



An investigation to determine the efficacy and safety of lentivirus mediated *FXN* gene delivery for the correction of Friedreich ataxia

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Scientific summary

Lentivirus vectors (LV) provide stable and long-term gene expression in several cell types and are therefore highly suited to the treatment of genetic disease. We have previously shown that LV can be used to correct haemophilia B, a genetic disorder of the liver. More recently, we have also shown that novel envelope pseudotyped LV can efficiently reach other tissues, including the cerebellum, dorsal root ganglia, spinal cord, heart and pancreas. These are the primary tissues that show frataxin deficiency in Friedreich ataxia. Therefore, our aim is now to use LV to deliver the *FXN* gene to these tissues, to restore normal frataxin levels and to correct the disease phenotype. To show proof of principle that this can be achieved we will use HIV-1 based LV to deliver the *FXN* gene initially to cultured FRDA fibroblasts and neurons and then to FRDA transgenic mice. We will create LV carrying the *FXN* gene driven by the spleen focus forming virus and ubiquitously acting chromatin opening element promoters to achieve high-level and long-term *FXN* expression. In parallel we will examine LV safety by profiling vector effects on the mouse genome using a series of genotoxicity assays developed in our laboratory.

Lay summary

Friedreich ataxia (FRDA) is an inherited neurological disorder for which there is currently no effective therapy. It is caused by both parents passing on a DNA mutation in the frataxin (*FXN*) gene, known as a 'repeat expansion'. This leads to reduced levels of an essential protein called frataxin within cells in the body. Neurons in certain regions of the brain and spinal cord, heart muscle cells and pancreatic cells appear to be particularly susceptible to damage because of this reduction in frataxin.

Although potential treatments for some of the later symptoms of FRDA are now being investigated using antioxidants and iron chelators, it may be more effective to treat the early stages of dysfunction. Such a treatment could be achieved by frataxin gene therapy, where extra frataxin genes are artificially introduced into the body with the help of viral vectors to supplement the defective gene, thereby increasing the frataxin protein levels in the cells.



Successful gene therapy clinical trials have recently been carried out for other inherited disorders, such as a form of blindness known as macular degeneration. However, before gene therapy clinical trials can be considered for FRDA, preclinical studies in mice are necessary to determine the best system that will result in the safest delivery of the *FXN* gene to the appropriate affected tissues, resulting in a permanent increase in frataxin protein levels within the cells.

This project aims to undertake some of these preclinical mouse studies. Firstly, the efficacy of introducing the *FXN* gene into cultured FRDA cells by means of a viral delivery system will be examined. Then the safety and efficacy of introducing the *FXN* gene into newborn mice via a number of different routes will be investigated. It is important that the expression of the frataxin protein is long-lived in the mice and to measure this, we will analyse different tissues taken from mice up to six months after administration of the gene therapy. In addition, any potential benefits of increased frataxin levels on FRDA-like symptoms in the mice will be assessed. The results that we obtain will provide very valuable information when considering future gene therapy clinical trials.

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