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REGENERATIVE MEDICINE

Regenerative medicine aims to restore the function of diseased or damaged tissues or organs by a variety of approaches, from cell-based therapies through tissue engineering to developing new medical devices. This offers potential medical benefits, but also poses regulatory challenges. This POSTnote looks at recent developments in this area and analyses the issues they pose for UK researchers and regulators.

Background

Diseased, degenerating or damaged organs and tissues give rise to a wide range of chronic illnesses. Patients suffering from such illnesses are currently faced with a relatively short list of options. These include:

- long-term drug therapy, which may allow a disease to be managed but rarely cures it;
- organ transplant (there is a shortage of donor organs);
- medical devices such as pacemakers.

Regenerative medicine aims to restore the function of tissues and organs by a variety of approaches. The idea is not new; the first bone marrow transplant took place in 1956, to treat a young boy suffering from leukaemia. A key issue with this type of medicine is to prevent the patient's immune system from rejecting the regenerative tissue. In the 1956 transplant, doctors got round this problem by using bone marrow from the patient's identical twin. By the late 1960s and early 1970s, they were able to match donor tissues to patients by tissue typing. This meant that tissues could be sourced from matched donors who were not necessarily related to the patient. Much of the recent interest in regenerative medicine arises from developments in stem cell research, but there are also promising possibilities in biomedical- and tissue-engineering. The following sections look at some of the possible approaches.

Different Types of Regenerative Medicine

Cell Therapies

Each of the 200 plus cell types in the human body has been derived from a single cell: the fertilised egg. As the fertilised egg develops it forms embryonic stem (ES) cells, each of which has the potential to become any of the different cell types found in adults. As the early embryo develops, the ES cells differentiate into more specialised cell types and organise into structures that will become tissues and organs. Most cells fully differentiate into highly specialised cells, but some remain in a "semi-differentiated" state. These are adult stem (AS) cells that can turn into a more limited range of cell types.

Box 1. Stem Cells and Cirrhosis

Researchers based at Imperial College and Hammersmith Hospital, London have been using stem cells to treat patients with cirrhosis of the liver.[1] They recruited nine patients with severe alcoholic liver cirrhosis. For each patient, blood stem cells were isolated and cultured in the laboratory to achieve a fivefold increase in cell number. Each patient then received an injection of their cultured cells back into the main artery serving the liver. All patients tolerated the procedure well, and significant improvements in liver function were observed in seven of the nine patients. The exact mechanism by which the stem cells helped to restore liver function is unknown.

Therapy using a patient's own cells

Therapies that use a patient's own cells to regenerate their organs or tissues are called "autologous" therapies. An example of one such approach is given in Box 1. Other approaches include an on-going trial at two London hospitals to treat 100 heart attack patients with stem cells from their bone marrow to help to repair damaged heart tissue. While initial results from such studies are encouraging, large clinical trials are needed to prove that such approaches work.

Therapy using cells from another person

Therapies that use cells or tissues derived from a person other than the patient are called "allogeneic" therapies. Examples include using bone marrow or blood stem cells from matched donors or the use of established ES cell lines for therapy. For instance, the London Project to Cure Blindness, launched in June 2007, aims to develop a cure for Age-related Macular Degeneration using ES cells to regenerate damaged retinas (Box 2). Allogeneic therapies may pose more concerns than autologous therapies as they have the potential to cause immune rejection and may be given to more than one person.

Box 2. Age-related Macular Degeneration (AMD)

AMD is a common cause of poor vision among people aged 60 plus. It is caused by damage to cells in the macula, a region of the retina located in the middle at the back of the eye. The macula is responsible for central vision (what we see in front of us), which is key to activities such as reading and writing. The most common form of AMD (so called dry AMD) occurs when a particular type of photoreceptor (the retinal pigment epithelial or RPE cells) in the macula degenerate and starts to thin out. This causes a progressive loss of vision, and can cause blindness in some cases. Researchers have found that embryonic stem (ES) cells can be used to derive RPE cells. Animal experiments have shown that RPE cells can restore visual response when injected into mutant mice lacking functional photoreceptors. The London Project to Cure Blindness aims to develop RPE cell lines from human ES cells and test them as possible therapeutic agents in patients with AMD. Such an approach should not cause problems with immune rejection as this part of the eye is "immunologically privileged" and tolerates foreign cells and tissue. The group at University College London recently announced a collaborative deal with Pfizer to advance this work.

Tissue Engineering

Tissue engineering involves modifying cells or tissues in some way so that they can repair, regenerate or replace tissue in the body. Perhaps the best known example of such an approach was the tissue engineered section of windpipe (trachea) made for a patient whose airways had been severely damaged by tuberculosis (Box 3). Other examples of tissue engineering include artificial skin, made using human cells (fibroblasts) seeded into a protein matrix (fibrin) and cartilage membranes for implantation into patients who have torn the meniscal cartilage in the knee.

Biomedical Engineering

Another approach to regenerative medicine is to make biomedical devices that mimic the function of a tissue or organ. For instance, Type 1 diabetes results from destruction of the insulin-producing beta cells in the pancreas. Patients with this type of diabetes have to monitor their blood glucose levels regularly and inject the hormone insulin to maintain the level within the normal range. While some research groups are working to restore beta cell activity (using beta cell transplants or stem cells to establish a new beta cell population), others are using biomedical engineering to develop an artificial pancreas. Using ultra-low power electronics originally developed for mobile telephones, they are developing a tiny chip with a built-in glucose sensor that would be implanted into the patient. The chip would constantly monitor blood glucose levels, work out the optimum dose of insulin required to maintain stable levels of glucose and send wireless signals to a pump to secrete the appropriate amount of insulin.

Gene Therapy

Although there are different approaches to gene therapy, the most obvious is to identify a medical condition that can be treated by a specific protein, and then to deliver the gene coding for that protein to the affected cells. In practice, getting active genes into cells for long enough to get a sustained therapeutic effect is very difficult.

Box 3. Claudia's Trachea

In March 2008, Claudia Castillio, a 30 year old Colombian woman was admitted to hospital in Barcelona suffering from collapsed airways following a severe case of tuberculosis. Previous attempts to surgically replace large airways have proved unsuccessful; the only conventional option for such patients is to remove the affected lung and airway. However, the doctors offered to try and tissue engineer a new section of trachea. A scaffold was prepared by Italian scientists in Padua who took a section of trachea from a donor and removed all of the living cells by a process involving 25 washing cycles. Two types of cell were used to line this scaffold to make it bio-compatible with the patient:

- Epithelial cells taken from the patient's trachea were used to line the inner surface of the scaffold;
- Chondrocytes (cartilage cells) derived from stem cells from the patient's bone marrow lined the outer surface.

The cells were cultured at the University of Bristol, and flown to Barcelona where scientists reseeded the cells onto the scaffold. Spanish doctors extracted the damaged section of trachea from the patient and replaced it with the tissue engineered section in June 2008. No immune-suppression was required because the cells used to tissue engineer the scaffold came from the patient herself. Within 2 months of the operation the patient had a normal lung function and was able to lead an independent life.

Nevertheless, recent years have seen some progress in using gene therapy to regenerate tissue, particularly in the area of cardiovascular disease. For instance, UK researchers have developed a therapy based on the gene coding for vascular endothelial growth factor. This protein protects adult blood vessels against damage and is being tested to see if it prevents arteries from narrowing in heart disease patients. A key part of the research has been the development of a bio-degradable reservoir that delivers the therapy in a sustained, localised manner.

Current Regulation

Until recently, medical products were regulated either as medicinal products (such as drugs), or medical devices (such as pacemakers). Products developed for regenerative medicine often fell between these two categories, so a new class of medicinal products has been defined: Advanced Therapy Medicinal Products (ATMPs). Relevant legislation is outlined in Box 4 and its implications for research are discussed below.

Research

Research that involves procuring, testing, processing, storing, distributing, importing or exporting human cells or tissue for treating patients requires a licence from the Human Tissue Authority (HTA, Box 4). Any tissue or cells for use in treating patients must be handled in licensed laboratories conforming to strict standards of Good Manufacturing Practice (GMP). Other regulatory bodies may be involved depending on the research:

- researchers establishing new human ES cell lines will need a licence to conduct embryo research from the Human Fertilisation and Embryology Authority (HFEA).
- research involving genetic modification of cells/tissue, will need Health and Safety Executive notification.
- if the research involves work using animals, then Home Office approval must be obtained.
- it is non-statutory good practice for the researchers to deposit any new cell lines in the UK Stem Cell Bank.

Clinical Trials and Marketing

Moving research on cell/tissue based treatments from the lab into the clinic is complex. The first step for researchers is to consult with the Medicines and Healthcare products Regulatory Agency (MHRA) and the European Medicines Agency (EMEA) to decide whether the product/treatment in question is an ATMP (Box 4). In practice, the key test for deciding if a product/treatment is an ATMP is whether there has been any substantial manipulation of the cells/tissue.

ATMPs

If the regulatory authorities decide the cells/tissue have been manipulated, the product/treatment will be classified as an ATMP. The effect of the new regulation outlined in Box 4 is to apply the principles of existing legislation on medicines to ATMPs. Thus, to market an ATMP researchers must:

- Apply to the EMEA for market authorisation via the centralised procedure (Box 4). This allows products to be marketed throughout the EU.
- Present data to the EMEA to demonstrate the quality, safety and efficacy of their product.
- Collect and present data on the product after it has been authorised (vigilance data).

The HTA is responsible for ensuring that human cells or tissue used in ATMPs are donated, procured, and tested in an appropriate manner. However, the subsequent stages of clinical research involving ATMPs, including the manufacture, storage and distribution of products will be regulated (and licensed) by the MHRA. The Gene Therapy Advisory Committee (GTAC) advises on all proposals to conduct clinical trials involving stem cells as well as those involving gene therapy.

Non-ATMPs

If there has been no manufacturing step that substantially manipulates the cells/tissue, then the product is *not* an ATMP. It will *not* require market authorisation from the EMEA, but other regulations in Box 4 relating to medical devices, human tissues and transplants may apply. Once researchers have obtained clearance from an appropriate Research Ethics Committee for the proposed work, it will be licensed by the HTA to ensure that the procedures meet the required quality and safety standards. An example of this type of work might be a trial of the type described in Box 1.

Funding Issues

Basic Research Funding

In 2004-05 the government invested around £25m in basic stem cell research and associated support such as the UK Stem Cell Bank. Following publication of the UK Stem Cell Initiative (UKSCI) report[2] in 2005, the government pledged to increase this by up to £100m between 2006-08.[3] Funding is distributed between the MRC, BBSRC, EPSRC and ESRC.[4] The MRC includes regenerative medicine as one of its key areas under its Molecular and Cellular Medicine Board and spent £25.5 million on stem cell research last year. The BBSRC and EPSRC have jointly funded a Stem Cell Science and Engineering Initiative. All four Research Councils support the UK National Stem Cell Network.

Box 4. Regulation of Regenerative Medicine

Medical devices

Regenerative medicine approaches that do not contain human cells or tissue, but which involve implanting a device in the human body, are regulated by the MHRA under the Medical Devices Regulations. An example of such a device would be the artificial pancreas described on page 2.

Human cells and tissue

Use of human cells and tissue is regulated by the Human Tissue Authority under the EU Tissue and Cells Directives. These three Directives were implemented into UK law in July 2007, via the Human Tissue (Quality and Safety for Human Application) Regulations 2007. These cover the procurement, testing, processing, storage, distribution and import/export of tissues and cells for human application (treatment of patients).

Transplantation

Transplantation is regulated by the HTA under the Human Tissue Act 2004 which came into force in September 2006, and covers the donation by living people of solid organs, bone marrow and stem cells.

Advanced therapy medicinal products (ATMPs)

Directive (2001/83/EC) defines three categories of ATMP:

- Tissue engineered products – engineered cells/tissues that can be used to treat or prevent disease in humans. The cells/tissue can be of human or animal origin, may be viable or non-viable, and the product may contain other components such as one or more medical device (such as a scaffold).
- Advanced somatic cell therapy products – include any treatment based on living cells that have been altered in some way to obtain a therapeutic effect. The cells may be autologous, allogeneic or from an animal.
- Gene therapy products – many of which work by inserting genes (DNA) into cells.

Regulation (EC) No 1394/2007, which came into force in December 2008, requires anybody wishing to market an ATMP within the EU to seek authorisation from the EMEA. Applications will be considered by a Committee for Advanced Therapies (CAT). The EMEA published a guideline[5] on Human Cell-based Medicinal Products in May 2008 outlining the information required. This covers risk analysis, quality and manufacturing, and both clinical and non-clinical development.

Other sources of funding include the Wellcome Trust, which has stem cell research as one of its priority areas, and research charities. Researchers have welcomed the increase in public sector funding. However, many make comparisons with the US. For instance, the State of California alone has allocated $3billion for stem cell research since 2004 and President Obama's stimulus package increased funding for the National Institutes of Health by 34%. There are concerns that, without further increases in research funding, the UK could fall behind in this area, particularly now that the US ban on federal funding of ES cell research has been lifted.

Infrastructure

One of the recommendations in the UKSCI report was that the government should strengthen the infrastructure supporting UK stem cell research. In its response, the government said that it would provide resources to redevelop and maintain the UK Stem Cell Bank and increase funding for Centres of Excellence and cell production facilities. In March 2008, the MRC Centre for

Regenerative Medicine opened to develop therapies for human disease, using stem cells as a starting point.

Translational Research

Another issue highlighted by researchers is the difficulty in obtaining funding for translational research. While funding is available for basic research and for "proof of principle" trials in small numbers of patients, it is very difficult to obtain funding for the large-scale clinical trials required for regulatory purposes. Such trials are time-consuming, very expensive and, in the case of conventional medicines, usually funded by pharmaceutical companies.

However, these companies may be reluctant to fund clinical trials in new markets where likely returns on investment are uncertain. For instance, an (autologous) therapy involving a patient's own cells has a potential market of one. Funding of clinical trials involving allogeneic therapies may be more appealing because at least there is the prospect of developing a product that can be marketed to many patients. Trials involving drugs that act on growth or other factors controlling the activity of therapeutic cells within the body may also find it easier to attract funding for similar reasons.

Several initiatives have sought to improve the availability of funds for translational research:

- The Wellcome Trust supports translational research through its Strategic Translational Awards.
- The Technology Strategy Board's announcement of a 'Cell Therapy' competition in November 2007 for projects which look to translate bioscience research into more robust methods for regenerative healing.
- The MRC's announcement of a new translational stem cell research programme which aims to fund translational stem cell research to the tune of £10 million per year by 2010/11.
- The creation of the new virtual Office for Life Sciences within the Department for Innovation, Universities and Skills to address key issues affecting the pharmaceutical, medical biotech and devices sectors.

Regulatory Issues

Number of Agencies Involved

Moving research from the laboratory into the clinic involves dealing with a wide range of different regulatory bodies. For instance, a researcher wanting to derive a new ES cell line, test it in animal models, do clinical trials in humans, and then apply for marketing authorisation would have to interact with the HFEA, Home Office, HTA, MHRA, GTAC and the EMEA. Many researchers argue for clearer guidance and a single point of contact to guide them through the regulatory process.

Definition of an ATMP

Whether a product is an ATMP or not is decided on a case by case basis against the criteria set down in EU legislation. But there is scope for different interpretations of the legislation. For instance, the Directive makes it clear that certain routine operations (such as cutting, grinding, shaping, filtering, freezing, etc.) are not substantial manipulations. However, it is not clear whether simple procedures such as the overnight culture of cells isolated from a patient would result in a product being classed as an ATMP. The distinction between certain types of tissue engineered products and medical devices is also a grey area. Further guidance on such issues is being prepared by the EMEA to help researchers to navigate their way through the regulations. The EMEA held the first in a series of workshops on ATMPs in April 2009 to explain key points of the new Regulation.

Information required for licensing

It is important for researchers to know what information is required for licensing a product so that they can design their clinical trials accordingly. In the USA, the relevant department of the Food and Drug Administration (the Center for Biologics Evaluation and Research) typically arranges a meeting with prospective applicants to discuss the information required on a case-by-case basis and to agree a specific protocol for clinical trials. In the UK, the EMEA has set up an Innovation Task Force to provide a forum for early dialogue with applicants.

The main guidance available from the EMEA is the Guideline[5] outlining the general information required for approval of human cell-based medicinal products. This includes requirements to test the biological activity (potency) and find the optimal dose of cell/tissue products. Some researchers question the relevance of such requirements for preparations like certain tissue engineered products, which are designed to have a structural function rather than a biological activity.

Overview

- Regenerative medicine includes approaches such as cell therapy, tissue engineering, gene therapy and biomedical engineering, that aim to restore the function of diseased or damaged tissues and organs.
- It has the potential to deliver benefits to patients across a wide range of conditions.
- The UK is a world leader in the field of regenerative medicine, but is in danger of slipping behind the US due to funding and regulatory considerations.
- Regulation of regenerative medicine requires a balance between protecting patients on the one hand and encouraging innovation on the other hand.
- Difficulties in obtaining funding for clinical trials is a major obstacle in moving UK research on regenerative medicine from the lab to the clinic.

Endnotes

1 Pai, M et al, American Journal of Gastroenterology (2008) 103, 1952–1958
2 www.advisorybodies.doh.gov.uk/uksci/uksci-reportnov05.pdf
3 www.dh.gov.uk/en/Publichealth/Scientificdevelopmentgeneticsandbioethics/Stemcell/Stemcellgeneralinformation/DH_4124082
4 MRC is the Medical Research Council; BBSRC is the Biotechnology and Biological Sciences Research Council; EPSRC is the Engineering and Physical Sciences Research Council; ESRC is the Economic and Social Research Council
5 www.emea.europa.eu/pdfs/human/cpwp/41086906enfin.pdf

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