THE HARTWELL FOUNDATION

2013 Individual Biomedical Research Award

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Nucleotide Repeat Disorders: Rescuing Misregulated MicroRNA With Targeted Drug Therapy

In 20 of the most prevalent and debilitating of inherited pediatric diseases, including Fragile X Syndrome, Huntington's disease and myotonic dystrophy (DM1), there is a fundamental genetic defect that occurs within the deoxyribonucleic acid (DNA) of certain genes: along small stretches of the DNA three or more consecutive nucleotides are inappropriately repeated. Although such repeats occur normally within DNA, in these devastating diseases, collectively referred to as a nucleotide repeat disorder (NRD), the number of repeats has expanded well beyond the normal range, causing altered biological function of affected genes. In many cases, the number of repeated sequences is correlated with the severity of disease. Neurologic dysfunction often accompanies NRD, which characteristically leads to lifelong disability and/or early mortality. Worse, with each successive generation, the number of inherited repeats can expand, producing more severe disease that manifest earlier in childhood. Unfortunately, there are no known treatment strategies to target this type of inherited disease. Based upon Erin's 2012 discovery that nucleotide expansions in each NRD have predicted homology to unique short sequences of ribonucleic acid called microRNA (miR), she submits that every NRD expansion should bind with high affinity to a specific miR. Given that small changes in miR have profound effects on cellular functions by regulating gene expression and protein production, she proposes that "sponging" up a specific miR by the regions of DNA with expanded nucleotide repeats would prevent miR from performing its usual role and thus account for each unique NRD disease. In contrast, blocking the sponging process in an NRD should prevent pathology. To test her hypothesis that sponging occurs in NRD and that targeted drug therapy will increase miR levels, she proposes to model the sponging mechanism in a cell culture model system. She will then seek to demonstrate in a mouse model whether selective miR delivery can ameliorate the effect of NRD disease. Erin offers a completely novel paradigm for a group of pediatric diseases thought previously to be connected only by the nature of shared genomic expansion — a potentially unifying strategy for treatment and relief of associated symptoms and disabilities in children affected by NRD. If Erin is successful, rescuing misregulated miR will make it possible to offer for the first time a therapeutic intervention for children suffering the otherwise debilitating and fatal effects of congenital disease brought on by nucleotide repeat disorders.