

Novel FcγR humanized mouse models enabling efficacy and PK/PD of therapeutic antibodies

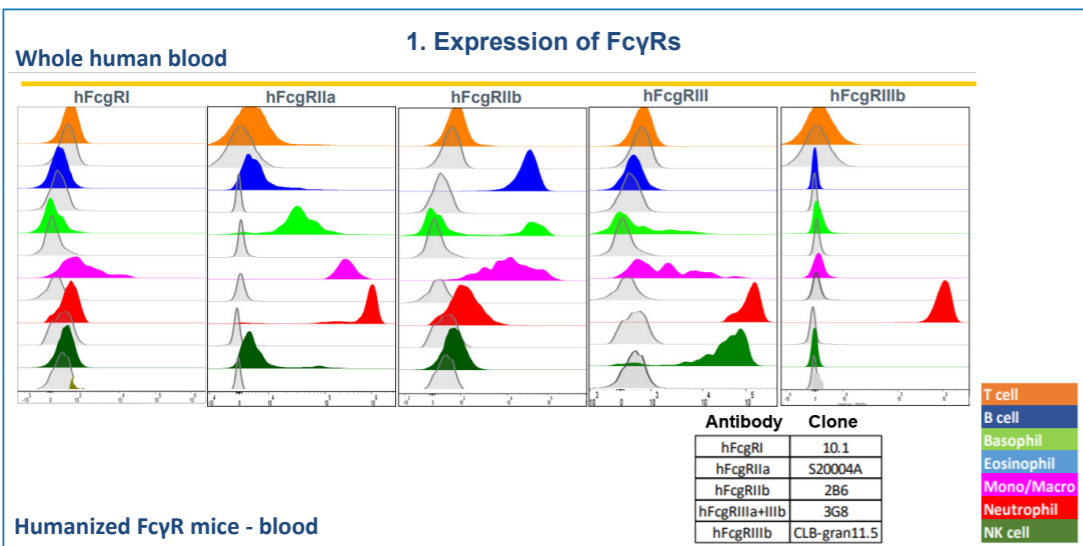
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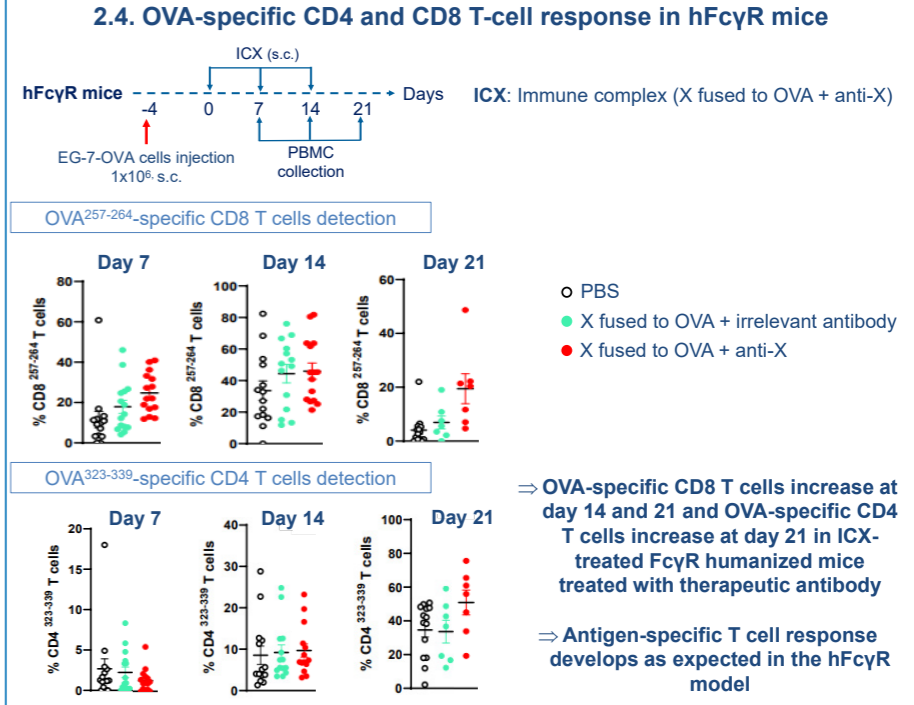
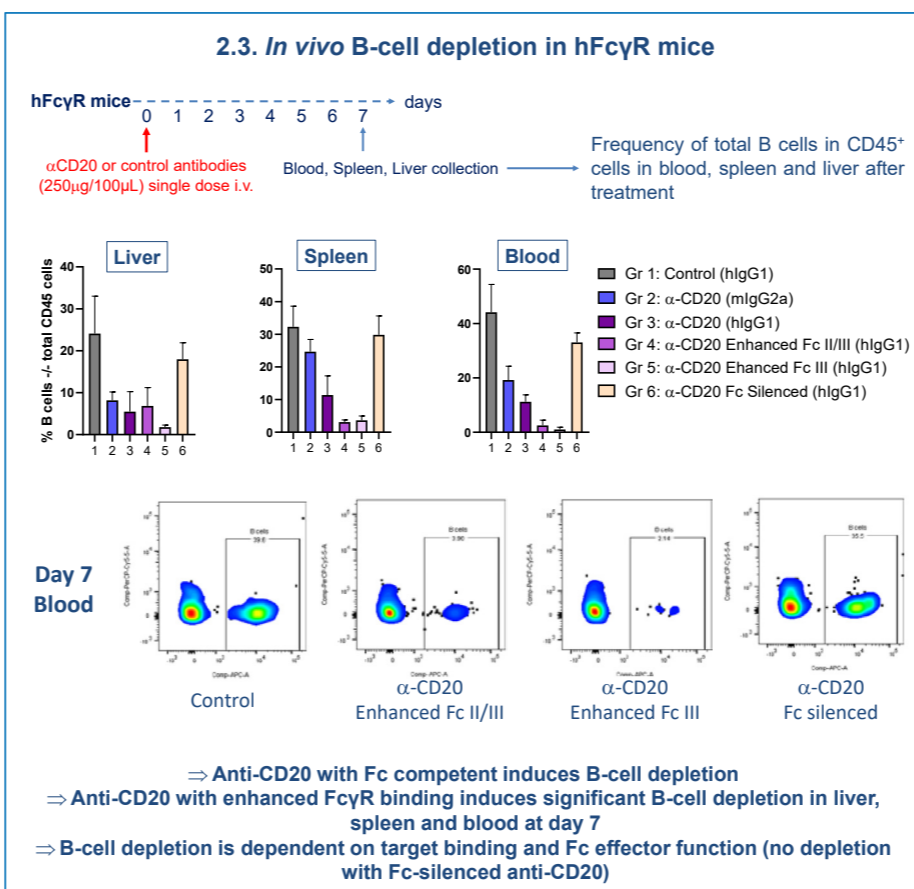
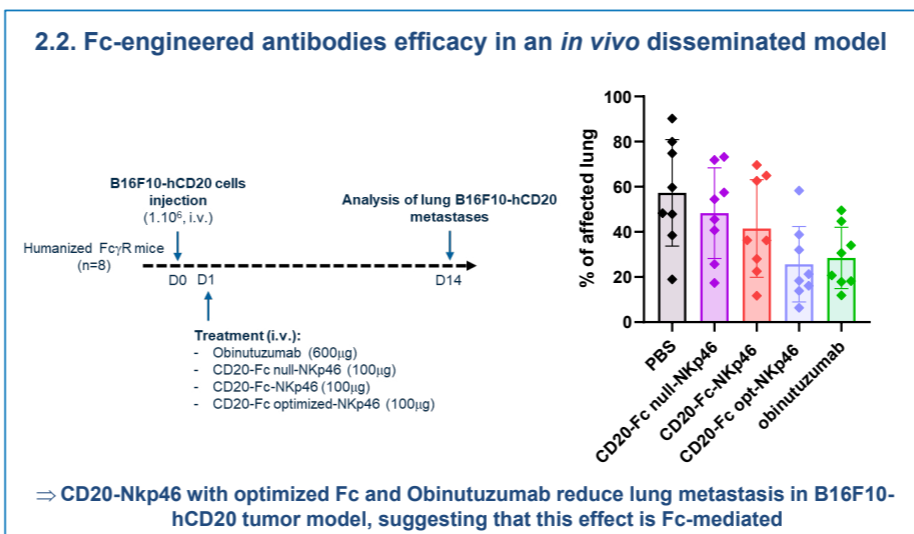
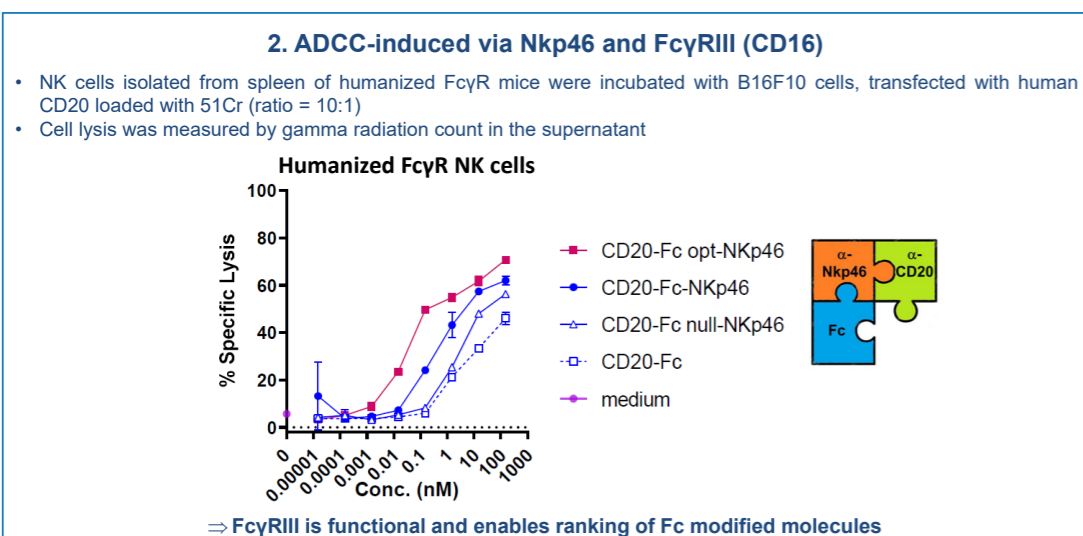
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Background: Enhanced activity of therapeutic IgG can be achieved by the modulation of Fc binding to Fcγ receptors (FcγR) which consequently modulate the Fc-effector function triggered upon crosslinking of target and effector cells by these antibodies. Assessment of therapeutic antibodies' pharmacodynamics in preclinical models is challenging, as the FcγR differ between mice and human, as well as in their expression pattern.

Humanized FcγR (hFcγR) model features a human-like expression pattern, in which humanized FcγRI, FcγRIIA, FcγRIIB, FcγRIIIA, FcγRIIIB are expressed and replace their mouse orthologs. We have previously reported that humanized FcγR expression pattern in hFcγR mice is consistent with their expression on human PBMC, with a few exceptions. Test of antibody-dependent cell cytotoxicity (ADCC) *ex vivo* in NK cells showed that Rituximab, an anti-hCD20 chimeric IgG1 with regular Fc, induces higher ADCC efficacy in NK cells from hFcγR than in NK cells from WT mice. Obinutuzumab, which also targets hCD20, but features an optimized Fc portion to enhance binding to FcγRIII, showed higher tumor cell lysis than Rituximab in NK cells from hFcγR mice, suggesting this model enables the ranking of antibodies⁽¹⁾.



⇒ hFcγR expression pattern in hFcγR mice is consistent with the expression in human PBMC, with a few exceptions (i.e., absence or low levels of FcγRIIA and FcγRIIB on basophils)
⇒ Intensity of FcγR expression also differs in cells from whole human blood and hFcR mice



3. Model upgrades

Model upgrade	Rational
hFcγR/hFcRn	Better translatability of PK study of therapeutics with enhanced half-life through binding to hFcRn ⁽²⁾
hFcγR/hlgG1	Tolerability to human IgG1 therapeutic antibodies
hFcγR/hFcRn/Rag1 ^{-/-}	Assessment of translational PK/PD in immunodeficient model for engraftment with human cells/tolerability to therapeutic human IgG
hFcγR/hTFRC	Better biodistribution of therapeutics to the brain through TFRC-mediated drug shuttling
hFcγR/Pan hCD3	Assessment of anti-CD3's efficacy
hFcγR/ICP humanized models from genOway's catalog	Flexibility of therapeutics assessment: bispecific or combotherapies targeting immune checkpoints (ICP)

Conclusion: The humanized FcγR model is a new tool to investigate efficacy of Fc-engineered molecules and is being improved to enable tolerability to hlgG1 antibodies, biodistribution in the brain, and test of therapeutics targeting human-specific immune checkpoints.

References:
⁽¹⁾ Sônego F et al., Novel FcγR humanized mouse models enabling efficacy and PK/PD of therapeutics antibodies, AACR 2024, 5341
⁽²⁾ Viuff D, Antunes F, Evans L, et al., Generation of a double transgenic humanized neonatal Fc receptor (FcRn)/albumin mouse to study the pharmacokinetics of albumin-linked drugs. J Control Release. 2016,10,1016