

Friedreich's Ataxia Research Update

There is a large amount of research into Friedreich's ataxia taking place across the world and an overview of this is given below. In 2010, a group of European researchers (the European Friedreich's Ataxia Consortium for Translational Studies; EFACTS) successfully secured a large grant from the European Commission for translational research; for a report of this project please click [here](#).

EXPANDING OUR KNOWLEDGE

Since the discovery of the genetic defect that causes Friedreich's ataxia (FRDA or FA) in 1996, much research has been focused on how this manifests as a neurological disorder. The disorder results from an abnormal expansion of the FA gene (Campuzano V et al 1996). Normally, the gene may be expanded up to ~33 repeats (GAA trinucleotide repeats), but when the sequence is longer than 59 repeats it appears to alter the architecture of the DNA sequence by causing the usual double-helix structure to fold back on itself into a triplex formation ('sticky DNA') (Sakamoto et al 1999). This interferes with transcription of the gene, resulting in a deficiency of the protein encoded in that gene, in this case named frataxin (Bidichandani SI, et al 1998). Increasing length of the repeat expansion correlates with greater reduction in levels of frataxin and increased severity of the disorder (Campuzano et al 1997).

Research looking at equivalents of frataxin in other organisms has shown that a decrease in frataxin is associated with a reduction in energy production in the mitochondria, an accumulation of free iron, and an increase in susceptibility to oxidative stress from free radicals (Wong A et al 1999). We know that whatever its precise function is in the body, frataxin protein is essential for survival. Cossee et al demonstrated that when mouse models were generated by completely deleting the frataxin gene and therefore preventing any frataxin protein being produced, the mice died whilst in the embryonic stages (Cossee M et al 2000). A paper published in 2007 showed that removing frataxin from a *C.Elegans* (roundworm) model of FA reduces oxygen consumption and respiration in the worm and shortened lifespan (Zarse et al 2007).

In the last decade, researchers have delved further into the function of human frataxin, suggesting lots of possible roles for the protein, and increasing our

knowledge of the protein itself; for instance we now know that it is a 210-amino acid protein (Musco et al 2000), which is found in the mitochondria, the energy producing units or 'batteries' inside cells. Highest levels of this protein are found in the heart, liver, skeletal muscle, pancreas, brown fat (present in newborn babies and very rich in mitochondria) and in the nervous system predominately in the dorsal root ganglia (Campuzano et al, 1996), structures containing groups of cell bodies of the sensory nerves that relay information along the spinal cord to the brain.

Until recently, the main theories were that frataxin acts as a chaperone for iron, delivering it for the assembly of enzymes containing iron-sulphur clusters and for heme synthesis, while also having an excess iron detoxification function which helps to protect cells from oxidative stress (Stehling et al 2004; Gakh et al 2005).

However a recent study revealed a more involved role in iron metabolism. Work by Adinolfi and colleagues revealed that frataxin is an an integral part of the cluster-assembly machinery; it participates in the regulation of iron-sulphur cluster formation by inhibiting the formation of clusters in response to high iron levels.

The creation of animal models of FA helps scientists to learn about the effects of frataxin and is crucial for testing potential treatments. A number of animal models of FA exist, each having specific uses. Simple models such as yeast and the *C.Elegans* worm have provided much valuable information about how genes work and because of their relative simplicity and short life cycles enable scientists to study disease processes much more quickly than would be possible in humans. Now there are also more advanced mouse models. The first mouse models created have one specific organ completely without frataxin, for example the heart, producing only the cardiac symptoms associated with FA or in other models only the neurological problems (Puccio 2001). A more 'realistic' mouse model which produces mice with low levels of frataxin throughout the body and symptoms more similar to that seen in the human condition was produced by Dr Mark Pook and his team at Brunel University, with funding from Ataxia UK (Al-Mahdawi et al 2006). Although this model is a good system in which to test novel therapies, the FA-like phenotype is rather mild, with no overt ataxia and no reduction in life span. Therefore, the researchers are now developing an improved model with more severe symptoms in a further Ataxia UK -funded project; click [here](#) for details.

RESEARCH INTO TREATMENTS

ANTIOXIDANTS AND IRON CHELATORS

Oxidative stress is thought to be central to the disease mechanism in FA and thus ways to reduce this stress are being investigated. FA cells are more susceptible to oxidative damage due to several reasons:

- the abnormal use of iron leads to changes in metabolism and increased production of harmful free radicals (via the Fenton reaction), (Radisky et al 1999; Koenig and Mandel 1997)
- because cells which are deficient in frataxin appear to be less efficient at generating natural antioxidant defences (Chantrel-Groussard et al 2001)

Antioxidants are molecules which help 'mop up' free radicals and prevent other molecules undergoing damaging oxidative reactions. Antioxidants come in many different types (eg Glutathione, vitamin C, vitamin E, beta-carotene, Coenzyme Q10) and may be important in many diseases, as well as being used in many dietary supplements and anti-ageing beauty treatments.

Preliminary results from a trial of vitamin E and Coenzyme Q10 (CoQ10) showed some stabilisation of the progression of ataxic symptoms when the therapy was taken over 47 months (Hart et al 2005). In this trial, funded by Ataxia UK, 10 adults received high doses of vitamin E and CoQ10 (2,100 IU/day, 400mg/day respectively). At the end of the study period testing showed that energy production in heart and skeletal muscle had improved and in 8 out of the 10 patients their clinical symptoms had remained stable or even improved. The researchers went on to conduct a larger trial with 50 patients and results of this Ataxia UK-funded study can be found [here](#) (Cooper et al 2008).

Idebenone is a variant of CoQ10 and is a powerful synthetic antioxidant. The first major studies on idebenone for FA were carried out by Pierre Rustin's research team (Rustin P et al 1999) and showed that when given to patients with FA and hypertrophic cardiomyopathy, idebenone could decrease the abnormalities in the heart muscle. In 2004 a group of researchers demonstrated the effects of administering idebenone to mice which had been engineered to be deficient in frataxin in their heart and muscle cells. These mouse models displayed an inactivation of mitochondrial iron-sulphur cluster proteins and an accumulation of iron in the mitochondria, as seen in human patients, but developed a much more severe disease than humans with FA with a rapidly progressing, lethal cardiomyopathy. Administration of idebenone delayed the progression of the disorder in the mice and delayed death by 1 week, suggesting that idebenone can be cardioprotective even when there is a complete lack of frataxin, but cannot overcome the primary deficiency of iron-sulphur proteins (Seznec et al 2004).

Small, open-label trials in various countries have since tested idebenone in patients with no serious side effects detected (Artuch et al 2002; Buyse et al 2003; Di Prospero et al 2007; Hausse et al 2002; Ribai et al 2007; Rustin et al 2002). Other small scale studies looking at cardiomyopathy in FA showed modest benefits from idebenone therapy (Hart et al 2005; Mariotti et al 2003; Rustin et al 2002; Artuch et al 2002; Buyse et al 2003; Hausse AO et al 2002).

A clinical trial of idebenone (trade name Catena) in the US was recently completed. Although treatment with idebenone improved FA symptoms, unfortunately no statistically significant difference was found between treatment and placebo groups. This could be due to unexpected improvements in the placebo group which occurred during the first three months of the six-month study. Despite these results, however, idebenone remains a promising treatment for the cardiac and neurological symptoms of FA; when the results of this study are pooled with those from a previous US trial, a significant improvement in ataxia is seen, compared to placebo. The US trial has been extended on an open-label basis (where each participant is openly given idebenone) for a further twelve months.

There is also currently a large, multicentre, phase III trial running in Europe that is being sponsored by the pharmaceutical company, Santhera. See their latest press release [here](#). Idebenone is being tested at doses ranging from 450-2250mg/day and its safety, tolerability and efficacy at treating the neurological symptoms in FA are being investigated. This study is also being extended on an open label basis. It is hoped that taken together, the results from the US and European studies will provide satisfactory results for the registration of idebenone in Europe and Switzerland. In the meantime, Santhera, the pharmaceutical company who make Catena, will make the drug available on a named patient basis which will allow healthcare professionals to prescribe it to individual patients. For information on the worldwide trials see <http://www.clinicaltrials.gov>.

Another antioxidant that has been put forward for testing in FA is mitoquinone (MitoQ), a compound which is selectively targeted to concentrate antioxidant action in the mitochondria. New Zealand's Antipodean pharmaceutical company is developing the compound to take it to phase II trials in patients with FA, whilst currently investigating the treatment in Parkinson's disease. Meanwhile, a coenzyme Q10 analogue called EPI-A000, which improves mitochondrial energy production and reduces oxidative stress in yeast cells, has received orphan drug status from the FDA and been accepted onto the National Institute of Health's 'fast-track' program to advance into early clinical trials. Preliminary results from a phase IIa clinical trial of EPI-A0001 in people with FA were released in June 2011. They suggest significant improvements in neurological function at both low and high doses of EPI-A0001, although further studies are required to prove the safety and efficacy of the treatment. For more information see the [press release](#) from the pharmaceutical company, Edison Pharmaceuticals, which is developing the drug.

EPI-743 is another small molecule with anti-oxidant properties that is also being developed for mitochondrial conditions by [Edison Pharmaceuticals](#). EPI-743 has recently been granted orphan drug status by the US Food and Drug Administration (FDA) (for more information see the [press release](#)). The FDA has also approved the drug for an Expanded Access program which means it will be provided to seriously ill people diagnosed with inherited respiratory chain

diseases of the mitochondria who meet specific clinical criteria. Preliminary data from a trial looking at the safety and efficacy of the compound in people with mitochondrial conditions looks promising, but needs to be confirmed in randomised, controlled trials. (See the [press release](#) for more details about the preliminary results.) A phase II trial in the US looking at the safety and efficacy of EPI-743 in patients with severe mitochondrial respiratory chain conditions is now recruiting and will include people with Friedreich's ataxia, see [here](#).

The antioxidant 5-carboxy-1,1,3,3-tetramethylisindolin-2-yloxy (CTMIO) has previously been shown to have positive effects in mice models of ataxia telangiectasia, an inherited condition that shares some similar symptoms with FA (Gueven N et al 2006). However, when the compound was tested in animal models of FA no improvements were seen; click [here](#) for details.

A new clinical trial looking at the effectiveness of EGb 761, a Ginkgo biloba extract, in FA is starting at the Hospital Necker Enfants Malades in Paris, France. EGb 761 is a standardised extract from the leaves of the Ginkgo biloba tree that contains well-defined quantities of its active components. In the body, EGb 761 increases blood flow through blood vessels, modulates neurotransmitters and protects the brain from nerve cell degeneration. EGb 761 also has antioxidant and free radical scavenging properties, making it of possible therapeutic benefit in the treatment of FA. The study is a Phase II clinical trial that will compare the efficacy of EGb 761 (120 mg) against placebo in people with FA. Volunteers are currently being recruiting for the study and further details of the trial can be found [here](#).

Because of the abnormal accumulation of iron seen in FA, another potential approach to treatment is iron-chelating therapy- using compounds which bind to iron and remove it from the mitochondria. The main challenge in this approach is to find compounds which prevent iron building up to excessive levels and increasing free radical formation and oxidative stress, whilst not removing iron from other parts of the body where it has an essential role (eg the blood). The iron-chelating agent Deferiprone has received some attention lately, since in 2007 researchers in Paris published results of a six-month study conducted in nine adolescent patients. Their results showed that treatment with deferiprone reduced iron accumulation seen with MRI scanning in certain parts of their brain, and in the youngest patients improved their neurological symptoms (Boddaert N 2007).

Recently a study was completed looking at a combination therapy of low oral doses of deferiprone (20 mg/kg/day) and idebenone (20 mg/kg/day) as a treatment for FA. The open-label single-arm study (meaning all participants were knowingly taking the combined therapy) was done in 20 people with FA aged 8 – 25 over a period of 11 months. The results indicate that overall neurological function stabilized (measured by ICARS; posture and gait scores worsened but fine motor function improved). Additionally, abnormal heart muscle enlargement

and iron levels in the brain were both significantly reduced. Side effects were mild, apart from the risk of neutropenia (an abnormal decrease in levels of a particular type of white blood cell), which was experienced by two participants and ceased after discontinuation of the deferiprone (Velasco-Sanchez et al, 2010).

There are some concerns about iron-chelation therapies, namely that iron removing agents could have toxic effects in people with FA, who have iron accumulation in specific places instead of generalised iron overload, and that they may cause increased abnormalities in the iron-sulphur cluster proteins which are already deficient in FA. A much larger trial is now being instigated at research centres across Europe, including the UK, and the USA to test the safety and tolerability of deferiprone for people with FA. For more information see the trial information page on www.clinicaltrials.gov .

In April 2008 a study was published looking at a new iron-chelating agent called PCTH (2-pyridylcarboxaldehyde 2-thiophenecarboxyl hydrazone) (Lim et al 2008). In experiments on cells from patients with FA, researchers found that PCTH more rapidly penetrated cells inducing faster iron removal, and was more effective at protecting cells from free radical toxicity than other iron chelators and more effective even than existing antioxidants. The researchers hypothesised that the rate at which the iron-chelating agent penetrates the cell is the important factor in their effectiveness at protecting cells; therefore PCTH is posed as a potential treatment for iron-overloading conditions such as FA.

INCREASING FRATAXIN

Since we now know that FA causes a deficiency of frataxin, an essential protein for life, some researchers are looking at ways to directly stimulate the production of frataxin in FA cells.

On these lines, encouraging research published by Pianese et al in 2004 showed that people with FA had residual frataxin levels of between 13-30%, whilst asymptomatic carriers of the gene (people with one normal gene and one affected gene who have no symptoms, as opposed to people with the condition FA who have two affected genes) also had reduced levels at around 40% of normal. This suggests that any therapy aimed at increasing the levels of frataxin may only need to increase levels to 40% to prevent symptoms.

In Austria, trials have been carried out using rhuEPO (recombinant human erythropoietin), a treatment known for its use in stimulating blood cell production in patients undergoing dialysis for kidney failure (Boesch S et al 2007; Boesch S et al 2008). Its potential benefit for Friedreich's ataxia was recognised when patients receiving it during dialysis experienced unexpected neuroprotective and

cardioprotective effects, although it is still not properly understood how rhuEPO exerts this effect.

In laboratory tests, treatment of different cell types with rhuEPO (including neurones and cells taken from people with FA) showed increases in frataxin protein (Sturm et al 2005). Further investigation in a small pilot study (eight participants), showed that rhuEPO could increase frataxin protein in people with FA. The treatment also appeared to reduce DNA damage and oxidative stress. In this study the rhuEPO was given by subcutaneous injections three times a week over a six month period (Boesch S et al 2008).

Another trial is now underway in Naples, Italy, to further study the efficacy of rhu-EPO on levels of frataxin and assess its safety in people with FA; see www.clinicaltrials.gov for details. Preliminary results from this show that rhuEPO increased frataxin protein in all participants, although significant increases in frataxin protein were not seen until approximately three months after a single injection of the drug.

However, EPO treatment can also have other effects in the body. It can increase red blood cell production and lower iron levels in the blood. Further investigation of EPO, in larger, placebo-controlled studies, is therefore required before it can be confidently recommended as a treatment for FA. Interestingly, a clinical trial is starting soon in Italy, which is looking at a new, chemically modified form of EPO called Lu AA24493 which does not have these side effects. Lu AA24493 is a carbamylated form of EPO, which is being developed by the pharmaceutical company Lundbeck for the treatment of stroke. It has neuroprotective actions in a number of animal models of neural damage and has been shown to increase frataxin levels in cells from people with FA. However, it does not have the side effects on red blood cell production that EPO has. The clinical trial will evaluate safety, tolerability and efficacy of Lu AA24493 in people with FA; for more details see www.clinicaltrials.gov.uk.

A biopharmaceutical company in California, US, STATegics, Inc, is also developing small molecules similar to erythropoietin for the treatment of FA. This work is being supported by the US charity Friedreich's Ataxia Research Alliance (FARA).

An alternative way to increase frataxin levels would be to deliver a version of the deficient protein straight to affected cells. Whilst this technique is still in the early stages of research, researchers in the USA are hoping to synthesise frataxin and target it to the mitochondria in cell models of FA.

OTHER DRUGS

A two year clinical trial looking at pioglitazone in FA is underway in France (Husson I, see details on www.orpha.net or www.clinicaltrials.gov.uk). Pioglitazone is a drug used as a treatment for diabetes, and is being tested for other neurological disorders (such as spinal injuries and MS) as well as for FA. A case study of an MS patient receiving pioglitazone had promising results as they noticed an improvement in coordination and strength, and improved memory, although there were no changes on the MRI changes which are seen in MS suggesting it was not correcting the pathology. For FA, the potential beneficial actions are thought to be a combination of inducing proteins involved in energy production, conferring neuroprotection, an antioxidant action and increasing the stability of iron-sulphur clusters. The trial, which is taking place in Paris, is open to people from other countries.

Varenicline is another drug that recently entered clinical trials. It is normally prescribed as a smoking cessation drug under the trade name Champix, but it also showed some benefits in people with ataxia in some case studies; when a clinician in the US gave the drug to people with different types of ataxia, including two people with FA, she noticed improvements in their ataxic symptoms. A small trial looking at varenicline in people with FA started in 2009. However, the trial was terminated in April 2010 at the advice of the Data Safety Monitoring Board (DSMB) which raised concerns about the safety and intolerability of varenicline and insufficient evidence of its efficacy in people with FA; worsening of gait and imbalance was seen in some study participants. Click [here](#) to see the press release.

GENETIC APPROACHES

Since the gene causing FA has been found, it is apparent that an ideal therapy for the condition would be to replace or remove the underlying genetic defect. If the abnormal GAA repeat expansion could be removed or shortened by a sort of genetic surgery, or a normal copy of the gene inserted, it may allow the gene may be read as normal and frataxin production to carry on uninterrupted. In this way, it is thought to eventually be possible to 'infect' cells with bacteria or viruses containing DNA or RNA coding for frataxin.

Scientists at the Children's Medical Research Institute in Sydney, Australia showed that it was possible to create viruses containing human frataxin DNA which would increase frataxin expression in cells from FA patients and make cells more resistant to oxidative stress (Fleming J et al 2005). In 2007, researchers published a study showing that mouse models that had been modified to be deficient in frataxin, appeared to recover from their symptoms after injection with Herpes Simplex virus type 1 (HSV-1) amplicon vectors

expressing human frataxin complementary DNA (Lim F et al 2007). In more simple terms this means that modified viruses (such as Herpes Simplex) could be used as a carrier to infect cells with specific pieces of DNA (eg the frataxin gene) and cause them to express the protein encoded in that DNA (eg frataxin). In 2007 Ataxia UK awarded funding to a group of the researchers working in this area to further investigate the effects of using harmless versions of Herpes Simplex viruses to deliver a correct version of the frataxin gene to mice with FA. More information on this research can be found [here](#).

Whereas some researchers are investigating ways of "adding in" correct DNA to the cells, others are trying to find ways of eliminating the defective protein from cells using a relatively new mechanism called RNA interference or RNAi. This method involves using a piece/sequence of RNA (an RNAi construct) that specifically recognises the defective RNA and targets it for destruction. In this way, the defective RNA can be eliminated from the cell before it is translated into the defective protein. Researchers at the University of Pennsylvania, Philadelphia, USA have received funding to test a large number of different RNAi sequences in FA cells (several hundred thousand). By screening and optimizing these RNAis, the researchers hope to establish RNAi sequences that are potential treatments for FA. Their aim is to bring them to clinical development with the help of one or more companies who are already involved in clinical trials of RNAi therapeutics for other diseases.

Another option, which has been investigated for Duchenne's muscular dystrophy, might be to use short pieces of DNA or RNA as a 'patch' to skip over the genetic defect (Arechavala-Gomez V 2007).

Another avenue of research which is being looked at is using drugs to directly target the structure surrounding the gene. In FA the deficiency of the protein frataxin occurs because the gene responsible for producing the protein appears to be 'switched off'. Research from Ataxia UK-funded researcher, Professor Richard Festenstein (see [here](#) and [here](#) for past related projects), has demonstrated that the abnormal GAA repeat expansion in the FA gene leads to the DNA becoming unusually packaged by dense heterochromatin structures, preventing the DNA from being read (Saveliev, A 2003). Researchers have been investigating whether substances that alter heterochromatin structure can reverse the silencing of the gene and a group of compounds called histone deacetylase inhibitors (HDAC inhibitors) looks promising.

In 2006 Professor Joel Gottesfeld's team at the Scripps Institute in California published the results of a lab-based study showing that HDAC inhibitors could reverse silencing of the frataxin gene in patient cells (Herman et al 2006). In their experiments, particular compounds from the HDAC inhibitor family were able to restore frataxin levels to normal in cells taken from FA carriers (people who carry a copy of the faulty gene but do not have FA). Additionally, in cells from people

with FA, frataxin levels were increased to up to 50% of normal, which may be sufficient to prevent symptoms.

Since then, new HDAC inhibitors have been developed and tested in animal models of Friedreich's ataxia and favourable results have been produced with a HDAC inhibitor called compound 106. When this compound was given to mice with FA, frataxin levels were restored to normal, with no apparent toxic effects (Rai et al 2008). This suggests that these compounds could correct the pathological process underlying FA.

A pharmaceutical company called Repligen has become involved with these newly developed HDAC inhibitor compounds, forming an exclusive commercial licensing agreement with the Scripps Institute. Repligen's input is important for performing the necessary animal trials and safety tests which are the first stage in bringing a new drug to human trials. Repligen recently announced that the first human trial of its lead HDAC inhibitor compound will begin in Italy soon. Click [here](#) for more news about this Phase I study.

Meanwhile, researchers are continuing to investigate other HDAC inhibitor compounds to find the most effective treatments. In an Ataxia UK-funded project, Professor Festenstein is investigating a HDAC inhibitor that is capable of increasing frataxin in cells taken from people with FA. The compound has been previously administered to humans without significant ill effects and in this project he will evaluate the ability of the compound to increase frataxin levels when given to people with FA. The safety of the compound will also be tested (for more information see [here](#)).

Researchers in Italy have recently begun tests to assess the efficacy of HDAC inhibitors and rhuEPO in combination and individually, in cell models of FA. It is thought that the up-regulation of frataxin protein observed with these two drugs may be complementary because they act at different stages in the production of the protein (Cocozza 2008).

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