Debate continues over human immune system's role in blocking therapeutic genes delivered using AAV vectors

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The hypothesis that memory T cells formed in response to childhood infections may be to blame for the loss of expression of therapeutic genes delivered via viral vectors has been hotly debated, but recent clinical trials of adeno-associated viral (AAV) vector-based gene therapies designed specifically to avoid T-cell responses to AAV have shown the ability to correct debilitating diseases such as hemophilia in some patients. The scientists who proposed this hypothesis discuss the ongoing controversy and progress in developing approaches to overcome AAV-vector-induced T cell responses in an article in *Human Gene Therapy*.

Hildegund Ertl, Wistar Institute and Katherine High, Spark Therapeutics, Philadelphia, PA, are coauthors of the article entitled "Impact of AAV Capsid-Specific T-Cell Responses on Design and Outcome of Clinical Gene Transfer Trials with Recombinant Adeno-Associated Viral Vectors: An Evolving Controversy." They describe the evidence that first led them to look more closely at how T cell responses could interfere in successful therapeutic gene delivery using AAV vectors and why their hypothesis was initially met with much skepticism. The researchers also discuss some of the strategies developed that have shown that it is possible to avoid a T-cell response. These include immunosuppression, use of rare AAV serotypes that the immune system would not typically have previous exposure to, or modified versions of AAV vectors that can deliver and achieve expression of sufficient levels

of the therapeutic gene without eliciting an immune response.

"Understanding immune responses to AAV vectors will be the key to fully and safely exploiting their therapeutic potential for diseases like 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.

More information: Hildegund C.J. Ertl et al. Impact of AAV Capsid-Specific T-Cell Responses on Design and Outcome of Clinical Gene Transfer Trials with Recombinant Adeno-Associated Viral Vectors: An Evolving Controversy, *Human Gene Therapy* (2016). DOI: 10.1089/hum.2016.172

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