

## **Action Duchenne Conference London, 12<sup>th</sup>-13<sup>th</sup> November 2010**

In November, MDI's Information Officer and Respite Coordinator attended Action Duchenne's eighth annual conference in London. Over the course of the two days there were presentations from some of the world's foremost clinicians and scientists involved in the care of people with Duchenne muscular dystrophy and research into potential therapies. The following is a report on the topics covered at the conference in 3 parts:

- Part 1: Diagnosis and Management of DMD
- Part 2: Research
- Part 3: Clinical Trials

### **PART 1: Diagnosis and Management of DMD**

#### **Standards of care for young people living with Duchenne**

**Prof. Kate Bushby**, Professor of Neuromuscular Genetics in Newcastle emphasised that appropriate management improves survival in DMD. DMD is now a treatable condition and multidisciplinary management is key. The consensus document on the diagnosis and care of DMD is a tool to lobby for a level playing field with appropriate management for all, to raise standards, encourage excellence and research.

The multidisciplinary model of care places the person with DMD at the very centre surrounded by their family and clinical care coordination. All the services that they need to access radiate from here, including diagnosis, genetics, physiotherapy, occupational therapy, cardiac and respiratory management etc.

There is a new initiative, CARE-NMD to take the care standards into the clinic. Their aims are to:

- Determine the current levels of care and barriers to improvement
- Improve training and education
- Monitor levels of improvement clinically and with patient satisfaction
- Redefine the natural history of DMD to inform the development of new therapies.

In the UK, new GP Consortia are being set up to make decisions about treatment and funding. The hope is that specialist neuromuscular services will be protected from the new GP Consortia but that local services such as physiotherapy will probably come under this model.

**Dr. Adnan Manzur** from the Dubowitz Muscle Centre in London followed up on the issues raised by Prof. Bushby. He said that the natural history of DMD has been altered over the last 30 years but have support services kept pace? The multidisciplinary model of care means that good clinical care should interface with research. Research can learn from clinical practice audits and clinical networks are important in ensuring standards of care. The care and clinics that Great Ormond Street aim to provide are:

- Speedy diagnosis on referrals
- Age specific clinics, e.g. young DMD under 7 years of age

- Problem specific clinics, e.g. orthotics
- Joint speciality clinics, e.g. scoliosis surgery
- Therapy input, e.g. physiotherapy, occupational therapy, dietician
- Close links with cardiac and respiratory services
- Treatment monitoring, e.g. steroids
- Involvement of a nurse specialist and Muscular Dystrophy Campaign care advisor
- Transition of care to adult team

There has been debate over whether assessments should be done all on one day or over multiple days. All on one day is helpful for people who need to travel long distances to get to the clinic but having all the assessments on one day can sometimes be tiring. There is also room for improvement. The hospital was designed decades ago and accessible toileting and hoisting facilities are not uniformly available in all clinical areas. There is a lack of psychology services, and occupational therapy and seating could also be expanded. The management is still quite “motor focused” – specialist care for learning and behaviour is quite limited. Great Ormond Street Hospital is also at risk from £16 million funding cuts after an NHS funding review so there may be challenges to face in the future.

Excellence in the care of DMD is an ongoing project.

**Stuart Wickison**, a young person living with DMD then spoke about his experiences. He compared the improvements in care for people with cystic fibrosis and an increase in lifespan for people with that condition to what could happen with DMD if improvements in care were invested in.

Stuart said that he is not a sufferer of DMD. He is much more than the condition.

He believes that while fundraising and looking for treatments and cures is important, you can't just concentrate on this as medical treatment is not the only thing that is important in maintaining quality of life. Family support is essential. The problem is not just that family support services and counselling are limited, it also parents' difficulty dealing with the diagnosis and feelings of guilt. Not being able to cope at times is understandable and it is not a failure. However, not accepting that you cannot cope is a failure. It is important that parents accept any help or support that is offered when they need it for their own good and for the good of the whole family. There should also be more investment in counselling services for individuals with DMD and family members to improve everyone's wellbeing.

### **Speaking to your Child and the Community about Duchenne**

**Dr. David Schonfeld** from Cincinnati Children's Hospital, USA, presented a workshop on how to speak to your child about DMD. This can be difficult but Dr. Schonfeld and colleagues have written a booklet to help – “Talking with Your Children about Duchenne Muscular Dystrophy”. There are 10 myths about this:

Myth 1: My child isn't upset because he doesn't understand his medical condition and its complications.

- Dr. Schonfeld recommends that you should tell your child when you receive diagnosis or from today onwards.
- Start talking about it before they understand.
- Introduce vocabulary.
- Talk about here and now, not the future.
- Information given at a simple level.
- Ill-informed is not good!
- Most kids do better if they are informed.
- Kids learn not to talk about it as they know it will upset parents – they end up dealing with it alone.

Myth 2: If you don't know exactly what to say, it's better to say nothing at all.

Myth 3: Talking about his condition will just upset him

- In fact, boys are upset about having the condition – not talking about it.

Myth 4: My son is doing well. I can tell when my child is upset / I would be the first to know.

- Kids protect parents!

Myth 5: Children are resilient & therefore don't need assistance – they'll bounce back.

Myth 6: I can't be of any assistance to my son if I am still struggling myself. I need to wait until I am ok with his diagnosis.

- You could be waiting for ever. Will you ever be ok with the diagnosis?

Myth 7: I don't know how to help my child with something this upsetting.

Myth 8: It is most important to have quality time with my child – talking about or thinking about something that is unpleasant is not quality time.

- This is not to be used to avoid important things like education, rules, guidance and friendships or you will end up with an unhappy, unpleasant child that nobody wants to be around.

Myth 9: I need to treat every day as if it were his only day. Treat every day as a gift versus treating every today as compensation for something owed.

Myth 10: What we are experiencing is just a normal reaction to an abnormal situation – we don't need counselling.

- It is painful & people will accept help if offered.

A copy of Dr. Schonfeld's booklet is available from the MDI office.

### **Caring for the Heart**

**Dr. John Bourke** from Newcastle spoke about the fact that just about all boys with DMD develop cardiomyopathy, a weakness of heart muscle. The primary cause, the lack of dystrophin, leads to problems in the cells and a repeated

cycle of cell injury and repair. As time passes, cells lose the ability to repair themselves and the consequences are damage to heart muscle with a loss of beating power, leading to a downward spiral in heart function. When left ventricular function is measured using an ECG we can see what is not functioning properly. However, obtaining good images by ECG as boys get older becomes more difficult because of problems with positioning etc. "Simple" assessments are probably sufficient.

In a cardiac MRI, it is possible to see that there is scarring in the heart before evidence of heart dysfunction is noticed, suggesting that the heart is affected earlier than symptoms appearing. An ENMC workshop in 2002 suggested that it was time to stop measuring the heart dysfunction and to start trying to treat it. This led to a number of publications demonstrating benefits of using ACE inhibitors and beta blockers in DMD when the heart is involved.

The experience in Newcastle is to use an ACE inhibitor quite early as soon as they see effects in the heart, and this can be followed by a beta blocker. In a long term follow up between 1997-2009, this showed that there was a gradual slippage in heart function over time with more deterioration around age 24-25 instead of 10-15 without treatment.

There is a question in relation to what would happen if treatment is started even earlier, before heart dysfunction occurs. A French study using perindopril suggested that early treatment was beneficial, but there were some problems with the methodology in this study.

As well as ACE inhibitors, there are other drugs which can be used to treat the heart. Anti scar agents can be used and so can ivabradine, which slows the heart rate. Boys with DMD will gain a faster heart rate so heart rate slowing is important to reduce damage. Heart failure agents such as diuretics and nitrates can also be used but the real aim is to treat the heart before it gets to this stage.

What they are looking at now, is how to reduce or prevent fatal arrhythmias from occurring as a result of severely damaged hearts becoming progressively more unstable electronically.

The good news is that while we wait for new disease modifying treatments to become available, heart protection and support is already there.

### **New Methods for Detailed Genetic Analysis**

**Dr. Steve Abbs** from Guys Hospital in London spoke about the importance of identifying the pathogenic variant in the dystrophin gene in order to confirm the clinical diagnosis, perform carrier testing, perform prenatal diagnosis for carriers, perform pre-implantation genetic diagnosis (this is currently not available in Ireland) and carry out gene specific therapy research. The dystrophin gene is one of the most complex and long, with 79 exons. Various mutations can result in DMD:

- Whole exon deletions ~60%
- Whole exon duplication ~10%
- Point mutations (substitutions, small deletions or insertions) ~ almost 30%
- Complex rearrangements, inversions and deep intronic variants <1%

In order to detect whole exon deletions or duplications, testing is carried out to see how many copies of each exon are present using an assay called MLPA.

In males who have one X and one Y chromosome, 1 copy of each exon is normal. No copies would signify a deletion and two would signify a duplication. In females who have two X chromosomes, two copies would be normal, one would signify a deletion carrier and three would signify a duplication carrier.

The genetic code is made up of three letter words called codons, with the letters A, C, G and T being the four bases. Genetic testing could detect a substitution, e.g. C would be changed to a T and also an inversion, e.g. where TAC would be changed to CAT.

There are also methods to detect small mutations and these would involve sequencing. This compares a patient's DNA to a normal reference sequence. However, it is not always possible to identify if a particular change will lead to the disease or not.

Genetic testing can detect around 98% of DMD mutations. This compares to a success rate of less than 10% in SMA and around 60% in neuromuscular disease in general. The reasons why some diagnoses may be missing could include:

- Limitations in current methodology: MLPA kits are not available for all genes involved in neuromuscular disease and we cannot look at all the introns
- Alternative diagnoses e.g. overlapping symptoms with conditions like limb-girdle muscular dystrophy
- Other causative genes are not yet known or understood.

There is a new method of genetic testing now to try to overcome some of these issues, a high density array called comparative genomic hybridisation. The benefits of new genetic technologies are:

- New technology should increase mutation detection rates
- Number of people with genetic confirmation of diagnosis should increase
- Additional tests will characterise mutations in more detail
  - informing clinical trials using targeted gene therapy.

Looking to the future, we could also see next generation sequencing looking at the whole genome including introns.

### **Autonomy: The Transition to Adulthood**

**Emily Ballard**, a specialist physiotherapist who coordinates the Neuromuscular Transition service at Guy's and St. Thomas' Hospital (GSST) in London, spoke about the fact that DMD is no longer a childhood condition. In the teenage years there is a high risk of respiratory deterioration so screening is essential. Screening and management of respiratory problems in the Lane Fox Respiratory Unit has meant that since January 2009 there have been no unplanned first crisis admissions and no admissions requiring tracheostomy or ITU in their own patient cohort, although they still see this from outside their cohort.

The work of the transition service is to link between the paediatric and adult services. A questionnaire that had been issued to 39 young people with DMD showed that they were concerned about the transition to adult services. They were told little by the paediatric team and did not meet the adult team in

advance. To enhance the link between the services, the GSST model of transition is that:

- All services are managed by one trust on one site
- There is a care coordinator between hospital and community neuromuscular teams

Early planning is essential, as is a team approach with joint clinics. As the young person gets older, the size of their care team will increase as they need access to more services. Each person should have a care plan in place which is flexible according to individual needs. It is essential to involve community teams and the care package must be reviewed as this is a progressive condition. It is important to also look at social care and consider issues such as independent living, further education and access to work. The overall aim is to maximise the quality of life.

The transition service is looking at how to keep young people out of hospital. One of the most important things is to provide portable equipment (for example, there is a new cough assist machine with a battery). There must also be 24hr technical support for maintenance of equipment. It is essential to plan chest crisis management and there should be provision of community outreach.

This transition service is unique and would need to be replicated in other areas. Health coordination at the age of transition is essential for all with DMD.

**Gordon McClurg** from Care Management Services spoke about the importance of autonomy and supports to access independent living, as a person living with DMD himself. Autonomy starts with you decide what you want to do. But it is not easy as you may have been conditioned to look to others e.g. parents, clinicians, etc.

What does Autonomy mean?

- Self governing
- Freedom to act
- Free will
- Freedoms are limited due to boundaries, resources – freedoms need resources.

The UK Government launched the “Big Society” drive to empower communities, but what about “My Society”:

- Same stake in society as everyone else – I can give back to society
- My choices – society is good to me, I can make it better
- My contribution – improve chances, publicise, campaigns, lobby parliament.

**Autonomy – its damned hard work!!!!**

### **Physiotherapy: Exercise and Fitness**

**Marian Main** from Great Ormond Street Hospital spoke about the importance of fitness and of keeping fitness relevant and interesting. Boys with DMD should be getting physiotherapy in addition to doing PE in school, so schools

need to ensure that PE is accessible to all. No matter how weak you are, there are still some types of exercise that you can do. To make it interesting, it is important for the physiotherapist to set out activities and play around the exercises they want the child to do, not to set out a formal exercise plan.

The best exercise for fitness is aerobic exercise. This is anything which increases the heart rate and respiratory rate (not excessively however). It is important not to use weights in children or do eccentric exercise (e.g. squats). However, be realistic. Do not stop a child walking downstairs or jumping. It is important to be sensible. The aim is not to improve function, but for the person to be as good as they can at a particular time.

Good forms for exercise would include swimming, horse riding, tricycling and non-contact martial arts (they tend to be symmetrical). Exercises to avoid would include trampolining, running, use of scooters (very asymmetrical), weights and real contact sports (such as rugby).

Respiratory fitness is also important. There are various exercises which can be done to help respiratory fitness, including swimming, singing and blowing bubbles.

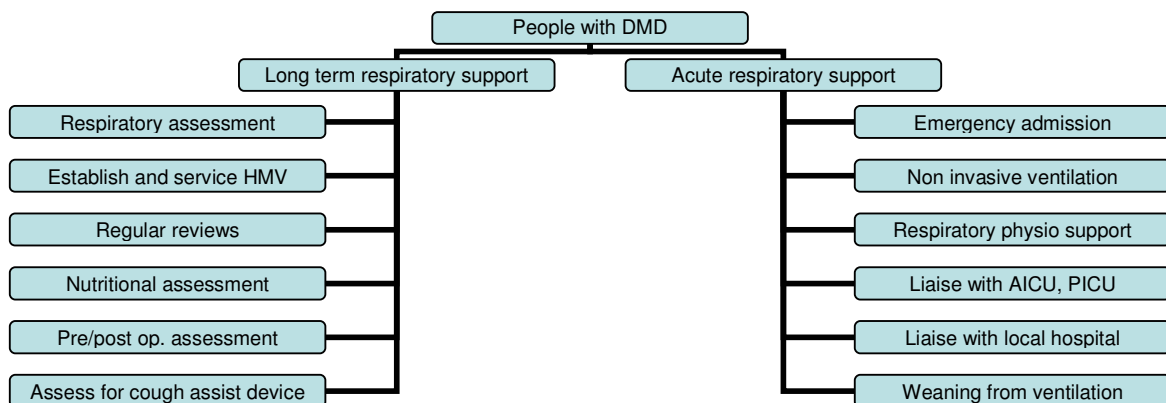
Contractures prevent effective exercise and cause pain. Stretching is important but this should be done afterwards. Before exercise the muscles should be warmed up. No exercise should be done until it causes pain and cramps.

Parents and carers also need to look after their fitness. Poor posture and bad lifting techniques can lead to problems so training in effective techniques is useful.

It is very important to remember that there are no lazy children. There may be children who are demotivated and frustrated or who don't understand the importance of exercise, and there are also times when parents / carers' expectations are too high, but this is something that can be worked on.

## Respiratory Care for Duchenne

**Dr. Nick Hart** spoke about the services provided at the Lane Fox Respiratory Unit. This is a 14 bedded purpose built unit with two outpatient rooms. It is not specifically for people with DMD but they do have expertise in this condition. The supports provided to people with DMD are outlined below:



Until research produces new treatments, the unit also covers ICU admission, tracheostomy and end of life care.

It is very important to have a respiratory review prior to a first respiratory crisis admission. Without this, there can be a longer hospital stay and more people requiring invasive ventilatory support and tracheostomy. Collaboration between paediatric neurology and specialist respiratory support will ensure timely intervention to reduce the severity of a crisis.

People should be aware of the symptoms of nocturnal hypoventilation. These include a disrupted sleep pattern, early morning headache, daytime fatigue and impaired concentration. If any of these symptoms are noticed, there should be a respiratory assessment. Machines such as the NIPPY and a Cough Assist as well as chest physiotherapy can be very beneficial in managing respiratory symptoms.

Tracheostomy is an option that some people consider. It has some benefits, including the fact that it does not obstruct the face as masks can, but it does require proper suctioning and cleaning etc to prevent infection. The problem in the UK at present is that it is difficult to sort out home care for someone with a tracheostomy.

### **Bone Protection for Children with DMD Treated with Corticosteroids**

**Dr. Ros Quinliven**, Consultant in Neuromuscular Disease at the National Hospital for Neurology and Neurosurgery and Great Ormond Street Hospital, spoke about the importance of bone protection. Weak bones mean that there is a greater risk of fractures with the risk of more discomfort and loss of function. Fractures are more common in children with DMD who are using steroids.

In order to look at bone density, a scan called a DXA is used, and this should be repeated every 1-2 years. This looks at bone mineral content, bone mineral density and bone mass. The usual result is shown as a T-score but this is not applicable to children as it is a measure of the results as compared to an average 30 year-old, and bone mass is still growing until the mid 20s. Therefore, a Z-score is used, which is corrected for the age and size of the child.

A North Star database audit (Manzur, 2009) looked at vitamin D levels in 152 people with DMD. 15% were found to have a severe deficiency, 43% were deficient and 22% were vitamin D sufficient. It is therefore important to not only make sure a person with DMD has enough calcium in their diet but also that they have enough vitamin D, and if necessary, take a vitamin D supplement daily. Vitamin D also comes from exposure to the sun, but a total sunblock stops it being absorbed. In summer therefore, a suncream to prevent burning is fine but a total sunblock is not helpful for vitamin D absorption.

Studies have suggested that the use of bisphosphonates can protect bone, particularly when used along with vitamin D. A study by Hawker et al (2005) in boys with DMD found that bone mineral density remained stable and even improved in younger patients treated with bisphosphonates and it was reasonably well tolerated. However, it was not a long enough study to show if it reduced fractures. Another study by Bushby et al (2009) suggested that there could be a window of opportunity for bisphosphonate treatment and that

it might not be useful for those who had been on steroids for over 6 years. The effect of the drugs on a growing skeleton over time is not known and there are side effects, so these must be monitored and further study carried out.

### **Duchenne, ADHD, Dyslexia and Autism**

**Prof. Veronica Hinton** from Columbia University in the USA spoke about the fact that the dystrophin protein can affect many things including the muscle and the brain. We do not know what causes ADHD (attention deficit hyperactivity disorder), dyslexia and autism, but there may be different causes that result in similar symptoms. Diagnosis is based on observable behaviours. Having DMD means that there is an increased risk of having one of these diagnoses but it does not mean that a person with DMD will have them.

Development dyslexia is when the reading ability is significantly lower than expected given the child's intellect and other skills. Reading skills are lower in boys with DMD as a group, lower even when compared to children who have a different neuromuscular condition. Boys with DMD have also been shown to perform more poorly than their siblings on tests of phonological awareness and phonological memory.

It is important that every child is evaluated on the basis of their own performance as an individual. If there is a problem, it should be treated as dyslexia would in anyone else, not as something special connected to DMD.

There is some evidence that DMD and autism occur together with greater than random frequency. Once again, diagnosis must be based on the individual's performance and behaviour. One study suggested that 15-19% of children with DMD and BMD have an autistic spectrum disorder (ASD). However, as this was not a randomized trial there could have been a selection bias.

For those who do have some ASD qualities, there are improvements with age in reciprocal social interactions and communication.

**Dr. James Poysky** from Baylor College of Medicine in Houston, Texas, spoke about ADHD. The prevalence of ADHD is around 1% of the population in the UK (3-10% in USA where the statistics include milder cases), and it is around 2-3 times more frequent in males. It is estimated that around 12-30% of boys with DMD could have symptoms of ADHD but this is only an estimate.

ADHD is diagnosed by criteria set out in the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders). Treatment includes parent training and group therapy (social skills training) but this is better for mild cases. The first line of treatment for moderate to severe cases is medication, and approximately 85% of people benefit from medication. As the medication may have potential cardiac side effects it is very important to consult with your cardiologist prior to starting any treatment.

Accommodations at school such as extra time for tests and assignments, a quiet test-taking environment (e.g. another room) preferential seating and giving directions one step at a time can reduce the impact of ADHD on academic progress.

## **PART 2: Research**

**Dr. George Vella** from Charley's Fund spoke about Pilot Trials Now which is an initiative focused on developing treatments by repurposing drugs approved by the FDA for other conditions that have shown real potential in DMD animal models. The value of this is that safety and toxicity profiles are already well known to regulatory agencies. These drugs may help to keep boys with DMD strong until new therapies hit the market.

Pilot Trials Now is necessary because while several FDA approved drugs show promise, few are tested in DMD patients due to cost, time and interest levels:

- Many approved drugs affect the same disease pathways
- Clinicians lack the time to raise funds to run trials
- There are burdensome administrative requirements
- There is a low profit margin since the drugs are already approved and IP (intellectual property) is owned.

One of the compounds that they have identified is sildenafil (Viagra). This was first studied for hypertension and angina and has been found to be safe in paediatric pulmonary hypertension (in this case it is called revatio). The question is, can sildenafil reduce cardiac hypertrophy and fibrosis induced by DMD? ECG analysis in the mdx mouse has shown that early treatment reduced heart dysfunction. To determine this, Pilot Trials Now funded a trial and Pfizer agreed to supply the drug. They are currently recruiting participants and hope for 30. This will be a randomized double-blind placebo controlled trial with a duration of 12 months. It would involve an oral dose of the drug.

There is also a trial of IGF-1 in Cincinnati. The hypothesis here is that IGF-1 therapy will improve or preserve muscle function in DMD vs. controls. The status is that the trial is active but not yet recruiting, and it will be a 6 month open label trial.

They are also testing five additional drug candidates in the mdx mouse and have identified four potential drugs that are currently in clinical trials for other indications.

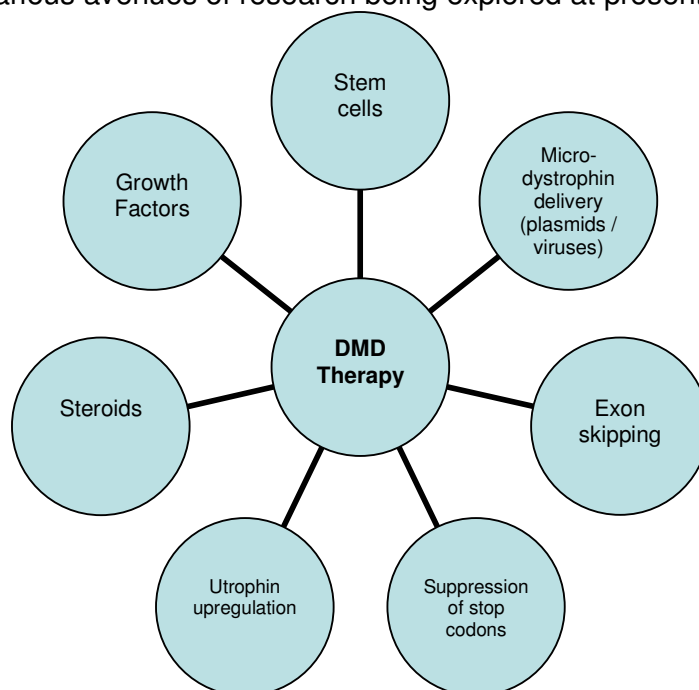
**Dr. Brad Hodges and Richard Cloud** from Prothelia spoke about their mission: to increase longevity and quality of life in people with muscular dystrophy. Richard Cloud especially understands the issues as his daughter has congenital muscular dystrophy. Prothelia's aim is to treat all patients regardless of the mutation and to treat multiple forms of muscular dystrophy. LAM-111 is their lead drug candidate and the aim is to restore the lost cellular adhesion in muscle cells. LAM-111 can be delivered systemically and has excellent efficacy with no toxicity. It can get to skeletal, diaphragm and cardiac muscle and is being investigated for DMD and congenital muscular dystrophy. At the moment, double knockout mice (missing dystrophin and utrophin) need to be treated at least once per week and it is not yet known how this would translate to humans. Future development will focus on the preclinical development of human LAM-111.

**Prof. Kay Davies** gave an overview of research taking place into DMD. There are challenges in developing a therapy for DMD:

- Dystrophin is a large protein

- Need to replace at least 20% of normal levels
- Need to target all muscles (heart, skeletal muscles, diaphragm)
- Muscle can make up 40% of a person's body mass so systemic delivery is necessary
- Need to avoid immune response
- Life long treatment is needed

There are various avenues of research being explored at present:



Prof. Davies spoke about issues with stem cell research, which shows promise but needs much more work before it can get to the clinical trial stage. For reasons not yet understood, introduced stem cells do not fuse with muscle cells correctly in humans while it works very well in the mouse.

Prof. Davies has been very involved in utrophin upregulation research. While the drug being developed by Biomarin has been stopped due to poor results, the idea has not been abandoned. Summit is now developing a new formulation of the drug independently of Biomarin. They are also using a new technique, live animal imaging with a utrophin luciferase knock-in mouse model. A firefly gene is inserted into the utrophin gene and when imaging, the intensity of the light signal indicates an increase in utrophin levels. This new technique will allow more efficient drug development.

DMD treatment is likely to be a combination therapy and how this works (e.g. treatments in parallel or one after the other) remains to be seen.

### Exon Skipping Research

**Prof. Steve Wilton** gave an overview of exon skipping. The concept of exon skipping is to skip over the disease associated / causing exons, using antisense oligomers which act like a sticking plaster or a “molecular spanner” which is specifically designed to modify dystrophin splicing.

The diagram below shows exons 48 to 53 and you can see that the end of each exon joins up with the next. However, if there was a deletion of exons 49 and 50 for example, you can see that 48 could not join up with 51 meaning that the disruption of the reading frame would result in DMD. With exon skipping, there would be a targeted removal of exon 51 and then exon 48 could join with 52, which would restore the reading frame but the resulting protein would be shorter. This would lead to a condition more like Becker (BMD).



Becker MD mutations are in-frame and there is a spectrum of severity. The aim is to achieve as mild a form of BMD as possible. Prof. Wilton reiterated that if a boy's mutation is already in-frame then this exon skipping will not apply, but other strategies such as utrophin upregulation may apply. He suggested that when looking for future exons to focus on, that they choose those that can be skipped most efficiently rather than the most common so they can get the best results and ensure that they can progress to other exons. They are also looking at multi-exon skipping. There are advantages with this such as that it would address clustered mutations and fewer oligomer preparations would be needed. However, there may be limitations to do with efficiency, dystrophin gene variation, cost and the potential for off-target effects.

Prof. Wilton referred to the MDEX systemic trial in the UK, which has now completed but unfortunately AVI BioPharma is not extending the study at present (meaning that participants who were receiving the therapy are no longer getting it). The next phase of the trial will take place in the USA.

**Dr. Mike Gait** spoke about peptide enhancers of exon skipping oligonucleotides. It is suggested that they may have to generate at least 30% of normal levels of dystrophin in all muscle types to obtain the best clinical benefit. Naked PMO (morpholinos, the antisense technology used in the AVI clinical trials) may not be able to reach this level in some tissues (e.g. the heart) unless very high doses are used. Therefore to enhance cell delivery, they are looking at cell penetrating peptides (CPP), which help the PMO to pass through the complex cell membrane system into the nucleus. A repeated dose of a CPP enhanced oligonucleotide called B-MSP-PMO has been shown to complete muscle protein production, but crucially not enough in the heart. A second muscle specific peptide however (peptide 9) is showing higher heart activity (Dr. Matthew Wood's lab.).

Peptide-PMOs will have to satisfy stringent safety criteria. There are some toxicity issues that will have to be looked at in future preclinical studies.

The MDEX Consortium currently has grants in place to advance a peptide-PMO to the clinical trial stage within 3 years.

**Dr. Aurélie Goyenvale** focused on AAV vectors which can deliver genes to muscle very efficiently. Their research involves inserting antisense sequences into viral vectors to induce exon skipping. This would have a more long-term effect, and it is also possible to deliver multiple oligonucleotides. One dose in the mouse meant that dystrophin was still being produced one year later.

Efficient systemic delivery has been shown in the mouse and dog. However, challenges remain regarding the optimal dose and potential immune response.

Regarding multi-exon skipping, the multiple skipping of exons 45-55 would be applicable to 63% of people with DMD. To do this, they need to design a single “plaster” for each exon and then combine it into a single vector. Optimisation of multi-vectors is still ongoing.

**Prof. Haifeng Yin** spoke about research in China. The challenge is that methods of diagnosis are not standard. Treatment in China focuses on Chinese medicine but there are also clinics claiming to offer stem cell therapy. Dr. Yin has worked on exon skipping, particularly peptide mediated AO delivery, for 6 years and is based in Tianjin Medical University where they have a laboratory of gene therapy joined with Oxford University. Dr. Yin believes that basic research is essential to provide a base for the development of new drugs.

### **Microdystrophin Gene Therapy**

**Prof. George Dickson** spoke about microdystrophin gene therapy which is coming from research into exon skipping and myostatin inhibition. A combination therapy is being looked at because trying to bulk up a muscle which is intrinsically weak will not work without some amount of dystrophin expression. Gene transfer involves use of AAV, a safe method for delivering the compound. The result would be non-integrating but could last over 6 years in muscle. The disadvantage is that immunogenic and human seropositivity exists.

AAV 8/9 can be delivered IV to treat multiple muscles and the heart in a canine model. Extensive microdystrophin expression was found which lasted 2 months post single injection. Improvements such as reduced cell “leakiness” and inflammation and improved force generation were noted. There was no evidence of inflammation or immune reaction.

Vascular delivery is now planned in the canine model.

### **PART 3: Clinical Trials**

**Dr. Pavel Balabanov** from the EMA, European Medicines Agency, spoke about the misunderstanding that the clinical view and the regulatory view oppose each other, with the question being asked “Are the regulators being too stringent?” While clinicians and patients are often ready to accept higher potential risks with only signals of benefit, the EMA’s main responsibility is the protection and promotion of public health. They believe that a clear clinical benefit must be proven to balance any potential risks.

There are challenges when looking at rare conditions:

- The population is restricted due to the rare condition. Competition for different trials and dropout rates can be problematic. However, the EMA has guidelines on research using small populations.
- The heterogeneous clinical state, e.g. how do we compare older vs. younger patients? Clinicians can help to educate the industry in relation to this.

- Statistics: if formal statistics cannot be used then it may be possible to discuss descriptive data.
- Endpoints: a clinical endpoint to assess a clinical trial is a must. A validated endpoint is preferred but discussion with the EMA could be held on any clinical endpoint demonstrating benefit. It is acceptable to show maintenance of effect and stop in progression but a long term clinical endpoint as a secondary measure will be needed.
- The EMA recognizes that traditional study designs can be irrelevant so innovative designs are acceptable but they must be based on scientific principles and data. More natural history studies of DMD are necessary.

When planning a clinical trial, early dialogue with the regulators is essential. This enables potential pitfalls to be identified early and can also educate the regulators. Informal support is also available from the EMA.

Dr. Balabanov could not predict how long it would take to get potential treatments for DMD from concept to the clinic. He believed that it could take longer than the development of enzyme replacement therapy for example, due to the complicated nature of the condition, but we need more data than is currently available. Indications of benefit in a phase 1 trial is not enough, they need to see data showing clinical benefit and this needs more work.

**Prof. Kate Bushby** spoke about improving clinical trial design and outcome measures. While we can now identify genes, diagnose DMD clearly and understand a fair amount of the pathophysiology, we need to understand animal models better, patients better, biomarkers and clinical outcomes. It is important to step back and think about the mouse model. *Why are there good therapeutic effects in mice that are not replicated in humans?* Better animal models means more robust studies with a better indication of what to take forward for development. TREAT-NMD is helping to develop experimental protocols. We also need to understand biomarkers better – how do these relate to disease progression or drug response?

The issue with outcome measures is that no one size fits all. It depends on trial design and phase and the patient group under study. Primary and secondary outcomes need to be defined upfront and a clinically meaningful change is key. Examples of outcomes that have been used in DMD are:

- Strength (manual testing or using machines)
- Functional scales (the North Star database)
- Timed tests (walk, stair climb)
- The 6 minute walk test
- Quality of life measures
- Dystrophin data

We need to understand how these outcomes relate to the clinical experience of the patient and their family.

There is now a new natural history of DMD. A meeting in Washington DC in June 2010 examining data from over 1500 boys has resulted in consistent natural history data. The relationship of core measures to clinical endpoints has been clarified, e.g. the loss of ability to get up from the floor or climb stairs is very clinically relevant.

While slowing the progression of DMD is clinically relevant, it is difficult to show so this needs to be kept in mind when running trials.

Prof. Bushby was asked about alternative approaches. She stated that if something shows promise it should be properly trialed to rule out a placebo effect which can be very strong, even in children. She very strongly does not advocate clinics around the world that are currently claiming to offer stem cell treatments for DMD, charging vast amounts of money for “treatment” with no data available.

**Nick Catlin**, CEO of Action Duchenne, spoke about managing expectations of research. Clinical trials are experiments, not treatments. They can have good results, bad results or something in the middle. The placebo effect is very powerful. Parents reporting back their opinions is useful but to assess trials properly we need definite objective outcome measures. Unfortunately there is no magic bullet and it will take time for therapies to have effects.

An important question to ask when going into a trial is what happens at the end of the trial? We need to ask industry these questions. We must work together with industry and transparency is essential. It is important to remember that there are regulations meaning that industry has to be very careful when presenting at patient group meetings as it can be seen as promoting a product to patients, which can result in large fines.

**Richard Cloud** from Prothelia emphasized that it takes \$1.4 billion to take a drug to market and only 1 in 10 drugs trialed actually gets there. More clinical trials are necessary to have a better chance of a drug making it.

### **Exon Skipping Trials**

**Dr. Steve Shrewsbury** spoke about the AVI Biopharma trial using AVI 4658. The systemic delivery study was completed in 2010, which was an open label study with no placebo control. An IV infusion was given over 60 minutes weekly for 12 weeks. Participants were between 5 and 15 years old and ambulant. Results have shown that the drug seems to behave in a dose proportional and predictable way. However, there was not a consistent response in terms of dystrophin expression and a higher dose may be the way to go in future. They believe it is safe up to doses of 100mg/kg. In terms of an immune response, inflammatory T cells were reduced in the top 2 cohorts which is good news but this still needs to be looked at.

Lung function remained stable over the course of the study, although it is not known what the natural progression would have been if they had not participated in the study.

The problem is that there was no clear correlation between 3 patients who showed substantial dystrophin positive fibre increases and clinical measures. Also, the open label design and small patient numbers prevent efficacy conclusions being drawn.

The next study is a phase 2 trial in the USA. They will push the dose up to 50 and 100mg/kg and will test IV infusion (taking around 60 minutes) and IV bolus (taking around 2 minutes) weekly for 12 weeks. They hope to start this in the coming weeks. There are plans for an extended dose study but this is not available yet.

There was a great deal of anger from parents whose sons had participated in the trial in the UK and are not on an extension study when they believed that this was going to happen. Some of these boys had shown substantial

dystrophin positive fibre increases but are no longer receiving the compound. Dr. Shrewsbury said that they are doing the next phase in the USA as they have saturated the exon 51 patients in the UK. They had planned to run an extension study but because they did not see a consistent dose effect they could not do this. It was disappointing that only 1 in 4 in the high consort had the best results and if even 3 out of the 4 had it then the extension study could have possibly gone ahead. They believed the logical step would be to start a new higher dose study and hope that they see more consistent results, although it may take around a year for this new study to be completed. They have given a commitment to transparency and discussing the way forward with the DMD community however as there may have been miscommunication.

**Dr. Pdraig Wright** leads the team in GSK that are developing the Prosensa drug. Earlier this year, GSK announced that they were putting together a team to look at therapies for rare conditions. They are doing this because:

- The medical need is overwhelming
- Rare diseases collectively are not rare
- New technologies offer hope (e.g. Human Genome Project, personalized medicines)
- There are highly committed advocacy groups.

The Prosensa drug is now called GSK 2402968. Phase 2 and 3 clinical trials for regulatory approval have commenced. The phase 2 trial (study DMD 114117) will run in Australia, Belgium, France, Germany, Netherlands, Spain, Turkey and the UK. Approximately 50 boys with DMD will be involved and the study will look at the dosing regime. There will be 3 groups; one receiving a placebo, one receiving injections every week and one receiving injections 6 weeks on and 4 weeks off.

The phase 3 trial (study DMD 114044) will run in Belgium, Canada, Chile, France, Germany, Italy, Japan, Korea, Netherlands, Poland, Russia and Taiwan. The hope is that this phase will show a clinical benefit. They need to confirm not just an effect, but maintenance of the effect. They don't yet have approval from the FDA to run this trial in the USA but hope to get this in the coming months. They are however doing one study in the USA at present and this is a pharmacokinetic study on non-ambulant boys (DMD 114118).

**Dr. Giles Champion** spoke about Prosensa's development of exon skipping, in addition to the work that GSK is doing. They are currently looking at exon 44 (PRO 044) but also looking at exons 45, 53, 52 and 55. In addition, they are working on myotonic dystrophy, spinal muscular atrophy and Huntington's Disease.

The phase 1/2 study of PRO 051 which GSK is developing as GSK 2402968, showed successful systemic delivery with dose related dystrophin expression and there was an extension study using a dose of 6mg/kg delivered weekly sub cutaneously. This was a small open label study with 12 boys and over 5 weeks the number of dystrophin positive fibres was 60-100% in 10 of 12 patients. Testing after 12 weeks revealed a mean improvement in the 6 minute walk test of 35 metres and after 24 weeks the mean change was 36.8 metres. While there were encouraging gains in some boys, this was a small number of patients and was not controlled so results must be read cautiously.

It is positive that no dystrophin antibodies were detected at present. There is now a need to start definitive placebo controlled trials.

The next compound to be developed is PRO 044. 12 boys have been recruited and the design is the same as PRO 051. They hope that exon 45 will be in trial by 2012.

Practical considerations for the future are that extensive clinical studies are not feasible for rare mutation groups. After the potential launch of the first exon skipping compound, patients and families will be keen to get a treatment for their mutation. Personalised medicine in orphan disease needs a new approach and they will need to work with the regulators.

### **Idebenone**

**Dr. Raffaele Robino** from Santhera spoke about the development of idebenone (catena) which they hope will preserve muscle cells. A phase 2 study in Belgium showed that it is safe and well tolerated and there was an improvement in cardiac and respiratory function. A DELPHI-Extension study is due to end in January 2011 and this should give more long term data on the safety, tolerability and efficacy of high dose idebenone in DMD. A phase 3 – DELOS trial is now ongoing to assess the efficacy of idebenone compared to placebo in improving or delaying the loss of respiratory function. Idebenone has a larger therapeutic effect on peak expiratory flow in people not receiving steroids at the same time, so this study is in 2 parts:

<u>Patients off steroids</u>	<u>Patients on steroids</u>
~ 40 patients	~ 200 patients
Enrolment nearly completed	Starting in 2011

Sites will be in the UK, Europe, USA and Canada. There will also be an open label extension study.

### **Ataluren**

**Dr. Stuart Peltz** from PTC Therapeutics spoke about ataluren, which was being developed to treat people with DMD as a result of a premature stop codon in the dystrophin gene (10-15% of cases). A phase 2b trial was stopped however, as no relationship between clinical benefit and dystrophin expression was determined. When further examination of the data was carried out though, ataluren was found to slow the loss of walking ability in people in the low dose group but there was no benefit in the high dose group, so this will require further investigation. PTC, with the support of the FDA in the USA, has implemented an open label safety study for people who had previously participated in ataluren trials at US sites. Unfortunately this study is not available in Europe, where Genzyme is responsible for developing the drug. Genzyme is working with EU regulatory authorities to determine the next steps.