

Highlights of 4th International Friedreich's ataxia conference Strasbourg, France 5-7 May 2011

Lay report written by Ataxia UK

Introduction

Over 200 researchers convened in Strasbourg in May to attend a large research conference solely dedicated to Friedreich's ataxia (FA). This was organised by the US ataxia charity Friedreich's ataxia research alliance with researchers in Strasbourg and sponsored by many organisations including Ataxia UK. This conference was held in conjunction with the annual meeting of the European FA Consortium for Translational Studies and euro-ATAXIA's annual meeting and conference highlighting the amazing collaborations amongst all the organisations involved in FA research.

The three days were packed full of presentations, with 58 talks and 53 posters. This report provides a summary of some of the research presented. Scientific summaries of the research are being prepared for publication. More information can also be found on the FARA website (www.curefa.org).

Research areas

There was much emphasis on the **development of new therapeutic targets** for FA as a result of basic research studies. This is an overarching aim throughout many of the talks.

Regulation of the frataxin gene and its silencing in FA

Since Professor Festenstein's initial discoveries on the way the FA gene is switched off and the potential for use of histone deacetylase inhibitors (HDACi) as a means of switching the gene back on, there has been much progress in this area of research. Professor Festenstein's team updated us on the role of an HDACi in increasing frataxin levels which has now moved to a human trial stage. He also spoke about the role of another mechanism that could potentially be targeted for therapy. This is the novel use of a drug which increases the levels of frataxin by preventing the destruction of the enzyme, RNA polymerase II, which is essential for switching the gene on.

Another important discovery regarding gene regulation is that the GAA repeat expansion in the frataxin gene changes with time and researchers are looking at ways to prevent this increase in GAA repeat size. Mismatch repair genes (such as one called MSH2) have been studied as a potential target. For example Dr Gottesfeld has been studying small molecule polyamides as a potential therapy and these result in a decrease in GAA repeat expansions in Friedreich's ataxia cells and this could possibly be via displacement of MSH2 from the frataxin gene.

The US pharmaceutical company Repligen provided update on their work on HDACi. They are starting a phase I human trial in Turin (Italy) to test for safety of their lead compound. Although mainly testing for safety, as this trial will actually be done on people with FA, they will also be able to test whether the drug is effective in increasing levels of frataxin. They are also working on new second and third generation HDACi with better properties in case the lead compound fails. Ataxia UK and other charities have partly supported this work at the Scripps Institute.

Models of FA

The conference highlighted how Dr Pook's mouse models, funded by Ataxia UK, have been used extensively by many researchers. Dr Pook has currently a grant jointly funded by Ataxia UK and GoFAR to develop models with increased GAA repeats and showing more progressed stages of FA. As soon as they are developed they are immediately made to good use by many researchers due to their extensive collaborations with one another. Dr Puccio's team has also created more mouse models (see euro-ATAXIA conference report).

A large section focused on the development of induced pluripotent stem (IPS) cells as models of disease. Three groups have worked on their development (in the US, France and Australia) and they have been distributed widely to many researchers worldwide. Now they are all working on the protocols to differentiate these cells into cells of interest such as nerve cells and heart cells. There seems to be consistency between the labs in the results obtained. These models are thought to be very useful for screening and as models of disease.

Interesting talks were presented from two researchers in Australia on the differentiation into heart cells (cardiomyocytes). Researchers in Brussels have succeeded in making a type of cell found in the cerebellum (Purkinje cells).

Stem cells

The current status of stem cell research was described by a world expert from Australia. He gave a keynote lecture describing the challenges faced in developing stem cells for the clinic; obtaining high numbers of pure cells, optimising delivery methods and integration into the host tissue. He was cautionary about the claims made by clinics offering stem cell therapy, saying their procedures are often costly, use a poorly defined product and are not based on positive clinical trial data. He recommended the 'Closer Look at Stem Cell Treatments' website for more information (www.closerlookatstemcells.org).

There were also two posters presenting results of FA stem cell research; one testing the effects of bone marrow stem cells in FA cell lines and one using stem

cells derived from adipose (ie: fat) tissue in mouse models of FA. The former is being funded by Ataxia UK and is taking place in Bristol and the latter is from a team in Spain.

Screening for drugs

A number of researchers spoke about screening studies to find drugs that increase frataxin levels. This is done using different 'libraries' of drugs that act on different pathways within the cell. For example Ataxia UK-funded researcher Dr Lufino from Oxford described his work in developing a cell model of FA and using this in a screening study with a library of drugs that are structurally similar to HDAC inhibitors. Two drugs from this library were found to increase frataxin levels in a specific manner and these will be therefore studied further.

A researcher from Australia presented results on a screening study that he did in which he discovered that resveratrol (an antioxidant found in grapes) increased frataxin levels in cells taken from patients. This has now led to the development of a phase I trial testing the effect of resveratrol in people with FA in Australia. Researchers in the US also did a screening study with a different library and identified some potential compounds of interest for FA.

Diagnosis

Researchers in the US reported the development of a new test to accurately measure frataxin levels in whole blood or dried blood spots that would be relevant for population screening. They mentioned an ongoing newborn screening pilot study in the US that is funded by the NIH. The aim of the study is to determine a suitable method of screening newborn babies for FA so that future therapeutic developments can be implemented from the earliest point possible and obtain maximum effect.

New drugs

A research team was working on developing synthetic CoQ10 analogues that work better than CoQ10 and idebenone at reducing oxidative stress. They had succeeded in developing some.

For more support or information please contact: Ataxia UK, Lincoln House, Kennington Park, 1 – 3 Brixton Road. London SW9 6DE

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.