

**Neuron-validated Approaches for Developing Friedreich's Ataxia Therapeutics**  
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**Scientific abstract**

Friedreich's ataxia (FA) is the most common recessive genetic ataxia affecting 1-2 per 50,000 Caucasians. The disease is caused by GAA triplet repeat expansions in intron 1 of the *FRDA* gene, repressing transcription and reducing levels of frataxin protein within the cell. The main affected organs are the central nervous system and the cardiac tissue. In this proposal we focus on developing models and treatments to treat the neurodegeneration seen in FA patients. The proposal is highly collaborative in nature, to be carried out in laboratories at the University of Oxford and the Universidad Autonoma de Madrid. We will focus in two areas. First, we will study the molecular mechanisms underlying repeat expansion in neurons and how increased repeat sizes affects gene expression using a reporter gene assay in a differentiated human neuronal model. We will then screen compounds for their ability to elevate gene expression from the expanded disease locus. Second, we will develop gene therapy for FA in a pre-clinical mouse model using the neurotropic herpes simplex virus type 1 (HSV-1) amplicon vector. We will use vectors carrying the *FRDA* cDNA and also, in parallel, the complete *FRDA* genomic locus, exploiting the unique high transgene capacity of HSV-1.

**Lay summary**

Friedreich's ataxia is one of the most common causes of inherited ataxias in Western Europe, affecting about 1-2 in 50,000 Caucasians, and there is currently no effective treatment. The main affected areas are the central nervous system and cardiac tissue. Treatments based on antioxidants have had some success at alleviating the cardiac conditions, but there remains no treatment for the neurodegenerative aspect of Friedreich's ataxia. This collaborative project jointly undertaken by laboratories at the University of Oxford and the Universidad Autonoma de Madrid in Spain is focussed on developing improved models and therapies of neurodegeneration in Friedreich's ataxia.

We will first study more about the genetic basis of the disease. It is known that the disease is caused by expansions of a DNA sequence in the gene which prevents enough of the correct protein (called frataxin) being made. The lower than normal level of the protein leads to cell death. What is not known is why expansions occur in cells, and how this happens in the brain. We will grow human neurons in cell culture dishes to study how the gene expansions occur. The expansions are known to occur between generations, but are also thought to happen actually inside cells of the brain during a patient's life. Work in Oxford will try to better understand this process.

The second part of the work will happen in Oxford and Madrid. We will again work in neurons cultured in dishes and investigate drug treatments which will help to alleviate



the repressive effect of the gene expansion and allow enough of the frataxin protein to be made.

Finally, in the third aspect of the project the Oxford and Madrid laboratories will work together on developing a novel gene therapy strategy to treat Friedreich's ataxia. We will use a modified harmless version of a virus which naturally infects neurons in the brain to deliver a correct version of the frataxin gene to the cells which are dying because not enough frataxin is being made. Improved viruses will be made in Oxford and then will be injected in mice with Friedreich's ataxia in Madrid. Previous work of this kind was able to cure mice of the movement problems associated with the disease.

Critical to the whole success of the project is the interaction of the Oxford and Madrid laboratories and the development of better cultures of human neurons. In

Oxford we will use reagents available from the Human Genome Project to try to better understand how the frataxin gene works. In Madrid part of the work will involve culturing neurons from patients with Friedreich's ataxia, a wholly novel approach. The laboratories have a long record of successful collaboration and look forward to working together for this project.

### **What does this mean for patients?**

If it is shown that this type of gene therapy can improve levels of frataxin in mouse models and in human neurons, further research could progress to the possibility of using this therapy in humans to overcome the core defect in Friedreich's ataxia.

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