

Gene Transfer for Hemophilia and Viral Infection

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Abstract

The goal of our work has been to establish an experimental basis for gene transfer as a method of treating hemophilia, an inherited bleeding disorder that results from the absence of functional Factor VIII or Factor IX. We have carried out pre-clinical and clinical studies of AAV-mediated gene transfer of the Factor IX gene in animal models and in human subjects with severe hemophilia B. Target tissues in humans have included both skeletal muscle (via direct intramuscular injection) and liver (via hepatic artery infusion). Our preclinical efficacy studies have demonstrated a life-long correction of the bleeding diathesis in hemophilia B in mice, and long-term therapeutic reconstitution of canine factor IX in deficient dogs after AAV-mediated gene transfer into the liver. To date, hemophilia B dogs have been followed for over 4 years and still maintain their initial levels of factor IX following the administration of AAV-2. As a result, a number of preclinical studies of AAV into the liver of various species were performed to generate the appropriate safety data to support a Phase I liver-based clinical trial. The comparative results from the two clinical trials, the correlative results of the preclinical studies from the animal models, and the potential advantages/disadvantages of the two approaches will be discussed. Hepatitis C Virus (HCV) infection is a major health problem world-wide. We have recently evaluated different gene transfer approaches for targeted disruption of the viral life cycle. RNA interference (RNAi) is a recently discovered RNA surveillance mechanism used in lower animals and plants to silence specific genes. We have recently demonstrated that RNAi can function in adult mammals. By adapting this to a gene transfer strategy, we have established selective suppression of a HCV-reporter chimeric gene in mouse liver. RNAi has potential for use as a gene therapeutic to treat HCV infection as well as a large number of other acquired and genetic disorders.
