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Sustained Expression of C5mAb in Presence of Murine and Human FcRn

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Adeno-associated virus (AAV) gene therapy has the potential to offer a long-term solution for diseases that rely on chronic dosing. For paroxysmal nocturnal hemoglobinuria (PNH) and other complement disorders, Homology has developed its Gene Therapy-mAb (GTx-mAb) platform, focused on a one-time dose to deliver an investigational vectorized C5 monoclonal antibody. The C5 GTx-mAb achieved dose dependent sustained expression of functional C5 mAb in two immunocompromised models: NOD-SCID mice, which lack murine C5, and FRG® liver-humanized mice, which express physiological levels of human C5 (Sharma et al, ASGCT-2021).

In this study, we asked if the steady state levels achieved with our GTx-mAb platform would be influenced by the presence of human neonatal Fc Receptor (FcRn) since both NOD-SCID and humanized FRG mice express the endogenous murine FcRn. The receptor is widely expressed in humans and mice and is primarily responsible for the unusually long immunoglobulin G (IgG) half lives in circulation. FcRn protects IgGs from degradation by binding to their Fc region in the acidified endosome and recycling the IgGs back into circulation at physiological pH. While human FcRn only binds to human IgGs, murine FcRn is more promiscuous and can bind IgGs from humans and other species with high affinity. For evaluation of human/humanized mAb therapeutics, mice expressing a human FcRn transgene and lacking endogenous FcRn are considered the best translational models, as their IgG half-lives translate closely to clinical findings.

We expanded our animal studies to include several strains, including immunocompromised and immunocompetent transgenic strains containing the human FcRn receptor. We found that the species-specific differences in mouse vs human FcRn did not significantly impact the overall circulating antibody levels at steady state. Circulating levels of C5 mAb in all mouse strains tested were comparable or higher than those found in NOD-SCID mice, suggesting that the continuous synthesis and secretion of antibodies by hepatocytes is the key determinant in achieving sustained antibodies levels. Furthermore, we showed that murine C5 can contribute to an *ex vivo* hemolysis assay mediated by human serum. Using a modified *ex vivo* hemolysis assay that corrects for hemolysis due to murine C5, we confirmed that *in vivo* produced C5 mAb was functional in all mouse models investigated.
In conclusion, we have demonstrated that our results with the GTx-mAb platform are translatable to immunocompetent as well as mouse strains containing a human FcRn. Further, these data support additional studies to evaluate the potential of single dose C5 GTx-mAb in the development of therapeutics for PNH and other complement-related disorders.