Stem cell research has fuelled hope of a treatment for a variety of conditions. This information sheet explains what these cells are and includes details of the current development of them as treatments.

It also covers how they may be used to create new models of disease, to screen for potentially beneficial treatments and to be used towards the goal of an effective treatment for motor neurone disease (MND).

### Content

<table>
<thead>
<tr>
<th>What are stem cells?</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Types of stem cell</td>
<td>2</td>
</tr>
<tr>
<td>Stem cells as a treatment</td>
<td>3</td>
</tr>
<tr>
<td>Stem cell clinical trials</td>
<td>5</td>
</tr>
<tr>
<td>Stem cells for research into MND</td>
<td>6</td>
</tr>
<tr>
<td>MND Association funded stem cell research</td>
<td>6</td>
</tr>
</tbody>
</table>

### What are stem cells?

Stem cells are cells that have not yet become specialised to perform a particular function. They can renew themselves and have the ability to give rise to various different cell types, for example blood, muscle or nerve cells.

Stem cells have generated much excitement and media attention because of the possibility that they could eventually be used as a therapy to repair or replace cells damaged by disease.

Scientists are also interested in using stem cells to generate motor neurones in the laboratory so that they can be used to learn more about MND.

For the latest news on stem cell research and related issues visit [www.mndassociation.org/stemcells](http://www.mndassociation.org/stemcells)
Types of stem cell

The main types of stem cells are embryonic, induced pluripotent stem (iPS) cells, adult and umbilical cord stem cells. Their uses in medicine include research to understand underlying causes of disease, such as MND, and the development of new therapies.

Induced pluripotent stem cell (iPSC)
Researchers can ‘turn back the clock’ on adult human skin and blood cells to reprogramme them into stem cells that have the same wide potential as other types of stem cells. These cells are known as induced pluripotent stem cells (iPSCs) and avoid the controversial use of embryos. Of all the types of stem cell iPSCs are used most frequently in MND research funded by the MND Association.

Researchers funded by the Association have already used human skin cells to create iPSCs, which have then successfully been turned into motor neurones and their support cells. These skin cells are collected from people living with MND by means of a skin biopsy. Researchers then introduce a cocktail of chemicals to reprogramme the skin cells into stem cells.

When skin cells from people with the inherited form of MND are reprogrammed into nerve cells, these cells contain the genetic changes that cause MND and therefore display characteristics of the disease. These cells provide researchers with a model of MND, enabling them to study living human motor neurones in the lab.

As well as learning more about what kills motor neurones, researchers can use these cells to screen potential drugs, before they go on to human clinical trials. By using human motor neurones in drug screening this could potentially increase the chance of successful clinical trials in humans.

Embryonic
Embryonic stem cells have the potential to develop into any type of cell in the body. They are found during the earliest stages of development, around 4-5 days after an egg has been fertilised. Human embryonic stem cells are currently not being used in any MND research funded by the Association.

Human embryonic stem cells present a number of ethical and religious concerns as well as technical challenges.

- Gathering embryonic stem cells results in the destruction of the embryo from which they came. Unwanted embryos from IVF procedures are sometimes used in research but the most controversy surrounds the use of embryos that have been created specifically for research.
- The wide potential of embryonic stem cells means that scientists must learn how to control their development to produce the right type of cell needed for research or treatments.
- Embryonic stem cells have the potential to generate tumours.

Adult and umbilical cord
After the very earliest stages of development, more specialised ‘adult’ stem cells develop that go on to form all the cells in a particular body system or tissue. For example, there
are muscle stem cells (mesenchymal), blood stem cells (haematopoetic) and nerve (neural) stem cells.

Adult stem cells are often relatively easy to obtain and in some cases raise fewer ethical issues than embryonic stem cells. For example, blood stem cells found in umbilical cords and adult bone marrow are already used to treat diseases of the blood and immune systems, such as leukaemia.

The adult human nervous system contains some specialised stem cells, known as neural stem cells, which have the potential to develop into neurones and support cells known as glia. However, they are limited in the numbers you can create and activities they can perform (such as self-renewal). They require manipulation by using nourishing factors (trophic factors) in order to get them to turn into a specific cell type such as neurones or glia cells.

**Stem cells as a treatment**

At present, there is no reliable evidence to suggest that stem cells can be used as an effective treatment for MND. Currently there are three American Food and Drugs Administration (FDA) approved clinical trials for stem cells in MND – see page 5 for more information on two of these.

The gold standard for testing both the effectiveness *and safety* of a treatment is a series of carefully controlled clinical trials, which build on the conclusions reached in the laboratory. **No stem cell treatment has yet completed such rigorous testing for MND.**

**What about the stem cell treatments advertised by clinics?**

It is important to note that the stem cell treatments being offered by clinics at considerable cost have not undergone proper clinical trials to prove their efficacy and may carry the risk of serious side effects.

Claims by clinics that stem cells are a successful treatment are rarely backed up with sufficient clinical evidence. Comparisons of outcome measures such as ALSFRS-R scores before and after receiving treatment are not shared, making it hard to validate their claims of the treatment being effective.

For clinics that use stem cells to treat many illnesses, it is hard to know if their claims are specific or applicable to MND. Where stem cells are approved for use in other conditions it does not mean the same can be assumed for MND.

If you are considering pursuing stem cell treatment, please discuss it with your neurologist first.

More information on questions to ask when considering unproven stem cell treatments: Research Information Sheet C: Unproven treatments and MND
Stem cells as a potential future treatment

Researchers still do not fully understand how stem cells might exert their beneficial effects in diseases such as MND. Some of the possible ways in which stem cells might be used to treat MND are as follows:

- Replacement of damaged neurones
- Replacement of support cells (glia)
- Delivering treatments and nerve-nourishing substances
- Protection and nourishment
- Dampening down inflammation

Challenges to overcome

Stem cells that have been administered to repair damaged motor neurones in animal models have given promising results. These have suggested that stem cell transplants are more likely to be effective in protecting existing motor neurones than in actually replacing or repairing them. However, these studies generated many unanswered questions.

Safety:
- What are the risks? (some stem cells have the potential to form tumours)

Feasibility / Practicalities:
- What is the best source of stem cells for transplantation? (It might be a combination of stem cells from different sources works best)
- What is the best route for delivering stem cells to treat MND? (eg into the spinal cord or muscles)
- How many stem cells do you need to give to have an effect?
- How many doses of stem cells need to be given to maintain any beneficial effect?
- Do additional factors (such as nerve nourishing factors) need to be given in conjunction with stem cells?
- Can stem cells be transplanted at any stage of MND, or do they need to be given at a specific stage of the disease to see a beneficial effect?

Effectiveness: Short- and long-term
- If stem cells are transplanted what is to stop them from developing MND?
- Once transplanted, do stem cells function normally and if so for how long?
- How can we stop the patient’s immune system from rejecting the transplanted stem cells? (like patients sometimes reject other donor tissue such as after having a kidney transplant)
Stem cell clinical trials

The first rigorous clinical trials to examine the safety of stem cell treatments in people with MND are taking place in America and Israel. These early clinical trials will assess safety only in Phase 1, with later studies (Phase 2 onwards) beginning to include measures of effectiveness in treating the disease.

**Neuralstem**

**Method:** This study uses nerve (neural) stem cells, injected into the spinal cord.

**Results:** The results from the Phase 1 American Neuralstem clinical trial involving 18 people suggested that the procedure was both safe and well tolerated by people with MND.

In the latest, Phase 2 clinical trial, 18 people were given injections of stem cells and at increasing doses (greater number of stem cells). Results from this phase confirmed that the transplantation can be safely performed at high doses, to both lumbar (lower back) and cervical (neck) regions.

**Brainstorm**

**Method:** This study uses bone marrow (mesenchymal) stem cells in combination with nerve nourishing factors (called NurOwn), injected into the muscle and/or spinal cord fluid.

**Results:** The results from the Phase 1 study involving 12 people with MND suggested stem cell treatment was safe and well tolerated over a 6-month follow up period. The results from the Phase 2a trial, where increased doses of cells were given to 14 people, suggested that the best location to inject stem cells is into the spinal cord.

A Phase 2 trial of NurOwn in America involving 48 people looked at the safety of stem cell transplantation, with injections given into the spinal cord and also the muscle. Results from this phase announced in July 2016 revealed that NurOwn treatment was safe and well-tolerated. While not a primary objective of this trial phase, the study also showed beneficial effects of NurOwn as assessed by lower levels of inflammatory biomarkers in the cerebrospinal fluid (CSF).

A Phase 3 trial is now being planned to investigate the effectiveness of NurOwn treatment.

**More information**
Read the latest stem cell trial news on the MND Research blog: [www.mndresearch.wordpress.com/tag/stem-cell-treatments](http://www.mndresearch.wordpress.com/tag/stem-cell-treatments)

For an explanation on how trials work see: Research Information Sheet D: Clinical trials, what are they and how are they organised?
Stem cells for MND research

Stem cells have a real potential to help drive MND research forward through the creation of new disease ‘in a dish’ models and as drug screening tools.

In order to find an effective treatment for MND, it is essential for scientists to understand what goes wrong in diseased motor neurones. However, it is extremely difficult to obtain human motor neurones, or to grow them in a laboratory dish. Stem cells provide researchers with a unique platform for studying MND on a cellular level as they can be encouraged to develop into living motor neurones in a laboratory dish.

Of particular value for this type of research would be human motor neurones with MND. These provide a more efficient and, in some aspects, superior alternative to existing animal and cellular models for studying the disease process and testing potential drugs. Motor neurones and their support cells can now be created from induced pluripotent stem cells (iPSCs).

MND Association funded stem cell research

As of March 2016, the Association is currently funding seven research projects using iPSC technology to create human motor neurones grown in a laboratory dish from skin samples of people living with MND. Some of these are described below.

These projects aim to develop iPSC derived motor neurones into new and better models of MND that can be used to further our understanding and test potential drugs.

Using iPSCs to study the low-complexity domain of TDP-43

Dr Martina Hallegger (University College London) was awarded a Non-Clinical Fellowship by the Association in January 2016.

Abnormal deposits of the TDP-43 protein are found in the majority of cases of MND, and cause damage to the motor neurones. There is a part of the TDP-43 protein heavily linked to the development of TDP-43 deposits, this is called the low-complexity (LC) domain.

Dr Hallegger will look at how mutations in the LC domain are linked to MND. She will do this by studying motor neurones generated from iPSCs. Understanding the ‘knock on’ effects of LC domain mutations and how these might lead to protein deposits could enable the development of more targeted drugs.
Using iPSCs to understand what happens to human motor neurones in MND

Dr Gareth Miles (University of St Andrews) has previously found that motor neurones lose their ability to produce an electrical nerve impulse. In this new project with Prof Siddharthan Chandran (University of Edinburgh) he is investigating why these electrical properties change by looking at proteins called ‘ion channels’ that regulate the flow of electrical messages.

By understanding the reasons why motor neurones lose their normal function, we can aim to design and develop new treatments that target this process.

Using iPSCs to understand the interplay between C9orf72 and TDP-43

In previous research, Prof Kevin Talbot and Dr Ruxandra Mutihac (both University of Oxford) have begun to understand more about how the C9orf72 gene defect causes human motor neurones to die. These studies were conducted using nerve cells created from patients’ skin cells using iPSC technology.

In this research project they are looking at the electrical activity of the nerve cells, how the nerves connect to muscle and how different parts of the cell contribute to the cells dying. They are using motor neurones from people with two different forms of inherited MND (those with C9orf72 and TDP43 mutations respectively) to see any differences and similarities between them.

Using DNA Bank samples to create iPSC models of MND

Prof Chris Shaw, Prof Jack Price (both King’s College London) and Prof Siddharthan Chandran (University of Edinburgh) are carrying out a project using the already collected white blood cell samples within the UK MND DNA Bank. From these they will create a large number of new iPSC models of MND. Ultimately creating an MND iPSC cell bank, these models will enable researchers to better understand the disease and screen potential new drugs.

More information on these projects and other stem cell research we fund:
Research Information Sheet E: Research we fund

More information on how we are using stem cells to understand MND please visit our research blog: http://mndresearch.wordpress.com/tag/ips-cells/

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