

Target Research

**Muscular
Dystrophy**
Campaign



Advances in science

An overview of 50 years of research

From genes to drugs

How researching genes has led to the development of potential new treatments

Stem cells

What are they?

MP comments on the HFE Act

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- More than 60,000 babies, children and adults in the UK have a neuromuscular condition.
- More than 300,000 people are indirectly affected as family, friends and carers.
- The Muscular Dystrophy Campaign supports more than 60 different neuromuscular conditions.
- The Muscular Dystrophy Campaign has pioneered the search for treatments and cures for 50 years.
- Each year we invest more than £1.7 million into high quality research in the UK and an equal amount is invested into the provision of care and information.
- We currently fund 27 research projects with each project lasting between two and four years.
- Many research advances for neuromuscular conditions in the last 50 years have been by Muscular Dystrophy Campaign-funded scientists including vital pre-clinical research for the exon-skipping trial for Duchenne muscular dystrophy.

Welcome to the first ever edition of *Target Research*. The production of a magazine devoted entirely to stories on scientific research past, present and future fulfils a longstanding ambition of ours. We also hope the articles provide answers to some of the questions you may have about research.

The publication of *Target Research* is part of the charity's 50th anniversary launch activities. Founded in 1959, the Muscular Dystrophy Campaign was set up as an initiative to boost research into Duchenne muscular dystrophy. At the time little was known about this form of muscular dystrophy even though it was first described more than 100 years earlier. Now 50 years on, with a large contribution from the Muscular Dystrophy Campaign, this situation has changed remarkably. We are proud to have invested over £10 million into research for Duchenne muscular dystrophy and more than £50 million into neuromuscular conditions in total.

Clinicians and researchers today have a much better understanding of how muscles function and the underlying factors that cause muscle disease. So far, more than 30 different types of muscular dystrophy have been described and, thanks to investment in basic science, the genes causing many of them have been identified. This has given clinical experts the knowledge to accurately distinguish between different types, which in turn gives those affected an idea of how the condition might progress. Most importantly this knowledge is helping scientists to develop treatments and we hope, in time, cures. The next few years will see the start of several clinical trials that would not have been possible without the research carried out in recent years.

The Muscular Dystrophy Campaign supports 60,000 people in the UK with neuromuscular conditions, of which the muscular dystrophies account for about 13%. The charity has significantly grown over the last 50 years and today provides care, support and research funding for over 60 different muscle conditions including Charcot-Marie-Tooth disease, spinal muscular atrophy and myasthenia gravis.

One of the challenges we faced when writing this magazine was to provide information that suited everybody. Since it would have been an extremely difficult task to give you an update for every condition (unless we were to turn this magazine into a book) we have concentrated on topics that we hope will be of interest to everybody, including the ins and outs of clinical trials and stem cells, and ethical considerations around animal and embryo research. For more information about research into specific conditions please visit our newly revamped research updates at www.muscular-dystrophy/research

We plan to publish *Target Research* every year and so we welcome your feedback. Please do complete the form at the back of the magazine – your thoughts are important to us.

A big thank you to everyone who has supported our work over the last 50 years. Without you none of the research that has taken place would be possible.

We hope you enjoy reading the first issue.

The Research Team
Muscular Dystrophy Campaign
February 2009



The research team on a lab visit – Dr Marita Pohlschmidt (Director of Research), Dr Kristina Mills (Research Communications Officer) and Dr Olusola Oke (Grants Manager).

Target Research

The research magazine for families and supporters of the Muscular Dystrophy Campaign

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50 years of neuromuscular research – an overview

Emeritus Professor Alan E H Emery

As the Muscular Dystrophy Campaign marks its 50th anniversary, we ask long-term supporter and vice-president Professor Alan Emery to give us an overview of how the field of neuromuscular research has evolved in that time. Professor Emery is emeritus professor of human genetics at the University of Edinburgh, founding member of the European Neuromuscular Centre and an Honorary Fellow at the University of Oxford. Professor Emery's research into neuromuscular conditions has resulted in the publication of more than 200 scientific papers and he is the author of a number of books on neuromuscular conditions, including *Muscular Dystrophy: The Facts*.

The early history of research into neuromuscular conditions by such notables as Edward Meryon in England, Duchenne in France, and Wilhelm Erb in Germany, led to the definition of the commonest neuromuscular disorder in children, namely Duchenne muscular dystrophy. The work of John Walton and colleagues clearly defined the clinical features and inheritance of Duchenne muscular dystrophy in the late 1950s. Also Peter Emil Becker in Germany defined a different form of dystrophy similar to Duchenne muscular dystrophy but milder, which was subsequently named after him.

It was around this time that I became interested in this group of diseases while pursuing post-graduate research in America. It was in 1962 that, by chance, I met John Walton at a meeting in Edmonton, Canada. He was of course internationally known by this time and it was through his encouragement, for which I shall always be grateful, that I decided to concentrate entirely on the subject of muscular dystrophy.

And incidentally his encouragement and advice at an early period in my career became a model I tried to emulate when later wishing to help my own research students.

Around the mid-1960s I reported two apparently new observations: firstly that female carriers of Duchenne muscular dystrophy may exhibit certain mild features of the disease, and secondly a relatively mild form of dystrophy exists which is different from Becker muscular dystrophy but inherited in the same way. Fritz Dreifuss, a neurologist in Virginia introduced me to the original family who presented with this condition.

I still remember loading up my station wagon with all the equipment I would need to examine the family and driving more than 500 miles to a remote community in

in the Manchester Royal Infirmary, where we concentrated on diagnosis and carrier detection using the serum level of creatine kinase (SCK) which would become the standard diagnostic test (I wish I had patented the method in 1964!). Then in 1968 I moved to Edinburgh to the post of Chair of Human Genetics and, with support from the Muscular Dystrophy Campaign (then known as the Muscular Dystrophy Group), the Medical Research Council and the Scottish Health Board, set up a research unit with in-patient facilities for clinical investigations, electromyography and muscle pathology – and later gene studies. It was around this time that everyone in the field realised the importance of genetic counselling and several units, including our own, set up

The most exciting event in the history of these diseases occurred in the late 1970s and early 1980s with scientists locating the Duchenne muscular dystrophy gene

the Appalachian Mountains in north eastern America. There I enjoyed the hospitality of these kind people and was privileged to be able to carry out clinical, genetic, serum creatine kinase (SCK), and ECG studies on all 19 family members in the local school house in a VERY long weekend! But it wasn't until about 20 years later that the condition was widely accepted as a distinct form of muscular dystrophy and named Emery-Dreifuss dystrophy, after myself and Fritz Dreifuss. Subsequently the defective protein was identified by Sylvia Bione and colleagues in Italy and named 'emerin'!

In 1964 I set up a small research unit

procedures for prenatal diagnosis for families who requested this.

But by the 1970s it was becoming very clear that the muscular dystrophies as well as various other neuromuscular disorders, such as the peripheral neuropathies and spinal muscular atrophies, were clinically and genetically diverse. Even then it was thought that there might well be over 20 different types of dystrophy alone. It was essential to be able to diagnose these different forms for two reasons. Firstly, in order to provide a good idea of the prognosis and for reliable genetic counselling in individual cases. Secondly, for genetic research aimed at identifying



Above: Professor Emery in Edinburgh, 1970

the specific genes involved. Furthermore other specialists, such as physiotherapists, respiratory physicians and orthopaedic surgeons for spinal surgery, were becoming involved in the management of patients.

The most exciting event in the history of these diseases occurred in the late 1970s and early 1980s with scientists locating the Duchenne muscular dystrophy gene on the short arm of the X chromosome (at position Xp21). The gene was then isolated and characterised and subsequently the protein product was identified and named dystrophin. The key players at this time, Kay Davies, Tony Monaco, Peter Harper, Lou Kunkel, Ron Worton and Eric Hoffman, are all now household names in the field. Soon afterwards the genes for many other forms of neuromuscular conditions were identified along with their protein products

and the idea soon emerged that specific therapies might be possible by somehow repairing the genetic defect that causes disease, a process we know as 'gene therapy'.

These new approaches required close collaboration between the physicians and scientists involved. For this reason I was invited in 1989 by the European Alliance of Muscular Dystrophy Associations (EAMDA) to set up the European Neuromuscular Centre (ENMC). The aim was to organise small workshops of around 10-15 experts in a particular field. They would discuss a specific research topic, agree to collaborate and share patient and scientific data, and draw up a summary report for publication. I was its first Research Director and Chairman of the Research Committee with much valuable help from Ysbrand Poortman and Michael Rütgers in the Netherlands. From 1999 I have been its Chief Scientific Advisor.

Though originally envisaged as essentially a European organisation, medical scientists

from all over the world are now attracted to these workshops, something which can only benefit the research community and of course, ultimately we hope, the families affected.

To me each of these steps in the last 50 years of research into neuromuscular conditions has had its challenges and rewards – from the clinician's recognition of the various forms, to the identification of the causative genes and now to the real possibilities of effective treatments. A challenging but very rewarding period in medical history. ●

*Professor Emery is the author of *Muscular Dystrophy – The Facts* published by Oxford University Press and now in its 3rd edition. It is written specifically for patients and their families. All proceeds from its sale are donated to support research and education into neuromuscular conditions and its sale is promoted by the Muscular Dystrophy Campaign*

To buy any of Professor Emery's books, please contact Oxford University Press, +44 (0)1536 741727

From genes to drugs

By Prof. Caroline Sewry and Dr Ros Quinlivan
The Wolfson Centre for Inherited Neuromuscular Disorders,
Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry

We are living in revolutionary times – years of laboratory-based research into neuromuscular disease is finally being transferred into the clinic setting. The European Union has invested several million Euros in a European network for translational research called TREAT-NMD [see page 20], which is co-ordinated from the Newcastle Muscle Centre. Clinical trials of potential new drug therapies for the treatment of some neuromuscular conditions are currently in progress, and others are being developed.

Since its foundation in 1959, the Muscular Dystrophy Campaign has worked tirelessly towards finding treatments for neuromuscular conditions by funding research and clinical studies. For many people it may seem a long time coming but years of hard work and effort are now reaping their reward. In this article we look at the scientific advances that have been made in recent years and discuss why finding and understanding the gene mutations that cause muscle disease were, and still are, so important for the development of drugs and treatments.

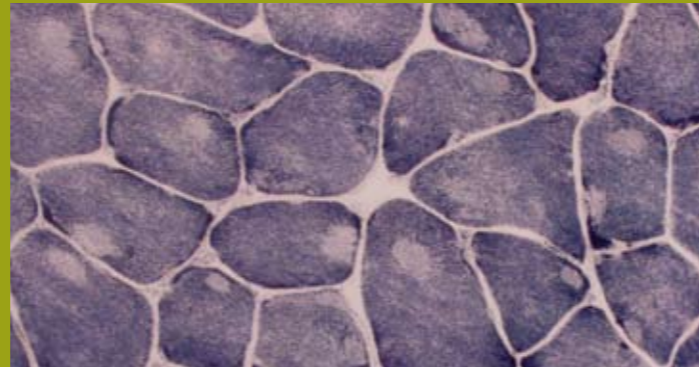
Searching for genes

Clinical differences between neuromuscular conditions have been recognised since the 19th century, but identifying the underlying causes and understanding how they are inherited has come from molecular research conducted since the 1980s. This has led to the identification of over 100 genes that cause different neuromuscular conditions.

Not knowing what the genetic defect is makes it difficult for clinicians to make an accurate diagnosis and give patients and families information about how their condition might progress. Accurate genetic diagnosis also means that families can receive proper genetic counselling so that they can make choices, for example prenatal diagnosis. Developments in molecular science are advancing rapidly and better ways of accurately and quickly finding a genetic defect are currently being developed.

Duchenne muscular dystrophy was first described in the 1850s but it was not until the 1980s that the first major breakthrough occurred – when researchers were able to locate the gene in the genome. In 1986 the gene for Duchenne muscular dystrophy was identified. It was one of the first genes identified by a technique called “positional cloning”. This technique involves DNA analyses of families who are affected by a particular condition. The gene that carries the mutation is identified by comparing the DNA of family members who have the condition to the DNA of unaffected relatives.

As more genes have been discovered, a complicated picture has emerged such that it isn't always just one gene causing one condition.



Above: microscope image of muscle fibres from a person with central core disease

In some cases the same gene can cause different severity of symptoms depending on what kind of mutation the gene carries. For example, the severe form of Duchenne muscular dystrophy and the milder form of Becker muscular dystrophy are caused by mutations in the same gene. In muscles of boys with Becker a reduced amount of dystrophin protein is produced which works to some extent. However, in Duchenne little or no dystrophin protein is produced. In other cases a muscle disease can be caused by defects in different genes, for example, limb girdle muscular dystrophy can be caused by mutations in any one of more than 10 different genes. More than 30 genes have also been identified which when mutated can Charcot-Marie-Tooth disease, a condition that affects the nerves that run from the spinal cord to all other parts of the body.

Other neuromuscular conditions result from a different type of genetic mutation. For example, research has shown that myotonic dystrophy is caused by a small repeat sequence within a gene being repeated many more times than usual. Healthy individuals normally have up to 30 copies of the repeat, but individuals with myotonic dystrophy can have many hundreds of copies. This leads to the production of toxic molecules in the muscle cells which in turn have an influence on other genes. This explains why people with myotonic dystrophy have a variety of symptoms such as cataracts, muscle weakness and heart rhythm disturbances.

Although a large number of genes causing muscle disease have been found there are still many for which no genetic defect has been identified or is still poorly understood. For example, it is known that facioscapulohumeral muscular dystrophy (FSHD) is caused by the

deletion of highly repetitive DNA on chromosome 4. This means that in unaffected people the same piece of DNA is repeated up to 100 times while in people with FSHD the number is reduced to less than 10 copies. Scientists have not come to a conclusion yet as to what this piece of DNA does and why its deletion causes muscular dystrophy. The genetics of FSHD are extremely complex and more work needs to be done to fully understand the processes involved before clinicians are able to offer an accurate diagnosis and prognosis.

The function of muscle proteins

Genes contain the instructions for making proteins – the basic building blocks of our bodies. Studying the function of a protein encoded by a particular gene can help us to begin to understand how a gene mutation leads to disease.

The discovery of the dystrophin protein marked the beginning of a series of discoveries of other neuromuscular conditions. Dystrophin was found to interact with other proteins at the muscle fibre membrane – the sheet that surrounds the muscle cells to give them stability and protection. This led to the identification of a group of genes that can cause several forms of limb girdle muscular dystrophy when they are mutated. The identification of these proteins, their location within the muscle fibre and the characterisation of their interaction has led to a greater understanding of how the proteins work. It is thought that these proteins have a structural function – stabilising the muscle fibre and protecting it from damage during muscle contraction.

Muscle disease is not only caused by mutations in structural proteins, they can also be caused by mutations in proteins that control the biochemical reactions in muscle cells. For example, defects in enzymes that supply muscle cells with energy from fuels (sugars and fat) can cause metabolic muscle diseases such as Pompe's disease and McArdle disease. Mitochondria – the machinery in the cell responsible for the final steps of converting energy into a form which can be used by the cell, can also be affected by mutations which can cause mitochondrial myopathy.

In some forms of congenital muscular dystrophy the process of adding sugar molecules to a protein called alpha-dystroglycan is defective. This protein needs many sugar molecules in order to function properly. At least six different genes are involved in adding sugars to this protein and research has shown that misprints in each of these genes can cause congenital muscular dystrophy. Looking for a reduction of sugars on this protein in muscle biopsies is now an important way to detect these conditions. As yet, not all the genes that control the addition of these sugars have been identified, and in about a third of children and adults with congenital muscular dystrophy the genetic defect cannot be found. More research is needed to discover all the genes involved so that one day it will be possible to provide a diagnosis for all families that are affected by congenital muscular dystrophy.

Knowledge of the proteins involved in muscle disease has also led to improvements in diagnosis using small samples of tissue, known as a ‘muscle biopsy’. When seen under a microscope specific features of the muscle tissue can suggest a diagnosis and there are now special stains ▶

Research we fund

Discovering new genes:

- Researchers in **Prof. Francesco Muntoni** group at the University College London are searching for new genes responsible for **congenital muscular dystrophy**. At least 14 different types of congenital muscular dystrophy exist and in approximately 30% of cases the gene defect is not known.
- **Prof. Kate Bushby's** group of researchers in Newcastle aim to identify new gene mutations causing **Bethlem myopathy** and **Ullrich congenital muscular dystrophy**. In approximately half of the individuals with the symptoms of these conditions, a genetic cause is unknown.

How mutations cause disease:

- **Prof. David Beeson's** research group at University of Oxford is currently working to understand how a newly identified gene mutation is involved in causing the symptoms of **congenital myasthenic syndromes**. Understanding the gene mutations is essential for the design of future treatment strategies
- **Prof. Jane Hewitt** at the University of Nottingham will be embarking on a project in late 2009 to further understand the mutations causing **facioscapulohumeral muscular dystrophy (FSHD)**. For many years scientists have known that FSH is caused by the loss of a repeated sequence of DNA but the function of this repeat is not fully understood.
- Researchers in **Prof. Darren Monckton's** laboratory at the University of Glasgow are conducting two projects to further understand the genetic defect causing **myotonic dystrophy**. This is important for families to be given an accurate prognosis so they can plan for their future. The studies will also help to provide patient data for future clinical trials.
- A protein called tropomyosin is being studied in **Dr Charles Redwood's** laboratory at the University of Oxford. Mutations in this protein are known to cause at least four different conditions including **nemaline myopathy** and **cap disease**, all having a wide variety of symptoms. The researchers will investigate how mutations in the beta-tropomyosin gene alter the stability of muscle fibres and their ability to contract. This may be able to explain how the different mutations cause different symptoms.
- **Dr Roland Robert's** research group at Kings College London is working to understand how dystrophin interacts with other proteins in muscle and how these interactions are affected by the mutations causing **Duchenne and Becker muscular dystrophies**. This will help to improve our understanding of why the severity of symptoms between individuals is so different and may also be useful in the design of gene therapy reagents.

For more information about research projects funded by the Muscular Dystrophy Campaign, visit www.muscular-dystrophy.org/research

Key dates in Duchenne muscular dystrophy research

Fifty years ago the Muscular Dystrophy Campaign was set up by Professor Nattrass, Lord Walton and Joseph Patrick originally to fund research to help boys with Duchenne muscular dystrophy. Since then our charity has grown to cover more than 60 neuro-muscular conditions and has invested more than £50 million into research. Below are some key achievements in Duchenne muscular dystrophy research. The achievements are an international effort and the Muscular Dystrophy Campaign played a major part by supporting and funding world-class scientists in the UK.

1852	first clinical description
1868	clinical features further described and named after the French neurologist Guillaume Duchenne
1954	Walton and Nattrass clearly define the clinical features and inheritance
1964	serum creatine kinase diagnostic test set up
1981	first prenatal diagnosis with DNA markers
1982	causative gene precisely located on the X chromosome
1986	causative gene isolated and sequenced
1987	dystrophin protein identified and named
1989	discovery of utrophin
1989	characterisation of the dystrophin-glycoprotein complex
1990	first gene therapy experiments successful in mouse model
1998	increasing levels of utrophin in mice prevents symptoms
2000	first gene therapy clinical trials in France using technology developed in the UK
2001	exon skipping technique demonstrated in cells in the lab
2003	company set up to pursue drug leads for increasing levels of utrophin (now called Summit plc)
2004	body-wide delivery of micro-dystrophin by a virus in mice
2005	PTC124 clinical trials begin in USA
2005	gene therapy clinical trial in the USA begins using a virus to deliver micro-dystrophin
2006	PTC124 clinical trial begins in UK
2007	exon-skipping clinical trial starts in UK

Honorary Life President of the Muscular Dystrophy Campaign, Lord Richard Attenborough visits a lab in the 1960s



to test whether a particular muscle protein is involved. This can help to identify the most appropriate genetic test for precise diagnosis.

The development of treatments

Discovering genes and understanding how they cause disease is not only essential for providing families with an accurate diagnosis, the knowledge is also at the heart of the development of new exciting drugs and treatments.

The principle of gene therapy is to add a healthy copy of the faulty or repair the genetic defect in muscle fibres. A virus which has been modified so that it is not harmful is often used as a vehicle to deliver the healthy gene. There are still many technical problems to overcome before gene therapy can be considered in people with muscular dystrophy – 30 percent of the human body is muscle and it is a challenge to deliver the healthy gene to as many muscle fibres as possible. Targeting the virus to muscle cells, rather than other cells where it might have unwanted effects, also poses a challenge. And finally, although the viruses do not cause illness, the body's immune system may still recognise them as foreign, so it is necessary to carefully select a type of virus that minimises this complication. There are currently three phase 1 clinical trials investigating whether gene therapy for muscular dystrophy will be possible and safe. One trial is for Duchenne muscular dystrophy (USA) and two are for limb girdle muscular dystrophy – type 2D (USA) and type 2C (France).

Other promising potential treatments are also on trial. Antisense oligonucleotides are small DNA fragments that have been developed as patches to restore dystrophin production in boys with Duchenne muscular dystrophy. This potential treatment is often called 'exon skipping'. A very detailed knowledge of the gene mutation is required for this approach as the therapy has to be tailored to a particular mutation.

The pharmaceutical company PTC Therapeutics is currently testing a new drug called PTC 124 that might potentially overcome "nonsense mutations". This type of mutation creates a premature stop signal in the dystrophin gene so that no protein can be produced. PTC124 allows the cells to ignore this stop signal and make a functional dystrophin protein. This approach would potentially work for the 10 to 15% of boys who have this type of mutation. For more information on the clinical trials of these approaches, see page 15.

The discovery of dystrophin in the 1980s led to the discovery of a similar gene called utrophin. Research also revealed that as a consequence of lacking dystrophin, boys with Duchenne and Becker muscular dystrophy have significantly more utrophin protein than normal. Scientists are currently looking for drugs that increase the amount of this protein to even higher levels in these boys. This is another good example of where the study of genes has led to the identification of a potential therapeutic approach. However, we won't know if a higher level of utrophin is able to compensate for the lack of dystrophin in boys with Duchenne muscular dystrophy until clinical trials are performed.

Although, the scientific developments are very exciting, we should not forget the tremendous improvements in clinical care which have significantly improved the quality and length of life for children and adults who have muscle disease. There is now a much better

understanding of the natural history of these conditions that has led to improved care. For example, better management of breathing difficulties, treatment of joints to reduce contractures and surgery that corrects spinal deformity. There is a greater understanding of the specific heart problems that can occur in different neuromuscular conditions – early intervention with medication and/or pacemakers or defibrillators can save some people's lives, and regular cardiac monitoring is now part of routine care. The use of corticosteroids for Duchenne muscular dystrophy is routine clinical practice and although we don't fully understand how these drugs work, there is good evidence that they improve muscle strength and prolong walking. They do have a number of significant side effects so finding alternative forms of treatment is a priority for researchers.

Since the Muscular Dystrophy Campaign was founded in 1959, scientists and clinical researchers, including those funded by the charity, have taken great steps forward. Potential new therapies are being developed and although this is very exciting the scientific community remains cautious until the results of clinical trials are known and we have a better understanding of the impact these therapeutic interventions might have. ●

Prof. Caroline Sewry is a leading muscle pathologist who has worked in the field for nearly 40 years as a researcher funded by the Muscular Dystrophy Campaign and has developed diagnostic techniques for studying muscle biopsies. Dr Ros Quinlivan is a leading paediatrician in the neuromuscular field and has developed the multidisciplinary service at the Muscular Dystrophy Campaign centre in Oswestry, where she also runs the only UK clinic for McArdle disease.

Research we fund into the development of new treatments

Therapeutic approaches:

- **Prof. David Brook's** group is developing methods to screen thousands of drugs for their potential to treat **myotonic dystrophy**.
- **Prof. Kate Bushby's** researchers are testing in the laboratory the potential of a drug called 'Poloxamer 188' to treat several types of muscular dystrophy
- Scientists in **Prof. Dame Kay Davies'** laboratory are continuing their work on the upregulation of utrophin as a therapy for **Duchenne muscular dystrophy**.
- **Dr Ian Graham** is leading a project to improve methods of exon skipping for **Duchenne muscular dystrophy**.
- **Prof. David Rubinsztein** is testing several drugs in the laboratory for their potential to treat **oculopharyngeal muscular dystrophy**.

- **Prof. Doug Turnbull's** team of researchers are investigating the use of IVF techniques to prevent the transmission of **mitochondrial DNA disease**.
- **Dr Mary Reilly** is co-ordinating a clinical trial of Vitamin C as a treatment for **Charcot-Marie-Tooth** disease (see p15 for more information).
- **Prof. David Beeson** was awarded a PhD studentship for the development of a gene therapy approach to potentially treat **myasthenia gravis** more efficiently.
- **Prof. Dominic Wells and Prof. Volker Straub's** groups are working together to develop tools to assess the efficacy of potential new therapies for **Duchenne muscular dystrophy**. Dominic's group is creating a new mouse model to test approaches such as exon-skipping prior to clinical trial while Volker is developing non-invasive methods such as magnetic resonance imaging (MRI) to assess muscle damage and repair in patients.

Clinical management:

- The use of new orthoses and other footwear is being investigated by **Dr Ros Quinlivan** and collaborators to improve walking and stability in children with **Duchenne muscular dystrophy**.
- **Dr Mary Reilly** is leading a project investigating exercises to strengthen hip flexors in people with **Charcot-Marie-Tooth** disease.
- **Prof. Doug Turnbull** is co-ordinating a study to determine if exercise therapy is beneficial for people with **mitochondrial myopathies**.
- **Dr Michael Rose** is conducting a questionnaire survey to find out the psychological and social factors that influence the quality of life of people with muscle disease – information that can be used by clinicians to give appropriate advice.

For more information on these projects please see page 19 and visit our website for more detailed summaries www.muscular-dystrophy.org/research

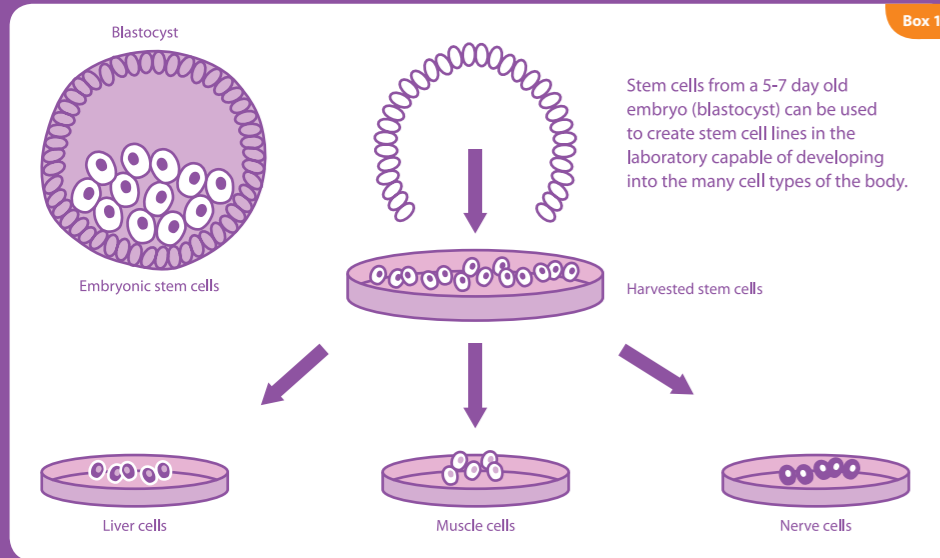
Dystrophin and utrophin

Professor Dame Kay Davies' team at the University of Oxford was involved in the discovery of dystrophin in the 1980s and soon afterwards they started searching for the existence of similar genes. From this work they reported the discovery of a gene, closely related to dystrophin, which was named 'utrophin'. This has subsequently formed the basis of a treatment approach. The Muscular Dystrophy Campaign has helped to fund Prof. Davies' work for more than 25 years.

She commented, "One of the major strategies we are using to develop an effective therapy for Duchenne muscular dystrophy is using drugs to increase the levels of the protein utrophin, which is very similar to the missing dystrophin. We have shown that increased levels of utrophin in the mdx mouse (a rodent model for the disease which also lacks the dystrophin protein) can prevent the disease. We test the drugs on cells grown in the laboratory first to optimise their efficiency. This work is being carried out in collaboration with the biotechnology company Summit plc and we also collaborate with colleagues internationally to standardise the way this type of preclinical research is conducted. During the last screens we successfully found one drug which is now moving forward to clinical trials."

Stem cells – the ultimate body repair kit

By Dr Kristina Mills, Research Communications Officer, Muscular Dystrophy Campaign.



We all have about 300 million skin cells, and every minute we shed up to 40,000 of them!

Given that most of the mature cells of the body such as skin cells are not able to divide and replace themselves, where do new cells come from? The answer lies with stem cells, a special type of cell present throughout the body. These amazing cells have the ability to divide almost indefinitely and can specialise into many cell types. These characteristics make them perfect for the job of developing, maintaining and repairing the human body. They also offer great promise for studying and curing many human diseases.

Embryonic stem cells can be isolated from embryos between five and seven days after the egg has been fertilised and are responsible for the miraculous creation of a new human being from a single egg and sperm. At this stage the microscopic embryo consists of around 100 cells and is called a blastocyst. Embryonic stem cells are termed

‘pluripotent’ because they have the ability to develop into the more than 200 different cell types of the body. A single embryonic stem cell isolated from a blastocyst can divide and renew itself in the laboratory for an indefinite period of time; this is called a stem cell line. These embryonic stem cell lines can then be coaxed to specialise into different cell types (see box 1).

Embryonic stem cells are very useful **tools for research**. Muscle cells from biopsies can only survive in a Petri dish for a limited time making it difficult to perform some experiments. Embryonic stem cells however, can be grown almost indefinitely and induced to form muscle cells in large quantities. Such a plentiful source of muscle cells can help researchers study the biology of muscle cells. Of even more value are stem cells which contain a genetic mutation causing disease because then the development of disease can be studied and therapeutic strategies explored. Several stem cell lines have been created from embryos identified

by preimplantation genetic diagnosis as having a genetic mutation, including those causing Duchenne and Becker muscular dystrophy. However, there are more than 60 different neuromuscular conditions covered by this charity and many more exist. These conditions are all relatively rare, so it would be difficult to obtain embryos to create stem cell lines representing all the conditions. Recent scientific advances have provided two potential alternatives – both are ways of transforming adult skin cells into cells which mimic embryonic stem cells. The first is the creation of hybrid embryos (see box 2) and the second is induced pluripotent stem (iPS) cells (see box 3). Embryonic and embryonic-like stem cell lines containing a genetic mutation will allow scientists to test thousands of drugs to find those that have potential to treat disease.

Adult stem cells are unspecialised cells found in small numbers in many organs and tissues. Unlike embryonic stem cells, adult stem cells usually only have a limited range of cells that they can specialise into. Generally they develop into the cell types of the tissue that they reside in. For example, skin stem cells give rise to cells called ‘keratinocytes’, which form the outer layer of the skin. In some ways, this is an advantage of adult stem cells because their development is easier to control and they are less likely to become an unexpected cell type, for example a liver cell in muscle. Recent research has found however, that some adult stem cells are more versatile than previously thought. For example, stem cells from blood vessels and even from fat tissue can be converted to muscle cells.

Satellite cells are the main type of stem cell residing in muscle. They earned their name due to their location attached to the outside of the muscle fibre (see right).

Embryonic stem cells are responsible for the miraculous creation of a new human being from a single egg and sperm.

Satellite cells lie dormant until disease or injury trigger them to regenerate the muscle.

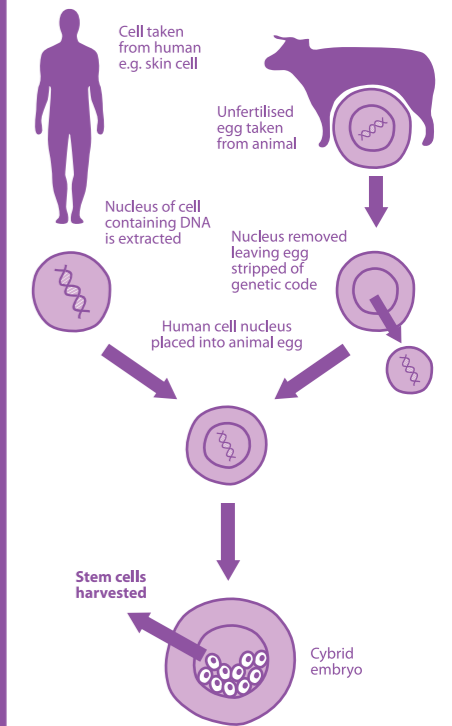
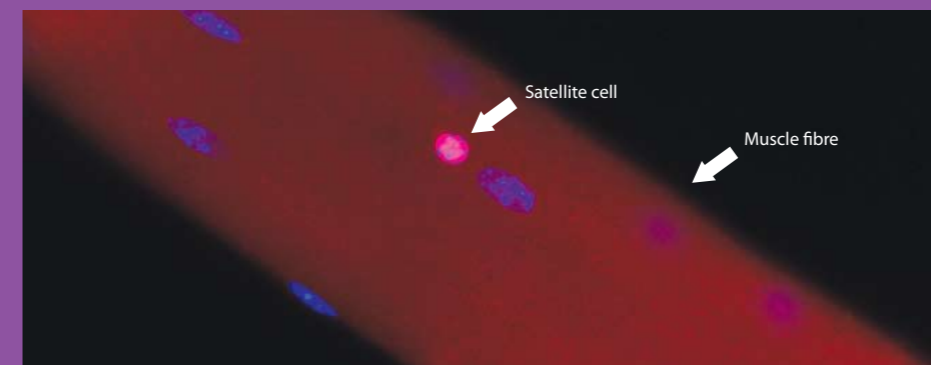
Obtaining the large numbers of adult stem cells needed for research and potential therapeutic applications is still a major hurdle as they are present in such small numbers and are difficult to identify, isolate and grow in the laboratory. Once removed from the body they also tend to lose some of their stem cell properties. Despite these difficulties, adult stem cells in bone marrow have been used for transplantation since the 1970s and can offer a complete cure for conditions such as leukaemia. In cases of severe burns, areas of undamaged skin can be removed and grown in the laboratory to create new skin that can then be grafted back onto the patient – a life-saving procedure. The success of these procedures and the tangible prospect of curing other diseases is spurring on researchers worldwide to investigate ways of harnessing the potential of adult stem cells.

There are currently several hundred **clinical trials** investigating stem cell therapy for various conditions including one neuromuscular condition – a phase 1 trial for **myasthenia gravis**. This debilitating condition is caused by a faulty immune system where the body attacks specific receptors located on the surface of muscle cells. Nerve impulses are then unable to transmit properly to the muscle which causes muscle weakness. The clinical trial involves

collecting the patient’s bone marrow stem cells before destroying their immune system with chemotherapy. Reintroduction of the patient’s own bone marrow stem cells regenerates a new immune system which hopefully won’t attack the receptors.

The ability of stem cells to divide and self-renew over a long period of time means that they could represent an efficient **treatment for muscle disease**. If doctors could transplant healthy muscle stem cells into patients then they could potentially set up residence in the muscle and constantly repair muscle – replacing fragile muscle cells with healthy ones. Similarly, for those conditions that affect the nerves – such as spinal muscular atrophy (SMA), healthy nerve cells could be transplanted. One way of achieving this would be to transplant stem cells from a donor. However, similar to an organ transplant, rejection of introduced stem cells would be a problem. In this situation careful matching of the donor to the recipient and immune suppression would be necessary. Scientists are studying different types of stem cells and ways of modifying them to minimise the risk of this complication. Alternatively the patient’s own stem cells could be used but the genetic mutation would have to be corrected before reintroducing them.

In some forms of muscular dystrophy such as fascioscapulohumeral muscular



What are hybrid embryos?

The genetic information (DNA) contained within the nucleus of a skin cell from an adult is placed inside the unfertilised egg from an animal, which has had its own DNA removed. The animal’s egg is essentially a shell that provides an environment for the human embryonic stem cells to form. By law the hybrid embryo is only allowed to grow in the laboratory for up to 14 days. During this time human stem cell lines can be created from the hybrid.

Cybrid embryos could be a very valuable tool for studying muscle disease. Stem cell lines could be created from people with and without a particular genetic condition. Since these embryonic stem cell lines would be able to renew themselves almost indefinitely they could be studied over a long period of time and used to screen thousands of drugs for their potential to treat the condition.

dystrophy (FSHD) and Emery–Dreifuss muscular dystrophy scientists believe that the genetic defect directly affects the satellite cells. Research is under way to find out why muscle stem cells in these conditions may fail to efficiently repair muscle damage. If this failure could be prevented then the patient's own stem cells could be encouraged to repair damaged muscle more efficiently and, hopefully, reduce symptoms.

The potential of stem cells to cure genetic disease is clear but are embryonic or adult stem cells more likely to provide a future therapy? The answer is that we don't know. This research is still in its infancy and we don't yet know which strategy will give the best results so it is important to study all stem cell types to maximise the chances of success. Dr Jenny Morgan (see box below) says: "Although stem cells hold great promise for the treatment of muscular dystrophies we still need to identify the best stem cell – one that can be isolated easily and expanded to large numbers in the laboratory without losing stem cell potential. In addition, the stem cell must be able to reach all the muscles of the body via the

blood system, then repair or replace damaged muscle fibres. Ideally, the stem cell should also give rise to more satellite cells, so that one stem cell transplant will give lifelong treatment. As well as using the best stem cell, factors in the dystrophic muscle environment will have to be altered in order to allow optimal stem cell function."

Dr Peter Zammit (see box below) says: "In muscular dystrophy the regenerative process carried out by the resident satellite cells initially maintains muscle function but then gradually fails. So investigating the regulation of satellite cell function is central to understanding this regenerative process. Furthermore, the genetic defects underlying conditions such as facioscapulohumeral muscular dystrophy and Emery–Dreifuss muscular dystrophy not only affect muscle fibres, but have recently been shown to also compromise satellite cell function, thus directly contributing to symptoms. In theory, manipulating satellite cells could both improve and prolong muscle function, which also has the advantage of maintaining an environment still capable of responding to other forms of therapeutic intervention." ●

Stem cell research we fund

Dr Jenny Morgan, University College London Institute of Child Health:

- 1) Is it the muscle environment in dystrophic and aged muscle that causes satellite cells to eventually fail to repair damage, or the satellite cells themselves that fail? Understanding this will allow scientists to create the best environment for muscle regeneration.
- 2) Studying satellite cell behaviour in mouse models of a group of muscular dystrophies – called the dystroglycanopathies, in which satellite cells are impaired. Studying these satellite cell defects may determine whether manipulation of satellite cells could be used as a therapy in some forms of muscular dystrophy.

Dr Peter Zammit, King's College London:

- 1) Investigating the different sub-types of satellite cells in both healthy and dystrophic muscle. This will help understand why regeneration eventually fails in diseased muscle and may lead to the identification and isolation of satellite cells that have the greatest ability to regenerate muscle.
- 2) Studying factors which affect how well satellite cells can regenerate muscles. Manipulating these factors could form a basis for potential therapies for muscular dystrophy.

Dr Lesley Robson, Barts and The London School of Medicine and Dentistry:

- 1) Investigating a protein called *Bmi1* in satellite cells. This protein might play a role in the ability of muscle stem cells to multiply and regenerate tissue, and could lead to the discovery of ways to improve the efficiency of muscle regeneration.

Induced pluripotent stem cells (iPS)

Box 3

Recently scientists have made a remarkable breakthrough in reprogramming cells which have already taken on a specialised function. Under normal circumstances, a specialised cell cannot alter its function. For example, a skin cell can not normally develop into a nerve cell or a liver cell. However, it has been shown that it is possible to coax skin cells to revert back to a state which is similar to the stem cells found within the early embryo.

These cells no longer have a specialised skin cell function and are known as induced pluripotent stem cells (iPS cells). These iPS cells appear to have many of the properties of embryonic stem cells, including the ability to specialise into many different cell types (which is known as pluripotency) and self-renew for long periods of time.

For genetic conditions, the use of iPS cells for stem cell transplants may be a long way off, but they have immense potential now for the study of disease processes and for drug discovery. For example, US scientists recently reported the creation of iPS cells from the skin cells of a boy with spinal muscular atrophy. These cells were then induced to form motor neurons – the cells adversely affected by the condition. The cells displayed the hallmarks of the condition and eventually degenerated.

These cells will be a very powerful tool to study what is causing the affected cells to die. This almost limitless supply of cells which model the disease process could also be used to screen thousands of drugs for their ability to treat the condition.

These cells will be a very powerful tool to study what is causing the affected cells to die

What does the new Human Fertilisation and Embryology Act 2008 mean for medical research?

In November 2008 the Human Fertilisation and Embryology (HFE) Act was passed in parliament to replace the Act of 1990. It contains changes to the legislation of assisted reproduction and the use of embryos in research and therapy. The Muscular Dystrophy Campaign played a vital role in campaigning for the safe passage of the Act through parliament.

Much has been written about the new act and its implications for research into conditions such as muscular dystrophy. We asked **Dr Evan Harris MP**, Liberal Democrat Science Spokesman, who was heavily involved in the passage of the Bill through Parliament to set the record straight.

Is the Act a good thing for medical research?

Undoubtedly. It is a very progressive measure and the Government needs to be congratulated for what it contains, especially since the earlier draft version of the Bill was far from satisfactory. Having said that, it is not perfect and there is a real worry that another Bill will be needed within 10 years – otherwise medical research and the developments of new treatments may be held back.

Does the Act now allow embryo research?

As with the old HFE Act – passed in 1990 – the new Act continues to allow research to take place using early human embryos under a licence granted by the Human Fertilisation and Embryology Authority (HFEA). The licence is subject to the same specific conditions as in 1990 – that no embryo is kept beyond the 14 day stage; that the research is necessary or desirable for medical advance; and that it is necessary to use embryos, as opposed to other forms of tissue.

What about human-animal hybrid embryos?

The Act makes it clear that creating embryos with human nuclear DNA but with the "shell" of an animal egg is legal. These 'cytoplasmic hybrids' or 'cybrids' (see box on page 9), as they are called, are felt to be a useful way of overcoming the shortage of human eggs which are difficult to extract – as one can imagine – and are much needed in fertility treatment. Embryonic stem cells can only be derived from embryos and the techniques to do so need a lot of work to perfect them. The Act permits embryos combining animal and human tissue to be created and used by scientists – subject to the same regulations as for human embryos.

Why was the issue of hybrid embryos so controversial and how do you argue against claims that it is immoral and unnecessary?

Firstly, the majority of MPs and peers feel that such research is moral and agree with the vast bulk of scientific opinion that it is necessary. I always make the point that if there is a good chance of serious medical diseases being better understood, or treatment ideas being developed, then it would be immoral not to allow it simply on the basis that some people – and a minority at that – place the status of the human embryo on the same level as people.

What does the Act mean for people with muscular dystrophy and their families?

It is hard to say. I have always argued against claiming that cures or treatments are certain or even likely. But we can be confident that the passage of the Act opens up new lines of research as it will encourage investment in medical research and scientists studying



stem cells. The point of being able to make cybrid embryos and derive stem cells is that it would, in theory, enable cells from patients with, for example, Duchenne muscular dystrophy, to be made into stem cells and the development of the condition looked at closely. Drugs to treat the condition can then be tested in the test tube.

What about adult stem cells and these new "iPS" cells? Shouldn't we be looking at them as well?

We are. It is not an either/or situation. About half of public funding for stem cell science goes to adult stem cell work which does not use embryos. It should, of course, be the best science that gets the funding in any event. Embryo research is only allowed if using adult cells would not be as effective. The prospect of induced pluripotent stem (iPS) cells (see page 10) is exciting as it offers the same potential as using embryonic stem cells without having to actually use embryos or harvest eggs. But it is too early to say where this is going to lead and when. ●

Dr Harris spoke at the charity's national conference in September 2008. Listen to the podcast at www.muscular-dystrophy.org

Animals in research

by Dr Marita Pohlschmidt, Director of Research, Muscular Dystrophy Campaign

Almost everybody will agree that we do not like to see animals suffering. And many of us will have read reports that animal experiments are unnecessary, unreliable and do not have any benefit for medical research. In this article we will look at some key questions and give you the opportunity to make up your own mind on the use of animals in research.

Is animal research necessary?

Many key developments in 20th century medical history have involved, at some stage, testing on animals. More than 70% of the Nobel prizes for physiology or medicine involved animal research. Examples of such medical advances which have transformed healthcare around the world include antibiotics, vaccines, chemotherapy, penicillin, blood transfusion, kidney transplants, insulin for diabetes and asthma inhalers. Of particular relevance to us, new technology such as gene therapy for muscular dystrophy

would not be possible without pre-clinical development in animals (see box 2).

Although the results of tests on animals don't give scientists a watertight answer as to whether a treatment will work in a human body, it does provide initial evidence of its safety and efficiency as well as its limitations. Results of animal experiments also show researchers which aspects of the new approach need improvement and help to plan the next set of experiments.

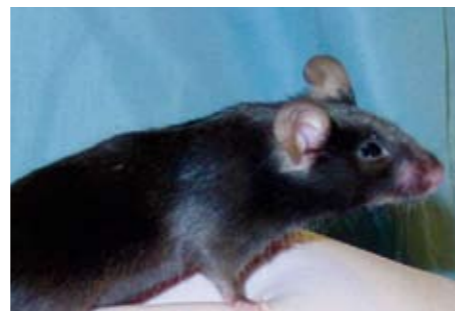
However, animal research is not only important when it comes to developing a treatment. Medical research also aims to understand the human body and what actually causes disease. Animal research is vital throughout the whole process, from understanding the biological mechanism of a disease to the development of treatments. As well as extending and improving the quality of life for millions of people, this research has also had a huge impact on veterinary medicine for pets and farm animals.

What is an animal model?

An animal model is a laboratory animal useful for medical research because it has specific characteristics that resemble a human disease or disorder – the biological similarity between animals and humans means that if an animal has a gene mutation similar to that which occurs in humans, they can present a similar set of symptoms.

Animal models of genetic diseases such as most neuromuscular conditions can be:

- spontaneous (naturally occurring in animals) for example, a commonly used model of Duchenne muscular dystrophy is the *mdx* mouse (see photo above) which has a mutation in the dystrophin gene which naturally occurred OR
- bred in the laboratory to have a similar gene mutation as that present in the human condition for example, a mouse model of Emery–Dreifuss muscular dystrophy was created by introducing a mutation into the lamin A gene of mice.



“Although cell culture experiments can help us to assess the potential of novel approaches to treatment, only by understanding and testing such therapies in the complex environment – the whole organism – can we develop clinically useful protocols. As clinical trials develop into effective treatments, the Duchenne community will have a lot to thank the *mdx* mouse for.”
Prof. Dominic Wells

Do animal experiments give scientists the right information?

Animals and humans have more biological similarity than often believed – 90% of our DNA is the same as mice – and animals often get the same diseases as us. So it stands to reason that studying a disease in an animal model gives scientists vital clues of what goes wrong in a human body.

Since the first gene for a muscle disease was identified in 1987 – the gene for Duchenne muscular dystrophy – scientists have discovered more than a 100 genes for other muscular dystrophies and related muscle diseases, like Charcot-Marie-Tooth and spinal muscular atrophy. For many of these diseases an animal model exists – either certain species can fall ill naturally like humans, or alternatively the models have been created in the laboratory (see box 1). The research advances made in the last 20 years have been impressive – scientists now understand a lot more about how a healthy muscle functions and the biological

mechanisms that lead to disease. Animal research has played a vital role in getting to this stage and will continue to be important as we look for further treatments and, one day, cures.

Are there other research methods?

Yes, other methods are available and researchers make sure they have exhausted these methods before moving on to animal experiments. These methods however, can not be regarded as alternatives; they are complementary methods and each has their value in the development of treatments.

The study of cells and tissues in the laboratory – in vitro experiments – can give first insights into biological processes. The body though, is very complex and is more than the sum of its cells and tissues. For example, if we were to study single muscle cells, from somebody with muscular dystrophy, grown in a Petri dish we would not necessarily detect anything wrong with them. It is only when we see the whole picture – when the cells are part of a muscle – that it becomes evident that they don't work properly and break down because of muscle contractions.

How many animals are used for research in the UK?

Approximately 3 million animals are used in animal research each year. In the last 30 years this number has nearly halved, although there has been a small increase in the last six years. This is because of a boost in funding for medical research and the increased number of animal models that have become available for genetic diseases. Since 1995 funding has increased by 50% whereas the number

Zebrafish are a common and useful model organism for studies of animal development and gene function.



© Steve Bastkauf

The “Exon Skipping” Study

A clinical trial to test new exciting technology to treat Duchenne muscular dystrophy started in 2007 with Department of Health funding. This therapeutic approach uses short DNA fragments to restore dystrophin expression in muscles of affected boys. Muscles make up more than 30% of our bodies and the challenge is to efficiently deliver these small fragments to all the muscle cells including the heart. It was only because of the availability of the *mdx* mouse – an animal model with the same gene defect as Duchenne muscular dystrophy – that scientists were able to test and refine this technology in a living organism and ensure that it moved into a clinical trial.

Vitamin C clinical trial

A clinical trial started in 2006 after it was reported that a mouse model of Charcot-Marie-Tooth disease showed convincing improvement in symptoms after treatment with Vitamin C. Without animal research the potential of this safe and easily available treatment would not have been highlighted and would not have progressed to clinical trial. The trial will be the first large trial of a therapy for Charcot-Marie-Tooth disease, which is one of the most common inherited neuromuscular conditions.

“When I learned that my boy had Duchenne muscular dystrophy I was devastated. My only hope is that scientists will win the race against time to develop a treatment that at least will stop this devastating disease progressing so quickly.”
Phillippa Farrant, mother of a son with Duchenne muscular dystrophy

of animals used increased by less than 18% (www.rds-online.org.uk).

Eighty-three per cent of the animals used are rats, mice and other rodents. Most of the remaining animals used are fish (10%), and birds (4%). Dogs, cats, horses and primates were used in less than 1% of all medical experiments involving animals (www.scienceandresearch.homeoffice.gov.uk).

All animals are specially bred for research and no unwanted pets or strays are allowed to be used.

Is animal research regulated in the UK?

The UK has some of the strictest regulations in the world. All animal research has to adhere to the 1986 Animals (Scientific Procedures) Act

which means that welfare is considered while still allowing medical research to progress. Any institution that wants to carry out animal experiments has to apply for a special license from the Home Office. Inspectors employed by the Home Office make surprise visits to the laboratory to ensure standards are met.

At the heart of any animal research are the 3 Rs that describe the basic principles every researcher should think about to avoid unnecessary use of animals.

- **Replace** animal research by the use of alternative methods.
- **Reduce** the number of animals used as much as possible.
- **Refine** experimental procedures so that animal suffering is reduced to a minimum.

The Muscular Dystrophy Campaign funds research that involves animal research because we believe that the use of animals in research is necessary to develop effective treatment and cures. We acknowledge concerns about animal welfare and do not fund animal research unless it is essential. Our grant application process ensures that scientists have the legal requirements in place, as defined in the 1986 Animals (Scientific Procedures) Act, which allows them to carry out animal experiments at their institution. ●

All about clinical trials

by Dr Marita Pohlschmidt, Director of Research,
Muscular Dystrophy Campaign



©Stockphoto.com/Marcelo Wain

Since the first gene for Duchenne muscular dystrophy was discovered in 1987, scientists today have a better understanding about how muscles function and what goes wrong when disease strikes. The world of science is buzzing and researchers are starting to express cautious optimism that treatments might be available in the near future. Here we take a look at clinical trials in general and some new developments in the field of muscle disease.

What is a clinical trial?

In the science world, the term that currently resonates throughout the country is "Translational Research". It describes the transition of novel technology from the laboratory to the clinics. Clinical trials are at the

centre of this process, because they represent the fastest and safest way to answer questions about the safety and effectiveness of a drug or treatment. Participation in clinical trials is voluntary and the clinical protocol – the detailed plan of the study – has to follow strict ethical guidelines. The mere fact that a clinical trial is starting is cause for optimism, however it must be remembered that only 20% of clinical trials are successful and it is not a guarantee for a treatment.

What are the phases of a clinical trial?

Phase I involves evaluating the drug or treatment for its safety in a small number of healthy people or patients. This phase shows how the

body copes with a drug, what dose is safe and what its side effects are. About seven out of 10 drugs or treatments will successfully make it through this phase.

Phase II, which can last up to two years, tests the effectiveness of a treatment on a larger number of patients. Participants are sometimes divided into groups and the benefit of the drug is compared to a placebo, which could be described as an "empty" drug. Usually the patients don't know whether they have been given the real drug or the placebo. The trial is then known as a 'blinded study'. Phase II trials are sometimes divided into phase IIa and IIb. **Phase IIa** is specifically designed to assess how much of the drug should be given, what's known as 'dosing requirements'. **Phase IIb** is specifically designed to study how well the drug works at the prescribed dose(s).

Phase III involves a larger number of patients and follows the same process as Phase II. This step can take two to three years. The aim is to obtain a more thorough understanding of the effectiveness and benefit of the drug.

Phase IV evaluates the long term risks and benefits of the drug once it's available on the market.

Why participate in a clinical trial?

People have different reasons. Some want to have a more active role in their own health care or would like to benefit from new research developments before they become more widely available. Clinical trials inevitably carry a risk though and so it is very important that an informed decision is made. Understanding the details of the clinical trial process and the impact it has on participants and their families is essential before a final commitment is made.

Ongoing clinical trials

An increasing number of clinical trials into treatments for people with muscle disease are taking place all over the world. Find out more about three of them here:

Exon skipping

The MDEX or Exon Skipping study is a clinical trial, run by a consortium of scientists, that tests a new gene therapy approach that might halt or even reverse the progressive muscle weakness in boys with Duchenne muscular dystrophy. This new approach uses short DNA fragments – known as 'molecular patches' – to restore production of the defective protein dystrophin. The technology is very specific and its application depends on the mutation that a boy with Duchenne carries in his DNA. A phase I/II study that involved nine boys has taken place, with the full results due to be published in April 2009. The Muscular Dystrophy Campaign was instrumental in setting up the consortium in 2005, securing £2.1m from the Department of Health and the Medical Research Council.

"The results of the first MDEX clinical trial shows that exon-skipping works without significant side effects in patients treated locally (injected into a muscle in the foot) with the molecular patch produced in collaboration with AVI Biopharma. We look forward to starting the intravenous trial in the first quarter of 2009 which will show if body wide treatment is possible and safe"

Prof. Dominic Wells, Imperial College London.

The mere fact that a clinical trial is starting is cause for optimism, however it must be remembered that only 20% of clinical trials are successful and they are not a guarantee for a treatment.

PTC124

PTC Therapeutics, a US-based biotechnology company is currently testing a drug called PTC124 which targets a specific type of mutation in the DNA. The mutation is called a "nonsense" mutation which creates a premature stop signal in the dystrophin gene so that no protein can be produced. Approximately 10-15% of all boys with Duchenne muscular dystrophy have this type of nonsense mutation. Following promising results in a small group of boys, PTC Therapeutics is conducting a larger international study involving 37 medical centres across the world including three in the UK, which are in London, Newcastle and Oswestry.

PTC Therapeutics recently completed enrolment ahead of schedule for its Phase 2b trial of PTC124 in nonsense mutation Duchenne/Becker muscular dystrophy. *"Early achievement of this goal, thanks to the extraordinary efforts of our investigative teams, patients and families, means that study results will be available that much sooner to the broader community,"* explained Diane Goetz, PTC's director of patient advocacy. *"We will be providing periodic updates about the progress of the study through our email update list. To join our list, please visit www.ptcbio.com and check the 'Contact us' section."*

Vitamin C

A clinical trial conducted by Dr Mary Reilly and funded by the Muscular Dystrophy Campaign aims to assess whether Vitamin C can help improve the symptoms in people with Charcot-Marie-Tooth (CMT). CMT affects the peripheral nerves – that is the nerves that run from the spinal cord to all other parts of the body – and impacts upon the movement and feeling in the arms and legs. It affects 1 in 2,500 people in the UK. The study is part of a bigger European trial and involves more than 40 people in the UK. This is the first large clinical trial of a therapy for CMT and if the study shows that Vitamin C is of benefit, a safe and low-cost medicine will be available.

"We are now 18 months into a two year therapeutic trial of Vitamin C in CMT 1A. Data analysis begins mid 2009, providing an answer to whether Vitamin C, shown to be effective in slowing animal models of this inherited neuropathy, is also effective in slowing the progression of the disease in our patients. In addition, the trial expands our knowledge of the natural history of CMT, best parameters to monitor change in function, and the creation of a local and international network of expert CMT centres. These are vital to improve patient care by accelerating the translation of lab research to clinical practice."

Dr Mary Reilly, University College London •

SNT-MC17/idebenone in development as treatment for Duchenne muscular dystrophy

Written by Thomas Meier PhD, Santhera Pharmaceuticals, Switzerland
Gunnar Buysse MD PhD, University Hospitals Leuven, Leuven, Belgium

In Duchenne muscular dystrophy progressive muscle weakness results in respiratory and cardiac illness which are life threatening complications of this disease. Subclinical or clinical cardiac involvement is seen in approximately 90% of Duchenne muscular dystrophy patients with dilated cardiomyopathy being the most commonly observed cardiac pathology. Assisted ventilation has become a standard of care in Duchenne muscular dystrophy management, but respiratory complications and insufficiency remain a major cause of morbidity and early mortality in Duchenne muscular dystrophy patients.

SNT-MC17/idebenone is a small molecule which has been developed for its efficacy to increase the production of cellular energy in mitochondria, the “powerhouses” of each cell in the body. The molecule is also cell protective due to its anti-oxidant properties. In Duchenne muscular dystrophy lack of dystrophin causes mitochondrial dysfunction, impaired energy homeostasis and oxidative stress, which contributes to the cellular pathology in skeletal muscle and heart tissue. Therefore, there is a good scientific rationale to investigate SNT-MC17/idebenone as a potential treatment option for Duchenne muscular dystrophy, specifically for its therapeutic efficacy in cardiac and respiratory functions.

As a first step to test the potential efficacy of SNT-MC17/idebenone in this disease, a long-term blinded, placebo controlled study was conducted in the dystrophin-deficient mdx mouse, a well established animal model for Duchenne muscular dystrophy (1). For this, SNT-MC17/idebenone or placebo was given from age 4 weeks until 10 months in mdx and normal mice. Presymptomatic-

initiated and long-term idebenone treatment significantly corrected cardiac diastolic dysfunction and significantly improved cardiac systolic contractile reserve (as such preventing mortality from cardiac pump failure during pharmacological dobutamine stress). In addition idebenone significantly reduced cardiac inflammation and fibrosis, and significantly improved voluntary running performance in mdx mice.

Encouraged by these positive preclinical data, a phase 2 clinical trial in Duchenne muscular dystrophy boys was conducted (DELPHI trial). In total 21 Duchenne muscular dystrophy patients (8-16 y) with cardiac dysfunction were enrolled in the double-blind randomized placebo-controlled trial. Comedication with glucocorticoids was allowed at stable dosage and both ambulatory patients and wheelchair-dependent patients were included. Thirteen patients received SNT-MC17/idebenone as a daily dose of 450 mg for 52 weeks, 8 patients were randomized to the placebo group. All subjects completed the study; the frequency and type of adverse events was comparable in the active and placebo treatment groups indicating good safety and tolerability of SNT-MC17/idebenone.

Patients receiving active drug significantly improved in myocardial deformation properties of the left ventricular inferolateral wall of the heart to a greater extent than patients on placebo. This improvement is clinically relevant as it assesses the function of the region of the heart, which in Duchenne muscular dystrophy patients is affected early and most severely. In addition and of equal potential clinical importance, patients receiving SNT-MC17/idebenone improved on respiratory strength parameters (peak flow and peak flow as % of predicted values) while



Above: Thomas Meier and Gunnar Buysse

patients on placebo deteriorated during the 52 week study period.

In summary, this is the first indication of clinical efficacy with SNT-MC17/idebenone on functional cardiac and respiratory parameters in Duchenne muscular dystrophy. Further research is required, and the DELPHI trial results provide a strong basis and guidance for the planning of additional clinical development studies with SNT-MC17/idebenone in Duchenne muscular dystrophy. Accordingly, Santhera Pharmaceuticals is currently planning to conduct such a Phase III clinical program in Europe and North America starting next year.

1) Buysse G., et al. (2008) Long-term blinded placebo-controlled study of SNT-MC17/idebenone in the dystrophin deficient mdx mouse: cardiac protection and improved exercise performance. Eur Heart J. 2008 (Epub ahead of print 2008 Sep 10) doi:10.1093/eurheartj/ehn406

The technical terms in this article are defined in the glossary on page 25.
See also www.santhera.com

From donation to innovation – how is our research money spent?

By Dr Julia Ambler*, Head of Grants, Muscular Dystrophy Campaign

* Dr Ambler is currently on maternity leave

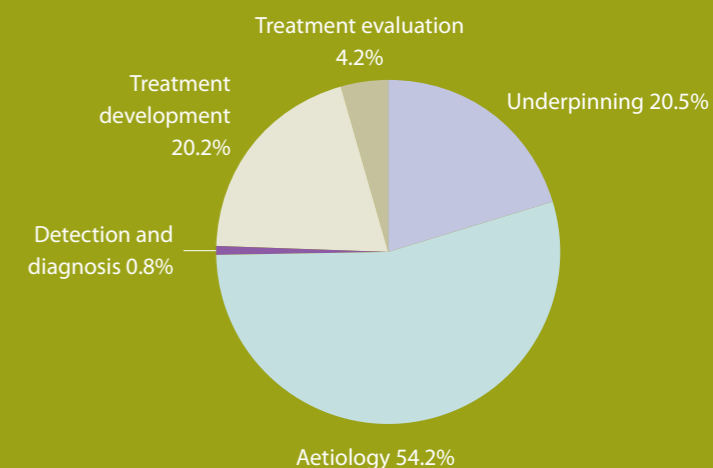
Charities are important contributors to research funding and the Muscular Dystrophy Campaign is no exception. Each year we contribute around £1.7 million to research with projects varying from basic science to clinical trials. Since you – our families and supporters – donate the money for research we feel that it is important to demonstrate which areas have been invested in and how relevant and timely these investments are.

In 2007 the Association of Medical Research Charities (AMRC) and the UK Clinical Research Collaboration (UKCRC) invited us to take part in an exercise called “From Donation to Innovation”. The exercise was a follow-on from an analysis of the research portfolios of the 11 largest UK charities and government funders including the Wellcome Trust and the Medical Research Council. “From Donation to Innovation” gave 29 smaller and medium sized charities the opportunity to analyse their research funding and compare it to other charitable and government funders.

All participants used the same classification system developed by UKCRC that allowed them to code their research investments by health (and disease) category and the type of research activity. As in the initial analysis of the biggest UK funders, this exercise covered directly funded, peer-reviewed research in the UK between 1 April 2004 and 31 March 2005. During this time the Muscular Dystrophy Campaign funded – as a medium size charity – 36 research projects with annual costs of £1.52 million.

A number of interesting observations arose from the report. The spread of research funding was representative of the conditions we cover with the focus on musculoskeletal research (88%) and the next largest share going to neurological research (6.6%). When it

Muscular Dystrophy Campaign Investment by Research Activity



comes to research activity (see graph above), we invested more than half of our funding (54.2%) into understanding the cause of disease (known as “aetiological research”). This type of research covers the discovery of disease genes and understanding how mutations in these genes can lead to disease. The second largest investment (20.5%) was in ‘underpinning research’ an area that includes projects to increase understanding of normal muscle and nerve function. Aetiological research forms an important step for diagnosis and, combined with underpinning research, is essential for the development of treatments. We spent about 20% of the research budget to investigate new approaches to treatment.

The report has provided us with an excellent snapshot of where our money was invested in 2004-2005. In summary, the results are reassuring because they show that we invested similar proportions of our

research budget in line with other UK funding institutions. It showed that the way we allocate research funding works well and that the charity has made the right strategic decisions.

In the coming years we will continue to analyse our research funding so that we can monitor how our funding changes with time. This way we ensure that we invest in line with our research strategy or alternatively it helps us make the necessary changes. We might find in the future that our investments into basic research has paid off and we spend a bigger chunk of research funding on the development of treatments; something we know is very close to the hearts of our families and supporters. ●

You can download copies of the report from the UKCRC website at www.ukcrc.org/publications.aspx

Lab visits

Receiving yearly updates from our scientists is one way of ensuring that we keep up to date with the research we fund but we also decided that we wanted to visit them face-to-face. This allowed us to hear directly about their groundbreaking research and helped us to build our relationship with them.



Dr Peter Zammit, Kings College, London

We popped around the corner from the Muscular Dystrophy Campaign offices to visit Peter's lab in July. Presentations were given to update us on their work which aims to identify muscle stem cells in animal models of muscular dystrophy and characterise their biology more accurately. All this work is essential for the therapeutic potential of these cells to be unlocked. We have invested £419 000 into the two, three year projects which both started in 2007.



Prof. George Dickson, Royal Holloway

On a sunny Autumn day we visited George's group in the magnificent surroundings of Royal Holloway. We heard updates from the scientists working to refine gene therapy and exon skipping approaches for Duchenne muscular dystrophy. They have improved the efficiency of these methods dramatically in mouse models which is essential to give these approaches the greatest chance of success in clinical trial. We invested £296,000 in the three year project which started in October 2005.



Prof. David Brook, the University of Nottingham

In August 2008 we visited David Brook who was awarded a research grant to develop a screen to identify drugs with the potential to treat myotonic dystrophy – the most common form of muscular dystrophy affecting adults.

On this visit we were joined by colleagues from the Trusts & Supporter Development team, and representatives from the Cranbury Foundation – long time supporters of research into myotonic dystrophy. This was so successful that we would like to take more supporters with a keen interest in research to visit laboratories and see first hand the research that they support.

After tea, coffee and biscuits the research team presented their latest results. We then donned lab coats to inspect the tissue culture facilities and the "robotic equipment" that will make it possible to test several thousand drugs for their ability to treat myotonic dystrophy. We invested £24,000 in the two year project which was started in October 2008.

The supporters' visit was so successful that we would like to take more people to visit research labs.



Dr Roland Roberts, King's College London

In November 2008 we made the short journey to Guy's Hospital to visit Rolie and his PhD student, Sabrina Boehm, the first recipient of our new PhD studentships.

They updated us on their work investigating dystrophin and other related proteins. Studying the proteins' structure and how they interact will give us a better understanding of exactly how dystrophin works and provide new therapeutic targets. We have invested £78 000 in the three year studentship which started in October 2007.



Prof. Francesco Muntoni, Institute of Child Health, University College London

In December 2008 we visited Francesco's lab for the first time since they moved to their new home at the Institute of Child Health. Clinical fellow Emma Clement updated us on the brain scans and muscle MRI being investigated to improve congenital muscular dystrophy diagnosis in the clinic. PhD student Caroline Godfrey updated us on their continued search for new gene mutations. We have invested £156 000 in the three year project which was started in November 2006.

Research projects currently funded by the Muscular Dystrophy Campaign

Principal Investigator	Institution	Project Title	Total project cost	For more info
Prof. David Beeson	University of Oxford	Mutations of MuSK-interacting proteins and molecular mechanisms underlying inherited myasthenic syndrome	£336,712	p5
Prof. David Beeson	University of Oxford	RNAi in vivo for treatment of neuromuscular junction disorders	£92,556	p7
Prof. David Brook	University of Nottingham	Assays for drug discovery in myotonic dystrophy	£24,000	p7
Prof. Kate Bushby	University of Newcastle Upon Tyne	Identifying novel molecular pathways and therapeutic targets for Bethlem myopathy and Ullrich congenital muscular dystrophy	£95,485	p5
Prof. Kate Bushby	University of Newcastle Upon Tyne	Long-term application of Poloxamer 188: A potential therapeutic agent in muscular dystrophy?	£96,884	p7
Prof. Kay Davies	University of Oxford	Upregulation of Utrophin for Duchenne muscular dystrophy therapy	£179,063	p7
Dr Ian Graham	Royal Holloway – University of London	Antisense oligonucleotides for therapeutic skipping of dystrophin exons: Pre-clinical and translational development of new targets and improved delivery methods.	£213,744	p7
Prof. Jane Hewitt	University of Nottingham	Investigation of molecular mechanisms in facioscapulohumeral muscular dystrophy	£98,280	p5
Prof. Darren Monckton	University of Glasgow	Defining progenitor allele length and somatic mosaicism in myotonic dystrophy type 1	£165,020	p5
Prof. Darren Monckton	University of Glasgow	Complex repeats in myotonic dystrophy type 1 and Charcot-Marie-Tooth disease	£184,007	p5
Dr Jenny Morgan	Imperial College London	The role of extracellular matrix components in satellite cell function	£158,507	p10
Dr Jenny Morgan	Imperial College London	Factors affecting the self-renewal of mouse satellite cells	£195,100	p10
Prof. Francesco Muntoni	University College London	A combined SNP mapping and RNA profiling approach to identify novel genes responsible for congenital muscular dystrophy	£113,489	p5
Dr Ros Quinlivan	RJAH Orthopaedic Hospital	Pilot project investigating the use of novel anklefoot orthosis and footwear combination to improve walking stability in children with Duchenne muscular dystrophy	£32,418	p7
Dr Charles Redwood	University of Oxford	Analysis of the effects on contractile function of mutations in beta-tropomyosin that cause different inherited myopathies	£150,097	p5
Dr Mary Reilly	University College London	Randomised double blind placebo controlled trial of long-term ascorbic acid treatment in Charcot-Marie-Tooth disease type 1A	£210,602	p7
Dr Mary Reilly	University College London	Strengthening hip flexors to improve walking distance in people with Charcot Marie Tooth disease	£115,950	p7
Dr Roland Roberts	Kings College London	Interactions of the dystrophin protein	£78,240	p5
Dr Lesley Robson	Barts and The London School of Medicine and Dentistry	Polycomb gene family member Bmi1 in the specification and maintenance of myogenic satellite cells	£116,179	p10
Dr Michael Rose	King's College Hospital	A UK study of psychosocial determinants for quality of life in muscle disease	£43,555	p7
Prof. David Rubinsztein	University of Cambridge	Oculopharyngeal muscular dystrophy – pathogenic mechanisms and therapeutic strategies	£171,814	p7
Prof. Volker Straub and Prof Dominic Wells	University of Newcastle upon Tyne Imperial College London	Assessment of muscle fibre damage in patients and in animal models for muscular dystrophy by MRI	£469,497	p7
Prof. Douglass Turnbull	University of Newcastle Upon Tyne	Exercise therapy for patients with mitochondrial myopathies	£153,502	p7
Prof. Douglass Turnbull	University of Newcastle Upon Tyne	Prevention of transmission of mitochondrial DNA disease	£166,897	p7
Dr Peter Zammit	Kings College London	Relating satellite cell heterogeneity to stem cell function	£191,381	p10
Dr Peter Zammit	Kings College London	What controls the efficiency of muscle regeneration?	£173,113	p10

Update on the 2009 research grant round

Every August the research team at the Muscular Dystrophy Campaign invites researchers and scientists to submit project proposals as part of the annual grants round process. In 2008 we received 34 proposals for research projects and our brand new PhD studentships.

The Muscular Dystrophy Campaign uses a strict peer review system to make sure we fund only high-calibre research that will contribute

significantly to major global research advances into neuromuscular conditions. Each grant application is sent to carefully selected reviewers around the world. These prominent researchers, who have relevant scientific expertise, are asked to evaluate the grant applications.

The Muscular Dystrophy Campaign has its own committee of independent scientists and clinicians that makes recommendations for research funding to the Board of Trustees, based on the reviewers' comments. Decisions are made in June and July and successful projects usually start in Autumn. ●

TREAT-NMD

European network creates worldwide partnerships to improve treatments for muscle disease.

by Rachel Thompson, TREAT-NMD, PR and Communications Officer



Funded by the European Commission, TREAT-NMD is a 'network of excellence' which was launched in 2007. It aims to accelerate cutting-edge treatments for neuromuscular conditions. Working closely with scientists, healthcare professionals, the pharmaceutical industry and patient groups around the world, the network is bringing forward new therapies and advancing diagnosis and care. The network has 22 core "partners" (universities, patient organisations and pharmaceutical companies) in Europe and close collaborations with many more across the world.

Improving "trial readiness"

Recent advances in cutting-edge therapies mean that clinical trials are already starting to take place in some neuromuscular conditions, such as Duchenne muscular dystrophy. But even though researchers are continuing to identify promising new therapies, it is still a challenge to get these therapies into clinical trials to prove whether or not they are effective.

TREAT-NMD is an important new approach to collaborative research in neuromuscular conditions. It aims to create the infrastructure to ensure that the most promising new therapies reach patients as

"It's really exciting to see how timely this initiative has been. The need to work together on the next phase of delivery of treatments for these devastating conditions is something that has caught the imagination of groups across the world. TREAT-NMD is the catalyst for this collaboration and provides a crucial platform for it to become a reality."

Professor Kate Bushby, TREAT-NMD network coordinator, Newcastle University

quickly as possible. The network is active in a wide range of areas, from preclinical research to diagnostic standards to patient care, but the driving force behind all of its activities is to build up the tools that are needed to bring new therapies more quickly from the lab to the clinic – from the bench to the bedside.

Bringing down the barriers

Neuromuscular conditions are comparatively rare and this creates additional barriers to getting a clinical trial off the ground. To recruit enough patients, trials often have to be multi-national, multi-centre studies, which makes the situation even more complex because of differences in legislation and even the differing ways patients throughout the world are treated. The difficulty finding both the right patients and the specialist clinical centres with the necessary expertise means that setting up a trial is an excruciatingly slow process, often taking years to complete. All of this means that running a neuromuscular clinical trial is an expensive



Above: TREAT-NMD is based at The Centre for Life, Newcastle-Upon-Tyne

and time-consuming business, and not one that is very attractive to pharmaceutical companies.

TREAT-NMD aims to change all this by setting up an infrastructure that makes it much easier to find the centres to conduct the trials and the patients to recruit into them. The patient registries initiative and the network of trial sites are two key parts of this "trial-readiness" strategy.

The TREAT-NMD patient registries and trial sites network

Until recently, in most countries, there has been no centralised database which contains genetic and clinical information about patients with a particular disease. In the UK this means that while each doctor knows about their own patients, no-one has an overview of all patients across the country. This is a problem because the information is essential for a clinical trial to be set up.

In collaboration with clinicians and patient organisations across the world, TREAT-NMD has created national patient registries of patients with Duchenne muscular dystrophy and spinal muscular atrophy. These databases contain the information needed to establish whether a particular patient might be eligible for a trial, together with the means of contacting them. Registries for other conditions are also in preparation. These individual national registries feed into a global database that can be accessed by researchers planning trials.

The database is safe for patients since it complies with all EU and national data protection legislation and has full ethical approval. Importantly, the information it

contains means it is a tool that will save the pharmaceutical industry valuable time and resources when recruiting patients for clinical trials, and thus in the end make sure treatments are approved more quickly. To find out more or to register yourself or your child in one of the UK registries, please visit www.treat-nmd.eu/patientregistries.

As well as finding patients for trials, TREAT-NMD has also set up a centralised source of information about clinical sites with the expertise to host a clinical trial. When a researcher or pharmaceutical company is planning a trial, this registry means they have all the data they need at their fingertips.

In all its activities, TREAT-NMD is not replacing the existing clinical centres, research groups and patient organisations who are doing so much valuable work in the field. Instead, it is helping them work together more effectively on a global scale. The network is working closely with patient groups, including the Muscular Dystrophy Campaign, to lobby for the implementation of best-practice care nationally. TREAT-NMD is already regarded as a model by groups outside Europe, such as the US National Institutes of Health and patient groups worldwide, who can see that the tools the network is creating are already making a tangible difference to researchers and clinicians, to the pharmaceutical industry, and ultimately to the patients themselves. ▶

Visit the TREAT-NMD website at www.treat-nmd.eu to find out more and to sign up for its fortnightly newsletter or call +44 (0)191 241 8605.

"By providing carefully designed infrastructure to support all stages of therapy development, and promoting necessary collaborations among patients, advocacy groups, academic institutions, industry, and governmental agencies, internationally, TREAT-NMD is becoming the essential, go-to resource to advance novel treatments for devastating neuromuscular diseases."

John D. Porter, Ph.D. Program Director, Neuromuscular Disease, NINDS/NIH Office of Translational Research, USA

"The search for effective treatments is of prime importance for the 60,000 children and adults who live with these devastating conditions in the UK. The new network will hopefully accelerate the development of research in this area and take us closer to finding successful treatments for the future."

Philip Butcher, Chief Executive of the Muscular Dystrophy Campaign.

Below: Network Coordinators Prof. Kate Bushby and Prof. Volker Straub



The European Neuromuscular Centre

by Annette Boersen, M.Sc.,
ENMC research manager

From a patient's initiative to a successful European research institution: the importance of co-operation and sharing of knowledge.

"Knowledge is power. Information is liberating" so says Kofi Anan, former head of the United Nations. Scientists in the field of neuromuscular research have built up a mass of knowledge during the last 50 years and sharing that expertise is crucial in the search for effective cures for muscle disease.

In the late 1980s, European neuromuscular patient organisations like the Muscular Dystrophy Campaign saw the need to increase efficiency, co-operation and interaction between international researchers and clinicians. Identifying this need led to the setting up of the European Neuromuscular Centre (ENMC).

The patient voice is still key. The ENMC continues to be funded and steered by an international group of neuromuscular patient organisations, including the Muscular Dystrophy Campaign. A Research Committee, made up of scientists from all over Europe, steers the centre's scientific direction.

So how does the centre allow researchers, clinicians and scientists to share key information – research techniques, results, strategies – for example? Primarily through workshops.

Between eight and 10 interactive workshops are hosted each year with a different topic covered at each. The topics are decided through an application system and each application is assessed on scientific merit by the Research Committee.

Fifteen to 20 researchers and scientists attend each workshop. To date nearly 2,000 scientists and researchers from over 30 countries have taken part in more than 160 workshops.

The results of the workshops are communicated via the ENMC website and the journal, *NeuroMuscular Disorders (NMD)*. More than 150 publications directly related to these workshops have been published (as well as many indirectly related publications). The importance of these workshops is underlined by the fact that workshop reports are amongst the most cited articles in *NMD*.

The success of the science workshops means that the centre is now embracing wider issues around patients' lives and well-being. A programme of practical care workshops, which will run alongside the science workshops, is planned for 2009.

The ENMC's crucial work now also feeds into a growing European research network. The centre is a partner of the TREAT-NMD network, which works on communicating information and knowledge to scientists, researchers and patient organisations throughout Europe. ●

Find out more at www.enmc.org or contact ENMC's research manager Annette Boersen at boersen@enmc.org



A communication platform for scientists and clinicians

Led by Professor Mike Hanna – **MRC Centre for Neuromuscular Diseases** is a joint initiative between University College London's (UCL) Institute of Neurology and Institute of Child Health, other departments of UCL and the University of Newcastle upon Tyne. It brings together basic science and clinical research to promote translational research in the UK. Scientific discoveries are currently revealing an increasing number of treatment avenues but to maximise the benefit for people with neuromuscular conditions a speedy bench-to-bedside transition is required.

In February 2008, in partnership with the MRC Centre for Neuromuscular Diseases, the Muscular Dystrophy Campaign organised a two day conference at the Institute of Child Health in London. More than 320 international scientists, clinicians and patients' groups attended to hear the latest research advances into muscle disease. Professor Dominic Wells, Imperial College, said: "This congress represents probably the densest concentration of UK specialists I have ever come across."

Following the success of this first meeting, the second UK Neuromuscular Translational Research Conference will be held on 26 and 27 March 2009 at the International Centre for Life, Newcastle.

Young scientist under the microscope

Sabrina Boehm, a Muscular Dystrophy Campaign-funded PhD student in Dr Roland Roberts' group at King's College London is carrying out research into the function of the protein dystrophin. Mutations in dystrophin are the cause of Duchenne and Becker muscular dystrophy.

Where were you born?

I was born and grew up in Augsburg, Germany, and came to London to do a Masters project in 2006 in Roli's lab. I returned to start my PhD in London in October 2007.

What or who inspired you to pursue a career in science?

I think it was my biology course at school and the teacher who taught the course. She was very passionate about science and I suppose she passed it on to me. From that time on I knew I wanted to do science.

Can you tell us more about your research?

I am studying the protein dystrophin and trying to find out what other proteins in the cell it interacts with. I concentrate on a particular region in the dystrophin gene, the so called rod domain, which is also the

location of a vast majority of mutations causing Duchenne and Becker muscular dystrophy. I'm trying to investigate the (so far very poorly understood) specific functions of the rod domain and thereby contribute to a better understanding of the cause of Duchenne and Becker muscular dystrophy.

What do you like about research?

I like the fact that you can find out things that no one knew before and contribute to general knowledge and progress. In my opinion basic research is extremely important, because I don't know how people would solve a problem if they didn't even know what they're supposed to look for. Our research tells them.

What are the challenges of working in research?

The daily challenge is to keep your chin up even if your experiment has not worked for the tenth time and you have to repeat it again. The overall challenge is wanting to discover something exciting and groundbreaking but also not to throw in the towel if it doesn't happen.

When do you aim to finish your PhD and what do you hope to achieve by the end?

I'm aiming to finish at the end of 2010 and I'm hoping to have found something by then that helps us better understand the



pathology of neuromuscular conditions. I would like to be able to contribute to the understanding of how mutations in the dystrophin gene cause disease, which could be used in the design of therapies in the future.

What did the award of the Muscular Dystrophy Campaign PhD studentship mean to you?

It was very exciting because it meant that I could come back to London and continue the work that I had started in my Masters project. Roli's lab is a great environment to work in and I'm very pleased to be involved in such a promising and important field of research. ●

Tell us what you think!

1) What is your overall impression of Target Research?

2) Are there any topics you would like to be covered in the next Target Research?

3) Was the science information understandable?

4) Do you have any other comments about Target Research?

Your details (optional)

Name

Age: 25 or under 26-40
41-59 60 or over

Address

Postcode

Telephone

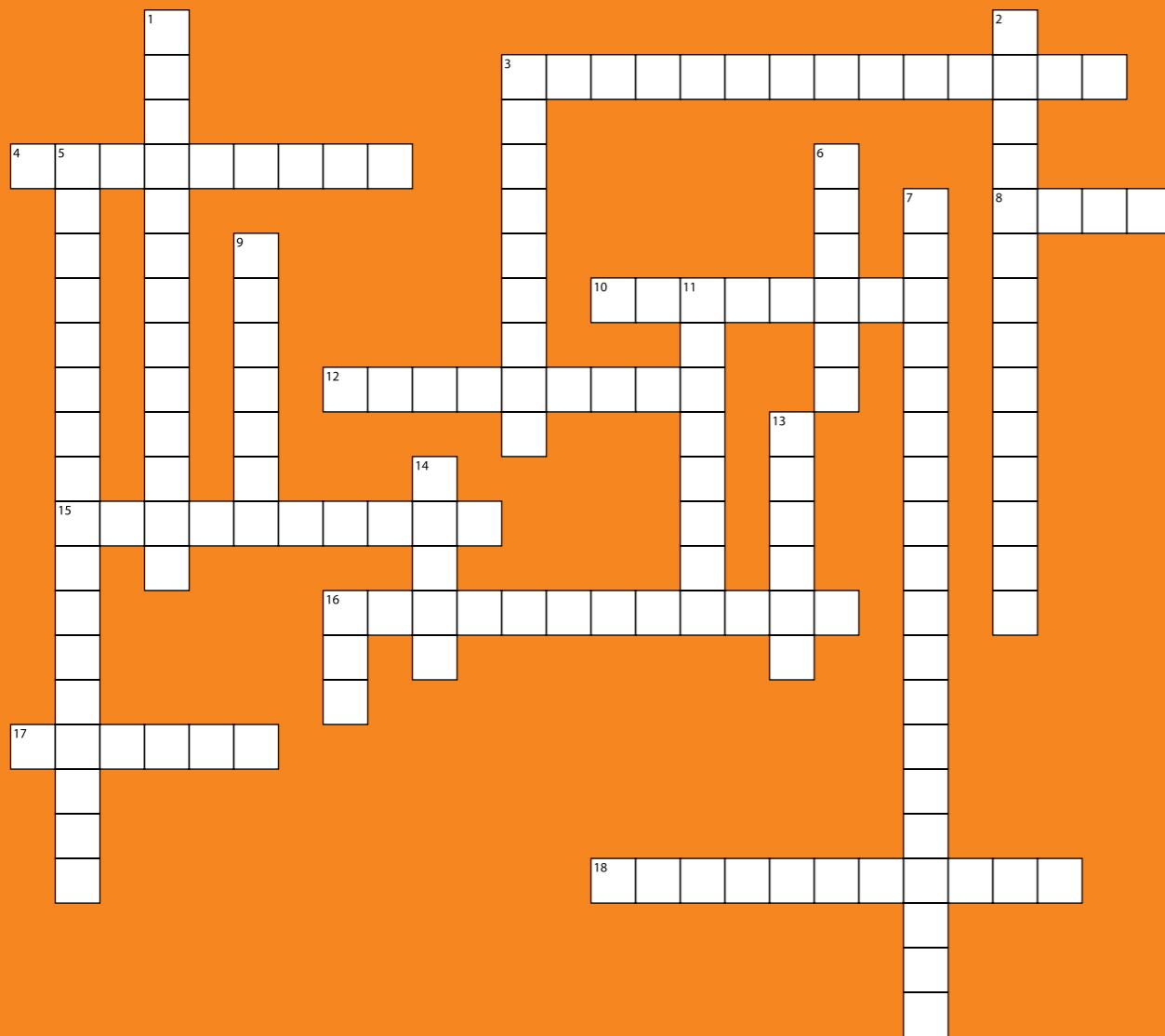
If you would like to be contacted by email, please write your email address here

Email

Please send your feedback to: **Research, Muscular Dystrophy Campaign, 61 Southwark Street, London SE10HL** or Email: research@muscular-dystrophy.org

We would like to keep you informed of our work. If you would prefer not to hear from us, please tick this box

Crossword



Across

- 3 What are muscle stem cells often called?
 4 Stem cells are either adult or
 8 The centre which funds and organises workshops clinicians and scientists involved in neuromuscular research.
 10 What is the treatment being tested in the Charcot-Marie-Tooth clinical trial?
 12 Name of the drug being trialed for Duchenne muscular dystrophy by Santhera
 15 Which protein does our young scientist Sabrina work on?
 16 Structures responsible for energy production in cells
 17 The only muscle in the body that is attached at only one end
 18 The number of research projects currently funded by the Muscular Dystrophy Campaign.

Down

- 1 What type of muscular dystrophy did Alan Emery help to discover?
 2 What is the largest muscle in the human body?
 3 Television presenter and former professional tennis player who is president of the Muscular Dystrophy Campaign

- 5 Neuromuscular condition being studied by Prof. David Brook
 6 The first name of the Director of Research at the Muscular Dystrophy Campaign.
 7 Type of muscular dystrophy that mostly affects the muscles of the face, shoulder blade and upper arm.
 9 Last name of Muscular Dystrophy Campaign chief executive
 11 The name of the 'network of excellence' whose aim is to speed the development of therapies for neuromuscular conditions.
 13 An embryo which is artificially created by combining animal and human components
 14 How old the Muscular Dystrophy Campaign is this year
 16 A commonly used mouse model for Duchenne muscular dystrophy

First correct answer wins a prize! Send your completed crossword along with your name and address to **Research crossword, Muscular Dystrophy Campaign, 61 Southwark Street, London SE1 0HL.**

Glossary

This glossary is intended to help with some of the scientific and technical terms used in this magazine.

1986 Animals (Scientific Procedures)

Act – In the UK this law safeguards laboratory animal welfare while allowing important medical research to continue. These controls are widely regarded as the strictest in the world.

Aetiology – The causes or origins of a disease.

Anti-oxidants – Molecules that slow down or prevent the damaging process of oxidation in our cells.

Basic research – Research that is carried out to increase the understanding of fundamental principles, for example, the identification of genes causing muscular dystrophy. Although, it has no direct or immediate therapeutic benefit, they are essential in the long term for the development of many therapeutic approaches, for example – gene therapy.

Biomedical research – The area of science devoted to the study of the processes of life, the prevention and treatment of disease, and the genetic and environmental factors related to disease and health.

Cardiac diastolic dysfunction – Diastolic dysfunction occurs when blood cannot pass efficiently into the heart's ventricles. This reduces the amount of blood that can be pumped around the body under sufficient pressure to reach all the tissues of the body.

Cardiac pathology – The study of the changes in the heart tissue, which can lead to a heart disease diagnosis.

Cardiac systolic contractile reserve – The ability of the heart to respond to increased demand beyond its usual workload.

Cellular pathology – The study and diagnosis of disease on the cellular level.

Clinical cardiac involvement – When the symptoms associated with deterioration of the heart muscle have begun to present themselves.

DELPHI – The name of Santhera's clinical trial, it stands for Duchenne Efficacy

Study in Long-Term Protocol of High Dose Idebenone.

Dilated cardiomyopathy – A condition in which the heart muscle becomes weak and enlarged, and fails to pump blood efficiently round the body.

DNA – Deoxyribonucleic acid is the chemical basis of genes. DNA contains the information needed for constructing proteins.

Double-blind clinical trial – A way to eliminate bias by prohibiting both patients and clinicians from knowing which people are receiving the treatment, and which are receiving a placebo during a clinical trial

Dystroglycanopathy – A group of congenital and limb-girdle muscular dystrophies caused by defects in the addition of sugar molecules a protein called 'alpha-dystroglycan'. This muscle protein forms an important link between the muscle cell and its surroundings and the sugars are required for it to properly function.

Dystrophic – Muscles affected by weakness or degeneration.

Dystrophin – The protein missing in people with Duchenne muscular dystrophy and reduced in those with Becker muscular dystrophy. Dystrophin is important for maintaining the structure of muscle cells.

Electrocardiogram (ECG) – Examination of the heart's electrical activity captured through electrodes placed on the skin.

Electromyography (EMG) – A method of recording the electrical activity of muscles. It assesses the health of muscles and the nerves controlling them.

Electron microscope – Invented in the 1930's, an electron microscope uses focused beams of electrons to create extremely magnified images. It can magnify images 300,000 times which is at least 150 times more powerful than a traditional light microscopes.

Embryo – The early life stage of a developing organism after fertilization. In humans, the embryo begins after fertilization of an egg by a sperm and persists up until week eight of pregnancy

Energy homeostasis – The maintenance of the balance between the production and expenditure of energy, in order to maintain a stable, constant energy level.

Fibrosis – This refers to the formation of excess fibrous connective tissue within an organ or tissue. Fibrosis is caused when the body is trying to repair damaged tissue.

Genome – All of the genetic information or DNA contained within an organism.

mdx mouse – This is a mouse model of Duchenne muscular dystrophy. It is a strain of mouse which has a mutation in the dystrophin gene – the gene that is found mutated in people with Duchenne. The muscles of these mice have features in common with the muscles of boys with Duchenne muscular dystrophy.

Mitochondria – These are the 'energy factories' of cells. They are structures that are found within most of the body's cells. They have their own DNA, and are passed down from the mother.

Morbidity – Poor health or illness.

Mortality – Death

Myoblasts – Cells that develop into muscle fibres. They are the intermediate cell type between satellite cells and muscle fibres.

Myocardial deformation – The myocardium is the muscles that surround and power the heart. Myocardial deformation occurs when these muscles become altered or diseased, causing them to not work properly.

Pharmacological dobutamine stress test – This test involves taking medication called dobutamine to stimulate the heart and creates the same effect as exercising. The test is used to evaluate heart and valve function in people who can't exercise on a treadmill.

Placebo-controlled clinical trial – Trial where some participants take a placebo and the others take the drug being investigated. The placebo is an inactive substance designed to resemble the drug being tested. It is used as a control to rule out any benefits a drug might exhibit because the recipients simply believe in it.

Pluripotent – Stem cell having the ability to give rise to all of the various cell types that make up the body

Protein – The building blocks of our bodies which are required for the structure, function, and regulation of the body's cells, tissues, and organs. Proteins are composed of one or more long chains of smaller units called amino acids in a specific order. The information of this specific order is stored in genes.

Randomised clinical trial – A trial where treatments and placebo are allocated randomly to participants.

Respiratory insufficiency – When the lungs cannot take in sufficient oxygen or expel sufficient carbon dioxide to meet the needs of the cells of the body.

Respiratory parameters – These are a set of tests that measure the strength of the breathing muscles

Serum creatine kinase test (SCK) – A blood test to detect muscle damage due to disease or injury. Creatine kinase is an enzyme normally only present in the muscle. When muscles are damaged however, the creatine kinase leaks into the bloodstream, and is therefore detected at higher levels than normal.

Sub clinical cardiac involvement – When the heart muscle has begun to deteriorate as a result of the disease process, but the symptoms are yet to manifest themselves.

Translational research – The clinical application of scientific medical research, from the laboratory to the bedside

Ventricular inferolateral wall – This is the region of the heart that is the earliest and most severely affected in people with Duchenne muscular dystrophy.

Hopefully she'll never
hear the name Santhera
as she grows up...



...but if she needs us,
we'll be with her
every step of the way.

As an emerging speciality pharmaceutical company, Santhera believes that the development of small molecules has a big future.

Unmet medical need is what drives our work. Particularly rare diseases and the development of orphan drugs where there are no current alternatives.

That's why we are busy developing novel solutions to improve the lives of patients with severe neuromuscular diseases.

At Santhera we care about people – every step of the way.

when it comes to science

we know how to move people



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**Muscular
Dystrophy**
Campaign



Front cover image: Scanning electron micrograph (SEM) of muscle fibres. Muscle is formed from bundles of muscle fibres. Running the length of each fibre are thin threads called myofibrils. Myofibrils contain alternating bands of the proteins actin and myosin, which give the fibres their striped appearance. The proteins slide over each other during muscle contraction
Credit: Dr Gopal Murti / Science Photo Library