Tailoring gene replacement therapy for MECP2-related disorders

Colleen Niswender, PhD
Vanderbilt University
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Rett syndrome (RTT) is a neurodevelopmental disorder that results from loss of MeCP2 protein function. The disease progression of Mecp2 knockout mice can be reversed if MeCP2 levels are increased, even in advanced disease states. Buoyed by this discovery, gene therapy efforts have begun to develop viral vectors capable of delivering MeCP2 to the brains of RTT patients. However, this approach is complicated by fact that even modest increases in MeCP2 dosage over baseline can result in phenotypes from a related disorder known as MECP2 Duplication syndrome (MDS). While most studies demonstrating the efficacy of MeCP2-gene therapy have been performed in Mecp2 knockout mice, many of the over 200 reported pathogenic mutations in MECP2 do not result in total loss of protein, or even full ablation of methyl binding or transcriptional repression, but rather create a hypomorphic protein with diminished function. The goal of this proposal is to determine how these hypomorphic alleles affect the therapeutic index of MeCP2-replacement strategies. Specifically, we hypothesize that mice expressing the T158(A) allele, which retains ~30% methyl binding, and the R133(C) allele, which preferentially affects hydroxymethyl binding, will present with MDS-like phenotypes when bred to a mouse overexpressing a human MeCP2 transgene (MECP2-TG1). Additionally, we will test the theory that pathogenic mutations in MECP2 mutation-negative RTT create a cellular context that is analogous to MECP2 mutation-positive RTT, and thus will be responsive to increased MeCP2 protein levels. The overarching goal of this proposal is to establish a framework for patient stratification based on how mutation type affects both the potential for efficacy as well as adverse effect liability.