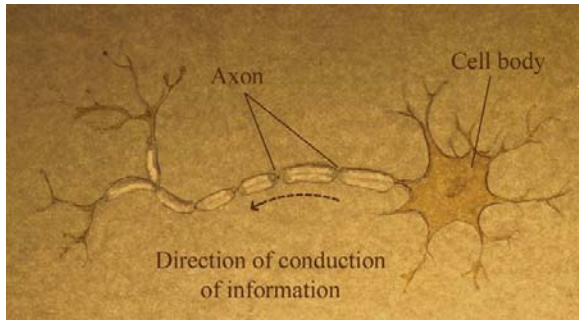


# Ready or not? A role play on taking stem cells to the clinic

Application for clinical trial, background on stem cells & spinal cord injury

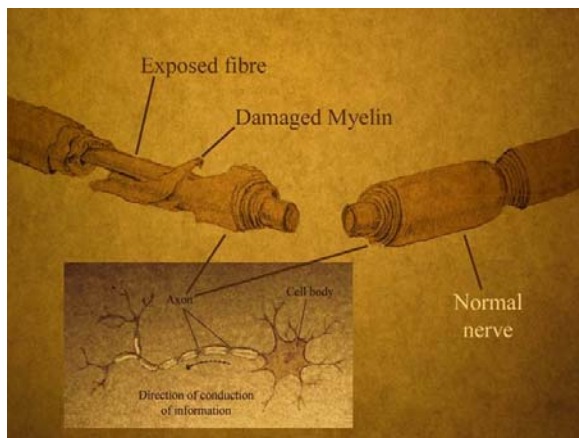
## 1. Application overview

Stem Cell Therapeutics is a biotechnology company set up in 2002 by a group of leading stem cell scientists, who want to use their knowledge and expertise to develop effective therapies for intractable diseases, such as cancer, Parkinson's disease, stroke, and for injuries that affect the spinal cord.



Stem Cell Therapeutics' scientists have developed a way of making a type of support cell of the nervous system from human embryonic stem cells. These support cells, called oligodendrocytes are the cells that make up the insulation sheath of nerves without which signals would not be conveyed along the spinal cord. The oligodendrocytes wrap themselves around the axon forming a sheath of myelin.

## Promising treatments for spinal cord injury



When the spinal cord is injured, axons are crushed, the myelin sheath is destroyed and the exposed axons degenerate. The connection between neurons is disrupted and the flow of information in the spinal cord is blocked.

By transplanting new oligodendrocytes into the spinal cord, scientists hope to restore the damaged myelin sheath, which should allow axons to regenerate and re-establish their connections.

Several experiments, using mice and rats which have undergone spinal cord injuries, have shown that transplanting oligodendrocytes into the site of injury

seems to be effective: after the transplant, animals are able to move much more easily, they are able to bear weight and are sensitive to touch.

However, this application was put on hold initially. Tiny spinal cysts of unknown significance developed in some of the mice receiving the treatment. But in another animal study no cysts developed.

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## Human embryonic stem cells treat spinal cord injury in animals

Stem Cell Therapeutics scientists have recently shown, for the first time, those human oligodendrocytes, made from human embryonic stem cells, can help improve recovery of rats that have suffered spinal cord injury.

The scientists showed that the injected oligodendrocytes did indeed wrap themselves around the axons of the injured rats, thus effectively rebuilding the nerves' insulation sheath (see Box A). They believe these re-insulated nerves have regained their capacity to transmit information along the spinal cord, restoring movement to the rats.

### Box A. Results of experiments of injecting oligodendrocytes into injured rats

Scientists carried out two parallel experiments:

- one in which four rats with spinal cord injury received injections of human oligodendrocytes;
- another in which four injured rats received no cells.

The first group of injured rats were injected with either 1.5 million oligodendrocytes or with 250,000 oligodendrocytes.

They compared the number of axons with rebuilt insulation sheaths (myelin sheaths) in each set of animals. The scientists found that:

- in animals that had received oligodendrocytes, there was a 136% increase in the density (number of axons per mm<sup>2</sup>) of insulated axons, compared to those animals that had not received any cells. This showed that injecting the oligodendrocytes stimulated re-insulation (that is, remyelination);
- the scientists concluded that the injected oligodendrocytes performed at least 63% of the total re-insulation that occurred. The remaining 37% of re-insulation was carried out by the oligodendrocytes produced by the rats themselves.

After receiving these cells, rats were able to take longer, wider strides and spread their toes (Box B).

Stem Cell Therapeutics scientists now wish to inject these same cells into patients who have recently suffered spinal cord injuries to test their safety and efficacy. Thus, the company has applied to the Research Ethics Committee for permission to run a clinical trial in humans.

# Ready or not? A role play on taking stem cells to the clinic

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### What are the phases involved in a clinical trial?

Clinical trials are conducted in phases. Each phase has a different purpose and helps scientists answer different questions.

In Phase I, researchers test an experimental drug or treatment in a small group of people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

In Phase II, the experimental study drug or treatment is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety.

In Phase III, the experimental study drug or treatment is given to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the experimental drug or treatment to be used safely.

In Phase IV, post marketing studies delineate additional information including the treatment's risks, benefits, and optimal use.

All of this does not guarantee success nor does it guarantee that no harm will result. This is biology in the real world, not a computer simulation. In light of the promising pre-clinical findings, Stem Cell Therapeutics has filed patents for the process of obtaining oligodendrocytes from human embryonic stem cells and their use in treating spinal cord injuries.

#### **Box B. Pre-clinical Trials: Survival and behaviour of experimental animals**

All four rats that were injected with oligodendrocytes survived the treatment.

The rats were examined before and after injury and treatment, by two independent observers. Once again, two experimental groups were compared: animals that were injured and received no treatment and animals that received injections of oligodendrocytes after injury.

Oligodendrocyte-treated rats showed considerable improvements in their ability to walk and move, when compared to non-treated rats. Treated animals continued to improve their walking abilities until one month after the injury, while the non-treated rats stabilised after two to three weeks.

Injured animals showed typical defects such as smaller rear paw stride length, increased rear paw stride width, and increased rear paw toe spread, as measured with the assistance of video.

Animals that were not injected with oligodendrocytes maintained these defects, while those rats that received oligodendrocyte injections after injury showed remarkable improvements, and were able to perform almost as well as non-injured rats.

There was no difference in the walking and moving ability between rats that had been injected with 1.5 million oligodendrocytes or 250,000 oligodendrocytes.

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## What will the clinical trial assess?

Scientists are not promising to cure any patients; they expect to see some improvement, and will be assessing the types of response to the treatment. Stem Cell Therapeutics seeks to establish a reasonable regulatory pathway for human embryonic stem cell treatments for spinal cord injury that currently has only very adequate therapies, if any effective available at all. The clinical trial will try to answer the following questions:

- Is it safe to inject these oligodendrocytes into humans?
- Do these cells cause any undesired side-effects or toxic effects when injected into humans, either healthy people or patients?
- How many cells is it safe to inject into humans?
- How many cells have to be injected to obtain an effect in patients?
- Do the benefits of the treatment outweigh the risks or inconveniences?
- Is this treatment better than the currently available treatments?
- Will the treatment benefit a large number of patients suffering from spinal cord injury, or only some?

These questions will not be answered in one go, but rather through a multi-phase process, in which both healthy volunteers and patients are recruited as volunteers.

## Who will be able to take part in the clinical trial?

After the pre-clinical phase, in which the safety of the cells will be tested, phase 1 will include 70 patients, all of which will have suffered a spinal cord injury within the previous weeks, the acute phase of the injury.

## What treatment will the clinical trial entail?

The patients enrolled in the clinical trial will be treated with immunosuppressant drugs to dampen the response of their immune system to the “foreign” oligodendrocytes they receive. This immunosuppressive treatment may make the patients more susceptible to infection, since their immune system will be working less efficiently. It is expensive. The greatest concern that experts have about the trial is that potent cells injected into the spine might develop into tumours, such as teratomas. This explains the cautious approach.

Although there are non-embryonic stem cell treatments for spinal cord injury that have been tried, they have been criticized for inadequate safety data from animals and unclear explanations of surgical procedures. By contrast, owing to the potential harm, novelty and public controversy, this trial is among the most intensively reviewed proposed clinical trials in history.

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## How will the trial be regulated?

If approved, the trial will follow all the established rules and guidelines of the European Union and the national government. Regular progress reports will be submitted to the Research Ethics Committee, during the trial, and the results will be made available to the international scientific and medical community, through publication in appropriate journals. The Research Ethics Committee can stop the trial at any time if there are any concerns about the welfare of the patients taking part.

## Who will benefit from the treatment, if the clinical trial is successful?

The scientists have made clear that they do not expect this treatment to be helpful for patients who suffer from old injuries. Research using rats has shown that when oligodendrocytes are injected 10 months after the injury, the rats show no improvement.

## Who will have access to treatment, after the clinical trial?

If the trial is successful, that is, if patients who receive the embryonic stem cell-derived treatment show improvements and there are no undesired side effects, then Stem Cell Therapeutics will begin talks with the Department of Health, looking to further develop this treatment and make it available through the health service. This will involve a commitment, from the Department of Health, to partially fund the studies needed to take this treatment into the clinic.

## Why use embryonic stem cells instead of foetal or tissue (adult) stem cells?

Stem Cell Therapeutics scientists want to use embryonic stem cells in their trial (instead of foetal or tissue /adult stem cells) so that they will be able to produce large amounts of a single type of cell – the oligodendrocyte.

Tissue (adult) and foetal stem cells are not as appropriate since they are more difficult to obtain in large amounts and grow in the laboratory.

## Where will the embryonic stem cells come from?

The proposed trial will use oligodendrocytes made from a human embryonic stem cell line (a population of stem cells that are able to survive and divide indefinitely in the laboratory). The stem cell line was made from surplus IVF blastocysts obtained at a fertility clinic with informed consent by couples undergoing treatment.

Depending on the results of the trial, Stem Cell Therapeutics considers using either other existing cell lines or establishing new ones from additional surplus IVF embryos.

In the future, Stem Cell Therapeutics will consider using patient-specific, integration-free iPS cells. These cells will be used as a source from which to generate oligodendrocytes. The oligodendrocytes obtained in this way will eliminate the need for immunosuppression treatment, since they will not be rejected by the patients' immune system.

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## Why inject oligodendrocytes instead of embryonic stem cells?

The scientists plan to inject oligodendrocytes instead of the embryonic stem cells from which they are made in order to reduce the risk of tumour formation in patients. Because of their unlimited ability to divide, embryonic stem cells often form tumours when transplanted into animals.

Stem Cell Therapeutics scientists feel certain that they are able to make nearly pure populations of cells that will become oligodendrocytes, with hardly any embryonic stem cells. They are currently testing these cells in rats, looking for any signs of tumours.

## Could the cells pass on animal viruses?

The stem cell line from which the oligodendrocytes have been made has been grown on human feeder cells for a year (the cells that support the growth of embryonic stem cells in a dish). Stem Cell Therapeutics scientists feel confident that their cells are not contaminated with any animal products (including viruses) which may be harmful to patients.

## What does all of this cost?

According to the National Spinal Cord Injury Statistical Centre (February 2010), it is estimated that up to 311,000 people in the U.S. are living with spinal cord injury with the average health care and living expenses cost for the first year following the injury as much as \$ 830,000 per patient.

Stem Cell Therapeutics is reported to have spent €110 million to get through the pre-clinical testing stage.

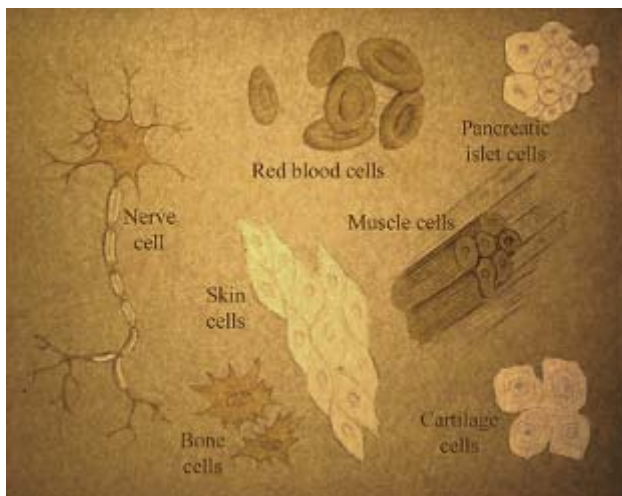
# Ready or not? A role play on taking stem cells to the clinic

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### 2. What are stem cells?

There are over 200 different types of cell in the human body. Each type of cell is specialised to perform a specific function. For example:

- Red blood cells carry oxygen through the blood stream;
- Liver cells remove toxins from the blood stream;
- Nerve cells carry information in the nervous system.



Functional tissues and organs of the body are maintained through the production of new cells through the process of cell division. In some organs, cells are continuously dying and being replaced by new cells. A red blood cell, for example, lives for only 120 days. Our skin cells are replaced every 35 days.

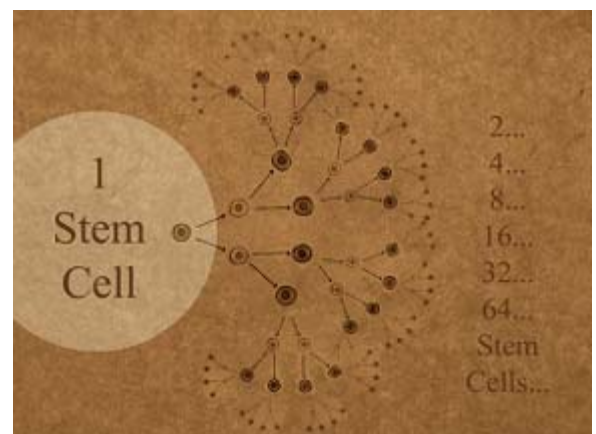
Sometimes disease or injury can cause cells to die or be lost. For example, when part of the liver is removed in surgery the remaining cells divide profusely and eventually replace the portion of liver that has been removed. Liver cells are special in their ability to divide and give rise to new identical cells (mitosis).

In contrast, most of the body's specialised cells are unable to divide and produce copies of themselves. Instead they are replenished from populations of stem cells which have the unique ability to divide to produce both copies of themselves and other cell types:

- Red blood cells are replenished from stem cells found in the bone marrow;
- Bone tissue is regenerated after injury by osteoblasts;
- Skin cells are replenished from stem cells in the deeper layers of the skin.

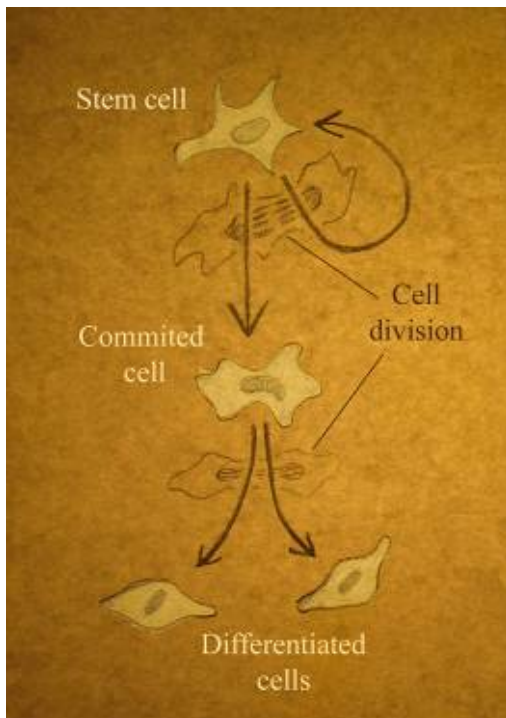
Stem cells are therefore unspecialised cells. They do not have a specific function (i.e. carrying oxygen) (Box C).

The ability of stem cells to produce identical copies of themselves, over and over again is truly remarkable. This process of **self-renewal** continues throughout the life of an organism. In addition to self-renewal, stem cells can also divide to produce more specialised cell types, such as blood and muscle cells. This process is called **differentiation** and happens naturally in the body.



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## Box C. What are the goals of stem cell research?

Scientists are trying to understand how a stem cell decides between self-renewing and differentiating into a more mature, committed cell.

Another goal of research is to direct cells down certain pathways, so that they become specific cells, such as the nerve cells that are damaged when the spinal cord is injured, or insulin-producing cells of the pancreas.

## Where can we find stem cells?

### Embryonic stem cells

Stem cells are found in early embryos (about 5-6 days old, in the case of human embryos), in foetuses, in the umbilical cord, and in some tissues of the adult body, including the skin and bone marrow.

Scientists have successfully grown stem cells from mice and humans in the laboratory. Although we end up with about 75,000,000,000,000 cells when we reach adulthood, we all start off as a single cell – the zygote, formed when the male sperm fuses with the female ovum during fertilisation. The fertilised egg then divides and forms two cells; each of these divides again (to form four cells), and so on. Five days later, a hollow ball of approximately 150 cells is formed called the **blastocyst**.

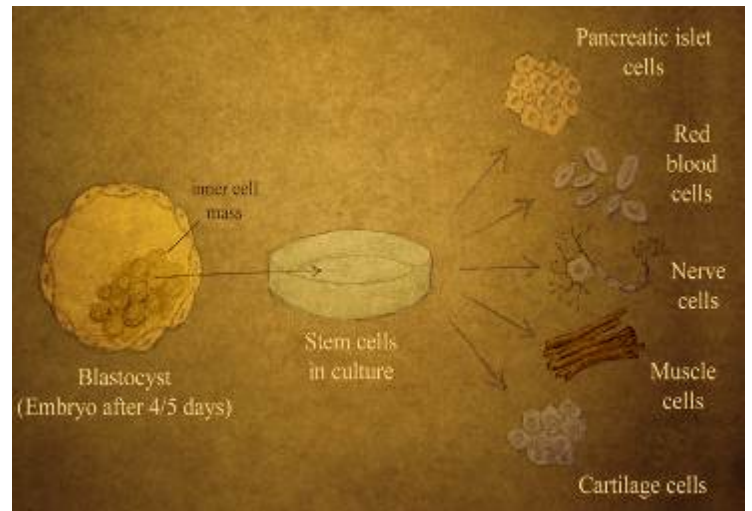
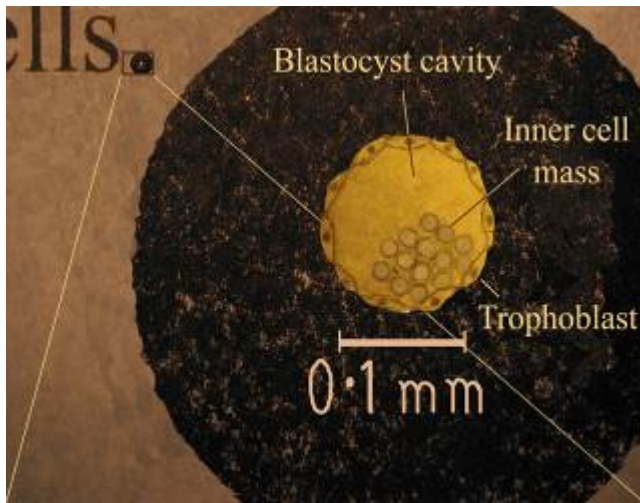
Embryonic stem cells are obtained from a group of cells in the blastocyst (Box D). Embryonic stem cells play a central role in the normal growth and development of animals and humans; since they go on to produce all the cell types of the embryo, the foetus and subsequently the adult.

In theory, embryonic stem cells could be guided in the laboratory to become any of the 200 or more types of cell in the body. This ability of embryonic stem cells is known as **pluripotency**.



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## Box D. The blastocysts from which embryonic stem cells are obtained

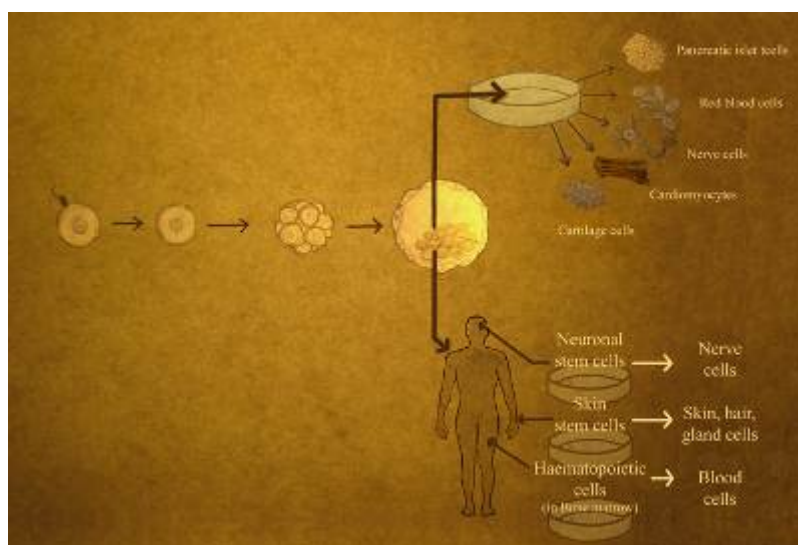
The blastocyst is the size of a pinhead. It contains two types of cell: the trophoblast and the inner cell mass.

The trophoblast will go on to form the placenta and other supporting tissue for the growing foetus.

The inner cell mass will give rise to the embryo proper and it is from these cells that **embryonic stem cells** are obtained.

Although the cells of the inner cell mass can form all the tissues in the human body, they cannot alone form an organism because they cannot make the placenta and supporting tissue that is necessary for development of the embryo and foetus.

In reality, the blastocyst can only develop into a foetus if it is implanted into the uterus of a woman.



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### Adult (or tissue) stem cells

Small amounts of stem cells can also be found in various tissues of the body such as bone marrow, skin, blood, muscle, brain, and the lining of the gut.

These are called **adult stem cells**, or **tissue stem cells**. The main role of these cells is to maintain and in some cases, repair the tissue in which they are found.

Tissue stem cells are pre-programmed to give rise to specific cell types when they differentiate. **Tissue stem cells usually only produce cells specific to the tissue in which they are found.** Stem cells found in muscle, for example, will normally only give rise to muscle cells. This more restricted ability is known as **multipotency**.

Scientists are actively investigating a process whereby a tissue stem cell from for example skin, under the right conditions, can be encouraged or induced to differentiate to cell types of another tissue (iPS cells, Box E). This ability of tissue stem cells would make them more widely used for therapy. iPS cells would circumvent many of the ethical issues surrounding the use of embryonic stem cells.

### Box E. iPS cells: induced pluripotent stem cells

Induced pluripotent stem cells (iPS cells) are a relatively recently discovered type of stem cells that are generated in vitro. Technology developed in 2007 allowed scientists to reprogramme adult human cells to a pluripotent state, making them similar to embryonic stem cells in terms of research and therapeutic applications. These iPS cells are genetically modified by the integration of up to four DNA-transcription factors into the adult cell genome. iPS cells can be generated from a wide variety of adult cells. Although the first versions of iPS cells were riddled with viruses, researchers have now managed to make them virus-free. However, these integration-free reprogramming methods have still to be optimised before their clinical application becomes possible. Please consult: <http://eurostemcell.org/factsheet/reprogramming>

### Foetal stem cells

These are found in the tissues of the developing foetus. From the end of the 8th week of pregnancy until birth, a developing human is classified as a foetus. At this stage, the major structures have formed. Foetal stem cells are similar to tissue stem cells, in that they are capable of giving rise to a limited number of cell types (they are **multipotent**). They are less mature than adult cell types, and so are easier to identify and grow in the laboratory.

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## Umbilical cord blood stem cells

A newborn baby's **umbilical cord** blood contains blood stem cells. Until recently, after every birth, the umbilical cord was disposed of in the delivery room. Some countries have cord blood banks to save these cells for future therapeutic use. Large numbers of samples increase the chances for finding the right donor tissue for a patient. Does your country have a cord blood bank?

There are fewer stem cells in umbilical cord blood than can be obtained from bone marrow. Cord blood has been used to treat children suffering from leukaemia and other blood diseases (Box F).

## Can stem cells be used to treat disease?

Tissue stem cells have the ability to replace damaged cells in the body that would otherwise not be replenished. This property led scientists to investigate the potential use of stem cells in supplying cells to treat diseases such as Parkinson's, heart disease, and diabetes, in which cells are irreversibly lost, and for which there are currently no treatments.

Scientists are working to direct stem cells to become the appropriate specialised cells, for example, brain cells. It is hoped that by transplanting these cells into the damaged or diseased tissue of an individual, they will regenerate the various cell types of that tissue.

**Bone marrow transplants** and **skin grafting** are established examples of therapeutic uses of stem cells. During a bone marrow transplant, for example, blood (haematopoietic) stem cells are removed from the bone marrow of a donor and transplanted into the patient to generate new blood cells. Bone marrow transplants have been used for 50 years to treat several blood diseases, such as leukaemia and anaemia.

This approach of replacing diseased cells with healthy cells is called **regenerative medicine**, or cell therapy. It is similar to the process of organ transplantation except that the treatment consists of transplanting cells rather than whole organs.

Most scientists believe that the use of stem cells to replace other types of damaged cells and tissues is still years away. Other, equally important, uses of stem cells are closer at hand. (Box G)

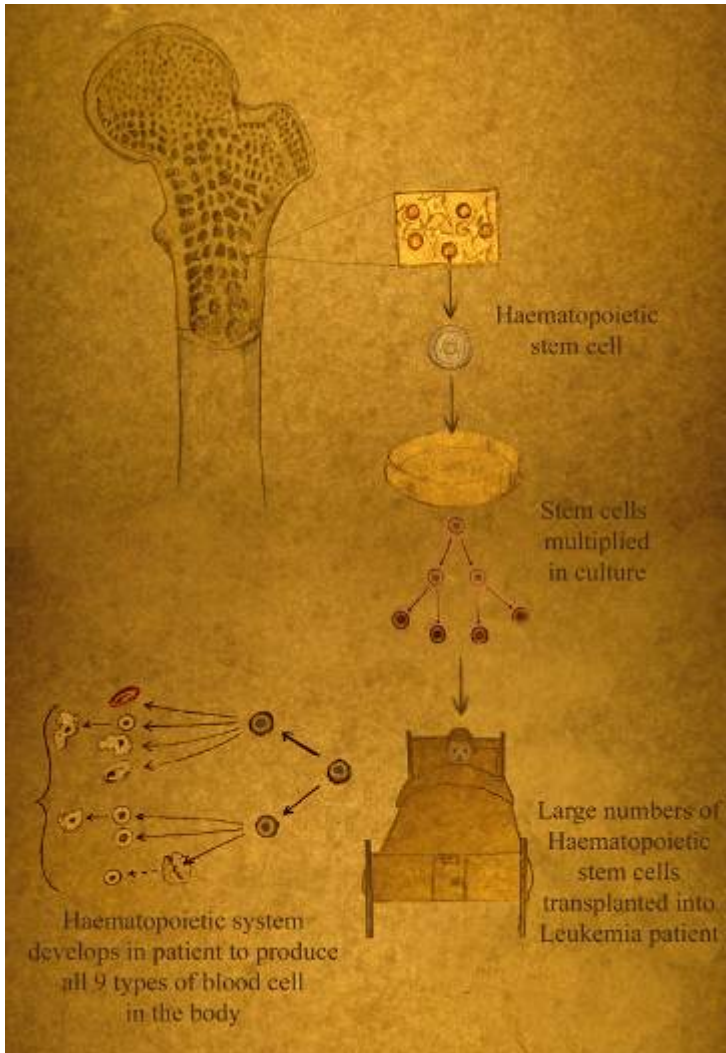
### Box F. Umbilical cord blood stem cells

Scientists are working to develop ways to increase the number of stem cells that can be obtained from umbilical cord blood, so that it may be used to treat adults, too. The potential of these blood stem cells to form other types of cell, such as nerve cells, is currently being investigated.

Scientists are also trying to find out whether other stem cells, similar to embryonic stem cells, are present in umbilical cord blood. Either discovery would increase the potential of umbilical cord blood for treating a wider variety of diseases.

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## Box G. Short term applications of stem cells

**Stem cells can be directed to produce specific cell types in the laboratory that can be used for drug testing and screening.**

If scientists are able to grow huge amounts of identical cells then pharmaceutical companies could use them to test the medicines they have developed. Consequently, the amount of testing done in animals could be considerably reduced.

**Stem cells can also be used to study disease processes.**

In many cases it is extremely difficult to obtain the cells that are damaged due to disease in order to study them in detail. They could be made from stem cells and engineered to carry the disease gene. For all purposes, these would be diseased cells, which scientists could use to model the disease, and use to better understand the processes that are causing the disease and its damage.

## Where do the stem cells used in research come from?

### Embryonic stem cells

The blastocysts from which embryonic stem cells are obtained come from several sources.

1. **Surplus embryos created for fertility treatment through in vitro fertilization (IVF)** involve fusing the female egg and sperm in the laboratory.

When a couple decides to undergo fertility treatment, several IVF embryos are created, to increase the chances of a successful implantation in the uterus, and subsequent pregnancy.

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The surplus embryos that are not implanted in the woman's uterus may be discarded or stored. Alternatively, they may be used for research, with full consent of the couple undergoing treatment. Between 1991 and 2005, a surplus of over 1.2 million embryos was stored in the U.K. These will be destroyed unless used within 10 years of their creation.

2. **Embryos can be created specifically for research purposes through IVF.** Donated female egg cells and sperm are collected separately, and then fused in the laboratory to create blastocysts from which embryonic stem cells can be obtained. Only certain countries allow embryos to be created in this way.

3. **Embryos can be created for research by the technique of somatic cell nuclear transfer** (also called therapeutic cloning).

- The nucleus of a tissue cell (for example, a skin cell) is transferred into an unfertilised egg that has had its nucleus removed.
- The 'fertilised' egg is activated and starts dividing and gives rise to an embryo. The embryo has the same genetic makeup as the individual from whom the nucleus was taken. This is the technique used to create Dolly the sheep.
- A major difference between the research that created Dolly and that carried out in humans is that the human embryos created using cell nuclear transfer are never implanted in a woman's uterus and so never go on to form a foetus or a baby.

They are used solely to grow embryonic stem cells from the blastocyst. This process is banned in some countries. (See "What does the law say?") To date, several research teams have been successful in obtaining 'cloned' human blastocysts but no-one has been able to grow human stem cells from the embryos.

## Foetal and Adult/ Tissue stem cells

Tissue (adult) stem cells are obtained by taking some of the relevant tissue from the body. They are often very difficult to obtain. Imagine how difficult it is to identify and reach the stem cells in the brain!

Blood stem cells are an exception. They are found mainly in bone marrow. They can be aspirated directly out of the bone marrow or stimulated to move into the blood stream where they can be easily collected.

Scientists are also exploring ways to stimulate adult stem cells *inside* the body. They hope to induce signals in the tissue that will get the stem cells to divide, multiply and make the appropriate specialised cells without having to move the stem cells into the laboratory.

Foetal stem cells are obtained from five to nine week old foetuses from elected pregnancy terminations, with full consent for research.

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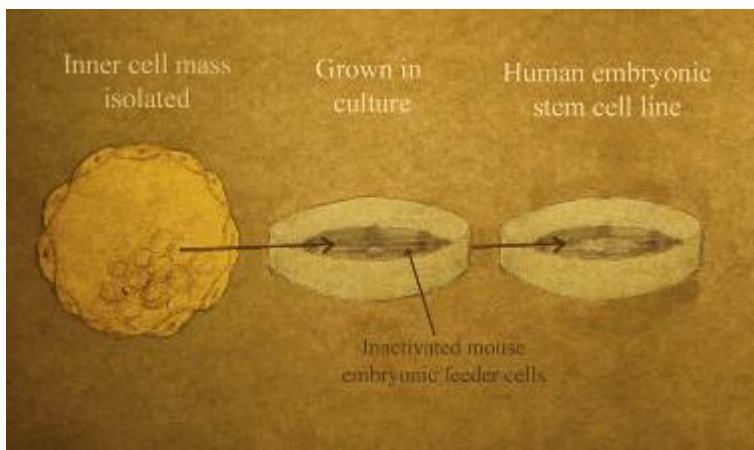
## Umbilical cord blood stem cells

Umbilical cord blood is an alternative source of blood stem cells. It has several advantages: the process by which the blood is harvested is not invasive at all (unlike harvesting stem cells from an adult). Millions of babies are born each year, making umbilical cord blood very abundant.

Several countries have set up umbilical cord blood banks (similar to blood banks). The stored cord blood is available to whoever may require treatment with blood stem cells and also for research purposes.

## What are stem cell lines?

In the laboratory, stem cells are grown in liquid culture media containing nutrients and growth-factors that act like food for the cells allowing them to survive, grow and divide.



The cells are grown in special flasks in incubators where the temperature and mixture of oxygen and carbon dioxide are similar to those found in the human body. The aim is to maintain the cells in just the right conditions to support their growth and proliferation.

Embryonic stem cells can be maintained in these culture media indefinitely. These cell cultures are called **stem cell lines**, because the **cells are able to replicate themselves for long periods of time, outside the body** (See Box H).

At any time, scientists can make the stem cells stop dividing and drive them to make specialised types of cell (blood, brain, muscle) simply by changing the make-up of the medium. They are, therefore, very valuable to scientists, because they can be used for a variety of experiments, including **modeling diseases** and **testing new drugs**.

Embryonic stem cells are grown on layers of support cells called 'feeder cells' in the presence of serum from the blood. The serum provides the nourishment the embryonic stem cells need to survive and divide.

Traditionally, mouse fibroblast cells (connective tissue cells) were used as feeder cells, and the serum was obtained from calves or other animals. Scientists are working to completely replace the mouse feeder cells with human cells, or to grow the embryonic stem cells without feeder cells at all guarding against possible transmission of animal viruses into the human cells, and, subsequently, into patients who receive these cells.

Tissue stem cells can also be grown in a liquid culture. However, unlike embryonic stem cells, tissue and foetal stem cells tend to spontaneously make more specialised cells in the dish. Consequently, it is very difficult to make cell lines from tissue and foetal stem cells.

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### Box H. How are stem cell lines stored in the laboratory?

Once an embryonic stem cell line is established, the cells can be harvested into vials and stored at ultra-low temperatures (-180°C). The stock of frozen cells is called a cell bank.

At any time, the frozen cells may be thawed and used for research or therapy. Stem cell banks are therefore very useful resources for scientists, especially when the cell lines are freely available to all researchers, as is the case with public cell banks such as the UK Stem Cell Bank.

It is estimated that in the whole world, there are 64 human stem cell lines. Scientists have been improving the way in which the stem cell lines are established, making new, safer lines to be used in therapy.

### Where is stem cell research now?

Much research is being done on identifying and isolating human tissue stem cells, which are few in number in human tissue. It is not easy to find the tissue stem cells among the many other types of cells in the brain, the liver or the skin, for example.

#### *Generating specialised cells from stem cells*

Embryonic stem cells need to be stimulated to become specialised cells, before they can be transplanted into patients. Many laboratories are working at developing the proper conditions for this specialisation, as well as understanding how the whole process takes place.

When directing embryonic stem cells to become specialised cells it is crucial that no embryonic stem cells remain in the final population of cells. Because of their unlimited ability to divide, a **single embryonic stem cell that is introduced in the body may grow uncontrollably and give rise to tumours.**

#### *Integrating cells into the body*

Once specialised stem cells are obtained, other obstacles arise when transplanting them into a person (or an animal). The new cells need to integrate into the tissue or organ where they are placed, so that they function properly. Heart cells, for example, need to beat in rhythm with the patient's own heart cells. Nerve cells need to become wired into the brain's circuit in order to work properly.

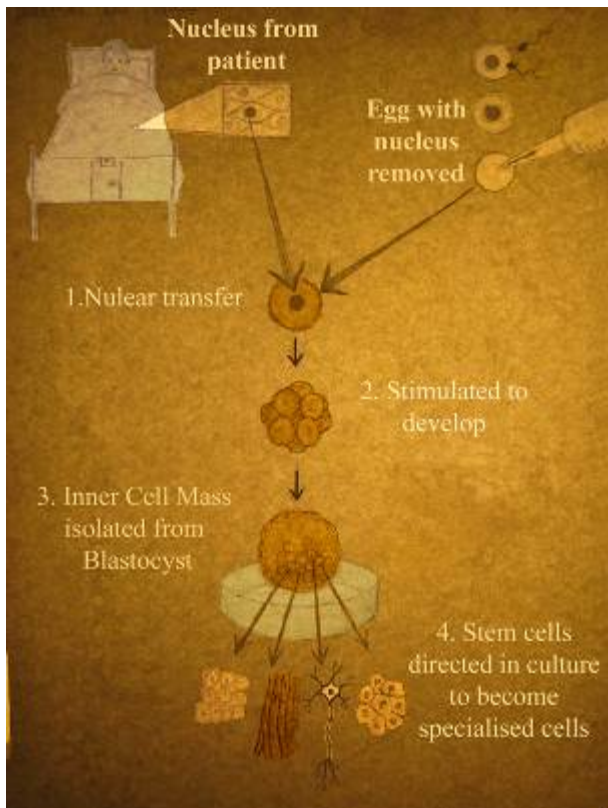
#### *Overcoming rejection by the immune system*

Stem cell therapies, like organ transplants face the problem of being rejected by the patients' immune system.

The immune system protects the body against disease by recognising micro-organisms that are not its own and destroying them. The immune system also rejects human cells and tissues that do not belong to the body. This has resulted in the failure of many organ transplants, and is an obstacle that must be overcome if stem cell therapies are to succeed. To overcome this, organ transplant patients are given drugs to dampen their immune system, which in itself can be quite dangerous as it leaves patients more vulnerable to infections.

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Alternatively, using the patient's own cells and tissues is expected to overcome the concern of immune rejection.

This could be achieved using iPS cell technology. Because the iPS cells are obtained from the patient's own cells, they will not be rejected by the patient's immune system when transplanted back into the body.

Questions about the business feasibility of prospects for stem cells in medicine remain. These include intellectual property, cost-effectiveness and regulatory affairs. At the production stage, issues of end product standardisation and purity, scalability, and timeliness have to be worked out.

To be therapeutically effective in transplantation it needs to be shown that cells and their subsequent daughter cells will function normally in the intended site for significant periods of time. This requires extensive testing first in animals, and then in appropriately designed clinical trials.

Despite these questions, it is ethically and morally responsible for scientific research to address the need to develop treatments for injuries and illnesses that are currently untreatable with pharmaceuticals and surgery.

### What does the law say?

Currently, there is no international consensus on embryo research or therapeutic cloning, and European nations vary in their legislation.

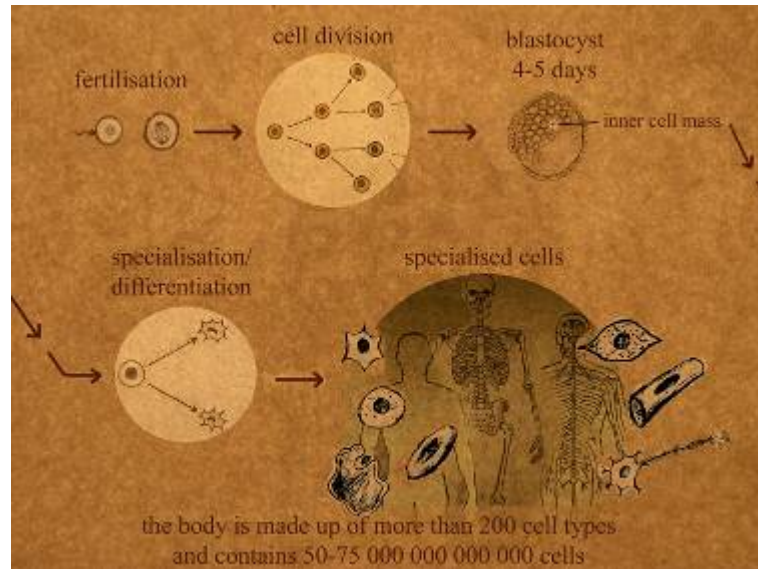
For example in the U.K., under the Human Fertilisation and Embryology Act (1990), and an extension in 2001, it is legal to carry out research on human embryos up to 14 days after fertilisation to help understand the development of embryos, or to help understand and treat serious disease.

Licensed research can only take place on embryos up to 14 days. Stem cells are isolated from the blastocyst much sooner than this – at 5-6 days. Licensed research can only take place on embryos created in vitro. That is, embryos which have developed from eggs fertilised outside the body. Most embryos used in stem cell research are embryos that were initially created for use in IVF treatment, but not used. These "surplus" IVF embryos can only be used for research if they are donated with full consent of the parents.



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By contrast, Ireland is the only country in the EU whose Constitution affirms the right to life of the 'unborn' and that this right is equal to that of the mother. The Commission on Assisted Human Reproduction report in 2005 recommended that embryo research be allowed up until 14 days after fertilisation on surplus embryos donated specifically for research, and that producing embryos specifically for research purposes should be prohibited. No legislation has been put in place in this area since then.

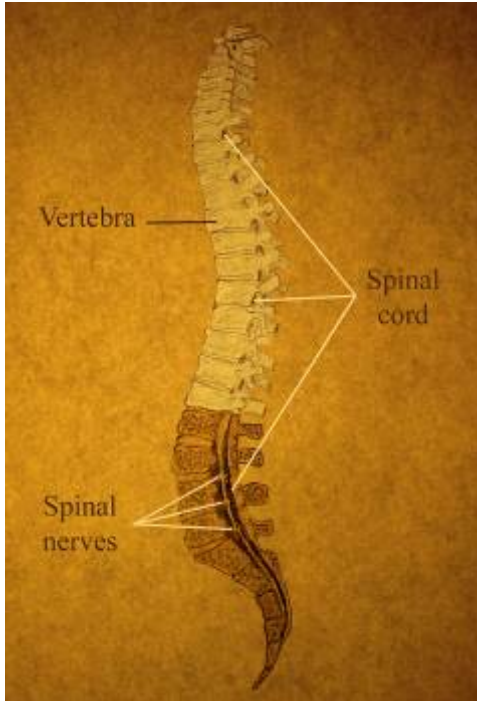
## Religious influences?

The question over whether an embryo deserves the respect and protection of a human person from the time of conception varies between religions. Some religions believe that the embryo is created by God and is a person in its own right with the same moral status as an adult human from the moment of conception. Other religions perceive acquiring full personhood, and the moral rights that go with this status, as gradual during the process of development between conception and birth. It follows from this belief that it might be ethically acceptable under certain circumstances to use embryos for research. For further information please consult: <http://www.eurostemcell.org/factsheet/embyronic-stem-cell-research-ethical-dilemma>

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## 3. What is a spinal cord injury?



The spinal cord is the delicate tissue encased in the spinal column.

It runs from the base of the brain to the middle of the back. The spinal cord conveys information between the brain, the limbs, the trunk and organs of the body.

Any injury to the spinal cord damages this information highway and therefore leads to paralysis, loss of sensation and loss of function of several internal organs (see Box I).

The spinal cord is made up of millions of nerve cells that send projections up and down the cord, and out into other parts of the body. The information that allows us to sit, run, go to the toilet and breathe travels along these projections called nerves.

Although the hard vertebrae of the spinal column protect the spinal cord, the bones can still be broken or dislocated, causing damage to the nerves and/or loss of cells.

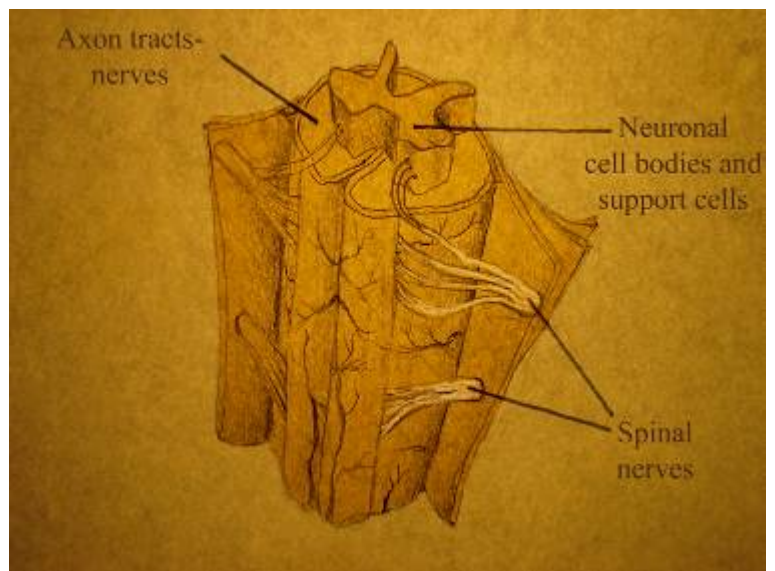
Cells that are lost in the spinal cord cannot be replaced by the body. Consequently, the function of the spinal cord becomes impaired permanently.

Road traffic accidents, falls, sporting accidents (like being thrown from a horse or a diving accident), and gunshot or knife wounds are all possible causes of spinal cord injury. One important preventative strategy is to maintain good driving and passenger habits. Specifically, always wear seat belts even in back seat.

Few injuries sever the spinal cord completely; most injuries cause vertebrae to compress or fracture crushing the nerves in the process.

Infections, cysts and tumours, if they develop in the spinal cord, can also lead to injury, without actually damaging the vertebrae.

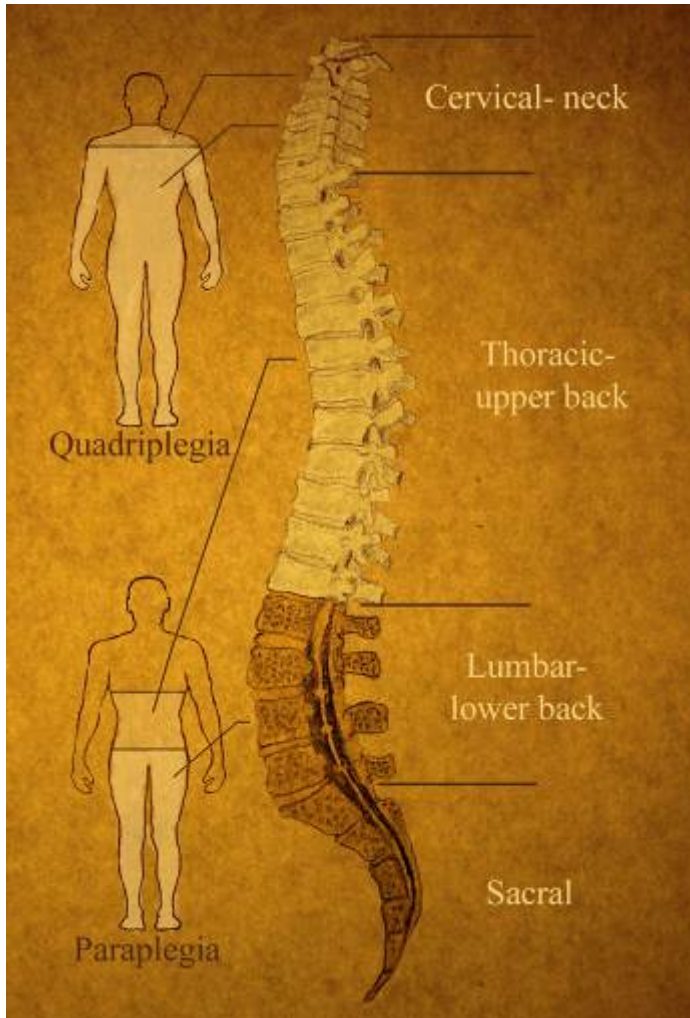
Some congenital diseases (those that are present at birth) affect the structure of the spinal column and may also cause damage to the spinal cord.



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Damage to the blood vessels that supply the spinal cord can also injure the spinal cord if the nerve cells are starved of oxygen and food/nutrients carried to them by the blood vessels.



The severity of the injury and the segment of the spinal cord which it affects determines the degree of impairment.

Injuries to the vertebrae of the neck can lead to paralysis of most of the body from the neck down, including arms and legs. This is called tetraplaegia.

Damage to the vertebrae of the middle back leads to paralysis of the lower body and legs. This is called paraplegia.

Until 50 years ago spinal cord injury meant certain death for most victims. Those who survived the initial injury faced a lifetime confined to a wheelchair or a bed, fighting off infections and complications (such as blood clots).

Today, thanks to research, improved emergency care, improved medical treatments and aggressive rehabilitation, scientists, doctors and therapists are optimistic that spinal cord injury will eventually be repairable.

## Box I. Currently, there will be no functional recovery at all in 40% of patients with spinal cord injury

Depending on the localization and the extent of the spinal injury patients suffer from complete or incomplete paralysis, loss of feeling, sexual function and bowel control.

Many have spasms, recurrent urinary tract infections, chronic pain, loss of confidence and depression 82% of these patients are male, 18% are female.

The mode (most frequent) age at injury is 19.

**Causes:** motor vehicle accidents (44%), acts of violence (24%), falls (22%), sports (8% and 2/3 of these are from diving) and other (2%).

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## How does the spinal cord work?

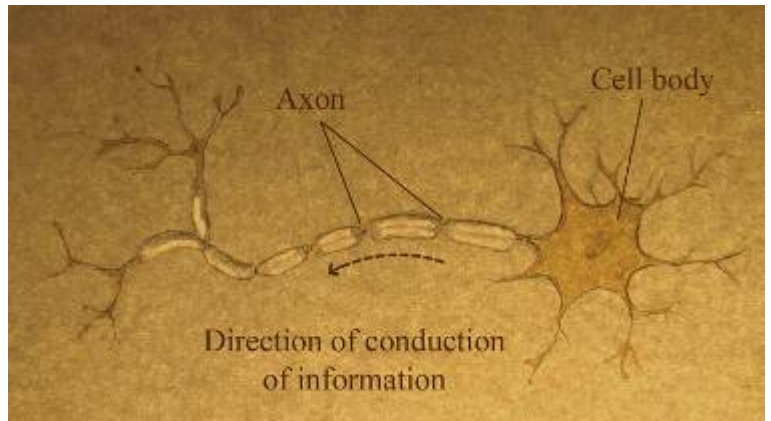
The spinal cord is often described as a cable made up of millions of wires, running between the brain and the rest of the body. The cells that carry the information are called neurons; the “wires” of the spinal cord are the projections of the neurons, called axons.

Axons carry signals either downward from the brain or upward towards the brain.

Some of these axons can be very long, so that they run the length of the spinal cord, which can be up to 45cm in an adult man.

Axons that carry similar signals, or extend to similar areas, bundle together in tracts, or nerves.

Each axon can make connections with many other neurons simultaneously, thus setting up a network of messages and information.



The nerves that carry messages down the spinal cord (from the brain) cause some sort of action at the final destination; they are called motor nerves. They control the muscles of internal organs (heart, stomach, intestines, etc) and those of the legs and arms. They also help regulate blood pressure, body temperature, and the response to stress.

The nerves that travel up the cord (to the brain) carry sensory information from the skin, joints and muscles (touch, pain, temperature) and from internal organs (heart, lungs, etc). These are the sensory nerves.

The spinal cord also contains circuits of neurons that control reflex movements, such as the knee jerk reflex that causes the lower part of your leg to automatically shoot up when your knee is tapped. These circuits are self-contained in the spinal cord; therefore they function without any input from the brain (see Box J).

### Box J. More on the structure of the spinal cord

The nerves leave or enter the spinal cord at the segment that is appropriate for their final destination through small openings between the vertebrae. For example, the motor axons that connect to arm muscles will exit the spinal cord through openings between the vertebrae of the neck. Those that connect to trunk muscles exit from vertebrae along the back.

The axon tracts run on the outside of the spinal cord. The bodies of the neurons, their support cells (called glia) and blood vessels all gather at the inner portion of the spinal cord.

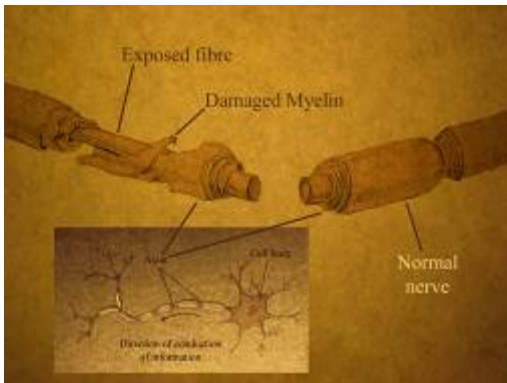
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### What happens when the spinal cord is injured?

The initial damage to the spinal cord triggers a cascade of events that spread around the injury site and last for days.

Any effort to develop strategies that will halt this cascade of events or repair the inflicted damage requires a thorough understanding of the processes involved, how they succeed each other, and how they interact.



The trauma of the injury itself directly pulls nerve cells apart; the cells burst open, releasing toxic substances that kill neighbouring cells. The axons lose their insulation (called myelin) and eventually disintegrate. Cells that die or are lost in the spinal cord cannot be replaced, and so the information pathway is blocked.

Blood vessels may be crushed, become leaky or even burst, causing heavy bleeding at the site of injury which may spread to other areas of the spinal cord.

Within minutes, the spinal cord swells to fill the entire space within the spinal canal. As a result, blood flow is cut off. The swelling and the excessive bleeding interrupt delivery of oxygen and nutrients to cells, causing many of them to die.

Cells of the immune system gather at the injury site, causing uncontrolled inflammation. The immune system's role is to protect the body from infection; the white blood cells circulate in the blood vessels and do not usually come into contact with cells of the nervous system.

However, after injury to the spinal cord, because vessels burst, the white blood cells accumulate near the nerve cells and trigger inflammatory responses, including more cell death.

Days or weeks after the injury, cells in the injury area begin to undergo a 'programmed cell death' through a process called apoptosis.

The nerve cells that are most prone to apoptosis are those that make up the insulating myelin sheath around axons, called oligodendrocytes. Without this insulation, axons are unable to carry signals, and eventually disintegrate.

The cumulative toll of all these events is that, a few weeks after the injury, a scar tissue is formed across the injury site. This scar acts as a physical barrier which any re-growing axons cannot cross to connect to cells on the other side.

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## How are spinal cord injuries treated?

The most important considerations when dealing with spinal cord injuries are to minimise the amount of damage to the spinal cord, on the one hand, and prevent additional damage, on the other. These concerns apply both when moving a patient and during the first weeks after the injury, during the so-called acute phase.

There are, as of yet no treatments that completely revert the damage caused to the spinal cord. However, doctors agree that high-quality medical care immediately after the injury and aggressive rehabilitation strategies can go a long way in helping patients regain both physical and emotional independence.

Medics report a window of 48-72 hours to address the initial injury and then must wait for the extent of the injury to become apparent. In the first 48 hours there is a need to address the acute inflammation and spinal instability. Many doctors see rapid surgical spine stabilization as a priority.

The steroid methylprednisolone is often given to patients within the first eight hours after their injury. This drug seems to significantly limit the extent of damage and improve patients' recovery. It appears to work by reducing cell death near the injury site by decreasing inflammation at the site and reducing the edematous swelling of the spinal cord. The use of steroids is controversial. There is evidence of benefit but this treatment can be accompanied by severe side effects. Many patients are poor candidates for high doses. Specifically, in a patient with poly-trauma resulting from an auto accident, the risk of infection when giving the steroid is too high and offsets the neurological gain with risk to life with sepsis (blood poisoning) and prolonged hospitalization. Also, wound healing is slowed after steroid use.

During the acute phase of the injury, which covers the first few weeks after the initial damage, braces, rods or ties are applied to the patient. The aim is to apply traction to the spinal column to stabilize it and prevent further damage.

Rehabilitation programmes are a central part of treating spinal cord injuries. They combine physiotherapy with skill-building activities and counselling. Their aim is to provide physical, social and emotional support to the patients.

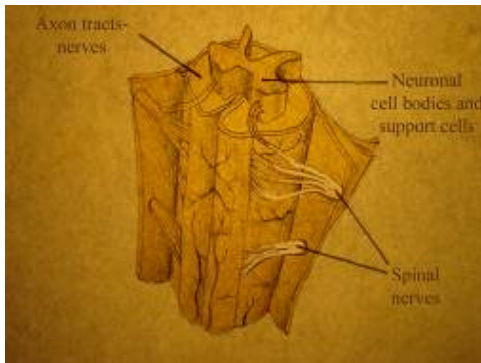
A rehabilitation team will typically include a physiatrist (a doctor specialising in rehabilitation), physical and occupational therapists, recreational therapists, rehabilitation nurses and psychologists, vocational counsellors, nutritionists and other specialists.

For the patient to get the most out of a rehabilitation programme, it is crucial that he/she is actively supported by family and friends.

Many research teams, all over the world, are working to understand what actually happens when the spinal cord is injured. Their hope is that, in dissecting out the different phases of spinal cord injury, it will be possible to identify targets for therapeutic interventions that will halt or even reverse the devastation triggered by the initial damage.

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A spinal cord injury is complex: it involves different kinds of damage (cell death, inflammation); different types of cells are damaged (neurons and their supporting cells, glia); the environment of the spinal cord changes drastically during the first few weeks after injury (immune cells flow in, toxic substances are released, a scar is formed).

It is therefore likely that a combination of therapies will need to be developed, acting at the appropriate time-point, and on the correct targets.

Any attempt to develop a treatment entails thoroughly understanding the physical environment of the injury.

Researchers are trying to find answers to one or several of the following questions:

- How can surviving cells be protected from further damage?
- How to replace nerve cells that have died or are non-functional?
- How to stimulate re-growth of axons and make them establish the correct connections?
- How to retrain the circuits of neurons so that body functions are restored?
- How can the glial scar be minimized; how can we remove this inhibitor to axon growth and promote axon regrowth?

## Spinal cord repair using stem cells?

A stem cell has the capacity to give rise to many different types of cells. Because of this amazing capability, there is great potential for the use of stem cells to treat the damage inflicted on the cells of the spinal cord, after injury. There are three ways in which stem cell derived neurons and oligodendrocytes may potentially contribute to repair the spinal cord:

- When introduced into the spinal cord shortly after injury (See Box K.), these cells may protect the cells at the injury site from further damage, by releasing protective factors. Stem cells may also stimulate self-repair by producing growth factors.
- They may be used to generate new supporting cells that will re-form the insulating myelin sheath.
- They may be used to replace the neurons that have died as a result of degenerative disease.

All research into the use of stem cells in spinal cord injuries has been undertaken using animal models (mainly mice and rats). The first clinical trial has started in October 2010. Several questions remain to be answered, but each new study brings scientists a step closer to applying stem cells, and the specialised cells grown from them, to the treatment of human spinal cord injuries.

### Box K. How are stem cells delivered to patients with spinal cord injury?

- Lumbar puncture delivery.
- Direct cell injection into the spinal cord
- Delivery on an implantable, polymer scaffold

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### Useful links

EuroStemCell

Europe's stem cell hub: information, education, conversation

<http://www.eurostemcell.org>

An animation showing how embryonic stem cell lines are made

<http://www.dnalc.org/stemcells.html>

The House of Lords report on the Human Fertilisation (Research Purposes) Regulations 2001

This extensive report covers several topics, including the science of stem cells, regulation and ethical issues

<http://www.parliament.the-stationery-office.co.uk/pa/ld200102/ldselect/ldstem/83/8301.htm>

Human Fertilisation & Embryology Authority (HFEA)

<http://www.hfea.gov.uk/home>

Institute for Stem Cell Research (ISCR)

To know more about the stem cell research carried out at the ISCR

[www.iscr.ed.ac.uk](http://www.iscr.ed.ac.uk)

NHS Cord Blood & Transplant (NHSBT)

Here you can find information on banking of umbilical cord blood

<http://www.nhsbt.nhs.uk/cordblood/cordblood/>

The UK Stem Cell Bank

Here you can find out more about stem cell lines and stem cell banks

<http://www.ukstemcellbank.org.uk/>



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## Acknowledgements



This role play draws on research funded by the MRC and the ESRC, and further developed by REMEDI.



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