Dr Anna Buj-Bello
Gene therapy approaches for X-linked Myotubular Myopathy

X-linked Myotubular Myopathy (XLMTM) is the most severe and most common form of the group of muscle diseases known as centronuclear myopathies (CNM). Babies born with XLMTM have such severe muscle weakness that they appear floppy and have difficulties in breathing. This disease arises from mutations in a gene termed MTM1, which makes a protein called myotubularin. When scientists look at the muscle cells from patients they see two major defects. Firstly, the cells are smaller, suggesting myotubularin is important for muscle cell growth. Secondly, the nuclei instead of being at their normal position at the edge of the cells, they are located in the centre. In humans, it has been suggested that the disease results from a defect in muscle maturation, however, this is not clear. It is unknown what role myotubularin plays in muscle cell growth that occurs during gestation and childhood or for keeping muscle in working order throughout adult life.

Mouse models for XLMTM

One way we can learn about how this disease arises is by making an animal model. Dr Anna Buj-Bello, INSERM, Strasbourg, France, has done just that. In fact, her research group have made two animal models, both in mice. The first mouse model has the MTM1 gene removed from every single cell in its body, whereas the second mouse has the MTM1 gene removed from just the muscle; it is still present in all other body tissues. By comparing these two models side-by-side, it allows one to look at the function of myotubularin in muscle alone and to examine if it has other functions outside of muscle. This is important since patients also experience non-muscle clinical symptoms, such as liver problems. These mouse models also allow studies to try and reverse the symptoms of the disease. These are known as 'rescue' experiments. To this end, Dr Buj-Bello has just been awarded £102,290 to fund a two year project to try and find out more about how myotubularin works and to test out various 'rescue' approaches.

Proposed research

The first set of experiments involve trying to 'rescue' the mice with XLMTM using the following two approaches:

i) Gene therapy: MTM1 replacement

Gene therapy is the introduction of a normal gene alongside its faulty counterpart in diseased cells, so as to alleviate the symptoms of disease. The principle of the technique can be likened to building a by-pass to reduce traffic congestion from a town centre. This is a relatively new form of therapy, requiring complex medical and technological procedures, which still need to be perfected, but initial trials are encouraging. In this instance, Dr Buj-Bello will reintroduce the normal MTM1 gene into her mice models for MTM1. There are many ways this can be done, but none are easy. The strategy this research group has chosen to use is to take a virus, such as those causing 'flu or the common cold. They remove all the bad genes which cause the infection and replace these genes with the normal MTM1 gene. This genetically modified virus, as it is now called, is then directly injected into the mouse models so that the normal MTM1 gene gets into each cell where it is needed. She will treat mice that have already developed the symptoms of XLMTM as well as those which are still asymptomatic. Therefore this approach will not only tell her whether the treatment can reverse the disease, but also whether it would stop the development of symptoms in the first place. Subsequent to injection, both sets of mice will be monitored over time for muscle strength and general health.

ii) Gene therapy: Growth factor treatment

Growth factors are molecules which make our cells increase both in number and in size, in the same way that farmers put fertilisers on their crops to increase quality and yield. Patients with XLMTM have muscle cells which are smaller than normal and this makes a large contribution to the muscle weakness they experience. To try and revert this, Dr Buj-Bello will treat her mice suffering with myotubular myopathy with a growth factor called insulin-like growth factor-1 or IGF-1 for short, which is already known to increase muscle size under other circumstances.

The second type of experiment involves so called, 'knocking-out' the MTM1 gene from healthy adult mice. So these mice have myotubularin from birth and whilst they are growing-up and then it is removed in adult hood. This really is similar to a boxer knocking out his healthy opponent so that he can no longer fight! These mice will then be monitored for the development of changes in muscle cell pathology as they age. This will tell us whether myotubularin is also important for muscle function in adults as well as in growing foetuses/children.

Overall Dr Buj-Bello's research is using different approaches to try and ameliorate the muscle problems associated with XLMTM in mice. Her findings are likely to suggest therapeutic approaches suitable to treat patients with these conditions.