Target Research

Muscular Dystrophy Campaign Research Magazine Issue 2 – December 2009

Also inside... groundbreaking research we fund, research news from around the world, and more

Clinical trials
Views from an expert and a patient

Exercise for muscle disease
A shift in the way we think?

Drug discovery
How new technology is aiding the search for new drugs

Genetic testing
Understanding what the future holds
Almost a year has gone by since the first edition of Target Research landed on your doorsteps. It has been a year of progress in the world of science with the identification of more genes that cause muscle disease; the development of new treatment approaches; the initiation of further clinical trials and the growth of new partnerships that promote the speedy translation of new research advances into patient benefit.

However, it was also a difficult year and, like other charities, the economic downturn has posed a challenge to our support of the research community - support that we have consistently provided for the last 50 years. So, we are all the more proud of our ongoing research programme that currently provides funding for 24 research projects. The only way we have achieved all this is with your help. The charity was set up in 1959 by a family and a scientist, and this key partnership continues today; indeed this magazine is an excellent example of how the charity, our supporters and our scientists work together. You can help us to continue our vital work by making a donation and registering an interest to get involved – simply fill out the form in the magazine.

In this issue you will find articles about genetic testing, exercise for people with muscle disease, a summary of the projects we are currently funding, and much more. Thank you to Talk Research members and everyone else who contributed to the second issue of Target Research.

The Research Team
Muscular Dystrophy Campaign

Dr Marita Pohlschmidt – Director of Research (centre),
Dr Kristina Mills – Research Communications Officer (right) and Dr Julia Ambler – Grants Manager (left)

Welcome
New project grants

New Patrick Research Fellowship to aid in the search for therapies for Duchenne muscular dystrophy

Professor Dame Kay Davies’ laboratory in Oxford has been awarded the first Patrick Research Fellowship which is funded through the generous support of Mr. Alexander Patrck and his family, who are long-term supporters of the charity. The fellowship will fund a post-doctoral researcher – Dr. Aurelie Govenvalle – in Prof. Davies’ laboratory. Dr. Govenvalle’s project aims to improve the efficiency of exon skipping which is currently in clinical trial for Duchenne muscular dystrophy. One of the challenges of this technique is to deliver sufficient amounts of the molecular patches to all of the muscles of the body. To address this, researchers will use a virus called the adeno-associated virus (AAV) to deliver the genetic information for a molecular patch into muscle cells where it can then be produced in large quantities over a long period of time. This approach will be tested on muscle cells grown in the laboratory and in mouse models.

Work on limb girdle muscular dystrophy continues in Newcastle

Prof. Kate Bushby will continue her work to investigate why a reduction or absence of the dystrophin protein leads to the group of muscle diseases known as dystrophopathies, which includes limb girdle muscular dystrophy type 2B and Miyoshi myopathy. Following on from recent progress in understanding the involvement of the immune system in these conditions (see p3), Prof. Bushby will use a mouse model to find out more about the cellular processes involved and potential avenues for treatment.

London grant to move Duchenne therapy closer to clinical trial

Prof. George Dickson and his colleagues at Royal Holloway are investigating the use of gene therapy to treat Duchenne muscular dystrophy. They will use the adeno-associated virus as a means to deliver a healthy copy of the dystrophin gene to the muscle. This approach has previously been hampered by the large size of the dystrophin gene so this project will investigate various methods for overcoming this hurdle and improve the efficiency of the gene therapy. If successful, this treatment will be applicable to all boys with Duchenne no matter what their mutation is, and possibly also to those affected by Becker.

New PhD Studentships

Sheffield scientists to investigate new therapeutic approach for Duchenne

Prof. Steve Winder at the University of Sheffield will supervise a project to investigate the function of a protein called the dystroglycan can help it to stay in the muscle cells. Without dystrophin – as is the case in Duchenne muscular dystrophy – the stabilising scaffold, including dystroglycan, is lost from the cells. Prof. Winder will investigate whether making small changes to the dystroglycan can help it to stay in the muscle cells and restore some stability to the muscle fibres. Experimental models will be used to investigate if this has potential as a future therapy for Duchenne.

Investigating new treatment approaches for the myasthenias

Prof. David Beeson at the University of Oxford will supervise this PhD studentship to investigate treatment approaches for myasthenia gravis and congenital myasthenic syndromes. The team wants to further understand the underlying causes of these conditions and investigate if decreasing the levels of a protein called GaQ is a feasible approach for a treatment. This is important since present treatments tend to become less effective over time and may result in serious side effects.

Improving the quality of life for people with muscle disease

We know that muscle disease can reduce quality of life but the degree to which it does is not only related to the severity of the muscle disease; factors such as how the individual perceives their illness can also play a part. Prof. John Weinman at King’s College, London will oversee this study aimed at understanding how negative perceptions of illness can impact upon quality of life. The overall aim is to devise a programme of education and training, which will be tested to see if it can alter an individual’s negative perception of their muscle disease and so improve their quality of life.

Research results

Updates and highlights from research funded by the Muscular Dystrophy Campaign this year.

Stem cell progress

Three key papers were published this year from the stem cell research we fund. Dr Peter Zammit’s group (King’s College, London) studied the role of two proteins called Pax3 and Pax7 in muscle stem cells. These proteins are ‘transcription factors’ which bind to DNA, turning genes ‘on or off’, and so are able to control how a cell behaves. This study underlined the importance of Pax3 and Pax7 in maintaining the muscle stem cell population and keeping it in a state which is ready to repair muscle when disease or injury occurs. Another study by Dr Zammit’s group further defined the specific ‘molecular signature’ of muscle stem cells when they are in their dormant state. The muscle stem cell population is normally dormant and only activated when it is needed to repair muscle. It is very important to be able to identify and isolate these dormant stem cells because they are likely to be of the most therapeutic value in future therapies involving stem cells.

In a third study, researchers in Dr Jenny Morgan’s group (Imperial College, London) provided evidence that transplanted muscle stem cells might be able to repair muscle damaged by muscular dystrophy. It was previously thought that muscle affected by muscular dystrophy might not be a suitable environment where stem cells could work efficiently because the damaged muscle is inflamed and gradually replaced over time with scar and fat tissue. To study this, the researchers used mdx mice. The muscle stem cells transplanted from healthy mice were able to regenerate older damaged muscle just as well as young muscle. However, pre-treatment of the muscle with radiation was required for the transplant to be successful so the team is now investigating what specific effects radiation has on the muscle.

Exon skipping for Duchenne muscular dystrophy

Researchers at Oxford University, led by Dr Matthew Wood, have reported improvements to exon skipping technology. They modified the molecular patches (antisense oligonucleotides) by chemically joining them to very small protein molecules known as ‘peptides’. These peptides help the molecular patches to penetrate cells more efficiently and direct them to specifically target the muscle cells. The researchers injected the modified molecular patches into the bloodstream of mdx mice and were able to show that dystrophin production was efficiently restored. Importantly, dystrophin was produced in the diaphragm and heart muscle, two areas which have been largely unsuccessful with previous molecular patches. The mice also had improved muscle strength. Further research is required to determine if this technology is safe and effective in humans.

Exon skipping for Duchenne muscular dystrophy 2B (dysferlinopathy)

Research led by Prof. Kate Bushby in Newcastle has identified a biological process involved in causing dysferlinopathy. The researchers examined a mouse model of dysferlinopathy and found that the normal process of inflammation and clearing away of damaged muscle fibres after injury was defective. Without this process the damaged muscle is not repaired, which leads to progressive muscle weakness. The findings of this study will help researchers more thoroughly understand the underlying biological processes that cause dysferlinopathy and allow the development of treatments in the future.

Research funded by donors

Researchers at Sheffield have successfully shown that muscle stem cells might be able to repair muscle damaged by muscular dystrophy. Importantly, the research was led by the late Dr. Kay Davies, who was a key figure in the development of Duchenne muscular dystrophy research. The researchers injected the modified molecular patches into the bloodstream of mdx mice and were able to show that dystrophin production was efficiently restored. Importantly, dystrophin was produced in the diaphragm and heart muscle, two areas which have been largely unsuccessful with previous molecular patches. The mice also had improved muscle strength. Further research is required to determine if this technology is safe and effective in humans.

New insights into limb girdle muscular dystrophy 2B (dysferlinopathy)

Research led by Dr. Kate Bushby in Newcastle has identified a biological process involved in causing dysferlinopathy. The researchers examined a mouse model of dysferlinopathy and found that the normal process of inflammation and clearing away of damaged muscle fibres after injury was defective. Without this process the damaged muscle is not repaired, which leads to progressive muscle weakness. The findings of this study will help researchers more thoroughly understand the underlying biological processes that cause dysferlinopathy and allow the development of treatments in the future.

See also: www.muscular-dystrophy.org/
currentgrants
Since the gene for Duchenne muscular dystrophy was found in 1986 the discovery of many more genes that can cause other forms of muscle disease has followed. The completion of the Human Genome Project in 2003 greatly accelerated this process because it gave scientists access to all the information that is stored in our DNA.

DNA is the chemical that carries the instructions for our bodies to grow, develop and function. It is the book of life, a string of building blocks of our bodies. In the human body, it is 2 meters long and contains about 6 feet of code. The instructions are coded in chains of 3-letter units. Each chain is called a gene and each gene has information for a specific protein. Proteins are the building blocks of our bodies; they are required for the structure, function and regulation of cells, tissues, and organs. Just as the letters “A”, “T”, “G” and “C” can be combined to form words, the order of these letters is the key to knowing what a person is going to do.

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Genetic testing – understanding what the future holds

Finding the genes that carry the mutations that cause muscle disease is vital to understanding what goes wrong in the muscles. This knowledge helps to develop treatments and cures but it also has an immediate benefit – it makes genetic testing possible.

Finding the genes that carry the mutations that cause muscle disease is vital to understanding what goes wrong in the muscles. This knowledge will in future help to develop treatments and, eventually, cures but it also has an immediate benefit – it makes genetic testing possible.

Different types of genetic tests are currently available. Whether a particular test is appropriate depends on the personal circumstances of the individual and how the condition is inherited. The three broad categories of genetic tests are described in this article: genetic testing possible.

Genetic tests are generally performed on a blood sample. However, every cell in our body carries the same DNA and so a genetic test can be performed on any type of cell or tissue. Sometimes a genetic test is straightforward, but sometimes it is possible to directly the geneticist straight to the gene causing the condition. The reason for this might be that the symptoms are very specific and, in the future, cures are also likely to develop a condition, and genetic testing for family planning purposes which includes carrier testing and prenatal diagnosis.

The gold standard for diagnosis

In the past a diagnosis was often based on clinical judgement alone, but since the arrival of genetic testing a more precise diagnosis can be made for an individual who is thought to have a muscle disease. This allows clinicians to give patients more accurate information about how the condition will progress during their lifetime, which allows for better preparations to manage the symptoms on a day-to-day basis. It also allows researchers to develop targeted, efficient treatments and, in the future, cures are also likely to develop a condition, and genetic testing for family planning purposes which includes carrier testing and prenatal diagnosis.

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from other muscular dystrophies, such as Becker or Emery-Dreifuss. In addition, limb girdle muscular dystrophy can be caused by more than 16 different genes. In this case the clinician follows a certain diagnostic path, which is sometimes also described as a diagnostic algorithm. The gene most likely to be mutated will be tested first and if no mutation is found the next likely one will be checked, and so on. In this case a diagnosis can take months, depending on how many genes need to be tested. Occasionally if a genetic test is not yet available through the diagnostic service, samples are sent to experts for that particular condition, either in the UK or abroad. DNA is then analysed as part of ongoing research projects.

Although enormous progress has been made in identifying and characterising the genes that cause muscle disease there are still people without a definite diagnosis. This number, however, continues to drop and the hope for the future is that a genetic test will be available for every condition. At the end of the last century it took more than a decade to sequence the human genome. Researchers more than a decade to sequence the human genome.

In this case the find the condition start before a couple begin trying to conceive. Prenatal testing is carried out because a couple may want to consider whether or not to continue the pregnancy if the foetus is affected. Amniocentesis allows them to know the foetus is affected so that they can carry on with the pregnancy armed with the knowledge that will help them to prepare and plan for the future. To carry out a prenatal test the clinician needs to take a tissue sample from the foetus from which DNA can be prepared. There are different ways of obtaining this sample; the ones currently used are amniocentesis and chorionic villus sampling.

Amniocentesis

Amniocentesis is usually done between 14 and 16 weeks of pregnancy, but under some circumstances could be performed earlier. A fine needle is passed through the abdomen and about 20ml (four teaspoons) of the amniotic fluid surrounding the foetus in the uterus is taken. This fluid contains cells from the foetus from which DNA can be prepared. The woman is awake during the procedure, which should be no more painful than having a blood test and only takes a few minutes. The risk of miscarriage is 1 in 200, but otherwise it is not thought to harm the foetus. Results are generally ready in one to two weeks.

Chorionic villus sampling

This test can be performed earlier in pregnancy, between 10 and 12 weeks. A sample is taken from the chorion, the tissue surrounding the foetus in early pregnancy. The cells in the sample are of foetal origin and therefore contain the same DNA as the foetus. Taking a sample involves passing a needle through the abdomen in a similar way to amniocentesis. It normally takes 20 to 30 minutes and is done under local anaesthetic. There is a one to two percent risk of miscarriage which is slightly higher than for amniocentesis. Results from this test can take from a few days up to two weeks.

Non-invasive prenatal diagnosis (NIIDP)

Both amniocentesis and chorionic villus sampling procedures carry a small risk of miscarriage so in recent years scientists have investigated a new non-invasive approach that eliminates this risk. Non-invasive prenatal diagnosis is based on the recent finding that fetal DNA circulates in the blood of pregnant women. However, it is only a very tiny amount and preparations of this DNA are always contaminated with the mother’s DNA which makes it very difficult to analyse. The development of this test is at an early stage and may be used in the near future to test whether a foetus has Down’s syndrome. Researchers might be able to further develop this test for inherited diseases, but its use will always be limited by the technical difficulties. At the moment this test is not available for any form of muscular dystrophy or other inherited muscle disease.

Pre-implantation genetic diagnosis (PGD)

PGD was developed in the early nineties and allows for very early embryos to be tested for a specific condition before they are implanted into the womb. Couples undergo standard in vitro fertilisation (IVF) during which eggs are fertilised by sperm outside the womb, in vitro. The embryos are grown in the laboratory until they are at the eight cell stage. A single cell is then removed from the embryo (see photo p6) and the DNA is tested for the presence of the mutated gene using very sophisticated molecular genetic techniques. The removal of the cell has not been known to affect the development of the embryo. Unaffected embryos are then implanted in the uterus or can be frozen for future use. A non-invasive prenatal diagnosis is a relatively new test, however; its provision is already embedded in the NHS. It has been successfully used to test for conditions such as Duchenne muscular dystrophy, myotonic dystrophy and spinal muscular atrophy. If you are interested in using this test you should ask a genetic counsellor whether it is suitable for the condition that you or your family is affected by.

The future of genetic testing

Currently individuals can only be tested for one gene at a time, but researchers are developing more sophisticated methods such as ‘whole genome sequencing’ which can rapidly decode all of the information in the DNA. In the future this technology might allow the testing of a person’s DNA for the presence of many genetic mutations at the same time. Genetic testing would then be much easier and quicker, although it will be years before a test like this becomes widely available.

For more information go to: www.muscular-dystrophy.org/factsheets

www.gig.org.uk

Amniocentesis

Image courtesy of Dr Sue Pickering
Clinical trials

An interview by Dr Kristina Mills, Research Communications Officer, Muscular Dystrophy Campaign

The first clinical trials for muscle disease are now underway. We asked Prof. Francesco Muntoni, from the Dubowitz Neuromuscular Centre in London, to explain how a clinical trial is set up and how patients can get involved. Prof. Muntoni is the lead scientist for the MDEX UK Exon Skipping clinical trial for Duchenne muscular dystrophy.

Where do you start?

The first step is to produce a clinical trial protocol – a document which describes in great detail how a particular clinical study will be performed, why, and by whom. The clinical trial protocol covers:

- the rationale for using a particular drug or treatment
- the safety profile of the study drug based on tests on cells grown in the laboratory and studies in animal models
- inclusion and exclusion criteria (which patients to include in the trial)
- how the study drug will be administered
- what measurements will be performed, how often, by whom and where
- how long the study will last
- what the expected outcomes are.

The clinical trial protocol document is written in close consultation with the trial coordinators, specialist trial nurses and the drug manufacturer. Wherever possible patients (or their parents) are also consulted. Besides making the journey of individuals recruited into the study as smooth as possible, a key purpose of the protocol is to confirm what will be measured before and after treatment, otherwise known as ‘outcome measures’. How to assess whether the study drug is safe must also be set out in the clinical trial protocol.

How do you decide who can and can’t participate in a trial?

The study protocol indicates clearly what characteristics the trial participants must have. These are called the ‘inclusion criteria’ and may include, for example, a minimum distance the participants must be able to walk. Also, in some studies, such as the current exon skipping study, the drug will only have an effect on boys with Duchenne muscular dystrophy who carry a specific mutation, so having that mutation is essential.

Attributes that exclude someone from participating are called ‘exclusion criteria’ and factors such as having another illness, or recently participating in another trial might mean someone can’t take part. The exclusion criteria aim to keep the participants safe, for example if you have another underlying condition it could be dangerous for you to participate in the trial.

Inclusion and exclusion criteria are not used to reject people personally; they help ensure that the researchers are able to produce reliable results and therefore get the treatment to market as quickly as possible so that the wider population can benefit. The criteria increase the reliability of outcome measures by ensuring that everyone taking part has similar symptoms at the beginning of the trial. Otherwise it is difficult for the researchers to interpret the results because they won’t know if the reason one patient responded to treatment and another didn’t is due to the drug or differences in their condition to begin with. This is especially helpful in the early phases of a clinical trial when only a few participants are involved (see box on p 10).

Who decides whether a clinical trial is allowed to go ahead?

The first stage is always finding funding! For example, the MDEX consortium applied for funding for the exon skipping study from the Department of Health and, more recently, the Medical Research Council. When we approach a grant-giving body, our proposal is sent for review by experts in the field – a process called ‘peer review’.

After obtaining funding, the protocol is sent to a series of committees that look at whether the proposed study might cause any unnecessary or avoidable risks to people taking part. Committees that might need to give approval include the Medicines and Healthcare products Regulatory Agency (MHRA), the Gene Therapy Advisory Committee (GTAC) and the relevant NHS Trusts. An ethics committee ensures the protocol meets the high standards that apply to experimental therapy, and that the information provided to parents and patients is well balanced and written in a comprehensible way.

How can people with neuromuscular conditions take part in a trial?

Register your interest in taking part in trials with your doctor and remind him or her regularly.

It is also important to join national registries if they are available for your condition. The two main registers currently available in the UK are for Duchenne muscular dystrophy and spinal muscular atrophy (see p 28). Patients or their parents can fill out an online form to register. For other rarer neuromuscular conditions, registries are in development or are run by clinicians in other countries. You may be able to register with these registries but you might need your doctor to help with this. Links and contact details for all of the registries can be accessed via the TREAT-NMD website.

Finally, you can also directly contact the centre involved in the clinical study. For example, you could contact the MDEX consortium for the exon skipping study. They will get in touch with your local doctor whose involvement is essential.

What are the risks and disadvantages of taking part in a trial?

Many patients are understandably eager to get involved in clinical trials. However, it is very important that they understand what is involved. They should discuss the study in detail with the trial doctor or nurse before giving their consent to take part.

The main disadvantage is that studies often involve multiple and frequent visits to hospital. This is obviously not always easy or practical. Procedures could be painful, for example injections and biopsies, and, of course, there is always the risk of an adverse reaction to the treatment. Participants in a trial also have to keep in mind that the treatment they receive might not provide any direct benefit for them – there is a chance they might be given a very low dose of the drug, or even a placebo.

Are there any benefits?

Most people get involved in clinical trials to gain access to new treatments before they are made widely available. They should keep in mind that although the start of a clinical trial is a very promising sign, it isn’t a guarantee for a treatment. One other advantage is that people taking part in clinical trials are followed up using even more stringent assessments than usual, even after the trial has finished. This close medical attention could result in better management of their condition.

Who funds clinical trials and is there enough funding available?

Clinical trials are expensive. In the early phases (see box on p 10), the Government and charities may be in a position to provide funding but as a trial continues and involves more participants the involvement of a pharmaceutical company is generally needed. The effort required to secure funds for clinical trials is considerable, and often we need to look at potential sources outside the UK.

The first clinical trials for muscle disease are now underway. We asked Prof. Francesco Muntoni, from the Dubowitz Neuromuscular Centre in London, to explain how a clinical trial is set up and how patients can get involved. Prof. Muntoni is the lead scientist for the MDEX UK Exon Skipping clinical trial for Duchenne muscular dystrophy.
What are the phases of a clinical trial?

Phase I evaluates the safety of the drug or treatment 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.

Phase II tests the effectiveness and safety of a treatment on a larger number of patients in comparison to a placebo. This phase also aims to determine the most effective does.

Phase III involves a larger number of patients 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 is available on the market.

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If all goes to plan, how long does it take for a potential treatment to pass through the clinical trial process and be made available for patients?

There is not a fixed answer. It depends on how innovative the treatment is. For example, a drug used for another illness is beneficial for muscular dystrophy the possibility of registering it for that purpose is more straightforward than bringing entirely new compounds into the clinical arena.

One example is Ataluren® (also known as PTC124) which is one of the experimental drugs currently in clinical trials for Duchenne muscular dystrophy. Studies in healthy volunteers were performed in 2005 and 2006 and in boys with Duchenne muscular dystrophy in 2007. This has been followed by a large study in which the extent of the clinical benefit is being explored in lots of boys with Duchenne muscular dystrophy around the world. This study will be completed by the end of 2009, and results available early in 2010. If everything goes according to plan the drug may be approved in 2011 and will then be available for the 10-15 percent of boys with Duchenne muscular dystrophy who have the particular type of mutation that this drug treats (nonsense mutation).

Is there any way that a patient can get access to a treatment before it has been tested and approved?

No, and this is for a good reason. Drugs that have not been tested could have very serious side effects and it is certainly advisable to stay away from them.

Does the time it takes to develop a treatment differ depending on the rarity and seriousness of the condition?

Not necessarily. The type of intervention planned plays a more significant role. If the treatment is similar to other drugs developed in the past it should progress more quickly. If however the treatment uses brand new technology, such as gene therapy, it is certainly advisable to stay away from them.

Can anything be done to speed up the clinical trial process?

There are three main areas that could speed up the clinical trial process:

1. Patients should register with trial sites and patient registries, and regularly discuss clinical trial opportunities with their doctor to increase the pool of potential participants.
2. Training in how to conduct clinical trials should be made available for clinicians.
3. Increased funding from the Government and pharmaceutical companies to allow the clinical trials to progress quickly from one phase to the next.

What is it like to participate in a clinical trial?

As research projects begin to move to clinical trial stage, many people are curious about what it is like to actually take part in one. We asked Oxford-based care advisor Jane Stein to visit ten-year-old William Arnott and his mother Katie at their home in Berkshire to ask them about their experience. William has Duchenne muscular dystrophy and has been taking part in the 12-week systemic exon skipping clinical trial at Great Ormond Street Hospital in London since July 2009. This trial involves injecting a molecular patch into the blood stream.

Why did William take part in the trial?

Katie Arnott: William’s name had been on the Duchenne muscular dystrophy registry for several years when I received an email from the database co-ordinator about the trial. I asked for more information about it and talked to William’s consultant before deciding it was something I could discuss with William himself.

William says that when it was suggested to him he felt ‘a little bit happy that they had found something that might work’. The trial started at the beginning of the summer holidays so instead of missing school he was missing holidays.

William Arnott: It’s annoying to have to go to the hospital every week but nice to know that it might help.

What is involved?

KA: Researchers need a sample of muscle from everyone taking part. As William had never had a muscle biopsy that was the first step. He wasn’t daunted and has no complaints. He knows that like everyone else in the trial he will also need another muscle biopsy at the end of the trial. Other tests that were done before the trial started included heart tests (an ECG and an echocardiogram) and lung function tests. Height, weight and blood pressure measurements were taken and a physiotherapist also assessed William with tests such as how far he could walk within a certain amount of time and testing grip strength with a hand held monitor.

The trial itself involves weekly, day-long visits to Great Ormond Street Hospital. William has to be at the hospital by 9am so we stay at a nearby hotel the night before. All our expenses associated with being in the trial – accommodation, meals and travel – are met.

The routine can vary a little depending upon which week of the trial it is, but usually the day starts with his weight and blood pressure being checked. Then “magic cream” is rubbed in before a needle is inserted in his arm for the delivery of the medication.

For information on ongoing clinical trials for muscle disease visit our website: www.muscular-dystrophy.org/clinicaltrials

for more patient experiences
www.trial-mdc.eu/patientstories
More about the meeting with EMEA
www.muscular-dystrophy.org/emea
More about the NDER consortium
www.nder.org
Link to our trial trial database:
www.muscular-dystrophy.org/clinicaltrials

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Is there any way of moving more quickly from research in the laboratory to trials with patients?

Studies in relevant animal models of muscular dystrophy have significantly increased the speed of testing potential treatments prior to clinical trials. The availability of suitable animal models and our understanding of them is increasing all the time, which will hopefully move treatments more quickly from the ‘bench to the bedside’.

With the exon skipping trial we found meeting with the regulatory authorities early in the process very helpful. We have very recently hosted such a meeting at the European Medicines Agency (EMA) which gave us the opportunity to inform the authorities of the specific issues involved with rare neuromuscular conditions, and also bring researchers up to speed with the current legislation. This should make the road to getting treatments into clinical trial and approved by the authorities smoother.

More about the MDEX consortium:
www.muscular-dystrophy.org/emea
More about the meeting with EMEA:
www.muscular-dystrophy.org/emea
More about patient experiences:
www.trial-mdc.eu/patientstories
More about the NDER consortium:
www.nder.org
Link to our trial trial database:
www.muscular-dystrophy.org/clinicaltrials

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With the exon skipping trial we found meeting with the regulatory authorities early in the process very helpful. We have very recently hosted such a meeting at the European Medicines Agency (EMA) which gave us the opportunity to inform the authorities of the specific issues involved with rare neuromuscular conditions, and also bring researchers up to speed with the current legislation. This should make the road to getting treatments into clinical trial and approved by the authorities smoother.
Researchers in America have published encouraging results of a study which tested a potential treatment for myotonic dystrophy. They injected short strands of DNA, known as morpholinos, into a mouse model of myotonic dystrophy.

DM1 - the most common form of myotonic dystrophy - is caused by the expansion of a repeated section of DNA in a gene called DMPK. A three-letter code in this gene is repeated many hundreds of times instead of the usual single copy, which is less than 30. This repeated genetic code gets stuck inside the nucleus of the cell and interferes with the function of other proteins. This leads to the wide range of symptoms of myotonic dystrophy. Prof. Charles Thornton’s research group at the University of Rochester showed in a treated mice the morpholinos specifically bound to the repeated section of genetic code like a magnet and blocked it from interacting with proteins. The muscle stiffness (myotonia) in the treated mice was also markedly reduced. These results in mice prove the principle that this treatment might be able to not only prevent the symptoms of myotonic dystrophy occurring but also reverse them. More research is required however before the effectiveness of this potential treatment can be tested in humans. In particular, how to administer the morpholinos to all of the muscles of the body and any potential side effects will need to be investigated.

Treatment for actin congenital myopathies proves successful in mice

Researchers in Australia have effectively treated mice that have a severe form of congenital myopathy caused by mutations in the skeletal alpha-actin gene. These mutations can cause several different types of congenital myopathy, including nemaline myopathy, core myopathies and congenital fibre-type disproportion. The actin protein is a major structural component of muscle cells and is required to generate the force for muscles to move. Mice without any skeletal muscle actin were used as a model to study whether a similar protein from the heart - cardiac actin - could be used to replace the missing skeletal muscle actin. These mice had severe muscle disease and died by the time they were nine days old. In this study these mice were then genetically modified so that their heart actin was switched on in their muscles. These mice were able to survive very actively for more than two years, which is old age for mice! Their muscles were also shown to work as well as normal mice.

This work relates to the 20-25 percent of nemaline myopathy cases caused by actin gene mutations and currently specifically only to those rare patients with the recessive disease caused by complete absence of skeletal muscle actin. The team, led by Prof. Nigel Laing, will now test whether heart actin can overcome the more common dominant actin mutations. The researchers are also screening for drugs which might be able to ‘switch on’ the production of heart actin in the skeletal muscle of patients.

Alzheimer’s research could lead to inclusion body myositis treatment

A team of researchers in California is taking a closer look at the role of a protein called amyloid-beta in inclusion body myositis. The results of this study are very similar to those seen in Alzheimer’s disease. It is known that clumps of proteins, including amyloid-beta, accumulate in the muscles of people affected by IBM, causing the muscles to deteriorate. This study investigated whether clearing away the clumps of amyloid-beta could improve symptoms in a mouse model of IBM. The researchers, led by Prof. Frank LaFerla, made the mice produce antibodies that bind to the amyloid-beta which in turn signalled to the immune system to clear the clumps of protein away. This led to an improvement in muscle function in the mice.

Looking at utrophin for Duchenne from a different angle

It is thought that a protein called utrophin may be able to compensate for the lack of dystrophin in boys with Duchenne muscular dystrophy since both proteins are structurally similar and appear to have many similar functions. Professor Dame Kay Davies’ laboratory in Oxford is searching for drugs which ‘switch on’ the utrophin gene to produce more utrophin protein in muscle. Meanwhile new research, led by Prof. James Evasti in Minnesota, has shown that an alternative or complementary approach might be to injectively modify a modified form of the utrophin protein. The researchers modified the protein to make it shorter and added a tag which allows the protein to penetrate cells. The researchers then injected the mice with the modified form of utrophin over a period of three weeks with the mini-utrophin and found that their muscles were healthier and stronger. Urophin, and not dystrophin, is injected because dystrophin might be recognised as foreign and rejected by the immune system of boys with Duchenne who do not normally produce any dystrophin. However, everybody produces some utrophin (including boys with Duchenne muscular dystrophy) so the body would be tolerant of it.

The findings of this research are very promising and may provide a new way to prevent muscle damage in Duchenne muscular dystrophy and may also be of benefit for those with Becker muscular dystrophy.

Potential heart drug for Emery-Dreifuss muscular dystrophy

Researchers in the US used a mouse model of the autosomal dominant form of Emery-Dreifuss muscular dystrophy (EDMD) to search for a treatment for heart conditions particularly associated with the condition. Prof. Howard Worman’s team injected the mice with a drug called PD98059 that is being investigated as a treatment for cancer. The treated mice had improved heart function and lived longer.

The results of these studies show that PD98059 might be able to delay or prevent the onset of the heart condition, which can be a cause of death in early adulthood or middle age for people with EDMD.

However, before PD98059 is available for medical use it has to be tested for safety and efficacy in humans in clinical trials. This will take many years, but it is an encouraging step in the right direction.

Parasite provides potential new drug for myasthenia gravis

Researchers at St Louis University have been studying tick saliva to find out if it’s properties could hold treatment answers for people with myasthenia gravis.

Myasthenia gravis is caused by a fault in the transmission of nerve impulses to muscles. It is an autoimmune condition where the immune system incorrectly attacks proteins on the muscle called acetylcholine receptors (AChRs) which normally receive the signals from nerves to tell the contract. This causes weakness and excessive muscle fatigue.

The researchers, led by Dr Henry Kaminski, studied a protein in tick saliva called rEV576 which allows ticks to avoid an immune response in humans. They treated two different rat models of myasthenia gravis with rEV576 and saw dramatic improvements in muscle strength compared to untreated rats. The treated rats were also generally healthier and lived longer.

This is a new class of drug which may, if proven to be effective in humans, be a very useful addition to the drugs already available to treat myasthenia gravis. Drugs currently available, such as corticosteroids and anti-cholinesterase drugs, bring a risk of serious side effects and can lose their effectiveness over time.
Moving our muscles – it is one aspect of our everyday lives that most of us take for granted; yet it is one of the most important. For the majority it is simple: move more during the day, spend less time sitting and you can protect your heart and the rest of your body against clogging up.

You will feel a bit happier, your blood pressure will go down and your life expectancy will increase. In simple terms, that is what exercise can do for you. What exercise is not so clear. It is clear that people with muscle disease move less. If muscles do not get used, they get smaller – the smaller the muscles are, the harder it is to move. This creates a vicious circle where low levels of movement make subsequent movement more difficult.

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This is where exercise as a clinical therapy fits in. But, before we start sending everyone with muscle disease to get an exercise prescription, more knowledge is needed.

Each muscle disease is associated with its own particular changes in the muscle although they can be classified into three broad groups. Some disorders do not allow the muscle to contract or relax properly (such as myotonic dystrophy, Charcot-Marie-Tooth disease, spinal muscular atrophy and myasthenia gravis). Another group of disorders causes a problem with the structure of muscle cells, which makes them more fragile (for example Duchenne muscular dystrophy). The final group of muscle diseases is caused by problems with burning fuels, like fat and sugar (for example Pompe disease and mitochondrial myopathy).

As you would expect, physical movements are affected slightly differently in each of these groups. Likewise, the response to becoming more physically active or doing exercise is different in each of these groups.

This is where research can help answer some very practical questions and is now starting to open some doors.

Over the past 15 years medical researchers have been collecting information to help answer the principal research question: is exercise in muscle disease safe?

Recent advances in identifying changes in DNA, the programme each of us holds for the structure of our muscles, has dramatically increased our knowledge about muscle disease. Defining these subtle changes in the DNA has led to a better understanding of the alterations in muscle function. The differences in muscle structure may make exercise safer for one condition than another, a factor which has refuelled the debate.

The other side of the argument is also being driven by the concept that doing nothing may actually harm the muscles. A practical consequence of muscle disease is that movements can be tiring and difficult. Indeed, for some people, physical movements are reduced or impossible. If movement is difficult, it is not surprising that people with muscle disease move less. If muscles do not get used, they get smaller – the smaller the muscles are, the harder it is to move. This creates a vicious circle where low levels of movement make subsequent movement more difficult.

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This is where research can help answer some very practical questions and is now starting to open some doors.

Where are we now?

Over the past 15 years medical researchers have been collecting information to help answer the principal research question: is exercise in muscle disease safe? The answers to this are different for different muscle diseases so it is difficult to give a categorical “safe” or “not safe” in a couple of paragraphs.

Most studies to date have looked at whether aerobic exercise, like cycling, is safe. Cycling has been chosen as it doesn’t have any “jarring” movements, as in jumping or running which can cause damage in the muscle. This is particularly the case for people who have structural problems in their muscles, as found in muscular dystrophy. Cycling is also good because exercise bikes don’t take up much room, they are easy to sit on and relatively easy to get on and off. The studies have mainly looked at whether the exercise caused any muscle damage and whether it improved fitness.

Of all of the muscle diseases we probably know the most about exercise in mitochondrial disease. In this group of patients the energy for muscle contraction is not produced as well as it should. As a result, people with mitochondrial disease find movement hard and exercise can be very difficult. However, the data from these groups in the USA, Europe and Australia clearly show that aerobic exercises like cycling do not damage the muscles and that energy production actually improves.

People with mild structural abnormalities of their muscle cells, like Becker muscular dystrophy, may also be able to exercise on a bike reasonably safely. The same is true for a handful of other conditions too but the data is not very substantial. So, although recent research has given us some information about whether exercise is safe for some conditions, more research is required before a clear-cut answer can be given about the safety of exercise for people with muscle disease.

Where are we going?

The next few years could be very interesting. There has been an important change in the way that we think about movement in muscle disease.
Supporting people with muscular dystrophy

One centre leading the way when it comes to physiotherapy and exercise is the NeuroMuscular Centre (NMC) in Winsford, Cheshire. For the last 10 years the centre’s physiotherapy team has been providing and supporting exercises that are tailored for people with muscle disease.

Since 1990 the centre has conducted full individual physiotherapy assessments for more than 400 registered clients. Where appropriate, clients have also been given a treatment plan with outcome goals.

Lyne Groves, Senior Physiotherapist at the NMC, comments: “Exercise programmes can be undertaken at the centre or at home. The NMC also has access to a local swimming pool for hydrotherapy, which has the advantage of relaxing the muscles with the warmth of the water while exercises are performed.

“Exercise can have cardiovascular benefits as well as strengthening limbs and muscles and improving balance and stability. Passive stretching exercises maintain joint range, muscle flexibility and length and prevent contractures. Wheelchair users are also helped to stand for short periods of time which stretches the legs, can help prevent oedema and aids respiratory and digestive function.”

Although the centre is based in the North West of England, it provides support to people from all over the UK.

The NMC also hosts a social enterprise – NMC Design+Print, it provides support to people from all over the UK.

In the past 12 months exercise trial units funded by the Medical Research Council were established in London and Newcastle. This will provide world-class facilities where patients with neuromuscular conditions can take part in exercise trials conducted jointly by these centres.

Patients have always strived to make their voices heard, but the concept of patient and public involvement (PPI) in research was only developed in the 1970s with the advent of informal Patient Participation Groups. The NHS initiated more formal arrangements for PPI in 1996. Support for involving the public in research decisions has continued to grow since then with many organisations such as the Medical Research Council (MRC) including PPI as an important part of their strategic direction. In 2007 the Muscular Dystrophy Campaign joined the ‘Natural Ground’ project, an initiative of the UK Association of Medical Research Charities (AMRC) to develop strategies for involving the public in charities such as ours.

PPI allows patients and their families to have a say in what research is funded and how the results of research are disseminated. In 2008 we started our own programme of PPI, an initiative called Talk Research. Initially this has focused on harnessing the experience of our supporters to ensure we provide research information that people are looking for, written in a way that they can understand.

This year we have extended the remit to consult patients and families on which research to prioritise for funding. We are keen to get a feedback process in place to ensure the entire research programme takes into account what is important to people affected by muscle disease.

If you would like to get involved please call 020 7803 4813 or email research@muscular-dystrophy.org

Talk research

A voyage round two grandsons

We asked John Kelly, who recently joined the Muscular Dystrophy Campaign’s Talk Research group, to tell us about how he developed an interest in and became involved in research.

“Our two grandsons, now 11 and 10, were born with myotonic dystrophy type 1 (MDM1), though none of us actually realised it at the time. The word ‘myotonic’ didn’t even enter our collective vocabularies until 2004 when one uncle found he was having difficulty in relaxing his grip after shaking hands. Fortunately, his doctor recognised this as a classic symptom of adult-onset myotonic dystrophy. Blood tests followed, and so our voyage of discovery began.

‘Professor Sir Peter Harper’s book ‘Myotonic Dystrophy – The Facts’ was an invaluable first port of call. This was closely followed by an interview with Dr Mark Rogers at Cardiff University, while our grandson was visiting us from California for Christmas. We were now beginning to perceive, albeit dimly through our amateur looking glass, what might lie ahead.

So we, as grandparents on this side of the pond, decided to become involved by joining the Myotonic Dystrophy Support Group (MDSG) in 2005, subsequently to become trustees. My son and I also attended the 5th International Myotonic Dystrophy Consortium (IMDC) in Quebec in the same year. There he became a founding member and is now the chairman of the Myotonic Dystrophy Foundation (MDF), the MDSG’s sister care group in America. We have since attended the 6th international conference in Milan in 2007 and have just returned from the 7th in Wurzburg, Germany.

The DMC is held biannually over four days. Uniquely, it attracts the largest gathering of worldwide some of 150 DM research scientists and clinicians who present their latest findings and exchange ideas. Only by attending the IDMC have we been able to appreciate the true scale of international collaboration that exists in DM research, and where else would we have had the opportunity to meet so many of the brilliant and dedicated people who are striving to find a solution. I do believe a treatment will be found one day, not only for DM but for all the dystrophies and it is this conviction which keeps my family, like countless others, heading forwards on the same voyage.

In the meantime, I am delighted to have been asked to join the Muscular Dystrophy Campaign’s Talk Research group. I believe that input from patients and families will become an evermore important component of research as the approaching era of human trials develops.”

For further advice and exercise guidelines go to www.muscular-dystrophy.org or contact the information service for an Adult Self-Management pack on 0800 652 6352 (freephone).
The challenges of developing therapies for rare diseases

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

Case study: Pompe disease

Pompe disease is a muscle disorder which affects about one in 40,000 births. It is caused by a deficiency of the enzyme α-glucosidase, which leads to accumulation of glycogen (a type of sugar) in the muscles. The most severe infantile form of Pompe disease results in early death. Less severe forms can occur at any age. Myozyme (a drug which replaces the missing enzyme) was licensed by Genzyme in 2006. It has been shown to be effective at clearing glycogen from muscles, leading to a considerable improvement in symptoms.

Small patient numbers required clinical trial sites to be set up all over the world with the initial study including 18 infants under six months old and a more recent study with 21 older children. None of the patients were treated with placebo because it was deemed to be unethical to deny these infants a potentially life-saving therapy. Instead data from treated patients were compared with previously gathered data from untreated babies.

More than £300 million was invested in developing and licensing Myozyme with ongoing costs, such as further clinical studies, totalling £37 million per year. This money must be recouped from sales to a limited number of patients worldwide, so costs per patient are high.

This is offset by the small number of patients treated, resulting in a low overall total cost.

Practical challenges

Drug development requires an understanding of the underlying biological processes causing a disease. For rare diseases though, gaining this knowledge is often hindered by less research funding and therefore fewer scientists working in the field. It is also important to be able to predict and measure how the disease will progress in order to accurately assess therapy effectiveness. This knowledge is not always available because fewer patients exist to document it. Double blind, randomised, placebo controlled trials are the ‘gold standard’ for testing any drug. However, this might not be possible for orphan drugs and alternative trial designs need to be considered. This is because fewer patients are available to take part in clinical trials, and if the disease is life threatening it might be unethical to treat patients with placebo. Often regulatory authorities will give ‘conditional approval’ of an orphan drug if patients are rigorously followed up after the drug is approved.

Looking ahead

There are many challenges associated with the clinical development of therapies for rare diseases. These challenges must be met because patients with rare diseases have an equal right to safe and effective therapies. Increasing partnership and collaboration between all stakeholders (physicians, patients and their families, industry and regulatory authorities) will continue to encourage research into rare diseases and offer hope to those in need of treatment.

The long-awaited first clinical trials are now under way to test the benefits of new therapeutic approaches to treat people affected by muscle disease. For the last 16 years the Muscular Dystrophy Campaign has played a crucial role in ensuring that funds are available to treating scientists in the UK so they can continue their vital research.

New therapies – building the case for NHS funding

By Robert Meadowcroft, Director of Policy and Operations, Muscular Dystrophy Campaign

In the future, however, once new treatments are proven to be safe and effective a new challenge emerges as we work to ensure that they are available for patients. As most of the conditions we support are classified as rare, given the relatively few numbers of people affected, drugs are likely to be expensive, so NHS funding must be assured. Second, after the first 10 years for the new drugs will be a major focus of the charity’s future campaigning activities.

What is the case we are building?

Once a drug or treatment comes to the market we anticipate two broad arguments that NHS commissioners could use to refuse access to new treatments – the high cost of the new treatments and the relatively small numbers of children and adults who will benefit.

The reality is that there are pressures within the NHS to spend its funds in areas that benefit the most patients. However, we do have powerful arguments on our side. First, NHS services are based on equity and fairness, and the need to follow an ethical approach – the first principle in the NHS Constitution is unambiguous:

The NHS provides a comprehensive service, available to all irrespective of gender, race, disability, age, sexual orientation, religion or belief. It has a duty to each and every individual that it serves and must respect their human rights.1

There is no caveat here that allows the NHS to refuse to provide a treatment on the grounds that another patient would be denied access to that treatment. There is not a ‘get out’ clause that those who have the misfortune to be diagnosed with a rare or very rare condition can be denied treatment because that treatment is too expensive.

Further, and perhaps more persuasively, most of the conditions we support are life-long progressive conditions and the current financial burden on the NHS to provide adequate care is significant. There are likely to be savings, given the potential of new treatments to slow down or even halt disease progression, and to extend the years of healthy and independent life. So, the cost of a new treatment must be offset by the reduced demands on health care, including costly palliative care. Furthermore, when health economists calculate the benefit of potential treatments they often overlook the impact that caring for somebody with muscle disease has on family members – an impact which could be reduced by an effective treatment.

We should also not forget that the Government, charities, industry and most importantly the families themselves have invested the funds necessary into research for the development of these treatments. It would be outrageous if this long-term, sustained effort and investment was simply cast aside by NHS commissioners who would deny patients access to life-saving new treatments.

Finally, there is a precedent in the NHS for the funding of an expensive therapy for a rare disease. Enzyme replacement therapy for Pompe disease costs in the region of £200,000 per patient per year. This is fully met within the NHS through the National Commissioning Group’s central funds set aside to ensure patients receive this life-saving treatment. We can use this blueprint to build future campaigns for access to treatments.

The Muscular Dystrophy Campaign is working hard to build a coalition of families, researchers, clinicians and politicians to put the case to NHS decision makers. Additionally, our campaigning work starts even before new drugs and treatments come to the market by ensuring that the design of clinical studies and the approval process consider the exceptional circumstances of the neuromuscular conditions we support (for more information, see p18). We put patients and families at the heart of this work as it is critically important that their plight is fully understood and their hopes are not dashed yet again. The Muscular Dystrophy Campaign is determined to win this fight on behalf of all people living with neuromuscular conditions.

The Muscular Dystrophy Campaign is determined to win this fight on behalf of all people living with neuromuscular conditions

1. NHS Constitution, Department of Health, HGOS (January 2009)

Find out more about our campaigns:
www.muscular-dystrophy.org/campaigns

More about EMEA and drugs for Duchenne
www.muscular-dystrophy.org/emea
High throughput screens

Molecular biology is a little like cookery. It is important to add the right amount of ingredients, mix thoroughly and leave for the required amount of time at the correct temperature to produce a successful outcome. After a little practice, most people can master baking a cake, but how many can manage baking 20 cakes or even 200 or 2,000 cakes in a single session? In most domestic kitchens it would be impossible but with a degree of automation much more can be achieved (how else could Mr Kipling succeed?). In the same way that automation and robotics have transformed many industrial processes, such as car production, they are now being applied to molecular biology and in particular to the quest to identify drugs to treat diseases, including neuromuscular conditions.

Where scientists previously performed single experiments in small plastic tubes they are now, with the help of automation and robotics, able to miniature experiments and perform several hundreds or even thousands of reactions simultaneously. The pharmaceutical industry uses robots capable of performing multiple repetitive tasks accurately, and now researchers in universities are also making use of this technology to transform the process of drug discovery.

In order to conduct a successful drug screen a robust test (or assay) is required. This could be based on a biochemical interaction between molecules or on cells grown in the laboratory. In either case it is essential to have good understanding of what goes wrong in muscle cells when they are affected by a particular condition. For many neuromuscular conditions a clear picture of the underlying molecular mechanism is now known, which has made possible the development of suitable screening assays.

Screening assays for drugs often involve growing cells which have the genetic mutation that causes a disease. The cells are grown in rectangular plates which are around 6” by 4” in size and contain 96 wells, 384 wells or as many as 1,536 wells. A different drug can then be added to each of the wells. It would be impossible for an individual researcher to perform reactions on that scale without being driven to distraction. The liquid handling robots however, can deal with dozens of plates in a single session, day after day, which allows very high throughput screens to be conducted. For example, the effect of one million different compounds on a particular cell line could be assessed over the course of just a few weeks.

When developing a drug screening assay, researchers must take into consideration how they will observe or measure the improvement in cell function after treatment. In many cases assays involve monitoring changes in the amount or location of fluorescent proteins within cells.

Developing screening assays for myotonic dystrophy

In the Nottingham laboratory two assays are under development, both of which use fibroblast cells from the skin of myotonic dystrophy patients. They have been transformed in the laboratory so that they can grow indefinitely and be used for multiple experiments.

One of the assays is based around trying to find a drug to eliminate the nuclear spots seen in myotonic dystrophy cells. The assay involves a technique called ‘in situ hybridisation’ in which fluorescent tags stick to the spots in the myotonic dystrophy cells, which allows them to be observed down the microscope.

The second assay is based on the faulty processing of genes (‘splicing’) which occurs in myotonic dystrophy cells. For this, genetically engineered cells which fluoresce red or green are used to indicate whether genes have been processed correctly. Myotonic dystrophy cells produce mostly green fluorescent proteins whereas unaffected cells fluoresce red and green (see above). The aim of the assay is to identify a compound that makes the myotonic dystrophy cells fluoresce both red and green, instead of just green, which would indicate that the normal processes had been restored by the treatment.

Using state-of-the art imaging and tissue culture robotics the Nottingham group has been able to produce assays that will allow thousands of compounds to be screened per week. The aim is to test large numbers of compounds with the assays to see whether any of the chemicals can reduce the number of spots in the patient cell lines and restore normal gene processing.

Libraries of drugs and future prospects

Some obvious questions arise, including how are the screens funded and where do the libraries of drugs come from?

Screening for drugs to treat myotonic dystrophy and other neuromuscular conditions

by Prof. David Brook and Dr Javier Granados Riveron

University of Nottingham

‘Spots’ in the nuclei of myotonic dystrophy cells

The development of robots for dealing with cells in culture also coincides with improvements to microscopes such that cells in a 96 or 384 well format can be analysed down the microscope in an automated fashion to monitor changes. Taken together these developments offer great potential in our search for drugs to treat neuromuscular conditions. In the rest of this article we will consider one example to illustrate this: screening for drugs to treat myotonic dystrophy.

Myotonic dystrophy (DM)

DM is the most common form of muscular dystrophy in adults. Its symptoms include muscle weakness and wasting, cataracts, diabetes and an irregular heartbeat. In particular, individuals with myotonic dystrophy have difficulty relaxing certain muscles, especially the hands, after use – this is called myotonia. Myotonic dystrophy was first described as a distinct clinical condition in 1909. The mutation responsible for the most common form of myotonic dystrophy – DM1 – was identified 17 years ago and it is eight years since the mutation for DM2 was published. Over this period researchers have understood an increasing amount about the underlying molecular basis of DM1 and DM2, both of which are caused by the expansion of a repeated section of DNA.

In DM1 the underlying mutation is the expansion of a three-letter code in a gene called DMPK. In an unaffected individual this code is repeated 30 or fewer times whereas in a person with myotonic dystrophy it is repeated many hundreds of times. This repetitive piece of DNA is made into RNA – the carbon copy of DNA which normally carries genetic messages from the cell nucleus to the rest of the cell (the cytoplasm) where proteins are made. However, the faulty RNA containing the extra repeats is trapped in the nucleus of DM1 cells and is not processed properly. It does not move to the cytoplasm as it should, and instead appears as distinct spots that can be seen using a microscope (see photo p20). The trapped repetitive RNA tends to bind to other proteins in the nucleus which prevents them from performing their normal functions. In particular, a protein called ‘muscleblind’ is trapped in these spots. This protein is involved in the processing or splicing of several other genes which code for proteins that have important roles around the body, such as controlling muscle contraction.

Using state-of-the art imaging and tissue culture robotics the Nottingham group has been able to produce assays that will allow thousands of compounds to be screened per week.

Above: Cells used to screen for drugs to treat myotonic dystrophy. The cells have been modified so that myotonic dystrophy cells fluoresce only green whereas unaffected cells fluoresce red and green which appears yellow when the images are merged. Unaffected cells are shown.

Robot dispensing liquid into a plate containing cells
The Cranbury Foundation
– supporting myotonic dystrophy research

by Mr Tom Chamberlayne-Macdonald, Cranbury Foundation

We have supported the work of the Muscular Dystrophy
Campaign for over ten years and continue to invest in vital
research into myotonic dystrophy. We have been fortunate to
visit a number of leading researchers over the years and were
delighted when the charity’s grant team took us to meet Prof. David Brook at
the University of Nottingham in 2008. We had a guided tour and were
given the opportunity to ask questions directly to Prof. Brook about
his work. Visiting the laboratory and seeing the research processes
and techniques in operation was extremely valuable to us as we could
really see the impact of our contribution. We were very impressed
by the work and we could see that Prof. Brook’s research findings are
making great strides towards treatments and cures for people with
myotonic dystrophy.

The work in Nottingham has gone through several phases of
development. Initial funding by a small grant from the Myotonic
Dystrophy Support Group allowed the patient cells lines to be
established and preliminary data to be generated. The Muscular
Dystrophy Campaign provided a grant of £24,000 for the development
of the assays, which in turn led to a recently awarded grant of £160,000
from the Medical Research Council that will allow 50,000 different
compounds to be screened.

Compound libraries come from several different sources. Pharmaceutical
companies have large collections of molecules and many academic
chemistry departments also have substantial collections of their own. The University of Nottingham has bought
a collection of 20,000 compounds (each in the form of a tiny volume of solution) from a commercial company.

The Nottingham group is also collaborating with the
National Institutes of Health (NIH) in the USA which have established
a collection of 3,000 compounds that have already received approval
by US regulatory bodies to be used as medicines. These are the
compound libraries used by the laboratory.

Other high throughput screens

The research described here for myotonic dystrophy is just one
example of the use of this new technology to screen for drugs to
treat a neuromuscular condition. Another pertinent example is the
high throughput screen being used by UK-based drug discovery
company Summit plc in collaboration with Prof. Dame Kay Davies in
Oxford. They are searching for drugs which increase the amount of the
protein ‘trophinin’ in muscle cells – a potential treatment approach for
Duchenne muscular dystrophy. One promising drug candidate has
already been found and is being developed further.

As our knowledge of the biology of muscle disease increases and
this valuable but expensive technology becomes more widely available, it is
anticipated that drug screens could be developed and conducted for many more neuromuscular conditions.

Prevalence of muscle disease in the UK

<table>
<thead>
<tr>
<th>Group of conditions</th>
<th>Number of patients in the UK</th>
<th>Percentage of total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscular dystrophies e.g. Duchenne muscular dystrophy, congenital muscular dystrophy, FSHD</td>
<td>6,000-10,000</td>
<td>12.0</td>
</tr>
<tr>
<td>Myotonic disorders e.g. Myotonic dystrophy, myotonia congenita</td>
<td>9,500</td>
<td>13.3</td>
</tr>
<tr>
<td>Congenital myopathies e.g. nemaline myopathy, myobutular myopathy</td>
<td>1,000</td>
<td>1.4</td>
</tr>
<tr>
<td>Distal myopathies e.g. Werdnig-Hoffmann disease, Charcot-Marie-Tooth disease, M. myotonica</td>
<td>300</td>
<td>0.4</td>
</tr>
<tr>
<td>Mitochondrial myopathies</td>
<td>3,500</td>
<td>4.9</td>
</tr>
<tr>
<td>Metabolic myopathies e.g. Pompe disease, McArdle disease</td>
<td>700</td>
<td>1.0</td>
</tr>
<tr>
<td>Periodic paralyses</td>
<td>400</td>
<td>1.3</td>
</tr>
<tr>
<td>Myositis e.g. inclusion body myositis, dermatomyositis</td>
<td>5,000-6,000</td>
<td>7.7</td>
</tr>
<tr>
<td>Spinal muscular atrophies (SMA)</td>
<td>1,200</td>
<td>1.7</td>
</tr>
<tr>
<td>Hereditary neuropathies e.g. Charcot-Marie-Tooth disease</td>
<td>23,000</td>
<td>32.0</td>
</tr>
<tr>
<td>Inflammatory and autoimmune neuropathies e.g. Guillain-Barré syndrome</td>
<td>6,403</td>
<td>8.9</td>
</tr>
<tr>
<td>Disorders of the neuromuscular junction e.g. myasthenia gravis</td>
<td>10,500</td>
<td>14.7</td>
</tr>
<tr>
<td>Myositis ossificans progressiva (MOP)</td>
<td>60</td>
<td>0.1</td>
</tr>
<tr>
<td>Total number (prevalence)</td>
<td>70,060-73,060</td>
<td>100</td>
</tr>
</tbody>
</table>

The numbers behind the conditions

The Cranbury Foundation funds research and provides support for over 60 muscle conditions, some of which are extraordinarily rare with as few as 10 known affected individuals in the UK. Although research into muscle disease has made incredible advances for many of the conditions, particularly in the last 20 years, little information on the exact numbers of children and adults affected is available.

The rarity of the conditions and the absence of reliable scientific data highlighting the numbers of people affected by a particular form of muscle disease are two of the reasons why children and adults with these conditions are often overlooked by the NHS. In several reports prepared by the Muscular Dystrophy Campaign and leading clinicians in the field, it has become evident that specialist health services in the UK are extremely patchy and health professionals often do not understand that a multi-disciplinary team is essential to improve length and quality of life.

The relatively low number of patients with neuromuscular conditions means that any drugs or treatments that are developed are expected to be costly. This makes the need for a reliable source of patient numbers even more urgent as it gives NHS commissioners key information with which they can allocate funds to maximise patient benefit. Although there are currently no effective treatments or cures available for most conditions, a number of clinical trials are under way. Scientists and clinicians are beginning to express cautious optimism that treatments might become a reality in the near future.

Together with leading clinicians in the field of muscle disease, the Muscular Dystrophy Campaign has written a report that represents the first estimate of the number of people with muscle disease in the UK. The detailed results of this review are shown in the table below.

The data in this report are essential for health care commissioners to plan and budget specialist services effectively to ensure that affected individuals and families receive the necessary multi-disciplinary health care within their own communities.

What the report highlighted

- The Muscular Dystrophy Campaign covers more than 60 diseases and provides support for approximately 70,000 children and adults in the UK.
- The severity of the conditions is highly variable – for the most severe disorders children can die at birth or in their first year of life while the mildest forms only slightly affect elderly people and have no life-limiting impact.
- About 70 percent of the people we provide support for are affected by muscle diseases that are inherited, while the remainder have an acquired muscle disease.
- The number of people in the UK affected by a given disease varies from 23,000 (hereditary neuropathies) to as low as 10 (some forms of lipid storage myopathies).

For more information about clinical trials, visit www.muscular-dystrophy.org/clinicaltrials

For more information about clinical trials, visit www.muscular-dystrophy.org/clinicaltrials
Ask a scientist

Q1. I have heard that Coenzyme Q10 supplements might be of some use for different types of muscle disease. I have facioscapulohumeral muscular dystrophy (FSHD), should I try it?

A. Coenzyme Q10 is an essential chemical within mitochondria, the tiny batteries within cells that generate the chemical ATP, which is the main energy source for all bodily activities. Coenzyme Q10 has been used to treat a very rare group of muscle disorders caused by problems in the mitochondria. However, when it comes to other more common types of muscle disease such as FSHD there is no evidence to suggest any benefit, and indeed no theoretical reason why it might work. In this article we posed some of the questions we have received recently to top researchers for further expert opinions.

Q2. What does this mean in the near (and potentially more distant) future as an effective treatment for spinal muscular atrophy (SMA)?

A. The cause of SMA is a lack of the SMN protein, which is critical for motor neuron survival. As the main research on SMA is to increase SMN levels. One way of achieving this would be to ‘deliver’ the SMN gene to motor neurons using viruses. Studies in mice show that it is technically possible to do this but it is likely to involve direct injections into the nervous system which we don’t have a lot of experience with, so safety issues will need to be considered. However, this is still a promising approach. Second, scientists are using the fact that all patients with SMA have at least one copy of the closely related SMN2 gene, which can produce small amounts of the fully functional SMN protein, but mostly makes a shortened version which doesn’t work. They are trying to find ways to make the SMN2 gene produce more fully functional, full length SMN protein. This can be achieved in cells grown in the laboratory by using small DNA molecules called antisense oligonucleotides to alter the processing of the SMN2 gene so that it makes full length SMN protein. The problem here is similar – how to best deliver the antisense oligonucleotides to the nervous system?

Third, there are drugs, such as HDAC inhibitors, which can increase the production of functional SMN protein from the SMN2 gene by altering the way that DNA is folded up into cell-like structures in the nucleus of the cell. DNA is naturally coiled which inactivates the genes. For a gene to be switched on to produce protein it needs to be uncoiled by the action of certain molecules in the nucleus. This is like a scrunched up piece of paper that can only be read once it is smoothed out. HDAC inhibitors interfere with this process of coiling and uncoiling and cause genes to be ‘switched off’. Several of these drugs have already shown positive effects in mouse models and have been tried in patients. However, they carry the risk of toxicity as they will affect other genes in addition to SMN2.

In the more distant future it might be possible that stem cells will allow the connections between muscle and nerve that are lost in SMA to be reformed by regenerating the spinal cord with new motor neurons. The technical challenges associated with directing these cells to find new connections are formidable and ‘rewiring’ the nervous system in this way is still a distant prospect.

Dr Kevin Talbot, Reader in Clinical Neurology, University of Oxford

Q3. I understand that FSHD is caused by the deletion of a highly repetitive piece of DNA called D4Z4 on chromosome 4. Is it possible that there could be different sub-types of FSHD that are caused by different variations of the D4Z4 deletion?

A. Your understanding is correct – almost all FSHD patients have a deletion of the D4Z4 repeat on chromosome 4. The number of repeated DNA segments is usually between 12 and 100 but people affected by FSHD have less than 12 repeats. FSHD patients who have a very small number of repeats (one to three copies) do tend to have a more severe form of the disease with onset earlier in life. However, this is not always the case and we do not know all the factors that contribute to the clinical severity of FSHD.

About five percent of FSHD patients do not have any deletion within D4Z4. We now know that in all FSHD patients, including those without the D4Z4 deletion, the way that the D4Z4 DNA is folded and packaged in the cell nucleus is altered. This can affect which genes are switched on or off and therefore change the way the cell behaves. Studying these molecular changes that are common to all FSHD patients may help us understand the processes occurring in the cell which lead to the symptoms of FSHD.

Prof. Jane Hewitt, Co-director Institute of Genetics, University of Nottingham

Q4. Research into some types of muscular dystrophy has identified that multiple genes are involved. Does this mean that there may be different causes within patients for a specific type of muscular dystrophy? If so does this mean that a treatment developed for a specific type of muscular dystrophy may work for one person but not another with the same type of muscular dystrophy?

A. In any one individual, there is most likely only one gene that causes the muscular disease; however the type of genetic fault can vary from person to person. In the past diagnosis was based purely on the symptoms particular patients had, but with the advent of techniques to analyse DNA, researchers have found that the picture is more complicated. This has resulted in reclassification into subtypes based on which genes are affected, such as the more than 16 different types of limb girdle muscular dystrophy (LGMD) which are known as LGMD1A, 1B, 2A, 2B and so on. Sometimes treatments will be specific to one type of mutation. For example, the recent clinical trial of gene therapy for LGMD2D conducted in the UK. In this clinical trial a virus containing a healthy copy of the gene that is mutated in LGMD2D – ‘alpha-sarcoglycan’ – was injected. This wouldn’t work for another type of LGMD such as LGMD1C which is due to a mutation in the ‘caveman 3’ gene. Therefore, it is now even more important for people with muscular dystrophy to check with their doctor that they really know the type of their disease has been diagnosed and, if not, that referrals are made for the appropriate tests. This will enable any new treatments that are developed to be made available to the appropriate patients.

Other treatments may be more generally applicable to a range of conditions regardless of the gene mutation, such as stem cell therapy or treatments that are managing the symptoms of a condition such as steroids or exercise therapy.

Prof. Katie Bushby, Co-director of the Newcastle Muscle Centre and Action Research Professor of Neuromuscular Genetics at Newcastle University

Q5. Exon skipping appears to be showing promising results for Duchenne muscular dystrophy by masking the fault in the dystrophin gene. Could research in this field be extended to cover other types of muscular dystrophy for which the specific gene or genes are known?

A. Most Duchenne muscular dystrophy cases are due to a mutation that disrupts the reading frame of the dystrophin gene (see box, above). This means that the information beyond the mutation cannot be translated into a protein. By using antisense oligonucleotides, researchers have found that one or more additional parts of the gene (exons), the reading frame can be restored and a
protein can be produced. The protein does however have a segment missing in the middle. Fortunately, the dystrophin protein has a large red region in the middle that does not appear to be absolutely essential. We know this from mild Becker muscular dystrophy patients and laboratory studies.

Thus missing parts of this rod as a result of the mutation and exon skipping will still allow production of a largely functional protein. In principle, exon skipping could be used for other genetic mutations but only if the treatment produces a functional protein. Unfortunately, unlike dystrophin, any loss of the internal structure of other proteins may prevent normal function. Therefore this limits the use of exon skipping in other muscular dystrophies.

Antisense oligonucleotide technology is however being applied in different ways to some other neuromuscular conditions. For SMA the antisense oligonucleotides are being used to alter the activity of the SMN2 gene (see Q2 above). In myotonic dystrophy antisense oligonucleotides are being used to block certain genes and proteins (see World Research News, p12).

Q6. If the genes for Duchenne muscular dystrophy can be caused by mutations in many different genes and the symptoms are highly variable from patient to patient, identifying new genes that cause these conditions is challenging.

However, our knowledge of how muscle works, how to study muscle in the laboratory and how mutations in genes cause disease has advanced greatly in the last 20 years. Technological advances, especially in the last five or so years, have allowed us to find mutations in DNA much faster than ever before. So, for conditions where the causative gene is not known or not fully understood, we hope that the research, once the necessary resources are available, would move at a faster pace by taking advantage of the knowledge, techniques and technology available today.

Q7. The reason why some muscles are affected and others not so badly affected in people with FSHD is, I believe, unknown. What research is being done to identify the reason for this and by which groups?

A. In people with FSHD the face and shoulder muscles are predominantly affected, however foot, upper arm and pelvic muscles are often also affected. It is not unusual for muscular dystrophy to affect only a subset of muscle groups. For example, oculopharyngeal muscular dystrophy (OPMD) affects the eye and swallowing muscles while limb-girdle muscular dystrophy affects the hip, thigh and shoulder muscles first. The reasons for these patterns of muscle weakness are not well understood.

A number of research groups around the world are looking at how different muscle groups develop in the embryo and how this development is controlled. This work might show that the formation of some muscles during fetal development in the womb is affected by mutations in certain genes. For example, it might be that the FSHD mutation affects the development of the face and shoulder muscles before birth, which shows itself as muscle weakness later in life.

The role of muscle stem cells is also being explored in FSHD research. Scientists suspect that muscle stem cells might be less able to survive or replace damaged muscle in people with FSHD, which results in muscle weakness. Perhaps stem cells in the face and shoulders are more impaired than in other muscles, resulting in the characteristic muscle group involvement in FSHD.

The North Star Project for Duchenne muscular dystrophy

The North Star Project was started in 2004 by the Muscular Dystrophy Campaign. Twenty specialist paediatric neuromuscular centres in the UK are currently part of the network.

Clinicians collect information, including genetic reports, steroid use, muscle function and symptom progression, from boys with Duchenne muscular dystrophy who attend these centres. Currently the database only holds information on boys who are still to walk. Of course, no information is stored without the patients’ or their parents’ consent.

How are patients’ symptoms assessed?

Doctors and physiotherapists conduct a standard interview at patients’ clinic appointments. This includes the evaluation of steroid use, the monitoring of potential complications and assessing the physical abilities of the children. Ensuring that the data is collected in a standard way is paramount to the success of the database. As part of the assessment the North Star clinical network developed and implemented a new scale – the ‘North Star Ambulatory Assessment’ (NSAA). This sets out a standard way for clinicians to assess the ability of the child to perform 17 activities, including standing, head raising, hopping and running.

What does it mean for Duchenne patients and their families?

The wealth of information stored in the database has now been made available for analysis by clinicians from the Network and other researchers who have successfully applied for access to the anonymised data. Auditing the use of steroids in Duchenne muscular dystrophy is one of the key aims of the North Star project and will allow the network clinicians to make recommendations on the best use of steroids.

The database has also provided information for several other projects. For example, an audit of vertebral fractures and of Vitamin D levels in boys with Duchenne muscular dystrophy will inform clinicians on how best to manage these issues.

The next step for North Star is to develop standardised assessment techniques for boys and young men who are no longer walking and expand the database to accommodate this further information.

Clinical databases are a vital tool for doctors, physiotherapists and other health professionals to understand the progression of symptoms or natural history of a condition. Analysis of the information stored in the database allows for the best possible care practices to be identified. The data can also be used in clinical trials as they provide a picture of the disease progression in different individuals before treatment is administered – this is known as ‘baseline data’.

We asked Elaine Scott and Dr Anna Mayhew, research physiotherapists and project co-ordinators for the North Star and Smartnet networks respectively, to update us on the progress of these clinical databases.

Prof. Francisco Munoz and Dr Adnan Manzur, consultant paediatric neurologists from the Dubowitz Neuromuscular Centre lead both of these projects.

The Muscular Dystrophy Campaign will endorse these projects.

Q6. If the genes for Duchenne muscular dystrophy and spinal muscular atrophy were known more than 15 years ago, why do we still not have a cure?

Do this mean that forms of muscular dystrophy where we don’t know the gene will take even longer to find an effective treatment?

A. Finding a treatment for Duchenne muscular dystrophy has taken a long time because the...
Partnerships

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

TREAT-NMD is an international initiative with two key aims: to develop the tools and services that doctors, scientists and the pharmaceutical industry need to bring new therapies from the lab to the patient with greater speed, and to establish best practice care for neuromuscular conditions worldwide. The Muscular Dystrophy Campaign is working closely with TREAT-NMD to help achieve these aims.

Advising researchers
Academic research often forms the base for new therapies, but assessing which of the promising new ideas in the lab are the most suitable to take forward to trials on patients is a challenge.

To address this issue TREAT-NMD has recently set up an ‘advisory committee for trial planning.’ Working in partnership with TREAT-NMD to help achieve these aims.

Working with pharmaceutical companies
For new therapies to become a marketed treatment for patients they usually need to be taken on by a pharmaceutical company for testing in a clinical trial. Strong working partnerships with the companies involved in the development of drugs for neuromuscular conditions are therefore very important.

TREAT-NMD has helped with the initial stages of their trial planning.

Final decisions about where to run a trial and which patients will be taken by the companies themselves, but TREAT-NMD’s comprehensive and unbiased information speeds up this process, as well as allowing patients fairer access to clinical research.

The new MRC Centre for translational research into neuromuscular diseases: A London-Newcastle partnership to form a UK-wide translational research network

The new MRC Centre for translational research into neuromuscular diseases is in the field of neuromuscular conditions, there is a large gap between major science discoveries and patient benefit. This gap is known as the ‘valley of death.’ For many neuromuscular diseases, there are no treatments on the horizon. TREAT-NMD has been working to reduce this gap by establishing multidisciplinary translational research activities.

The centre is building on long-established research and clinical links between University College, London and Newcastle (UCL Institute of Neurology, the UCL Institute of Child Health and the University of Newcastle) to create a network of clinicians and researchers to work together to bring treatments from the laboratory to patients. The centre has also established collaborations with other neuromuscular research groups and patient organisations throughout the UK, including the Muscular Dystrophy Campaign.

Prof. Michael Hanna, Director of the MRC Centre for Neuromuscular Diseases

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Supporting cutting-edge clinical research

In the past year the MRC centre has initiated and supported over 14 separate neuromuscular UK clinical trials, natural history studies and MRI studies. This includes clinical trials in Duchenne muscular dystrophy, inclusion body myositis (IBM) and muscle channelopathies (periodic paralysis and myotonia).

Patients registries
In collaboration with patient organisations and doctors across the world, TREAT-NMD has set up global patient registries for Duchenne muscular dystrophy and spinal muscular atrophy. Registries for other conditions are now in preparation including myotonic dystrophy, congenital muscular dystrophy, myotubular/centronuclear myopathy and those conditions caused by mutations in the FKRP gene (such as limb girdle muscular dystrophy type 2).

The global Duchenne muscular dystrophy registry currently holds details of more than 10,000 patients and contains the key information needed to establish whether a particular patient might be eligible for a trial. The same time the feedback that registered patients receive helps improve their access to relevant information and details of new developments that relate to their condition.

Working with pharmaceutical companies
For new therapies to become a marketed treatment for patients they usually need to be taken on by a pharmaceutical company for testing in a clinical trial. Strong working partnerships with the companies involved in the development of drugs for neuromuscular conditions are therefore very important.

TREAT-NMD has recently completed feasibility studies to help three companies in the field – Novo Nordisk, Prosensa and Acceleron. Using information from our global patient registries and care and trial sites registry, TREAT-NMD has helped with the initial stages of their trial planning.

Final decisions about where to run a trial and which patients will be taken by the companies themselves, but TREAT-NMD’s comprehensive and unbiased information speeds up this process, as well as allowing patients fairer access to clinical research.

Charities combine forces to secure research funding

Ann Patterson, secretary of the Duchenne Family Support Group (DFSG)

The DFSG was started in 1987 by a small group of parents whose children had been diagnosed with Duchenne muscular dystrophy. Since then we have grown into a national support network of parents, families and professionals who come together for mutual support, sharing information and social activities.

The DFSG has always tried to keep families abreast of the latest research as part of our ethos of supporting our members. So, when we were approached three years ago to join the Muscular Dystrophy Campaign in a partnership to apply for research funding from the Big Lottery Fund (BLF) we did not hesitate in agreeing. We realised that as a relatively small charity we would be unable to attract this sort of funding by ourselves and therefore our Management Committee wholeheartedly agreed to participate. Even though funding for research has never been one of the main aims of the DFSG, we know that news of research into treatment for Duchenne is of primary importance to our families.

The partnership application was successful and, in 2005, the research project, led by Prof. Volker Straub and Prof. Dominic Wells, was launched. The remit was to investigate novel approaches to therapies for Duchenne muscular dystrophy with particular focus on exon skipping. The project also includes research into non-invasive imaging – an invaluable tool for assessing whether treatments are working.

The DFSG’s role was to disseminate information on how the project was progressing and publicise the findings of the research. With the help of the funding from the BLF, we have produced articles in our quarterly newsletter and on our website. Prof. Wells also gave presentations at two of our national conferences, most recently in York in June 2009.

Providing resources, training and a communication platform for researchers
The MRC centre has established the ‘UK neuromuscular biobank’ – a collection of skin, muscle, nerve and stem cells from people with neuromuscular conditions. This is a valuable resource for research and for testing potential new therapies.

The centre aims to train the neuromuscular researchers of the future, so this year it started a translational research PhD programme for eight science and two clinical PhD students in London and Newcastle.

In March the second annual UK Neuromuscular Translational Research conference was held in partnership with the Muscular Dystrophy Campaign in Newcastle, attracting over 250 clinicians and scientists and showcasing the best neuromuscular science.

More information is available at www.treat-nmd.eu and www.muscular-dystrophy.org/research/treat_nmd_network

For more information go to www.dfsg.org.uk

For more information go to www.muscular-dystrophy.org
## Research projects currently funded by the Muscular Dystrophy Campaign

<table>
<thead>
<tr>
<th>Principal Investigator</th>
<th>Institution</th>
<th>Project Title</th>
<th>Description</th>
<th>Total project cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Ros Quinlan</td>
<td>Royal Orthopaedic Hospital</td>
<td>Pilot project investigating the use of novel ankle foot orthotics and footwear combination to improve walking stability in children with Duchenne muscular dystrophy</td>
<td>Investigating the use of new orthoses and other footware to improve walking and stability in children with Duchenne muscular dystrophy</td>
<td>£156,100</td>
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<tr>
<td>Prof. Charles Redwood</td>
<td>University of Oxford</td>
<td>Analysis of the effects on contractile function of mutations in beta-tropomyosin that cause different inherited myopathies</td>
<td>Investigating how mutations in the beta-tropomyosin gene alter the stability of muscle fibers and their ability to contract. This may be able to explain how the different mutations cause conditions such as nemaline myopathy.</td>
<td>£32,400</td>
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<tr>
<td>Dr Mary Reilly</td>
<td>University College, London</td>
<td>Strengthening hip flexors to improve walking distance in people with Charcot-Marie-Tooth disease</td>
<td>Investigating whether a home-based exercise programme to strengthen hip flexors in people with Charcot-Marie-Tooth disease can help to improve walking distance. See p15 for an update.</td>
<td>£116,000</td>
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<tr>
<td>Prof. Roland Roberts</td>
<td>King's College, London</td>
<td>Interactions of the dystrophin protein</td>
<td>Investigating how dystrophin interacts with other proteins in muscle and how these interactions are affected by the mutations causing Duchenne and Becker muscular dystrophies.</td>
<td>£78,200</td>
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<tr>
<td>Dr Lesley Robinson</td>
<td>Burns and the London School of Medicine and Dentistry</td>
<td>Polyclonal gene family member 1A in the specification and maintenance of myogenic satellite cells</td>
<td>Investigating the role of somatic cell function in muscle stem cells with the aim of determining if it can be used to improve the efficiency of muscle regeneration.</td>
<td>£114,200</td>
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<tr>
<td>Prof. Volker Strab</td>
<td>University of Newcastle</td>
<td>Assessment of muscle fibre damage in patients and in animal models for muscular dystrophy by MRI</td>
<td>Developing non-invasive methods such as magnetic resonance imaging (MRI) to assess muscle damage and repair in patients. These tools could be used to assess the efficacy of potential new therapies such as those currently in clinical trials for Duchenne muscular dystrophy.</td>
<td>£170,200</td>
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<td>Prof. Douglas Turnbull</td>
<td>University of Newcastle</td>
<td>Prevention of transmission of mitochondrial DNA disease</td>
<td>Investigating the use of IVF techniques to prevent transmission of mitochondrial myopathy.</td>
<td>£200,000</td>
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<tr>
<td>Prof. Douglas Turnbull</td>
<td>University of Newcastle</td>
<td>Exercise therapy for patients with mitochondrial myopathies</td>
<td>Investigating if exercise therapy is beneficial for people with mitochondrial myopathy. See p15 for an update.</td>
<td>£153,500</td>
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<td>Prof. John Wiseman</td>
<td>King’s College Hospital Trust</td>
<td>Changing adverse beliefs in those with social factors</td>
<td>Exploring how negative perceptions and other social factors can impact upon quality of life of people with muscle disease with the aim of devising a programme of cognitive behavioural therapy. See p15 for more information.</td>
<td>£61,000</td>
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<tr>
<td>Prof. Steve Winder</td>
<td>University of Sheffield</td>
<td>Regulation of dystrophinulin function</td>
<td>Investigating the function of a protein called dystrophinulin in order to further understand its role in healthy muscle and its potential use in Duchenne muscular dystrophy. See p15 for more information.</td>
<td>£100,800</td>
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<td>Dr Peter Zammit</td>
<td>King’s College, London</td>
<td>Relating satellite cell heterogeneity to stem cell function</td>
<td>Investigating the subtypes of muscle stem cells (satellite cells) which may lead to the identification and isolation of the cells that have the greatest ability to regenerate muscle.</td>
<td>£186,400</td>
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<tr>
<td>Dr Peter Zammit</td>
<td>King’s College, London</td>
<td>What controls the efficiency of muscle regeneration?</td>
<td>Studying the factors which affect how well muscle stem cells can regenerate muscle. Manipulating these factors could provide a basis of potential therapies for muscular dystrophy.</td>
<td>£191,500</td>
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</table>

*membership

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For more information go to www.muscular-dystrophy.org/currentgrants

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### Principal Investigator

- **Dr Jenny Morgan**
  - Imperial College, London
  - The role of extracellular matrix components on satellite cell function
  - In a group of muscular dystrophies known as the dystroglycanopathies the muscle stem cells (satellite cells) are impaired. Understanding this impairment could help scientists to develop a therapy using muscle stem cells.
  - £154,500

- **Dr Jenny Morgan**
  - Imperial College, London
  - Factors affecting the self-renewal of mouse satellite cells
  - Investigating the muscle environment so that scientists can determine which factors can be used to improve muscle stem cell (satellite cell) regeneration of damaged muscle.
  - £191,100

### Institution

- **University of Oxford**
  - Targeting CR24 as a cause of disease and as a novel therapy in myopathic disorders.
  - Improving diagnosis and investigating new avenues for treatment for people with myopathic signs and symptoms. See p12 for more information.
  - £92,000

- **University of Nottingham**
  - Axars for drug-discovery in myosteat dystrophy
  - Developing methods to screen thousands of drugs for their potential to treat myosteat dystrophy.
  - £24,000

- **University of Newcastle**
  - Identifying novel molecular pathways and therapeutic targets for Beleem dystrophy and Ullrich congenital muscular dystrophy.
  - Identifying new gene mutations that cause Beleem dystrophy and Ullrich congenital muscular dystrophy. This may lead to the identification of potential therapies for these conditions.
  - £95,500

### Project Title

- **Upregulation of utrophin for Duchenne muscular dystrophy therapy**
  - Continuing research to find drugs to increase the amount of protein ‘utrophin’ in muscle. This protein may be able to substitute for the missing dystrophin protein in Duchenne muscular dystrophy.
  - £179,000

- **Optimisation of U7 snRNA assays for therapy of Duchenne muscular dystrophy**
  - Investigating new, more efficient ways to deliver enzyme replacement treatments to all the muscles of the body, with the aim of improving on current even skipping treatment for Duchenne muscular dystrophy. See p12 for more information.
  - £170,000

- **Enhancing the therapeutic functionality of aden-associated virus (AAV) vectors encoding dystrophin for preclinical Duchenne muscular dystrophy gene therapy studies**
  - Investigating ways to optimise a gene therapy approach using a virus to deliver a shortened version of the dystrophin gene to muscle cells as a potential treatment approach for Duchenne muscular dystrophy. See p12 for more information.
  - £151,000

- **Investigation of molecular mechanisms in facioscapulohumeral muscular dystrophy**
  - Investigating further the mutations causing facioscapulohumeral muscular dystrophy (FSHD). Understanding the underlying mechanism behind FSHD will help towards the development of potential therapies in the future.
  - £98,300

- **Defining progeria allele length and somatic mosaicism in myosteat dystrophy type I**
  - Investigating why symptoms can vary so much from person to person in myosteat dystrophy by examining the different genetic mutations causing the condition.
  - £194,000

- **Complex repeat in myosteat dystrophy type I and Charcot-Marie-Tooth disease**
  - Investigating the genetic fault that causes Charcot-Marie-Tooth disease: See p12 for more information.
  - £165,000

- **Studying the genetic fault that causes nemaline myopathy**
  - Investigating how mutations in the beta-tropomyosin gene alter the stability of muscle fibers and their ability to contract. This may be able to explain how the different mutations cause conditions such as nemaline myopathy.
  - £32,400

- **Studying the genetic fault that causes nemaline myopathy**
  - Investigating how mutations in the beta-tropomyosin gene alter the stability of muscle fibers and their ability to contract. This may be able to explain how the different mutations cause conditions such as nemaline myopathy.
  - £32,400

- **Regulation of dystrophinulin function**
  - Investigating the function of a protein called dystrophinulin in order to further understand its role in healthy muscle and its potential use in Duchenne muscular dystrophy. See p15 for more information.
  - £100,800

- **Relating satellite cell heterogeneity to stem cell function**
  - Investigating the subtypes of muscle stem cells (satellite cells) which may lead to the identification and isolation of the cells that have the greatest ability to regenerate muscle. Manipulating these factors could provide a basis of potential therapies for muscular dystrophy.
  - £186,400

- **What controls the efficiency of muscle regeneration?**
  - Studying the factors which affect how well muscle stem cells can regenerate muscle. Manipulating these factors could provide a basis of potential therapies for muscular dystrophy.
  - £191,100

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For more information go to www.muscular-dystrophy.org/currentgrants
Glossary

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

Acquired disease – a condition which develops during your lifetime and isn’t due to a particular gene mutation. One example is those conditions where the body’s immune system mistakenly attacks itself (autoimmune conditions).

Adverse associated virus (AAV) – a small virus which affects humans. It is not known to cause disease which makes it an attractive vector for delivering genes into cells for gene therapy.

Antisense oligonucleotides – short sequences of genetic material (DNA or RNA) which can bind to a specific piece of genetic code and change how the code is read. They can be used to overcome small errors in the genetic code or to block parts of the gene.

Antibodies – proteins made by the body to protect itself from foreign substances, such as bacteria or viruses.

Assay – a procedure in the laboratory for measuring the activity of a substance, such as a drug.

Biochemical test – a test which measures the amount or activity of a particular enzyme or protein in a sample of blood, urine or other tissue such as muscle.

Cell line – cells of a single type that are genetically identical grown in the laboratory. They are often allowed so that they can grow and divide indefinitely.

Chromosome – cylindrical shaped bundles of DNA found in the cell nucleus. They consist of long, threadlike strands of DNA coiled upon themselves many times.

Cytoplasm – the jelly-like substance that surrounds the nucleus of a cell. It contains mitochondria and other structures responsible for functions such as energy and protein production.


Dysferlinopathy – a condition caused by a reduction or an absence of the protein dysferlin. Includes limb-girdle muscular dystrophy type 2B, Miyoshi myopathy and distal anterior compartment myopathy.

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.

Echocardiogram – a test which records the electrical activity of the heart through electrodes attached to the skin.

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

Exon – genes are divided into regions called exons and introns. Exons are the sections of DNA that code for the protein and are introns that are cut out, along with introns, to make a protein-coding ‘gene’.

Exon skipping – a technique which involves masking the exon of a gene that carries a mutation in order to restore the complete or partial function of the gene. See also ‘antisense oligonucleotides’ and box 2.5.

Fibroblast – one of the major cell types found in skin.

Foetus (also spelt fetus) – the term used to describe the human or animal embryo after the eighth week of development until birth.

Gene therapy – treatment of a disease by introducing a new gene into a cell. Viruses are often used to deliver the new gene into the cells. Can also refer to treatments such as gene silencing which involve modifying existing genes.

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

HDAC (histone deacetylase) inhibitors – a drug that affects the way DNA is folded into cell structures. This changes the activity of some genes. They have a long history of use as mood stabilisers and anti-epileptics, and are being studied as a treatment for many other conditions.

Immune system – the body’s defence system against foreign material, such as bacteria or viruses. The immune system includes white blood cells and chemicals and proteins in the blood, such as antibiotics.

In-vitro fertilisation (IVF) – a process by which the egg is fertilised by sperm outside the womb.

Magnetic resonance imaging (MRI) – a non-invasive body imaging procedure that uses powerful magnets and radio waves to create pictures of the internal structures of the body.

Male mouse – a mouse model of Duchenne muscular dystrophy. These mice have a mutation in the dystrophin gene – the gene that is mutated in boys with Duchenne.

Mouse model – a strain or breed of mouse which has a disease that is similar to a human disorder. It is used as a control to rule out any benefits a drug might exhibit because the recipients believe they are taking it.

RNA – ribonucleic acid, a substance very similar to DNA. When a gene is ‘switched on’ RNA copies of the DNA code are made which move outside the nucleus into the cytoplasm where they direct the manufacture of proteins.

Nucleus (plural nuclei) – the centre of a cell, which contains the cell’s chromosomal DNA.

Placenta – 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 believe they are taking it.

Skeletal muscle – muscle which applies force to bones and joints to move the body. Other types of muscle include cardiac (heart) and smooth muscle (blood vessels, stomach, intestines).

Skeletal muscle – muscle which applies force to bones and joints to move the body. Other types of muscle include cardiac (heart) and smooth muscle (blood vessels, stomach, intestines).

Splicing – the process of cutting out and joining together the exons of a gene.

Stem cells – cells that have not yet specialised to form a particular cell type, and can become other types of cell such as muscle cells. They are present in embryos (embryonic stem cells) and in small numbers in many adult organs and tissues, including muscle.

Translational research – the application of knowledge gained from scientific medical research in the laboratory to studies in humans.

Urothelial – a very similar protein to dystrophin. Low levels of urothelium are present in everyone – including people with Duchenne muscular dystrophy – but in insufficient amounts to compensate for the loss of dystrophin.

Vertebral – relates to or relating to the vertebrobe, the bones of the spinal column.
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