

## **STEM CELL RESEARCH: MEDICAL PROGRESS WITH RESPONSIBILITY**

### **A REPORT FROM THE CHIEF MEDICAL OFFICER'S EXPERT GROUP REVIEWING THE POTENTIAL OF DEVELOPMENTS IN STEM CELL RESEARCH AND CELL NUCLEAR REPLACEMENT TO BENEFIT HUMAN HEALTH**

#### **➤ EXECUTIVE SUMMARY**

1. This report has been produced by an Expert Group established by the Government and chaired by the Chief Medical Officer. The Group was asked to undertake an assessment of the anticipated benefits of new areas of research using human embryos, the risks and the alternatives and, in the light of that assessment, to advise whether these new areas of research should be permitted.
2. It must be emphasised that the report considers and makes recommendations on aspects of cellular research and development. This is basic research which if permitted would precede, probably by many years, any possible application to treatment.

#### **• THE STEM CELL**

3. Many of the scientific issues central to the Expert Group's deliberations concern stem cells, unspecialised cells which have not yet differentiated into any specific type of tissue. The successful application of stem cell research would depend upon:
  - whether stem cells can be successfully isolated and grown in the laboratory;
  - whether stem cells grown in the laboratory can be influenced to turn into specific cell types;
  - whether stem cells that have formed particular cell types could be used to treat patients whose tissue was diseased or damaged through injury;
  - whether tissue grown in this way would develop normally or whether there might be risks to the patient.

## ➤ **POTENTIAL SOURCES OF STEM CELLS**

4. Scientists consider that stem cells could be derived from a number of sources:

- from early embryos (blastocysts) created by in vitro fertilisation - either those which are not needed for infertility treatment (sometimes called 'spare embryos') or created specifically for research;
- from early embryos created by inserting the nucleus from an adult cell into an egg with its nucleus removed - cell nuclear replacement (sometimes called 'cloning');
- from the germ cells or organs of an aborted fetus;
- from the blood cells of the umbilical cord at the time of birth;
- from some adult tissues (such as bone marrow);
- from mature adult tissue cells reprogrammed to behave like stem cells.

5. These different types of stem cell are unlikely all to have the same properties or the same potential to develop into particular tissues. Theoretically, stem cells derived from early embryos have the greatest potential to develop into most types of tissue (they are often referred to as 'pluripotent'). Stem cells taken from fetal tissue or umbilical cord blood appear to be more limited in the type of tissue they can be developed into. Stem cells can be extracted from some adult tissues but their potential to develop into other kinds of tissue is also likely to be limited. It may in the future become possible to reprogramme adult cells to behave like stem cells but at the moment this remains largely hypothetical and requires greater understanding of the mechanisms of reprogramming.

## ➤ **TREATMENT POSSIBILITIES**

6. In the long term there could be considerable potential for the use of tissues derived from stem cells in the treatment of a wide range of disorders by replacing cells that have become damaged or diseased. Examples might include the use of insulin-secreting cells for diabetes; nerve cells in stroke or Parkinson's disease; or liver cells to repair a damaged organ. One means of deriving stem cells which are genetically compatible with the person being treated could be from cells created by the cell nuclear replacement technique. Further advances in understanding of how organs regenerate would increase the range of possible treatments that could be considered.

7. In addition to this potential to develop tissue for use in the repair of failing organs, or for replacement of diseased or damaged tissues, the technique of cell nuclear replacement might be applied to treat some rare but serious inherited disorders. Repairing a woman's eggs (oocytes) by this technique gives rise to the possibility of helping a woman with mitochondrial damage to give birth to a healthy child which inherits her genes together with those of her partner.

➤ **THE SCIENCE IN PERSPECTIVE**

8. Most scientists in this field see many technical and scientific hurdles to be overcome before the potential benefits of stem cell techniques could be realised. Consequently, it is very difficult to put a timescale on the developments in stem cell research outlined in this document.

9. However, research has shown that stem cells can be derived from embryos in a range of animal species (and, more recently, from human embryos), from fetal tissue, and from adult tissue including bone marrow, skin and blood. Studies, mainly in mice, have demonstrated that stem cells can then be made to differentiate into specific cell types and that cells derived in this way can be successfully transplanted. Applying this work to humans will take considerable time since it would be necessary to identify the chemicals required to encourage the growth of the cells and the appropriate conditions to obtain the required cell type. The research to date does, however, demonstrate why stem cells are regarded as having such considerable potential.

10. Embryos have been created by the technique of cell nuclear replacement in a range of animal species although it is not possible to predict how easy it would be to replicate the work in humans.

11. There are a number of technical and safety issues that have been raised by the early work on stem cells and cell nuclear replacement. These include whether the supply of spare eggs (oocytes) for therapy would be adequate; whether cells and tissues derived from cell nuclear replacement would develop normally or whether defects are likely to arise; whether stem cells and subsequent tissues will "age" normally; whether such tissues will be more prone to develop malignancy; and whether tissues generated from a reprogrammed adult nucleus would overcome the problems of rejection after transplantation as theory suggests they

should. All these safety issues would need to be clarified by research. Many would require further study in animals before studies using human embryonic tissue were considered. However, the differences between species mean that human research would be needed both to demonstrate the validity of the concept and to investigate the safety issues.

12. Most scientists consulted felt that the science was still several years away from being able to deliver many of the technical building blocks needed to make significant progress in achieving healthcare benefits. In particular gaining knowledge about how stem cells differentiate, and on how this process might be controlled to produce the particular kinds of tissue needed for treatment, is only just beginning.

➤ **LEGAL RESTRICTIONS**

13. The UK has a well-established system for regulating the creation and use of embryos, both in research and treatment, embodied in the Human Fertilisation and Embryology Act 1990 (the 1990 Act). This Act is administered by the Human Fertilisation and Embryology Authority (the HFEA). The 1990 Act allows for the creation and use of embryos for research, provided that the research is for one of the five purposes currently specified in the Act and is granted a licence by the HFEA. Before a research project can receive a licence, the HFEA must be satisfied, on a case by case basis, that the use of embryos is necessary for the purposes of the research. Research can only be pursued under the aegis of the Act and with a licence from the HFEA. Embryos used in research cannot be kept for longer than 14 days (excluding periods of storage). Some 48,000 embryos which were no longer needed for in vitro fertilisation treatment were used in research between August 1991 and March 1998 and 118 embryos were created in the course of research in the same period.
14. Research involving the creation of an embryo by cell nuclear replacement is not prohibited under the 1990 Act provided it is for one of the existing specified research purposes. In such circumstances, the HFEA would consider each application for a research licence on its merits and would need to be satisfied that the creation of an embryo by cell nuclear replacement was necessary for the purposes of the research. So far no applications for a licence for such research have been made.
15. At present the creation or use of embryos for research to improve understanding or treatment of non-congenital diseases is not permitted under the 1990 Act although there is scope within

the Act for additional research purposes to be added through Regulations (rather than new primary legislation).

16. There is no specific legislation currently in force in the UK to regulate research on stem cells once extracted from embryos or research aimed at deriving stem cells from other, non-embryonic, sources such as an aborted fetus or adult cells. A Code of Practice laid down by the Polkinghorne Committee in 1989 governs the use of fetal tissue, while guidance from professional and research bodies and from the Department of Health governs research more generally.

➤ **ETHICAL CONSIDERATIONS**

17. A significant body of opinion holds that, as a moral principle, the use of any embryo for research purposes is unethical and unacceptable on the grounds that an embryo should be accorded full human status from the moment of its creation. At the other end of the spectrum, some argue that the embryo requires and deserves no particular moral attention whatsoever. Others accept the special status of an embryo as a potential human being, yet argue that the respect due to the embryo increases as it develops and that this respect, in the early stages in particular, may properly be weighed against the potential benefits arising from the proposed research. The current restrictions and controls on embryo research reflect this latter view, providing the human embryo with a degree of protection in law but allowing the benefits of the proposed research to be weighed against the respect due to the embryo.
18. The derivation of stem cells for research from early embryos no longer needed for infertility treatment ('spare embryos') or created by in vitro fertilisation specifically for research does not raise any new ethical issues provided that existing ethical safeguards within the 1990 Act are adhered to. If, as Parliament has judged, it is ethically acceptable to use embryos for the five currently permitted purposes then those in the ethical middle ground would argue that using them to obtain stem cells to study the development of tissue for potential therapeutic purposes, which offers significant potential benefits in health terms, does not seem to raise fundamentally different ethical issues within the current legislative framework.
19. However, research involving embryos created by cell nuclear replacement raises new concerns for many people, including those opposed to all embryo research and possibly some of those in the middle ground. Even those who accept the current research uses of embryos

might express concern about the research use of embryos created in this way. Such embryos can be seen as being created simply as a means to an end and for use as a product source.

20. An alternative view is that the benefits of being able to develop an individual's own cells to create a new source of cells for their own future treatment make this action ethically justifiable. While research on embryos created by cell nuclear replacement does indeed involve using them as a means to an end, this can be said to apply to some degree to all research using embryos. The potential benefits of the research need to be weighed against these concerns. Research into cell nuclear replacement might well offer a means of producing compatible tissue for treatments and it may offer the only means of learning about the mechanisms for reprogramming adult cells. These benefits, if realised, would be substantial and may represent the best prospect of developing treatments for a number of degenerative disorders.
21. Concerns have also been expressed that allowing research on embryos created by cell nuclear replacement would be a first step on a 'slippery slope' towards human reproductive cloning. The Expert Group concluded that an inadvertent slide into reproductive cloning was not a realistic prospect because of the stringent controls operated in the UK by the Human Fertilisation and Embryology Authority in its licensing both of research involving embryos outside the human body and of infertility treatment. The 14 day limit on keeping embryos outside the human body and the very clear position adopted by the Authority that they will not license the implantation of embryos created by cell nuclear replacement, provide clear and effective controls to prevent any access to reproductive cloning. Additional controls would require a new Act of Parliament.

➤ **OOCYTE NUCLEUS TRANSFER**

22. Mitochondria are small energy-producing structures in the cytoplasm of every cell, which are only inherited from the mother. The DNA contained in the mitochondria affects a number of important functions in providing energy for the cell. Although the nucleus contains the vast majority of the DNA, defects in mitochondrial DNA are known to cause more than fifty inherited metabolic diseases. In theory it may be possible to prevent a child inheriting damaged mitochondria from the mother by inserting the nucleus of the mother's egg into a donor egg with healthy mitochondria which has had its nucleus removed (a form of cell

nuclear replacement). The egg formed in this way would then need to be fertilised by the father's sperm using in vitro fertilisation techniques. Any child born would inherit its nuclear DNA from the mother and the father plus healthy mitochondrial DNA from the donor egg. Very little research has been undertaken to investigate whether the theoretical promise of this form of cell nuclear replacement for the prevention of mitochondrial disorders is real.

23. Given the genetic make up of any child born as a result of this technique, it would not constitute reproductive cloning. The resulting child would not be genetically identical to anyone else. Nonetheless, concerns have been expressed that oocyte nucleus transfer represents a modification to the human genome which can be passed on to the next generation. Such modifications are subject to a moratorium in many countries, although basic research to modify eggs or sperm would be permitted under both international conventions and UK law. There does not appear to be any ethical objection to initiating this kind of basic research.

#### ➤ **CONCLUSIONS AND RECOMMENDATIONS**

24. The picture presented to the Expert Group by the scientific community was of the enormous potential of stem cells as a source of new tissue for therapeutic uses in the repair of damaged tissue and organs for a wide range of currently incurable disorders. Work in animals and early work to extract stem cells from human embryos support this position. At present, stem cells from embryos appear to have the greatest potential to be developed into the widest range of tissues. In the long term the scientific view is that it will be possible to reprogramme adult cells to make them behave like stem cells with the full potential of embryonic stem cells but without the morally more contestable need to create an embryo.
25. The Expert Group concluded that the great potential to relieve suffering and treat disease meant that research was warranted across the whole range of possible sources of stem cells in the first instance, including embryos.
26. The Expert Group recognised that ethical opinion on the use of embryos in research as a source of stem cells is divided. There are those who believe that an embryo is a human being from the moment of its creation. Others consider that an early embryo is simply a collection of cells. The middle ground, on which the current research uses are based, recognises the

special status of an embryo as a potential human being but accepts that it is justified to use early embryos for serious research purposes which may benefit others.

27. While respecting the views of those opposed to such research, the Expert Group concluded that the proposed new research uses to develop treatments for diseased tissues and organs did not raise fundamentally different ethical issues from the research uses currently permitted under the Human Fertilisation and Embryology Act 1990, at least as far as embryos no longer required for infertility treatment were concerned. The potential benefits of the research justified the use of such embryos as a source of stem cells at this early stage of their development.
28. The sensitivity of the issues associated with research involving the creation of embryos by cell nuclear replacement meant that even some people in the middle ground of ethical opinion may not accept that balancing the benefits of the research against the stage of development of the embryo is an appropriate basis for deciding whether to allow this form of research. Nevertheless, the science suggested that such research was desirable. Provided that the necessity of using embryos created by cell nuclear replacement is clearly demonstrated, on a case by case basis, with proper consent of the donors and under the regulatory control of the Human Fertilisation and Embryology Authority, the Expert Group was willing to support it. The Expert Group concluded that the potential benefit of discovering the mechanism for reprogramming adult cells and thereby providing compatible tissue for treatment justifies this transitional research involving the creation of embryos by cell nuclear replacement.
29. The Expert Group recognised that the Human Fertilisation and Embryology Act 1990 does not allow for distinctions to be made in Regulations between the research use of embryos created in different ways, although the manner of regulating any proposed research within the UK is sufficiently finely tuned to be able to take account of particular ethical concerns. Indeed, the UK enjoys a leading international position in the resolution of these difficult questions in that such research is mediated by the Human Fertilisation and Embryology Authority, a statutory body accountable to Parliament with the direct responsibility for reviewing and, if appropriate, licensing research proposals on a case by case basis.
30. The Expert Group considered that this well-established framework for the control of embryo research in the UK provides the necessary safeguards against the inappropriate use of embryos in research. In particular, the Human Fertilisation and Embryology Authority, in



considering an application for a research licence for a project involving the creation or use of an embryo by cell nuclear replacement would need to be satisfied that the use of such an embryo was necessary for the purposes of the research (i.e. that the aims of the project could not be met in other ways including the use of ‘spare embryos’ generated in the course of treatment services). In addition, specific consent should be sought from individuals whose eggs or sperm have been used in the creation of embryos donated for research to their embryos being used for research involving the extraction of stem cells.

31. The Expert Group noted that there was currently no mechanism for monitoring subsequent research involving cultures of stem cells once they have been extracted from embryos, whether created in the UK or abroad. The Expert Group concluded that while additional controls on individual research proposals were unnecessary in the UK given the controls which would apply to the extraction of stem cells from embryos, it would be desirable for the research to be monitored and progress assessed by an appropriate body to establish whether the research is delivering the envisaged benefits and to highlight any currently unforeseen concerns which may arise.
32. The potential of the technique of cell nuclear replacement to provide treatment to prevent mitochondrial disorders (by oocyte nucleus transfer) led the Expert Group to conclude that basic research should be allowed to investigate that potential. While treatments developed from such research could be seen technically as constituting a modification of the human genome which would be passed on to the next generation, this modification was likely to be of a modest nature. Considerable research would be necessary to investigate the feasibility and efficacy of the technique and the significance of any germ line effect before its use in treatment could be considered. Such basic research is allowed under international conventions.

➤ **RECOMMENDATIONS**

33. The Expert Group makes the following recommendations:

**Recommendation 1**

Research using embryos (whether created by in vitro fertilisation or cell nuclear replacement) to increase understanding about human disease and disorders and their cell-based treatments

should be permitted, subject to the controls in the Human Fertilisation and Embryology Act 1990.

**Recommendation 2**

In licensing any research using embryos created by cell nuclear replacement, the Human Fertilisation and Embryology Authority should satisfy itself that there are no other means of meeting the objectives of the research.

**Recommendation 3**

Individuals whose eggs or sperm are used to create the embryos to be used in research should give specific consent indicating whether the resulting embryos could be used in a research project to derive stem cells.

**Recommendation 4**

Research to increase understanding of, and develop treatments for, mitochondrial diseases using the cell nuclear replacement technique in human eggs, which are subsequently fertilised by human sperm, should be permitted subject to the controls in the Human Fertilisation and Embryology Act 1990.

**Recommendation 5**

The progress of research involving stem cells which have been derived from embryonic sources should be monitored by an appropriate body to establish whether the research is delivering the anticipated benefits and to identify any concerns which may arise.

**Recommendation 6**

The mixing of human adult (somatic) cells with the live eggs of any animal species should not be permitted.

**Recommendation 7**

The transfer of an embryo created by cell nuclear replacement into the uterus of a woman (so called 'reproductive cloning') should remain a criminal offence.

**Recommendation 8**

The need for legislation to permit the use of embryo-derived cells in treatments developed from this new research should be kept under review.

**Recommendation 9**

The Research Councils should be encouraged to establish a programme for stem cell research and to consider the feasibility of establishing collections of stem cells for research use.