A legal and ethical tightrope

Science, ethics and legislation of stem cell research • by Alan Colman & Justine C. Burley

Among the many research fields that have found their way into the focus of public interest, seldom has one become such a hotly debated topic as research on embryonic stem cells. It has set churches and abortion opponents against scientists and patient advocates. Walking a tightrope, Western governments find it hard to draft regulations for this research field that address the concerns of both sides. Here, we will discuss the current state of stem cell research, potential clinical applications and comment on recent public policy decisions to regulate the research and use of embryonic stem cells.

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Stem cell technology is by no means new—bone marrow transplantation has been carried out for over 20 years. Stem cells are so interesting because they have the unique dual capacity of both self-renewal and the production of specialised cells. After birth, most somatic cells have a limited lifespan, and it is widely accepted that in most tissues stem cells are responsible for replacing lost cells. Thus, there is a large clinical potential for their use. But research on stem cells has been bedevilled by a paucity in stem cell numbers *in vivo*, difficulties in culturing them and inadequate means of identifying them accurately. But recent improvements in culture and purification methods, as well as the identification and directed use of growth factors, have now enabled biologists to grow almost pure cultures of stem cells and some of their differentiated descendants. Indeed, the analysis of the behaviour of such populations after their exposure to growth factors

and the examination of the fates of stem cells after transplantation into animal models is uncovering unexpected plasticity in the lineage restrictions of various adult stem cell types. It is this plasticity that has caused the current excitement in adult stem cell research.

when they are introduced into early mouse and chick embryos. Previously, such pluripotentiality had only been associated with embryonic stem cells.

Such unexpected potentialities have been found in other adult stem cells too. Human bone marrow stromal cells can

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The star performer is the adult neural stem cell (NSC). These cells can be extracted from the adult brain and cultivated *in vitro* as aggregates (neurospheres) for long periods (Reynolds and Weiss, 1992). Not only can such cells differentiate into neurons, oligodendrocytes and astrocytes *in vitro*, but it has also been shown in sophisticated transplantation studies that they can promote widespread reconstitution of damaged CNS regions. Yandava *et al.* (1999) demonstrated this by injecting cloned murine NSCs into the brains of the dysmyelinated *shiverer* mouse; these mice have a mutation in the myelin basic protein, an important component of normal myelin. This treatment resulted in extensive production of new brain tissue by the transplanted cells, and more effective myelination of host neuronal processes. Suggestive, though not definitive, changes in behavioural phenotype were also reported. Another surprise is the plasticity these cells show when they are exposed to new environments. Bjornson *et al.* (1999) systemically injected clonal murine NSCs into sub-lethally irradiated mice and found that they were able to produce a variety of blood cell types. Even more spectacular are findings of Clarke *et al.* (2000) that murine NSCs contribute to cells of all germ layers,

become astrocytes when injected into rat brain (Azizi *et al.*, 1998). Murine, muscle-derived stem cells can reconstitute the haemopoietic compartment of irradiated mice (Gussoni *et al.*, 1999). Intravenous injection of murine bone marrow stem cells into a mutant mouse line with progressive liver failure has led to the formation of hepatocytes and restoration of liver function (Lagasse *et al.*, 2000).

Although therapeutic applications of stem cells have been cited as imminent, such claims may be premature. Much of the data cited above has not yet been replicated. Moreover, apart from the results with NSCs, no clonal cell populations have been used, which leaves open the possibility that the observed plasticity is due to a rogue stem cell with NSC-like properties. A further caveat to future therapeutic uses of adult stem cells is the finding that some cell types, e.g. NSCs, appear to lose part of their potentialities during the long-term culturing that is required to produce sufficient cell numbers (McKay, 2000). These disadvantages may not apply to embryonic stem cells. These truly pluripotent cells, first recognised in the mouse, are also able to form any specialised cell in any adult tissue. And unlike adult stem cells, their multiple potential properties seem to be sustainable long-term in culture. For example,

Fig. 1. Cellular therapy will probably require the conversion of one cell type into another. Starting with either specialised cells (e.g. fibroblasts) or adult or embryonic (ES) stem cells, general strategies are displayed in which cells of desired phenotype can be generated by directed differentiation from stem cell progenitors involving reprogramming where necessary (e.g. starting from specialised cell types). Reprogramming can be achieved by somatic nuclear transfer and might be achieved using cytoplasmic transfer or, ultimately, by direct interconversion of specialised cell types. Red arrows show potentially autologous routes; dotted lines indicate hypothetical routes.

Brustle *et al.* (1999) obtained pure populations of glial precursor cells from mouse ES cells successively cultured with different combinations of growth factors. Transplantation of these cells into myelin-deficient rats resulted in enhanced myelination of axonal sheaths in the host animals.

Embryonic stem cells have been derived from 'spare' human embryos (Thomson *et al.*, 1998) and from the primordial germ cells of aborted fetuses (Shamblott *et al.*, 1998). In addition to supplying vital insight into early human development, these cells and their derivatives could have many therapeutic uses, such as cell replacement therapy, tissue repair and drug testing. But enthusiasm for the clinical benefits of embryonic stem cells has been tempered by concerns that, because of a genetic mismatch, such cells or their derivatives would be rejected by the patient. One apparent advantage of using adult stem cells therefore is that they could be derived from and applied to the same patient, thereby avoiding potential tissue rejection. But, if it proves necessary, we may be capable of producing autologous (i.e. genetically matched) embryonic stem cells as well. Transfer of somatic cell nuclei, which has successfully been used in the reproduc-

tive cloning of a variety of mammals (Colman, 2000), could be used to establish embryonic stem cell lines with genetic material from the patient (Figure 1), albeit with very low efficiency and consequently the requirement for large numbers of human oocytes. A proof of principle test of this strategy—'therapeutic cloning'—has recently been reported in mice (Munsie *et al.*, 2000).

The origin of embryonic stem cells has sparked ethical controversy over, and prompted legislative responses to, stem cell research

The origin of embryonic stem cells—aborted fetuses, 'left-over' IVF embryos or embryos specially created for the purpose—has sparked ethical controversy over, and prompted legislative responses to, stem cell research. In a pluralist society, people hold divergent and deep-seated convictions about the point(s), at which human life begins to have value, and how this value might be respected. Hence the dispute about the morality of the creation and use of embryos in stem cell research. Anti-abortionists in the USA and members

of the Catholic Church in Europe ardently oppose any research on human embryos because they regard the fertilised oocyte as warranting the same protection as that of adult human beings (Mieth, 2000). Others accord no moral status to embryos at all. Most take the middle ground, according to which embryos assume moral status at a certain age. In the UK, for example, the threshold is 14 days, well after stem cells would be harvested. But the potential medical applications of stem cell research should not be ignored in this debate—treatments for Parkinson's disease, diabetes and spinal cord injury, to name but a few, might all be improved. The social and financial impact of stem cell research must also be assessed. In the USA, more than 10 million people have diabetes, more than 500 000 have Parkinson's disease and 200 000 are paralysed due to spinal cord trauma. Prominent activists, such as the actors Christopher Reeve, paralysed after an accident, and Michael J. Fox who suffers from Parkinson's disease, lobby Congress and the public to support research on embryonic stem cells (Fox, 2000).

Sound policy-making should not simply follow public opinion. It has to address two questions: have the possible consequences of a policy been considered adequately? How cogently are both the

consequences themselves and the route to their achievement, defended in moral terms? Within the last six months, three policy documents endorsing stem cell research have been published and these are discussed below.

New Technologies (EGE), an independent advisory body which reports to the President of the EU, published its Opinion on 'Ethical Aspects of Human Stem Cell Research and Use'. Among other topics, the EGE recommends European funding

committee and the NIH of the potentially huge beneficial consequences of stem cell research is commendable.

The UK report, in contrast, is a relatively good example of sensible policy-making for two reasons. First, the possible clinical benefits of stem cell research have been appropriately considered. Secondly, the use and creation of embryos for stem cell research is correctly identified as not being different in any morally meaningful way to embryo experimentation currently allowed by the Act. In fact, it is hard to see how the Expert Group could have concluded other than they did. The opinion offered later by the EGE, which covers a more extensive range of issues, reaches roughly the same conclusions as the UK Expert Group regarding the use of embryos. The EGE focuses on the potential benefits of stem cell research and, in the light of these, accepts the need for stem cell research using embryos, although it insists that—for the time being—spare embryos should be employed. The EGE's opinion does, however, suffer from constant use of vague statements about autonomy, respect and dignity, typical of EU documents.

With regard to the new NIH guidelines, the public/private split on stem cell research rings decidedly schizophrenic

In August 2000, the Chief Medical Officer's Expert Group on Therapeutic Cloning in the UK issued its report to the government (<http://www.doh.gov.uk/cegc/stemcellreport.htm>). They make nine recommendations regarding experimentation with embryos, which—if ratified by Parliament—would extend the scope of existing legislation. Currently, the Human Fertilisation and Embryology Act of 1990 (the Act), administered by the Human Fertilisation and Embryology Authority (HFEA), permits research that involves the creation and use of embryos for only five research purposes, including the improvement of infertility treatment, provided that a license for any such research has been granted. The recent report advocates broadening the range of permissible research to understand better human disorders and diseases, and supports research using embryos whether these are created by *in vitro* fertilisation or somatic cell nuclear replacement (SCNR). The group also recommended that public funding should be made available for the launch of stem cell research programmes. It should be noted that the Act already requires the HFEA to establish that embryos are essential to any research that it is empowered to license. The report makes it clear that this requirement should remain for any broader research aims that the group is recommending.

In the wider European context, no laws are in place that specifically govern stem cell research, although draft legislation is being prepared in the Netherlands, Belgium and France. In Ireland, Austria and Germany, embryo experimentation is not permitted. It is authorised under specific conditions in Finland, Sweden and Spain, and—although not formally legal—in France. At the level of the European Union, the European Parliament on September 7 expressed its discomfort with the UK report. Later in November, the European Group on Ethics in Science and

for stem cell research and the use of 'spare' embryos from IVF for the derivation of embryonic stem cells. The creation of embryos through SCNR, at least while stem cell research is in its infancy, is thought to be premature.

The approach taken by the UK and other Member States in the European Union contrasts sharply with that of the USA, where different rules apply in the public and private sectors. Until recently, no public funds from the NIH could be used for research involving embryos, although such research is legal in the private sector. Following the proposal of the National Bioethics Advisory Committee's report in 1999 that public funding for the derivation and study of human embryonic stem cells should be allowed under certain conditions, the NIH drafted new guidelines in August 2000 (Powledge, 2000). Stem cell research using embryos can be funded as long as frozen surplus embryos from IVF treatments are employed, but no federal funds can be used to destroy any embryos for the harvesting of these cells.

Compared to the UK and the rest of Europe, the USA has the most permissive policy on embryo experimentation. This has the important advantage of not impeding scientific innovation unduly. But there are drawbacks to the absence of regulation, as Andrews has shown in her study of the IVF industry in the USA (1999). With regard to the new NIH guidelines, the public/private split on stem cell research rings decidedly schizophrenic. Public funding is not deemed legitimate for research involving the destruction of embryos, but funding is legitimate as long as others perform the act of destruction! The NIH Guidelines may be the product of admirable political tightrope walking but fail the tests of consistency and cogency so essential to sound moral argument. That being said, the recognition on the part of the advisory

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Controversy and legislation notwithstanding, it is unlikely that embryonic stem cells will benefit patients in the near future as many technical problems remain to be solved. For clinical applications it will be essential to generate or select pure populations of the desired cell type in culture. Cell populations will have to be validated for the absence of neoplastic tendencies. In acute clinical cases, it may be necessary to use pre-accumulated stocks of non-autologous stem cells since growing cultures of freshly isolated adult or customised embryonic stem cells would take too long. But despite these limitations, it is clear that there are strong scientific and practical reasons for simultaneously pursuing both embryonic and adult stem research, since neither route currently assures future clinical success. And this is the view the policy advisory documents/guidelines discussed above have adopted.

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Exploring the unknown

The silent revolution of microbiology • by *Eduard Kellenberger*

Comparing shape and development has permitted biologists to classify all known animals and plants into more than one million and some half a million species, respectively. For micro-organisms, however, such morphological criteria are much less suited. Complemented by biochemical criteria, taxonomists were at least able

change as soon as it is accepted that micro-organisms produce substances beneficial in the therapy of human diseases or for industrial applications.

The biomass of micro-organisms on our planet is estimated to be much more important than that of plants. Prokaryotes are the basis of every food chain on this planet.

The interest in microbiology will grow as soon as expectations become confirmed that micro-organisms produce substances beneficial in the therapy of human diseases or in industrial applications

to order the micro-organisms responsible for infectious diseases in humans, plants and animals. But only about 5000 prokaryotic organisms have so far been formally described, which represents barely one percent of the existing bacterial species (Pace, 1997). This situation will probably

They still dwell where higher organisms cannot survive, not only on the surface, but also deep in the oceans and in the earth. But even today, the popular view of micro-organisms is focused nearly exclusively on those that cause disease. Few are aware of their additional benefits, namely in the fer-

mentation of dairy products, sausages and beverages. But their indispensable presence and necessity in natural biotopes—which includes our digestive tract for instance—is still not commonly accepted. During an excursion to a Swiss lake, I recently heard a perfect exposition of aquatic food chains by a young biologist: to my great surprise he started with the plankton and completely omitted the important role of micro-organisms in feeding and thus sustaining it. This narrow view has certainly something to do with the obsolete taxonomy, which, as we have seen, is restricted to pathogenic micro-organisms or to those few others that are responsible for alimentary fermentation. And non-medical microbiology faces yet further adversity. Molecular biology, before it got its name, was based on studies of bacterial genetics and bacteriophages, generally carried out by microbiologists. Gene technology and