STEM CELL RESEARCH

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Research in animals suggests that stem cells – the precursors of the more specialised cells that make up organs and tissues – may be used to repair diseased or damaged tissue. Cells derived from early stage embryos may be particularly useful. While it is not clear whether this research can be repeated in humans, any such move would raise legal and ethical issues.

This briefing outlines recent developments in stem cell research, looks at the potential applications and analyses the issues that arise.

STEM CELLS

What are stem cells?

Stem cells are characterised by two main properties:

- they have the capacity to renew themselves;
- and to develop into more specialised types of cell.

As outlined in **Box 1**, stem cells can be categorised according to their 'plasticity' – i.e. the range of different cell types they are capable of producing. As a general rule of thumb, the earlier the stage of development of the tissue from which a stem cell is derived, the greater the range of cell types it can give rise to. Animal research (mainly in mice) has shown that it is possible to derive pluripotent (Box 1) stem cells from embryos and fetuses. These can be cultured and multiplied in the laboratory, and used to produce a very wide range of different cell types.

Pluripotent human stem cells

Recent research in the US and Australia has suggested that it may also be possible to isolate pluripotent human cells. Two research groups have derived cells from human embryos (ES cells, see Box 1) and cultured them in the laboratory. Another research group has managed to derive cells from human fetal tissue (EG cells, see Box 1) and maintain them in stable cell cultures.

Researchers are fairly confident that these cell cultures are actually pluripotent human stem cells. The human embryo cells give positive results in a standard test for stem cells[1]; one of the groups has also managed to differentiate them into nerve cells in culture. However, both the human embryo- and fetus-derived cells have different growth characteristics than the mouse stem cells (they are more difficult to grow and multiply in culture in the laboratory)

BOX 1 DIFFERENT TYPES OF STEM CELLS

Stem cells are often categorised according to the extent to which they are differentiated (i.e. how committed they are to develop into cells of a particular type). A newly fertilised egg is **totipotent** – it has the capacity to turn into **all** types of cells needed for full embryonic development. After the first three rounds of cell division the egg's daughter cells start to differentiate into two main cell types: those that will go on to form the placenta and the **stem cells** that will go on to form the embryo. These embryonic stem cells are **pluripotent** – they have the capacity to turn into all of the cell types found in the adult animal, but cannot give rise to placental cells and thus cannot develop into embryos. As explained in more detail below, more highly differentiated (**multipotent**) stem cells may also be isolated from fetuses and adults.

- **Pluripotent stem cells.** Research in mice and other species has identified two main types of pluripotent cells. **Embryonic stem** (ES) cells are isolated from the blastocyst - a ball of 50-100 cells that forms about 5 days after fertilization and contains an inner cell mass of 20 or so pluripotent stem cells. **Embryonic germ** (EG) cells are derived from the primordial sex cells (those cells that will eventually develop into eggs and sperm) present up to about 6 weeks of development. Researchers have cultured and multiplied ES and EG cells from mice in the laboratory; both types have demonstrated the capacity to produce a wide range of cell types.
- **Multipotent stem cells** – may be derived from fetuses and also comprise a progressively diminishing proportion of adult cells. They are already partially differentiated (e.g. as neural stem cells, or blood stem cells) and may thus have a more limited capacity to produce different cell types. For instance, blood stem cells can produce all of the various different types of blood cell needed in the body. Recent research suggests that it may be possible to reprogramme multipotent stem cells of one type (e.g. neural cells) into another type (e.g. blood) although this has yet to be confirmed.

Sources: http://bioethics.gov/stemcell_exec_intro.htm; "Therapeutic Cloning. A Submission by the Royal Society to the CMO's Expert Group", February 2000; and "Stem Cell Therapy: The Ethical Issues", Nuffield Council on Bioethics, April 2000.

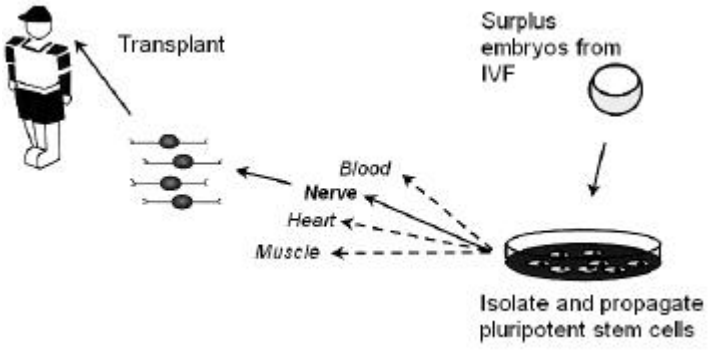
Multipotent human stem cells

As organs and tissues grow, stem cells become more differentiated and thus have a more limited capacity for giving rise to different cell types (they are multipotent, Box 1). In adults, stem cells constitute a diminishing proportion of total cells, although this varies from tissue to tissue. Tissues such as skin, intestine and blood that are continually renewed, maintain a population of partially differentiated stem cells throughout life. Others (e.g. muscle) may retain a dormant population that divide only when required (e.g. if the tissue is damaged). Some tissues (e.g. heart) do not appear to retain stem cells into adulthood.

Adult stem cells (e.g. blood stem cells) have been used in various therapeutic applications, partly because they are readily accessible. To date, efforts to isolate, multiply and culture adult stem cells in the laboratory have met with only limited success.

1 The (human) cells are injected into mice with no immune system; under such circumstances stem cells form multi-differentiated tumours.

FIGURE 1 STEM CELL THERAPY (SCT)



Source: Centre for Genome Research, Edinburgh University

POTENTIAL APPLICATIONS

Although research is still at a very early stage, human stem cells have a wide range of potential therapeutic applications. These include:

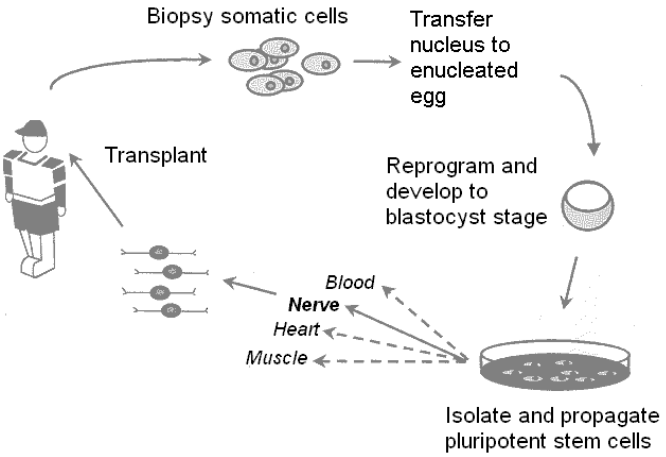
- repair of organs damaged by trauma or disease;
- treatment of degenerative diseases such as Parkinson's (brain), hepatitis (liver), diabetes (pancreas) and leukaemia (blood);
- treatment of burns and complex fractures;
- use of genetically modified stem cells to treat diseases caused by lack of secreted gene products (e.g. cystic fibrosis);
- use of blood stem cells to treat blood disorders.

An idealised scheme for stem cell therapy is shown in **Figure 1**. Although the Figure shows the production of nerve cells, in theory pluripotent cells would have the capacity to produce any of the 216 different types of cell that make up the human body. Whichever type of human stem cells were used in such applications, their ability to renew themselves offers two main advantages:

- A stem cell transplant should continue to deliver its therapeutic effect long-term, even in tissue undergoing continuous turnover.
- Production of cells for transplantation on a large scale in the laboratory. Such cell lines might eventually only require fetal or embryonic tissue to set them up in the first place. They could be used to establish banks of differentiated and undifferentiated cells and tissues for transplantation.

It should be emphasised that such developments are still a long way from being realised. For instance, while researchers may have managed to isolate and culture human ES and EG cells, they do not yet understand the (chemical, physical and genetic) factors that trigger stem cells to differentiate into one cell type or another.

FIGURE 2 PATIENT-SPECIFIC STEM CELL THERAPY



Source: *Centre for Genome Research, Edinburgh University*

IMMUNOLOGICAL REJECTION

As with conventional organ transplants, one of the main problems with stem cell transplants is likely to be immunological rejection. A recent submission from the Royal Society[2] outlined a number of potential ways round this problem:

- Tissue matching – establishing banks of different types of stem cells representing the main tissue types within the population. This is analogous to the current situation with blood groups.
- Genetic manipulation of stem cells to reduce immune recognition in the human host.
- Giving the cells or tissues used for a transplant the same immunological profile as the patient receiving them.

In theory, this latter option could be achieved using somatic cell nuclear transfer (SCNT). The nucleus of a donated egg is removed (enucleation), and replaced with a nucleus from an adult somatic (non-sex) cell. If this was implanted into the uterus, it could go on to develop into a clone of the adult from which the somatic cell was taken. This is known as **reproductive cloning** - the technique used to create Dolly the sheep. But if the egg is allowed to develop to the blastocyst stage (Box 1) and not implanted, it can be used as a source of embryonic stem cells for culture (**Figure 2**). This is known as **therapeutic cloning**; ES cells produced in this way could be used for therapy in the adult donating the somatic cell without fear of rejection. No such procedures have been licensed in the UK using human cells. While many scientists see benefits in research on SCNT for therapeutic purposes, all agree that human reproductive cloning should remain banned.

2 'Therapeutic cloning: A Submission from the Royal Society to the CMO's Expert Group', Royal Society, London, Feb 2000.

THE LEGAL FRAMEWORK

Research on tissue derived from human embryos is regulated under the Human Fertilisation and Embryology (HFE) Act 1990 by the Human Fertilisation and Embryology Authority (HFEA). As outlined in **Box 2**, this Act allows the licensing of certain types of research involving human embryos up to the 14th day of development. At present, the Act only allows the licensing of such research for specific purposes concerned mainly with studies on infertility, miscarriage, and congenital disease. Research on human embryos for therapeutic purposes – e.g. the production of stem cells derived from ES cells (Figure 1) or via SCNT (Figure 2) for transplantation - is **not** currently allowed.

ISSUES

Recent years have seen considerable debate over whether research (including SCNT) involving the use of cells derived from human embryos or fetuses should be allowed for therapeutic purposes. The debate has focused on the availability of alternatives to research on human embryos, the legal and ethical implications of such research, and the potential risks and benefits to human health.

Availability of alternatives

There are three potential sources of stem cells for transplants to repair damaged or diseased tissue:

- Multipotent stem cells taken from the patient.
- Pluripotent stem (ES) cells from embryos.
- Pluripotent stem (EG) cells from fetuses.

Those opposed to the use of embryo- or fetal-derived cells point to the advantages of using multipotent cells from the patient's own body. This not only avoids the ethical and legal issues associated with ES/EG cells but also gets round any problems with immunological rejection. But some adult tissues may not contain stem cells and those that do are not always readily accessible. They are also difficult to grow (so there is a delay between harvesting and therapy) and have only a limited potential to produce different cell types. To date, therapeutic applications have been largely limited to treating blood disorders using blood stem cells.

Many scientists see research on pluripotent ES cells as being the way forward. They suggest that ES cells offer a number of potential advantages. ES cells can give rise to many more cell types than adult stem cells, and may be easier to isolate, grow and multiply. There is also a wealth of knowledge about the behaviour of animal ES cells that may be transferable to humans. Ultimately, the hope is that such research will lead to a full understanding of how cells differentiate and develop, and how such processes can be controlled. This may eventually lead to a situation where research on ES cells is no longer required. For instance, it may one day be possible to obtain stem cells by directly 'reprogramming' normal adult cells. But research on ES cells raises a number of legal and ethical issues; these are discussed in more detail below.

BOX 2 STEM CELL RESEARCH AND THE UK LAW

Human Embryonic Tissue – under the HFE Act 1990 the HFEA may license the use of human embryos in research only where it considers their use to be necessary or desirable:

- to promote advances in the treatment of infertility;
- to increase knowledge about the causes of congenital disease;
- to increase knowledge about the causes of miscarriage;
- to develop more effective methods of contraception;
- to develop methods for detecting gene or chromosome abnormalities in embryos before implantation.

This list may be extended in regulations by the Secretary of State for Health. Under the terms of the Act, any new categories established must have a view to increasing knowledge about the creation and development of embryos, or increasing knowledge about disease, or enabling such knowledge to be applied.

Human fetal tissue - there are no specific UK statutory provisions governing the use that can be made of tissues derived from fetuses. However, the Abortion Act (1967) governs the legality of the abortion that makes fetal tissue available. Subsequent use of fetal tissue for teaching, therapy and research is the subject of a code of practice issued by the Polkinghorne Committee in 1989. This concluded that research ethics committees should examine all proposals for work with fetal tissue.

Somatic cell nuclear transfer (SCNT) – the HFE Act expressly prohibits only cloning that involves '*replacing the nucleus of a cell of an embryo with a nucleus taken from a cell of any person*' or an embryo. SCNT is excluded from this prohibition since it involves nuclear substitution into an egg (not an embryo). Nevertheless, because the technique involves the production and use of embryos outside the body, it falls within the general terms of the HFE Act and thus comes under the jurisdiction of the HFEA.

Source: 'Stem Cell Therapy: The Ethical Issues', Nuffield Council on Bioethics, April 2000.

Legal/ethical issues

Techniques such as SCNT and ES cell culture/reprogramming were not envisaged when the HFE Act 1990 was drafted. A number of bodies have thus examined whether the 1990 Act and the HFEA can adequately regulate this rapidly progressing research area. These include the House of Commons Science and Technology Select Committee[3], Human Genetics Advisory Commission and HFEA[4], Nuffield Council on Bioethics (NCB)[5] and the Chief Medical Officer's (CMO) Expert Advisory Group on Therapeutic Cloning.

3 5th Report, The Cloning of Animals from Adult Cells, Session 1996-97
4 HGAC/HFEA, Cloning: Issues in Reproduction, Science and Medicine, 1998
5 NCB, Stem Cell Therapy, The Ethical Issues, NCB, 2000

Reproductive cloning

Those opposed to human embryo research in general, and SCNT in particular, often portray such procedures as the 'thin end of the wedge'. They claim that allowing SCNT for therapeutic purposes would pave the way for full reproductive cloning in humans. In contrast, most scientists see a clear distinction between reproductive and therapeutic cloning, regarding the former as ethically unacceptable in humans, and the latter merely as a means of reprogramming adult cells into stem cells.

Concerns over the possibility of using SCNT for human reproductive cloning have prompted scrutiny of the existing regulatory framework by the Commons Science and Technology Committee and the HGAC/HFEA. As noted in Box 2, the HFE Act does not explicitly prohibit SCNT, but all such procedures do fall within the HFEA's remit. The Government has explicitly ruled out human reproductive cloning and the HFEA has stated that it will not licence SCNT for such purposes. Both the Commons Science and Technology Committee and the HGAC/HFEA reports concluded that the existing safeguards were wholly adequate to forbid human reproductive cloning. However, both recommended that the government consider passing legislation explicitly banning reproductive cloning so that the full ban is enshrined in statute rather than depending upon the decision of a statutory body.

Changes to the HFE Act 1990

HGAC/HFEA also recommended that regulations made under the HFE Act 1990 (Box 2) be extended to allow research involving human embryos for developing methods of therapy for:

- diseased or damaged tissues or organs;
- mitochondrial diseases.

The first of these would allow research on ES cells for therapeutic purposes. Priorities include:

- understanding mechanisms of differentiation and development;
- identification, isolation and purification of different adult stem cell types;
- controlling differentiation of stem cells;
- preventing rejection of transplanted stem cells;
- demonstrating the safety of stem cell transplants (normal cell development, function and growth);
- confirming successful animal research in humans.

The second proposed change would allow research to correct rare disorders caused by faults in DNA present in structures (mitochondria) that float in the fluid surrounding the cell nucleus. Faults in this mitochondrial DNA (inherited from the mother's egg) can cause metabolic disorders. It might be possible to transfer a nucleus from a woman with 'bad' mitochondrial DNA into an egg donated by a woman with 'good' mitochondrial DNA. Such an egg could be fertilised *in vitro*, and implanted in the mother's uterus.

In its response to the HGAC/HFEA report, the Government noted that possible changes to the legislation should be considered, and asked the CMO to set up an expert advisory group in June 1999. The group's report is expected by summer 2000, and will address issues such as:

- the current state of play of stem cell research in humans and animals;
- which applications are potentially most beneficial;
- potential safety or technical problems;
- ethical and social implications of such research and its potential therapeutic application;
- potential impact on the provision of health care;
- whether alternatives to research on human embryos are available to achieve the same ends, and if so, when these will be available.

Source of embryos

Should research be restricted to using 'surplus' embryos from IVF programmes or should researchers be allowed to create embryos specifically for research? NCB considered this issue and concluded "*while there are sufficient and appropriate donated embryos from IVF treatments for use in research…there are no compelling reasons to allow additional embryos to be created*". However, some have suggested it may be necessary to produce some embryos specifically for establishing cell banks. Once established, cell banks would require the use of fewer embryos.

Safety

Other concerns over human stem cell therapy have focused on the potential risk of proliferating stem cells causing tumours. Studies in animals have already shown that neural stem cells can be integrated into nerve tissue in a stable manner; further animal studies are needed before such procedures are tried in humans. Some researchers suggest genetically modifying stem cells to contain a 'suicide gene' to protect against such risks. Others note that human genome data might allow stem cell screening to assess their potential to cause tumours.