

A new cell and gene therapy approach to treat common bleeding disorder

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In a new study from the Wake Forest Institute for Regenerative Medicine (WFIRM) researchers have developed an optimized cellular platform for delivering Factor 8 to better treat patients with hemophilia A.

Hemophilia A is a [genetic disorder](#) caused by a deficiency in, or the absence of, coagulation Factor 8), an essential protein for blood to clot.

Hemophilia A is an x-linked genetic disease, and thus almost always affects males, and it occurs in 1 in 5,000 live male births. Roughly 20,000 individuals in the United States suffer from [hemophilia A](#), and it is estimated that more than 400,000 people worldwide have this devastating disease, according to www.hemophilia.org. Hemophilia A is currently treated with infusions of expensive Factor 8 products 2-3 times per week for the entire life of the patient.

While these treatments have dramatically improved the life expectancy of patients with hemophilia A, they are unavailable to nearly 75% of the world's patients, they cost well over \$250,000 a year (per patient), and complications can send the price tag to more than \$1 million. Moreover, as many as 30% of patients with the severe form of hemophilia A develop an immune response (inhibitors) to the infused Factor 8 protein, rendering subsequent treatments ineffective and placing the patient at risk of life-threatening bleeding events. In addition, and perhaps most important, these treatments are not curative.

The delivery of Factor 8 through gene and/or cellular platforms has, therefore, emerged as a promising approach to provide long-term correction of hemophilia A. For this study, the researchers investigated the suitability of human placental cells as delivery vehicles for Factor 8 and determined an optimal Factor 8 transgene to secrete therapeutic Factor 8 levels from these cells. Using cells that are modified to over express Factor 8 allows safeguards in production that are not possible when direct vector injection is used to treat patients.

"This is about the quality of life for these patients," said lead author Graca Almeida-Porada, MD, Ph.D. of WFIRM. "We are trying to develop not just a treatment, but a cure."

The research group demonstrated, for the first time, that human placental cells constitutively secrete low levels of Factor 8, confirming

these cells possess the machinery necessary to express and process this challenging protein, and suggesting they may be ideally suited as a cellular platform for delivering and producing Factor 8 to correct hemophilia A.

"We demonstrated human placenta-derived mesenchymal cells possess a set of several fairly [unique properties](#) that make them ideal both for cellular therapies/[regenerative medicine](#), and as vehicles for Factor 8 delivery," said Almeida-Porada. "In addition, because the pharmaceutical properties of Factor 8 can be markedly enhanced by changing the coding sequence to facilitate Factor 8 processing and secretion by the cells, we identified a modified Factor 8 transgene, amongst the several developed by our colleagues at Emory, that yielded optimal Factor 8 expression and secretion from placental [cells](#)."

While our initial goal is to use this treatment to correct hemophilia A prior to birth, Almeida-Porada said the approach could also be used in those pediatric and adult patients who develop Factor 8 inhibitors during their lifetime. Further preclinical studies will be needed to establish in vivo safety and efficacy of this therapy, for both prenatal and postnatal recipients, she added.

"It is our hope this approach can be moved forward as a long-lasting and curative treatment option for patients with hemophilia A," added co-author and WFIRM Director Anthony Atala, MD.

More information: Nadia El-Akabawy et al, Defining the Optimal FVIII Transgene for Placental Cell-Based Gene Therapy to Treat Hemophilia A, *Molecular Therapy - Methods & Clinical Development* (2020). [DOI: 10.1016/j.omtm.2020.03.001](https://doi.org/10.1016/j.omtm.2020.03.001)

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