THE ROYAL SOCIETY

# Stem cell research – second update

The Royal Society issued two documents on the subject of stem cell research in 2000: 'Therapeutic Cloning' and 'Stem Cell Research and Therapeutic Cloning: an update' (available on www.royalsoc.ac.uk). The following further update has been prepared in response to the inquiry by the House of Lords Ad Hoc Committee on stem cell research and specifically addresses the questions set out in the call for evidence, it should be read in conjunction with the other two publications on the subject.

The response has been prepared by a working group chaired by Professor Richard Gardner FRS (Dept Zoology, University of Oxford), and comprising Dr Maeve Caldwell (MRC Centre for Brain Repair, Cambridge), Professor Christopher Graham FRS (Dept Zoology, University of Oxford), Sir John Gurdon FRS (Wellcome CRC Institute, Cambridge), Dr Robin Lovell-Badge FRS (National Institute for Medical Research, London), Dr Anne McLaren FRS (Wellcome CRC Institute, Cambridge), Dr Robert Moor FRS (Babraham Institute, Cambridge), Dr Austin Smith (Centre for Genome Research, University of Edinburgh), and Professor Azim Surani FRS (Wellcome CRC Institute, Cambridge) with support from Dr Rebecca Bowden and Dr Josephine Craig (Secretariat, Royal Society). The response has been endorsed by the Council of the Royal Society.

**1 Do the additional purposes in the 2001 Regulations raise issues of principle different from the purposes specified in the 1990 Act?**

The additional purposes in themselves do not raise additional issues of principle. Serious degenerative diseases are at least as worthy an objective as infertility or contraception.

However one impact is that some of the research initiated under the additional purposes may require the use of embryos produced specifically for research (somatic cell nuclear transplantation) rather than 'spare' embryos. In addition the aim of extending the regulations is to explore the prospects of using cells derived from early human embryos as enduring grafts for effecting repair of damaged tissue in humans. This principle is only novel with regard to the use of early embryos since employing human fetal tissue for grafting was sanctioned some years ago under conditions set out by the Polkinghorne Committee.

**2 There is a range of different views world-wide on the acceptability of research on embryonic stem cells. What considerations underlie these differences? Do changes in the law here have implications for practice overseas and vice versa?**

This is a difficult question to address since attitudes are dominated by cultural, historical and religious considerations. The key issue here is when a new human life is deemed to begin, and there will inevitably be growing tension between this and the desire to participate in exciting (and possibly highly remunerative) new advances in medicine.

**Policy document 9/01**

**June 2001**

**ISBN 0 85403 560 5**

**This report can be found at www.royalsoc.ac.uk**

A number of other countries have great respect for the UK regulatory system in this field, and aim to modify their laws accordingly. Regulations allowing research on embryonic stem cells in the UK will give the UK a competitive advantage in the technology.

**3 Have increased globalisation and other international commercial developments, in relation, for example, to e-commerce and patenting, changed the context of the debate in the UK? Would issues relating to research on embryos benefit from more attention at international level?**

Commercial considerations have not played any significant role in the debate in the UK. The pharmaceutical industry has maintained a fairly low profile throughout. Most of the debate and work on this issue has been carried out in the biomedical research community, among whom there is an almost universal determination to ensure that human embryonic stem cell lines for research and therapeutic purposes are derived and maintained as a public rather than private resource. The Donaldson Report recommended that the Research Councils set up and maintain a Stem Cell Bank, something that the Wellcome Trust may be interested in. Such a bank could be run on a similar basis to the Human Genome Project in that cell lines would be stored in the bank, available to the scientific community on a non-commercial basis and funding and ethical permission on stem cell research could be conditional on any lines being put in the bank. In the US, of course, such cell lines can only be derived within the private sector and this has inevitably meant the imposition of a host of restrictions on their use.

It would be very difficult to develop legislation for research on embryos on a global level due to vast differences in socioeconomic and ethical considerations between countries and cultures. The European Parliament Committee on Human Genetics is currently considering this issue at a European level. The European Science Foundation are also considering the issue and aim to produce a policy statement soon.

**4 What are the potential medical benefits of stem cell research? What is the most likely time-scale for realising them? What are the potential risks?**

Although the medical benefits have not changed since the first Royal Society statement ('Therapeutic Cloning'), the rate at which new advances are being made on somatic stem cells is startling. It is also worth noting that there have been advances with human embryonic stem cells since the working group report - for example it is now clear that they can be clonally propagated (Developmental Biology 227:271-278), and genetically manipulated (Current Biology 11: 1-20) and that functional cardiomyocytes and neurons can be produced from human embryonic stem cells (Molecular Medicine 6: 88-95). From an objective scientific viewpoint this area of research can surely be pursued with every confidence of delivering appropriate cell types for pharmaceutical development and reasonable expectation of providing at least some forms of cell therapy.

The implication is that time-scales for the use of stem cells may well be shorter than those anticipated in the documents enclosed. However, two points should be emphasised: (i) the occurrence of unexpected adverse reactions to stem cell transfer (eg tumour formation or the loss of cell function or control) would seriously delay the exploitation of these therapies; and (ii) that time-scales for realising medical advantages of stem cell therapy are likely to be different for different organs (eg brain repair therapies are likely to take longer to develop than islet cell replacement in the pancreas). Time-scales are always difficult to predict. Adult stem cells are already in routine use, in the form of bone marrow transplants and it is likely that the first clinical trials (probably in USA) of both adult and embryonic stem cells will take place within the next 5, certainly 10, years.

**5 There are differing views on the extent to which potential treatments could be developed from non-embryonic stem cells, such as adult and umbilical cord stem cells. What are the advantages and disadvantages of working with these alternative sources of stem cells?**

It is often presented that there is an either/or choice between adult verses embryonic stem cell research. The Royal Society believes that adult stem cell research and embryonic stem cell research **are not alternatives** and **both** must be pursued. In all likelihood each will yield distinctive therapeutic benefits but (i) we cannot predict which will be first or better and (ii) work on one system may help work on the other.

Recent developments in adult stem cell research are very exciting and may offer great promise for the future. In the submission to the Donaldson inquiry ['Therapeutic cloning' ] the Royal Society urged that the potential of umbilical cord stem cells should be explored vigorously as a high priority. The disadvantages of adult stem cells is that they are small in number and often hard to access. By the time they have been multiplied up in culture to a therapeutically useful stock of cells, their proliferative lifespan may have become dangerously short. An important issue that needs to be acknowledged is the fact that, with very few exceptions like bone marrow, adult stem cells will only be obtainable from organs of very recently deceased individuals. Given the difficulty of recognizing and enriching for the relatively modest proportion of stem cells in such organs, the task of getting useful numbers of such cells is not going to be easy. Since there is already an acute shortage of donors of organs for transplantation, work in this area is going to entail even more competition for scarce resources.

At present embryonic stem cells are much better characterised and understood - in particular they can actually be grown in the laboratory. Since the Royal Society report 'Stem cell research and therapeutic cloning: an update' (Nov 2000) there have been advances with human embryonic stem cells (see answer to previous question for references). From an objective scientific viewpoint this area of research can surely be pursued with every confidence of delivering appropriate cell types for pharmaceutical development and reasonable expectation of providing at least some forms of cell therapy. The Royal Society believes that we cannot wait to see whether either source will provide all the urgently needed therapies: both lines of research should be pursued in parallel.

**6 What are the commercial interests involved in research in this area? Does increased commercial involvement create additional ethical difficulties?**

At present research on human embryonic stem cells is confined almost exclusively to the commercial sector, with the exception of the Israeli groups. In the US, Geron Corporation have an exclusive licence to a patent on human embryonic stem cells and therefore have a monopoly position. This is compounded by the fact that the US Government will not allow any research with public sector funding. In Australia, the Australian/Singapore group who have also isolated human embryonic stem cells have set up a company called Stem Cell International. Therefore at present almost the only way anybody can get access to human stem cells is by entering into an agreement with one of these two companies which inevitably involves surrendering intellectual property rights and, probably more importantly, means that this field is not currently subject to open scientific debate, scrutiny and challenge. In addition to the problems of scientific validation this raises, the Society believes that transparency and accountability are absolutely essential in an area that is of such public concern and also has such major implications for future healthcare. It is therefore vital that the UK academic (and commercial biotechnology and biopharmaceutical) sectors are allowed to contribute and compete openly.

Other companies involved in stem cell research are Stem Cell Sciences (UK) Ltd whose activities are currently confined to mouse ES cells and nuclear transfer and there are a host of companies pursuing various fetal and adult stem cell research e.g. Reneuron, NeuralStem, Neuronova, Systemix, Cardion, PPL, etc, in contrast to the exclusivity of the human embryonic stem cell field.

**7 Human reproductive cloning (the transfer of an embryo created by cell nuclear replacement into a woman's uterus) is unlawful in the UK, and the Government has announced its intention of reinforcing this ban by specific primary legislation. Is there likely to be any pressure to resist such a ban? What are the principal ethical (and scientific) arguments against human reproductive cloning?**

The Society has confined itself to commenting on the scientific issues. One concern is that when people talk about the possible use of human cloning, for example, to replace a beloved child or partner lost in an accident, they betray wholly unrealistic expectations of the outcome. While the clone is likely to bear a striking physical resemblance to the original, in terms of personality and other higher mental attributes the two will differ at least as much as monozygotic twins.

The scientific arguments against cloning relate to its ineffectiveness (1% success rate in mammals) its unpredictability, the high percentage of fetal deaths that occur and the evidence that many cloned animal offspring that have been produced show abnormalities of differing degrees of severity. The great majority of nuclear transplants (cloned embryos) develop abnormally. Some of these abnormalities are relatively small such that they are compatible with the birth and growth of a mammal, and some are not. Therefore there is a very real danger of creating seriously handicapped individuals. That possibility seems to constitute a strong ethical argument against the use of reproductive cloning. We consider that that a human cloning ban would have public support, is currently justified on scientific grounds and would assist in improving the public's confidence in science.

**8 Does the extension of embryonic stem cell research, and, in particular, the technique of cell nuclear replacement therapy (therapeutic cloning) - designed to grow tissue for therapeutic purposes - increase the likelihood of human reproductive cloning in the future?**

Improvements in cloning technology (and in the underlying scientific understanding of nuclear reprogramming) could increase significantly the likelihood that human reproductive cloning will be successfully carried out in countries where it is legally permitted. It could be argued that research on therapeutic cloning might lead to a higher success rate, and in particular, a higher rate of producing normal cells by this means. While cloning for therapeutic purposes might lead to an improved efficiency at very early stages of embryo development (blastocyst stages), this does not necessarily mean that it would allow post implantation problems to be overcome. Indeed the only way to know whether any new techniques might improve rates of normal development to term would be to implant the embryos back in the womb. This would not be allowed in the UK. It should be noted that technical improvements in nuclear transfer are more likely to come from reproductive cloning experiments in animals than from human 'therapeutic cloning'. Those trying to undertake reproductive cloning might use any such improvements in techniques.

In our view, there would be no merit in banning therapeutic cloning research for fear that it might give some benefit for (illegal) reproductive cloning. If there were to be a ban on therapeutic cloning research in this country, those interested in this would do it abroad. The only way to decrease the likelihood of human reproductive cloning would be an international ban or moratorium. Given the concerns one option is to explore the option of an international moratorium on human cloning. However provisions may need to be made to ensure that research on stem cells and cell nuclear replacement therapy is not jeopardized by any such moratorium.

**9 Has the regulatory framework established by the 1990 Act operated effectively? Is it likely to remain adequate for the foreseeable future? Have any gaps appeared in the regime as a result of developments since 1990?**

The regulatory framework established by the 1990 Act was modelled on a pre-legislation Voluntary/Interim Licencing Authority that was set up by the biomedical community to police itself before the legal framework was in place. This framework has worked very well and the Society believes that it is adequate for the foreseeable future.

**10 Do additional guidelines need to be developed to assist the Human Fertilisation and Embryology Authority in issuing licences in accordance with the new Regulations? If so, what should the guidelines contain?**

At present the existing guidelines are adequate. However the Committee should consider whether a subgroup of the Human Fertilisation and Embryology Authority needs to be established to oversee licences issued in accordance with the new regulations.

**Copies of Royal Society policy documents, including 'Therapeutic Cloning' and 'Stem Cell Research and Therapeutic Cloning: an update' can be obtained from the Royal Society's webpage www.royalsoc.ac.uk, or from the Science Advice Section (tel: 0207 451 2585).**