

## Human Fertilisation and Embryology Bill

Briefing for House of Lords Committee Stage, Monday 3 December 2007

*Prepared by the Academy of Medical Sciences, Medical Research Council, Royal Society and Wellcome Trust and supported by the Association of Medical Research Charities*

### Executive Summary

We support the aims of the Human Fertilisation and Embryology (HFE) Bill to modernise and update the Human Fertilisation and Embryology Act (the Act), ensuring it keeps pace with scientific and medical developments in the field whilst maintaining public confidence in the regulatory framework around such research. This will ensure that UK scientists working at the cutting edge of stem cell and embryo research will be able to continue their work under the tightly-regulated environment that has enabled this research to flourish in the UK. The UK's strengths in this field present valuable opportunities to influence the international agenda, drive the translation of basic research towards clinical benefits and attract skilled scientists and international investment in stem cell research.

We are satisfied that, in the main, the Bill introduces sensible and workable amendments that are important to achieve these overall aims. There are, however, a limited number of provisions that concern us.

This briefing provides details of those aspects of the Bill we particularly welcome, which include:

- Inclusion of inter-species embryos in the licensing regime
- Removal of the prohibition on altering the genetic structure of embryos for research
- Extension of the storage period for gametes and embryos from five to ten years
- Extension of the purposes for which embryos can be used for research
- Facilitation of the use for medical research of data on treatment held by the Human Fertilisation and Embryology Authority (HFEA).

The briefing also describes the main aspects that concern us (together with our recommendations for addressing those concerns), including:

- Definitions of gametes, eggs and sperm
- Consent requirements for artificially generated cell lines
- Consent provisions for children for storage and use of gametes or cells for research.

Further information about the need for stem cell research, sources of stem cells and the need to create inter-species embryos for research, is also provided in the Annex to this briefing.

## **1. Provisions we support**

### **A. Inter-species embryos (ISEs)** (Clause 4 page 4 line 21)

- 1.1 We support the provisions of the Bill that allow for the creation of inter-species embryos (ISEs) for the purposes of research under licence subject to key restrictions, including:
  - (a) prohibition of implantation in a woman
  - (b) prohibition of the development of the ISE past:
    - the appearance of the primitive streak; or
    - 14 days, whichever is sooner.
- 1.2 We support the inclusion in the definition of ISE of: true hybrid embryos (4(5)(a)), cytoplasmic hybrid embryos (4(5)(b)), transgenic human embryos (4(5)(c)) and chimeric human embryos(4(5)(d)).
- 1.3 We also support the inclusion of a regulation-making power (4(5)(e)) to make adjustments to the definition of ISEs in light of the difficulties of defining all the types of ISE which might be created in the future. We feel this is an important and sensible approach to future-proofing the legislation.
- 1.4 It is important to bear in mind the following. The scientific, ethical, safety and regulatory issues around ISE research have been rigorously reviewed. The Academy of Medical Sciences' report '*Inter-species embryos*' (June 2007) concludes that such research represents a valid and potentially important route to advancing the science of early human development, reprogramming, pluripotency and human embryonic stem (hES) cells. Regulating such research under the strict regulatory regime of the Act will ensure that it is undertaken in a responsible and appropriate manner and subject to rigorous, transparent review.
- 1.5 One of the major limiting factors in pursuing hES cell research is the availability of donated human embryos and oocytes. Using animal oocytes to create cytoplasmic hybrid embryos is a valid and potentially important route towards advancing the science of nuclear transfer and the creation of stem cell lines as disease models. Animal eggs could provide an essentially unlimited supply of oocytes with which to hone research techniques, allowing more rapid progress and sparing the use of more valuable human eggs.
- 1.6 Work on interspecies constructs is not new: mouse-human hybrid cell lines have been used to map human genes since the 1970s and eventually led to the successful Human Genome Project. Transgenic mice expressing human genes have led to key insights into understanding and treating diseases ranging from Down syndrome to Alzheimer's Disease to cancer, HIV and AIDS. No insurmountable ethical or safety issues have emerged in over three decades of this research.
- 1.7 We welcome recent advances in methods of direct re-programming of somatic cells without the use of oocytes or early embryos.<sup>1</sup> However, this work has not been developed to a stage where it can be translated into human therapies, indeed there is

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<sup>1</sup> Takahashi et al., Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors, Cell (2007), doi:10.1016/j.cell.2007.11.019

a long way to go before we know whether this might even be possible. Therefore other avenues of research involving ISEs should not be closed off. (See Annex A for further information)

**B. Removal of the prohibition on altering the genetic structure of embryos for research** Schedule 2 Clause 2 (3) page 54 line 33

- 1.8 We welcome the removal of the prohibition on the alteration of the genetic structure of the cell of an embryo. This change will enable research involving the genetic modification of embryos to be authorised under a research licence. This will allow experiments involving either the insertion of exogenous DNA or the genetic manipulation of human embryos *in vitro*. Such work may help to identify genes that are important in specifying early cell lineages, or those that are critical in specifying the earliest stages of embryonic development and could also lead to direct benefits for infertility treatments.

**C. Extension of storage limits from five to ten years** Clause 15 (3) page 11 line 45

- 1.9 We welcome the doubling of the maximum storage period for gametes and embryos from 5 to 10 years. The nature of research means that future needs cannot always be anticipated in advance and it will be important to maintain these precious resources. We emphasise that, particularly where genetic disorders are concerned, a generation may pass before the full value of a research sample is recognised.

**D. Extension of research purposes** Schedule 2 3A (1)(b) page 58 line 27

- 1.10 This provision gives welcome clarity around the permissibility and importance of fundamental and basic embryo research and ensures that research into serious conditions such as brain injuries (which may not be considered 'serious diseases' under the current Act) can be undertaken under licence where they meet the other requirements of the legislation.

**E. Facilitation of the use of data on treatment held by the HFEA for medical research** Clause 25 page 29 line 6

- 1.11 We welcome the introduction of this clause, which enables the Government to make provisions to regulate disclosures of information gathered by the HFEA for research purposes. A firm commitment from the Government to develop regulations and provide funding for the HFEA to facilitate custodianship and disclosure of information is imperative for vital research into long term consequences of IVF treatment and conception. Current research is reliant on information from overseas sources, which may not be of the same high quality or as comprehensive as that held by the HFEA. The MRC Review *'Assisted Reproduction: A safe, sound future'* (2004) argued there is an urgent need to obtain reliable information, currently unavailable for the UK to understand the longer term consequences of assisted reproductive technologies. We therefore support this move and urge the Government to develop and introduce the relevant regulations as swiftly as possible.

## **2. Provisions that concern us**

### **A. Definitions of gametes, eggs and sperm** Amendment to Clause 1 (4)(a) and (b) 4(2) and paragraph 14 of Schedule 3

- 2.1 Changes proposed to the definitions of gametes, eggs and sperm are inconsistent with the ordinary scientific meanings of these terms and with the use of the term gamete in the Human Tissue Act 2004. This creates confusion and the prospect of dual regulation by the HFEA and the Human Tissue Authority (HTA) in some cases. We support the removal of the reference to germ line cells in the definition of the terms, bringing the terms substantially back in line with their scientific meaning and ensuring consistency with the Human Tissue Act 2004.

### **B. Clarification of definition of 'human cell' in Schedule 3** Amendment to paragraph 14, Schedule 3

- 2.2 The Bill introduces the term 'human cell' throughout Schedule 3, but does not fully clarify its meaning in context. The clarification of this definition is pivotal to the consent provisions in Schedule 3. We believe it should be made clear on the face of the Bill that 'human cell' means cells that have come from a person and not cells generated *in vitro* (cell lines). Were the definition to extend to cell lines, the vast stores of cell lines, including those for individual rare diseases, that are held in public, charitable and commercial collections would be unusable for the purposes set out in Schedule 3. This would be a tragic waste of resources and contrary to the interests of patients and the public.

### **C. Special exceptions to consent provisions in relation to children and storage and use for research** Insertion of new paragraphs 12 and 16(4) of Schedule 3

- 2.3 The effective consent provisions that have been introduced do not make provision for consent to be given by parents on behalf of their children to use their gametes or human cells for the creation of an embryo or ISEs for research purposes. The effect of this is that research into childhood diseases, including lethal genetic disorders, using somatic cell nuclear transfer (SCNT) would be unable to go ahead. We recognise research using material from children should not be undertaken lightly and would advocate that the Bill makes provision for consent by those with parental responsibility, thereby permitting the use of children's gametes and cells for research in very limited circumstances, subject to strict safeguards.

#### ***Organisation Contacts***

*Academy of Medical Sciences:*

*Association of Medical Research Charities:*

*Medical Research Council:*

*Royal Society:*

*Wellcome Trust:*

*Helen Munn 020 7969 5234*

*Simon Denegri 020 7269 8820*

*Catherine Elliot 020 7670 5481*

*Anne Simpson 020 7451 2530*

*Nancy Lee 020 7611 8751*

## Annex A

### STEM CELL RESEARCH AND THE NEED FOR INTER-SPECIES EMBRYOS

#### The potential of stem cells and current research

Stem cells are unspecialised cells that can self-renew and differentiate into specialised cell types.

**It is hoped that stem cells could ultimately replace any damaged or degenerate tissue, for example, cardiac muscle after a heart attack, brain tissue in Parkinson's or Alzheimer's disease or pancreatic islet cells in type 1 diabetes.** Stem cells given to the patient would differentiate into the tissue which requires replacement or repair.

One difficulty with current organ transplants is that the human body can reject cells that do not exactly match those of the recipient. **Stem cells offer the potential to allow transplantation of cells or tissues containing a patient's own DNA** (autologous), thus avoiding the problems of tissue rejection.

Stem cells may also be used *in vitro* as models for cells and tissues with specific diseases enabling drug therapies to be tested or disease progression to be studied in detail. Many cancerous cells behave like stem cells and greater understanding of the mechanisms by which stem cells develop and function will be useful in oncology research.

Current stem cell research is directed towards:

- exploring the use of adult stem cells, such as the use of bone marrow stem cells in **heart repair**
- exploiting embryonic stem cells for the treatment of **paediatric, heart, pancreatic, liver and brain conditions**
- using fetal stem cells as **treatments for neurodegenerative conditions** and eye conditions
- exploring the use of endogenous stem cells, naturally resident in tissues of the human body, to **direct the repair of damaged or diseased cells and tissues**
- increasing our **understanding and treatment of cancer** through studies of endogenous adult stem cells
- generating embryonic stem cells with the same nuclear genetic material to that of the patient using therapeutic cloning techniques, to avoid the potential rejection of cell therapies
- using stem cell lines as **tools in drug discovery and development. Further information about current projects funded by the MRC and the Trust is given below.**

#### Sources of stem cells

There are three sources of stem cells:

**1. Embryonic:**

these are pluripotent cells (i.e. they can turn into any cell type). They could be used either

- a. To create autologous matched cell lines using somatic cell nuclear transfer (SCNT) or by direct reprogramming (see below). These would initially be used to provide models of disease and test therapies but eventually might be the source of stem cell therapies; or

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- b. To create cell lines that could be used by a large number of recipients. These lines can also be used to study the processes involved in cellular development and differentiation.

### 2. Fetal:

- a. Umbilical cord blood contains adult-type stem cells. Some organisations offer banking of this blood in the hope that in the future it may provide stem cells for the donor. At present the techniques do not exist to make this a reality.
- b. Fetal tissue has also been studied to provide multipotent cells to repair injured tissues such as neuronal cells in Parkinsons disease or spinal cord injury. After the embryonic stage most fetal stem cells, including cells from the amnion, will be, at most, multipotent, unless the cell can be modified to regain pluripotency.

### 3. Adult:

This is the most attractive route to remove many of the ethical arguments that arise over the use of gametes, embryos or fetuses.

- a. Adult stem cells are already widely used in bone marrow transplantation where the multipotent bone marrow cells are reimplanted following chemotherapy to replace bone marrow cells destroyed during therapy. Some success has been reported using similar cells to repair heart damage after infarction. There is however, dispute as to whether these cells actually differentiate into cardiac tissue or have other effects (for example, on the immune system) that improve outcomes in this situation.
- b. Work has also focused on processes that could allow adult somatic (not gametes – eggs or sperm) cells to be ‘reprogrammed’ to regain the properties of multipotency or, ideally, pluripotency. There have been some very recent reports of success in this research but, as yet, none have been sufficient to be certain that this technique will be an effective source of stem cell lines.

## **Somatic cell nuclear transfer (SCNT) - Creation of autologous ES cells**

**There are three main avenues of research attempting to derive autologous pluripotent stem cell lines** (ie stem cells exactly matched to a patient)

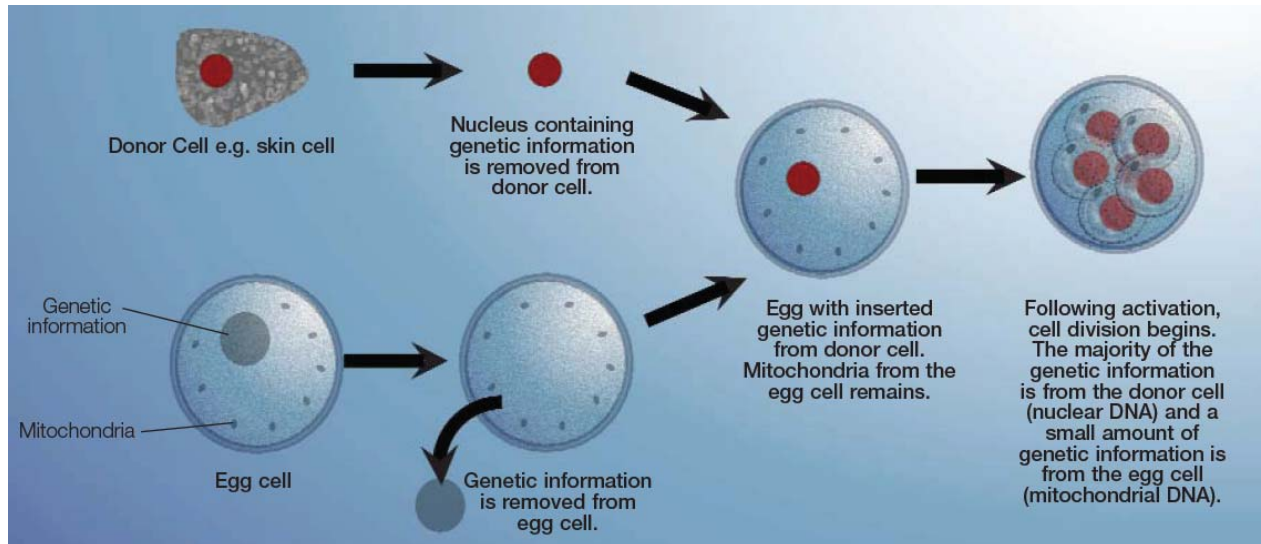
1. SCNT using human eggs
2. SCNT using animal eggs, creating an ISE
3. Reprogramming of adult somatic cells

To produce stem cells **exactly** matched to the recipient, researchers remove the genetic material (the nucleus) from a normal (somatic) cell in the patient’s body and place it into an unfertilised egg (see the figure below). The nucleus then behaves as it would in an embryo, and stem cells exactly matched to the donor of the nucleus can be cultured, and encouraged to grow into the specific cell type(s) needed to repair damage. However, the generation of embryos from which stem cells can be harvested using SCNT is still inefficient.<sup>2</sup> In addition, **the availability of human eggs for SCNT is limited because most donated eggs are used for fertility treatment rather than research.** The full technique has not yet been achieved in humans. A valid and potentially important avenue in overcoming these limitations is to use an animal egg with human DNA. This creates an inter-species embryo of the type described in section 4 (5)(b) of the Bill. This is sometimes termed a ‘cytoplasmic hybrid embryo’.

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<sup>2</sup> Promising research in non-human primates has recently been reported although with a success rate of just 0.7%.

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### Inter-species embryos

SCNT using animal eggs requires the creation of a cytoplasmic hybrid embryo, a type of inter-species embryo (ISE). The Bill defines four types of ISE which may be created under licence, with a regulation-making power to cover classes not yet defined which may arise in the future:

- a. **true hybrids:** created by the fusion of human and animal gametes [Clause 4(5)(a)]
- b. **cytoplasmic hybrid embryos:** created by transferring the nucleus of a human cell into an animal oocyte, from which the nucleus has been removed [Clause 4(5)(b)]
- c. **transgenic human embryo:** a human embryo into which animal DNA has been integrated [Clause 4(5)(c)]
- d. **chimeric human embryo:** a human embryo into which one or more animal cells have been integrated [Clause 4(5)(d)].

### **Research using ISEs**

a. We are not aware of any current scientific reasons to generate true hybrid embryos *in vitro* (by mixing human and non-human gametes or pronuclei - clause 4(5)(a)). However, given the speed of this field of research, the emergence of scientifically valid reasons in the future cannot be ruled out. As current legislation allows creation of hamster egg-human sperm hybrids to test sperm quality, we do not believe such entities would be deemed unacceptable on ethical grounds alone.

b. To date, proposals have been submitted to the HFEA to create cytoplasmic hybrid embryos for SCNT research (clause 4(5)(b)). These proposals suggest using cow eggs obtained from an abattoir. We know of no existing proposals to create the other types of ISE defined in the Bill.

c. There are already good scientific reasons to conduct experiments involving genetic manipulations (e.g. the insertion of exogenous DNA) of human embryos *in vitro* (clause 4(5)(c)). These techniques could facilitate the investigation of gene function in very early embryogenesis (i.e. up to the 14 day limit), thus aiding research into re-programming, stem cell derivation, early cell commitment, differentiation and early embryo development. For example, labels could be incorporated into early human embryos to trace the differentiation of cell types. Such work has already commenced in mouse models. This would allow

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scientists to investigate further how pluripotent cells become selected and differentiated into specific cell types. In addition to increasing understanding of cell potential, such work could be used to improve assessments of embryo quality prior to assisted reproduction and so potentially increase the chances of IVF success.

d. It is also possible that researchers may seek to introduce ES cells into human embryos *in vitro* to determine their relationship to normal embryo cells and to investigate how pathways to different lineages are triggered (clause 4(5)(d)).

### Reprogramming of adult somatic cells

We welcome recent advances in methods of direct reprogramming of somatic skin cells without the use of oocytes or early embryos as announced by teams in the US and Japan.<sup>3</sup> However, other forms of research should not be closed off. Knowledge of the factors required for reprogramming has depended on human embryos research and SCNT experiments and we must continue to explore a range of methods for reprogramming to further our understanding of hES cells and their pluripotency. We believe that the most likely route to achieving reliable techniques for creating stem cells requires understanding the mechanisms to reprogramming adult cells *back* to pluripotency and the mechanisms that programme embryonic cells *towards* differentiation.

### Summary

**It is our view that, at present, there is no conclusive evidence as to which method of producing pluripotent stem cell lines (SCNT with human eggs, interspecies embryos or reprogramming of adult cells) will ultimately prove most effective.** Techniques developed in pursuing one avenue will be applicable to the others. For example, creation of cytoplasmic hybrid embryos would allow researchers to work on much more easily available eggs from animals, such as cow eggs obtained from an abattoir. Techniques developed could then be applied to human eggs, donation of which is limited and subject to other considerations. Similarly, knowledge relating to the development of cells following SCNT may aid progress in reprogramming adult cells to 'regress' to become pluripotent.

For further information see:

Inter-species embryos. Academy of Medical Sciences (2007)

<http://www.acmedsci.ac.uk/download.php?file=/images/publication/118356622535.pdf>

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<sup>3</sup> Takahashi et al., Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors, *Cell* (2007), doi:10.1016/j.cell.2007.11.019 and J. Yu et al. *Science* doi:10.1126/Science.1151526;2007

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### Examples of current stem cell research funded by the MRC and the Wellcome Trust

#### **Disease Modelling**

Work undertaken by Wellcome Trust-funded scientists at the Wellcome Trust Centre for Stem Cell Research based at the University of Cambridge aims to focus on the genetic and biochemical mechanisms that control how stem cells develop into particular types of cells. This work will help provide the techniques and knowledge for the engineering of stem cells to model particular diseases, drug discoveries and regenerative medicine.

#### **Blindness**

MRC-funded scientists at the University College London Institute of Ophthalmology are researching stem cell transplants to treat people with hereditary retinal disease and age-related macular degeneration – two major causes of vision problems and blindness in the UK which have a lack of effective treatments. The investigators hope to use stem cells to generate replacement retinal cells that could be used to restore vision.

#### **Diabetes**

Dr Neil Hanley and his team at the University of Southampton are attempting to generate human embryonic stem cells that can be used to replace the insulin producing beta cells in patients suffering from type 1 diabetes.

#### **Osteoporosis**

Stem cell technology holds promise for many people with bone problems, such as arthritis and osteoporosis patients, people with bone injuries and those who need joint replacement operations. MRC-funded scientists at Imperial College London have successfully grown cartilage cells from human embryonic stem cells. Their achievement may mean that one day replacement cartilage could be grown for transplantation into patients.

#### **Biology of embryonic stem cells**

Researchers at the Wellcome Trust Institute for Stem Cell Research, at the University of Edinburgh are investigating the development of applications to understand how embryonic stem cells maintain their potential during self-renewal and how they then switch to the production of particular, specialised cells. Work in this field has the potential to lead to the ability to develop replacement cells and tissues for treatment of degenerative diseases including juvenile diabetes. This work could also lead to improved cell based assays as an alternative to animal tissue for screening new pharmaceuticals.

#### **Stem cell bank**

Based at the National Institute for Biological Standards and Control at South Mimms, Hertfordshire, the UK Stem Cell Bank was established in 2002 as the world's first stem cell bank. It is funded jointly by the BBSRC and the MRC. The Bank recently made its first four research-grade stem cell lines available, with the release of further research-grade lines imminent. It is also embarking upon the construction of its Good Manufacturing Practice (GMP) facilities for the deposition and ultimate distribution of clinical-grade stem cell lines for transplantation. Confidence in the UK oversight arrangements has persuaded a number of overseas labs to deposit lines – of the 40 registered some 20 are non-UK derived.