

## AAV and Liver-Directed Gene Therapy – Lili Wang, Ph.D.

Gene therapy is a promising tool for treatment of the human diseases that cannot be cured by traditional therapies. Because a large number of inherited metabolic disorders are a result of the deficiency of enzyme required to function in the liver or secreted by the liver, liver-directed gene therapy has become an active field. The two main categories of delivery vehicle are non-viral and viral vectors, and among the viral vectors, Adeno-associated viral (AAV) vector has emerged as an attractive vector for liver-directed gene therapy due to its non-pathogenicity, low immunogenicity and high efficiency. The initial success was demonstrated using serotype 2-based vectors that hepatic delivery of AAV-FIX vectors results in long-term high levels of FIX in normal and hemophilic mice, and therapeutic levels in hemophilia B dogs and primate models[1-6]. The success in animal models was further expanded since the discovery of a large number of novel AAV serotypes[7], among which AAV8 appears to be one of the most efficient vector for hepatic gene transfer. In murine models, sustained correction has been demonstrated in many disease models, such as familial hypercholesterolemia[8], hemophilia[9-11], lysosomal storage disorders[12-14], atherosclerosis[15], and glycogen storage disease[16], and ornithine transcarbamylase-deficiency[17]. Long-term therapeutic levels have also been achieved in large animal models[11, 18, 19]. Recently, the development of self-complementary vectors (scAAVs) further improves the transduction efficiency of the liver in mice by at least 20-fold over that achieved with comparable conventional AAV vectors[20], because of the elimination of the rate-limiting step for conversion of the single-stranded AAV genome into transcriptionally active double-stranded forms.[21, 22]. The combination of superior serotypes and self-complementary vectors demonstrated high level and stable factor IX gene expression in nonhuman primates[20, 23]. So far, the success in animal models has not been translated into human yet. The only clinical trial that has been conducted using AAV for liver-directed gene transfer is a phase I clinical trial for severe hemophilia B mediated by AAV2 vector. Therapeutic levels of factor IX was detected in one patient but it only lasted transiently due to development of cell mediated response to the input AAV capsid[24]. Besides, pre-existing neutralizing antibodies to AAV2 was found to greatly reduce the gene transfer efficiency. Thus, more efforts are required to translate the success in animal models to human. The newer generation of efficient vectors (scAAV and novel serotypes) may be able to evade the toxicity observed with AAV2 vector since they could work at a much lower vector dose.

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