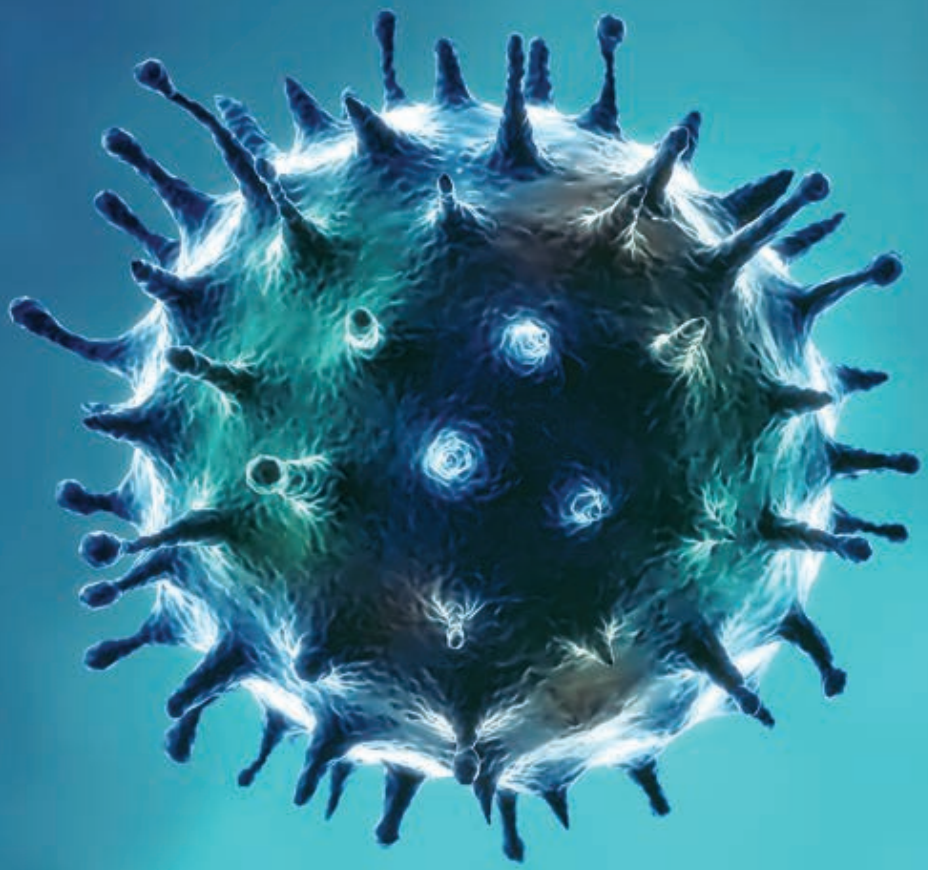
Muscular Dystrophy UK's research magazine
2016

Target Research



AAV therapy in muscle-wasting conditions

How does it work and can it be used to treat muscle-wasting conditions?

Translational research conference

Read the highlights of this year's conference.

Research news

A round-up of news stories from around the world

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Welcome to the 2016 edition of Target Research

As you may be aware, we will now be publishing one edition of *Target Research* every spring.

In this issue, you will be able to read about the use of harmless viruses (AAVs) for the treatment of muscle-wasting conditions such as Duchenne muscular dystrophy and spinal muscular atrophy. This has been written by a post-doctoral researcher, Dr Haiyan Zhou, whose research we are able to support thanks to your generous donations.

A junior scientist, Tayyibah Ali, writes about her Muscular Dystrophy UK-funded PhD project investigating cellular transport in centronuclear myopathy.

Finally, another of our junior scientists, Golnoush Golshirazi, has written about the ninth UK Neuromuscular Translational Research Conference held in March 2016.

As always, you will find a summary of the latest news, including Muscular Dystrophy UK-funded research and research from around the world, as well as updates on the most recent clinical trials. You can find a more detailed version of these and other stories on our website.

I very much hope you enjoy this edition of *Target Research*. Please get in touch, if you have feedback or any questions about any of the topics covered.

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About us

Muscular Dystrophy UK is the charity bringing individuals, families and professionals together to beat muscle-wasting conditions.

- We support high quality research to find effective treatments and cures; and lead the drive for faster access to emerging treatments for UK families.
- We ensure everyone has the specialist NHS care and support they need, with the right help at the right time, wherever they live.
- We provide a range of services and opportunities to help individuals and their families live as independently as possible.

We know we can beat muscle-wasting conditions more quickly by working together and hope you will join us.

AAV therapy in muscle-wasting conditions

Dr Haiyan Zhou, a Muscular Dystrophy UK-funded researcher writes about AAV therapies in muscle-wasting conditions. Dr Zhou is a Senior Research Associate in the laboratory of Professor Francesco Muntoni at The Dubowitz Neuromuscular Centre, Institute of Child Health, University College London.

Adeno-associated virus (AAV)

AAVs are small viruses that infect humans and other primates but that are currently not known to cause any disease. They contain their own DNA and can inject it inside human cells. In fact all viruses need to do this in order to 'survive'. A virus is just made of genetic material packaged in a capsule. It needs to infect a host in order to reproduce.

It is this feature of viruses that led scientists to think that they can be used as vectors, or carriers to deliver a new gene into cells. This approach is called gene therapy. In this approach, some of the viruses' own DNA is replaced by the gene of interest. The virus carries the gene into the cell and injects it inside the cell. The cell then produces the protein encoded by the gene that the virus was carrying. AAVs can infect both dividing and non-dividing cells.

However, there are a few disadvantages in using AAVs for gene therapy. One of these is the small size of their genome which is only 4,700 letters long. Therefore, they can only carry a small size DNA. Another disadvantage is the difficulty in producing them in large amounts in the laboratory.

Even though AAVs are harmless and do not cause disease, they are still foreign material for the body and may cause a mild immune response, especially if they are administered more than once. However, multiple administrations may not be necessary as the effect may be long-lasting (many years) because the virus may persist in the body. The immune system may also attack the protein encoded by the gene that is being transferred because it has never come across it in the past. These problems may be overcome by drugs that suppress the immune response.

To date, 12 naturally-occurring human AAV strains and more than 100 non-human primates' strains have been discovered. Different AAV strains have shown their preference in targeting different tissues. The availability of many strains increases the potential of AAVs as a delivery vehicle for gene therapy.

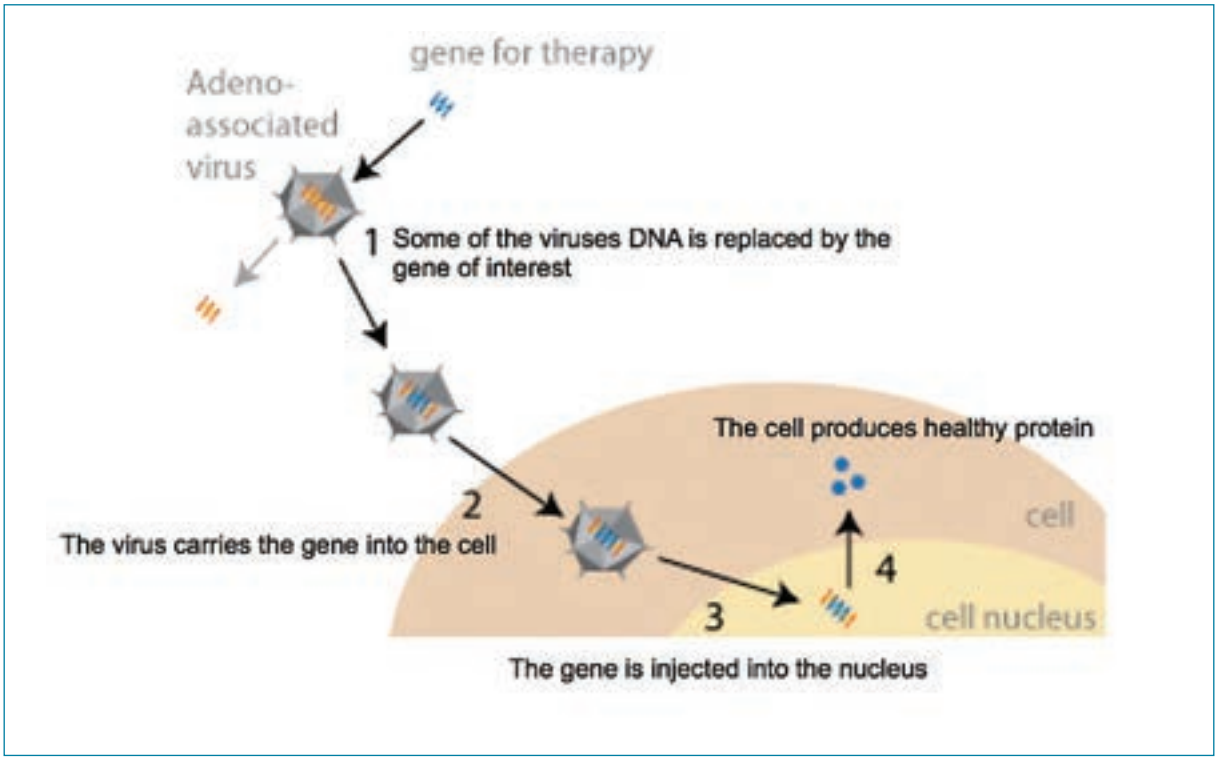


Diagram showing how an AAV is used for gene therapy

AAV therapy in spinal muscular atrophy

Spinal muscular atrophy (SMA) is caused by the loss of a protein called survival of motor neuron (SMN). Motor neurons are nerve cells that carry signals from the central nervous system to the muscle. In 95 percent of patients, the loss of the SMN protein is caused by a mutation in the survival motor neuron 1 (*SMN1*) gene. SMN protein is crucial for motor neuron survival. Lack of SMN protein in the spinal cord causes the spinal motor neurons to die and leads to skeletal muscle atrophy and paralysis.

The *SMN1* gene is small: its messenger RNA is made of only 1,500 letters. This is ideal for AAV gene therapy, as it can be comfortably packaged into the virus.

The primary cell type that is affected in SMA is the spinal motor neuron cells, or nerve cells located in the spinal cord. Therefore, a vector that crosses blood/brain barrier – a tight protective barrier between the blood circulation and the brain – is required in order to treat SMA by injecting the therapeutic agent into the bloodstream.

In pre-clinical studies, the scAAV9 (a certain type of AAV vector) has been shown to efficiently target motor neuron cells in the spinal cord when injected into the spinal canal or bloodstream.

Clinical trials

The vector is also being used as a vehicle to deliver a fully-functional human SMN1 gene into the body in a current gene transfer clinical trial in babies with SMA type 1. The preliminary observations from the ongoing clinical trial are encouraging. The treatment is generally safe and well-tolerated in the patients studied to date. Most encouragingly, there have been significant improvements in patients' survival and motor functions.

AAV therapy in Duchenne muscular dystrophy

Duchenne muscular dystrophy is an X-linked muscle-wasting condition, which generally affects only boys. It is caused by mutations in the dystrophin gene. These mutations disrupt the gene expression and stop the body making dystrophin protein.

Current research

Gene therapy for Duchenne muscular dystrophy, which adds a functional dystrophin gene to the body, has been explored as a therapeutic strategy since the 1990s. In theory, this approach could benefit everyone affected by Duchenne muscular dystrophy regardless of the nature of the mutations. Some AAV strains show high efficiency in getting inside skeletal muscle following injection in the bloodstream and would therefore be applicable as a therapy for Duchenne muscular dystrophy.

However, the full-length dystrophin gene is gigantic, with 14,000 letters in its messenger RNA. This is far beyond the packaging capacity of any AAV vector. Dystrophin mini- or micro-genes have therefore been designed to meet the needs of a smaller but still functional dystrophin gene.

Another approach is to divide the gene in three sections and put the different parts of the dystrophin gene in different vectors. The pieces would then be assembled in the muscle cells and code for a full-size dystrophin protein. This approach is called triple trans-splicing and Muscular Dystrophy UK is currently funding a project in Professor George Dickson's laboratory at Royal Holloway University of London to develop this approach.

Studies of viral gene therapy using mini- or micro-dystrophin genes have shown very encouraging results in mouse and dog models of Duchenne muscular dystrophy. Muscles in limbs, as well as those in the

diaphragm and heart, expressed dystrophin when the AAV was injected in the blood stream in these models. The treated animals exhibited considerable improvement in life span, muscle strength and body mass. Moreover, in mouse model, no immune responses have been observed from dystrophin mini-gene AAV vectors.

Clinical trials

In human trials, there have been variable immune responses. In a phase I clinical trial where an AAV mini-dystrophin gene was injected into muscle, immune response was observed in some patients who carried the pre-existing antibodies to the dystrophin protein. To overcome this in future clinical trials, pre-screening of patients for immune response to dystrophin before admission into trials has been proposed.

Currently a new phase 1 clinical trial using a new AAV strain and a muscle-specific signal to allow the delivery of the micro-dystrophin gene specifically to muscle is being planned. The aim is to test the safety and dystrophin expression in muscle tissue.

In addition to the dystrophin gene itself, viral gene therapies aimed at targeting other genes involved in Duchenne muscular dystrophy have been studied. Clinical trials include the delivery of a gene called GALGT2. This gene allows members of the dystrophin protein complex to be expressed widely in muscle cells and plays an important role in maintaining the integrity of muscle cells. Pre-clinical studies have shown that overexpression of GALGT2 inhibits muscular dystrophy in mdx mice.

Other approaches

A gene therapy approach as a potential treatment for Duchenne muscular dystrophy also includes follistatin gene transfer. Follistatin is a protein that inhibits the myostatin signalling pathway. Myostatin is a negative regulator of muscle mass. Therefore, scientists think that blocking it may increase muscle mass. In fact research has shown this to be the case in animal models.

AAV gene therapy is promising for the treatment of Duchenne muscular dystrophy. However, there are several challenges that have hindered the development of this treatment. These include the enormous size of the gene, the very large mass and body-wide distribution of the target tissue (muscle), the complications associated with immune response, and the complex nature of the condition.

Researchers are improving this method by exploring more functional short dystrophin genes and optimised viral vectors with high delivery efficiency, low immune response and long-term persistence of the delivered gene expression in muscle.

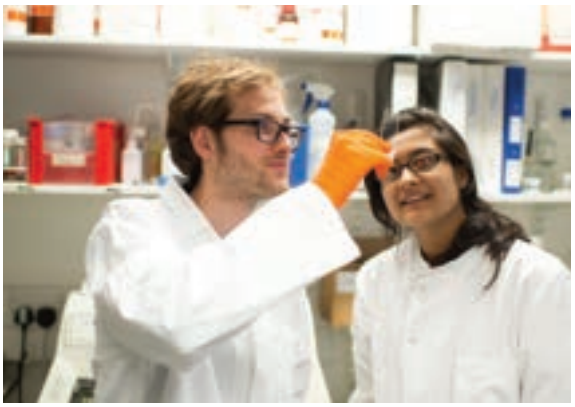
Conclusions

Gene therapy using AAV vectors has enormous potential as a therapeutic approach to replace defective genes that are responsible for conditions such as SMA and Duchenne muscular dystrophy. AAV gene therapy has shown promise in pre-clinical studies in animal models of these muscle-wasting conditions. The AAV vectors are safe and well-tolerated in patients in early phase gene transfer clinical trials. With further optimisation, AAV gene therapy could eventually be developed as a treatment for patients with SMA and Duchenne muscular dystrophy.

Dr Haiyan Zhou

Research news update

Muscular Dystrophy UK-funded research



New insights into the biology of the dystroglycanopathies

New research suggests that genetic defects causing the dystroglycanopathies affect the development of muscles even before birth. According to Dr Sue Brown, a Muscular Dystrophy UK-funded researchers and colleagues at the Royal Veterinary College in London, these findings are important for the development of future therapies for this group of conditions.

Cancer drug could help people with Duchenne muscular dystrophy

Funded by Muscular Dystrophy UK and other organisations, Professor Steve Winder and his team at the University of Sheffield, showed that dasatinib improved muscle function in a zebrafish model of Duchenne muscular dystrophy. This means that dasatnib, a drug already approved for the treatment of certain types of cancer, could also be beneficial for people with Duchenne muscular dystrophy. It is promising that dasatinib is already approved by the FDA for use in people, so trials testing its effect in people with Duchenne muscular dystrophy could start sooner. However, it is important to note that these experiments were performed on zebrafish. Even though it is a great animal model, the results would need to be tested in a higher organism, such as a mouse, before the drug can be tested in human clinical trials.

Some types of motor neurons are spared in spinal muscular atrophy

Scientists funded through a partnership between Muscular Dystrophy UK and the SMA Trust have published new research. They identified which specific type of motor neuron was affected and which type was able to survive in SMA. This knowledge will enable scientists to focus on studying the differences between these two types of motor neurons, which could lead to the development of therapeutic approaches.

Muscular Dystrophy UK-supported scientist gets multi-million pound award from the Wellcome Trust

Professor David Brook and colleagues at the University of Nottingham received a Seeding Drug Discovery Award from the Wellcome Trust. The award is more than £3m to develop a drug for myotonic dystrophy type 1. The project was initiated in 2008 with a small grant from Muscular Dystrophy UK. This is a great example of how a small project grant can generate the knowledge necessary for securing a large drug discovery award that could potentially lead to new therapies.

Muscular Dystrophy UK award allows junior scientist to attend international conference

A junior scientist working in the field of muscle-wasting conditions attended an international scientific conference thanks to a Muscular Dystrophy UK prize. Emma Wilson, from the Institute of Neurology, University College London, said about the prize, "It was a great honour that Muscular

Dystrophy UK deemed my work worthy of their best poster prize and to attend my first international conference. It allowed me to gain invaluable experience that I hope to carry forward into my future scientific career as I continue my research into neuromuscular conditions. Thank you Muscular Dystrophy UK!"

Research news from around the world

A new mouse model of spinal muscular atrophy

Professor Muntoni and co-workers at University College London generated a new mouse model of spinal muscular atrophy (SMA), mimicking the milder forms of the condition. This model will be invaluable in better understanding the condition and designing new clinical trials.

New potential therapeutic target for spinal muscular atrophy

US researchers showed that blocking the activity of an enzyme called JNK3 in a mouse model of spinal muscular atrophy (SMA) greatly improved life-span and growth. These results suggest that blocking the activity of the same enzyme in people with SMA may also improve the symptoms of the condition. JNK3 could therefore be a new therapeutic target for the treatment of SMA.

New blood biomarkers identified for three types of muscular dystrophy

Researchers from Newcastle University, together with Pfizer, have identified four new proteins that are higher in the blood of people with Duchenne, Becker and limb girdle muscular dystrophy (LGMD) than in unaffected people. These potential biomarkers could help to monitor the progression of the conditions, and measure the response to treatment.

New research on muscle stem cells

New research conducted by scientists in the US and France have given insights into why foetal muscle stem cells are better than adult muscle stems cells at repairing muscle tissue. The knowledge generated by this research may have implications for treating different muscle-wasting conditions.

Genome editing in stem cells as a treatment for Duchenne muscular dystrophy

Researchers at the University of California have developed a new approach using genome editing in stem cells. This approach could potentially be used as a treatment for Duchenne muscular dystrophy and could benefit 60 percent of people affected by the condition.

Genome editing improves muscle function in Duchenne muscular dystrophy

Three research articles appeared in the prestigious scientific journal *Science* showing that genome editing technology could improve muscle function in a mouse model of Duchenne muscular dystrophy. This was the first time the technique had been used to treat a genetic condition in a fully-grown animal.

Clinical trials news

Positive results from Duchenne clinical trial

Catabasis Pharmaceuticals have announced positive results from the first part of their MoveDMD trial. The phase I/II trial is testing

the compound CAT-1004 for the treatment of Duchenne muscular dystrophy. The second part of the trial is expected to start imminently.

Tragic death during clinical trial

On 26 January 2016 Akashi Therapeutics' HALO trial, testing the experimental drug HT-100 in Duchenne muscular dystrophy, was suspended. This was because one of the boys on the trial was experiencing serious, life-threatening health issues. On 9 February 2016, the boy died. Akashi Therapeutics is working closely with the FDA to analyse and investigate the situation to better understand the possible causes of this tragic outcome.

Phase II utrophin trial

The long-awaited phase II clinical trial of Summit Therapeutics' utrophin up-regulating compound SMT C1100 has received regulatory approval. SMT C1100 is for the treatment of Duchenne and Becker muscular dystrophy. The protocol of the trial, called PhaseOUT DMD, is now available on the EU Clinical Trials Register.

New clinical trial for potential spinal muscular atrophy drug

PTC Therapeutics has announced the start of a phase I clinical trial to test the safety of a new potential drug, RG7916. This is for the treatment of spinal muscular atrophy (SMA). The aim of the trial is to test whether the compound is safe and well-tolerated in healthy men aged 18 to 45, before it can be tested in people with SMA. It will investigate how the drug is absorbed, distributed and secreted by the body, as well as its mechanism of action.

New Duchenne clinical trial starts in the US for non-ambulatory boys

A new clinical trial testing the effectiveness of the anti-fibrotic compound FG-3019 in boys with Duchenne muscular dystrophy has started in the US. The trial is for boys who are 12 years or older and have lost the ability to walk. FG-3019 has been shown to reduce the formation of scar tissue and significantly improve muscle function in pre-clinical studies.

New clinical trial for the treatment of periodic paralysis

A new clinical trial for the treatment of hypokalaemic periodic paralysis started recruiting participants. The trial is taking place at the MRC Centre for Neuromuscular Diseases at the National Hospital for Neurology and Neurosurgery, Queen Square, London. It aims to understand whether the drug bumetanide may be useful in treating attacks of hypokalaemic periodic paralysis.

New study for myotonic dystrophy type 1 opens for recruitment

A new study investigating the relationship between genetic factors and the effects of myotonic dystrophy type 1 on the brain is now open for recruitment. The study aims to recruit 40 participants, in the West of Scotland, who have the adult-onset form of the condition.

Positive results from the eteplirsen extension study

The results of a phase IIb clinical trial of the exon skipping drug, eteplirsen, have been published in the scientific journal *Annals of Neurology*. The trial, conducted by Sarepta Therapeutics, showed that after three years of treatment, eteplirsen slowed the rate of progression of Duchenne muscular dystrophy amenable to exon 51 skipping. The FDA will now consider whether or not to grant accelerated approval for eteplirsen.

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Understanding cell membrane changes in centronuclear myopathy

Dr Andrew Shevchuk and his PhD student, Tayyibah Ali, from Imperial College London are investigating how mutations associated with centronuclear myopathy (CNM) affect endocytosis. This is an essential cell process that allows cells to take up nutrients and replenish their cell membranes. Findings from this study will increase our understanding of the role of endocytosis in CNM and could help us identify new targets to develop therapies in the future. Tayyibah writes about her project:

I study CNM using a novel microscopy technique. CNM is characterised by the weakness and wasting (myopathy and atrophy) in skeletal muscle cells, which are used for movement. An important feature of CNM is the location of the nucleus in muscle cells, which can be seen under a microscope. In normal circumstances, the nucleus is found at the edge of the rod-shaped muscle cells (Figure 1), but in CNM the nucleus is located in the centre of these cells Figure 2). (This is where the name for this myopathy is derived.) CNM is caused by mutations in a number of genes, including one known as Dynamin 2. The gene is made up of different segments, which have different functions. Mutations can occur in different segments of the gene causing effects on the protein it codes for.

The gene codes for a protein called Dynamin 2, which is involved in a process known as endocytosis. This process allows for the transportation of substances such as nutrients, hormones, and other essential proteins into the cell (see Figure 3 on p14).

This protein also helps in regulating the cell skeleton, which helps cells maintain their shape and internal organisation. It also provides mechanical support for cells to divide or move.

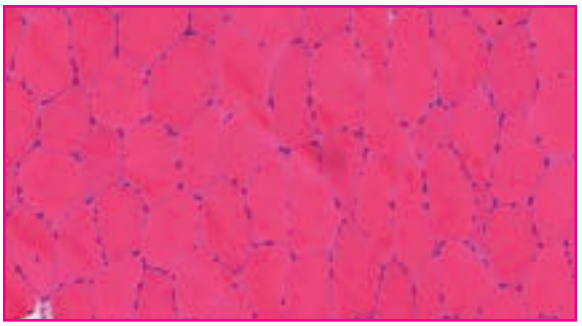


Figure 1. Healthy muscle cell (cross-section)
Photo credit: © Professor Janice Holton, UCL Institute of Neurolgy

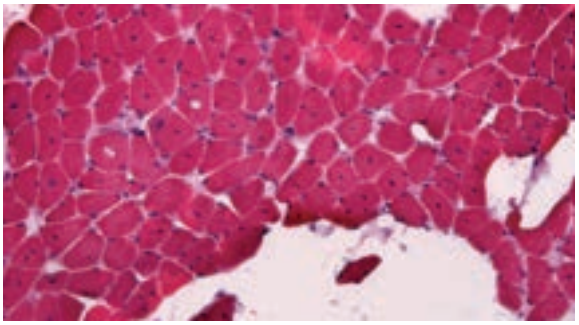


Figure 2. CNM muscle cell (cross-section)
Photo credit: Jensflorian

During endocytosis, substances that are to be taken up by the cell are bound to receptors, which are specific for that substance. This triggers the recruitment of a range of proteins, which allow for the uptake process to begin. The substance is surrounded by a cage-like structure that pulls the cell membrane containing the substance bound for internalisation into a pit, which begins to curve inwards and form a ball-shaped sac, called vesicle, by narrowing at the neck (see Figure 3 on p14).

Here, Dynamin 2 is recruited to the 'neck' to separate the vesicle from the cell surface, so it can travel further into the cell and deliver the substance it carries to its destination.

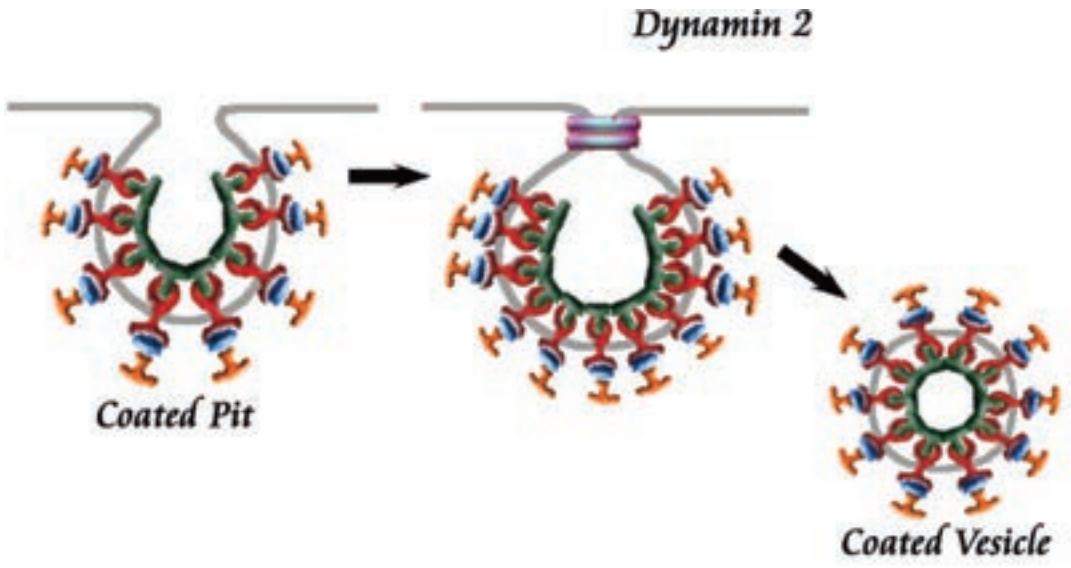


Figure 3. Endocytosis

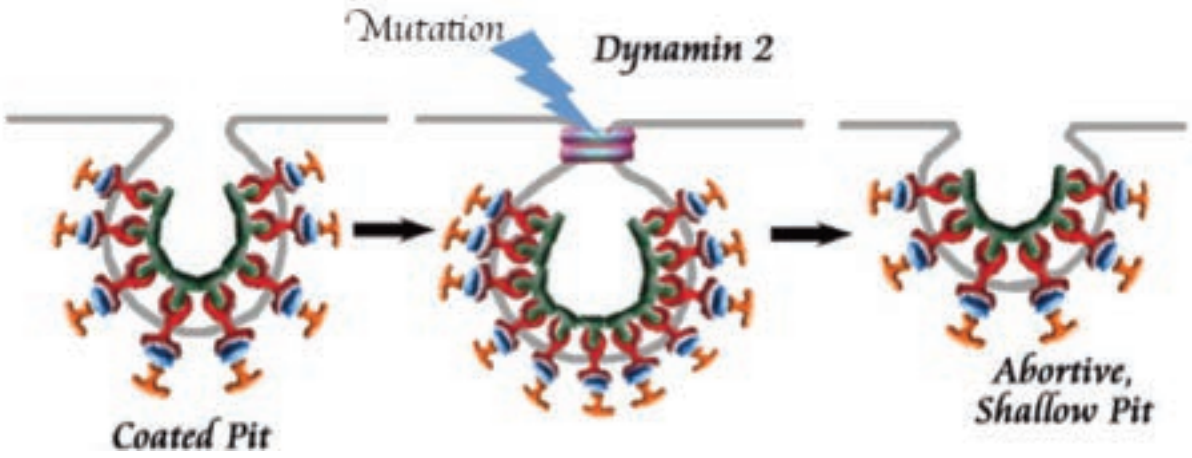


Figure 4. Abortive shallow pit formation caused by mutations in the Dynamin 2 gene

The challenge in studying endocytosis is the combination of multiple techniques needed to visualise the process. I am using a technique, called combined Scanning Ion Conductance and Fluorescence Confocal Microscopy. Developed by Dr Shevchuk in our laboratory, this is a nanoscale imaging technique that is able to scan the surface of cells and record a high-resolution time-lapse image of cell topography.

This image is simultaneously captured with fluorescent imaging, which visualises fluorescent proteins that are used to label molecular processes and structures. It allows for the observation of protein expression at the cell membrane. This is a powerful tool to visualise individual endocytic events in real time taking place on the cell surface in living samples.

So far the study has yielded new results which show that when mutations occur in the Dynamin 2 gene, this has an effect on the length of time is takes for a pit to form and for the pit to be separated from the cell surface. We have found that mutated Dynamin 2 protein is recruited to the cell surface at earlier than expected time points, and attempts to separate pits from the cell surface. It has been shown that in individual endocytic events, pits take longer to form.

At the late stages, these become abortive, i.e. the pit does not internalise successfully (Figure 4). The degree of pit abortion varies between different mutations in the Dynamin 2 gene.

The next steps in the study are to compare these with data gathered from other mutations and observe the effect this has on substance uptake by the cells. The aim of the study is to better understand the mechanisms that are perturbed by the rise of these mutations and identify alternative ways in which cells could compensate for this alteration in substance uptake ability. A better understanding of disease mechanism will be useful for future drug development work and may help identify new therapeutics targets for future interventions.

More information about the project can be found on our website at:
www.musculardystrophyuk.org/grants/shevchuck

A major step forward

As you might have already read on our website, on 15 April 2016, NICE announced that it was recommending Translarna for funding on the NHS in England, to treat Duchenne muscular dystrophy.

This was a historic moment. Translarna is the first drug coming to the clinic that addresses a specific type of genetic mutation in the dystrophin gene. The decision was the end of a long journey towards the development of a treatment for a rare condition, taking on all the challenges of carrying out clinical trials and demonstrating the drug's benefit to the regulators.

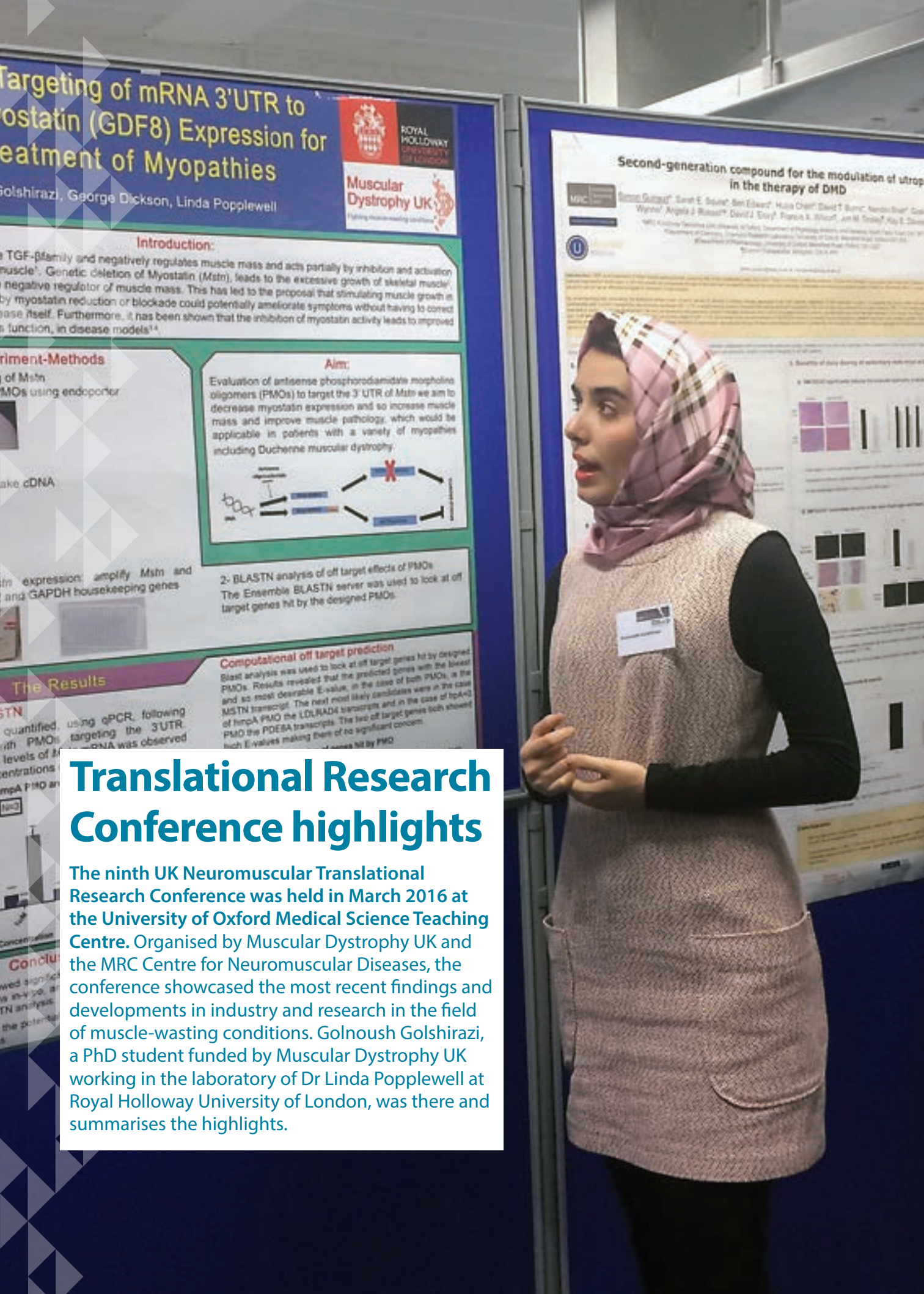
The company, PTC Therapeutics, started the clinical trials more than 10 years ago and it was a huge learning curve for the whole community. There was a lot to learn about how best to design these studies in order to understand whether the drug had a benefit for the boys.

However, the results of the clinical trial for Translarna have been persuasive enough for the NHS to agree to a managed access agreement (MAA). This means the drug is initially available for five years, after which its benefit will be assessed again.

Going forward, what can we learn from this? First of all, there is still a lot to learn about Duchenne muscular dystrophy – how it progresses and why there is such great variability between the affected individuals. Secondly, as the benefit of the first generation drugs might not be as great as we wished for, we need to be able to measure small differences in muscle health and function. Thirdly, we need to still invest heavily into research to develop improved second and third generation drugs to explore the full potential of those technologies that are currently in clinical trial.

And we need to make sure that the regulators better understand the nature of the condition and the urgency of bringing treatments to the clinic not only for Duchenne muscular dystrophy but for all muscle-wasting conditions. Only then will there be processes put in place for families to have access to first generation treatments while further data on their benefit can be collected. An MAA is certainly the right way forward and the charity is proud to have played a vital role in making this possible.

Dr Marita Pohlschmidt
Director of Research,
Muscular Dystrophy UK



Translational Research Conference highlights

The ninth UK Neuromuscular Translational Research Conference was held in March 2016 at the University of Oxford Medical Science Teaching Centre. Organised by Muscular Dystrophy UK and the MRC Centre for Neuromuscular Diseases, the conference showcased the most recent findings and developments in industry and research in the field of muscle-wasting conditions. Golnoush Golshirazi, a PhD student funded by Muscular Dystrophy UK working in the laboratory of Dr Linda Popplewell at Royal Holloway University of London, was there and summarises the highlights.

The UK Neuromuscular Translational Research Conference 2016 provided a platform for scientists, clinicians and industry partners to come together to share and discuss their latest findings.

The conference focused on three main sessions: genomic therapies, next generation biomarkers and big data. There were also poster guided tours and poster flash sessions led by eminent scientists.

Genomic therapies

The most recent findings on research into spinal muscular atrophy (SMA), facioscapulohumeral muscular dystrophy (FSHD) and Duchenne muscular dystrophy:

Muscular Dystrophy UK-funded researcher, Professor Francesco Muntoni, from University College London, presented recent findings on the role of survival motor neuron protein (SMN) and how its lack causes SMA. He also discussed the use of gene therapy approaches as potential treatments for SMA. (See the article from Dr Haiyan Zhou on p5 for more information about gene therapy approaches to treat SMA.)

Dr Julie Dumonceaux, from Institut de Myology, Paris, talked about the genetics of FSHD and how an increase in the expression of a gene called DUX4 could have a toxic effect in muscles and cause the condition. She presented recent work in targeting the DUX4 gene in order to block its expression and showed how such an approach could offer an effective therapeutic approach for FSHD.

Next generation biomarkers

This session covered advances in imaging technologies for Duchenne muscular dystrophy and Charcot-Marie-Tooth (CMT) disease.

Professor Andy Blamire, from Newcastle University, introduced the BIOIMAGE-NMD programme, which involves next generation in vivo imaging technologies for Duchenne muscular dystrophy and other rare muscle-wasting conditions. This technology offers a non-invasive way to assess tissue structure and it can reveal changes in tissue structure that cannot be seen in conventional muscle MRI. Ongoing work is focusing on translating this work to clinical scanners for human studies.

Professor Eric Hoffman, from ReveraGen BioPharma, Children's National Medical Center, Washington, presented his work on using blood biomarkers in drug development and how they could be used to monitor the mode of action of drugs. Advances are being made in finding biomarkers for people with Duchenne muscular dystrophy and inflammatory bowel disease, who are treated with corticosteroids such as prednisone. These biomarkers are now integrated into the clinical development programme of the anti-inflammatory drug vamorolone/VBP15 to measure safety and dose selection as well as confirmation of clinical outcome measures. Biomarkers are invaluable in helping clinicians to see how well the body is responding to a treatment.

Big data

Dr Ivo Gut, from the National Centre for Genomic Analysis (NCGA), Barcelona, discussed how analysing the hereditary information encoded in the DNA of an organism in its entirety is becoming increasingly important in biomedical research. This is because when the genome is analysed as a whole, interactions between genes can be studied. However, this type of approach generates a huge amount of data and there are challenges associated with handling such data. Dr Gut discussed how a set of standards and collaboration between laboratories could increase the value of the data generated in this way.

Professor Peter Robinson, from Charité Hospital, Berlin, presented on the potential of using genome sequencing to investigate non-coding variation of genes and how this could help diagnose muscle-wasting conditions. He and his team have developed a whole genome analysis framework, called Genomiser, which interprets non-coding variants in genetic conditions. Genomiser predicts the importance of a variation in the non-coding genome and, for the first time, offers the chance to detect and discover regulatory variants in genetic conditions.

Professor Henry Houldon, from University College London, Institute of Neurology, talked about a programme called Neuro-GeCIP. According to the programme, around 8,000 samples of DNA will be collected over the next two years from families with neurological and neurodegenerative conditions. These samples will then be used for whole genome sequencing. The aim is to improve our understanding of the genetics of rare neurological conditions and identifying new key biological pathways. This could allow scientists to identify new genes causing these conditions, better understand the disease mechanisms and develop potential therapies in the future.

The John Newsom-Davis Lecture

This was given by Professor David Beeson, from the University of Oxford, on congenital myasthenic syndromes. His talk covered the biology of the condition and how next generation sequencing had helped the discovery of new genes involved in the condition. He discussed the importance of tailored treatments to particular syndrome sub-sets. This was demonstrated with examples of dramatic patient improvement with tailored treatments.

Prof Beeson showed some remarkable videos of patients whose walking abilities dramatically improved after taking ephedrine and/or salbutamol. Prof Beeson stressed that these conditions could be treatable if they were targeted in the right way.

Poster presentations

Scientists presented their most recent findings through poster and platform sessions. The guided poster sessions were also a success with many interesting and high quality posters presented.

As a Muscular Dystrophy UK-funded PhD student, I presented a poster on targeting myostatin as a therapeutic approach for a wide range of myopathies, including Duchenne muscular dystrophy. Myostatin is a negative regulator of muscle mass. Therefore, blocking mysostain in individuals with myopathies could improve the symptoms of the condition. I designed and tested 'molecular patches' to block the production of mysotatin. My work has shown that these molecular patches are able to successfully block the production of mysostatin in cells grown in the laboratory and highlights their potential for therapeutic purposes.

Glossary

AAV – AAV (Adeno-Associated Virus) is a small virus, which infects humans and some other primate species. AAV is not currently known to cause disease and causes a very mild immune response. These features make AAV a very attractive vehicle for delivering genes into cells. To date, AAV vectors have been used in phase I and phase II clinical trials for the treatment of Duchenne muscular dystrophy, limb girdle muscular dystrophy types 2C and 2D and other non muscle-wasting conditions, including cystic fibrosis, haemophilia and Parkinson's disease.

Animal model – Animals (usually mice or rats) with conditions similar to those affecting humans, which can be used to study disease processes and test potential therapies. The animals have a similar gene mutation as the one present in the human condition. The mutation is either naturally occurring in the animals or they induced in the laboratory to have the mutation.

Biomarker – A biological substance found in blood, urine or other parts of the body that can be used as an indicator of health or disease. A biomarker may be used to help clinicians diagnose a condition and monitor how it is progressing, but can also be used to see how well the body responds to a treatment.

DNA – Deoxyribonucleic acid (DNA) is the molecule that contains the genetic instructions for the functioning of all known living organisms. The main role of DNA molecules is the long-term storage of information. DNA is often compared to a set of blueprints, a recipe, or a code, since it contains the instructions needed to construct other components of cells, such as proteins. DNA is divided into segments called genes.

Dystrophin – The protein missing in people who have Duchenne muscular dystrophy and reduced in those who have Becker muscular dystrophy. The dystrophin protein normally sits in the membrane that surrounds muscle fibres like a skin, and protects the membrane from damage during muscle contraction. Without dystrophin the muscle fibre membranes become damaged and eventually the muscle fibres die.

Exon skipping – A therapeutic approach currently in clinical trial for Duchenne muscular dystrophy. It involves small pieces of DNA called 'molecular patches' which mask a portion of a gene where there is a mistake, or mutation. The name comes from 'exon' which are the segments that genes are divided into. For example, the dystrophin gene (which is affected in Duchenne muscular dystrophy) is divided into 79 exons. It is called 'skipping' because the molecular patch causes the body to ignore or skip-over an exon.

Gene – Genes are made of DNA and each carries instructions for the production of a specific protein. Genes usually come in pairs, one inherited from each parent. They are passed on from one generation to the next, and are the basic units of inheritance. Any alterations in genes (mutations) can cause inherited disorders.

Gene therapy – Treatment of a disease by introducing a new gene into a cell. The new gene may be used to replace a function that is missing because of a defective gene. Viruses are often used to deliver the new gene into the cells.

Genome – The complete set of genes in a person or organism.

Immune response – The body's response to 'foreign' material, such as bacteria or a virus. The immune system includes certain types of white blood cells. It also includes chemicals and proteins in the blood, such as antibodies.

mdx mouse – A mouse model of Duchenne muscular dystrophy. These mice have a mutation in the dystrophin gene – the gene that is mutated in boys with Duchenne. The muscles of these mice have many features in common with the muscles of boys with Duchenne.

Mutation – A permanent change in the DNA code that makes up a gene. Depending on where the mutation occurs, and the type of mutation, they can either have no effect or result in genetic diseases such as muscular dystrophy. Mutations can be passed on from generation to generation.

Neuron – Also called a "nerve cell". The neurons are responsible for transmitting messages throughout the body. They are important for both involuntary functions (like your heartbeat) and voluntary functions (like walking).

Protein – Proteins are required for the structure, function, and regulation of the body's cells, tissues, and organs. They are the building blocks of our bodies. Each protein has unique functions. Proteins are large molecules composed of one or more chains of amino acids in a specific order. The order is determined by the gene that codes for the protein.

SMN gene (Survival Motor Neuron gene) – Mutations in the SMN gene are the cause of some forms of spinal muscular atrophy (SMA). There are two types of SMN genes- SMN1 and SMN2.

SMN protein – Survival motor neuron protein. Produced by the SMN genes and reduced in individuals with spinal muscular atrophy. This protein is necessary for normal motor neuron function. Evidence suggests that a lack of SMN might also directly affect muscle cells.

Stem cells – Cells that have not yet specialised to form a particular cell type, and can still become muscle cells or other types of cell.

Trial – An experimental run. Testing certain therapies on animals or humans, for example.

Utrophin – A very similar protein to dystrophin. Low levels of utrophin are present in everyone – including individuals with Duchenne muscular dystrophy – but in insufficient amounts to compensate for the loss of dystrophin.

Vector – A vehicle for transferring genetic material into a cell. Currently, the most common vector for gene therapy is a virus that has been genetically altered to carry normal human DNA. Non-viral vectors include plasmids into which specific genetic material has been added.

Zebrafish model – A tropical freshwater fish belonging to the minnow family. There are many advantages of using zebrafish to study human disease and development: Firstly, zebrafish are small in size, and are easy to keep and breed. They are more similar to humans than you think; many genes are shared between humans and zebrafish, including the genes used to make muscles. The genes of zebrafish can be modified, this means we can create mutations in genes which cause human diseases, such as muscular dystrophy. Importantly, zebrafish embryos are transparent, so we can easily observe their muscles developing. Finally, the embryos can be used too look for drugs which may prevent or slow the progression of a disease.

References and further information

Please contact us at **research@musculardystrophyuk.org** if you would like any further information or a link to the original research article. The articles are written in technical language with no summary in layman's terms; and some may require a payment before they can be viewed.

Disclaimer

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Muscular Dystrophy UK

Fighting muscle-wasting conditions

Muscular Dystrophy UK is the charity bringing individuals, families and professionals together to beat muscle-wasting conditions. We're providing a range of services and opportunities to help people live as independently as possible.

We're working with world-class researchers and won't stop until we find treatments and cures for all our conditions.

We're a first port of call for 4,000 families in the UK newly-diagnosed with muscle-wasting conditions every year. We offer a personal support system at their point of need, with a specialist helpline and free information.

For over 50 years, we've been here for families. This is only possible thanks to donations, gifts in wills and family fundraising.

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