



Evaluation of RNA *trans*-splicing therapy for spinocerebellar ataxia, type 1 – A pilot study

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Scientific Abstract

The aim of this project is to test the therapeutic potential of a novel genetic modification technology for spinocerebellar ataxia type 1 (SCA1). SCA1 is one of the spinocerebellar ataxias caused by an expanded polyglutamine tract in the protein ataxin-1. Phosphorylation of ataxin-1 at Ser⁷⁷⁶ is critical for its neurotoxicity. Ser⁷⁷⁶ phosphorylation together with the expanded polyglutamine sequence act synergistically in the regulation of the steady-state levels of ataxin-1, which, in turn modulates its activity as a putative transcriptional regulator. Our hypothesis is that steady-state levels of ataxin-1 can be reduced by preventing Ser⁷⁷⁶ phosphorylation by modifying its coding sequence by RNA *trans*-splicing. The specific aims are: (i) To engineer *trans*-splicing molecules to substitute Ser⁷⁵², the homologue of human Ser⁷⁷⁶, for alanine, in mouse ataxin-1; (ii) To reprogram *Sca1* transcripts in cultured neurons from wild-type mice; reprogramming will be demonstrated by RT-PCR, western blotting, immunoprecipitation and mass spectrometry; (iii) To analyze the consequence of reprogramming on steady-state levels of polyglutamine-expanded ataxin-1 in neurons from a knockin mouse model of SCA1. This project will serve as a proof-of-principle for other spinocerebellar ataxias for which genetic modification-based methods could offer a realistic therapeutic possibility.

Lay Summary

Spinocerebellar ataxia type 1 is an inherited neurological disease caused by the production of a protein toxic to nerve cells. The aim of this project is to test the potential of a novel genetic modification technology to reduce the toxic protein load. If successful, this proof-of concept project will have implications for the treatment of not only spinocerebellar ataxia type 1 but also some other spinocerebellar ataxias. Gene therapy for the nervous system is still at an early stage but if it was to start showing promising results could offer a realistic therapeutic possibility for rare diseases.

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