Humanized FcγR/FcRn mouse model exhibits immunological responses comparable to wild-type mice

AACR 2026
Abstract #3803

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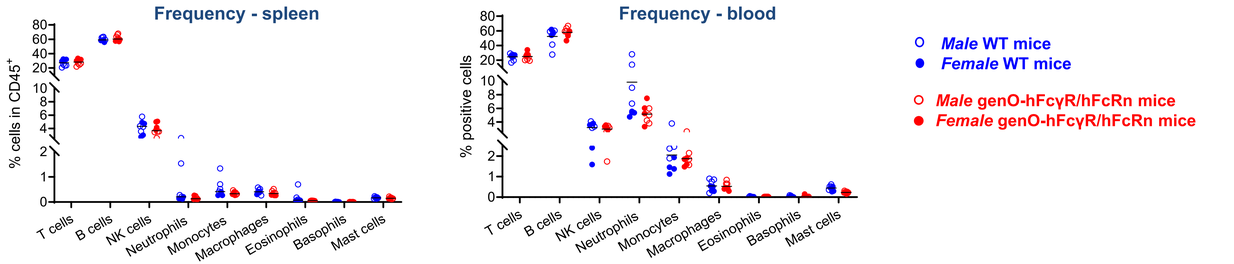
Background: Therapeutic antibodies have revolutionized cancer treatment by leveraging immune mechanisms such as Fc-effector functions, which depend on interactions between IgG and Fcγ receptors (FcγR). However, preclinical evaluation of antibody pharmacokinetics (PK) and pharmacodynamics (PD) remains challenging due to species-specific differences in FcγR and FcRn expression and function. We previously reported a FcγR humanized model that expresses a human-like pattern of FcγRs (including FcγRI, FcγRIIA, FcγRIIB, FcγRIIIA and FcγRIIIB – genO-hFcγR). These receptors are functional and enable accurate evaluation of Fc-effector functions such as ADCC and B-cell depletion. The model demonstrated Fc-dependent activity of therapeutic IgG, allowing differentiation between antibodies with regular versus enhanced FcγR binding and supports ranking of Fc-engineered antibodies in preclinical studies[1]. FcRn was also humanized in the model to enhance the translatability of PK studies by enabling human FcRn-mediated IgG recycling, while maintaining PD assessment of Fc-engineered therapeutic antibodies. Herein, we characterized the immunological competence of the humanized genO-FcγR/FcRn mouse model under inflammatory conditions by comparing its immune responses with those of wild-type (WT) mice following defined immunological challenges.

1. Humanization of Fcγ receptors and FcRn does not alter immune cell distribution in genO-hFcγR/hFcRn compared to WT mice in spleen and blood

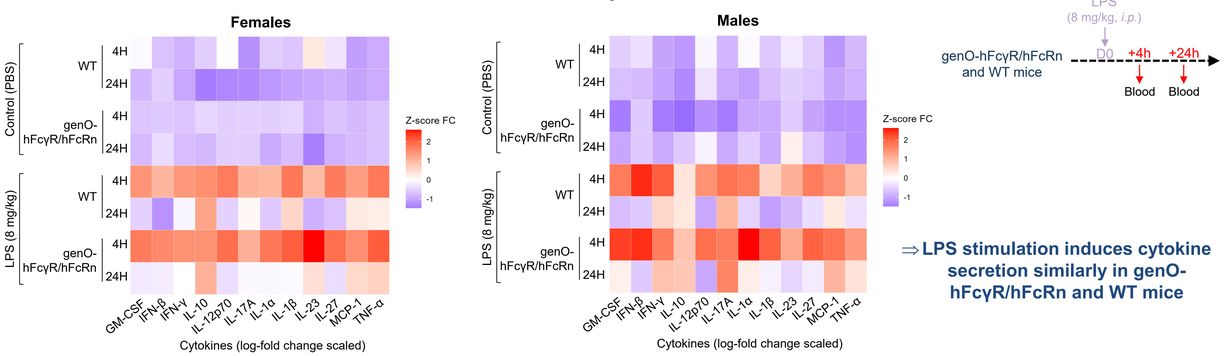


Freshly isolated splenocytes, gated on live CD45$^+$ CD200R$^+$ FcεRI$^+$ (Basophils), CD45^{low} CD200R$^+$ FcεRI$^+$ (Mast cells); in CD45$^+$ CD200R$^-$: CD3$^+$ CD19$^-$ (T cells) and CD3$^-$ CD19$^+$ (B cells); in CD3$^-$CD19$^-$cells: NKp46$^+$ (NK cells), Ly-6G$^+$ (Neutrophils), Ly-6G$^-$ SIGLEC-F$^+$ (Eosinophils), Ly-6G$^-$ SIGLEC-F$^-$ Ly-6C$^+$: F4/80$^-$ (Monocytes) and F4/80$^+$ (Macrophages).

⇒ **Similar results of immune profiling in bone marrow – *data not shown***

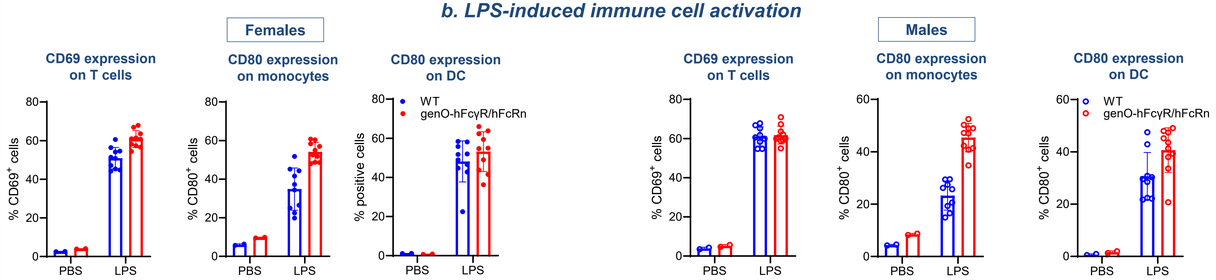
2. *In vivo* response to LPS is similar in genO-hFcγR/hFcRn and WT mice

a. LPS-induced cytokine secretion



⇒ **LPS stimulation induces cytokine secretion similarly in genO-hFcγR/hFcRn and WT mice**

b. LPS-induced immune cell activation

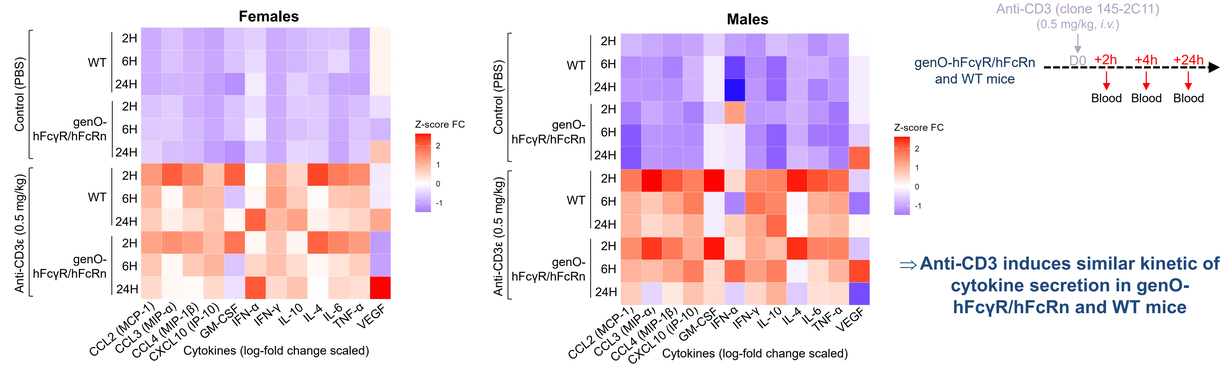


Freshly isolated splenocytes, T cells (gated on live CD3$^+$CD19$^-$ TCRαβ$^+$) and CD3$^-$CD19$^-$NKp46$^-$CD11b$^+$ (monocytes) and CD3$^-$CD19$^-$NKp46$^-$ CD11c$^+$ (DC cells) 24h post LPS injection (8 mg/kg, *i.p.*).

⇒ **LPS induces expression of CD69 on T cells and CD80 on monocytes and DC in both genO-hFcγR/hFcRn and WT mice, suggesting immune cells activation, which is in line with the increased cytokine production**

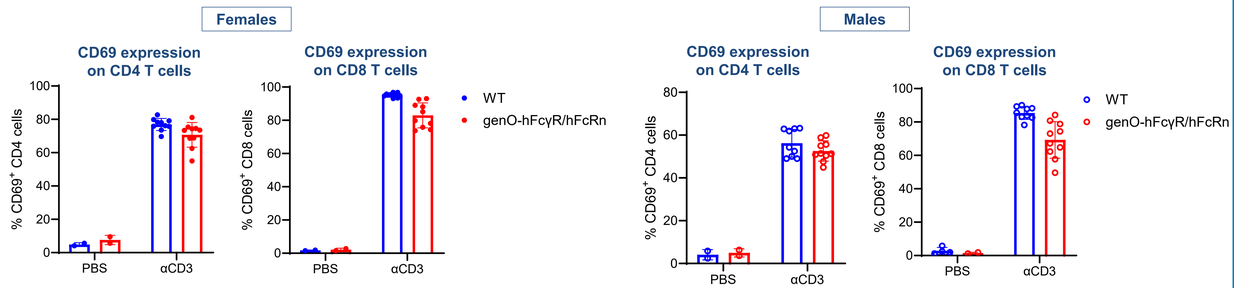
3. *In vivo* response to anti-mouse CD3 is similar in genO-hFcγR/hFcRn and WT mice

a. Anti-mouse CD3-induced cytokine secretion



⇒ **Anti-CD3 induces similar kinetic of cytokine secretion in genO-hFcγR/hFcRn and WT mice**

b. Anti-mouse CD3-induced immune cell activation



Freshly isolated splenocytes, T cells (gated on live CD3$^+$CD19$^-$ TCRαβ$^+$), CD4 (CD4$^+$ CD8$^-$) and CD8 (CD4$^-$ CD8$^+$) cells, 24h post anti-CD3 injection (clone 145-2C11, 0.5 mg/kg, *i.v.*).

⇒ **Overall similar induction of CD69 expression on CD4 and CD8 T cells from genO-hFcγR/hFcRn mice compared to WT mice, in line with cytokine production induced by anti-CD3**

Conclusion: These results demonstrate that genO-FcγR/FcRn mice are immunocompetent and mount immune responses comparable to those of wild-type mice. This model is a robust and reliable tool for studying Fc-engineered therapeutic antibodies in a context that preserves native immune functionality. The genO-hFcγR/hFcRn model is also being improved to enable tolerability to hIgG1 antibodies, and flexibility of therapeutics testing through expression of human immune checkpoints.

Reference: 1. Van Damme KFA, Sichien D, Van der Borght K, *et al*. Cross-species cellular mapping and humanization of Fcγ receptors to advance antibody modeling. *Sci Immunol*. 2026;11(115):eady7328. doi:10.1126/sciimmunol.ady7328

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