Therapeutics & Vaccines

Compounds and Methods for Modulating Frataxin Expression in Friedreich's Ataxia

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WARF: P160232US07

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The Wisconsin Alumni Research Foundation (WARF) is seeking commercial partners interested in developing new treatments for Friedreich's Ataxia (FRDA), a terminal neurodegenerative disease with no effective therapy. UW–Madison researchers have developed synthetic transcription elongation factors (Syn-TEFs) for increasing frataxin (FXN) expression in FRDA patients.

Overview

Friedreich's Ataxia (FRDA) is a neurodegenerative disorder without treatments to halt or reverse disease progression, affecting roughly 9,000 Americans. FRDA is caused by triplet expansion in the first intron of FXN (which encodes the protein frataxin). Disease severity correlates with the number of repeats, with affected patients typically having 100s to 1,000s of triplet repeats.

FXN mRNA drops 90% in FRDA patients while genetic carriers exhibit expression levels at about 40% and normal function, indicating that lower expression is tolerable. Published work suggests that transcriptional elongation (overcoming 'paused' transcription processes) is the major hurdle to making sufficient FXN mRNA. To data, no intervention has sufficiently raised FXN mRNA to combat FRDA symptoms. In the present invention, the researchers focused on resolving the transcriptional pausing hurdle as a means to improve FXN mRNA production.

The Invention

UW–Madison researchers have generated new chimeric complexes that selectively increase FXN mRNA production to eliminate the physiological cause of Friedrich's Ataxia. The synthetic transcription elongation factors (Syn-TEFs) of the present invention comprise a bromodomain inhibitor (such as Brd4), bound to a linker (such as PEG), which is further bound to a polyamide designed to target a gene sequence of interest near the repeats (see image below). Mechanistically, the complex binds selectively to the DNA near the triplet repeats in FRDA patients, and then the linked bromodomain inhibitor binds BRD4 and thereby recruits the elongation machinery to restart the paused transcription complex.

The inventors observed a 4.3-fold improvement at 500 nM after 1 day, which should be sufficient for real improvement, since FRDA carriers only have 40% of normal expression and show no symptoms. Increasing the dose to 1 μM increased FXN mRNA 8.5-fold after 1 day, with 3-fold improvement after only 6 hours.

Applications

- Specific and potent activation of FXN gene expression

Key Benefits

- Superior activation of FXN gene expression compared to existing approaches

Additional Information

For More Information About the Inventors

- Aseem Ansari

Related Technologies

- P160383US02 describes Artificial Transcription Factors and uses thereof.

Publications

- Erwin et al. Synthetic transcription elongation factors license transcription across repressive chromatin. 2017. Science 358, 1617-1622.

Tech Fields

- Therapeutics & Vaccines : CNS
- Therapeutics & Vaccines : Other therapeutic technologies

For current licensing status, please contact Rafael Diaz at rdiaz@warf.org or 608-960-9847

Figures