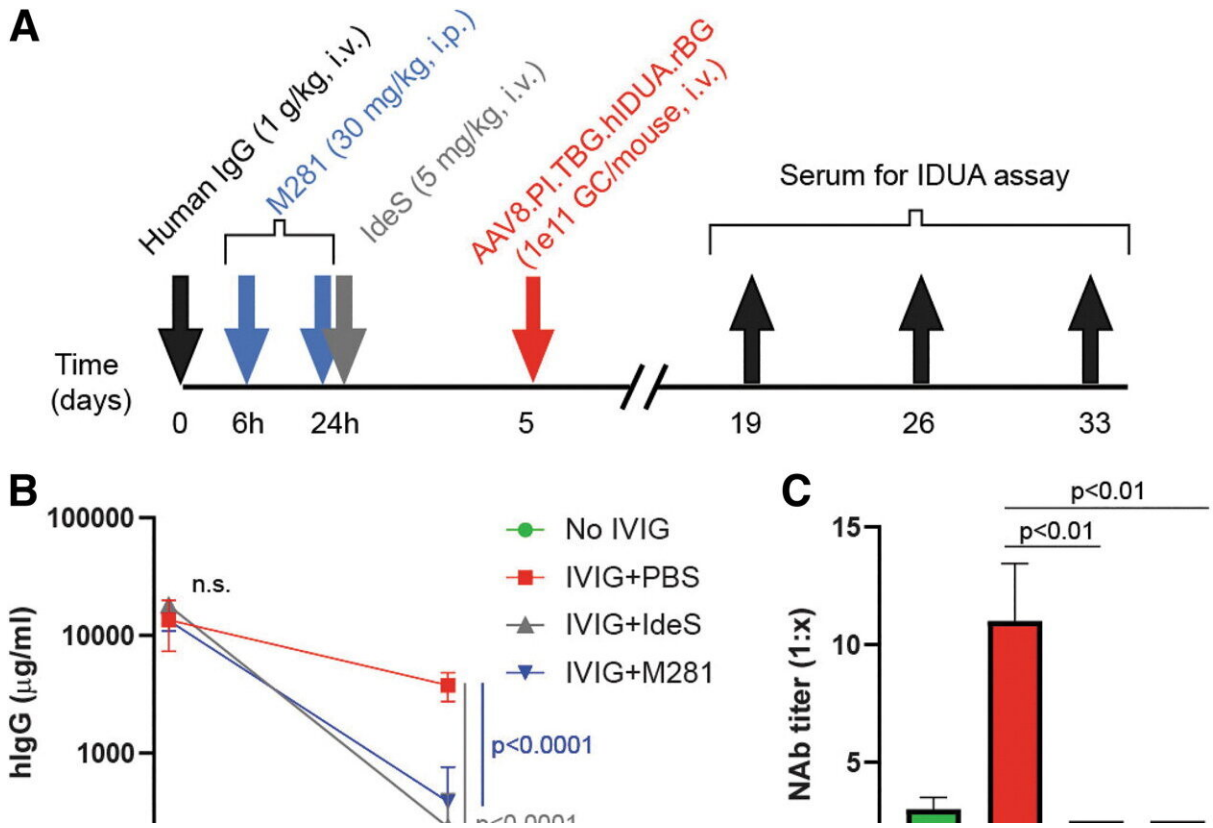
Enabling adeno-associated virus gene therapy despite preexisting humoral immunity

March 22 2023



M281 treatment prevents human NAb-mediated reduction of liver-targeted gene delivery after intravenous AAV administration in humanized FcRn transgenic mice. (A) Scheme of the in-mouse study assessing M281 effects on hIgG and anti-AAV NAb levels and subsequent systemic vector transduction to the liver comparing those by IdeS in hFcRnTg32.scid mice pretreated with hIgG. (B) hIgG concentrations in mouse serum samples over time. hIgG was undetectable in the No IVIG group (n = 5 per group). (C) AAV8 NAb titers at day 5 post-hIgG (n = 5 per group). (D) Serum IDUA activity post-AAV8.TBG.hIDUA.rBG

vector administration. Data were analyzed using ANOVA followed by a *post hoc* Tukey test. AAV, adeno-associated virus; ANOVA, analysis of variance; FcRn, neonatal Fc receptor; GC, genome copy; hIgG, human IgG; IdeS, imlifidase; IDUA, α-I-iduronidase; i.p., intraperitoneal; i.v., intravenous; IVIG, intravenous immunoglobulin; NAb, neutralizing antibody; PBS, phosphate-buffered saline; TBG, thyroid hormone-binding globulin promoter. Credit: *Human Gene Therapy* (2023). DOI: 10.1089/hum.2022.216

The use of a monoclonal antibody that reduced circulating IgG levels, led to a decrease in preexisting neutralizing antibodies (NAbs) to adeno-associated virus (AAV). The study, which showed that this strategy enabled gene delivery to the liver and heart via systemic AAV-based gene therapy in mice and non-human primates, is published in *Human Gene Therapy*.

AAV vectors represent the leading platform for gene delivery to treat rare genetic disorders. However, the prevalence of natural humoral immunity, with Nabs, prevents a significant proportion of the population from being treated with AAV-based gene therapy. IgG appears to be the predominant antibody class among Nabs. Inhibitors of the neonatal Fc receptor (FcRn) represent one group of IgG-reducing drugs in clinical development. M281 is a anti-human FcRn monoclonal antibody that can reduce IgG levels to less than 20% of the baseline level.

In the current study, James M. Wilson, MD, Ph.D., from the Perelman School of Medicine, University of Pennsylvania, and co-authors, evaluated the effect of M281-mediated IgG reduction on pre-existing NAb titers and gene transduction in the context of systemic AAV-based gene therapy in mice and non-human primates.

Based on their results, the investigators concluded that "mitigating pre-existing humoral immunity via disruption of the neonatal Fc

receptor–IgG interaction may make adeno-associated virus-based gene therapies effective in neutralizing antibody-positive patients."

"The presence of neutralizing antibodies to AAV can disqualify some patients from receiving gene therapy," says Editor-in-Chief Terence R. Flotte, MD, Celia and Isaac Haidak Professor of Medical Education and Dean, Provost, and Executive Deputy Chancellor, University of Massachusetts Chan Medical School. "This intervention has the potential to circumvent that limitation and allow more patients to benefit from gene therapy in the future."

More information: Makoto Horiuchi et al, Neonatal Fc Receptor Inhibition Enables Adeno-Associated Virus Gene Therapy Despite Pre-Existing Humoral Immunity, *Human Gene Therapy* (2023). DOI: 10.1089/hum.2022.216

Provided by Mary Ann Liebert, Inc