

Development of Treatments for Inherited Neuromuscular Disorders

We now know the genetic cause for many inherited Neuromuscular disorders, so why is it taking so long to find effective treatments or a cure? This is a frequent question at Neuromuscular clinics and remains a frustration for many people with Neuromuscular disorders.

We have accurate genetic diagnostic tests for most of the common inherited Neuromuscular disorders and these can be performed in Australian laboratories. However, testing for many of the less common disorders often has to be performed at overseas laboratories. Unfortunately there is no Medicare subsidy for many genetic tests and these are currently expensive with some testing costing up to \$8000. This is a significant problem as hospital departments are not funded to obtain genetic testing. The federal government has announced a consultation regarding genetic testing so there is a chance that this important problem will be addressed in the next 2-3 years. The other development that will lead to better and cheaper testing is Next Generation gene sequencing. This allows sequencing of the whole exome (most of the genetic material used for coding proteins) for about \$2000. This process produces such large amounts of information that it is still difficult to process all the information obtained but progress will be rapid. It also generates a lot of extra information and one of the challenges of Next Gen sequencing is deciding how to deal with this extra genetic information, or whether to ignore it.

Once the genetic defect is known, the next task is to work out the affect on the function of nerve and/or muscle. The biochemical pathways that underlie the functioning of cells and tissues are often very complex and it may take many years for scientists to be certain how and why a genetic abnormality results in a clinical disorder. Once this

is determined it is then possible to consider how to correct the defect.

One of the first steps is to reproduce the defect in an experimental model, which is usually done by introducing the abnormal human gene. The most frequently used models involve tissue culture of human muscle, rodents or zebra fish, however none of these are ideal. Tissue culture is problematic as the cells grow on a culture plate fed with an artificial medium, and are separated from other tissues. It is often crucial that they are associated with blood vessels and nerve tissue interaction to demonstrate the disease process. Both zebra fish and rodents may be useful models for human disease but can produce misleading results. The first step is to create something that looks and acts like the human disorder in the test model – this is known as producing a phenotype. Animal models with phenotypes (including rodents and dogs) for Duhenne and Becker dystrophy have been around for Duchenne and Becker Dystrophy for about 20 years and for about 10 years for Myotonic Dystrophy. While we have potential rodent models for FSH dystrophy we do not yet have one that demonstrates a definite phenotype.

Once we have an animal model, we can begin the process of finding a treatment, either drug-based or genetic, that will result in "cure" or improvement of the phenotype in the disease model.

Unfortunately, a treatment that is effective in a tissue culture or animal model may not be either safe or effective in humans. Rodents and zebrafish are short lived and tissue culture live for a few days only, so the life span of the disease model is short. This means that they may die long before developing evidence for the toxicity of a treatment. While muscular



*Prof. Alastair Corbett
Muscular Dystrophy NSW
Medical Director*

dystrophies may shorten life span, they are not rapidly fatal disorders and patients even with severe muscular dystrophies live for many years and lead enjoyable and productive lives. Therefore we are not justified in using treatments that are dangerous or may result in serious side effects, or be potentially life threatening. This is in contrast to some treatments for cancer. Many cancers are likely to prove fatal within months if not treated, so we can have a lower threshold with regard to the safety of medication. Medication or gene therapies for Neuromuscular disorders must be considered both safe and effective before introduced for general use. Ensuring effectiveness and safety is a long and involved process. Genetic treatments – exon skipping and stop codon read through - are now being tested in Duchenne muscular dystrophy. We do not yet know the effectiveness or possible long term toxicity and we await the outcome of these blinded and controlled trials.

At the present time, we can cure Myotonic dystrophy in the mouse model and work is proceeding on genetically curing it in human tissue culture using a short sequence of DNA called an Antisense Oligonucleotide. This gets into the cell and unblocks the

cell machinery that was malfunctioning due to accumulation of the expanded CTG repeats present in Myotonic dystrophy. If it continues to prove safe and effective it may need to be looked at in other Myotonic dystrophy disease models closer to humans before human trials can start. FSHD treatment investigation is not as advanced.

I am frequently asked why we don't use stem cells. There are many different types of stem cells and our own muscles contain stem cells which allow them to recover after damage. In inherited Neuromuscular disorders, our own stem cells have already failed. We can either use stem cells from another person (a tissue graft that might be rejected) or genetically modify the patient's own stem cells. We have 2

copies of each gene, a copy from each parent is inherited. There are 2 forms of inheritance - dominant and recessive. Recessive disorders occur when both copies (alleles) of the gene are abnormal - the gene product (protein) cannot be made and results in a loss of function. Autosomal dominant disorders usually occur because one allele makes an abnormal toxic product that causes damage to the cell resulting in a toxic gain of function. Stem cells could have a role in recessive disorders to replace the protein or function that is lost. They have been trialed in individual muscles in limb girdle dystrophies with some benefit. There is currently no way to administer muscle stem cells other than to inject them directly into muscle. Until some form of general

delivery by intravenous injection or similar becomes available, they are unlikely to prove useful. In dominant disorders, toxicity is problematic, due to an abnormal product from the defective allele. Adding stem cells is unlikely to do anything to counter this. The appropriate treatment is one which would suppress or counteract the abnormal gene or its toxic product.

We are entering an exciting time for patients and scientists with the very real prospect of effective treatment or cure. We should not however forget that conventional symptomatic treatment is also improving as we understand these disorders better, and that there is plenty to be done at the present time. We should not just wait for a cure.



On Wednesday 9 November, our Dukies all came together for a special lunch at the Novotel at Sydney Olympic Park following an invitation from the National Office of the Duke of Ed (DoE). The main aim of the lunch was for the DoE Ambassadors, Board and staff to meet each of our truly amazing young people who are doing their Award, and to also gain a better understanding of each person's individual journey. It was also a chance for Muscular Dystrophy NSW and the National Office of the Duke of Edinburgh's Award to acknowledge/celebrate the new partnership we have formed - ensuring young people with neuromuscular conditions have access to the Award program.

What a wonderful afternoon we all had! Sean started proceedings with an Acknowledgement of Country, and Hayley delivered yet another moving speech, outlining what her Adventurous Journey to the Pacific Islands taught her about how she wanted to live her life. There was a strong sense of Team as all the Dukies shared their journey achievements so far with the DoE guests, and also opened up about any challenges they had been having along the way. All in attendance were extremely impressed with our Team's drive and obvious enthusiasm for this pilot program, and Pene and I couldn't have been prouder of how each one of our Dukies rose to the occasion.

This is a strong team and we're really starting to make a huge



DoE Ambassadors and Board representatives with Members of Muscular Dystrophy NSW's DoE Team in their special edition jackets

difference together, which we hope will eventually pave the way for many more young people with a neuromuscular condition in the future.

Loretta Downie,
Event Manager

