Project Title: Refinement of allele-specific antisense oligonucleotides for spinocerebellar ataxia type 3

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Scientific Summary:
This project aims to develop a novel therapeutic approach for spinocerebellar ataxia type 3 (SCA3) using allele-specific antisense oligonucleotides (ASOs). The project will involve several key steps: first, the researchers will refine ASO sequences to optimise their efficacy and specificity while minimising toxicity. Second, they will establish a preclinical evaluation platform using SCA3 iPSC-derived brain organoids to assess the safety and efficacy of ASOs. Third, the researchers will investigate the effects of non-selective and allele-specific ASO treatments on ataxin-3 function. Finally, they will identify a potential treatment strategy through an in-depth analysis of lead ASOs, including an evaluation of the benefits of an ASO cocktail for the treatment of SCA3.

The project builds on previous work that has identified potential ASO targets, disease-associated SNPs, and demonstrated their efficacy in reducing mutant ataxin-3 levels. By combining these efforts with a robust preclinical evaluation platform, this research aims to accelerate the development of a promising therapeutic approach for SCA3 patients.

Lay Summary:
Spinocerebellar ataxia type 3 (SCA3) is the most common form of autosomal dominant ataxia. People with SCA3 inherit one copy of the disease-causing gene from either their mother or father. What is often overlooked is that those with SCA3 also inherit a healthy copy of the SCA3 gene from the other parent, which is needed for normal physiological function. Current treatment strategies aim to reduce the levels of both the mutant and healthy copies, which might lead to unintended side effects.

This project aims to target only the mutant protein that leads to SCA3 without affecting the healthy version. The researchers will do this by looking at small differences between the mutant SCA3 gene and its healthy version, which can be targeted. Small molecules called antisense oligonucleotides (ASOs) can selectively bind to the instructions for proteins (mRNA), in this case for the mutant SCA3 protein, blocking its production while all other proteins, including the healthy SCA3 protein, can be produced.

The researchers have reprogrammed SCA3 patient skin cells to become stem cells, which can be programmed into brain-like cells called organoids. The brain-like cells are good models for predicting drug side effects. They will test a range of ASOs on these brain-like cells to see which are most effective at suppressing the mutant SCA3 protein and are most tolerable.