



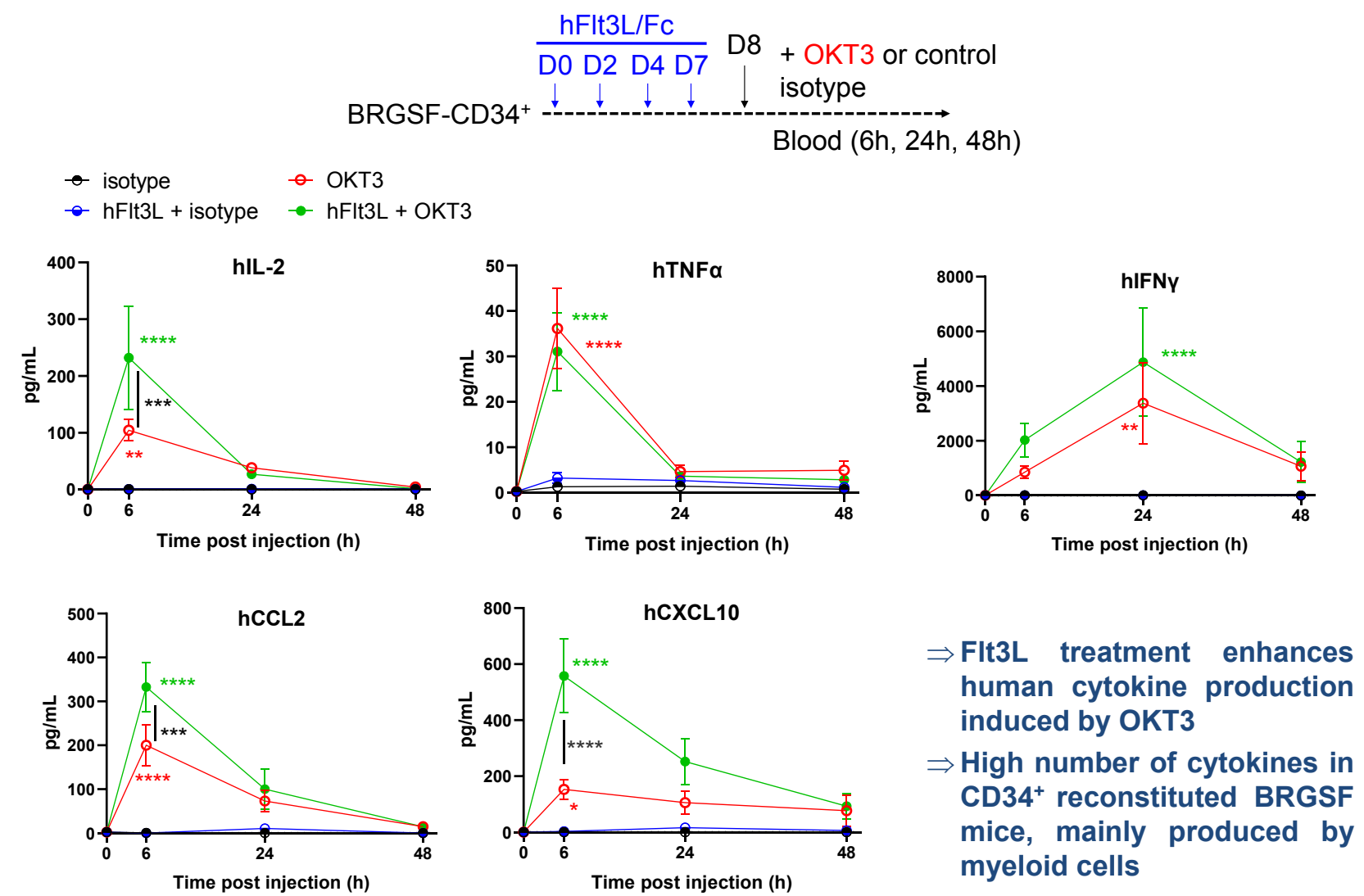
BRGSF-HIS mice as a predictive tool for safety assessment of biologics

Gaëlle MARTIN¹, Alexis GONON¹, Perrine MARTIN-JEANTET¹, Julie GORRY¹, Edward H. VAN DER HORST², Kader THIAM¹
¹genOway, Lyon, 69007, France, ²Sensei Biotherapeutics Inc., Boston MA 02210, USA

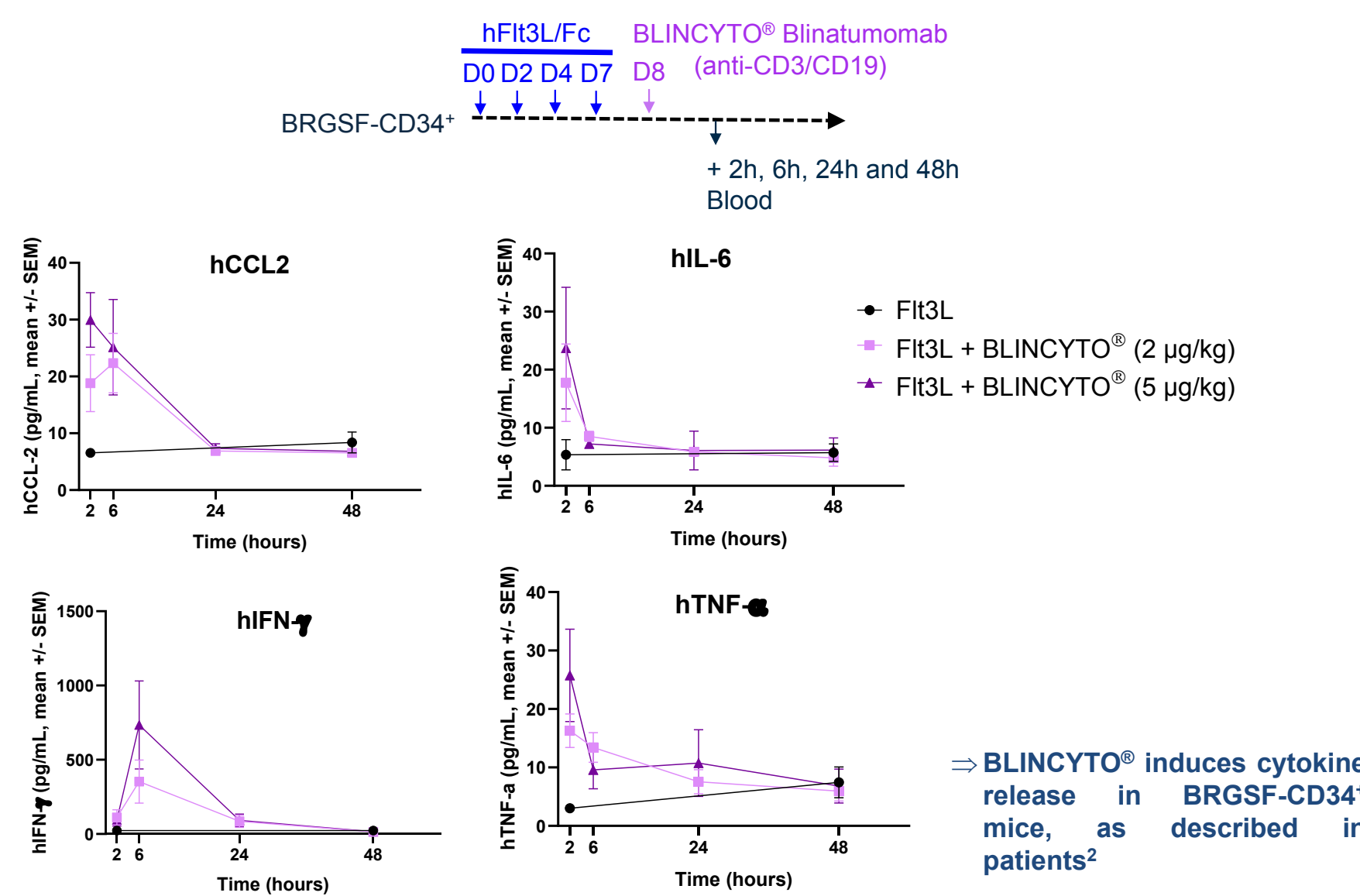
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Background: Immunotherapies are efficacious but are often associated to immune-related adverse events, such as cytokine release syndrome (CRS). Safety assessment of therapeutics in preclinical models remains challenging, as they should be relevant 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⁾.

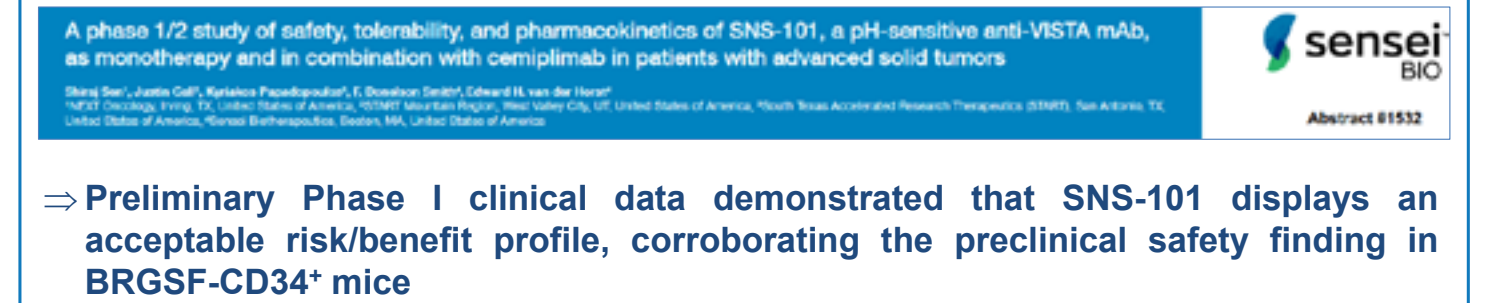
1. Myeloid cells enhance OKT3-induced cytokine release in BRGSF-CD34⁺ mice



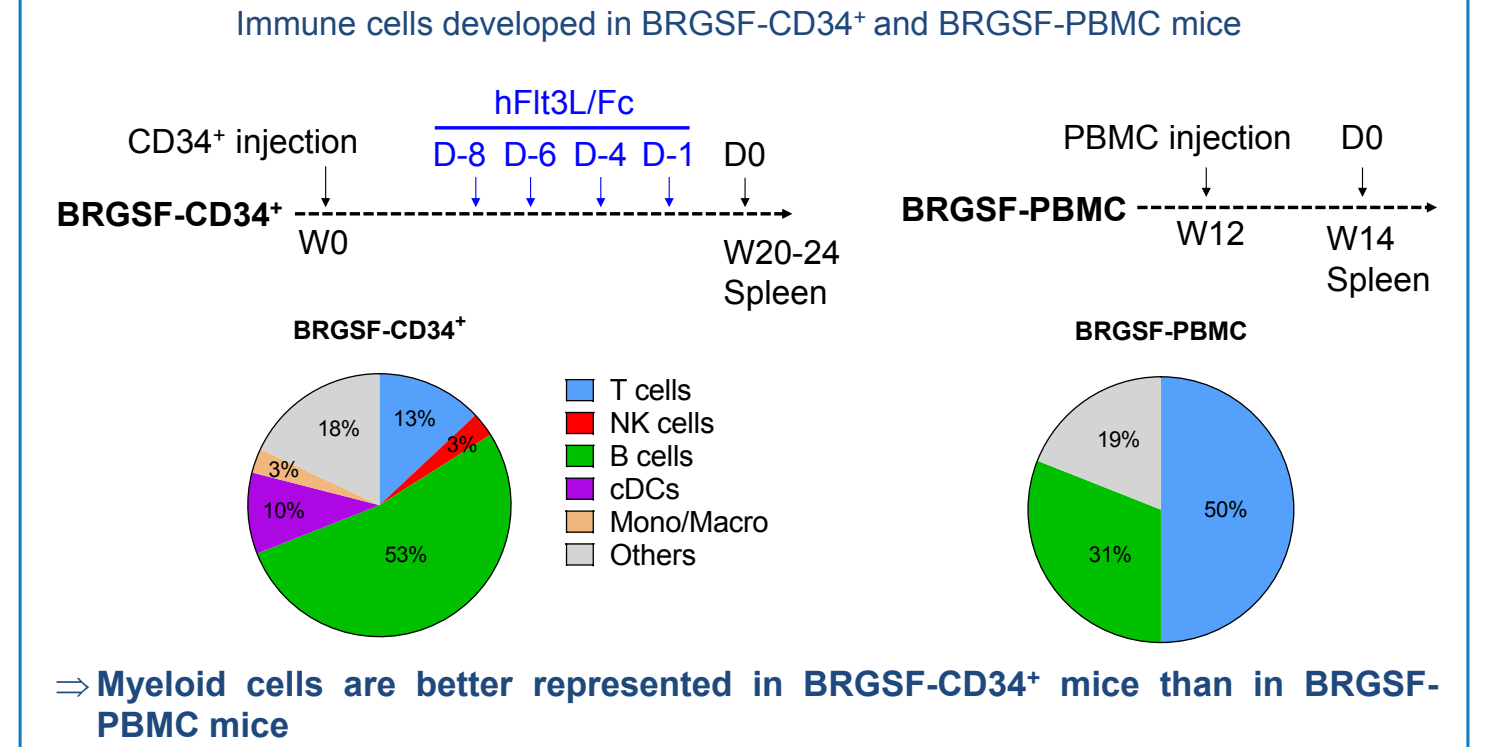
4. Safety assessment of Blinatumomab and anti-VISTA antibodies tested in the clinic



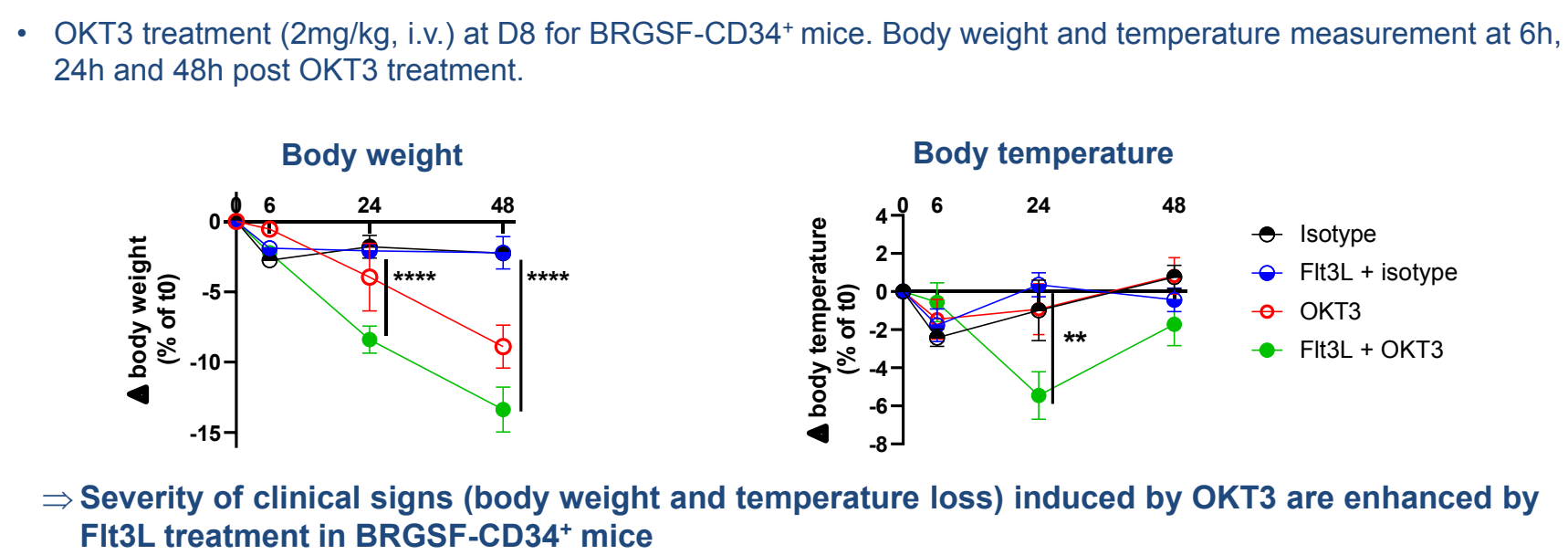
5. Correlation of preclinical and Phase 1/2 study findings



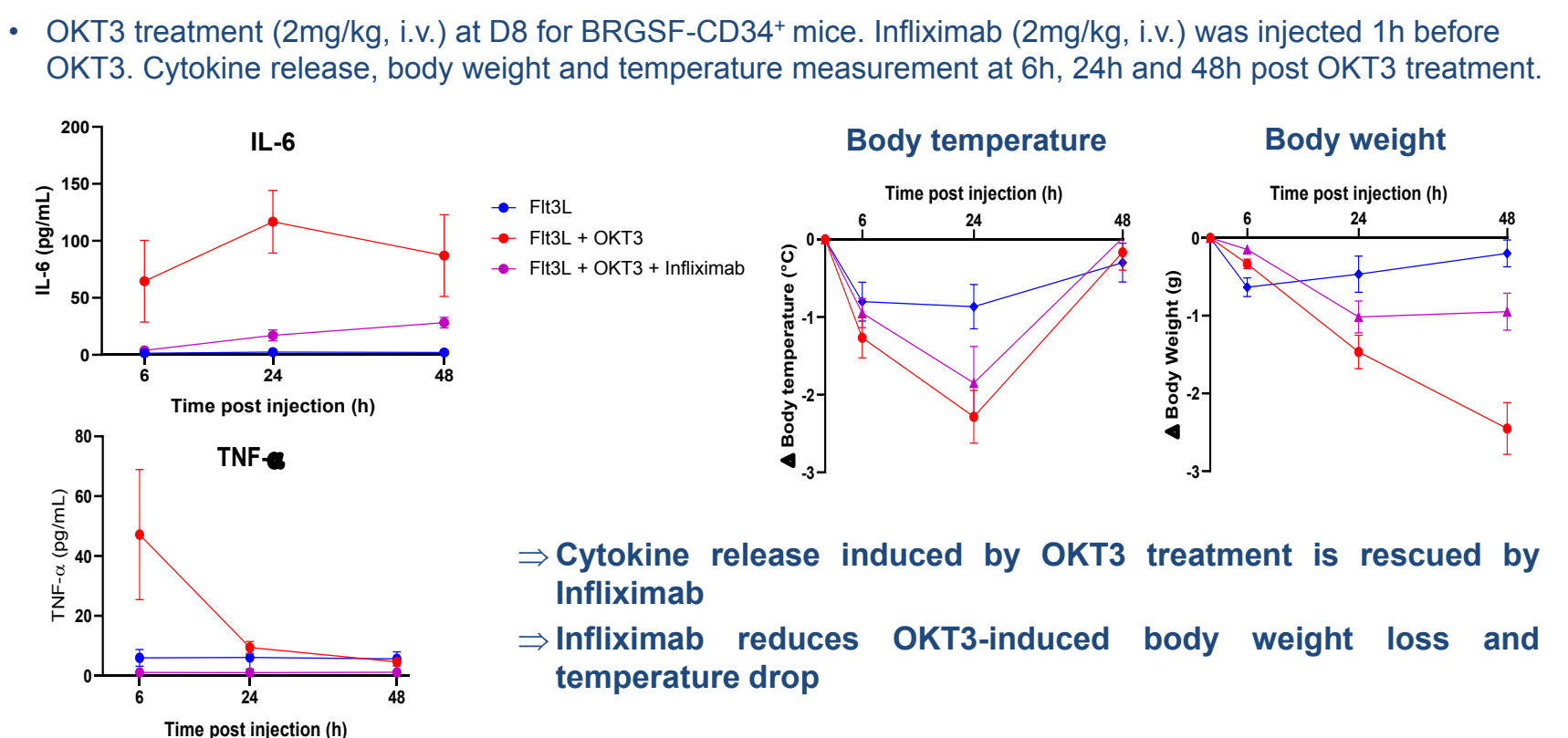
6. How does CRS in CD34⁺-reconstituted BRGSF mice compare to PBMC reconstituted BRGSF mice?



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

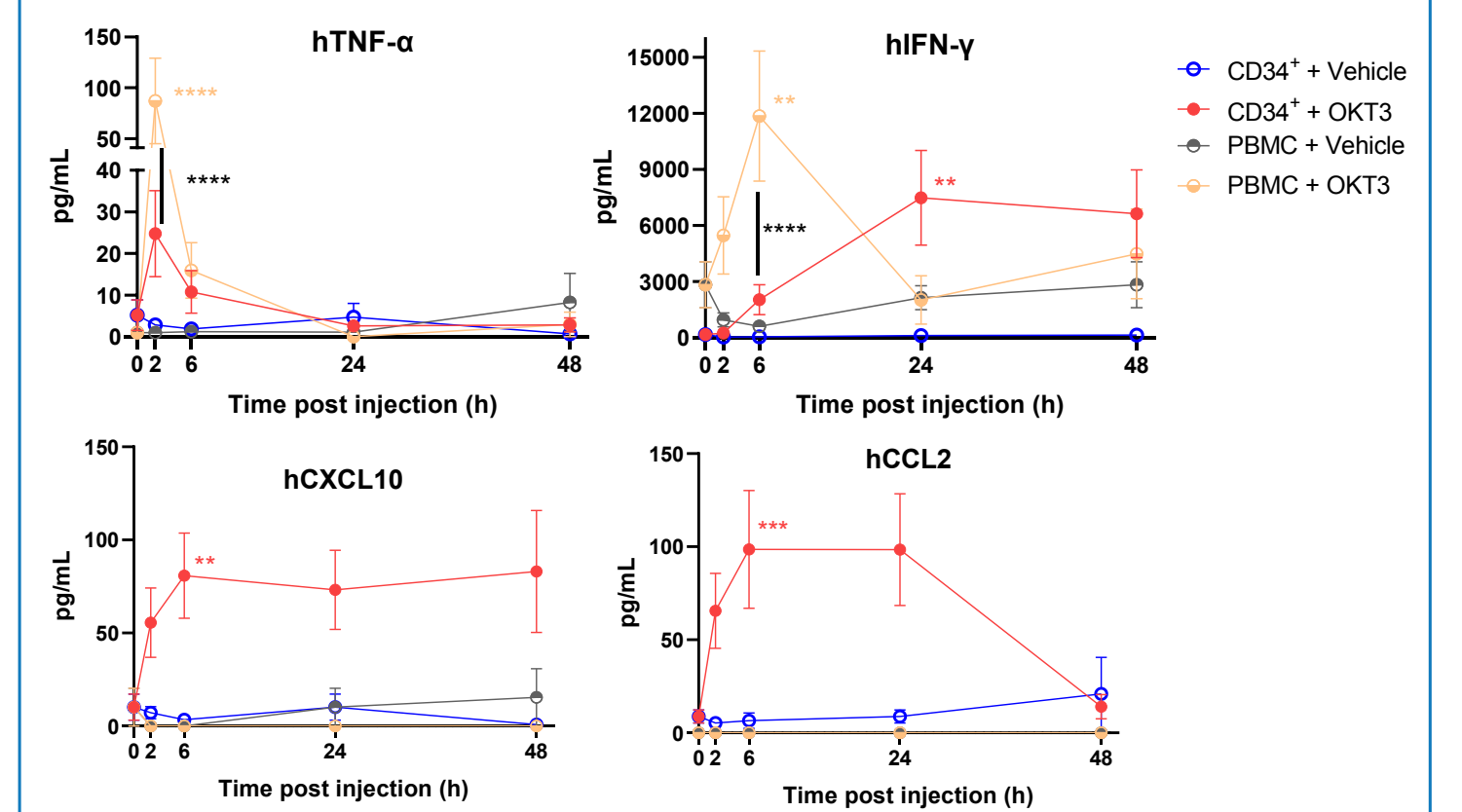


3. Infliximab induces rescue of OKT3-induced CRS



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.



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

Corresponding author: thiam@genoway.com
DOI: Kader THIAM is an employee and stock holder of genOway

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