Science and ethics of stem cell research*

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Stem cells may be defined as cells that are capable either of self-renewing or of giving rise to one or more differentiated cell types. Stem cells exist in most tissues of our body, including the brain, skin and muscle. Skin, gut and blood cells need to be renewed frequently. Stem cells for blood can be found in the bone marrow, and also in the umbilical cord blood, which can be recovered after the baby is born. Besides these so-called 'adult' stem cells, there is a class of stem cells which will proliferate indefinitely outside the body and which can give rise to every tissue in the body if cultured under appropriate conditions. These pluripotent stem cells include embryonic stem cells (ES cells), which in the humans were first reported by Thompson[1]. Human embryonic stem cell lines are derived from blastocyst stage embryos, 5–7 days after fertilization, containing 100–150 cells. The embryos are mostly donated by couples who are attending *in vitro* fertilization (IVF) clinics for infertility treatment, and who no longer require those particular embryos (fresh or frozen) for their own parental project.

Adult embryos tend to be a few in number (one in 10,000 blood-forming stem cells in the bone marrow) and are usually hard to maintain in culture. However, they could be useful for cell therapy, since it now appears that they may give rise to tissues other than those with which they are normally associated. The bone marrow also contains the so-called mesenchymal stem cells, which are today being used experimentally in a number of situations, including cardiac surgery and spinal cord repair. It is too early to know whether these treatments will be clinically useful. Already however, stem cells from the limbal region of the eye are being used routinely in the repair of damaged corneas.

The remarkable properties of embryonic stem cells imply that potentially they may be of even greater value than adult stem cells. Although they cannot on their own make an embryo, their derivation normally involves destruction of the early human embryo, which some people and some cultures regard as morally impermissible. In the UK, however, Parliament passed an Act in 1990 permitting research on these early human embryos for certain purposes which were of potential clinical value. The research was to be strictly regulated, and a statutory authority, The Human Fertilisation and Embryology Authority (HFEA), was set up to license and monitor all clinics carrying out IVF, and also all research projects on human embryos[2]. Today, the number of countries that allow human embryonic research on 'spare' embryos donated by couples undergoing IVF is large (Table 1).

In Europe, there are five countries (Italy, Germany, Austria, Norway and Ireland) where all human embryo research and hence ES cell derivation is prohibited, with Italy, Germany and Austria allowing research on ES cells imported from other countries where their derivation is allowed.

Stem cell therapy can, in principle, be valuable in a large number of serious and intractable degenerative diseases, such as Parkinson's, stroke, multiple sclerosis, hepatitis, ischaemic heart disease, diabetes and rheumatoid arthritis, since ES cells can give rise to all the required cell types (neural; liver; muscle, including cardiac; pancreatic islet cells; blood; cartilage). Apart from their use in cell and tissue therapy, ES cells could be valuable to pharmaceutical companies for drug development and toxicity testing, largely replacing the use of animals.

As with all new medical treatments, there would be clinical risks involved. Good manufacturing practice is essential, and animal products in feeder layers and culture media should be avoided. With stem cells, there is a possible risk of tumours, or the development of tissues of inappropriate type, or aberrant function. Unless stem cells are derived from the patient herself/himself (autologous), as in the use of bone marrow-derived cells for treatment of the same individual, there is a risk of transplant rejection. Various approaches to achieving graft compatibility stem cell therapy have been suggested. It may be possible to eliminate surface antigens from stem cells by genetic manipulation, or possibly to introduce specific immunological tolerance in patients. Given a large enough bank of pluripotent stem cells, it would be possible to find a reasonable match for the tissue type of at least a proportion of patients, thus allowing a lower dose of immunosuppressive drugs to be used. Pharmaceutical companies are also working on improved immuno-suppressive drugs that are less costly and with fewer side effects. A recent paper in *Lancet*[3] has discussed the number of stem cell lines that a bank would require to provide different levels of matching for patients in the UK. Clearly there is a need for more new ES cell lines from a variety of different ethnic groups.

The other possibility that has been suggested for avoiding transplant rejection is to derive an ES cell line using a nucleus from one of the patient's own somatic (body) cells, introduced into a donated egg from which the chromosomes have been removed. The reconstituted egg would then need to be induced to develop into an embryo. This somatic cell nuclear transfer (SCNT) technology is the same as that used in animal cloning experiments, e.g. Dolly, the cloned sheep[4]. However, in humans the cloned embryo would not be transferred to a woman's uterus (this would be a criminal offence in most countries) but would be used to make an ES cell line, which would be immunologically identical to the patient and hence could be used to derive tissues for their therapy. This so-called therapeu-

Table 1. Countries allowing licensed research on 'spare embryos' donated by couples in IVF clinics

UK	Czech Republic
Sweden	Hungary
Belgium	Israel
Netherlands	India
France	Australia
Finland	Japan
Denmark	China
Spain	South Korea
Switzerland	Iran
Portugal	Argentina
Greece	Brazil

*Based on a public lecture delivered at Raman Research Institute, Bangalore on 28 October 2006.

Table 2. Countries that allow embryos to be made for research using SCNT

United Kingdom	The Netherlands (but moratorium)
Sweden	Japan
Belgium	China
Finland	South Korea

tic cloning would need multiple eggs and much cost for each patient. Since many of the diseases involved are common, it seems unlikely that this procedure (which has never yet been achieved) would be clinically useful. On the other hand, ES cell lines cloned from patients with rare genetic diseases (e.g. 'stone man' disease), or more common diseases of complex genetic and/or environmental origin (e.g. motor neuron disease), would be of great research value, allowing biochemical and physiological investigations of the various conditions. In addition, research on the reprogramming process that must occur when the body cell nucleus is introduced to the egg cytoplasm is a hot topic for research, since in the future it is possible that nuclear reprogramming might allow direct somatic to stem cell conversion. A number of countries already allow SCNT for making cloned stem cell lines (Table 2).

One obstacle to such research is the supply of eggs, since egg donation involves both ethical and logistical problems. For research purposes, it may be possible to use animal eggs instead of human eggs. Alternatively, techniques may be found for maturing the very early oocytes in the human ovary, or perhaps using the 'eggs' that can be derived from ES cells in culture[5]. An exciting paper appeared recently[6] claiming to be able to derive pluripotent stem cells directly from ordinary body cells, but clearly this work needs repeating.

In conclusion, I believe that stem cells show great promise for regenerative medicine. ES cells proliferate indefinitely in culture and are pluripotent; some adult stem cell lines show unexpected plasticity and proliferative powers. Research on both adult and ES cells should be pursued. Countries that allow strictly regulated research on early human embryos will also allow ES cells to be made from 'spare' embryos donated by couples in IVF clinics. Stem cells from cloned embryos are unlikely to be useful in routine clinical practice, but could be valuable for research on rare genetic diseases, and common diseases of complex origin. For all stem cell therapeutic applications, it is important to keep in mind considerations of risk-benefit.

My most important plea, however, is that scientists, doctors and the media should beware of raising patients' hopes unduly, since clinical trials using human embryonic stem cells in relation to many of the diseases listed previously may well not be attempted within the next 10–20 years. Premature clinical application would be most undesirable, both for the patients and for the future of stem cell therapy in general.

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