Progress in gene therapy for hemophilia A and B

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For 35 years, since the Factor VIII and Factor IX genes were cloned, the dream of curing hemophilia via inserting normal genes into affected individuals has remained just out of reach, despite positive results in animal models for more than 20 years. The initial human trials in the 1990s-early 2000s identified adeno-associated virus (AAV) as the preferred vector system, and encouraging but transient results were obtained using AAV2-FIX. The transgene was lost via a T-cytotoxic cellular response toward hepatocytes containing the FIX gene recognized AAV capsid peptides displayed in the context of HLA class 1, the typical response in a viral infection. A subsequent trial employed steroids to manage the T-cell response, preserving hepatocytes containing the FIX transgene, resulting in an average ~5% FIX activity in 10 subjects. Subsequent studies have employed the Padua mutant of FIX, R338L, a natural mutation conferring 6-8-fold higher specific activity, to enable FIX expression following IV administration in the ~30% range. For years, B-domain deleted FVIII has been difficult to package in AAV vectors, resulting in low hepatic expression in animal models. More recently, a promoter/enhancer-BDD-FVIII construct has been developed that, when packaged in AAV5, has yielded ~100% FVIII activity at 1 year and ~50% activity at 2 years. These remarkable Phase 1/2 results for both FIX and FVIII have led to 2 HemB and 2 HemA Phase 3 trials, ongoing at present. Despite these promising results, many questions remain, including the duration of transgene expression, long term safety, managing the short term immune response, assessing direct hepatocyte toxicity, and what level of expression is sufficient. Further understanding of AAV transduction biology and exploration of more efficient and cell type specific AAV vectors, as well as alternative vector systems, will offer the continued advancement of the field, to the benefit of those affected by bleeding disorders.