



Development of an improved GAA repeat expansion mutation-based mouse model of Friedreich ataxia for therapeutic testing.

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Scientific summary

We have recently established a GAA repeat expansion mutation-based FRDA transgenic mouse model, which exhibits a representative FRDA-like phenotype, including similar DNA methylation and histone modification epigenetic changes. This model is a good system in which to test novel therapies, but the FRDA-like phenotype is currently rather mild, with no overt ataxia and no reduction in life span. Therefore, we aim to develop an improved model by increasing the number of mutational GAA repeat sequences and hence increasing disease severity. We plan to achieve this by performing genetic crosses of our FRDA model with (a) different inbred strains of mice, and (b) genetically modified mice that are deficient for the DNA methyltransferase 1 gene (*Dnmt1*). We will then carry out translational therapeutic research using FRDA mouse model primary fibroblast and neuronal cells, human FRDA primary fibroblasts, and the FRDA mouse model itself to test the effects of a number of potential frataxin-increasing compounds, including the class III histone deacetylase (SIRT1) inhibitor, splitomicin, the histone methylation reducing drug, mithramycin, the DNA methylation inhibitor, zebularine, and GAA-interacting compounds, pentamidine and DB221. All data from these preclinical studies will provide valuable information for future FRDA clinical studies

Lay summary

Friedreich's ataxia (FRDA) is a lethal inherited neurological disorder for which there is currently no effective therapy. The disease is caused by both parents passing on a DNA mutation, known as a "repeat expansion". This leads to reduced levels of an important protein, frataxin, within cells. Although potential treatments of some later symptoms are now being investigated, it may be more effective to treat the early stages of disease, producing an increase in frataxin protein. Within this application we firstly aim to obtain some indication of the effectiveness of potential FRDA therapies from studying cells that are cultured in the laboratory. However, ultimately this is an artificial situation that does not necessarily relate to how the therapy will work on a whole complex organism. Therefore, the use of a mouse model of FRDA to study potential therapies is considered essential. We have recently established a good FRDA mouse model that is useful for therapeutic studies. However, the symptoms of disease in this model are rather mild, so we would now like to develop an improved model that has more severe symptoms, thereby increasing the



effectiveness of preclinical therapeutic studies. In particular, we plan to test our FRDA mouse model with several different compounds that have good potential for frataxin-increasing FRDA therapy. The results that we obtain will be invaluable when considering which drugs may be suitable for future clinical trials.

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