Lay Summary Myotubular Trust Grant to Dr Jocelyn Laporte, IGBMC, France

Reducing DNM2 as a novel therapeutic target for centronuclear myopathy

Centronuclear and myotubular myopathies (CNM) are genetic diseases that can be caused by defects in several genes. Most cases are due to alterations (mutations) of either myotubularin (**MTM1**) or dynamin 2 (**DNM2**). The genetic link between these 2 genes was previously not understood. Also, while it is known that *a lack* of MTM1 leads to myotubular myopathy, the impact of mutations on the function of DNM2 was unclear.

Unexpectedly, we found that *too much* DNM2 leads to centronuclear myopathy in mice, suggesting that *increased action* of DNM2 is a cause of centronuclear myopathy. We hypothesize that reducing DNM2 may improve the symptoms of centronuclear/myotubular myopathy. Through a collaborative effort with researchers from Institute of Myology in Paris and Hautepierre hospital in Strasbourg, this rationale was validated** in diseased animals lacking MTM1 as we were able to **rescue the signs of centronuclear/myotubular myopathy by reducing DNM2**. Especially, an impressive improvement of muscle strength and respiratory function, as well as a full rescue of lifespan, was noted.

It is the first example of "**cross- therapy**" for a myopathy, where the decrease of a gene (DNM2) altered in one form of centronuclear myopathy, rescues another form of centronuclear myopathy which is due to the loss of a different gene (MTM1). The identification of DNM2 as a novel therapeutic target for myotubular/centronuclear myopathies paves the way for pre-clinical development, including how this strategy can be applied to other forms of centronuclear myopathies.

The aims of the 2-year research project being funded by the Myotubular Trust from early 2015 are:

1) **Targeting dynamin 2 as an innovative therapeutic strategy** in X-linked myotubular/centronuclear myopathy:
We will determine the best way to reduce DNM2 in order to achieve the most important improvement of the disease. Several technological approaches will be tested and the most potent one will be derived as an injectable product that could be ultimately used in clinical trials.

2) **Analyze long-term effects** of reducing DNM2 in X-linked myotubular/centronuclear myopathy:
Whilst reduction of DNM2 rescues myotubular myopathy in diseased animals, it is important to evaluate any side effects of long-term DNM2 reduction. To achieve this, it is planned to fine-tune the reduction of DNM2 to avoid any potential complications due to the treatment. We also aim to investigate if there are any problems that may develop once the myopathy is ameliorated.

3) Determine if reducing DNM2 can **rescue other forms of centronuclear myopathies**:
We will investigate if this novel therapeutic approach can be applied to other forms of centronuclear myopathy, therefore increasing the number of patients that can be treated with the same therapy.

**Read the journal article 'Reducing dynamin 2 expression rescues X-linked centronuclear myopathy.'

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FINDING STRENGTH

Dr Laporte has focused his research on myotubular and centronuclear myopathies since 1993 and discovered the MTM1 gene in 1996. Through a unique and interdisciplinary approach, his team has identified the genetic cause of a majority of MTM/CNM patients, characterized several molecular and cellular defects leading to the development of these diseases, and has recently validated strategies to improve the muscle alterations and shorter lifespan of mice with myotubular myopathy through fine tuning of gene expression. These achievements were obtained thanks to fruitful collaborations with national and international teams, and past team members subsequently seeded their own research in the field.

The Institute of Genetics and Molecular and Cellular Biology (IGBMC) is one of the main European research centres in biomedical research. In France, it is the largest research unit, involving the Inserm, CNRS and the University of Strasbourg. The Institute aims to develop interdisciplinary research at the interface of biology, physics and medicine, in order to understand the mechanism of cells in health and diseases. The IGBMC is located on the "Parc d'Innovation d'Illkirch" in the Strasbourg suburbs, an exceptional scientific, academic and industrial environment that is dedicated to scientific research and biotechnologies and largely favors collaborations and technology transfer