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BRGSF-HIS mice as a predictive tool for safety assessment of biologics

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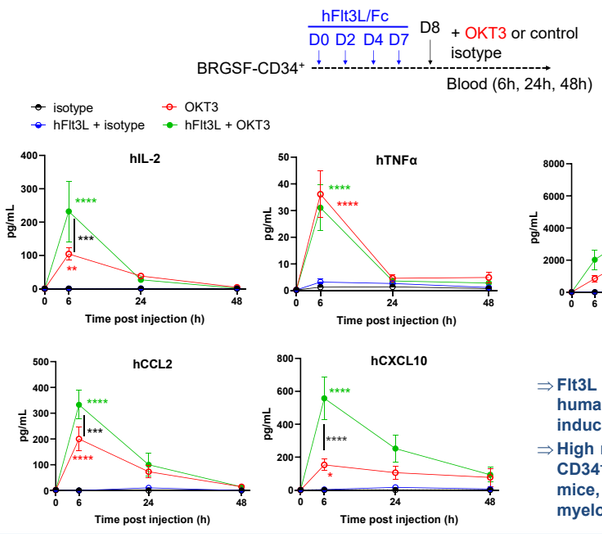
Background: Immunotherapies are efficacious but are often associated to immune-related adverse events, such as cytokine release syndrome (CRS). Safety assessment of therapeutics in preclinical models remains challenging, as they should be relevant and translational. Models exhibiting a human immune system are widely used, but the composition of the human immune system developed remains a concern. Here we report the use of BRGSF mice, an immunodeficient mouse model which can be reconstituted with human cord blood CD34⁺ cells (BRGSF-CD34⁺) or PBMC (BRGSF-PBMC). BRGSF-CD34⁺ develop functional human lymphoid and myeloid compartments, with systematic and persistent presence of plasmacytoid dendritic cells (pDCs), conventional dendritic cells (cDCs), and monocytes/macrophages. Their myeloid and dendritic compartments can be transiently boosted with exogenous human Flt3L injections. In contrary to other models which overexpress human cytokines to develop human myeloid cells, Flt3L-treated BRGSF-CD34⁺ mice do not show side effects(1).

1. Myeloid cells enhance OKT3-induced cytokine release in BRGSF-CD34⁺ mice

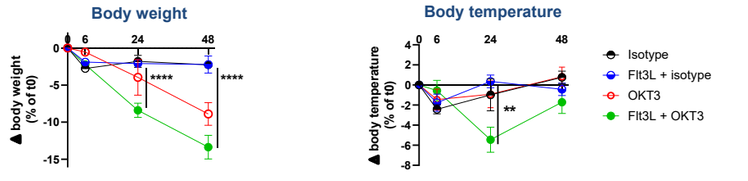


⇒ **Flt3L treatment enhances human cytokine production induced by OKT3**

⇒ **High number of cytokines in CD34⁺ reconstituted BRGSF mice, mainly produced by myeloid cells**

2. Myeloid cells enhance the severity of OKT3-induced clinical signs

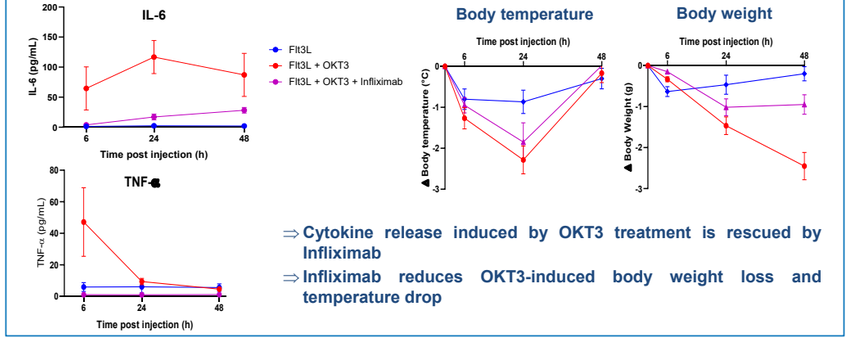
- OKT3 treatment (2mg/kg, i.v.) at D8 for BRGSF-CD34⁺ mice. Body weight and temperature measurement at 6h, 24h and 48h post OKT3 treatment.



⇒ **Severity of clinical signs (body weight and temperature loss) induced by OKT3 are enhanced by Flt3L treatment in BRGSF-CD34⁺ mice**

3. Infliximab induces rescue of OKT3-induced CRS

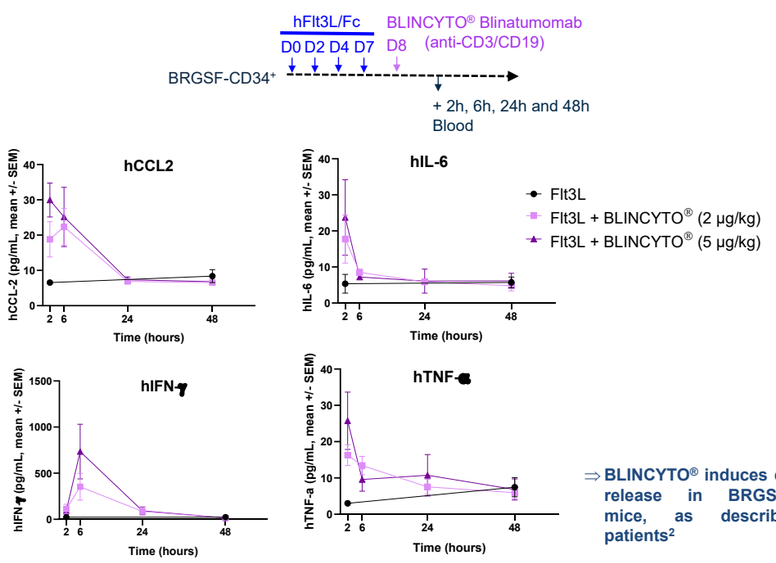
- OKT3 treatment (2mg/kg, i.v.) at D8 for BRGSF-CD34⁺ mice. Infliximab (2mg/kg, i.v.) was injected 1h before OKT3. Cytokine release, body weight and temperature measurement at 6h, 24h and 48h post OKT3 treatment.



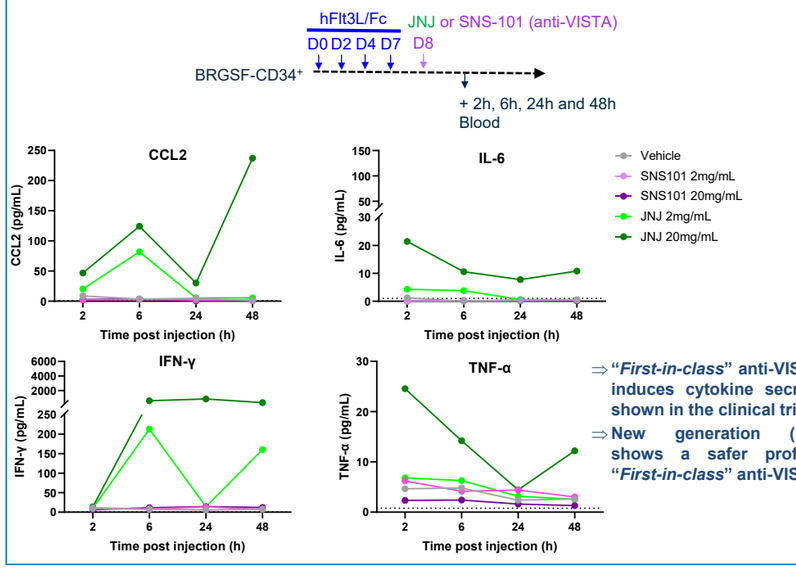
⇒ **Cytokine release induced by OKT3 treatment is rescued by Infliximab**

⇒ **Infliximab reduces OKT3-induced body weight loss and temperature drop**

4. Safety assessment of Blinatumomab and anti-VISTA antibodies tested in the clinic



⇒ **BLINCYTO® induces cytokine release in BRGSF-CD34⁺ mice, as described in patients[2]**



⇒ **"*First-in-class*" anti-VISTA (JNJ) induces cytokine secretion as shown in the clinical trials**

⇒ **New generation (SNS-101) shows a safer profile than "*First-in-class*" anti-VISTA(3)**

Conclusion: Altogether, the data suggest that CD34⁺-reconstituted BRGSF-HIS mice could be used as a predictive tool to investigate immunotherapies' safety.

References:
- (1) Martin, Gaëlle H et al. "Myeloid and dendritic cells enhance therapeutics-induced cytokine release syndrome features in humanized BRGSF-HIS preclinical model." *Frontiers in immunology* vol. 15 1357716. 7 Feb. 2024, doi:10.3389
- (2) Teachey, David T et al. "Cytokine release syndrome after blinatumomab treatment related to abnormal macrophage activation and ameliorated with cytokine-directed therapy." *Blood* vol. 121,26 (2013): 5154-7. doi:10.1182
- (3) Thisted, T., Smith, F.D., Mukherjee, A. *et al.* VISTA checkpoint inhibition by pH-selective antibody SNS-101 with optimized safety and pharmacokinetic profiles enhances PD-1 response. *Nat Commun* **15**, 2917 (2024). https://doi.org/10.1038

5. Correlation of preclinical and Phase 1/2 study findings

A phase 1/2 study of safety, tolerability, and pharmacokinetics of SNS-101, a pH-sensitive anti-VISTA mAb, as monotherapy and in combination with cemiplimab in patients with advanced solid tumors

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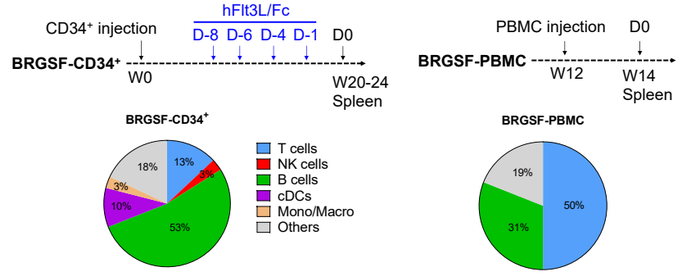
Abstract #1532

⇒ **Preliminary Phase I clinical data demonstrated that SNS-101 displays an acceptable risk/benefit profile, corroborating the preclinical safety finding in BRGSF-CD34⁺ mice**

6. How does CRS in CD34⁺-reconstituted BRGSF mice compare to PBMC reconstituted BRGSF mice ?

Immune cells developed in BRGSF-CD34⁺ and BRGSF-PBMC mice

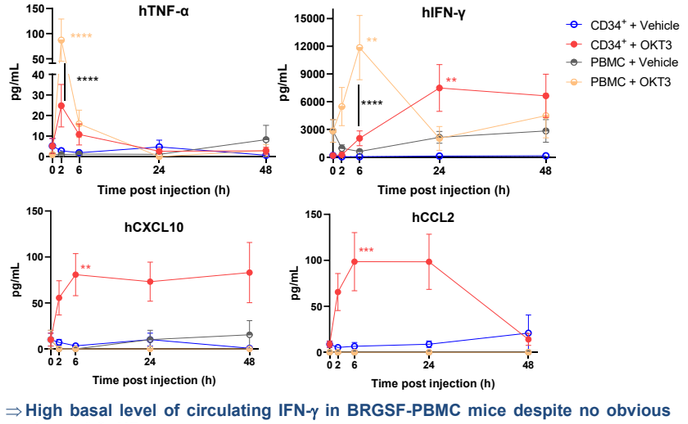


⇒ **Myeloid cells are better represented in BRGSF-CD34⁺ mice than in BRGSF-PBMC mice**

7. Cytokine release in BRGSF-CD34⁺ and BRGSF-PBMC mice

- OKT3 treatment (2mg/kg, i.v.) at D8 for BRGSF-CD34⁺ mice and at D0 for BRGSF-PBMC mice.

Cytokine release measurement at 6h, 24h and 48h post OKT3 treatment.



⇒ **High basal level of circulating IFN-γ in BRGSF-PBMC mice despite no obvious signs of GvHD**

⇒ **No cytokine from myeloid origin produced in BRGSF-PBMC mice**

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DOI: Kader THIAM is an employee and stock holder of genOway

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