

Stem cells

Fact Sheet

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Stem cells

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Contents

1. What are stem cells?	1
2. Potential uses	2
3. Possible risks	4
4. Clinical trials	5
5. Stem cell tourism	8
6. References	8
7. Glossary of terms	9

1. What are stem cells?

Stem cells are different from all other kinds of cells in the body:

- they are unspecialised - this means they are not modified to have a specific function in the body;
- they are able to divide and renew themselves for long periods of time - this is known as *proliferation*;
- under specific conditions they have the potential to develop into cells with special functions - this is known as *differentiation*. For example, stem cells have the potential to differentiate into the beating muscle cells of the heart, cells that produce insulin in the pancreas or nerve cells in the brain.

There are two main types of stem cells - *embryonic stem cells* and *adult stem cells*.

Embryonic stem cells

As the name suggests, embryonic stem cells are found in the developing embryo. These cells are capable of developing into all the cell types that make up the tissues and organs of the human body, such as the heart, skin and brain.

Adult stem cells

Stem cells are found in much smaller numbers in adults than they are in embryos. Adult stem cells are found in some adult tissues and organs, including the bone marrow, the blood and the brain. The role of adult stem cells is to maintain and repair cells that are lost through general 'wear and tear', injury or disease.

Adult stem cells are more limited in the types of cells they can differentiate into; they typically generate into the types of cell in the tissue where they are found. Some examples are:

- **Haematopoietic** (blood-forming) **stem cells** - found in the bone marrow, the blood and also the umbilical cord of newborn babies. They differentiate into all of the different types of blood cells including red blood cells, white blood cells and platelets.
- **Stromal stem cells** - found in the bone marrow. They differentiate into tissues including bone, cartilage and fat cells.
- **Neural stem cells** - found in the brain. Neural stem cells can give rise to the major cell types in the brain, including *neurons* (nerve cells) and *oligodendrocytes* (myelin-forming cells).

2. Potential uses of stem cells

Embryonic stem cells

Research on human embryonic stem cells only began in 1998 when it was discovered how to isolate them from embryos and grow them in the laboratory. Embryonic stem cells are said to be *pluripotent*, as they can differentiate into any type of cell found in the embryo or adult. By studying embryonic stem cells in the laboratory, scientists will be able to identify the factors that control when a stem cell differentiates and the type of specialised

cell it develops into. This will then give an insight into how they may be used therapeutically.

Adult stem cells

Research on adult stem cells started in the 1960s and haematopoietic stem cells from the bone marrow have already been used in transplantation for around thirty years for blood disorders such as leukaemia (a cancer of the blood).

Over the years, adult stem cells have been found in many more tissues than scientists originally expected. Originally, adult stem cells were thought to be *multipotent*; this means they are only able to differentiate into a few different cell types. However, more recently, experiments have suggested that some (but not all) adult stem cells might be pluripotent. This ability of some adult stem cells to develop into more cell types than expected is termed *plasticity*.

The following are examples of adult stem cell plasticity:

- brain stem cells that can differentiate into blood cells;
- stromal cells from the bone marrow that can become heart muscle cells;
- haematopoietic stem cells that can develop into liver cells.

Scientists are trying to find ways of growing adult stem cells in the laboratory. They also need to understand and to learn to control the signals that make adult stem cells differentiate into the required type of cell. This could enable them to manipulate the stem cells to develop into specific cell types to be used in stem cell therapies. Also if adult stem cells do prove to be more 'plastic' than was originally thought, they could be more useful for stem cell therapies than expected.

Stem cell research and MS

Stem cells are unlikely ever to be used to grow whole organs, but they may be able to repair areas of damage. This is the theoretical basis of their use in MS. Three possible theories have been advanced in relation to stem cell treatments in MS:

- the stem cells develop into nerve cells to repair damage to the brain;
- stem cells develop into oligodendrocytes to repair damage to the myelin;
- stem cells boost the immune system to prevent damage.

However, before stem cell treatment becomes routinely available for conditions such as MS, much more work is needed to ensure the stem cells can be controlled and are safe to use.

More recent research has taken a different approach – groups in Cambridge and Edinburgh have been investigating the potential for encouraging stem cells already present in the central nervous system to develop into oligodendrocytes capable of repairing myelin¹. Initial work in rats has identified potential targets for drug treatments but further work is needed to test whether this mechanism will also work in people with MS.

3. Possible risks of stem cells

The promise held out by the potential of stem cells is balanced by risks that still have to be assessed and overcome. These include:

- **Unwanted cell development:** large numbers of cells are needed for transplantation and whilst embryonic stem cells can be grown easily in the laboratory, care has to be taken, as there is a risk of uncontrolled cell development and the possible growth of tumours. Adult stem cells are rare in human tissues and methods for growing them successfully in the laboratory still have to be developed.

- **Immune rejection:** the source of the stem cells can have implications.

There are two main types of transplant that can be carried out:

- *autologous* transplants - recipients receive their own stem cells;
- *allogeneic* transplants - recipients receive stem cells from a donor who may be completely unrelated to the recipient.

In an autologous transplant the cells will not be rejected by the immune system because the person is receiving their own cells back. However, in an allogeneic transplant there is a risk of immune rejection and the cells have to be matched to the recipient as closely as possible to avoid this.

Transplantation of embryonic stem cells would be an allogeneic transplant and therefore there is a possibility that the recipient could reject the cells.

Whether this would actually happen has not been determined yet in human experiments.

- **Suppression of the immune system prior to transplantation:** typically before transplantation is carried out, the recipient undergoes treatment to suppress their immune system, for example using chemotherapy drugs. This can leave an individual more prone to infections and also the drugs used can be very toxic to the body.

In summary, the consensus is that any treatment based on stem cells is still some years away. To be useful for transplant purposes there are many questions that still require answering and there is a need for research that shows:

- sufficient numbers of stem cells can be grown;
- the cells can successfully be controlled to develop into the type of cell required;
- the transplanted cells survive, integrate and function in the recipient;
- the transplanted cells do not harm the recipient.

4. Clinical trials

Although work with stem cells is still at a very early stage, there have been some small clinical trials of stem cell transplantation in people with MS in both Europe and the United States. These trials investigated the benefits of transplanting haematopoietic stem cells harvested from the bone marrow or the blood of the participant, ie an autologous transplant of adult stem cells. Although this technique is termed a 'transplant', in reality the cells are actually infused via a vein into the blood stream.

These trials were initiated after it was observed that people with MS who had been treated with stem cells because they had a cancer of the blood, also saw an improvement in their MS. This method was also shown to induce remissions in animal models of MS.

Since 1995, more than 200 people with MS have been treated using stem cells from their own bone marrow or blood in clinical trials. These trials were classed as phase I/II trials as they involved small numbers of people. In all these trials the participants underwent intense treatment to suppress their immune system in the week prior to the stem cell 'transplant'. Below are the

results of some of the clinical trials that have been published on stem cell treatments for MS:

a) European Group for Blood and Marrow Transplantation

In 2002, the European Group for Blood and Marrow Transplantation carried out a comprehensive analysis of 85 patients who had received stem cell transplants for MS². Because this analysis looks at results from several different trials, the method for suppressing the immune system and infusing the stem cells was not the same for all 85 people.

The analysis showed that the transplantation of haematopoietic stem cells was a potentially useful treatment for some people with MS. Following treatment an anti-inflammatory effect was seen, as measured by MRI. However, the effect on stabilising symptoms and disease progression was less clear. It was also observed that in high-risk cases such as the over-45s, those with a high disability score or people who had undergone a more intensive immunosuppressive treatment, the procedure was associated with a 5% risk of transplant-related mortality.

The European Group for Blood and Marrow Transplantation is currently carrying out a phase III trial comparing autologous stem cell treatment to the immune suppressing drug mitoxantrone. This trial is called the ASTIMS (**A**utologous **S**tem Cell **T**ransplantation **I**nternational **MS**) trial. The results of this trial are not expected until the end of 2011 at the earliest.

b) Italian Group for Bone Marrow Transplantation

Results of a phase II trial carried out by the Italian Group for Bone Marrow Transplantation were reported in December 2005³. This trial involved 21 participants with MS who were beginning to have difficulty walking (with a score in the range 5.0-6.5 on the EDSS scale, a standard measure of disability in MS), and were rapidly deteriorating. Participants received stem cells harvested from their own blood. Following treatment 20 people had stabilised or improved. The remaining participant also improved initially, but began to deteriorate nine months after the procedure.

c) MS Group, Erasmus Medical Centre, Holland

In January 2006, the MS specialist group from the Erasmus Medical Centre in Holland reported the results of 14 people with MS treated with autologous bone marrow stem cell transplants⁴. Transplant recipients had an initial EDSS in the range 5.0-6.5. In the follow-up, up to 36 months post-transplant, it was observed that 3 patients stabilised and two patients improved. However, nine patients deteriorated, with six losing their ability to walk.

d) Division of Immunotherapy, Northwestern University

This study, reported in the *Lancet Neurology*⁵, involved 21 people with relapsing/remitting MS who had had two relapses in the previous year despite treatment with beta interferon. The injections of autologous stem cells followed courses of treatment with immune suppressing drugs.

Following treatment, the participants were followed for an average of three years. All 21 showed no worsening of disability as measured by the EDSS scale, and 17 improved by at least one point. 16 people experienced no further relapses following the stem cell treatment.

The researchers reported that this treatment is 'a feasible procedure that not only seems to prevent neurological progression, but also appears to reverse neurological disability'. They have initiated a second, larger, multicentre trial with study centres in North and South America⁶.

e) Institute of Clinical Neurosciences, Frenchay Hospital, Bristol

In a phase I study⁷, researchers assessed the safety and feasibility of treating six people with stem cells derived from their own bone marrow. In contrast to previous studies, stem cells were not pre-treated to increase certain subsets of cells and participants did not receive treatments to suppress their immune system before their bone marrow stem cells were infused.

Participants were followed up for a year and no serious adverse effects were found. Clinical measures indicated that their MS was stable. The Bristol team were encouraged by the results which now need to be investigated further in a phase II/III clinical trial with a longer follow up period.

5. Stem cell tourism

There has been a great deal of press coverage of stem cell treatments that are being offered commercially. A panel of British doctors and scientists has warned of the risk to health and finances of visiting private stem cell clinics around the world⁸. On 1 January 2007, the Dutch government introduced new regulations that banned commercial stem cell clinics offering unproven treatments as it had concerns that “centres in the Netherlands are offering this form of treatment as if it is common practice while in fact it is in the early stages of development.” The treatments that were being offered were very different from those described in the published clinical trials. Dr Robert Trossel, a doctor offering stem cell therapies at clinics in the Netherlands and Belgium has subsequently been struck off the UK Medical Register. The International Society for Stem Cell Research (ISSCR) has published a patient handbook⁹ to help people evaluate stem cell therapies they may be considering.

The MS Trust is not currently aware of any ethical, authorised clinics using stem cells to treat MS outside of clinical trials.

6. References

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7. Glossary of terms

Adult stem cell - an undifferentiated cell found within an adult tissue that has the potential to differentiate into a specialised cell type of the tissue it is found within

Allogeneic transplant - recipients receive cells/tissues that are taken from a different individual of the same species

Autologous transplant - the donor and recipient of the cells/tissue are the same person

Differentiation - the process by which a stem cell develops into a specialised cell

Embryonic stem cell - an undifferentiated cell found within an embryo that has the potential to differentiate into a wide variety of specialised cell types

Haematopoietic - an agent that promotes the formation of blood cells

Multipotent - able to develop into more than one type of differentiated cell

Neuron - nerve cell

Oligodendrocyte - myelin forming cell

Plasticity - the ability of stem cells from one adult tissue to develop into the specialised cell type of another tissue

Pluripotent - able to develop into any type of cell found in the embryo or adult of that species

Proliferation - the expansion of a population of cells by the continual division of individual cells to produce two identical cells.