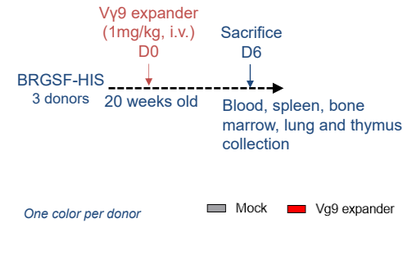


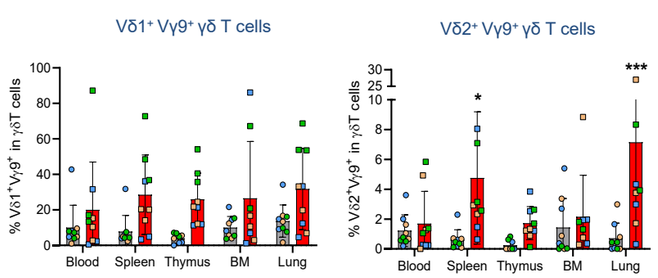
- Blood, spleen, bone marrow and lung collection
- *Ex vivo* activation with Vδ1 targeting compounds for 24h

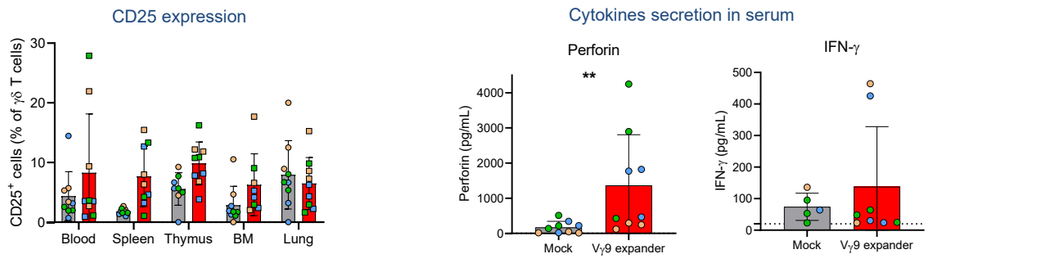


⇒ **Compound B targeting Vδ1 cells show similar activation profile on targeting Vδ1 cells developed in BRGSF-HIS mice and human PBMC from a healthy donor**

3. *In vivo* expansion of γδ T Vγ9$^+$ cells in BRGSF-HIS mice







⇒ **Vγ9$^+$ cells developed in the BRGSF-HIS mice**
⇒ **"Expander" activates Vγ9 proliferation in all tested organs and increases their frequencies**

Conclusion: The development of functional γδ T cells in BRGSF-HIS mice brings a new perspective to the assessment of therapies targeting this cell population in humanized mouse models.

References:
- (1) Labarthe L, Henriquez S, Lambotte O, Di Santo JP, Le Grand R, Pflumio F, Arcangeli ML, Legrand N, Bourgeois C. Frontline Science: Exhaustion and senescence marker profiles on human T cells in BRGSF-A2 humanized mice resemble those in human samples. J Leukoc Biol. 2020, 10.1002
- (2) Li Y, Li G, Zhang J, Wu X, Chen X. The Dual Roles of Human γδ T Cells: Anti-Tumor or Tumor-Promoting. Front Immunol. 2021 Feb 16;11:619954
- (3) Clark BL, Thomas PG. A Cell for the Ages: Human γδ T Cells across the Lifespan. Int J Mol Sci. 2020 Nov 24;21(23):8903

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