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SITC 2023 Abstract #1248

Myeloid cells' contribution is key in CRS pathophysiology induced by T-cell engagers in BRGSF-HIS model

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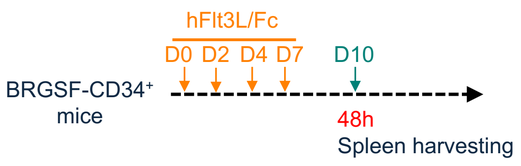
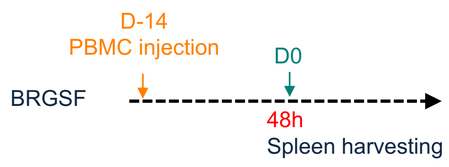
Background: T-cell engagers show high efficacy in B cell malignancies. High risk of immune-related adverse events, including cytokine release syndrome (CRS), is reported in patients treated with T-cell engagers due to on-target offsite effects. Thus, reliable and translational mouse models are required to predict potential safety issues and investigate their rescue. PBMC-reconstituted models are the most currently used as preclinical models to investigate CRS induction' while CD34⁺ reconstituted ones are more rarely described for this application.

1. BRGSF model features

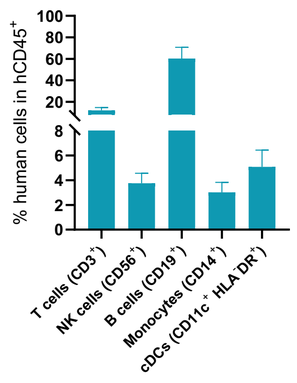
- **BRGSF** (Balb/C Rag2$^{-/-}$ IL2Rγ$^{-/-}$, SIRPα^{NOD} and Flt3$^{-/-}$):
  - Highly immunodeficient with reduced murine myeloid cells
  - Normal life span (no anemia, no weight loss, normal fur texture & integrity, normal activity & posture)

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

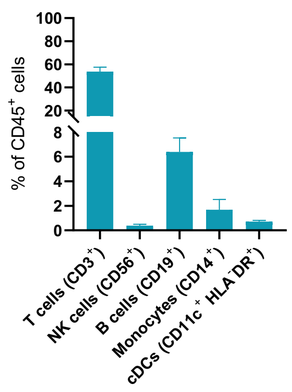




BRGSF-CD34⁺



BRGSF-PBMC

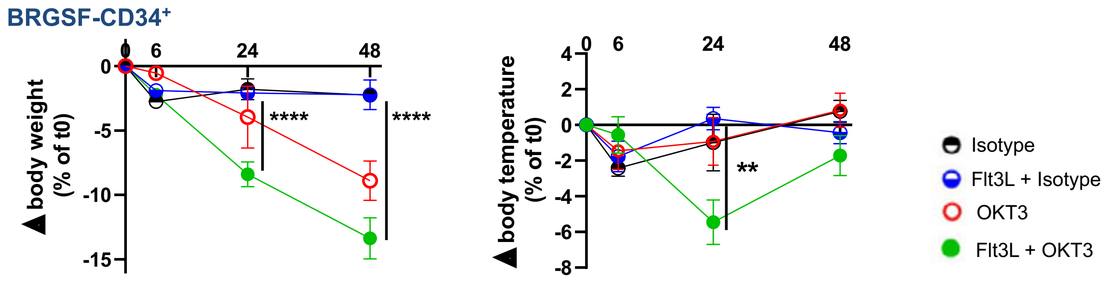


- **Myeloid cells are better represented in BRGSF-CD34⁺ mice than in BRGSF-PBMC mice**

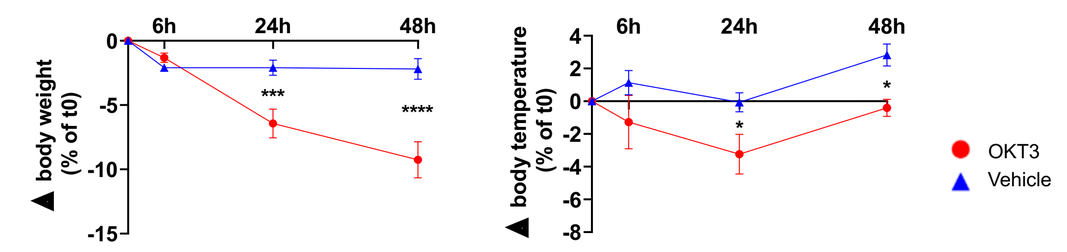
3. OKT3-induced clinical signs in BRGSF-CD34⁺ and BRGSF-PBMC mice

- OKT3 treatment (2mg/kg, i.v.) at D8 for BRGSF-CD34⁺ mice and at D0 for BRGSF-PBMC. Body weight and temperature measurement 6h, 24h and 48h post OKT3 treatment.

BRGSF-CD34⁺



BRGSF-PBMC

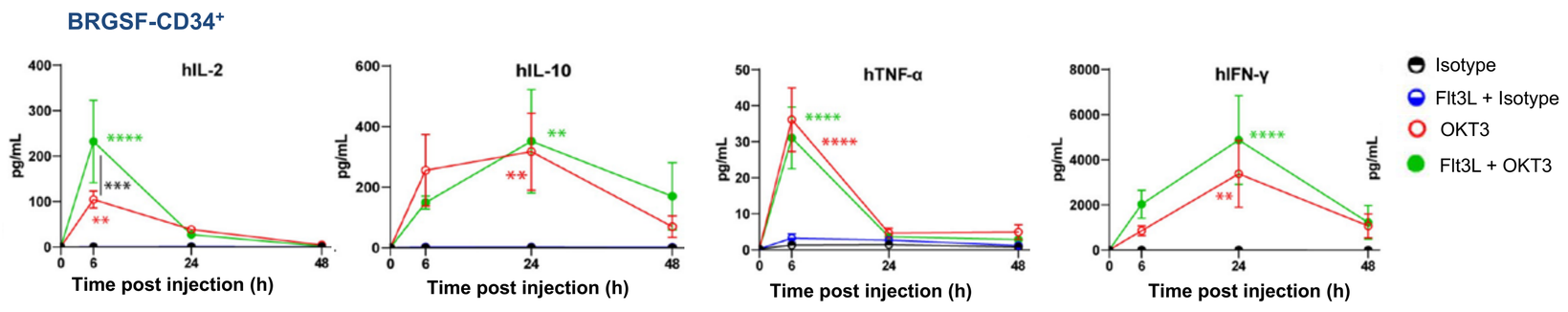


- **BRGSF-CD34⁺ mice show more pronounced clinical signs than BRGSF-PBMC mice**

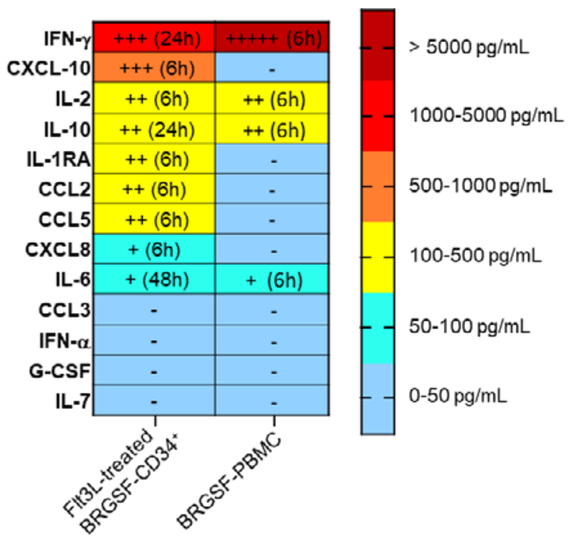
4. Cytokine release in BRGSF-CD34⁺ and BRGSF-PBMC mice

- OKT3 treatment (2mg/kg, i.v.) at D8 for BRGSF-CD34⁺ mice and at D0 for BRGSF-PBMC. Cytokine release measurement 6h, 24h and 48h post OKT3 treatment.

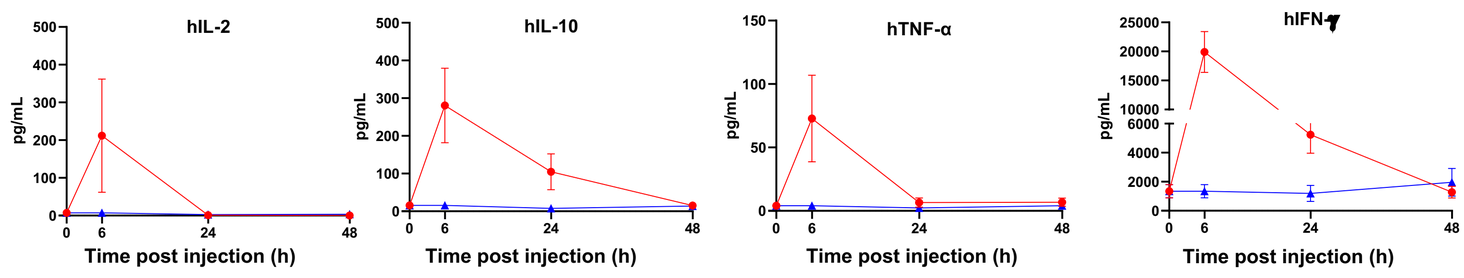
BRGSF-CD34⁺



- Summary of cytokine release

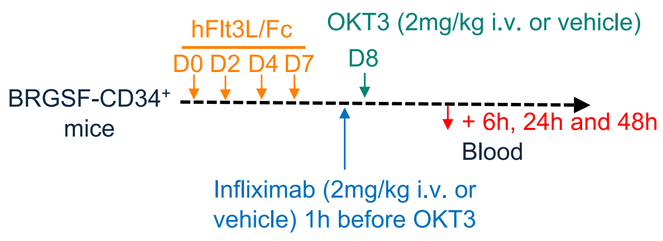


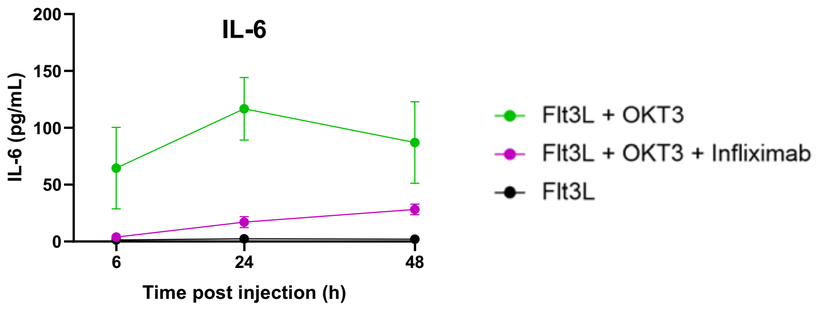
BRGSF-PBMC

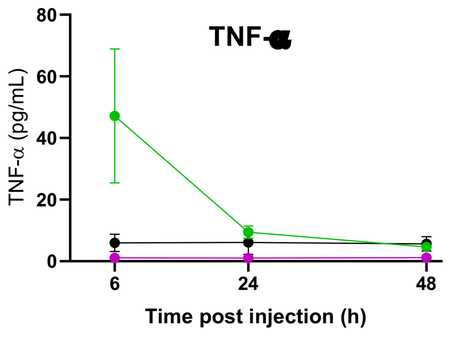


- **High number of cytokines in CD34⁺-reconstituted BRGSF mice, mainly produced by myeloid cells**
- **No cytokine from myeloid origin produced in BRGSF-PBMC mice**
- **High basal level of circulating IFN-γ in BRGSF-PBMC mice despite no obvious clinical signs of GvHD**

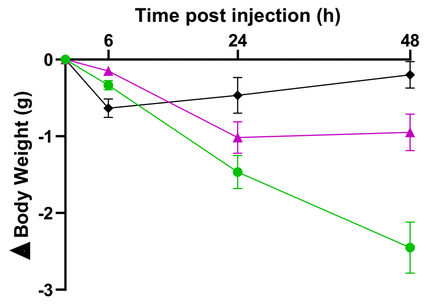
5. Rescue of CRS induction by Infliximab in BRGSF-CD34⁺ mice



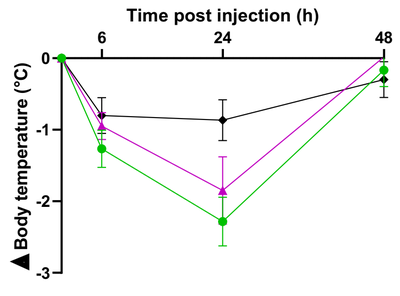




Body weight



Body temperature



- **Cytokine release induced by OKT3 treatment is rescued by Infliximab**
- **Infliximab reduces OKT3-induced body weight loss and temperature drop**

Conclusion: These data suggest that BRGSF-CD34⁺ enable a more translatable assessment of CRS induction by T-cell engagers than BRGSF-PBMC, mainly due to the presence of myeloid cells, which contribute to the physiopathology of CRS.

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