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**Poster Presentation**
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**Gene Therapy-mAb Platform Targets Complement Protein 5 Using AAVHSCs**

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Many diseases necessitate chronic dosing of therapeutic monoclonal antibodies (mAbs). Patients present with compliance-fatigue, discomfort and repeat-dosing related complications such as infusion-related reactions, and in minor instances, incomplete disease control during mAb troughs. A single dose of AAV-mediated gene therapy delivering vectorized mAb may mitigate these complications.

Establishing Homology's gene therapy-mAb (GTx-mAb) platform, we designed an AAV-mediated anti-C5 antibody for the treatment of the complement-related disorder paroxysmal nocturnal hemoglobinuria. Vector designs expressing C5mAb using liver-specific promoters were evaluated *in vivo* and *in vitro* and delivered by AAVHSCs (AAV capsids isolated from human hematopoietic stem cells).

We previously demonstrated that a single dose of GTx-mAb expressing anti-C5 antibody resulted in robust, sustained, functional antibody levels in NOD-SCID (C5-deficient) and in FRG® liver-humanized mice (reconstituted with human hepatocytes and expressing humanC5) for 26 and 12 weeks, respectively. Dose response studies with our best design achieved IgG levels > 20 mg/mL at the highest dose examined (Sharma et al, ASGCT-2021).

Here, we have focused on design optimization around coding and non-coding elements. Fully assembled mAbs were highly expressed *in vitro* in plasmid-transfected hepatoma cells and AAVHSC-transduced primary hepatocytes, and *in vivo,* in NOD-SCID mice. We achieved a further 3-fold increase in IgG expression at steady state with our lead construct, reflected in higher serum IgG/liver vector genome ratios.

In summary, we demonstrated that one-time treatment with an AAVHSC construct expressing a full anti-C5 antibody results in sustained therapeutic levels of serum mAbs that may alleviate the inconvenience and potential side-effects of repeat dosing.