Dr Manuela D'Alessandro
Unravelling the different pathways involved in myotubular and centronuclear myopathy

Myotubular and centronuclear myopathies (MTM/CNM) are rare diseases which cause severe muscle weakness and particularly target the muscles which are essential to maintain life i.e. to breathe and eat [http://www.myotubulartrust.org]. The most severe form of the disease is X-linked Myotubular Myopathy (XLMTM) where affected baby boys struggle to survive from birth.

In XLMTM the protein myotubularin is missing. When scientists look at muscle cells from patients they see two abnormalities. Firstly, the cells are smaller, suggesting myotubularin is important for controlling muscle cell growth and strength. Secondly, the nuclei have moved from their normal position at the edge of the cells into the centre. What causes this centralization of nuclei (as it is known) or its relationship to the absence of myotubularin is not understood. It is highly probable that deciphering this link will shed valuable light on the condition, and indicate possible drug therapies to treat the symptoms.

2010 Grant from the Myotubular Trust

The Myotubular Trust has awarded a three year post-doctoral fellowship to Dr Manuela D'Alessandro at The Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC), in Strasbourg, France, to address this important question. Dr D'Alessandro will be based in the lab of Dr Jocelyn Laporte, a pioneer in the MTM/CNM field. The award of £120,000 will cover the costs of 3 years of research to further understand the molecular relationships between the MTM/CNM genes and the issue of nuclei positioning.

Proposed Research

Dr D'Alessandro will be conducting her research in the following three areas:

i) To identify the genetic links between the genes that cause CNM/MTM and the position of the nucleus

We know that mutations in myotubularin (MTM1), amphiphysin 2 (BIN1) and dynamin 2 (DNM2) all cause various forms of MTM/CNM and so we can predict that all of these proteins are on the same signaling pathway inside muscle cells. Dr D'Alessandro's first aim will therefore be to further characterize the working relationship between all three of these genes by describing more precisely the molecular pathway(s) in which these genes function. She will also be investigating how nuclei move around cells, so called nuclear positioning and migration.

ii) Characterization of other proteins known to be involved in nuclear positioning

The physical interaction between the proteins known to be involved in CNM/MTM and other proteins also involved in positioning the nucleus is likely to be very helpful in understanding the condition. Dr D'Alessandro will use cell biology and biochemistry approaches to study this interaction

iii) Identification of novel (new) proteins on the MTM/CNM pathway.

Using a sophisticated technique known as a genetic screen, she will also try and identify new genes on the MTM/CNM pathway.

Complimentary Research Projects

In order to develop a possible treatment strategy for myotubular and centronuclear myopathy, researchers are working on developing the ability to replace the missing gene product through gene therapy.

However, realistically this may present a huge challenge for many reasons, not least that the immune system reacts against the protein that the replacement gene produces. Therefore, as well as pursuing gene therapy approaches, it seems appropriate to find out as much as possible about the function of these genes and their molecular partners in the cell as this might reveal alternative therapeutic possibilities to gene therapy.

To this end the Trust is funding three complimentary areas of research:

- Gene replacement therapy studies in the XLMTM mouse with Dr Anna Buj Bello (INSERM, France);
- Detailed structural studies of muscle from Labrador dogs and human patients affected by these conditions, to learn more about the physical changes that occur in the muscles (Dr Richard Piercy, Royal Veterinary College);
- This year's grant to understand more precisely the molecular pathway(s) in which the 3 genes (MTM1, BIN1 and DNM 2) function.

Collectively, these three grants use all the available animal models for the disease and address a number of the scientific questions most likely to lead to a therapeutic strategy to treat myotubular and centronuclear myopathy