

Spinocerebellar ataxia: RNAi therapy for Spinocerebellar Ataxia
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Scientific Abstract

Spinocerebellar ataxia type 7 (SCA7) is a dominantly inherited neurodegenerative disease caused by an expanded CAG repeat mutation in the Ataxin-7 gene, for which no curative treatment currently exists. RNA interference (RNAi) has potential as a therapeutic tool for silencing disease causing genes, specifically for the allele-specific silencing of dominant disease genes. Using RNAi to silence the mutant Ataxin-7 gene, we will target identified single nucleotide polymorphisms with tight linkage to the repeat mutation rather than the mutation itself. Building on exciting preliminary data, and using a novel double-luciferase screening system to identify highly functional RNAi molecules (shRNAs) with allele-specific discrimination for the mutant Ataxin-7 gene, we will; i) carry out further screens to optimise the shRNA selectivity and function; ii) Transfer these shRNAs into lentiviral vectors generating U6 and miRNA-based constructs; iii) Investigate these in cell culture using HEK cells, and lymphoblasts harvested from patients containing a range of CAG repeat lengths. This will lay the groundwork for future studies to test this RNAi therapy in an SCA7 mouse model, initially by attempting to correct the retinal degeneration phenotype. It will also underpin a future application to MRC for project grant level support.

Lay Summary

Spinocerebellar ataxia type 7 (SCA7) is a hereditary, chronic neurodegenerative condition for which no therapy exists at present. It is inherited in dominant fashion meaning that the mutant ataxin-7 gene is present in cells alongside the normal gene, and despite the presence of the normal gene the mutant gene causes the disease. A logical therapy for this condition would therefore be to remove or prevent the action of the mutant gene. A powerful new method for silencing or switching off genes has recently been discovered called RNA interference (RNAi), for which its discoverers received a Nobel Prize in 2006. Using RNAi we plan to selectively switch off the mutant ataxin-7 gene, in such a way that the presence and activity of the normal gene (which is essential) are largely unaffected. We have already made progress in identifying the RNAi molecules that could achieve this and we now wish to extend these studies to improve the function of these molecules and to see whether this method can work in cells, using genetically manipulated cells and also cells derived from SCA7 patients. A talented PhD student will carry out this work, and determine the feasibility of this experimental approach for patients with SCA7 within the next 12 months.

**For more support or information please contact: Ataxia UK, Winchester House,
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