

## **International Research Conference May 2007**

A Research Update by Laura Stewart

**GeNeMove (The German Network for hereditary Movement Disorders) held their international conference this year in Bonn, Germany. The conference consisted of two days of talks and was very well attended, with researchers from all over the world making up the audience. Being a German event, there was also a plentiful supply of Kuchen (German cakes) to keep us going through the long days. Here I will summarise the talks given on the first day, which was dedicated solely to hereditary ataxias.**

### **Spinocerebellar ataxias**

The first day of talks started bright and early at 8.30 am with a talk from Harry Orr about his research on SCA1. Dr Orr and his group have been studying biochemical signalling pathways and think that glycogen synthase kinase (GSK3) may be important in spinocerebellar ataxia. This would suggest that drugs which inhibit the GSK3 pathway could potentially be therapeutic for SCA1. There are already existing drugs which affect GSK3, (for example lithium), so if these were found to be beneficial for ataxia, therapies could very quickly be available for patients.

Dr Paulson then spoke about SCA3 (Machado-Joseph disease). SCA3 is part of a group of diseases known as polyglutamine disorders, which result from an abnormal expansion of certain tracts in the DNA. Other examples of these disorders include SCA7 and Huntington's disease.

The genetic defect in polyglutamine disorders usually causes accumulation of a toxic protein, and another speaker, Dr Rubinsztein talked about ways to decrease levels of these proteins utilising the body's own protein breakdown mechanisms. Researchers testing this idea in mice have found that their performance in neurological tests improves. However these drugs are associated with severe side effects, so research is now trying to identify safer compounds.

Thomas Klockgether discussed the extensive data becoming available thanks to the large EUROSCA project, which started in 2005. It now has 17 centres in 10 countries and more than 2000 patients on its database. Data from this project has revealed that the average age of onset for all SCAs is in the 30s and highlighted that the SCAs are not solely cerebellar diseases, as patients in this study have on average two extracerebellar symptoms, such as sphincter disturbance or swallowing difficulties.

Dr CM Gomez from San Diego pulled together the latest knowledge on ion channels relating to the ataxias. Ion channels help cells communicate with each other through the exchange of electro-chemical signals. Disorders thought to be caused by defects in ion channels are known as channelopathies and occur in many different body systems (eg the kidney, eye, brain or pancreas). In SCA6 there is an expansion of a

polyglutamine tract in the gene providing the code for a component of neuronal calcium channels. This means it is on the border between polyglutamine disorders (like SCA3) and channelopathies, suggesting two avenues to explore for potential treatments.

### **Friedreich's ataxia**

Dr Helene Puccio spoke about the work which has been done in her labs in Paris and in the UK by Dr Mark Pook (who was funded by Ataxia UK) creating mice models. The researchers have been learning more about the frataxin protein by creating mice that produce absolutely no frataxin (compared to people with Friedreich's ataxia who have decreased levels of frataxin but some residual protein remaining). These mice develop severe heart problems and ataxia. It is thought that lack of frataxin leads to iron-sulphur clusters and iron accumulation which makes the tissues more susceptible to oxidative stress. Dr Pook has now created humanised models of Friedreich's ataxia, where the mice have milder characteristics of the disorder. These mice have already been employed in research around the world.

The effects of decreased frataxin on other parts of the body were discussed further by Dr Lill, from Marburg, Germany. According to research, mice that do not produce frataxin develop a loss of islet cells, the cells in the pancreas that produce insulin, leading to diabetes. In addition, animals that were fed on a high-fat diet were more likely to become obese if they had the gene for frataxin knocked out compared to controls with normal frataxin levels.

### **Treatments**

Lately there has been much excitement around a group of compounds called histone deacetylase inhibitors. Joel Gottesfeld from the Scripps Institute in California has been looking at using these compounds in Friedreich's ataxia and he was at the conference to give us an update on his work. This work is based on the finding that genes showing a GAA TCC repeat mutation (as seen in Friedreich's ataxia) are associated with abnormalities in the structure of the proteins forming the backbone of DNA (called histones) that appear to silence or switch off the production of frataxin. Therefore compounds which modify the structure of histone could allow the gene to be switched back on. The histone deacetylase (HDAC) inhibitors are one such group of compounds and the latest research by Gottesfeld's team has found some specific molecules in this group which do appear to increase frataxin in cells from people with Friedreich's ataxia.

Gottesfeld also mentioned the work of Professor Pandolfo in Brussels, to whom Ataxia UK is currently providing funding for research in this area. According to Gottesfeld, Pandolfo's team has now shown that in mice which have been engineered to carry the Friedreich's ataxia gene, certain HDAC inhibitors can increase frataxin levels up to the level found in normal mice.



Another current area of interest in Friedreich's ataxia is antioxidant therapy, in particular the compound idebenone. Dr Kenneth Fischbeck told us about a recently completed trial in the US which tested high-dose idebenone in 48 young patients with Friedreich's ataxia. The trial found that there was a trend towards a decrease in ataxic symptoms whilst taking idebenone. Fischbeck mentioned the idebenone trial in Europe which is at various stages in different countries. In the UK, the trial has already begun in Newcastle. I was able to speak to a representative from Santhera, the pharmaceutical company involved in the trial and discuss Ataxia UK's involvement in recruiting participants.

*The conference showed that there is a lot of enthusiasm and optimism in ataxia research. It was wonderful to see people from all over the world working together towards finding causes and cures for the ataxias, and this gave me the opportunity to meet with leading researchers on behalf of Ataxia UK and catch up with other organisations working towards the same goals.*

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We have a number of other publications on the ataxias available free of charge. In addition we publish a quarterly magazine called *The Ataxian* containing articles on research, living with ataxia and other relevant information. Our website also contains news of research projects.

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