The Project: Novel therapeutic compound to treat neurodegenerative trinucleotide repeat diseases

The Investigator: Christopher E. Pearson, Ph.D.

The Background:

Genetic expansions of DNA repeat sequences in certain genes have been linked to at least 40 neurodegenerative and neuromuscular diseases, including Huntington’s disease, myotonic dystrophy, and amyotrophic lateral sclerosis. These repeat expansions tend to get larger as they are passed down the family tree, resulting in earlier age-of-onset, increased disease progression, and severity. Importantly, the expansions continue as the individual ages, with the largest expansions arising in affected tissues, and these ongoing mutation expansions are thought to drive the disease progression and severity.

Gene-specific CAG/CTG trinucleotide repeat expansions are responsible for 16 of the >40 diseases caused by unstable repeats, including Huntington’s disease (HD) and myotonic dystrophy. The larger the CAG repeat, the earlier the age of onset, the greater the progression and severity. In HD, the disease age-of-onset is tightly linked to CAG tract length, an association that is particularly true for individuals with the most common expansion sizes of 40-50 where age-of-onset can vary by decades. To this extent, a reduction of a few repeats could delay onset by years. Ongoing repeat expansions occurring in affected tissues correlate with disease age-of-onset, severity, and progression. Dramatic repeat length variations exist between tissues of the same individual, with differences >5,000 repeats, with the largest expansions in heart, cerebral cortex and striatum. The considerably larger expansions in the clinically affected tissues indicates that the somatic expansions are driving disease onset, progression, and severity. Recent studies reveal that, for at least six of the sixteen CAG diseases (HD, SCA1, SCA2, SCA3, SCA7, & SCA17), DNA repair proteins are major modifiers of age-of-onset, lending further support to the correlation between

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ongoing somatic expansions and age-of-onset. This association is likely to be true for all 16 CAG
diseases, each of which show somatic expansions. Thus, methods of arresting or reversing somatic
CAG/CTG repeat expansions could be used to arrest or reverse disease progression and would be
extremely beneficial in a therapeutic setting.

The Discovery

The Pearson Lab in collaboration with colleagues at Osaka University have discovered a small
molecule useful in treating these trinucleotide repeat diseases. Initial testing has demonstrated that
the compound not only arrests CAG/CTG expansions, but induces contractions of expanded CAG
repeats (reduces the number of repeats) in both cell models and in affected tissues of an HD mouse
model. Repeated administrations of this small molecule have additive effects of inducing contractions
of the CAG tract. Notably, the small molecule acts specifically upon the mutant expanded repeat,
without affecting either the non-expanded allele, and without damaging the rest of the genome.
Application of this small molecule may have important clinical benefits for preventing or reversing
disease disease-onset, progression and severity in numerous repeat diseases.

Development Stage

Preclinical in vitro and in vivo data in a disease-specific brain region, are promising. Next steps
include medicinal chemistry, pharmacokinetic, animal efficacy, and toxicology studies.

Intellectual Property

A US Provisional patent application has been filed.

Contact

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