Development of DNAzyme Gene Therapy for Huntingtons Disease

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Research Abstract
Clinical trials of pharmacotherapies to slow progression of the hereditary neurodegenerative disorder Huntington’s disease (HD) have not identified effective drugs. Partly because of this and because reducing levels of the pathogenic mutant huntingtin protein is likely to be the most effective treatment, gene therapy is being pursued by many investigators and clinicians, typically using either antisense oligonucleotides (ASOs) against mutant huntingtin mRNA, or RNA against mutant huntingtin mRNA that interferes with its expression (RNAi). Because ASOs

and RNAi delivery constructs (typically AAV expressing RNAi) cannot cross the blood-brain-barrier and because efficacy of any one treatment wanes with time, direct CNS delivery several times a year will be required to maintain efficacy. Such repeated injections pose safety risks and concerns about achieving high enough levels in the critical brain areas for therapeutic benefit. We have been testing an alternative approach using systemic delivery of DNAzymes in R6/2 HD transgenic mice, and found they have considerable efficacy and promise. DNAzymes are synthetic catalytically active DNA molecules that bind to and cleave targeted mRNA. They possess a central catalytic domain consisting of a specific sequence of 15 deoxynucleotides, and two variable flanking domains that can be designed to hybridize a DNAzyme molecule to a specific target mRNA. After mRNA cleavage, DNAzymes dissociate from the mRNA, and the cleavage products are further degraded by intracellular RNases. DNAzymes possess advantages over other gene therapies because: 1) they are catalytically active, leading to a better dose-response efficacy; 2) they are stable and cross the blood-brain barrier, and thus can be delivered repeatedly by systemic injections, thereby avoiding the need for direct CNS injection; 3) systemic administration yields DNAzyme delivery to both peripheral organs and brain, thus treating peripheral and central manifestations of disease; and 4) therapy can be discontinued in the event of adverse side effects. In the proposed studies, we will further develop systemic DNAzyme therapy as an HD treatment, by characterizing the extent and duration of its effectiveness using the rapidly progressing R6/2 mouse model expressing truncated mutant human huntingtin (Aim 1) and the more slowly progressing BACHD mouse model expressing full-length mutant human huntingtin (Aim 2). Studies in both mouse lines will evaluate how long the mutant huntingtin holiday lasts after a one-month daily intraperitoneal delivery period (out to a month post in R6/2 mice and two months post in BACHD mice), and assess benefit by extent of mutant huntingtin mRNA and protein knockdown in brain and peripheral organs (qPCR and Western blots), behavioral testing (rotarod and open field), and brain neurochemistry and pathology. We will also evaluate any possible DNZ6 toxicity or inflammatory effects, and determine the extent to which the DNAzyme(s) we test knock down human WT huntingtin in vitro and endogenous mouse WT huntingtin in vivo.

Further information available at:

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