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Role of hFlt3L in the development of myeloid and dendritic cells in genO-BRGSF-HIS mice

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OUTLINE

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THE genO-BRGSF-HIS MOUSE MODEL

- genO-BRGSF-HIS mice, generated on a BALB/c background, contain several mutations that render them extremely immunodeficient.
  - The Rag2^{tm1Fwa} mutation leaves mice without murine T and B cells
  - The mutation in the gamma chain of the IL-2 receptor (IL2Rγ_c^{tm1Cgn}) leads to a decrease in murine NK cells
  - The presence of the NOD-specific SIRPα polymorphism (Sirpα^{NOD}) induces the reduced effector function of murine macrophages
  - The Flt3^{tm1Irl} mutation leads to a decrease in murine myeloid cells

- These mice are then reconstituted with **CD34⁺ human hematopoietic stem cells (HSC)**, enabling the development of a human immune system (HIS). The administration of **hFlt3L** after reconstitution helps **boost the myeloid compartment for more relevant and translatable immune responses**.

- Model's main features:
  - Functional human myeloid and lymphoid compartments upon CD34⁺ HSC-reconstitution
  - Dynamic recruitment and activation profile of immune cells into the tumor microenvironment
  - Presence of functional γδ T cells
  - Large therapeutic window thanks to long life expectancy and stable engraftment
  - Highly permissive to PDX and CDX engraftment
  - Reduced number of murine myeloid cells

- The **genO-BRGSF-HIS model** is a key tool for the efficacy and safety assessment of both lymphoid and myeloid-targeted therapies, as well as for advancing your knowledge in tumor biology

Flt3L AND ITS IMPORTANCE

- The Fms-related tyrosine kinase 3 ligand (Flt3L) is a cytokine that synergises with other cytokines and growth factors.

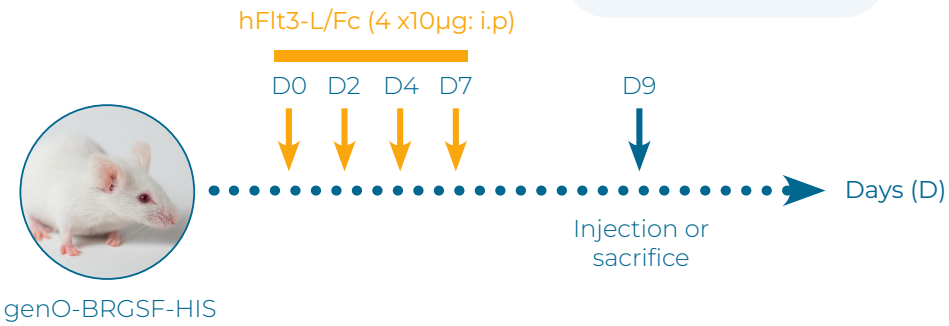
- This ligand is critical for robust human hematopoietic cell development in humanized mice, especially for dendritic and myeloid cells. Its absence results in severely impaired hematopoiesis and immune cell differentiation.

- **Flt3L also stimulates the proliferation and colony formation of $CD34^+$ hematopoietic cells**, both alone and synergistically with other cytokines such as IL-3, IL-6, GM-CSF, and EPO, making it valuable for transplantation and regenerative medicine.

- Bio X Cell provides a recombinant hFlt3L (Flt-3L-Ig) of high quality that guarantees a **robust experimental standard**.

PROTOCOL: hFlt3L ADMINISTRATION FOR THE DEVELOPMENT OF MYELOID AND DENDRITIC CELLS

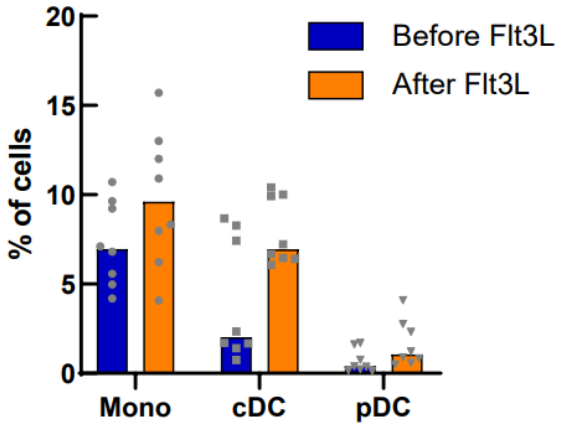
1. Prepare hFlt3L at a concentration of 66,7 µg/mL in a 1x PBS solution
2. Treat genO-BRGSF-HIS mice intraperitoneally with 10 µg of hFlt3L, in a volume of 150 µl of PBS
3. Do a total of 4 treatments, 2-3 days apart, as depicted in the scheme below
4. 2 days later, you can analyse the presence of myeloid and dendritic cells



RESULTS:

hFlt3L TREATMENT STIMULATES HUMAN MYELOID CELLS AND DC DEVELOPMENT IN genO-BRGSF-HIS MICE

- Reconstitution of genO-BRGSF mice with CD34⁺ HSCs leads to the development of human monocytes and dendritic cells (DCs). Nevertheless, the production of these cells can be boosted with hFlt3L treatment, leading to a more relevant and translatable immune response.

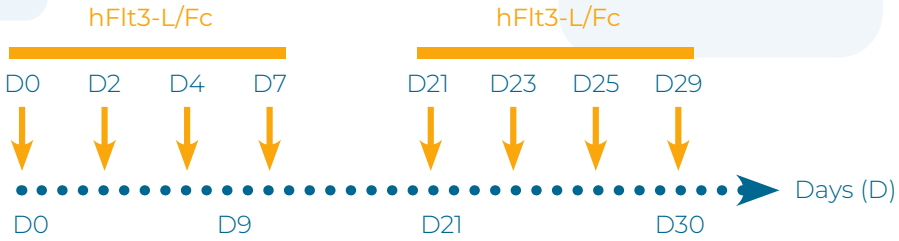


SITC poster, 2022

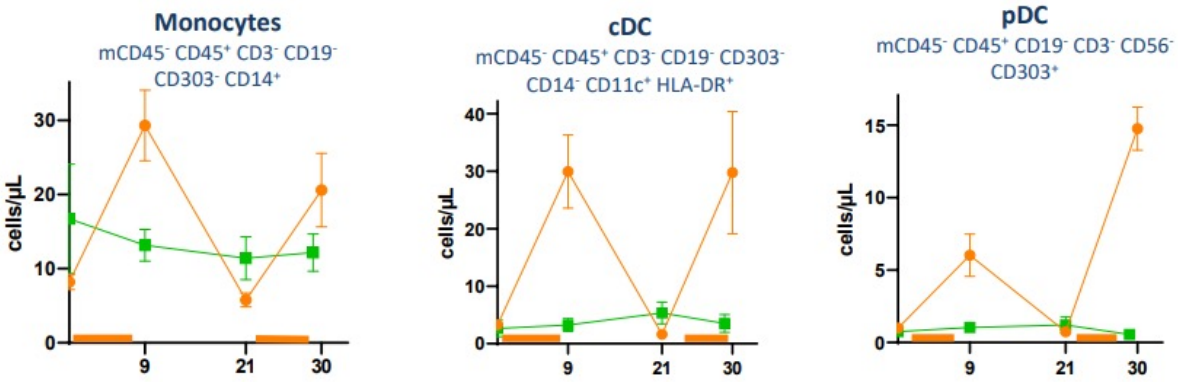
30 weeks old BRGSF-HIS mice treated or not with FLT3L (10µg, i.p.) every other 2-3 days for one week

hFlt3L TREATMENT CAN BE USED TO RE-BOOST MYELOID CELL PRODUCTION

- The effect of the hFlt3L administration is shown to be transient. A second round of treatment leads to another wave of dendritic and myeloid cell production, highlighting the flexibility of this model. This also demonstrates that the experimental window can be extended according to the experimental needs.



Increased numbers of monocytes and DCs following each hFlt3L treatment



AACR poster, 2024

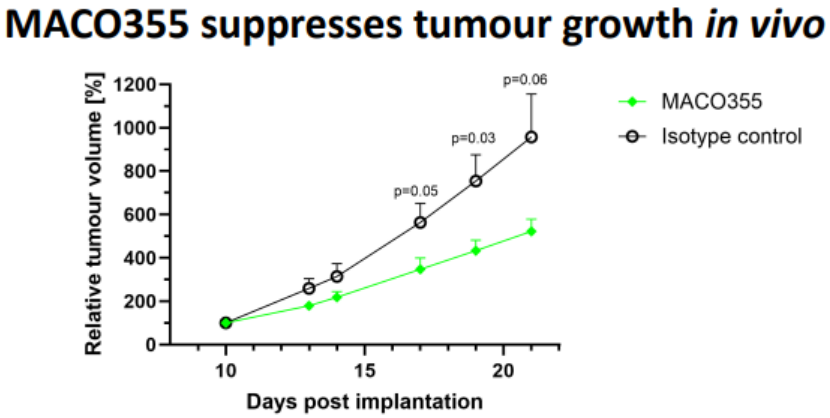
MODEL APPLICATIONS

EFFICACY ASSESSMENT

- Thanks to the hFlt3L-driven development of a functional myeloid compartment, the genO-BRGSF-HIS model enables efficacy testing of therapies targeting myeloid cells in solid and haematologic cancers.

- In their poster presented at the AACR 2024, Macomics used this model for testing a new myeloid-targeted therapy, MACO355, which repolarizes M2 macrophages into a pro-inflammatory state by binding LILRB1, LILRB2 and LILRB3.

- Macomics could confirm that their compound leads to a reduction in tumor growth, confirming the utility of this model for efficacy testing of myeloid-targeted therapies.



AACR poster, 2024

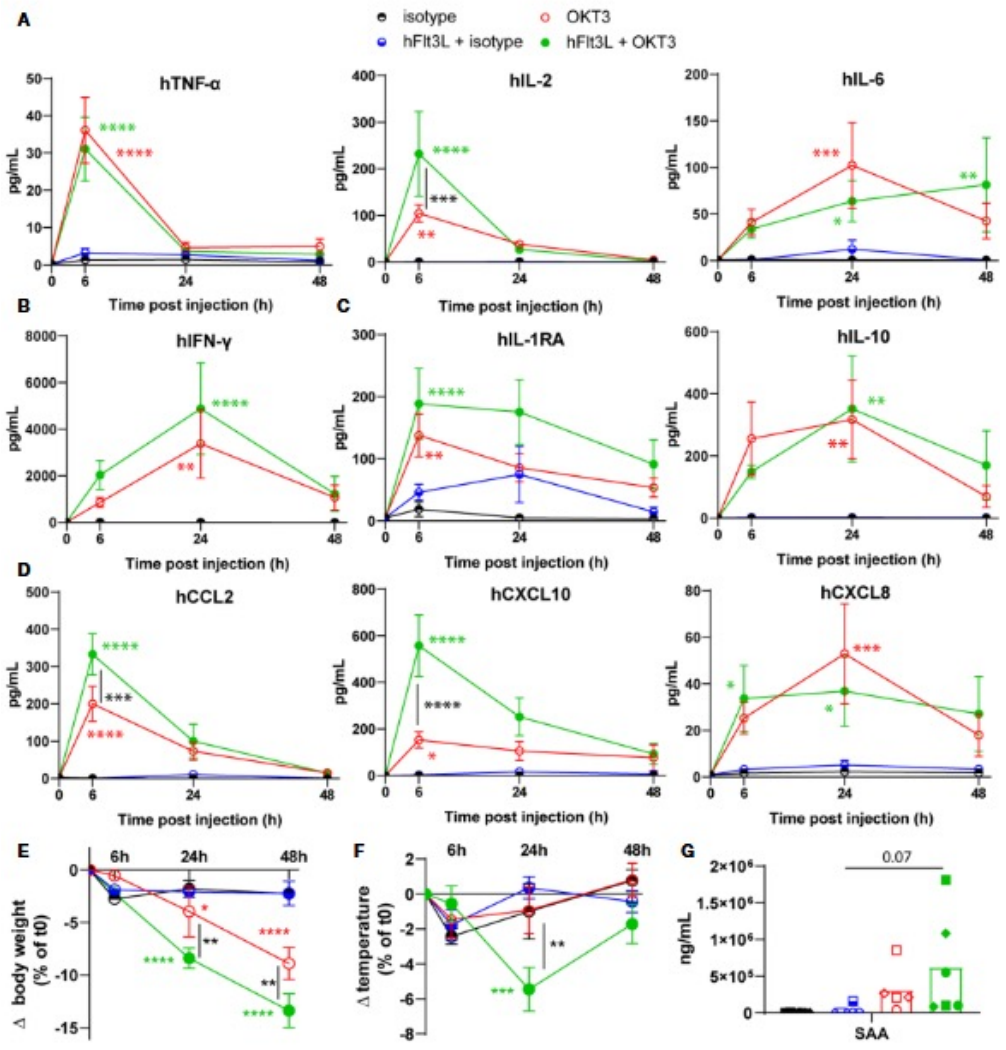
SAFETY ASSESSMENT

- In a recently published paper (Martin *et al.*, 2024), we demonstrated the value of the genO-BRGSF-HIS model for evaluating compound safety and highlighted the critical role of the myeloid compartment in this process. To this end, mice were treated with hFlt3L and various therapeutics known to trigger cytokine release syndrome (CRS).

- CRS is a potentially life-threatening immune-related adverse event associated with many immunotherapies, making reliable preclinical models essential for both risk prediction and therapeutic testing.

- Our findings establish the genO-BRGSF-HIS model as a robust platform that not only reproduces key clinical features of CRS, but also clarifies the contribution of myeloid and dendritic cells to its pathogenesis and enables evaluation of CRS-mitigating therapies.

Cytokine release and clinical features following treatment with hFlt3L and OKT3, an anti-hCD3 mAb



Martin *et al*, Frontiers in Immunology, 2024

SUMMARY

- The genO-BRGSF-HIS model is a translatable mouse model containing a functional human immune system following reconstitution with human $CD34^+$ hematopoietic stem cells, with no side effects.
- Treatment with hFlt3L provided by Bio X Cell enhances the development of myeloid and dendritic cells in the genO-BRGSF-HIS mouse model.
- The genO-BRGSF-HIS model boosted with Bio X Cell's hFlt3L enables efficacy and safety testing of new therapeutics.

GENOWAY AND BIO X CELL

- **genOway** is a biotechnology company providing preclinical models and solutions that increase the success rate in clinical trials. genOway develops "the most human-like" models - mice, rats, and cell lines - to bridge the gap between preclinical findings and clinical success. genOway collaborates with 17 of the top 20 pharma companies, leading biotechs and academic institutions, and has contributed to over 600 scientific publications. genOway is present in 28 countries and has breeding facilities in the USA and Europe.
- bioXcell For nearly 30 years, Bio X Cell has been the trusted partner of researchers pursuing groundbreaking discoveries. With nearly 30,000 peer-reviewed citations, our antibodies have set the standard for performance, quality, and reliability in translational and preclinical research. We specialize in providing researchers with high-purity, low-endotoxin, pathogen-free functional antibodies specifically formulated for robust performance in *in vivo* experiments, helping you achieve confident and reproducible results.