Inflammatory factors linked to inhibition of factor VIII gene therapy in hemophilia A

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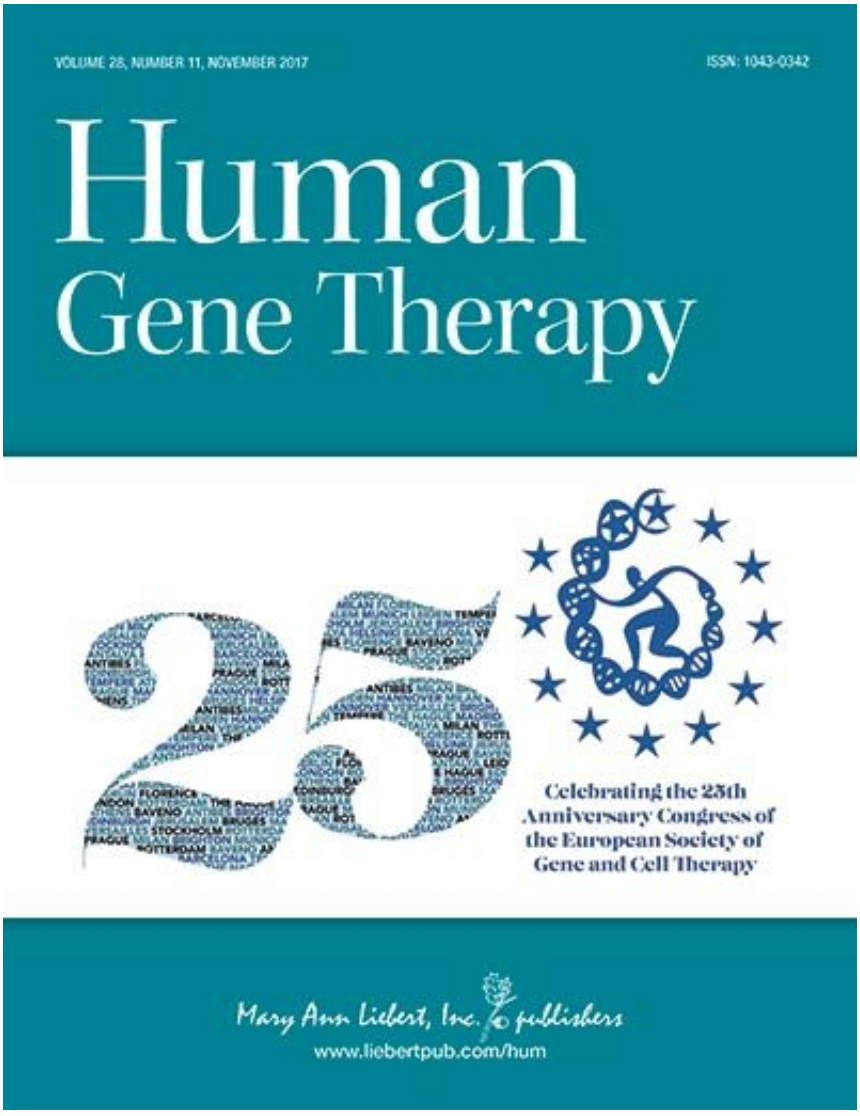

Credit: Mary Ann Liebert, Inc., publishers

As a gene therapy cure for hemophilia A moves closer to reality, a new study sheds light on a challenging complication in which a host autoimmune response inhibits the production of normal clotting factor VIII from the transferred FVIII gene. Researchers compared the levels of multiple pro- and anti-inflammatory cytokines in a mouse model of hemophilia A that received FVIII gene therapy at different ages and either did or did not exhibit FVIII inhibitor formation, as presented in an article published in *Human Gene Therapy*.

The article entitled "A Retrospective Study of Cytokine Profiles Changes in Mice with FVIII Inhibitor Development after Adeno-Associated Virus-Mediated Gene Therapy in a Hemophilia A Mouse Model" is coauthored by Junjiang Sun, Gene Therapy Center and Eshelman School of Pharmacy, University of North Carolina (UNC, Chapel Hill), and colleagues from UNC, University of Saint Joseph School of Pharmacy (Hartford, CT), Northern Jiangsu People's Hospital (Yangzhou, China), Chinese Academy of Medical Sciences, and Peking Union Medical College (Beijing, China). The researchers reported a shift in the cytokine profiles of mice with FVIII inhibitor development, including significantly increased levels of pro-inflammatory cytokines such as interleukin (IL)-1 and IL-6 and tumor necrosis factor (TNF)-alpha, among others. They also showed a negative correlation between risk factors for FVIII inhibitor development and age at which gene therapy was administered.

"Immune responses represent an important limitation to gene therapy for hemophilia," 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 Medical School, Worcester, MA. "The paper from Dr. Sun's group and their colleagues begins to address factors that may predispose certain individuals to mount a greater immune response against the therapeutic protein produced by the gene therapy vectors and thus benefit less from

the therapy."

More information: Junjiang Sun et al, A Retrospective Study of the Cytokine Profile Changes in Mice with FVIII Inhibitor Development After Adeno-Associated Virus–Mediated Gene Therapy in a Hemophilia A Mouse Model, *Human Gene Therapy* (2017). DOI: 10.1089/hum.2017.094