

Human Fertilisation and Embryology Bill

House of Lords Report Stage 15, 21 January 2008

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

Section 1: Summary

The aim of the Human Fertilisation and Embryology (HFE) Bill is 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 careful regulatory framework that has been established around such research.

The Academy of Medical Sciences (AMS), Medical Research Council (MRC), Royal Society, Wellcome Trust and Association of Medical Research Charities are confident that the Bill in its present form provides assurance to UK scientists working at the cutting edge of stem cell and embryo research that they can continue their work under the tightly-regulated environment that has made the UK a world-leader in this area.

This research has massive potential to provide treatments for serious debilitating disorders ranging from developmental abnormalities in young children, to stroke, cancer, HIV/Aids, diabetes and Parkinson's disease, as well as better and safer treatment for infertile couples. 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 to the UK.

Why this Bill is important

The provisions in this Bill will ensure important scientific and medical research can be undertaken. In this briefing, we focus on the following specific areas of the Bill that we support:

- The ability to create inter-species embryos at the human end of the spectrum under licence, for research purposes;
- Allowing scientists to alter the genetic structure of embryos for research purposes;
- The opportunity to use data collected by the HFEA on fertility treatment to examine the long-term effects on patients and their children.

Outstanding Issues

We believe there are a number of issues which remain outstanding in the Bill. In this briefing, we focus on a series of amendments tabled at Report Stage, that will ensure new legislation does not excessively constrain or limit important biomedical research.

These issues, summarised below, are detailed in section 3 of this brief.

- Replacement of the term 'inter-species embryo' with 'human admixed embryos'
- A defence in circumstances where it is reasonably believed that the Act does not apply
- An exception to the requirement for specific consent for use of existing holdings of cells and cell lines to create embryos or ISEs for research
- Special provisions in relation to children and consent to the use of cells to create embryos or ISEs and to the storage and use of embryos or ISEs for research

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Section 2: Areas of the current Bill we support

Interspecies embryos (ISEs) (Clause 4 Page 4 line 21)

We support the provisions of the Bill which allow the creation of inter-species embryos at the human end of the spectrum for the purposes of research under licence. We continue to support key restrictions placed on these licences, which reflect those placed on all human embryos used for research, namely:

- (a) prohibition of implantation in a woman or an animal
- (b) prohibition of the development of the ISE past:
 - the appearance of the primitive streak; or
 - 14 days, whichever is sooner.

The ability to create ISEs within a robust regulatory environment will enable researchers to develop potentially life-saving therapies for a number of debilitating human conditions including diabetes, cancer, HIV/AIDS, Parkinson's disease and spinal cord injuries and many others.

ISEs include cytoplasmic hybrid embryos, which enable human embryonic stem cells to be derived for research through the use of animal¹ eggs rather than human eggs. This removes the significant restraint on research brought about by the limited amount of human eggs available for research purposes. A cytoplasmic hybrid embryo is created when the genetic material from a human cell is placed into an unfertilised animal egg and starts to act like an embryo, and from which stem cells can be derived. This technique is known as somatic cell nuclear transfer (SCNT). Provisions in the Bill ensure that these entities are prohibited from developing beyond the earlier of 14 days or the development of a primitive streak (i.e. the same point after which research is no longer allowed on human embryos).

Further details of the importance of human embryonic stem cells to research are provided in Annex A.

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

We welcome this provision which will enable research involving the genetic modification of human embryos to be authorised under a research licence. This will allow experiments involving either the insertion of DNA into the embryo, or the genetic manipulation of human embryos *in vitro*. Such work will help us to identify genes involved in early development and could also lead to direct benefits for infertility treatment. Provisions in the Bill ensure that these entities are prohibited from developing beyond the earlier of 14 days or the development of a primitive streak.

Facilitation of the use of data on treatment held by the HFEA for medical research (Clause 25 page 29 line 6)

We welcome this provision, which will enable Government to regulate sharing of information on fertility treatments currently gathered by the HFEA for ethically approved research. A firm commitment from the Government to develop regulations and provide funding for the HFEA to facilitate custodianship and sharing 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 is unlikely to be as comprehensive, relevant or of the same high quality as that held by the HFEA. The Medical Research Council review '*Assisted Reproduction: A safe, sound future*' (2004)² argued there is an urgent need to obtain reliable information, currently unavailable for the UK, to understand the longer term

¹ For convenience, in the context of this briefing we use the term 'animal' to mean 'non-human animal'

² www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002393

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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.

Section 3: Amendments to the Bill we support

Replacement of the term 'inter-species embryo' with 'human admixed embryos' (Amendment to Clause 4, and all consequential amendments)

We support the amendments tabled by Lord Darzi, (specifically in regard to Clause 4, and all consequential amendments) which replace the term 'inter-species embryo' with 'human admixed embryo'. We believe this term better reflects the scope of what is to be regulated under subclause 4(5) (a) to (d) of the Bill.

Defence in circumstances where it is reasonably believed that the Act does not apply (Amendment to Clause 29)

A series of offences are set out in the current Bill, including the storage of gametes and the creation of embryos or interspecies embryos without a licence. Embryos are broadly defined under the Bill to include 'an egg that is in the process of fertilisation or is undergoing any other process capable of resulting in an embryo'. Gametes are also broadly defined to include germ line cells at any stage of maturity. Our understanding of the processes by which eggs develop into embryos and cells develop into germ line cells is incomplete. It is therefore possible that a researcher could store or carry out research on cells that are not currently known to be or destined to become germ line cells, or could carry out research on eggs that are (unknown to current science) capable of resulting in an embryo. We believe it should be a defence for a researcher to prove in such circumstances that they reasonably believed what they stored or were creating was not a gamete, an embryo or an interspecies embryo as defined in the Bill. The researcher would, of course, need to cease the activity and seek a licence, or destroy the material, as soon as it became reasonably clear that this was necessary. We note that a similar defence is contained in the Human Tissue Act 2004.

Exception to requirement for specific consent for use of existing holdings of cells and cell lines to create embryos or ISEs for use for research (Amendment to Schedule 3 - insertion of new paragraph 10A)

The consent provisions introduced in Schedule 3 of the Bill extend the requirement to obtain specific consent for the use of *any* human cells to create an embryo. As currently set out in the Bill, the consent requirements will block the use for research of many existing holdings of cell lines that have been collected over many years, often from patients with specific rare conditions. These existing holdings may be hugely important for research into the origins, development and treatment of the diseases from which the original patient donors suffered. Where possible, consent should be obtained from these patients. But this is not possible in *all* cases, for example, where a cell line has been irreversibly anonymised and the original donor cannot be identified. We are concerned that the significant time and resources invested in creating these collections of cell lines will be wasted, and that blocking their use for research is contrary to the interests of patients.

We suggest that the Bill is amended to include a limited exception allowing the use of existing holdings of cells and cell lines to create embryos or ISEs for use for research without consent where the following criteria are met:

- 1 Where the cells are lawfully taken
- 2 Where the cells are first stored or used prior to the relevant sections of the Act relating to Licence Conditions come into force
- 3 Where the donor cannot be identified

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- 4 Where it is not reasonably possible to obtain consent
- 5 Where there is no alternative source of tissue
- 6 Where there is no evidence that the donor has indicated an objection to such storage and use (as applicable)

The research would also need to meet the other requirements of the Act, including that the research would have to be necessary and relate to serious disease or other medical conditions. This will ensure that, in exceptional and deserving cases, vital resources are not wasted and important research can be carried out.

Special provisions in relation to children and consent to the use of cells to create embryos or ISEs, and to the storage and use of such embryos or ISEs for research (Insertion of new paragraphs 12A Schedule 3)

The consent provisions in Schedule 3 of the Bill do not make provision for consent to be given by parents on behalf of their children to use cells lawfully taken from them (e.g. left over from a blood test) to create embryos or ISEs for the purposes of research into serious disease or serious medical conditions. This would prevent research into childhood diseases, including lethal genetic disorders, using embryonic stem cells created through SCNT. We recognise research using material from children should not be undertaken lightly and advocate that the Bill makes provision for consent by those with parental responsibility, thereby permitting the use of children's cells only for research in very limited circumstances and subject to strict safeguards. The safeguards proposed borrow from other sources including protections included in the Mental Capacity Act 2005 and are in line with other regulatory arrangements for children in which consent can be provided for children by their parents.

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Annex A

Why are Embryonic Stem Cells Important

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

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 stem cells, to **direct the repair of damaged or diseased cells and tissues**
- increasing our **understanding and treatment of cancer**
- 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
- producing stem cell lines with the genetic mutations that cause specific diseases in order that the ways in which these diseases affect cells the body, and may be treated, can be more fully understood
- using stem cell lines as **tools in drug discovery and development.**

There are three types 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 (cell lines which match the donor) 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
- 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 which is important in tissue repair and has potential to treat degenerative diseases.

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 (meaning they can differentiate into different cell types, but these types are limited in number) to repair injured tissues such as neuronal cells in Parkinson's 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 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 heart attack. There is however, dispute as to whether these cells actually change 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 normal adult cells, such as skin cells, to be 'reprogrammed' to regain the properties whereby they can turn into other cells which are either very similar or entirely new. 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

SCNT describes the technique used to create embryonic stem cells using a donor nucleus. It can be used to create embryonic stem cells outside a human or animal and is also used in regenerative medicine.

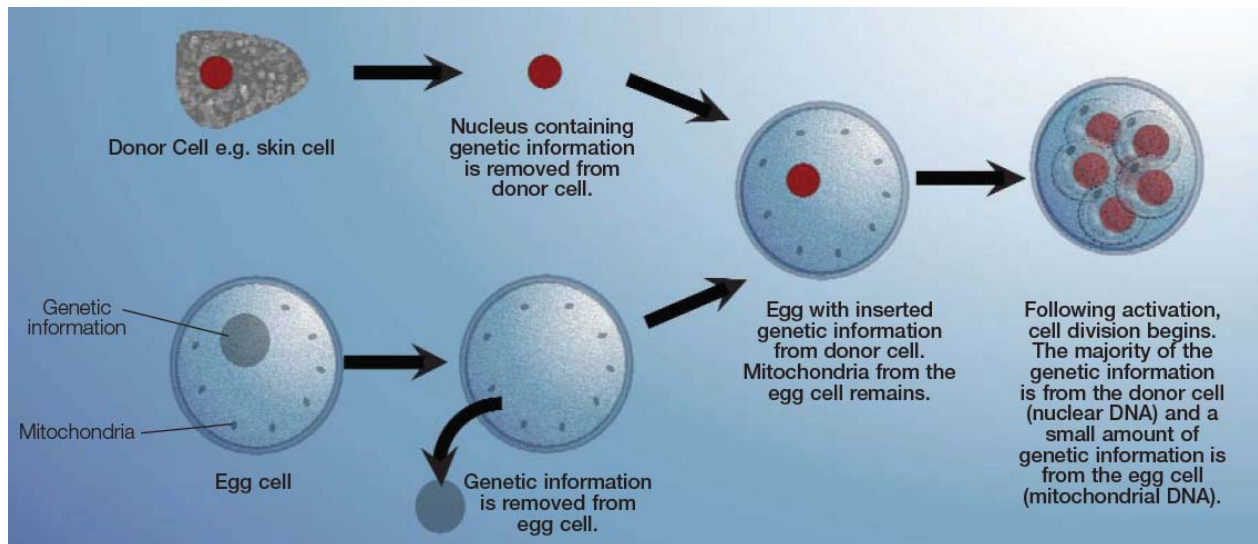
SCNT is a part of two of the three main avenues of research attempting to derive autologous pluripotent stem cell lines (ie stem cells exactly matched to a patient)

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.³ 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 a human admixed embryo of the type described in section 4 (5)(b) of the Bill (as amended). This is sometimes termed a 'cytoplasmic hybrid embryo'.

³ 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 (Human Admixed 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

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embryos to trace the differentiation of cell types. Such work has already commenced in mouse models. This would allow 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.⁴ 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>

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.

⁴ 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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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.