Action Duchenne – skipDuchenne Campaign

Nick Catlin, Founder and Head of Research at charity Action Duchenne, gives an introduction to the charity, the condition, how they aim to improve life for those living with Duchenne, and the important role that biotech, pharmaceutical and drug discovery companies have to play.

Established in 2001, Action Duchenne aims to support and promote innovative research into a cure and effective medicines for Duchenne/ Becker Muscular Dystrophy. The charity, which is led by Duchenne families, aims to promote awareness of the condition, to improve care services, and to provide access to a range of educational and support/ development programmes for people living with Duchenne at every stage of the condition. This is achieved by working in partnership with government agencies, NHS and care organisations, other charities, academic, scientific and research groups, and biotech/pharmaceutical/ drug discovery companies worldwide.

Duchenne Muscular Dystrophy (DMD) is an incurable muscle-wasting disease affecting 1 in every 3500 male births in the UK. Duchenne is the most common and severe form of muscular dystrophy, and is the most common genetic childhood killer disease. It is caused by a genetic variation in the dystrophin gene. In every town and every city in the UK there will be at least one boy or young man living with Duchenne; get care and research right for Duchenne and you've got it right for thousands of others with related conditions.

Since 2003 Action Duchenne has provided £4m for research projects and partnerships. The charity has worked with the MDEX consortium, Department of Health, and the Medical Research Council to deliver new clinical trials for Duchenne drugs. In addition, it has been instrumental in developing projects with biotech companies both in the UK and US, including key projects with Sarepta (previously known as AVI Biopharma) and Summit.

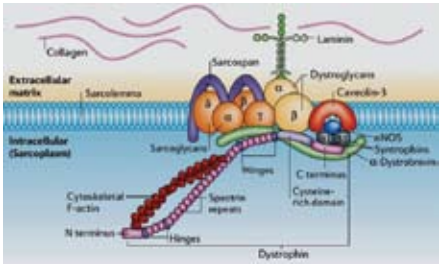
skipDuchenne

There are high hopes for the upcoming market approval of small drugs that are able to provide a genetic treatment for DMD by introducing a functional dystrophin protein into muscle cells. Leading the field in terms of advanced clinical trials are antisense oligomers developed by GSK, Prosensa and Sarepta and with a novel drug Ataluren developed by PTC Therapeutics. These molecules aim to trick the RNA splicing mechanism to produce a functional dystrophin protein.

Action Duchenne's skipDuchenne campaign (www.actionduchenne.org/skipduchenne) and funding programme will aim to ensure that the 83% of patients in the UK with DMD that can benefit will have immediate access to exon skipping drugs within the next three to five years.

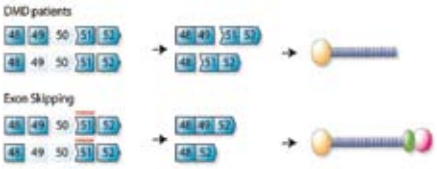
For those young people who are unable to benefit from antisense oligomers (AO) >20% skipDuchenne proposes an alternative strategy using gene replacement delivered via vectors.

DMD is caused by mutations in the dystrophin gene that leads to a failure to produce a functional muscle protein called dystrophin. Dystrophin acts as a "coat hanger" for a number of proteins in a complex that provides stability and healthy cells. Cell instability and death will occur when this complex of proteins is misplaced or missing.

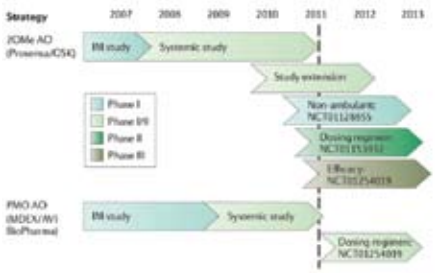


Exon Skipping

There have been many laboratory studies in DMD animal models over the last 10 years that have shown that by using small molecules called antisense oligomers (AOs) that target specific regions of the faulty gene, a shortened dystrophin protein can be expressed in muscle cells. In the related condition Becker Muscular Dystrophy such a shortened protein can restore the dystrophin complex and muscle function to near normal levels in many cases.



Human studies are now underway targeting the exon 51 region of the gene, and have been shown to be safe and also to successfully express a shorter dystrophin protein.



GlaxoSmithKline and Prosensa are currently conducting extensive Phase IIb and Phase III trials for exon 51 in ambulant and non-ambulant patients and the full data set could be available for 2014. Prosensa has been developing further studies in other exons:

Exon 44 Phase I study, Exon 45 and 53 to start in the next wave, 52 and 55 in another wave.

Sarepta is continuing with exon 51 human trials in the USA with an alternative AO chemistry that will build upon encouraging data

already published by the UK MDEX consortium http://www.mdex.org.uk/. Sarepta also has under consideration other exons 53, 45, 44 and 50. Further studies are planned with the new international exon skipping consortium http://idesc.info/

It is therefore conceivable that if all continues to go well, within the next two years there will be sufficient data available to bring the first genetic treatment for Duchenne Muscular Dystrophy using exon skipping technology to the market.

Antisense oligomers can potentially restore the reading frame of 83% of Duchenne patients (Treat NMD, 2009). Professor Steve Wilton has gone on to show that it is possible to sequence every single exon skip required to treat 83% of patients with a relevant AO (Wilton et al., 2007).

75% of patients have a deletion that occurs in the hotspot region between exon 43 and 55. Skipping the top 10 exons - 51, 45, 53, 44, 46, 52, 50, 43, 6 & 7 - would restore dystrophic expression for >40% of all patients (Rus et al., 2009).

Parents and patient organisations have so far backed the strategy for completing trials that will give compelling evidence for the use of one exon (exon 51).

PTC Therapeutics has also announced recently that it is undertaking a Phase III study in a number of US and European centres to further trial its drug Ataluren. This drug targets a small sub-population of Duchenne patients that have single base pair gene variations in the gene. Even a single point variation can result in an out of frame mutation resulting in no dystrophin. It is proposed that Ataluren acts by skipping over this tiny mutation to produce functional dystrophin.

Other exon skipping programmes are also underway using other chemistries, and while not yet at the human clinical trial stage, offer real promise for near-future application. These include conjugated AO's developed at Oxford and Cambridge. The Oxford and Cambridge teams have won grants from Wellcome and MRC to continue the work first established with Action Duchenne funding. PNA chemistries are under investigation and Action Duchenne has funded projects in the UK and China.

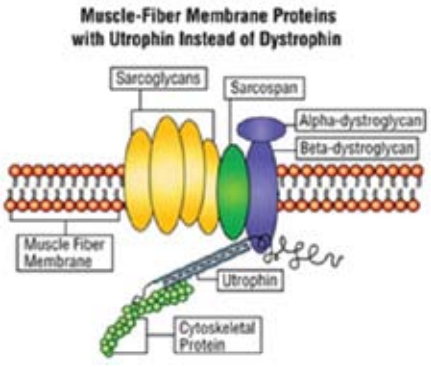
Gene Replacement

For those young people who are unable to benefit from antisense oligomers >20% skipDuchenne proposes an alternative strategy using gene replacement delivered via vectors. There is animal data to show that this method of delivery using AAV vectors could replace the faulty gene with a gene that could either promote exon skipping (AAV U7), replace the gene with a mini gene, or use a combination of vectors to restore the full gene at the membrane.

Action Duchenne is already funding research in this promising area of gene delivery with Royal Holloway University of London. The skipDuchenne research project will build upon this and other research and aim to bring a genetic treatment to those patients unable to benefit directly from AO exon skipping in the next five years.

Utrophin Upregulation

Professor Kay Davies at University of Oxford has pioneered an approach to develop an effective therapy for DMD through increasing the amount of the dystrophin-related protein utrophin in muscle. Utrophin is a protein that is present in muscle cells at the junction where the nerve meets the muscle cell.



They have already shown that utrophin can functionally replace dystrophin in the mouse and dog models of the disease. Upregulation of utrophin has the advantage of being applicable to all patients as it is not mutation-dependent. Furthermore, a small-molecule, orally administered drug can be more easily delivered to all affected muscle types including heart and diaphragm, and would not require the use of an immunosuppressant.

N=1 Clinical Trials

The current clinical trial programme for assessing the efficacy and safety of exon skipping antisense oligonucleotides follows the well established pathway of development. This involves the familiar phases of trial development through pre clinical, Phases I, II, III and IV, to drug marketisation. However, Action Duchenne, along with many others involved with the development of genetic medicines, question whether this framework is now fit for purpose for a rare disease like Duchenne.

Duchenne patients do not present as a homogenous group. Every child will have as a starting point a different dystrophin gene variation that has an impact on the clinical symptoms of the disease. Every Duchenne patient will have polymorphisms in all manner of other genes that may impact on the progression of the condition. Crucially, every child will be exposed to a complex array of environmental, class and cultural factors including diet, housing, education, parental expectations and known medical interventions and support.

Therefore, in clinical trial experiments, it is hugely difficult to achieve any reliable controls within the Duchenne population. It is highly likely that in a clinical trial, patients, for all the above reasons, will respond differently to any one drug. The current drive towards personalised medicines by drug companies is testament to the fact they have been unable for decades to find drugs that will treat a patient population in a uniform way. Consistently they have had to stop expensive trials because they have not been able to present uniform and consistent clinical data for a drug.

The slow and expensive clinical trial programmes for drug development for Duchenne are not just frustrating families, they are not giving us the data we need. There is also an elephant in the room. Many families who see little hope in this

process for their children are turning in increasing numbers to the internet for known drugs, supplements or devices that might help, and they would certainly buy AOs if they could. These are not crazy folk, but many who have seriously researched the subject and have the cash to buy drugs and devices online.

So far the regulatory authorities have been unable to stop this trade, and indeed it is growing faster. Clinicians, researchers and GPs have turned a blind eye or simply do not know that their patients are taking online-sourced supplements or drugs.

Apart from the obvious dangers of such experiments with drugs of unknown quality and guesstimate doses, it means that it is making it even more difficult to test a drug on a group of Duchenne patients. If patients taking these drugs or supplements were excluded from trials then we would certainly not have enough patients, as they are already thin on the ground. Combine this with the knowledge that some Duchenne patients are taking bisphosphonates, betablockers, ace inhibitors and steroids by agreed prescription, and the picture becomes even more complex.

How can the Pharmaceutical Industry Help?

We would suggest that rather than rejecting N=1 experiments, the answer lies in using as a starting point existing N=1 knowledge and patient data of every intervention (legal or not) and clinical assessment for the life of a single patient. New medicines can then be tested for safety and long-term efficacy for an individual patient, irrespective of their genome or current treatment regime. The research team's job would then be to data mine all patients taking that new drug over an extended period, and begin to tease out patterns of medical interventions or genomic suitability that would seem to be working most effectively across the whole Duchenne community. We need to radically rethink clinical trial protocols for Duchenne, and we need a database that holds the medical life history of a patient.

The embryos of such databases do exist in the UK. The DMD Registry and North Star database have been great examples of beginning to collect this information for individual patients. Frustratingly, in the UK we do not have a database in the NHS that could do this for every intervention for every patient, despite massive expenditure on NHS IT infrastructure. However, this is an idea supported by clinicians such as Sir Gordon Duff in his Lancet article.

Clinical experiments therefore become integral to a patient's treatment regime. Also, designing trials that start at Phase III/IV or IV in this way also offers the potential for biotech companies to gain conditional market approval for a medicine while under extensive trial. This could be a real incentive for smaller biotech companies to recoup R&D revenue and support further development. Such trials should be driven by risk management, not a slavish adherence to existing phased protocols.

Clinical trials could be seen as part of the clinical management process of every Duchenne patient, and this would be a marked improvement over the current system.

skipDuchenne – Aims and Objectives

Aims

1) To provide £5m of funding over the next five years to support the skipDuchenne research programme, that will aim to ensure that all patients living with Duchenne have access to a first genetic treatment in the next three to five years
2) To ensure that all those patients in the UK that could benefit from exon skipping using antisense oligomers (AO's) - 83%, have access to AO drugs within the next –three to five years
3) To support the development of an alternative gene replacement technology using vectors that can deliver a gene therapy for those unable to benefit from AO exon skipping

Objectives

1) To work with biotech and iDESC partners to ensure that by 2014 all potential human exon skipping sequences have been optimised
2) To fund further research and work with biotech partners to collect experimental data to show the potential for using two AO drugs to promote double skipping (eg using 51 and 45)
3) To bring together biotech companies, research groups, UK government and the UK and European regulatory authorities to agree funding and a strategy to roll out all exon skipping drugs that could benefit 83% of Duchenne patients directly following the publication of compelling data for the market approval of exon 51 by 2014.
4) To support efforts for regulatory approval for clinical trials using AAV vector technology to deliver gene replacements for patients in the UK.
5) To fund further pre-clinical research and trials for the development of AAV vector gene delivery for patients over the next five years
6) To continue to support alternative ways of delivering exon skipping drugs and enhancing delivery

Nick Catlin is founder and Head of Research of charity Action Duchenne. The charity was set up by Nick and his partner Janet Hoskin and other Duchenne families in 2001 to support and promote innovative research into a cure and effective medicines for Duchenne Muscular Dystrophy. Nick and Janet have a son Saul, aged 11, who has Duchenne.
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