Duchenne Muscular Dystrophy

Exciting new gene-based therapies are now being tested on patients in clinical trials

A general overview of the techniques, potentials and challenges of virally delivered genetic material designed to produce human microdystrophins

Please scroll down to see what trials and research are being done using this approach.

Introduction
In this brief document, we want to explain in a bit more detail, how gene therapy offers hope as a potential treatment for Duchenne muscular dystrophy. Our aim is to help parents, guardians and patients with DMD, who may not have a detailed science background, to understand what this new approach could deliver.

Children born with Duchenne muscular dystrophy have a fault, known as a mutation, on their dystrophin gene, the longest gene in the body. The fault means that they cannot produce dystrophin, a protein that is vital for muscle strength and function. Without enough dystrophin, skeletal and cardiac muscles become damaged as they repeatedly contract and relax with use. The damaged cells weaken and die over time, causing the characteristic muscle weakness and wasting and heart problems seen in Duchenne.

If the dystrophin gene could be replaced with a healthy gene (or section of the gene) then the hope is that muscles would produce dystrophin and any further damage caused by DMD would be much reduced.

How is Duchenne Muscular Dystrophy treated currently?

Corticosteroids (predominantly prednisolone and deflazacort) are prescribed routinely to patients with DMD, and are now part of the recognised standard of care. Medicines to tackle the onset of cardiomyopathy, are also prescribed, such as ACE inhibitors, angiotensin blockers, beta blockers and diuretics. Patients with DMD can also have weak bones or reduced bone mineral density, caused by decreased mobility, muscle weakness and the use of steroids. In recent years, patients have been given bisphosphonate treatments such as zoledronic acid - used successfully to treat osteoporosis. All of these treatments treat the symptoms of DMD; they do not address the underlying cause, which is a lack of dystrophin.

Currently the only drugs approved that target the disease itself are Exondys51 (previously known as eteplirsen), in the US, and Ataluren, in the UK. These drugs are designed to skip over or ignore the
mutation in the DMD gene. However, they can only correct specific mutations on the DMD gene and so are only suitable for small sub-populations of those living with Duchenne. In the last few years, huge strides have been made looking into the exciting possibility of delivering new genetic material to cells through gene therapy, to overcome the errors/deletions in the dystrophin gene. This approach has the potential to be beneficial to more DMD patients than etiplersen or Ataluren.

**Gene therapy - how could it work in Duchenne Muscular Dystrophy?**

DMD is an inherited, genetic disease. A gene is a very large molecule, and the gene for dystrophin is the longest known gene. So, we have a problem - how can we repair or deliver a new copy of this gene to every cell in the body where it is needed?

Our cells have evolved mechanisms to prevent intrusion of foreign molecules. To overcome this we use vectors, or carriers, to carry the new gene into the cell. Currently, the most promising approach is based on the use of a harmless virus called **Adeno-associated virus (AAV)** as a vector. Viruses have evolved to recognise certain cells and then insert themselves via the cell membrane, and deliver their genetic material into the cell (usually making us feel unwell). However, if scientists remove the unwanted, disease-causing genes and replace them with appropriate beneficial genes, they could restore gene expression. This is the basis of the ‘gene therapy’ that is causing great excitement at the moment.

One challenge of DMD gene therapy is that the dystrophin gene is the longest known gene. Because of this size, it is impossible to insert the entire dystrophin DNA into the AAV vector. So, researchers have created **microdystrophin** - a shortened version of the dystrophin gene which can fit into the AAV vector. Gene therapy using microdystrophin has successfully been tested in animal models of Duchenne muscular dystrophy. A shortened, but functional, dystrophin protein is produced using this method.

**Other types of gene therapy**

We can’t leave gene therapy without mentioning CRISPR /Cas9. This has been in the news recently and is a technique that could be used to treat a wide range of genetic diseases, including DMD. CRISPR/Cas9 is an exciting genetic engineering technique with two key components: 1) Cas9 which is an enzyme that can cut DNA at a precise point and 2) CRISPR, a short strand of RNA (a chemical messenger similar to DNA). Recent reports in the journal Science have used the CRISPR-Cas9 technique to treat mice with a defective dystrophin gene. The technique ‘cut out’ a specific portion of faulty gene. Without this piece, the muscle cells made a shortened but functional dystrophin protein. There are high hopes for CRISPR Cas9 technology for Duchenne, but for now the state of the science is classified as early stage.

**Technical challenges, limitations and potential risks associated with microdystrophin therapy**
Like almost all forms of medical treatment, gene therapy is not without risk. As described above, a viral vector may carry the replacement gene into the cell body, but this technique presents the risks. There are three main areas of risk and these are discussed below.

- **Unwanted immune system reaction.** The body’s immune system has evolved to recognise and remove unwanted viruses, to stop us getting ill. The microdystrophin-carrying viruses are seen by the immune system as intruders. If the immune system recognises the virus as an intruder it will try to attack and remove the virus. This often results in inflammation, and in severe cases can cause organ failure.

- **Targeting the wrong cells.** Because viruses may be capable of ‘infecting’ more than one type of cell, it’s possible that they may deliver their therapeutic genetic material to cells other than those they were designed for. If this happens, these healthy cells may be damaged, perhaps causing other illness or diseases such as cancer/tumours.

- **Infection caused by the virus.** It is not impossible that viruses, when delivered into the body, may after a while revert to their ‘wild type’ and cause the illnesses they were originally responsible for.

Gene therapy poses one of the greatest technical challenges in modern medicine. It is very hard to deliver new genes into cells and to keep them working. Once the gene reaches the correct destination, it must be activated or turned on, to produce the protein. Once the gene is turned on, it should stay turned on. Cells tend to shut down genes which are too active or are exhibiting unusual behaviours, to prevent problems arising such as cancer.

If gene transfer is approved by regulatory authorities, we don’t know how long any potential effect would last. The next challenge is re-administration. Gene therapy is a one-time treatment. In theory, a single administration of gene therapy treatment should be enough to induce dystrophin production. If the effect of the gene therapy does not last, it may be desirable to re-administer the drug. However, there are challenges with this. The first time your body ‘sees’ this virus the immune system will take a while to respond. However, the second time your body ‘sees’ this virus the response will be much more rapid and lead to neutralisation and removal of the virus before it has had a chance to deliver its genetic payload. This means that a second administration of beneficial virus cannot be carried out.

Some patients may have pre-existing antibodies to AAV, meaning they would not be able to receive AAV-mediated gene transfer.

There are always risks and challenges when developing a new treatment. Regulators such as the FDA in the US, and EMA in Europe, have strict scientific guidelines for clinical trials to ensure the intervention is...
as safe as it can be before tested on patients. It may be frustrating when new treatments take many years to develop but it is important that we are diligent about the drug development process.

What trials and research are being done using this approach?

There are several companies developing gene therapy for DMD, some of which are currently advancing the clinic. See the table below.

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<thead>
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<th>Clinical stage</th>
<th>In development</th>
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<td><strong>Solid Biosciences</strong></td>
<td><strong>Genethon</strong></td>
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<td><strong>IGNITE DMD trial: AAV microdystrophin SGT-01</strong></td>
<td>Genethon currently has an AAV microdystrophin programme in the pre-clinical phase. Genethon’s research has shown long-term microdystrophin gene therapy to be effective in a canine model for DMD, with no side effects.</td>
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In June 2018, Solid announced that the US Food and Drug Administrations (FDA) has lifted the clinical hold on IGNITE DMD, the company’s Phase I/II clinical trial for its investigations microdystrophin gene transfer for the treatment of DMD.

Read their press release [here](#).

In connection with the lifting of the clinical hold, Solid has made changes to the IGNITE DMD protocol, including the addition of IV glucocorticoids in the initial weeks post administration of SGT-001, and enhances monitoring measures that include a panel for complement activation. The amended protocol also specifies that eculizumab will be available as a treatment option if compliment activation is observed.

The company plans to enroll and dose several children prior to dosing additional adolescents. In addition, Solid now has the choice to obtain the intermediate muscle biopsy at 45 days’ post administration of SGT-001 to collect additional information about the time course of microdystrophin expression.

The microdystrophin is designed to treat patients...
with any DMD mutation.

IGNITE DMD will initially be conducted at clinical trial sites in the US.

Sarepta

Sarepta is currently supporting two different gene therapy approaches:

1. **AAV Microdystrophin**, AAVrh74.MHCK7.micro-dystrophin

In June 2018, Sarepta announced positive preliminary results from its Phase I/IIa gene therapy clinical trail, conducted by Jerry Mendell M.D of Nationwide Children’s Hospital.

   - Biopsies performed at Day 90 showed robust micro-dystrophin expression in muscle measured by all methods and observed in all three patients.
   - Significant decrease in levels of serum creatine kinase (CK), an enzyme biomarker strongly associated with muscle damage caused by Duchenne muscular dystrophy.
   - No serious adverse effects (SAEs) observed

Twelve patients have been enrolled in two cohorts to undergo gene transfer. Cohort 1 ranges from 3 months to 3 years of age. Cohort 2 ranges from 4 to 7 years of age.

The micro-dystrophin is designed for exons 18-58, which covers 60-70% of the DMD population.

Read their press release [here](#).

2. **GALGT2 gene therapy programme**.

GALGT2 gene therapy uses an AAV vector to deliver a GALGT2 gene. Pre-clinical work showed
an overexpression of GALGT2 led to normal muscle function, in animal models of DMD. This programme could potentially treat most cases of DMD, as well as other muscular dystrophies.

In June 2018, Sarepta announced positive preliminary data from the first patients dosed in the Phase I/IIa AAV.GALGT2 clinical trial.

Read more about Sarepta’s gene therapy programmes [here](#).

**Pfizer**

**PF-06939926 trial: AAV Microdystrophin**

On March 22nd 2018, Pfizer dosed its first patients with an infusion of mini-dystrophin.

Read their press release [here](#).

The trial will continue to enroll ambulatory, male patients between the ages of 5 and 12.

Two dose cohorts with up to 6 patients each will be dosed with PF-06939926. They will then receive a first year follow up and then a 4-year long term follow up with annual visits. The dosage will be staggered, so the patients are not all dosed at once.

Early data from this trial is expected in the first half of 2019.

If you would like any more information regarding this research please visit the company websites:

- Solid Biosciences: [https://solidbio.com/gene-therapy](https://solidbio.com/gene-therapy)
- Sarepta: [https://www.sarepta.com/our-pipeline](https://www.sarepta.com/our-pipeline)

**Any questions and where to go for more information**

We hope you have found this short document helpful in understanding a little more about some of the...
exciting developments in the treatment of Duchenne Muscular Dystrophy. If you’d like to know more then there are several approaches you can try.

Firstly, go to Duchenne UK’s website - you will find it here:  https://www.duchenneuk.org  There is a wealth of information about the disease, approaches to treatment, support groups, our people and of course information on how we in Duchenne UK are fighting our hardest to improve the lives of young people suffering from Duchenne.

If you want to speak with us we want to listen. Key contact information is found here:  https://www.duchenneuk.org/Pages/Contact.aspx

If you want to understand more about gene transfer, please take a look at this educational toolkit provided by Solid Biosciences: