



Overcoming the transcription defect in Friedreich ataxia with small molecules

Principal Researcher: Massimo Pandolfo, Université Libre de Bruxelles, Brussels, Belgium

This research, which was completed in early 2008, was jointly funded by Ataxia UK in collaboration with the US charities FARA/MDA, the Italian organisation GoFAR and the Irish charity FASI.

Here is a summary of the research, based on the researchers' final report submitted to Ataxia UK.

Background

Previous research (by Professor Festenstein in London) indicated that GAA repeat expansions seen in Friedreich's ataxia (FA) cause silencing of the gene because of a phenomenon known as the position variegation effect (PEV), which occurs when a gene is in the vicinity of a heterochromatin region- tightly packaged DNA which helps regulate the expression of genes. This in turn causes a deficiency of the frataxin protein produced by this gene.

Therefore, targeting the dense heterochromatin structure at the GAA repeat expansion seems to be a possibility for developing FA therapies. Histone deacetylase (HDAC) inhibitors could potentially prevent the silencing of the gene by making heterochromatin revert to a more open, 'readable' structure.

Present research and results

Through collaboration with Dr Joel Gottesfeld at the Scripps Institute, this project aimed to analyse the effects of a novel family of HDAC inhibitors in a mouse model of FA. The researchers previously created mice that had been genetically engineered to carry the GAA repeat expansion ('knock in' or KI mice), and showed that when they were engineered to carry two copies of the GAA repeat (KIKI mice), the mice had significantly lower levels of frataxin and the same changes in genetic and epigenetic features (i.e. dense heterochromatin remodelling) that were seen in cells from people with FA.

The mice were injected with a specific HDAC inhibitor called compound 106 over three days. The researchers found that increased histone acetylation was apparent in the brain for at least 24 hours after the last injection, and the effect had disappeared within a week. In further investigations they discovered that compound 106 increased the level of frataxin mRNA (which helps produce the protein frataxin) up to approximately the level seen in the natural 'wild-type' mice. When the compound was administered to wild-type mice it did not seem to have an effect on frataxin levels, suggesting that the effect was due to the removal of the gene silencing caused by the GAA repeat expansion in the mouse models of FA.

There was no apparent toxicity apparent in the mice treated with injections of compound 106.

A number of other drugs which increase the levels of frataxin in cells have been identified, including recombinant erythropoietin (rhu-EPO), 3-nitropropionic acid (3-NP) and haemin. It is not known how all of these work to increase frataxin but it is thought to be independent of the genetic GAA repeat expansion, and therefore it is proposed that these agents could be looked at to be used as a combination treatment with a heterochromatin targeting approach such as HDAC inhibitors.

The researchers have also started investigating the transcriptional control of the frataxin gene, including the identification of the involved factors and how it is altered in the disease. Possible new therapeutic targets may emerge from these studies. They are now applying to awarding bodies for funding to continue this work.

Benefits to people with ataxia arisen/likely to arise from this research:

These studies have represented important progress in the development of potential therapeutics for FA. We have proven that a class of HDACi is capable of increasing frataxin levels in a GAA expansion-based mouse model of frataxin deficiency. The correction of changes in gene expression profiles that we obtained with this treatment is a particularly important finding that indicates that cellular changes due to frataxin deficiency are reversible before pathology appears, suggesting that treatments that restore frataxin levels in FRDA individuals may completely rescue surviving cells. These findings are of course preliminary and need to be confirmed by further preclinical and hopefully clinical studies.

Publications arisen from this project

Rai M, Soragni E, Jenssen K, Burnett R, Herman D, Coppola G, Geschwing DH, Gottesfeld JM, Pandolfo M. HDAC Inhibitors Correct Frataxin Deficiency in a Friedreich Ataxia Mouse Model. PLoS ONE 2008; 3 (4): e1958.

Conferences/ meetings where this research has been presented:

Platform presentations by M. Rai at the American Academy of Neurology 2007 Annual Meeting, Boston, and at the Society for Neuroscience 2007 Meeting, San Diego.

For more support or information please contact: Ataxia UK, Winchester House, Kennington Park, Cranmer Road. London SW9 6EJ

Website: www.ataxia.org.uk.

Helpline: 0845 644 0606 **Tel:** +44 (0)20 7582 1444 **Fax:** +44 (0)20 7582 9444

Email: helpline@ataxia.org.uk.