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Transducing the Liver as an Antibody Factory using AAVHSCs

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Chronic dosing of therapeutic antibodies is used as a treatment for many diseases, including autoimmune disorders, complement-related diseases, inflammatory disorders, wet AMD and others. Repeat dosing is associated with complications, increased risk for the patient, discomfort, and lack of compliance. AAV-mediated gene therapies offer the potential to change the paradigm of antibody delivery. A single dose of a vectorized antibody may be able to overcome the peaks and troughs characteristic of antibody pharmacokinetics with persistent and durable antibody levels, alleviating the need for chronic dosing and its associated risks.

Taking advantage of the natural tropism of AAVHSCs (AAV capsids isolated from human hematopoietic stem cells (HSCs)), we designed AAVHSC vectors to produce functional antibodies *in vivo* using liver-specific promoters to preferentially express to this tissue. As a proof of concept, we focused on complement-related disorders and used anti-complement protein 5 antibody as payload. Antibody expression was demonstrated *in vitro* in transformed hepatoma cell lines (Hepa1-6, Alexander, HuH7, HepG2), primary hepatocytes (murine and human), and *in vivo* in mouse and human hepatocytes. In both *in vitro* and *in vivo* studies, the fully assembled antibodies were highly expressed (human IgG ELISAs and WB) and were functional (competitive ELISAs and *ex vivo* hemolysis assay).

Stable and robust IgG expression *in vivo* was successfully demonstrated in NOD-SCID mice for the duration of the study (up to 26 weeks). *In vivo* expression was dose-dependent and steadily increased during the first 5 weeks, reaching a plateau by ~7 weeks post dose. Analysis of the cellular lysates at the end of study demonstrated the antibody was efficiently secreted and that there were no protein aggregates in the liver even at the highest doses examined, with serum IgG levels >20mg/mL. IgG levels were dependent on vector design and capsid, and capsid-ranking differed in mouse vs human hepatocytes.

In summary, we showcase the potential for AAV-mediated gene transfer in transforming a liver to an antibody-producing factory. By utilizing AAVHSCs, which have broad tissue tropism across different cell types and species, we may be able to deliver an appropriate antibody payload to the liver and maintain durable levels of IgG production and therapeutic expression to meet the needs of patients with a variety of diseases currently managed with chronic antibody dosing.