Assessing T-cell engagers *in vivo*: How BRGSF-HIS mice can help

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Immuno-oncology is based on the decades-long knowledge that tumors can escape the patient's immune system in order to keep growing and metastasize. Immunotherapies have been developed to try and prevent cancer cells from "fooling" immune cells, and allow these last ones to fight back. One approach for immunotherapy is to target immune checkpoints, also called ICP blockade, to prevent tumor cells from cheating the immune system, so that it can eventually eliminate them.

T-cell engagers to bring the right cell to the right place

Another approach is to physically drive immune cells to the tumor by targeting, with a single compound, the T-cell co-receptor CD3 and a tumor-specific antigen. Such compounds are called T-cell engagers (TCEs), and they are used not only to recruit T-cells to the tumors but also enhance T-cell effector mechanisms. Interestingly, the additional targeting of the T-cell costimulatory receptor CD28 seems to enhance T-cell activation and thus increase TCE efficiency.[1] Considering the broad expression profile of CD3 and CD28, and the risks that their targeting entail, physiologically relevant models are of utmost importance to assess TCEs' efficacy, but also their toxicity. We have shown previously the value of CD3 and/or CD28 genetically humanized mouse models for anti-tumor efficacy assessment. Although these models can prove suboptimal for safety and toxicity assessment, one interesting alternative for such application exists: the reconstituted BRGSF-HIS mouse model.

T-cell engagers assessment in BRGSF-HIS model

BRGSF-HIS mice show specific features offering high versatility as a preclinical model: functional myeloid and lymphoid compartments, a broad therapeutic window, robust engraftment of cancer cells including AMLs, and no GvHD, just to list a few.

In a context of safety assessment, this model was treated with a CRS-inducing anti-CD28 compound (Fig.1A),[2] and exhibited an increased cytokine secretion (Fig.1B).

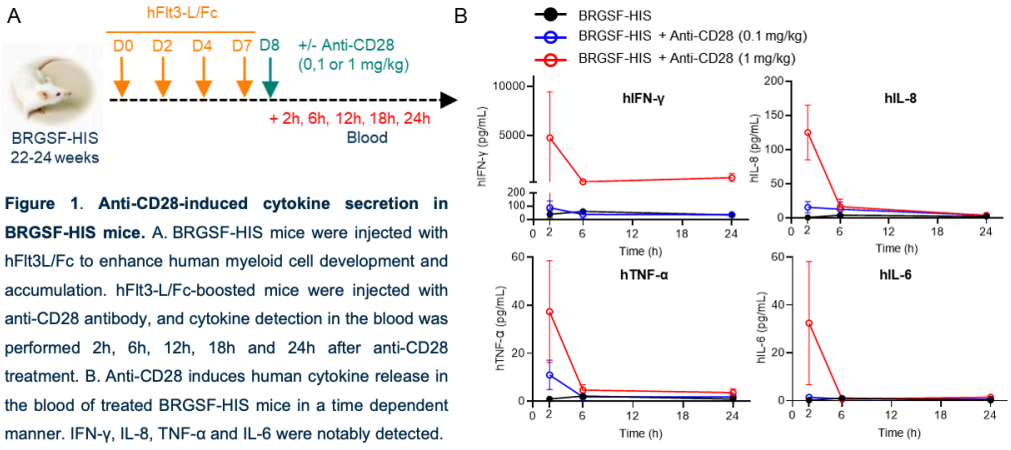

Figure 1. Anti-CD28-induced cytokine secretion in BRGSF-HIS mice. A. BRGSF-HIS mice were injected with hFlt3L/Fc to enhance human myeloid cell development and accumulation. hFlt3-L/Fc-boosted mice were injected with anti-CD28 antibody, and cytokine detection in the blood was performed 2h, 6h, 12h, 18h and 24h after anti-CD28 treatment. B. Anti-CD28 induces human cytokine release in the blood of treated BRGSF-HIS mice in a time dependent manner. IFN-γ, IL-8, TNF-α and IL-6 were notably detected.

Similarly, BRGSF-HIS mice treated with the monoclonal anti-CD3 antibody OKT3 (Fig.2A) developed an induced Cytokine Release Syndrome characterized by T-cell depletion in the blood and spleen (not shown), decreased body weight (Fig.2B), and a significant increase in cytokine secretion (Fig.2C).[3] OKT3-induced CRS in BRGSF-HIS mice is enhanced by the myeloid compartment and can be mitigated by the anti-IL-6R blocking antibody Tocilizumab (Fig.2C).

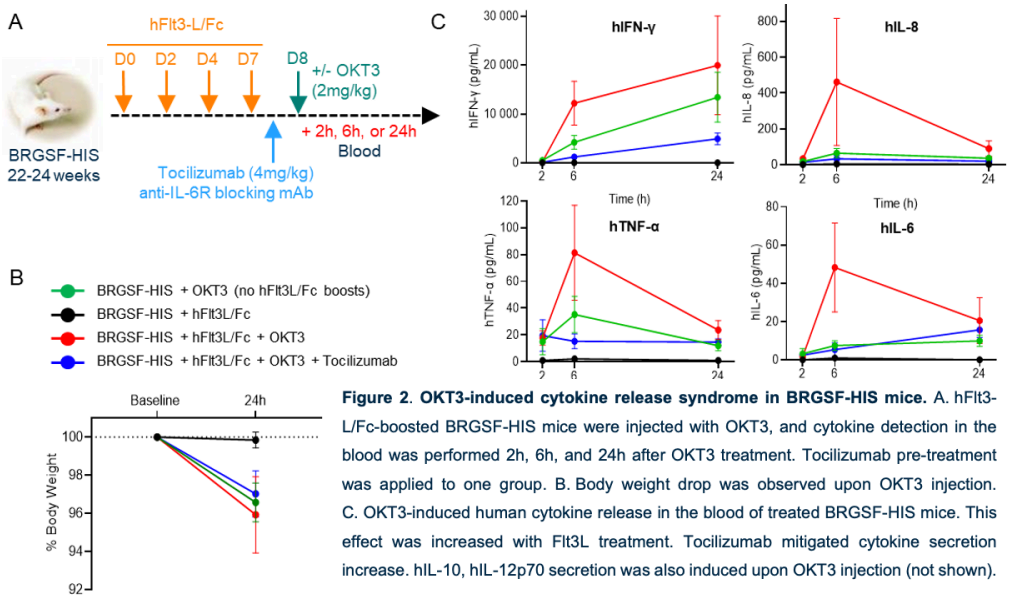

Figure 2. OKT3-induced cytokine release syndrome in BRGSF-HIS mice. A. hFlt3-L/Fc-boosted BRGSF-HIS mice were injected with OKT3, and cytokine detection in the blood was performed 2h, 6h, and 24h after OKT3 treatment. Tocilizumab pre-treatment was applied to one group. B. Body weight drop was observed upon OKT3 injection. C. OKT3-induced human cytokine release in the blood of treated BRGSF-HIS mice. This effect was increased with Flt3L treatment. Tocilizumab mitigated cytokine secretion increase. hIL-10, hIL-12p70 secretion was also induced upon OKT3 injection (not shown).

To test BRGSF-HIS mice response to a T-cell engager, FDA-approved TCE Blinatumomab was injected (Fig.3A). This treatment also induced cytokine release (Fig.3B), and body temperature drop (Fig.3C) in a dose-dependent manner.

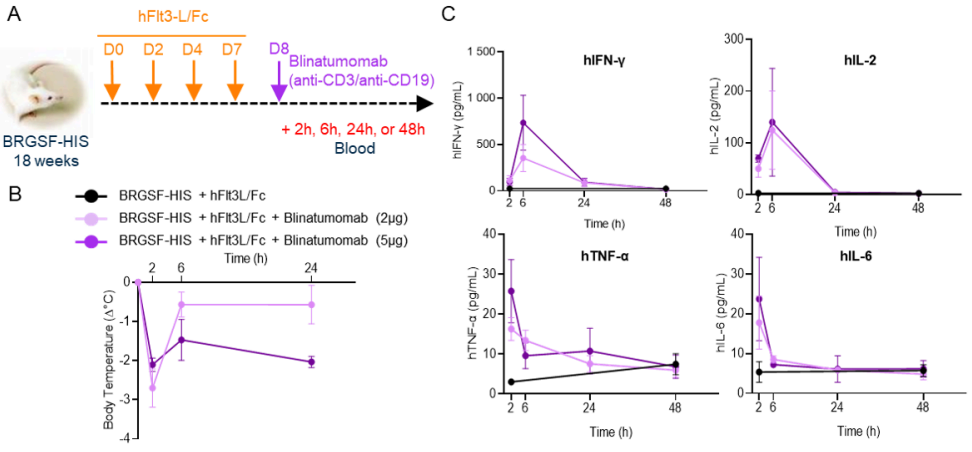

Figure 3. Blinatumomab TCE-induced cytokines release in BRGSF-HIS mice. A. hFlt3-L/Fc-boosted BRGSF-HIS mice were injected with Blinatumomab, and cytokine detection in the blood was performed 2h, 6h, 24h and 48h after TCE treatment. B. Body weight drop was observed upon Blinatumomab injection in a dose-dependent manner. C. Blinatumomab-induced human cytokine release in the blood of treated BRGSF-HIS mice. hCXCL-10 and hCCL-2 increased secretion was also observed upon Blinatumomab injection (not shown).

The reconstituted BRGSF-HIS model can thus be used for safety and toxicity assessment of a variety of compounds, including TCEs. BRGSF-HIS and genetically humanized mouse models are complementary to assess T-cell engager-induced CRS, in addition to efficacy.

Of note, genetically humanized CD3 and CD28 mouse models and the BRGSF-HIS model are available at genOway, designer and provider of multiple preclinical models in several research areas, including immuno-oncology, metabolism, cardiovascular diseases, and neuroscience.

References:

1. Zhou S, Liu M, Ren F, Meng X, Yu J. The landscape of bispecific T cell engager in cancer treatment. *Biomark Res.* 2021 May 26;9(1):38.
2. Ye C, Yang H, Cheng M, Shultz LD, Greiner DL, Brehm MA, Keck JG. A rapid, sensitive, and reproducible in vivo PBMC humanized murine model for determining therapeutic-related cytokine release syndrome. *FASEB J*. 2020 Sep;34(9):12963-12975.
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