Cleveland Clinic Innovations

PRODUCT
B-domain minimized Factor VIII sequence for gene therapy

INDICATION
Hemophilia A

VALUE PROPOSITION
B-domain minimized Factor VIII constructs which exhibit increased protein expression and secretion can have greater clinical impact than currently marketed Hemophilia A gene therapies.

DEVELOPMENT STAGE
Approach validated in human cell line.

INTELLECTUAL PROPERTY
Patent Pending.

RELATED PUBLICATIONS
Liu Z, Zhang Y, Zhu M, Zhang B. Identification of candidate nonsense mutations of FVIII for ribosomal readthrough therapy. Haematologica vol 104,12 (2019).

CONTACT INFORMATION
Saqib Sachani
Associate Director, Business Development and Licensing
sachans@ccf.org
216.672.1913
IDF# 2021-134

Efficient Gene Therapy Delivery of Factor VIII

Inventors: Bin Zhang, PhD, Yuan Zhang, PhD
Lerner Research Institute

UNMET NEED

Hemophilia A (HA) is an X-linked inherited disease caused by mutations in the gene encoding the blood coagulation protein Factor VIII which causes chronic and excessive bleeding. HA affects approximately 1 in every 5,000 male births worldwide and is typically managed through Factor VIII infusions and more recently via Factor VIII replacement via gene therapy for severe patients. Patients receiving Factor VIII infusions must do so for the rest of their life, and frequently experience complications and breakthrough bleeds due to inconsistent Factor VIII levels in their blood.

Current gene therapies remove the need for frequent Factor VIII infusions, but Factor VIII levels in blood decrease over time. This is typically compensated for by using a high dose of AAV vector during treatment, but this leads to an elevated immune response that reduces Factor VIII expression and secretion and leads to high levels of anti-AAV antibodies which prohibit repeat dosing. New strategies are needed which maintain high Factor VIII expression and secretion but allow for reduced dosing to prevent immune complications which lead to decreasing Factor VIII levels over time.

SOLUTION

Cleveland Clinic researchers have developed a library of B-domain minimized and codon optimized Factor VIII sequences which demonstrate an up to five-fold increase in protein secretion compared to a B-domain deleted standard (SQ). The B-domain connects the heavy chain and light chain of Factor VIII but is not necessary for final protein function and is typically removed to facilitate AAV packaging during gene therapy. Researchers have discovered that maintaining a 27 amino acid sequence from the middle of the B-domain (positions 1011-1037) drastically increases Factor VIII secretion while still maintaining the size of the construct within the limits of AAV delivery. Importantly, the increased Factor VIII secretion is independent of other strategies such as improved vector design and promoter/codon optimization and can have synergistic effect when combined with these efforts.