



# postnote

June 2004 Number 221

## REGULATING STEM CELL THERAPIES

As research on human stem cells continues apace, new frameworks may be required to regulate their use. Such cells can be used as medicines, as transplants or transfusions to regenerate organs and tissues, or in conjunction with more advanced therapies such as gene therapy. Some of these applications are already subject to strict regulation; others are not. This briefing examines recent developments in this field and considers future regulatory options.

### Stem cell therapies

Stem cells are unspecialized cells that can replicate themselves by dividing; in some circumstances stem cells can also be induced to become one of the 200 or more different types of specialized cells found in the body. As outlined in box 1, they can be derived from various sources. Regardless of source, scientists ultimately see stem cells being used for the treatment of degenerative diseases like Parkinson's, chronic illness such as diabetes and certain forms of heart disease, as well as traumas such as burns and fractures.

### Current treatments

Current treatment options for such diseases include:

- Long-term drug therapy. This generally does not cure such conditions, but rather allows them to be managed. It must be monitored over the life of the patient to respond to the changing disease.
- Transplants. Here the aim is to replace the damaged organ or tissue to restore normal physiological function. The number of patients needing transplants far outstrips the number of organs available for donation. Even when organs are successfully transplanted, there is a danger of rejection by the recipient's immune system.
- Medical devices such as pacemakers, vascular grafts, orthopaedic pins and prosthetic heart valves. Such devices may need replacing over the patient's lifetime.

### Box 1 Sources of stem cells

Stem cells are cells that have the ability both to replicate themselves and become other, more specialized types of cells (**differentiation**). Stem cells are of four major types, each with advantages and disadvantages.

#### Embryonic stem (ES) cells

- Derived from human embryos that are a few days old
- Have the potential to become almost any type of cell
- Difficult to manipulate
- Ethically contentious as the embryo is destroyed in the process of ESC creation

#### Foetal stem cells

- Derived from aborted human foetuses
- Have the potential to become many of the cell types
- Ethically contentious and limited availability

#### Cord blood and placental stem cells

- Derived from umbilical cord blood and placentas
- Already used in a variety of therapies
- Easily extractable
- Can currently only form a limited number of cell types
- Available in low concentrations

#### Adult stem cells

- Found in all humans
- Already in use for some therapies
- Sometimes difficult to access
- Can currently form a limited number of cell types

### Stem cell based therapies

Different regulatory frameworks apply depending on the mode of action of the treatment. A distinction is made between those treatments where the stem cells produce a therapeutic substance resulting in a medicinal action and those (non-medicinal) treatments where stem cells replace or augment normal tissue function.

#### Non-medicinal therapies

Most current stem cell therapies are non-medicinal in nature, and act principally by replacing, repairing or regenerating some function of the patient's body. As

discussed in more detail later, proposals for a new regulatory framework seek to distinguish between:

- **Unmodified stem cells used in transplants:** the simplest therapies involve transplanting tissue containing stem cells into a patient. Examples include bone marrow transplants, placental stem cells (which have been used in the US to treat a variety of diseases) and foetal stem cells (used to treat Parkinson's disease with limited success).
- **Stem cells that have been extensively manipulated/modified or subject to an engineering process:** such cells can be used to replace (bones, heart valves, blood vessels and arteries), repair (neurological tissue, skin, or muscle) or regenerate (liver and pancreas) human tissue. The European Commission has proposed new regulations to cover these **tissue engineered products**.

#### *Medicinal therapies*

As stem cell technologies mature, therapies that have a medicinal mode of action are likely to be developed. Any stem-cell based therapy designed to have a therapeutic, diagnostic or preventative effect would be classified and regulated as a **medicinal product**. Examples may include genetically modified cells (adding genes to produce therapeutic substances such as insulin, or 'knocking out' genes coding for immunological markers) and cells that have been differentiated or reprogrammed. As outlined in box 2, these are methods that may allow researchers to turn cells of one type into cells of another type.

#### **Potential safety issues**

Of the various approaches outlined above, the simplest therapies are transplants of unmodified stem cells derived from the patient receiving them. Such (autologous) approaches may be safer than traditional (allogeneic) transplants in which material is transferred from one person to another because the risk of transmission of disease and/or rejection of the material is eliminated. The risks of disease transmission or rejection are particularly high when the tissues or cells remain viable in the recipient.

Another area of concern may be manipulated stem cells, particularly those derived via reprogramming techniques such as cell nuclear replacement (CNR, see box 2). Experience from studies using CNR to clone animals suggests two potential issues. First, the technique is very inefficient, with overall success rates typically between 0 and 3%, largely due to difficulties in controlling reprogramming.<sup>1</sup> Second, even where CNR appears to have been successful, the resulting animal clones often suffer from abnormalities. There is currently no way of telling how successful reprogramming has been when CNR is used to make stem cell lines.

## **Regulation of stem cell research**

### **Embryonic stem cells**

The current legal framework can be traced back to 1978 and the birth of Louise Brown, the first 'test tube baby'. This prompted debate on how to regulate the creation of embryos outside the human body, and led to the Human

## **Box 2 Differentiation and reprogramming**

### **Directed differentiation**

Differentiation is the name given to the process that occurs when unspecialized (stem) cells give rise to cells with more specialized functions. Researchers think that the process is a response both to internal (e.g. genetic) and external factors (e.g. physical proximity to neighbouring cells, or chemicals released by other cells or encountered in the environment). If the nature of these internal and external factors is better understood, it may be possible to direct the differentiation of stem cells in the laboratory, and use the cells and tissues for therapeutic purposes.

### **Reprogramming**

Until quite recently it was thought that differentiation was a one way process, with cells becoming increasingly specialized. However, research has now shown that it is possible to reprogram cells, turning them from specialized cells back into unspecialized (stem) cells or cells of another type entirely. The best known example of this was Dolly the sheep, where a cell nuclear replacement (CNR) method was used to substitute the nucleus of an egg with a nucleus taken from a (specialized) adult mammary gland cell. During the process the adult nucleus was reprogrammed, and started to behave as if it were an embryo which, following implantation went on to develop into Dolly. Other experiments in recent years have suggested that stem cells from one tissue may be able to give rise to cell types of a completely different tissue. For instance, blood cells have become neurons, liver cells have been made to produce insulin, and blood stem cells developed into heart muscle.

Fertilisation and Embryology (HFE) Act 1990. The Act set up the HFE Authority (HFEA) to regulate and monitor any fertility treatment involving donated eggs, sperm and embryos created outside the body, the storage of eggs, sperm and embryos, and research on human embryos. Under the terms of the Act, all research involving the creation, storage or use of human embryos outside the body must be licensed by the HFEA. Such research will only be licensed where it is "*necessary or desirable*" and where use of human embryos is essential. Furthermore, the Act originally restricted embryo research to one of five permitted purposes related to reproductive medicine. Parliament approved the HFE (Research Purposes) Regulations 2001, which extended the permitted purposes to cover:

- increasing knowledge about development of embryos;
- increasing knowledge about serious disease;
- enabling any such knowledge to be applied in developing treatment for serious disease.

Concerns that permitting therapeutic research on stem cells might open the way to human cloning led to the Human Reproductive Cloning Act 2001, which prohibits such cloning. Regulation of embryo research in some other countries is outlined in box 3.

### **The national stem cell bank**

Following the debate over whether to extend the permitted purposes for research on embryos to include therapeutic research, a House of Lords Select Committee on Stem Cell Research was established in March 2001. This Committee reported in February 2002, endorsing "*the Department of Health's proposals to establish a stem cell bank overseen by a steering committee,*

**Box 3 Embryo research in other countries**

Belgium is the only other EU member state to permit the creation of an embryo explicitly for research purposes. Ten EU member states explicitly forbid the creation of human embryos for research purposes and the procurement of stem cells. Five of those nations also prohibit the procurement of ES cells from 'spare' embryos, although Germany does allow the regulated import of human ES cell lines. In the US, Government funding, including money from the National Institutes of Health, is permitted only on selected ES cell lines created before 9 August 2001. Private research on embryos and ES cells is not regulated at the federal level but all research is reviewed by institutional ethics committees.

*responsible for the custody of stem cell lines, ensuring their purity and provenance and monitoring their use".<sup>2</sup>* In September 2002 the Medical Research Council (MRC) and the Biotechnology and Biological Sciences Research Council announced funding to establish a National UK Stem Cell Bank (opened in May 2004). The bank is responsible for providing quality-controlled stem cell lines for research and for developing therapies. Its Stem Cell Steering Committee (SCSC) is currently consulting on a draft Code of Practice for the Use of Stem Cell Lines.<sup>3</sup>

Researchers wishing to use embryonic stem cells or to access stem cell lines from the bank would have to comply with the Code of Practice. All applications to deposit stem cells in, and to use cell lines from, the UK Stem Cell Bank (or those imported from abroad) would be considered by the SCSC. The Code of Practice lays down various measures to ensure the safety and quality of the cell lines used in the UK. For instance, it requires that research on stem cells is conducted in line with MRC and Department of Health (DH) guidance.<sup>4</sup>

## Regulating clinical stem cell research

### Quality and safety

Stem cells intended for clinical use are also covered by the SCSC's draft Code of Practice. It stipulates that they must be derived and processed in clinical facilities that have been inspected by the Medicines and Healthcare products Regulatory Agency (MHRA) and meet DH guidelines.<sup>5</sup> The institution must also implement an appropriate quality system and comply with the Code of Practice of the Medical Devices Agency (which is now part of the MHRA).<sup>6</sup> Finally, the proposal must be subject to formal risk assessment.

### Clinical trials and therapy development

All researchers planning to use stem cells in clinical trials must seek the MHRA's advice as to the applicability of current regulations for medicinal products or medical devices. As outlined in box 4:

- Clinical trials of all medicinal products must be conducted in accordance with rules laid down in the Clinical Trials Directive. Medicinal stem cell therapies are also regulated under the Medicinal Products Directive. This was recently updated to encompass advanced therapies including certain types of therapies ('somatic cell therapy medicinal products') involving manipulated stem cells.

- The Medical Devices Directive specifically excludes products derived from human tissue or cells, and does not apply to clinical research involving human stem cells as such. However, the non biological part of a stem cell-based device (e.g. the matrix in an artificial skin) would have to comply with the Directive.

### Consent

The SCSC Code of Practice currently requires researchers to seek consent as required by the Human Tissues Act (1961) and HFEA guidance (for research on embryos). However, a new EU Directive (2004/23/EC) on Human Tissues and Cells was adopted in March 2004 with a two year implementation period. As outlined in box 4, this sets out wide ranging requirements for ensuring the safety and quality of all tissues and cells used for human applications. It will be implemented principally by regulations provided for by the Human Tissues Bill, currently before Parliament. This would establish a new body, the Human Tissue Authority (HTA), and set the requirements for obtaining consent from donors of human organs, tissues and cells.

Scrutiny of the Bill has prompted debate over the scope and frequency of the consent required. The Bill is designed to protect donors by ensuring that tissue is used only for the purposes specified in the consent. But there are concerns that it could have far reaching implications for many areas of clinical research that involve routine re-use of samples. The Code of Practice will be updated to reflect the new Bill when it has been enacted.

## Regulation of tissue engineered products

Although existing EU and national regulations already cover some of the stem cell therapies described in this briefing, there is a gap on tissue engineered products. The following sections describe proposals for a new framework for marketing approval for such products and discuss whether there is a need for further regulation to control research in this area.

### Proposed framework for tissue engineered products

The European Commission is consulting on proposals for a new regulatory framework for tissue engineered products. It views EU regulation in this area as desirable, to ensure the quality, safety and efficacy of such products while allowing patients access to the potential benefits of new therapies. Following consultation with stakeholders, the European Commission published its most recent proposals in April 2004.<sup>7</sup> Key features of the new proposals include:

- Two main types of tissue engineered products are defined. **Autologous products** are those that are derived from cells/tissues removed from one person and used in (or on) that same person. **Allogeneic products** are derived from cells or tissues removed from one person and used in/on another person.
- All authorisations for the manufacture, marketing or use in clinical trials of autologous products would be handled at national level, by the appropriate national competent authority. This is designed to ensure that

### Box 4 Current EU stem cell regulation

#### Medicines

The Clinical Trials Directive (2001/20/EC) lays down rules for conducting clinical trials to establish the safety, efficacy and quality of medicines for marketing approval in the EU. It sets out the conditions required for regulatory approval/ notification, ethical review, informed consent, good manufacturing practice, safety reporting and inspection. Medicines are regulated by the Medicinal Products Directive (2001/83/EC), which defines a medicinal product as any substance or combination of substances presented for treating or preventing disease in humans or animals. It has recently been amended by 2003/63/EC to cover Advanced Therapy Medicinal Products which includes some of the therapies described in this briefing. The MHRA is the UK competent authority for approving new medicinal products and authorising clinical trials.

#### Medical devices

Medical devices are regulated under the Medical Devices Directive (93/42/EEC). This excludes products incorporating or derived from tissues or cells of human origin, and thus does not apply to stem cell-derived products as such, although the non-biological components of any stem cell-derived device would have to comply with the Directive. The Medical Devices Agency was the UK competent authority; it has now been subsumed into the MHRA.

#### Human tissues and cells

The Human Tissues and Cells Directive (2004/23/EC) establishes standards of quality and safety for the donation, procurement, testing, processing, storage, distribution and preservation of human tissues and cells. The Human Tissue Bill would establish the Human Tissue Authority (HTA) in the UK, to secure consent for the collection, storage and use of human tissue, including stem cells. It will also set up, under the HTA, the Inspectorate for Organs and Tissues for Human Use which will inspect and accredit tissue banks (the MHRA currently does this on a non-statutory basis).

authorisation is as accessible as possible, as such products are often produced by small facilities such as hospitals and tissue banks for local use.

- Authorisations for the manufacture or use in clinical trials of allogeneic products would also be handled by the appropriate national competent authority. But marketing authorisation for such products would be centralised at the EU level, conducted by the EMEA.<sup>8</sup> This reflects concerns that such products have the potential to cause immune reactions, and are likely to be used to treat more than one person. However, the same overall safety, quality and efficacy criteria would apply for both types of products.

Industry groups such as the BioIndustry Association (BIA) and EuropaBio support the introduction of an EU-wide regulatory framework for tissue engineered products. However, such groups have expressed concerns over the Commission's latest proposals. For instance, they have suggested that the proposals do not clearly distinguish between tissue engineered products and other (borderline) products derived from cells/tissues.

Such groups also suggest that the two-tier approach involving both national and European marketing approvals is overly complex and are concerned that the EMEA may not be able to fulfil both of the main roles

proposed for it (it will also act as a clearing house to decide which borderline products fall under which regulatory framework). Finally, industry groups point out that the proposals do not include any guidance on the conduct of clinical trials for tissue engineered products.

### UK regulation

When the proposed tissue engineered products regulation comes into effect, the UK will have to decide whether to:

- Create a new regulatory authority to be the national competent authority to consider applications to manufacture, market or conduct clinical trials using tissue engineered products.
- Expand the remit of an existing body to include tissue engineered products. Candidates could include the HFEA, MHRA and the proposed new HTA. This would be in line with recent developments in the UK (where the bodies regulating medicines and devices were merged to form the MHRA) and in the US (where the Food and Drug Administration acts as a clearing house for most products making health related claims).

There is also the question of how wide the remit of the competent authority should be. The Nuffield Council on Bioethics suggested that there should be some wider form of oversight over stem cell research in 2001.<sup>9</sup> The SCSC and its liaison committees perform this role to some extent, although its terms of reference are limited to depositing/accessing stem cell lines in the UK bank.

The House of Lords Stem Cell Committee recommended that DH "*should consider either establishing a body similar to the Gene Therapy Advisory Committee with oversight of clinical studies involving stem cells, or extending the membership and remit of GTAC to achieve the same ends*". The government's response acknowledged that the clinical use of cells derived from ES cells would be a '*new development*' and noted that it would "*consider whether any further oversight of such clinical trials is desirable*".<sup>10</sup>

#### Endnotes

- 1 [www.ri.bbsrc.ac.uk/public/webtablesGR.pdf](http://www.ri.bbsrc.ac.uk/public/webtablesGR.pdf)
- 2 Report from the Select Committee Stem Cell Research, HL 83(i), February 2002. The original DH proposal was in the Report of the CMO's Expert Group on Therapeutic Cloning, DH, August 2000
- 3 [www.mrc.ac.uk/index/public-interest/public-consultation/public-stem-cell-consultation.htm](http://www.mrc.ac.uk/index/public-interest/public-consultation/public-stem-cell-consultation.htm)
- 4 *Guidance on the Microbiological Safety of Human Organs, Tissues and Cells used in Transplantation* (DH, 2000)
- 5 *Code of Practice for Tissue Banks* (DH, 2001)
- 6 *Code of Practice for the Production of Human-derived Therapeutic Products*, Medical Devices Agency (2002)
- 7 [www.tecnet.ie/dbtecimngs/Consultation\\_document.pdf](http://www.tecnet.ie/dbtecimngs/Consultation_document.pdf)
- 8 European Agency for the Evaluation of Medicinal Products
- 9 *Stem cell therapy: the ethical issues*, NCB, December 2001
- 10 [www.dh.gov.uk/assetRoot/04/01/97/47/04019747.pdf](http://www.dh.gov.uk/assetRoot/04/01/97/47/04019747.pdf)

POST is an office of both Houses of Parliament, charged with providing independent and balanced analysis of public policy issues that have a basis in science and technology. POST is grateful to Bimal Chaudhari for preparing this briefing.