Docket #: S11-239

Supt4h – Novel target for Huntington's and PolyQ Diseases

Researchers in the laboratories of Prof. Stanley Cohen and Prof Tzu-Hao Cheng have discovered that Supt4h is a potential therapeutic target for reducing toxicity and restoring the functionality of deleterious proteins in Huntington's (HD) and other polyQ diseases. Targeting Supt4h could also decrease the synthesis of abnormal RNAs that result in other neuromuscular disorders. PolyQ diseases are dominant genetic conditions caused by expansion of a CAG trinucleotide repeat which then encodes protein with a long polyglutamine (polyQ) region. Transcripts containing expanded trinucleotide repeat segments in non-protein-coding regions of transcripts, or expanded segments of other trinucleotide repeats are similarly affected. These non-functional variants then lead to protein aggregation and result in debilitating neurodegenerative disease.

Targeting Supt4h (a transcription elongation factor) reduces the synthesis of long polyQ proteins – while still allowing for normal synthesis of non-mutant cellular proteins as well as proper folding of long polyQ stretches of protein. Small molecules or RNAi compounds targeting Supt4h could provide a new avenue for addressing the underlying cause of disorders such as HD, spino-cerebellar ataxia (SCA), dentatorubralpallidoluysian atrophy (DRPLA), or spinobulbar muscular atrophy (SBMA).

Stage of Research
The inventors have demonstrated that small molecules targeting Supt4h reduce aggregation and increased functionality of polyQ proteins in neuronal cell studies.

Applications

- **Drug development** for neuromuscular disorders, including polyQ diseases (HD, SCA, DRPLA, SBMA)

Advantages

- **Unmet medical need** - there is currently no effective treatment for HD or other neurological disorders caused by trinucleotide repeat expansions
- **Restored functionality** - studies in cell culture show that this approach is capable of restoring function to variant proteins that traditionally cause disease in a dominant fashion
- **Transcriptional control**

Publications

- Liu C et al. Spt4 Is Selectively Required for Transcription of Extended Trinucleotide Repeats. Cell. 2012-02-16, 148(4):690–701.
- patent application PCT/US2011/063997: Selective reduction of the deleterious activity of extended tri-nucleotide repeat containing genes

Patents

- Published Application: WO2012078906
- Published Application: 20130317088
- Published Application: 20160152978
- Published Application: 20180171336
- Issued: 9,211,303 (USA)
- Issued: 9,862,947 (USA)
- Issued: 10,760,077 (USA)

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