Allele-Selective Inhibitors for Expanded Trinucleotide Repeat Genes

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Country

USA

Title of project or programme

Allele-Selective Inhibitors for Expanded Trinucleotide Repeat Genes

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NIH (NINDS)

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1

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Trinucleotide Repeat Expansion, Trinucleotide Repeats, Huntington Disease, Antisense Oligonucleotides, MJD1 protein

Research Abstract
DESCRIPTION (provided by applicant): Background. Expanded trinucleotide repeats cause Huntington’s Disease (HD) and other degenerative disorders. There are no cures for these devastating illnesses and treatments are urgently needed. Trinucleotide repeat disorders are due to mutations in just one gene, and agents that block expression of the mutant gene offer a promising option for treatment. Antisense oligonucleotides (ASOs) or duplex RNAs can inhibit

expression of trinucleotide repeat genes in animal models, but inhibition of both the mutant and wild-type alleles may not be tolerated in patients. Selective inhibition of only the mutant protein would be ideal, but requires innovative approaches to gene silencing because of the need to discriminate between the two similar alleles. During the previous funding period we used single-stranded antisense oligonucleotides, single-stranded interfering RNAs (ssiRNAs), and duplex RNAs to achieve selective inhibition of mutant HTT. Objective. We propose to maximize the potential for clinical development by optimizing these newly discovered compounds and better understanding their mechanisms of action. We will extend our strategy to other trinucleotide-repeat diseases to identify additional therapeutic lead molecules. The mRNAs of trinucleotide repeat genes differ in many ways, and the challenge of inhibitor development will lead to insights into how repetitive sequence affects the mechanism of recognition. At the most fundamental level, the chemical properties and design features of the nucleic acids we use are novel and their study will offer important general insights into gene silencing by ASOs, ssRNAs, and duplex RNAs. Aim 1. Optimize potency and selectivity of duplex RNAs, ASOs, and ssRNAs. We will design and test new generations of compounds and assay their inhibition of HTT expression. The structure activity relationships we develop will allow us to select the best compounds for animal studies and offer mechanistic insights into allele-selectivity. Aim 2. Investigate the mechanism of allele-selective inhibition. Understanding the mechanism of allele-selectivity will facilitate the design of highly effective inhibitors of HTT expression. We will us biochemical and cell-based approaches to characterize the protein- and nucleic acid-interactions that occur during recognition of HTT mRNA by our inhibitory molecules. Aim 3. Application of inhibitors to other disease genes containing expanded repeats. Other disease genes contain expanded triplet repeats including ataxin-3, myotonic dystrophy protein kinase, and ataxin-7. Developing compounds to achieve allele-selective inhibition of these genes would widen the therapeutic potential of the approach and offer new perspective on mechanisms.

Further information available at:

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