

Human Embryonic Stem Cells and the Prospects for Human-Animal “Hybrids”

The UK must permit work on human-animal embryos if the therapeutic promise of stem cell research is to be fully realised, say Gary Uy and Linda Horton.

One of the principal aims of medicine has been to overcome the debilitating effects of loss of function of organs and tissues in order to extend the duration, and improve the quality, of human life. Until recently, tissue removal and replacement from a donor seemed to be the only option. With innovative medical discoveries appearing in the news with ever greater frequency, it no longer seems unrealistic to replace and restore organ and tissue function by simply transplanting healthy cells obtained from the very patient who needs them. Humans unfortunately have a low capacity to regenerate healthy tissues and organs, raising the hope that human embryo research will lead to promising human embryonic stem cell therapies.

It is beyond dispute that, in order for treatments to reach patients, the inventiveness of researchers must be supported by laws that promote scientific ingenuity and provide regulatory certainty. A prime example of this is the pioneering *Human Fertilisation and Embryology Act of 1990* (“the Act”). The Act governs the use of human reproductive technologies in the UK and is among the most advanced in the world. Whether it will remain so is unclear.

The Act was given royal assent in the UK on 1 November 1990 and came into force on 1 April 1991. It has since been used as the model for similar legislation in several other countries, including Canada. What has made the UK statutory framework a sound model is that it promotes both the pursuits of the medical community and the dignity of the human embryo. The Act is broad. It covers the collection, storage and donation of human sperm and eggs, the screening of potential sperm and egg donors, the consents required to store human embryos, sperm and eggs, human pre-implantation embryo testing, and counselling before *in vitro* fertilisation (IVF). Today, it remains one of the most permissive reproductive laws among the European Union (EU) member states.

Under the Act, a statutory licensing body, the Human Fertilisation and Embryology Authority (HFEA), was created on 1 August 1991. Its mandate includes the granting of licences for research projects using human embryos and IVF technology. The HFEA is composed of 18 members (including a chairman and a deputy chairman), appointed by the secretary of state, who are prominent figures in fields such as research, ethics and reproductive medicine. The HFEA has the authority to grant licences for human IVF treatment services (including the creation and storage of embryos *ex utero*), the storage of human embryos and human embryo research.

Except for an amendment to the Act in 2001 which widened the circumstances in which a research licence could be granted, the Act as it relates to experimentation has proven sufficiently flexible to accommodate the regulatory needs of the research community for a decade and a half without the need for further amendment. The durability of the statutory scheme seems especially remarkable when one considers the successive technical improvements in human embryonic research that have allowed scientists and clinicians to create, study and manipulate embryos with ever greater precision. Concerning research licences, the longevity of the Act is due partly to the foresight of parliament in legislative design and partly to the discretion granted to the HFEA in making its licensing decisions.

However, the Act will change. On 21 January 2004, the government announced that it would review the Act to ensure its relevance and fitness for purpose in the early 21st century. This consultation is part of a process of re-establishing a framework that is broadly acceptable to society. To this end, the government published a white paper in December 2006 outlining the various proposals it will make to parliament concerning amendments to the Act¹. Chief among them will be legislation clarifying the extent to which the law applies to human-animal embryos. The results of the consultation indicate that the government will argue that the creation of human-animal embryos should, in fact, be prohibited in the Act, with the possible inclusion of regulations, subject to conditions, to set out circumstances in which the creation of human-animal embryos might be granted a licence at some future point in time. The publication of the white paper follows a consultation commissioned by the Department of Health and includes the various conclusions and recommendations proposed by the House of Commons Science and Technology Committee dated 24 March 2005².

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...however, it is soon to change, with the government intending to argue that human-animal embryo creation should be prohibited

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Ethical controversies surround the use of human embryonic stem cells in research...

Understandably, one of the main controversies that has surrounded the use of human embryonic stem cells in research is whether such research is ethically acceptable. Although the state of human embryonic stem cell research has advanced impressively over the past decade and a half, things have not yet progressed to the stage where human embryonic stem cell lines can be reproducibly derived from a human embryo without destroying it, although there is some experimental evidence that it can be done. Even if embryos could routinely survive the process of deriving embryonic stem cells, there is a prohibition in section 3(a) of the Act against sustaining embryos beyond 14 days following fertilisation. At present, it is the HFEA that makes such inevitable ethical judgments before deciding if a research programme will receive a licence, as all research licence applications must first receive clearance from a "properly" constituted HFEA ethics committee³. This is contentious, as it has been suggested that the HFEA is not able to make such ethical judgments. Josephine Quintavalle, head of the public interest group Comment on Reproductive Ethics, has argued that ethical decisions concerning research applications should be debated and discussed at the parliamentary level rather than by an unelected group⁴. This is clearly impractical.

Although the government proposes to replace the HFEA with the Regulatory Authority for Tissue and Embryos, which is intended to be the single statutory regulator under both the Act and the *Human Tissue Act 2004*, it is not yet clear what the precise function of the new body would be. The white paper suggests that ethical experts be included on expert advisory panels of technical specialists to be set up for various disciplines, such as assisted reproduction and embryology. The House of Commons Science and Technology Committee went so far as to recommend the creation of a nationally co-ordinated network of clinical ethics committees alongside the establishment of local research ethics committees⁵. What is clear is that the government would like to see more uniform measures in place for ethical evaluations of research proposals. Whether this will result in an increase or decrease in successful licensing applications remains to be seen.

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While it is expected that much of the legislation governing research purposes will remain unchanged, the government has, crucially, proposed to ban research resulting in "human-animal chimaeras" or "human-animal hybrids". We await the results of the parliamentary debates to establish whether the proposals to prohibit human-animal chimaeras will be given the force of law. However, in order to appreciate the gravity of the government's proposal, it is first necessary to review the legality of human therapeutic cloning in the UK.

Human embryonic stem cell research – a revolution in the making?

Most of the hope in deriving stem cell lines for medical use rests with human embryonic stem cells derived from pre-implantation human embryos. This is because embryonic stem cells are "pluripotent" (ie they have the potential to develop into virtually all cell types in the human body *in vivo*, except for placental tissues). Human embryonic stem cells are fundamentally different from adult stem cells, which are obtained from certain parts of the fully formed body and have only limited potential to develop into the range of tissues that is theoretically possible with human embryonic stem cells.

In therapeutic cloning, sometimes referred to more technically as somatic cell nuclear transfer (SCNT), the nucleus from the cell of a patient (which contains its nuclear genome, or cellular DNA) is transplanted into a human egg whose own nucleus has been removed. The resulting cell is then artificially stimulated to commence cell division and undergo nuclear reprogramming (a phenomenon which effectively tricks the DNA into recapitulating normal embryonic development as if the DNA from the patient's cell had always been a part of the egg into which it had been injected). Such embryos are then developed *in vitro* until embryonic cell lines can be isolated. The virtues of therapeutic cloning, although widely hyped in the media, would be of little use to patients whose need for stem cell therapy is due to a disease caused by a genetic insufficiency such as cystic fibrosis, as it would be essential to ensure that the donor embryonic stem cells did not exhibit the gene defect which they were meant to correct.

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Central to embryonic stem cell transplantation therapy is the matching of donor and patient tissues to avoid immunorejection. The ideal stem cell therapy would therefore combine "Dolly the sheep" and embryonic stem cell technologies, and it is the cloning of cells and tissues that is the essence of therapeutic cloning. Although the prospects of therapeutic cloning have been widely reported to be revolutionary, with further years of research it would not be surprising to discover that embryonic stem cells were more appropriate for certain therapeutic uses and adult stem cells for others.

Therapeutic cloning is the most essential embryonic research tool permitted by the Act. Despite the wording of section 3(3)(d) which prohibits...*replacing a nucleus of a cell of an embryo with a nucleus taken from a cell of any person, embryo or subsequent development of an embryo*, the legality of

therapeutic cloning under the Act is beyond question. The ProLife Alliance, which brought a judicial review of the Act, argued that “embryo”, as defined in section 1 of the Act, should not apply to embryos created by SCNT and that as such, licences granted for therapeutic cloning studies were beyond the jurisdiction of the HFEA⁶. The House of Lords unanimously ruled in 2003 that the definition of “embryo” applies equally to those embryos created by methods other than by fertilisation, such as by SCNT, at once confirming the permissibility of therapeutic cloning experiments in the UK⁷. This ruling, by implication, also permits the application of the Act to parthenotes (unfertilised eggs which undergo cell division upon the application of certain external artificial cues), which offers other avenues to researchers in applying therapeutic cloning to patients.

At present, the UK remains one of a small minority of EU member states that permit therapeutic cloning, provided that certain conditions are met:

- a licence is obtained from the HFEA (section 3(1) of the Act);
- human embryos are surplus to IVF treatment, or eggs donated, with the appropriate consent (schedule 3 of the Act);
- the purpose of the experiments is to “increase the knowledge about the creation and development of embryos, or about disease, or enable such knowledge to be applied” (schedule 2, section 3(3) of the Act);
- the embryo is destroyed before 14 days after fertilisation (sections 3(a) and (4) of the Act); and
- the embryo is not placed in a woman (section 3(2)(a) of the Act).

However, so-called “reproductive cloning” experiments (ie embryos produced by SCNT resulting in a live birth) are illegal in the UK, whatever the purpose, as a licence cannot be granted for keeping or using an embryo after the appearance of the primitive streak beyond 14 days after fertilisation. The criminal offence is codified in the *Human Reproductive Cloning Act 2001*.

The initial excitement over human embryonic stem cells as the next frontier in treating a plethora of human diseases and conditions has been somewhat premature. In truth, there are some convincing results from research groups which document a greater plasticity and interconvertibility of adult stem cells than previously thought, which makes it difficult to justify the notion that embryonic stem cells offer the greatest prospects among stem cells for the treatment of human disease. In fact, much of the promise of human embryonic stem cells comes from our presently greater understanding of embryonic stem cells produced from the mouse, a species in which it has proven far simpler to derive and manipulate embryonic stem cells than humans.

Although much has been made of embryonic stem cell-based therapies, the science is still in the early stages of useable technologies and cures. This is principally because the routine abnormalities in animals produced by reproductive cloning experiments suggest that embryonic stem cells produced from SCNT are not yet safe to graft into human patients reliably. The scientific community is divided, with some claiming that the perceived risks are merely hypothetical, while others claim that they are very real. Another, no less important concern, of course, is the tendency for transplanted embryonic stem cells to exhibit characteristics typical of cancers, which grow and proliferate in an uncontrolled fashion *in vivo*.

In light of these uncertainties, it is essential that research into the possibilities of therapeutic cloning continue without disproportionate legal interference, as has been the case so far in the UK, and particularly that therapeutic cloning be conducted on a far greater experimental scale. Experimental programmes which depend on human eggs are inherently limited as humans are not especially fecund and are severely limited in the number of eggs that can be produced over a period of time. Therefore, a more efficient option is to isolate embryonic stem cells from embryos produced from the transplantation of human cell nuclei into animal eggs. Simply put, the more experimental data that can be generated over a period of time, the more information researchers will have on which to base and design purely human embryological experiments. However, this leads directly into the latest controversy surrounding human embryonic stem cell research. The prospective use of the as yet hypothetical human-animal “chimaeras” or human-animal “hybrids” as a source of embryonic stem cells has already been publicised in the media, even though such experiments have not yet been conducted in the UK.

The human-animal “hybrid” debate – the next advance in therapeutic cloning?

The HFEA has received two separate applications to conduct such research. The researchers proposed applying SCNT technology, by transplanting human cell nuclei into animal eggs as

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The scientific community is divided over the safety of grafting into humans embryonic stem cells produced from therapeutic cloning

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The widely used terms "human-animal hybrid" and "human-animal chimaera" misrepresent this technology to the public

described earlier, to produce human-animal chimaeras or human-animal hybrids. Although the terms chimaera and hybrid are now regularly used to describe the combination of human nuclear DNA and animal eggs, these terms are scientifically incorrect in a way that misrepresents this technology to the public.

Chimaera is a term which derives from Greek mythology to describe what is effectively a monster, composed of body parts made up of several different animals, and both "chimaera" and "hybrid", as they are used in scientific terminology, suggest first that the resulting organism is carried to term, and second that the resulting organism is the product of both animal and human DNA in more or less equal measure. In fact, what the researchers instead plan to investigate is whether it would be possible in the first place to create early embryos and derive embryonic stem cell lines by transplanting human cell nuclei into animal eggs whose own nucleus had been removed, with the intention of destroying the resulting embryo around the time when embryonic stem cells are isolated, and before 14 days after fertilisation. Because of the inaccuracy of these terms, the term "human-animal embryo" will be used in the remainder of this article.

The Act has not prohibited human-animal embryos outright. Section 3(5) of schedule 2 of the Act states: *A licence under this paragraph may authorise mixing sperm with the egg of a hamster, or other animal specified in directions, for the purpose of developing more effective techniques for determining the fertility or normality of sperm, but only where anything which forms is destroyed when the research is complete and in any event, not later than the two cell stage.* It is clear that embryos created in such a manner must be destroyed at the two cell stage of development, and are not to be implanted into a woman (section 3(2)(a) of the Act).

The creation of human-animal embryos, the correct term, is not expressly prohibited under the current law

Arguably, as currently drafted, the Act does not expressly prohibit embryos created by the transfer of human DNA into an animal egg where it is not for the purpose of *determining the fertility or normality of sperm*, but where the research is intended to...*increase knowledge about the creation and development of embryos, or about disease, or enable such knowledge to be applied* (schedule 2, section 3(3) of the Act). The HFEA has long taken the position that it will not grant a research licence using human embryos unless it is indispensable for the purposes of research, and the use of animal eggs in place of human eggs in these experiments is debatable. Nevertheless, Angela McNab, chief executive of the HFEA, has said that human-animal embryo research would not be prohibited by the Act and it would be within the remit of the HFEA to regulate and licence such research⁸. However, the HFEA has taken the cautious view that it will review applications to produce human-animal embryos once a public consultation into this particular issue has been completed later this year.

The issue of human-animal embryos is a particularly complex one, not only from a legal and ethical standpoint, but also from a biological one. First, although the DNA of the resulting embryonic stem cells would be primarily of human origin, its mitochondrial DNA would be of animal origin. It is a common misconception that each cell in the human body has only one genome. In fact, the human has two genomes: its "nuclear genome" which is the DNA present in the nucleus of each cell of the human body, and its "mitochondrial genome", the DNA present in particular cell compartments known as the mitochondria, which are found in the cytoplasm of the cell (ie the bulk of the material of the cell extrinsic to the cell nucleus, and bound by the cell membrane). However, there would be little chance of such animal DNA integrating into the nuclear DNA of the embryo, as mitochondrial DNA does not exhibit the same tendency to undergo recombination as the nuclear genome and it is physically confined in separate compartments away from the nucleus.

Certain human-animal cell fusion products have already been in use for some time in medical research

Second, early in development, certain "epigenetic" cues (ie stimuli which produce inherited changes in gene function, or other cell characteristic, that are not a result of genetic coding) have been shown to significantly influence mammalian embryonic development. In the context of human-animal embryos, such cues are likely to be found in the cytoplasm of the animal egg and, as such, might influence the development of the resulting human-animal embryo in a manner which is still unclear. Nevertheless, these uncertainties need not unduly concern the public, as certain human-animal cell fusion products have already been in use for quite some time in medical research, particularly in the development of cancer therapies.

Colin Blakemore, chief executive of the Medical Research Council (MRC), an influential publicly funded UK organisation that provides funding to various medical and bioscience research laboratories across the country, has stated: "The MRC recognises that the creation of such hybrids raises concerns among some members of the public. However, without robust evidence as to the basis or extent of such concerns, we're not persuaded that there is a case for changing the current legislation regarding research⁹." The prime minister, Tony Blair, has stated the government is not "dead set against" the creation of human-animal embryos for research, and that "research that's really going to save lives and improve the quality of life will be able to go forward"^{10,11}.

Conclusion

The use of human-animal embryos to generate experimental data on the biology of human embryonic stem cells will help to solve many of the problems associated with the safe use of embryonic stem cells in humans, which, of course, will help to advance the rate at which embryonic stem cell therapies can be brought to market. However, in addition to the possible ban on human-animal embryo experimentation, there is another challenge to the use of this technology in the EU – it is unclear whether it will be possible to patent such processes under the EU biotechnology directive, and this issue is in itself worthy of a separate discussion¹².

The UK has enjoyed its position at the forefront of human reproductive technologies and discoveries due in large part to the fact that the Act encourages research on human embryos to increase knowledge about the creation and development of embryos, or about disease, or to enable such knowledge to be applied. The main success of the Act as it concerns research has been its continuing relevance to advances in research from 1991 through to the present day. Arguably such relevance would be questionable should human-animal embryo experimentation be made unlawful.

The vision displayed by the government in authorising therapeutic cloning experiments at a time when certain other countries had banned them is evidenced by the number of countries that have since adopted substantial provisions of the Act in their own national legislation. This tradition should continue in order to enhance the possibility of using therapeutic cloning in the treatment of diseases such as Alzheimer's or Parkinson's disease in our lifetimes. Whatever amendments are made to the Act concerning human-animal embryos, they will be closely scrutinised. And the world will be watching.

Experimental data generated from the use of human-animal embryos will help with the safe use of embryonic stem cells in humans

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