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A Cross-Species Map and Humanized Mouse Model of Fcγ Receptors and FcRn

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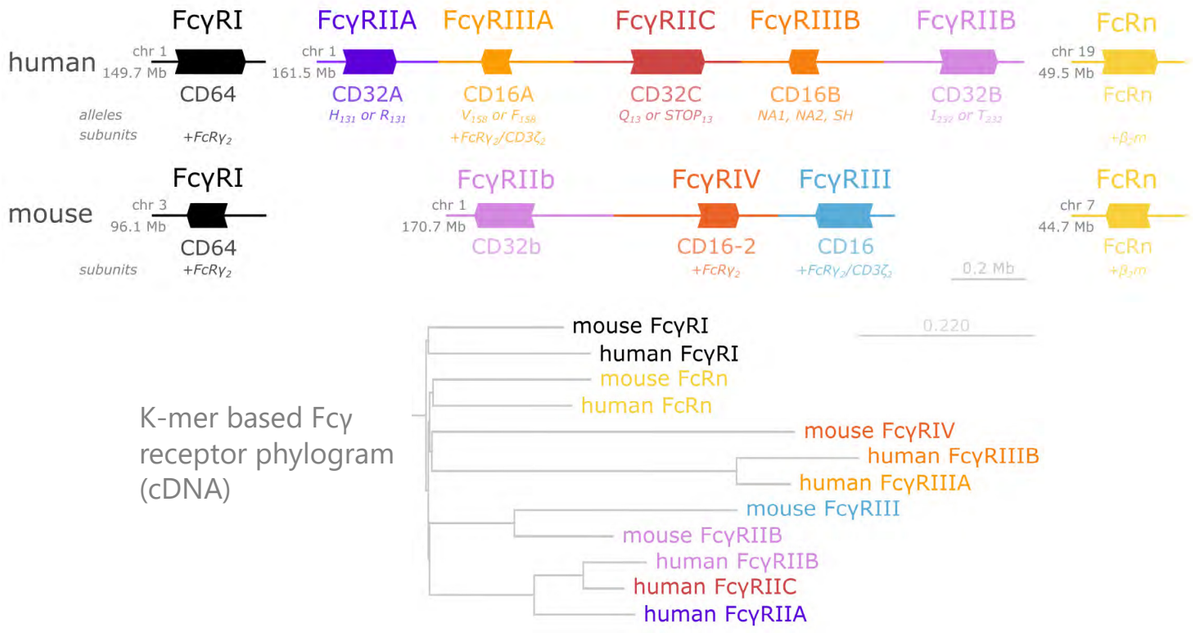
Fcγ receptors differ across species



Between-species differences in Fcγ receptors limit the use of mice as a preclinical model to study antibody function.

We **map** human and murine Fcγ receptors expression, and introduce a **novel mouse line** which expresses human FcγRI, FcγRIIA/B, FcγRIIIA/B and FcRn, replacing their murine counterparts. This resource and unique model will advance the preclinical assessment of antibody-based therapeutics.

Humanized Fcγ receptor mouse generation

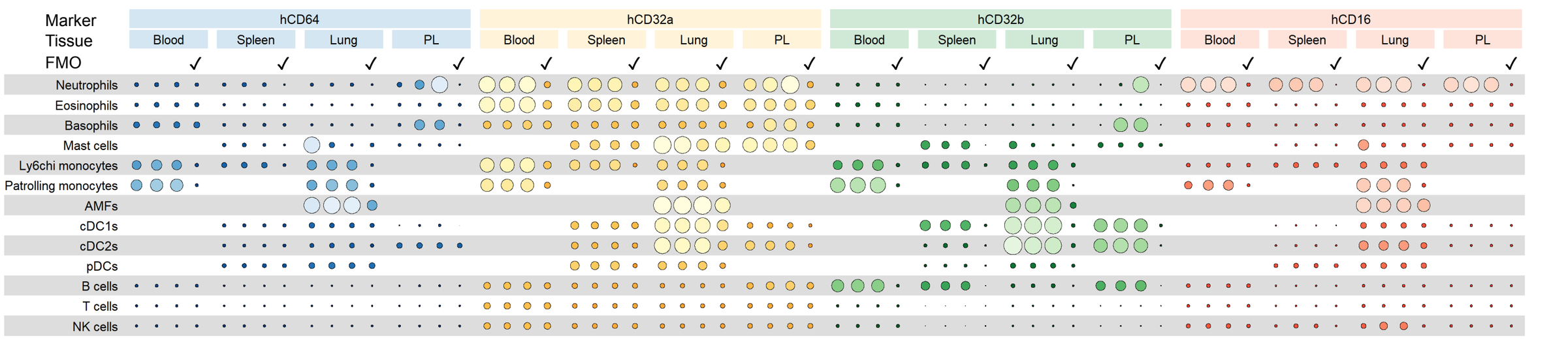
Human FcγRI was inserted into endogenous locus through homologous recombination and subsequent cre-mediated cassette exchange in embryonal stem cells.

Human FcγRIIA^{R131}, FcγRIIB^{I232}, FcγRIIIA^{F158}, FcγRIIIB^{NA2} were knocked-in into murine locus in two consecutive steps in embryonal stem cells.

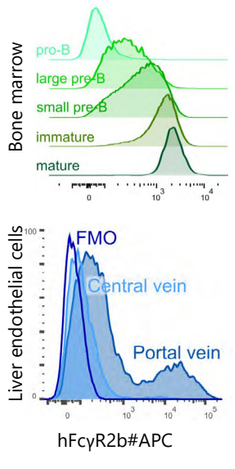
Homozygous humanized FcγR mice were interbred with a humanized neonatal Fc receptor (FcRn) line, the receptor which mediates IgG recycling and trafficking *(Viuff et al., 2016)*.

Knock-in FcγR genes are controlled by their human promotors, whereas FcRn is controlled by the mouse promotor.

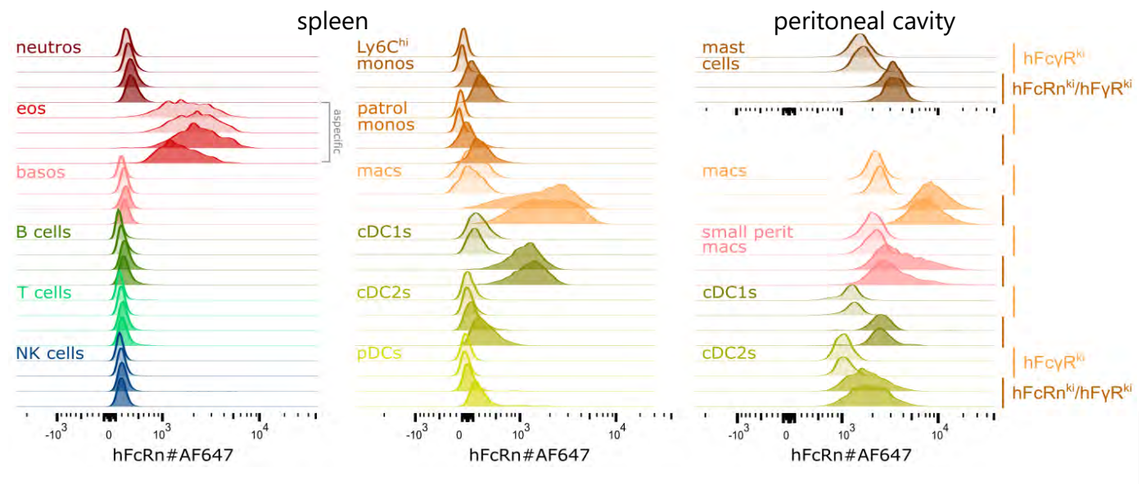
Humanized Fcγ receptor expression



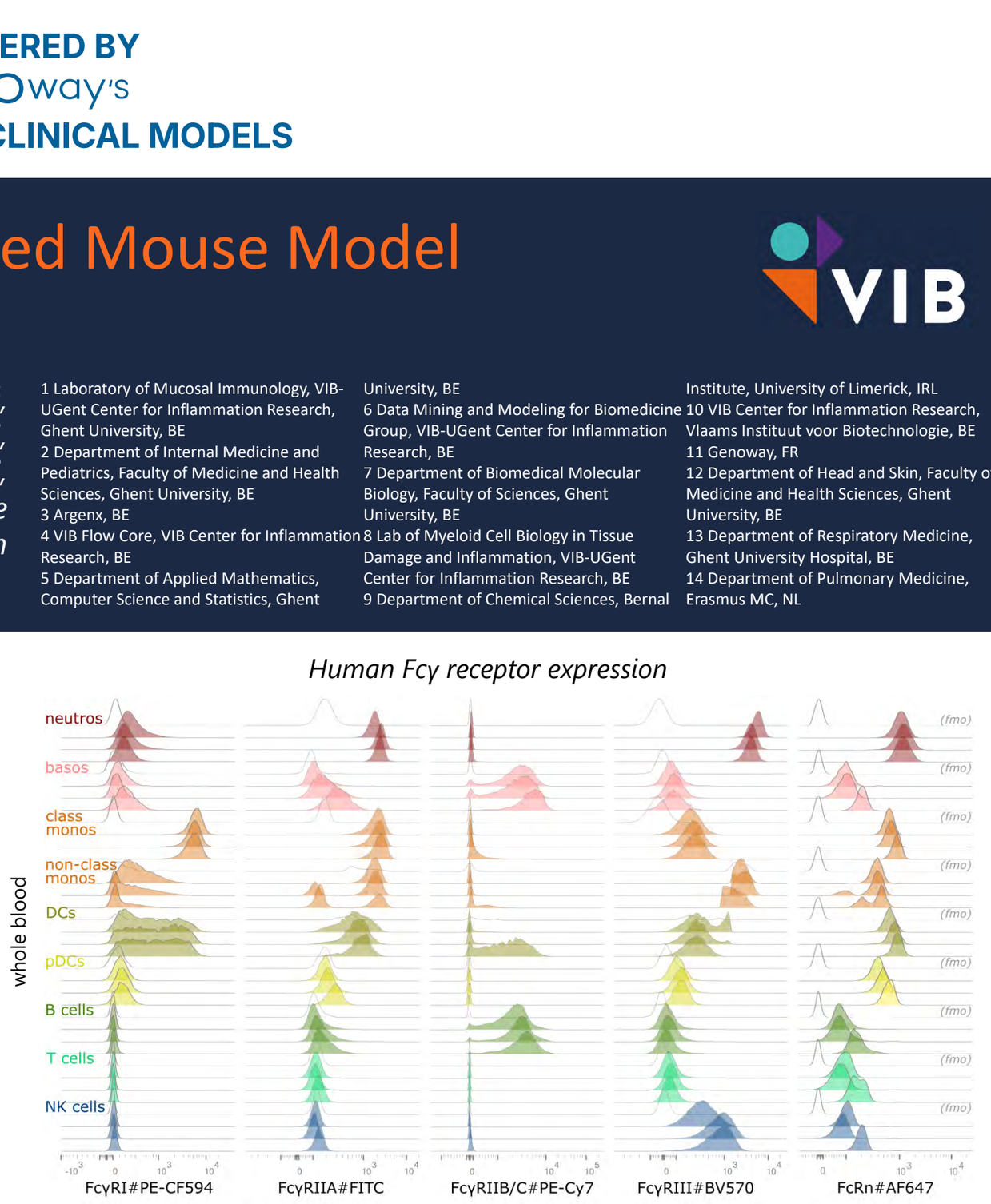
Humanized FcγR2b



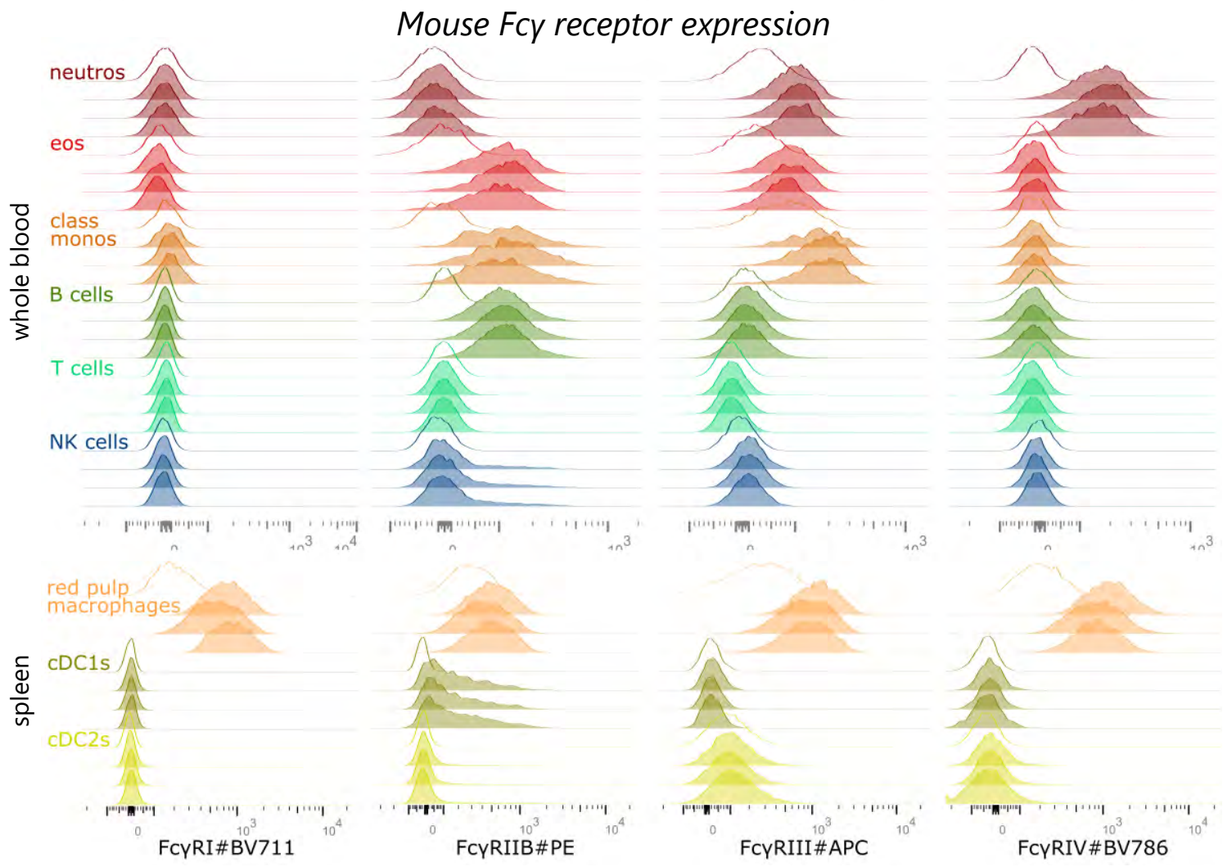
Humanized FcRn expression



Human Fcγ receptor expression

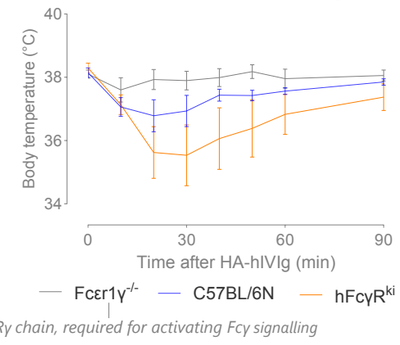


Mouse Fcγ receptor expression

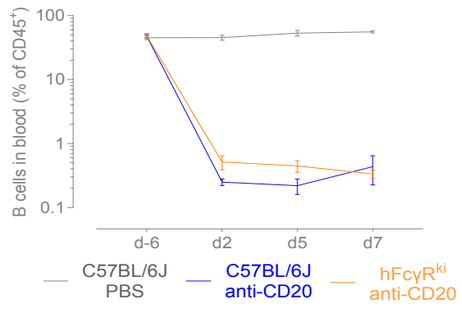


Functional validation of humanized Fcγ receptor functions

Systemic anafylaxis with heat-aggregated human intravenous immunoglobulins



B cell depletion using human anti-mouse CD20



Conclusion: These humanized mice display a fully functional Fcγ and FcRn repertoire, which will boost preclinical evaluation of monoclonal antibodies.

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