

# NEUROMUSCULAR DISORDERS IN THE 21<sup>ST</sup> CENTURY

## THE HOPE AND THE HYPE

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Professor North's talk covered three broad topics:

1. Gene discovery and genetic diagnosis
2. Understanding disease mechanism
3. Better symptomatic and specific therapies

### Gene discovery and genetic diagnosis

The identification of the underlying genetic cause of a particular neuromuscular disorder allows researchers to begin to understand the mechanism of disease, ie how a mistake in a particular gene causes the disease. This then enables us to develop therapies that target the specific disease process, and therapies that aim to replace the faulty gene or correct the mistake. Knowing the specific genetic change in a particular individual allows us to provide that person and their family members with accurate counseling about genetic risk, and the option of prevention or prenatal diagnosis.

The genetic basis of an enormous number of neuromuscular disorders has been identified in the last ten years. For example, in 1996 there were four known genes for limb-girdle muscular dystrophy (LGMD) - alpha-, beta- and gamma-sarcoglycan in addition to dystrophin (for Duchenne and Becker MD). Now, ten years later, there are at least 23!! Despite this there are still a significant number of LGMD in which the genetic basis remains a mystery.

### Understanding disease mechanism

Researchers are now studying all the genes known to be associated with muscle disorders to understand the complex process involved in the disease and the factors that lead to muscle wasting and muscle weakness. For example, dystrophin is known to be an important structural protein involved in protecting the muscle membrane from the forces generated when muscle cells contract. However, it is becoming clear that dystrophin's role is much more than just structural, and it is involved in the complex signaling pathways in the muscle cell itself.

### Management of muscular dystrophy: Better symptomatic and specific therapies

- Medical therapies: Although the focus in most people's minds at the moment is very much on the possibility of future curative therapies, it is important not to forget that excellent medical care continues to make a major impact on the quality of life and survival of children and adults with neuromuscular conditions. For example, the introduction of spinal surgery for scoliosis and respiratory support has significantly improved survival of boys with Duchenne MD (DMD).
- Drug therapy:
  - **Corticosteroids** have been used for some years now in DMD and in some boys result in rapidly improved strength. This is usually measurable in 10 days, and the maximum benefit is reached by about three months. Steroids slow the loss of function for up to three years, and can prolong the ability to walk for a number of years. The exact mechanism of action of steroids is not well understood, and we know that they have an effect on many different processes within the muscle eg. They promote muscle regeneration, stabilize the muscle fibre membrane, have an anti-inflammatory effect and decrease muscle degeneration
- Gene therapy: Most of these therapies aim to convert the disease to a milder form eg. from Duchenne MD to a milder disease like Becker MD by producing at least some dystrophin that is partially functional. **The biggest challenge for these therapies is to deliver enough of the therapy to the muscle cells themselves.** Many of these therapies are successful in mice – but a whole mouse only weighs 25g and a single mouse muscle weights a lot less than 1g!
  - *Cell replacement*: myoblast transfer therapy aims to introduce immature muscle cells with a normal or functioning gene into a patient's muscle – these normal cells can then differentiate into normal muscle tissue.

- *Gene replacement*: directly replacing the faulty gene using a carrier called a ‘vector’ – e.g. the aim is that the new gene can be put into an altered virus and given to the patient where it will multiply and spread into the muscle
- *Gene repair* – which aims to fix the patient’s own faulty gene
  - Drugs that cause ‘**read through**’ of early stop signals (called ‘nonsense mutations’): In some patients, the fault in the gene results in an early stop signal, so that the gene is not read all the way to the end, and the protein is not formed normally. **PTC124** is an example of one of these drugs, and is in an early trial currently starting in the UK.
  - Compounds that provide a ‘gene band-aid’ – and allow the muscle cell to ‘skip’ over the part of the gene where the mistake is (called ‘exon skipping’). At least some functional protein will be formed.
- *Gene up-regulation or inhibition*: We know that although there is degeneration of muscle cells in muscular dystrophy, there is also a lot of regeneration. This regeneration is not enough to keep up with the muscle damage. Therefore, rather than just trying to replace the missing or faulty protein, we can try to boost other pathways of muscle regeneration or dampen the degenerative pathways. For example blockade of the protein **myostatin** results in loss of the normal inhibition of muscle growth in mature muscle and results in muscle hypertrophy. Also there are other proteins that may be capable of taking over at least some of the function of the missing protein and we may be able to increase the production or activity (up-regulate) of these eg. **Utrophin** is an immature version of dystrophin that can replace some of its functions in skeletal muscle..

There is a huge amount of exciting research happening, and although progress seems slow, it is important that above all we do no harm. Side effects of experimental therapies can be severe, and therefore they need to be tested thoroughly before they become widely available. A catastrophic side effect will be a dramatic set back to the process, a set back that we cannot afford.