

Response to the Human Fertilisation and Embryology Authority consultation on the ethical and social implications of creating human-animal embryos in research: scientific questions

We welcome the opportunity to respond to the scientific questions posed by the Human Fertilisation and Embryology Authority (HFEA) in relation to the HFEA consultation on the ethical and social implications of creating human-animal embryos in research, launched in April 2007. This submission has been approved on behalf of the Royal Society by Sir David Read FRS, the Vice-President and Biological Secretary.

Summary

- The Royal Society is supportive of the creation of cytoplasmic hybrid embryos by cell nuclear replacement (CNR) into animal eggs for research purposes. This technique will provide a valuable experimental tool and may ultimately lead to therapeutic benefits.
- There is a scientific case for the creation of other human-animal embryos for research purposes.
- More research is essential to address scientific issues regarding chimaera and hybrid embryos and/or stem cells derived from them.
- Placing embryos created through CNR into a woman is prohibited under the Human Reproductive Cloning Act 2001. Whether embryos created through CNR would have the normal potential to develop if replaced into a woman is unknown but unlikely and impossible to determine without further research.

Q1 Do you think creating embryos by cell nuclear replacement (CNR) into animal eggs will be beneficial to research?

The Royal Society is supportive of the creation of cytoplasmic hybrid embryos by cell nuclear replacement (CNR) into animal eggs for research purposes. As defined below, this technique will provide a valuable experimental tool and may ultimately lead to therapeutic benefits.

The proposed technique is one of a number of routes being investigated to overcome the shortage of human eggs available for medical research. Furthermore, if animal eggs from abattoir material were used, this technique could contribute to the reduction of animal use in research. The Royal Society strongly endorses the principle of the three R's which means that every effort must be made: to replace the use of live animals by non-animal alternatives; to reduce the number of animals used in research to the minimum required for meaningful results; and to refine the procedures so that the degree of suffering is kept to a minimum (Royal Society 2006).

Whether the cell nuclear replacement technique will prove to be a viable method of generating stem cells and establishing stem cell lines is not clear at present. However, stem cell research is still in its early stages and it is essential that we do not close off this and other avenues for development given the potential benefit of such work.

Creation of embryos *via* this method will also provide experience in CNR technology using readily available animal eggs. Even if viable CNR stem cells cannot be recovered from cytoplasmic hybrid embryos, technical efficiency and expertise should be improved so that a much smaller number of human eggs could subsequently be used to generate stem cells.

Production of CNR stem cells through this technique would enable investigation of their basic biology. This technique may provide valuable experimental models of reprogramming of gene expression, facilitating further understanding of the mechanisms of reprogramming and of the factors required to establish pluripotency. Research using this technique may subsequently inform the development of alternative methods to derive embryonic stem cells directly from somatic cells, without the need for oocytes or early embryos.

CNR could also provide invaluable models of cellular disease, for example, motor neuron disease, Parkinson's disease, diabetes and Alzheimer's disease.

Q2 The applications that we have received relate to a very specific aspect of 'hybrids and chimaeras' (the creation of cytoplasmic hybrid embryos). Can you think of any reasons why scientists or researchers may wish to create other embryos where there is a mix of human and animal cells or DNA?

There is a scientific case for the creation of other human-animal embryos for research purposes, for example, transgenic and chimaeric embryos.

- Transgenics

There is support for the creation of transgenic animals by introducing certain human genes into animal embryos (non-human transgenic embryos, as defined by Academy of Medical Sciences 2007). This has been standard scientific practice for over 20 years and is an important tool for investigating the function of genes and their mechanisms of regulation. Also, there may be value in inserting one or more human genes, or entire human chromosomes, into animal embryos to produce models of various human genetic diseases, such as Down's Syndrome. There is also a case for the introduction of genes from other species into human embryos for research purposes only (human transgenic embryos, as defined by Academy of Medical Sciences 2007). Such approaches may allow an increase in the efficiency of the derivation of stem cells and also shed light on the molecular control of early patterning and differentiation processes in human embryos.

- Chimaera

The creation of non-human chimaeric embryos by transplanting human embryonic stem cells, or cells derived from them, into animal embryos may prove valuable for testing their developmental potential, safety and efficacy for research purposes and identifying signals that direct the earliest stages of differentiation before contemplating using them therapeutically. Chimaeras made with human cells are also a very valuable way of creating animal models of human disease or animals carrying human characteristics to explore human disease and therapeutic approaches. We are not aware of any current need to introduce animal cells into early human embryos (human chimaeric embryos, as defined by Academy of Medical Sciences 2007), but this approach could still prove of great value and we would not want to rule it out in the future.

- Hybrids

The Royal Society is not currently aware of a scientific need for the creation of true human-animal hybrid embryos (for example, as between a horse and donkey in the creation of a mule). However, in such a rapidly moving field, this situation may change. For example, initiation of hybridisation could be of great value for determining whether chromosomes of human sperm are normal/abnormal.

We have outlined a number of reasons why scientists may wish to create human-animal hybrid and chimaera embryos. As detailed above, this is a rapidly moving field. The Royal Society is therefore supportive of the approach recommended by the House of Commons Science and Technology Committee whereby legislation would allow all types of human-animal chimaera or hybrid embryos to be created for research purposes under licence by the Regulator (House of Commons Science and Technology Select Committee 2007).

Q3 Can you anticipate any biological problems with embryos, or stem cells derived from embryos, created by CNR using animal oocytes that will limit their use in research?

Whether this technique will prove to be a viable method of generating stem cells and establishing stem cell lines is not clear at present. Certainly, it remains to be seen whether a human nucleus can be fully reprogrammed in the cytoplasm of an animal egg.

Potential problems may also arise from non-concordance of the human nuclear genes and the predominantly animal mitochondria. It may well be that the human mitochondria would have a competitive advantage, and would outgrow the animal mitochondria in the course of stem cell derivation and passage, but this can only be ascertained by doing the relevant research. In addition, the possibility of recombination of DNA from human and animal mitochondria to produce mitochondria of mixed genetic constitution has not yet been discounted. It is possible to grow cells in culture conditions where mitochondrial function is not required. Indeed, most embryonic stem cell culture medium supports cells in this way. Given that much of the research will be conducted *in vitro*, this suggests that any problems with mitochondrial function may largely be overcome. However, *in vivo* experiments with the cells (which would include the production of teratoma, a non-malignant tumour consisting of different types of differentiated cells) might be compromised.

Some researchers have suggested that there is the possibility of activation of endogenous animal viruses. If this did occur, it could compromise the value of CNR using animal oocytes.

More research is essential to address these and other scientific issues regarding chimaera and hybrid embryos and/or stem cells derived from them. It is important to note that stem cell research is still in its infancy and it is essential that we do not close off this avenue for development given the potential benefit of such research.

Q4 Are you aware of any data or information that would indicate that embryos created by CNR using animal eggs would not have the normal potential to develop if replaced into a woman? NB: this is banned by the Human Reproductive Cloning Act 2001.

Ultimately, this question can only be answered by carrying out an illegal experiment. However, given the current state of knowledge about cloning, where there has been limited success within species and even less between species to date, it is unlikely that embryos created through CNR have the potential to develop if replaced into a woman. As discussed above, CNR would facilitate understanding of whether an adult human

nucleus can be reprogrammed so as to support normal development on an embryo. Without such research, it is impossible to determine whether such an embryo could survive if replaced into a woman.

Furthermore, for embryos created through CNR to develop if replaced into a woman, it is first necessary for implantation to take place. Successful implantation requires a highly co-ordinated series of cell and tissue interactions and, to date, there has been little success with animal interspecies embryo transfer. For example, mouse into vole and *vice versa* fail at implantation because the embryo and uterine tissues do not recognize one another, whilst interspecific transfers between the more closely related sheep and goat usually implant successfully but fail in mid-gestation for immunological reasons. In normal development, surface proteins of blastocysts are different from those of eggs. Whether implantation would be affected by differential display of animal proteins on the developing embryo and the human host is unknown. There is the possibility that relevant proteins would be replaced by human proteins once transcription of nuclear genes has begun, however, while this is very likely, details with respect to timing and extent are unknown. If implantation was to occur, but there were problems with mitochondrial replication or function it is likely that the embryo would fail at gastrulation stages.

Transfer of such embryos could also pose greater risk in humans than other species since cloned embryos of other species invariably show abnormal placental development and the human placenta is uniquely susceptible to malignancy.

Q5 Do you consider a cytoplasmic hybrid embryo to contain a complete human genome?

This is a linguistic and/or legal question, not a biological one. When the phrase 'human genome' is used, it usually refers to the nuclear genome. If the human mitochondrial genome is intended, it is usually specified as such. The term "complete human genome" could be construed as meaning either a nuclear genome not missing any chromosome or part of a chromosome, or a nuclear plus mitochondrial genome.

References

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