Muscular Dystrophy UK's research magazine

Issue 2 of 2015

Target Research

Genome editing

How does it work and can it be used to treat neuromuscular conditions?

Translational Research Conference

This year's conference showcased the latest developments in neuromuscular science

Research news

A round-up of news stories from around the world

Muscular Dystrophy UK
Fighting muscle-wasting conditions

Come to our 2015 conferences

You'll get to meet other families living with muscle-wasting conditions, take part in numerous workshops and find out about other work we are doing.

Ticket costs include lunch, morning and afternoon refreshments. There will be a crèche available for children up to the age of 16.

Get your tickets today at www.musculardystrophyuk.org/conferences

Our National Conference and AGM in London

Saturday 26 September at the Holiday Inn London Kensington Forum, 9.30am–4.30pm

As always, our President, Sue Barker will present our President's Awards.

The programme includes workshops on:

- physiotherapy and exercise
- psychology
- Trailblazers
- research updates
- care advisors
- emerging treatments.

Tickets cost £35/family, £15/adult and £5/child under 16.

There are some disabled parking bays at the front of the hotel and a NCP car park at the side of the hotel. Further parking is available close by.

For further information, contact Maureen at maureenw@musculardystrophyuk.org

Our Scottish Conference in Glasgow

Saturday 24 October at the Beardmore Hotel and Conference Centre, 9.30am–4.30pm

The popular Scottish Kite Awards will also be presented.

The programme includes workshops and advice surgeries on:

- transition
- planning short breaks, accessible travel
- research updates
- Carers Scotland
- Scottish Disability Sports
- Scottish Trailblazers and Campaigns
- advocacy support
- care advisors
- physiotherapy
- Family Funds.

Tickets cost £30/family, £10/adult and £5/child between 12 and 16 (children under 12 go free).

For further information, contact Lyn at lyni@musculardystrophyuk.org

Welcome

Welcome to the second edition of *Target Research* for 2015. This issue focuses on a new and exciting technique called 'genome editing' that has revolutionised the molecular biology field. The technique allows making changes to the DNA by adding, removing or replacing parts of it. Therefore using this technique, disease-causing mutations in the DNA can be corrected. Our feature article explains how the technique works and its potential to treat muscle-wasting conditions.

You can also read about the highlights of the eighth UK neuromuscular translational research conference that was held on the 19 and 20 March 2015 in Newcastle. This year's conference was attended by a large number of scientists from all over the world. It was a great platform to help drive forward translational research into muscle-wasting conditions.

As always you will be able to find a summary of the latest news, be it newly published research papers in the field or developments in clinical trials for new potential drugs. You can find a more detailed version of these news stories and others on our website.

I hope you enjoy this edition of *Target Research* and please get in touch with some feedback or if you have any questions about any of the topics covered.

Dr Özge Özkaya
Editor, Target Research
020 7803 4813
research@musculardystrophyuk.org
@MDUK_News

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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.

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FundRaising Standards Board

Genome editing

Genome editing is a new and exciting molecular biology technique that has the potential to be developed into therapies for genetic diseases – such as muscle-wasting conditions – that are caused by mutations. The technique can be used to make precise targeted changes to the DNA of living organisms, and can correct genetic mutations by adding, removing or replacing parts of the DNA.

There are more than 60 different types of muscle-wasting conditions. Although they are regarded as rare or very rare, all together they affect more than 70,000 people in the UK. They are all genetic conditions and are caused by errors – or mutations – in the DNA code.

Scientists have been trying for many years to find ways to correct these mutations. One possible approach is to add a normal gene to the cell alongside the faulty one. This approach is being explored for conditions such as Duchenne muscular dystrophy. Scientists are trying to make use of harmless viruses called AAVs to carry the healthy copy of the dystrophin gene to the muscle cells.

In some instances, a mutation in the DNA code results in the production of a toxic protein. The approach that is adopted in this case is called 'gene silencing' and aims to destroy the faulty message that encodes for such proteins.

However, with a newly developed technique, a person's own mutated gene that is causing the condition can be corrected. It is called 'genome editing' and has revolutionised the molecular biology field.

How does genome editing work?

Genome editing allows adding, removing or replacing parts of a person's own DNA. It uses enzymes called 'endonucleases' or 'molecular scissors' that have the ability to cut the DNA at precise locations. After the DNA has been cut, the cell will repair the cut by joining the two ends of the DNA together. Alternatively, the cell can be provided with a DNA sequence, which can then be inserted at the break point (see Figure 1).

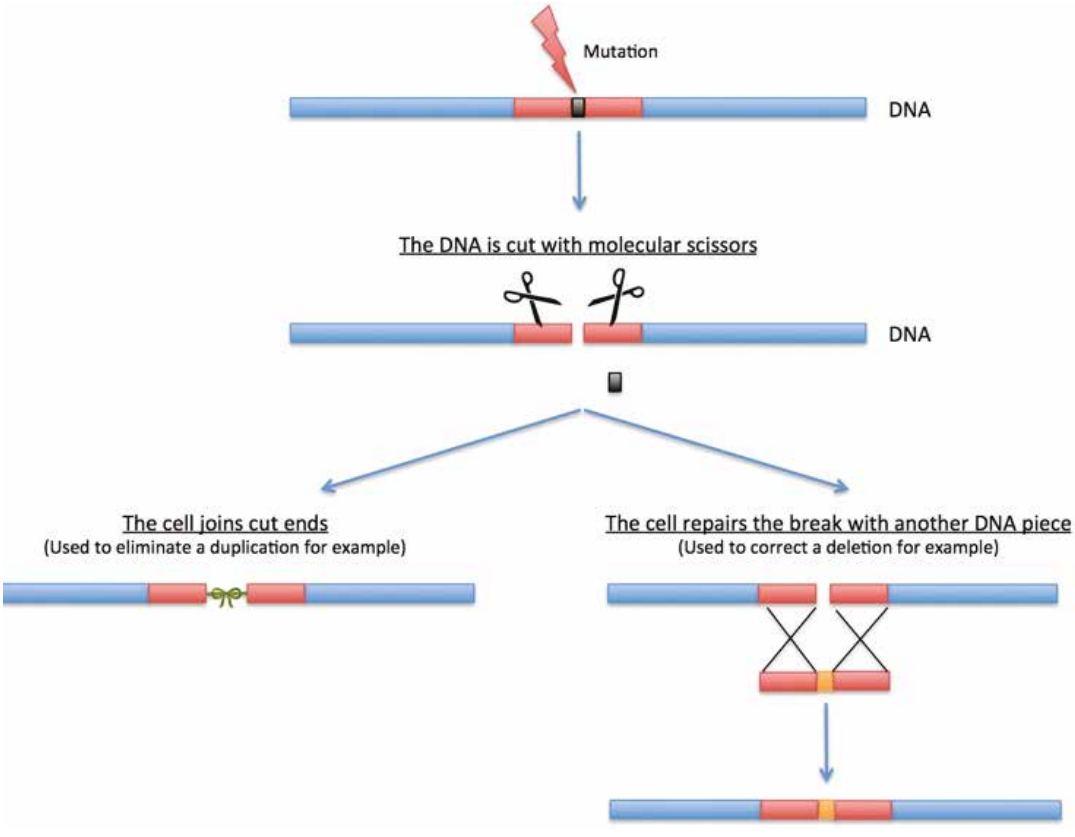


Figure 1: Molecular scissors cut around the mutation in the DNA. The cell then repairs the cut simply by joining the cut end or by using another piece of DNA.

What are the different genome editing techniques?

There are three main techniques that can be used to edit or change genomes. They all use DNA cutting enzymes or endonucleases but they differ in the way these enzymes are directed to the precise location in the DNA.

Zinc-finger nucleases

Zinc-finger nucleases recognise specific locations in the DNA through proteins called zinc-finger proteins. They are given this name because they curl around a zinc ion to form a shape that attaches itself to the DNA. Each zinc-finger binds three specific letters in the DNA, for instance 'ATG'. Therefore, by combining a number of specific zinc-fingers in a protein, a very specific region of the DNA can be targeted. For example, using four zinc-fingers that each recognise a different set of letters – say ATG TTG AAC TTC – the DNA scissors can be carried to the one and only location in the DNA where the message reads ATG TTG AAC TTC. However it is difficult and time consuming to engineer proteins that carry a specific sequence of zinc-fingers for each gene target. This has been an obstacle for the widespread use of this technique (see Figure 2).

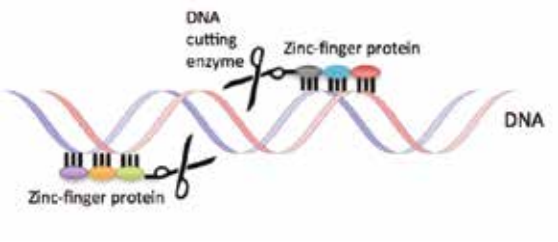


Figure 2: Zinc-finger proteins guide the molecular scissors to precise locations in the DNA.

TALENs (transcription activator-like effector nucleases)

In this case, particular amino acid repeats called TALE (transcription activator-like effector) repeats are used to carry the molecular scissors to the desired site in the DNA. Different combinations of several TALE repeats are used to recognise specific regions in the DNA. This strategy is very similar to zinc-finger nucleases but is simpler and cheaper to design. However, they can still be difficult to produce (see Figure 3).

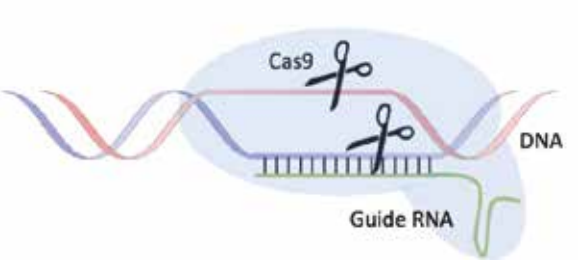


Figure 3: The molecular scissors are directed to a precise location in the DNA by a combination of TALE repeats.

CRISPR/Cas9 system

This is the latest method to edit genomes and is currently used by a very large number of laboratories across the world for different applications. The main difference is that it does not rely on proteins to recognise regions in the DNA but uses a small RNA molecule. RNA is very similar to DNA and is also made of four letters, A, C, G and U (instead of T). Small RNA molecules of a specific sequence can be engineered with the desired sequence, for example AUG UUG AAC UUC. They will then go and bind to the DNA where this particular sequence is found guiding the molecular scissors to that sequence. It is much easier and cheaper to design and can be used to target more than one gene at a time (see Figure 4).

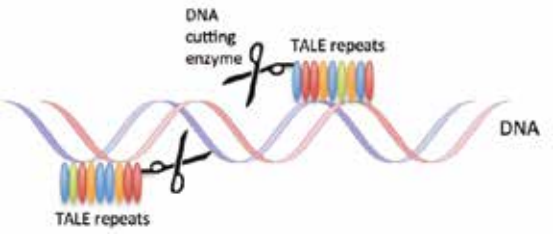


Figure 4: An RNA molecule guides the Cas9 nuclease to a specific location in the DNA.

Genome editing and muscle-wasting conditions

Muscle-wasting conditions can be caused by different types of mutations. Sometimes an additional piece of DNA is added into a gene – this type of mutation is called an insertion. Other times, a chunk of DNA is missing from a gene, and this is called a deletion. Finally, a piece of DNA might be repeated in a gene, this is called a duplication. In all three cases, the reading frame of the gene can be disrupted and no normal protein is produced. In addition, a single letter change in the DNA (a point mutation) might result in a premature stop signal and no full-length protein is made.

Genome editing could be used to correct all of the mutations described above. For example, in the case of a duplication or an insertion, the extra piece of DNA could be cut out and the DNA repaired by the cells. In the case of a point mutation, the mutated part of the DNA could be swapped with the correct sequence, and in the case of a deletion the missing piece of DNA could be inserted back in.

Duchenne muscular dystrophy, which can be caused by any one of the mutations explained above, could benefit from genome editing, so the cells revert to making fully-functional dystrophin protein.

How could genome editing be used to treat muscle-wasting conditions?

Genome editing could be used to correct mutations in affected tissues, for example in muscle. In this case, the idea is to use muscle precursor cells extracted from the muscle tissue, correct the genetic fault in the laboratory and implant the cells back into the muscle tissue. These types of experiments have already been done on animal models of Duchenne muscular dystrophy and it is hoped that they could be tried in humans in the future (see *Genome editing to restore the production of dystrophin* on page 11 and *Professor George Dickson's research project* on page 8).

Genome editing has also been tested in animal models as a potential therapy for muscle-wasting conditions called mitochondrial myopathies caused by mutations in the mitochondria. Mitochondria are the 'energy factories' of cells. They have their own DNA encoding for proteins, important for energy production. Mutations in mitochondrial DNA particularly affect the muscle tissue and the brain because of their high-energy demand. A version of genome editing could potentially be used to prevent the transmission of mitochondrial disease to future generations. Most people affected by mitochondrial disease have a mixture of mutated and healthy mitochondria in their cells. A special type of endonuclease that target mitochondrial DNA is used to specifically cut the DNA of the mutated mitochondria, eliminating the faulty type. This technique has already been tried in mice, and scientists are hopeful that it could potentially be used in the future as a therapeutic option for women with – or who have the potential to transmit – mitochondrial disease (see *Genome editing and mitochondrial disease* on page 11).

Although genome editing has been extensively studied in human adult cells and animal embryos, it has recently been tried in human embryos for the first time (see *Editing the genome of human embryos* on page 11). The advantage of this approach is that the mutation is corrected at embryonic stage and all the cells that derive from the fertilised egg have the corrected gene.

However, there are ethical concerns of using such a technique on human embryos as the alteration would be permanent and passed down the generations. The UK

has a comprehensive and well-established regulatory framework for the use of human embryos in research. The genetic modification of embryos can only be done with a licence from the Human Fertilisation and Embryology Authority (HFEA). The UK guidelines only permit experiments with human embryos as long as they are not allowed to grow for more than 14 days. Embryos modified by genome editing, therefore, could not be implanted back into a mother's womb under the current law.

Drawbacks of genome editing

One problem with each of the three techniques of genome editing is that they are not as specific as the scientists originally thought. Even though they are all designed to recognise a very specific region in the DNA, they can sometimes cut the DNA in unintended places. This could mean that unwanted mutations can be introduced in the genome at random places and cause more harm than good.

Conclusion

Genome editing is a powerful molecular biology tool that has the potential to correct disease causing mutations in the human genome. However, it is still in its infancy and far from being ready to be used in the clinic. Scientists are constantly working on ways to improve it, and in the meantime it is providing them with tremendous insight in understanding the functioning and interactions between genes in the laboratory.

Professor George Dickson's research project

Muscular Dystrophy UK, in partnership with five other charities, is funding a research project into genome editing in the laboratory of Professor George Dickson at Royal Holloway University of London.

The aim of the project is to develop molecular tools required for the technique and to test them in cell culture models – and mouse models – of Duchenne muscular dystrophy.

This approach has the potential to be beneficial for all boys with Duchenne muscular dystrophy regardless of their mutation. It has the potential to treat people with Becker muscular dystrophy and to be adapted for the treatment of other muscle-wasting conditions.

Professor Dickson said: "Recent astonishing advances in science have yielded 'molecular scalpels' and 'repair patches' to specifically cut open and correct the damaged X-chromosome in Duchenne muscular dystrophy patients' cells. With this new funding from Muscular Dystrophy UK, the exciting and pioneering technology of genome surgery will produce a universal gene repair system that could be applied to all types of Duchenne and Becker muscular dystrophy mutations."

Genome editing – the 'holy grail' of gene therapy

Some of you might remember the news story that broke some weeks ago about a team of researchers in China using genome editing to change the DNA in human embryos. The research was aimed at correcting a mutation in the gene causing β-thalassaemia, a potentially fatal blood disorder.

The news sparked a fierce debate in the scientific community about the ethical implications of such work. Researchers are split in their opinion, with some saying the technology has the potential to develop into a cure for genetic conditions while others are seriously concerned about the ethics.

The key concerns are around germline modifications, which are the introduced genetic changes in the embryo. These modifications will be present in every cell of the body including the germ cells, and would be inherited. They could have unpredictable consequences not only for the individual but also for future generations.

Whatever potential or risk scientists anticipate this technique might have, the common view is that currently it is far too unsafe even to consider developing for clinical use.

However genome editing could also be used to repair genetic defects in cells of adult individuals. There are few ethical issues attached to this, and there is huge potential for it actually to represent a cure.

Most of the gene therapy approaches developed so far are transient and would last only for a certain period of time. But genome editing ultimately repairs the genetic defect and each cell that would derive from such a repaired cell would carry the repaired gene. For me, this is the 'holy grail' of gene therapy.

Unfortunately the technique is still far from being safe to be used in adult cells and a lot of research will need to go into its further development before we can think about clinical trials.

A number of other promising treatment approaches are currently being tested in clinical trials, most of which – at best – have the potential of halting the progression of muscle-wasting conditions. So let's not lose sight of our final goal to find cures, and let's continue to invest in a range of technologies that might be able to do this.

Dr Marita Pohlschmidt
Director of Research, Muscular Dystrophy UK


DNA molecule

Research news

Genome editing


DNA

Genome editing to restore the production of dystrophin

Researchers at Duke University in the USA have managed to restore the production of dystrophin protein in cultured muscle cells using the groundbreaking technique known as genome editing. They extracted muscle cell precursors from people with Duchenne muscular dystrophy and implanted them back into mice after correcting the mutation in the dystrophin gene. The researchers saw that the mice were able to produce human dystrophin protein. Although the technique is still in its infancy, it could potentially be used one day to treat people with Duchenne muscular dystrophy.

Genome editing and mitochondrial disease

A different application of genome editing technology has been used to selectively eliminate mutated mitochondria in mouse embryos while sparing the healthy ones. The researchers transplanted the embryos back into the mother's womb. The mice gave birth to pups carrying only the non-targeted type of mitochondria and they themselves gave birth to a second generation of offspring carrying only the non-targeted type of mitochondria. This suggests that this technique could potentially be used to treat or even cure mitochondrial disease.

Editing the genome of human embryos

In a world first, Chinese scientists have used genome editing technology in human embryos. The team was aiming to correct a mutation in the gene causing ß-thalassaemia, an inherited blood disorder. The results of the study showed that the technique is not working efficiently because the genetic mutation was successfully corrected in only a small fraction of the embryos. Moreover, the scientists observed a large number of "off-target" genetic mutations on other parts of the genome which could be harmful. The paper has generated major ethical debate in the scientific community because any genetic change done to an embryo is heritable and could have unpredictable effects on future generations.

(Please also see our feature article on page 5 for a more detailed account of the genome editing technique.)

Exon skipping

Exon skipping could work for a range of conditions

A new study conducted by Professor Peter Zammit, one of the scientists supported by Muscular Dystrophy UK, has shown that exon skipping could be used to correct 'missense mutations'. Professor Zammit's research team used a molecular patch in

mouse and human cells grown in culture to skip exon 5 of the LMN gene that is associated with neuromuscular conditions, including Emery-Dreifuss muscular dystrophy, limb girdle muscular dystrophy 1B, congenital muscular dystrophy and dilated cardiomyopathy.

Professor Zammit said: "Our work shows that exon skipping could potentially be extended to treat patients that were hitherto thought unable to benefit from such a therapy."

Update on potential Exon 51 skipping drugs

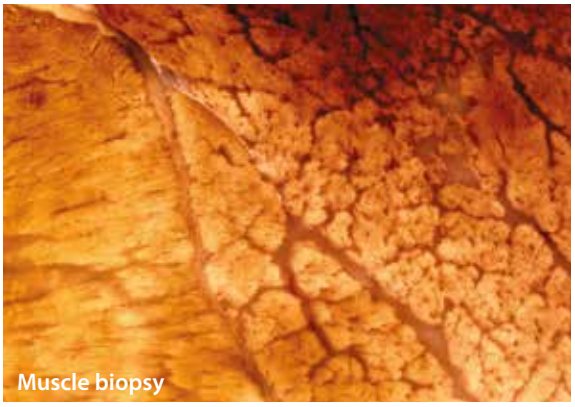
The pharmaceutical company BioMarin has completed a rolling submission of a New Drug Application (NDA) for drisapersen, an investigational exon 51 skipping drug for Duchenne muscular dystrophy, to the US Food and Drug Administration (FDA). This will allow the FDA to assess this part of the licensing application without waiting for the entire license application document to be submitted. The company also submitted a Marketing Authorisation Application (MMA), the European equivalent of an NDA, to the European Medicine Agency (EMA).

Similarly, Sarepta Therapeutics began the submission of a rolling NDA to the FDA for their exon 51 skipping drug, eteplirsen. The company is hoping to complete the submission by the middle of 2015 and once data compilation for the FDA is complete, to present additional data to EMA to seek approval for eteplirsen in the European Union.

New type of molecular patch could work better than existing ones

A study showed that a new type of molecular patch called tricyclo-DNA, to be used for exon skipping, is able to increase the amount of dystrophin in the body to much higher levels than the molecular patches developed so far. In recent clinical studies, exon skipping produced encouraging results. However, the delivery of the molecular patches has not been very efficient, which has limited their therapeutic benefits. The results of this new study show that tricyclo-DNA is much more efficient than other molecular patches. The experiments have been conducted on animals and more research is needed to further investigate the treatment potential of tricyclo-DNA.

Utrophin up-regulation

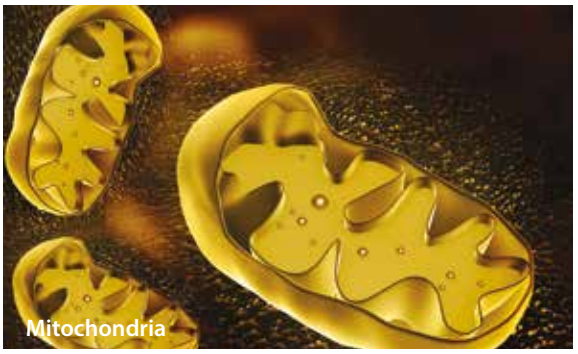

Muscle biopsy

Update on study

A new phase Ib clinical trial to test the compound SMT C1100 in boys with Duchenne muscular dystrophy, when they are on a particular diet, has finished recruiting participants. It has been shown in animal models that SMT C1100 increases the level of utrophin in the muscle.

Utrophin is a protein very similar to dystrophin and it is hoped that it might compensate for the lack of functional dystrophin in people with Duchenne muscular dystrophy. A previous clinical trial had shown that the compound was safe and well-tolerated. Summit Therapeutics, the company that developed the compound, recently presented new pre-clinical data on SMT C1100 and another second generation compound SMT022357 showing that they were able to increase utrophin along the length of muscle fibres in animal models of Duchenne muscular dystrophy.

Mitochondrial donation IVF


Mitochondria

Technique could benefit more women than previously thought

With support from Muscular Dystrophy UK, Professor Doug Turnbull and his team from Newcastle University have developed a technique called mitochondrial donation IVF. This technique has the potential to prevent women with mitochondrial myopathies from passing the condition to future children. Professor Turnbull and his team recently published a new study suggesting that the number of women who could benefit from this technique was higher than previously thought. Around 2,500 women in the UK and 12,500 women in the USA could potentially benefit from the technique and not pass on mitochondrial conditions to their children. The UK Parliament recently voted in favour of allowing the technique to be used in the clinic.

Clinical trials and potential new drugs

SMA clinical trial now recruiting participants

A phase I clinical trial for people with spinal muscular atrophy (SMA) is currently recruiting participants to test the effectiveness of a new oral drug called RO6885247. The trial will test whether the drug can increase the production of the survival motor neuron (SMN) protein that is not produced to sufficient levels in people with SMA. SMN protein is crucial for the survival of motor neurons and its absence leads to muscle wasting. The drug has already been tested on animals and has been shown to significantly increase the production of functional SMN protein.

New drug shown to reduce loss of respiratory function in Duchenne muscular dystrophy

The results of a phase III clinical trial have shown that the drug idebenone significantly reduces the loss of respiratory function in boys with Duchenne muscular dystrophy. The results of the trial demonstrate that idebenone represents an alternative treatment option for people with this condition, at an age when the decline in their respiratory function becomes clinically relevant. Santhera, the pharmaceutical company that developed the drug, recently announced that the US Food and Drug Administration (FDA) had granted Fast-Track designation for idebenone. This means that the drug could reach patients faster.

A new heart drug

Rimeporide, a potential drug for the treatment of Duchenne muscular dystrophy, recently received Orphan Drug Designation (ODD) from the European Medicine Agency (EMA). Rimeporide was originally developed for congestive heart failure. A clinical trial to test the safety, tolerability, pharmacokinetics and pharmacodynamics of rimeporide in boys with Duchenne muscular dystrophy is planned for the second half of 2015.

Eplerenone could slow the decline of heart function

A new study has shown that eplerenone, a drug traditionally used for high blood pressure and late stage heart failure, could slow the decline of heart function in Duchenne muscular dystrophy when taken in combination with other heart drugs. Further studies are needed to understand the effects of combination therapy to protect the heart muscle.

New therapeutic approach for myotonic dystrophy type 1

Researchers have discovered that a biological pathway – called the TWEAK pathway – is over-active in people with myotonic dystrophy type 1 (DM1). Moreover, they have seen that the level of activity correlates with the severity of the condition. The scientists have shown that blocking the pathway reduces the symptoms of the condition in mouse models. The antibody they used against the TWEAK protein has already been trialled in the clinic for other conditions. The scientists are hopeful that the antibody can be moved quickly to clinical trial for the treatment of DM1.

Myotonic dystrophy type 1 research full steam ahead

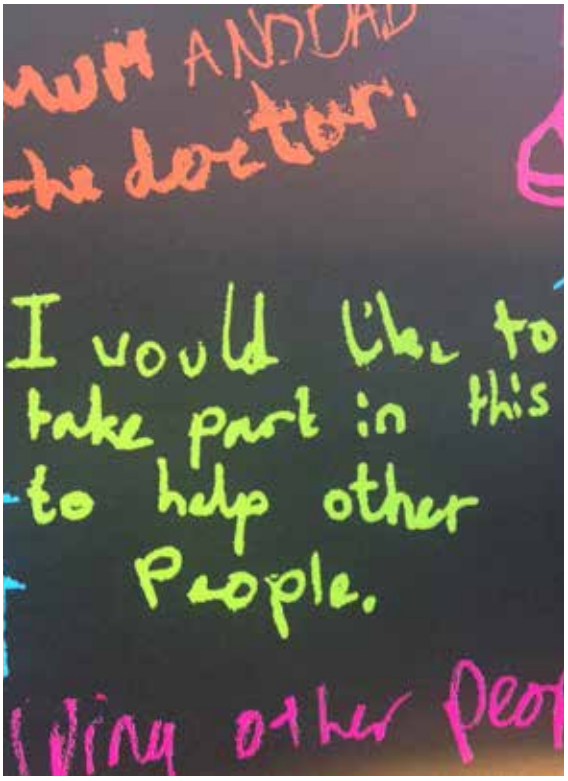
The largest multi-centre trial in DM1 to be carried out in Europe has closed recruitment earlier than expected, owing to high retention rates. The aim of the study, which is a collaboration between researchers and clinicians from the UK, Netherlands, Germany and France, is to improve clinical practice and standards of care for patients with DM1. The study will assess a combination of cognitive behavioural therapy and exercise to see if these can increase activity, reduce fatigue and improve quality of life in people with DM1.

Small beneficial effect of vitamin supplements for FSH

The results of a new clinical trial have suggested that vitamin supplements may have a small beneficial effect on the progression of facioscapulohumeral muscular dystrophy (FSH). However, these are preliminary results and further larger trials are needed to understand the precise benefit of the supplements.

Report on children and clinical trials

The Nuffield Council on Bioethics has recently published a report called *Children and clinical research: ethical issues*. The report focuses on the involvement of children in clinical research and how to achieve this in an ethical way. The report makes recommendations about the roles and responsibilities of children, their parents or guardians, researchers and others. As part of the report, the Council also produced an animation entitled *Health research; making the right decision for me*, conveying the key points of the report. It can be used to help researchers understand what things matter to young people, and to help children and families make decisions about taking part in a clinical trial.



You can find more detailed versions of these news stories and more on our website: **www.musculardystrophyuk.org/news-events/research**

Definitions

Food and Drug Administration (FDA): federal agency of the United States Department of Health and Human Services. The FDA is responsible for regulating and supervising food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs, vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices, cosmetics, animal foods and feed and veterinary products.

European Medicines Agency (EMA): European Union agency for the evaluation of medicinal products. The EMA is responsible to protect and promote public and animal health, through the evaluation and supervision of medicines for human and veterinary use.

New Drug Application (NDA): an NDA is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the USA.

Marketing Authorisation Application (MMA): an MMA is an application submitted by a drug manufacturer seeking permission to bring a newly developed medicinal product to the market. It is the European equivalent of the NDA in the USA.

Orphan Drug Designation (ODD): an ODD is a status assigned to a drug intended for use against a rare condition. The drug must fulfil certain criteria to receive the designation. An orphan drug benefits from incentives such as protection from competition once on the market.

Fast-Track Designation: designation of the FDA that facilitates the development of drugs which treat a serious or life-threatening condition and fill an unmet medical need.


Life

Translational Research Conference highlights

The eighth UK Neuromuscular Translational Research Conference, which took place at the Centre for Life in Newcastle in March 2015, brought together 200 scientists, clinicians and industry partners from around the world. Jointly organised by Muscular Dystrophy UK and the MRC Centre for Neuromuscular Diseases, the conference showcased the latest developments in neuromuscular science, and highlighted their potential translation into patient benefit.

The Conference is held every year in London, Oxford or Newcastle. It was established in 2008 with the aim to bring together scientists, clinicians and industry partners working in the field of neuromuscular conditions. It is a platform where they can showcase and discuss their latest findings in the field. This year's key themes were mitochondrial disease, genomic data, new drug targets and imaging techniques. The programme included more than 25 talks by experts in the field as well as from junior researchers, some of whose work is funded by Muscular Dystrophy UK. Alongside oral presentations, there were 124 poster presentations.

Mitochondrial disease

Professor Doug Turnbull, Professor of Neurology at the University of Newcastle, gave an update on mitochondrial donation IVF, the technique that his group pioneered. For many years, Muscular Dystrophy UK funded Professor Turnbull's research to develop the technique. He expressed his delight at the recent decision in the Houses of Parliament to approve the technique to be tested in the UK. Around 2,500 women in the UK and 12,500 women in the USA could potentially benefit from this technique. This was a great example of the importance of basic scientific knowledge and how basic research could be translated for direct patient benefit.

Professor Zeviani, Director of the MRC Mitochondrial Biology Unit, presented the latest developments in mouse models of the disease, and Professor Rob Taylor, Professor of Mitochondrial Pathology at the University of Newcastle, gave updates on molecular mechanisms of the disease.

Genomic data

Professor Stephan Zuchner from the University of Miami talked about the importance of cutting-edge sequencing techniques for the identification of new disease-associated genes. He outlined how next generation sequencing techniques increased the pace of discovery of new genes in neuromuscular conditions and how they allowed scientists to precisely describe and classify these genes.

Knowing as much as possible about the genetic cause of neuromuscular conditions is essential in designing and developing therapeutic approaches. This is a lengthy process and requires many years of basic research that can then be taken into the clinic. It also requires collaboration between scientists, clinicians and industry partners.

This idea was reinforced in a presentation by Professor Hanns Lochmüller, one of the scientists supported by Muscular Dystrophy UK, on the importance of data sharing between scientists in different countries working on neuromuscular disorders.

New drug targets

The second day of the conference focused on the identification and validation of new drug targets in neuromuscular conditions such as Charcot-Marie-Tooth disease (CMT) and spinal muscular atrophy (SMA). Dr Cristina Csimma spoke about TREAT-NMD's Advisory Committee for Therapeutics (TACT) that was established to provide the neuromuscular community with expertise on drug development and disease knowledge. TACT has had a very positive impact in bridging the gap between basic research and drug development and accelerating the development of new potential therapies for muscle-wasting conditions. It is now being considered for adoption by other rare diseases outside the neuromuscular field.

Imaging techniques

There were four presentations on the use of MRI (magnetic resonance imaging) in characterising and monitoring the evolution of neuromuscular disease, including facioscapulohumeral muscular dystrophy (FSH), hypokalaemic periodic paralysis and Duchenne muscular dystrophy.

A key highlight of the conference was the third John Walton Lecture given by Professor Carsten Bönnemann, a leading neuromuscular clinician scientist from the USA. In presenting an excellent overview of congenital muscular dystrophies, Professor Bönnemann outlined the progress in the clinical characterisation, natural history and genetic basis of these conditions.

There were also guided poster discussions and five-minute poster sessions, where junior scientists had the opportunity to present their findings to their colleagues. We were delighted that Louise Moyle – a PhD student supported by Muscular Dystrophy UK – won a prize for her poster on FSH.

The next Neuromuscular Translational Research Conference will be held in Oxford in March 2016.

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.

Amino acids – The 'building blocks' of proteins. The sequence of amino acids determines the shape, properties and role of the protein.

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 to the one present in the human condition. The mutation is either naturally occurring in the animals or induced in the laboratory to have the mutation.

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.

Embryo – A fertilised egg that has the potential to develop into a foetus.

Enzyme – A protein which initiates, facilitates or speeds up a reaction. Almost all of the processes that occur in our body require enzymes. Examples include the digestion of food, the growth and building of cells, and all reactions involving transformation of energy.

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 an error, or mutation. The name comes from 'exons' 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.

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

Mitochondria – The 'energy factories' of cells. They have their own DNA, inherited from the mother.

Molecular patch – A short piece of genetic material (DNA or RNA) that can bind to a specific gene and change how the code is read. They can be used to mask errors in the genetic code, this is known as exon skipping and this is in clinical trial for Duchenne muscular dystrophy. Also called an antisense oligonucleotide, which is often abbreviated to AO or AON.

Muscle cell – The basic unit of muscle fibres.

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.

Phase I clinical trial – The first stage of testing a drug or treatment in human subjects. Researchers test a new drug or treatment in a small group of people – often healthy volunteers rather than patients. This phase is to evaluate the treatment's safety, determine a safe dosage range, and identify side-effects. About 70 percent of experimental drugs pass the initial phase of testing.

Phase II clinical trial – This is designed to test how well the drug or treatment works as well as to continue safety assessments on a larger group of patients (20-300). When the development process for a new drug fails, this usually occurs during Phase II trials when the drug is discovered not to work as planned, or to have toxic effects. Only one-third of experimental drugs successfully complete both phase I and phase II studies.

Phase III clinical trial – This tests a new drug on a larger number of patients after it has been shown to be effective in a phase II trial. Phase III trials often enrol large numbers of people and may be conducted at many centres nationally or internationally. These phase III studies allow researchers to determine the tolerance and the effectiveness of the product and therefore to assess the benefit/risk ratio of the drug. Between 70 and 90 percent of drugs entering phase III will be candidates for a market approval application.

Point mutation – A type of genetic mutation that causes a single building block of DNA (nucleotide) to be replaced with a different one.

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.

Reading frame – The genetic code consists of a sequence of letters which are read in groups of three. There are three possible ways of reading the sequence, depending on the starting point. If the code reads AGCAGCAGC, for example, the three reading frames are AGC AGC, GCA GCA and CAG CAG.

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

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.

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
61A Great Suffolk Street, London SE1 0BU
020 7803 4800
info@musculardystrophyuk.org
www.musculardystrophyuk.org

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.

Muscular Dystrophy UK
61A Great Suffolk Street
London SE1 0BU

0800 652 6352 (freephone)
info@musculardystrophyuk.org

www.musculardystrophyuk.org

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