



British Fertility Society

Response to the

Human Fertilisation and Embryology Authority

Public Consultation on

**Hybrids & Chimeras: A Consultation on the ethical,
social implications of creating human/animal
embryos in research**

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This document represents the British Fertility Society (BFS) response to the Human Fertilisation and Embryology Authority Public Consultation “Hybrids & Chimeras: A Consultation on the ethical, social implications of creating human/animal embryos in research”.

The British Fertility Society is a multi-disciplinary organization representing professionals with an interest in reproductive medicine. The objectives of the society are:

- To promote high quality practice in the provision of fertility treatment.
- To provide a common forum for members of various disciplines having an interest in the science and treatment of infertility.
- To promote high quality scientific and clinical research in the causes and treatment of infertility.
- To provide professional leadership in the provision and regulation of infertility services.
- To promote the increase of NHS funding for and equity of access to fertility treatments.

Therefore the use of interspecies embryos in research studies is an important issue for BFS members.

To respond to this consultation, BFS membership were circulated by email and asked to send in their replies using the standard proforma. This response represents the majority view of those who replied and was compiled by Daniel Brison on behalf of the Executive Committee.

It is submitted by the Honorary Secretary whose contact details are:

Dr. Allan Pacey
c/o British Fertility Society Secretariat
22 Apex Court
Woodlands
Bradley Stoke
BS32 4JT

bfs@bioscientifica.com

The society **agrees** to the making its responses publicly available by the HFEA in accordance with the Cabinet Office Code of Practice on Written Consultation. In addition the society will be making this response available on its website (<http://www.fertility.org.uk>).

Hybrids & Chimeras: A Consultation on the ethical, social implications of creating human/animal embryos in research

A. General Questions in Consultation

1) The following types of embryo research are already legally permitted and licensed in the UK. Which of them, in your view, are acceptable?

a) Research using human embryos donated by IVF patients

Yes. The BFS supports research on so-called spare human embryos very strongly on the basis that these embryos would be discarded in any case, and the benefit to society from such research strongly outweighs ethical and moral concerns about the status of the embryo. To the best of our knowledge, no BFS member objects to research on spare human embryos.

b) Research using human embryos created specifically for research from donated eggs and sperm

Yes. The BFS strongly supports the creation of human embryos specifically for research purposes, on the basis that the benefit to society from such research strongly outweighs ethical and moral concerns. We would like to point out that the definition above should also include eggs activated artificially in the absence of sperm to yield a parthenogenetic embryo. Sources of eggs required may be: left over from IVF cycles, donated by patients undergoing IVF treatment (egg sharing for research), or from altruistic egg donors. It is likely that methods will be developed which allow the creation of embryos from eggs collected by non-invasive methods to be matured in vitro before fertilization.

c) Research using cloned human embryos created specifically for research through cell nuclear replacement (CNR)

Yes. Assuming that this category refers only to human nuclei into human eggs, the BFS supports research into human CNR cloning. The only caveat is that expressed in the paragraph above, concerning the ethical sourcing of such eggs. We would like to suggest that further research is carried out into using aged eggs discarded

from IVF cycles for CNR. This has recently been demonstrated to be effective in mouse by Wakayama et al. (2007; Current Biology 17:120-121).

2. Do you think that the HFEA should issue licences to allow research using cytoplasmic hybrid embryos?

Yes. Some BFS members are opposed to the mixing of animal and human embryos for philosophical reasons, while others would accept cytoplasmic hybrids but not true genetic hybrids or chimeras. However the great majority of members support cytoplasmic hybrid research, on the basis that the benefit to society far outweighs any moral/ethical concerns.

However we would like to emphasise our concern that such research must: (1) continue to be tightly regulated, (2) not lead to clinical application (i.e. research only and not been seen as a quick route to the production of human embryonic stem cells for therapeutic use), (3) not lead to replacement of hybrid embryos into a woman and (4) the 14 day time limit for studying such embryos must remain. We also point out that although the cytoplasmic hybrid embryo is >99% human, the remaining animal mitochondrial genes are in fact essential, without that animal contribution the pre-implantation embryo would die. Moreover, egg cytoplasmic proteins (and RNA's?) will regulate expression of the human genes contained in the CNR nucleus, making the early cytoplasmic hybrid embryo functionally animal to a greater degree than simply counting genes would suggest.

We take the view that CNR research in general is important, in order to improve understanding of somatic cell nuclear reprogramming and to generate embryonic stem cells as models of disease. The success rate of CNR in animals is very low, and gives rise to the production of embryos and fetuses with many abnormalities. These problems are well-documented in a recent book by Ian Wilmut and Roger Highfield (After Dolly: the uses and misuses of human cloning' Little Brown; 2006; especially chapter 8). It is therefore important to pursue research into CNR along all avenues in parallel, in animal CNR models, in cytoplasmic hybrids, and using human eggs. However it is the very fact that somatic cell nuclear reprogramming is a complex process which means that cytoplasmic hybrids, while important for

research in this field, are unlikely to yield human embryonic stem cell lines which are sufficiently genetically and epigenetically normal to be used in clinical disease therapy.

We would like to see consideration given by research teams to alternative sources of human eggs, e.g. aged, failed to fertilise from IVF cycles, egg sharing, altruistic donors, when submitting licence applications for cytoplasmic hybrid research. The donation of human eggs would be greatly facilitated by, and in fact requires, the presence of dedicated research nurses as part of the current MRC-funded human embryonic stem cell co-ordinators (hESCCO) group.

3. Do you think that the law should in future permit the creation of true hybrid embryos for licensed research purposes?

Yes, on balance. Some BFS members are opposed to the mixing of human and animal genomes, however, as the consultation document points out, this is common practice as many human genes are expressed in animals. The majority of BFS members would support the creation of true hybrid embryos for genuine scientific research purposes. We do not envisage any application of this work nor justification for allowing it at the moment, but the law must anticipate developments which would make applications in this area likely. The insertion of animal gene sequences into human embryos (defined as a true hybrid in the consultation document) is likely to cause concern among the public and we can see no scientific justification for creating such transgenic embryos at present. However, there might be justification in creating transgenic embryos in which human gene sequences were inserted into human embryos, for example to over-express a particular gene in order to study its function in early development. It is currently not permitted to modify the genome of the human embryo in this manner, but in the future this could be considered, for research purposes only.

4. Do you think that the HFEA should in future issue licences to allow research using human chimera embryos?

Again, yes on balance. We can see no requirement for this and no justification for allowing it at present, but one may well arise and therefore the potential to do this

should be in place. Regulation should be permissive to allow both this and the creation of true hybrid embryos in the future. After all, the law can be repealed if there is significant disquiet at the time.

5. If you have answered yes to questions 2 to 4, what limits do you think should be placed upon human embryo research?

- a) *It is absolutely necessary to retain the time limit of 14 days for all research on human embryos, in order to retain the confidence of the public in this field.*
- b) *It is necessary to absolutely forbid the implantation of CNR, hybrid or chimeric embryos into a woman.*
- c) *The restriction on not modifying the human embryo genome should remain at present.*
- d) *Human embryonic stem cells from CNR, including cytoplasmic hybrids, should not be used for clinical transplantation until such time as they can be shown to be genetically, epigenetically and functionally normal and to not carry a disease risk.*

B. Supplementary Scientific questions

1) Do you think creating embryos by cell nuclear replacement (CNR) into animal eggs will be beneficial to research? Please give reasons for your answer.

Yes. While some BFS members are opposed to the mixing of animal and human embryos for philosophical reasons, the great majority support cytoplasmic hybrid research, on the basis that the benefit to society far outweighs any moral/ethical concerns. Our response to the general consultation contains more detailed discussion of this.

2) The applications that we have received relate to a very specific aspect of 'hybrids and chimeras' (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?

Generally no, the BFS agrees with the views expressed in the consultation document that there is currently no scientific rationale for creating true genetic hybrids or chimeras.

The creation of transgenic human embryos would be useful to study the function of a particular gene during the pre-implantation period, e.g. by over-expression or knockout of the gene. However, we can see no reason why an animal gene sequence would be inserted into a human embryo for this purpose. The only credible scientific study would involve the insertion of human gene sequences into human embryos. It is currently not permitted to modify the genome of the human embryo in this manner, but in the future this could be considered, for research purposes only.

3) 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?

Yes. Somatic cell nuclear reprogramming is highly complex and in some species models works either only very inefficiently, or not at all. Some species animal CNR has a low success rate and gives rise to a high rate of abnormalities. In human CNR success has been extremely limited with only one blastocyst produced to date

as far as we are aware. These problems are certain to be magnified when attempting CNR across species (human nucleus into animal egg). Although this has been reported using rabbit and cow eggs, it is certainly not routinely successful. Problems are likely to arise from: mitochondrial heteroplasmy, epigenetics (incorrect remethylation of the genome) and possibly incorrect activation of the human embryonic genome in response to animal rather than human egg cytoplasmic factors. These problems, plus the risk of animal disease transmission, will mean that ES cells derived from such embryos are unlikely to ever be used in clinical therapies.

We would like to emphasise, however, that these problems are not a reason not to do this research, rather we would argue that this is a reason to pursue animal oocyte CNR, in order to improve its efficiency for use as a research tool and also to further our understanding of somatic cell nuclear reprogramming.

In order to address some of the legal points around whether or not the embryos would be considered to be live human embryos it would be useful for you to address the following two questions.

4) 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.

For the reasons stated in (3) above, such embryos are highly unlikely to have normal developmental potential. There are no data on this to our knowledge, but there may well be data on cytoplasmic hybrids between closely related animal species which would be relevant.

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

No, not unless it also contains human mitochondria. If we can be sure that no human mitochondria are transferred along with the human nucleus, then the cytoplasmic hybrid cannot have a complete human genome as it will be missing the 0.3% of genes which are mitochondrial. If however human mitochondria are transferred along with the nucleus, then the cytoplasmic hybrid will have a complete human genome, at least initially. How long this would persist would

depend on whether or not the human mitochondria survive destruction in the oocyte, and replicate during development. However, even though the human genome would be complete in this eventuality, it would not be exclusively human as there would also be animal mitochondrial genes present.
