

Report on the Medical Research Council's (MRC) Centre for Neuromuscular Diseases

1st Myotonic Dystrophy Workshop

1st December 2010

Introduction

Our Chairman, Vice Chairman, Mike Walker and I represented the MDSG at the 1st Myotonic Dystrophy Workshop held at the MRC Centre for Neuromuscular Diseases in London on 1st December 2010.

The Director, **Professor Michael Hanna** opened proceedings stating that the overall aim of the MRC Centre is to bring together clinicians, scientists, patient organisations, and patients in order to advance translational research in neuromuscular disease. He added this is a particularly exciting time as a range of basic science discoveries are revealing an increasing number of therapeutic targets and the Centre aims to work with all its partners to support the development of a trials culture for patients with neuromuscular diseases.

Aim

Dr. Chris Turner, a Consultant Neurologist, charged with developing the lead for Myotonic Dystrophy clinical service at the MRC Centre, then itemised the specific

Aims of MRC Centre Myotonic Dystrophy Workshops

- **Establish a DM network of UK clinicians/scientists/therapists**
- **Develop a National DM patient registry/database**
- **Develop National Clinical Guidelines for management of DM**
- **Groundwork for UK therapeutic and natural history trials in DM**
- **Seek and coordinate funding for basic science and clinical research in DM**
- **Develop international networks**
- **Establish a UK National Working Party for DM with key members**
- **Education and update in DM**

Morning Session

The following topics were addressed by **Dr. David Hilton-Jones**, **Dr. Perry Elliott**, **Dr. Chris Turner** and **Dr. Mark Roberts** respectively:

- Excessive daytime sleepiness and respiratory failure
- The heart in DM; cardiac monitoring
- Muscle and brain in DM
- Gastrointestinal involvement in DM

Afternoon Session

- **Professor Darren Monckton** spoke about “**Unstable DNA in Myotonic Dystrophy: Causes and Consequences**”. The size of the CTG repeat not only varies from generation to generation, but is also unstable throughout the lifetime of an individual patient and differs from tissue to tissue. Moreover, although each repeat within a person will be both expanding and contracting, on average an increase occurs over time. Continuing, he said variant repeats were yet another factor where an interruption of the CTG repeat by some other sequence, in around 5% of cases, may modify the range and severity of the symptoms. In conclusion he said his research indicates that the overall rate of increase in CTG repeat expansions in DM patients over time represents a classic “bell curve”. The majority are at the top of the curve, with an average increase in the rate of their repeat expansions over time, while the minority on the sides of the curve have either slower or higher than average rates of repeat increase. This has clear implications for trial design, as results may be biased if this effect is not accounted for.
- **Professor Charles Thornton** spoke about “**Treatments for Myotonic Dystrophy and target RNA**”. While the disease process in Myotonic Dystrophy is complicated and our understanding of it is still incomplete, events over the last 3 years are beginning to suggest that RNA mediated mechanisms could prove to be unusually susceptible to therapeutic intervention. Most researchers are using one means or another to target the toxic, repeat containing RNA. For example, several research groups are attempting to find “small molecule” drug - like compounds that can block the interaction of CUG repeats with RNA binding proteins. Another approach involves the use of antisense oligonucleotides (ASOs) where impressive results have been achieved in the laboratory. Although there are still significant hurdles ahead before these can be translated into clinical human trials, he thought it would be likely that the latter would commence in 5 years, possibly even 2 or 3.

- **Professor David Brook**, spoke about **“Developing Assays (Tests) for drugs to treat DM”**. His group and others have set about identifying small molecules that may be useful in DM therapy. So far, they have screened the entire collection of 2,1724 drugs approved by the National Institute of Health (NIH) in USA. This had produced 3 possible contenders. They have also screened about half of a further 6,080 drugs held at Nottingham. These have produced 6 more possible contenders, bringing the total thus far to 9. All reduce sequestration of the MBNL protein within the nucleus without cell toxicity in zebra fish models. Next steps will include mouse models.
- **Dr. Mark Rogers**, spoke about **“Clinical Databases and Registries”**. An **International Workshop** had been held in The Netherlands in **2009**. This had decided an **International DM1 Registry should be created to harmonize key patient data to facilitate translational research in DM1 by easing the path for industry and researchers to move therapies forward to the human clinical trial stage**. Work to set up this International Registry had commenced in collaboration between TREAT-NMD and existing registries in Canada, Finland, France, Germany, Italy, Netherlands, UK and USA which cover some 2,200 DM1 patients. Continuing, he said DM1 prevalence is approximately 1 in 7,000. This indicates that about **10,000 people within the UK have DM1** out a population of 70 Million. In contrast Cardiff’s registry, currently the largest in the UK, contains just 237 DM1 patients. **A UK Nationwide DM1 Registry is clearly required to support the International Registry and expedite translational research to the clinical stage** This National Registry will be developed at Cardiff. The Marigold Foundation, which is rolling out a similar national programme across 23 clinics in Canada, has offered to provide the necessary soft ware free of charge, but **start up and annual running costs of £40,000/annum remain outstanding**.
- **Margaret Bowler described how the MDSG had grown** from humble beginnings in 1989 into a National Support Group and is now a company limited by guarantee with 10 Directors, 8 Medical Advisors, helpline, quarterly newsletter, modern website and an office with 2 part time staff supported by a book keeper. Continuing, she said the MDSG had **1830 members throughout UK** and was positive it **will act as an excellent framework around which to base the formation the UK National DM1 Registry**, in conjunction with the Hanns Lochmuller of TREAT-NMD, Chris Turner at the MRC and Mark Rogers in Cardiff. She recognised that **generating the necessary funding will be critical to the development of basic and clinical research in UK**.
- **This critical funding issue will be addressed by the MDSG Directors at their next meeting in Cardiff with Dr. Mark Rogers on 15th January**

2011.

- *John Kelly*

10th January 2011