HUMAN-ANIMAL COMBINATIONS IN STEM CELL RESEARCH

A REPORT BY
THE BIOETHICS ADVISORY COMMITTEE

SINGAPORE

September 2010

FOREWORD

The use of laboratory animals has long been an essential part of biomedical research. Such use is closely regulated with the aim of ensuring the welfare of the animals, especially in the minimisation of pain or discomfort. Many of the uses of laboratory animals entail some mixing of human and animal biological material. Mouse 'feeder cells' are often used to culture human stem cells for basic research, and genetically modified mice with some human genes have long been valued as disease models for research.

Concerns relating to the humane treatment of animals in laboratory research have long resulted in laboratory research of this nature being closely regulated, yet there has been little or no ethical controversy arising from the fact of human-animal combinations as such. In recent years, however, and especially as a result of research with various kinds of stem cells, including pre-clinical research into stem cell treatment, there has been growing ethical concern over the diversified generation of human-animal combinations. Two directions appear to the BAC to merit attention.

The first of these new directions relates to the possible use of animal eggs and human genetic material to develop what are called 'cytoplasmic hybrids', which are formed when a human cell nucleus is inserted into an animal egg from which the nucleus has been removed. Such cytoplasmic hybrids are an artificial creation for research only. They provide a way to avoid the creation of human embryos for research, but there is clearly a need to limit the development of such entities beyond 14 days (or the appearance of the primitive streak, whichever is earlier) and prevent them from being implanted into a human or an animal. They should only be used as laboratory preparations for research into cell processes.

Another area of interest is human-animal chimeras, which are animal recipients of injected human stem cells. This has been done many times as part of the standard testing of stem cell properties using mice. There is however an increasing prospect that other species will be used in future, in an effort to better approximate the human case. This will be important in the development of therapeutic applications of stem cell research, but it is clearly necessary that such procedures should not risk producing animals with human characteristics.

This Report therefore reviews the scientific basis for research with both cytoplasmic hybrids and human-animal chimeras at various stages of development. The BAC considers these two types of human-animal combination as important for stem cell research in Singapore. It particularly considers the ethical reservations and regulatory installations that such research entails.

I hope this Report and its recommendations will help the development of a regulatory framework that ensures research with human-animal combinations is carried out ethically. I must thank all who have given the BAC their views, which have been helpful in shaping this Report. I would also like to thank the members of the Human Embryo and Chimera Research Working Group that produced this report, for their time and effort.

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September 2010

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About the Bioethics Advisory Committee

The Bioethics Advisory Committee (BAC) was established by the Singapore Cabinet in December 2000 to examine the ethical, legal and social issues arising from research in the biomedical sciences and to develop and recommend policies on these issues. It aims to protect the rights and welfare of individuals, while allowing the biomedical sciences to develop and realise their full potential for the benefit of mankind.

The BAC reports to the Steering Committee on Life Sciences (formerly the Life Sciences Ministerial Committee).

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     Genome Institute of Singapore

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   - *Associate Professor Nuyen Anh Tuan*
     Department of Philosophy, Faculty of Arts and Social Sciences, National University of Singapore

HUMAN-ANIMAL COMBINATIONS IN STEM CELL RESEARCH

EXECUTIVE SUMMARY

1. The term 'human-animal combination' is a broad one, and refers to any kind of living organism in which there is some mixing of human and animal material. Genes, cells or tissues from humans may be incorporated into animals (and *vice versa*) for the purposes of treatment or research. Although human-animal combinations have been used for several decades in biomedical research, their use has diversified significantly in recent years, especially in the field of stem cell research.

2. Human eggs are required to create embryos, from which stem cells can be derived for research. To overcome the shortage of human eggs, some scientists have started using animal eggs, which are more readily available. They have created embryo-like entities called *cytoplasmic hybrids* by injecting the nuclei of cells from the human body into enucleated animal eggs. Disease-specific or patient-specific stem cells can then be derived from these hybrids to study nuclear reprogramming and to understand genetic diseases. Cytoplasmic hybrids are thus useful tools for gaining a better understanding of stem cells and their possible clinical applications. Another alternative solution to overcome the shortage of human eggs and the controversial creation and use of human embryos for research, is to use induced pluripotent stem cells, which are created using adult body cells and require no eggs or embryos.

3. Besides cytoplasmic hybrids, researchers have also produced *animal chimeras* by injecting human stem cells into animals, to study stem cell biology as well as to find new and more effective ways to treat diseases. As the animals used are at various stages of development, from embryos to fully developed animals, and may be non-human primates (i.e. monkeys or apes), ethical concerns have arisen. Research involving the introduction of human stem cells into the nervous system of animals is a particular concern, as there is uncertainty over the extent of human contribution to the resulting animal's characteristics. Concerns have been expressed that living creatures with both human and animal

features, in particular animals with human consciousness or mental characteristics, might be created.

4. With increasing ethical debate on this subject internationally, the BAC formed a working group in 2006, to consider in detail and with respect to Singapore, the ethical, legal and social issues that arise from such research. Various types of human-animal combinations that have been created for research were studied, together with the scientific rationale behind such creations. The ethical issues and regulatory policies on such research in the major scientific jurisdictions were also examined.

5. Because this is a sensitive and complex subject with a wide range of views, a public consultation was conducted between January and March 2008 to ascertain and understand any concerns of the Singapore public. Stem cell scientists working in Singapore were also consulted, as were the BAC's International Panel of Experts. In addition, two public meetings were held, and the BAC also met research ethics committee members, representatives of regulatory bodies and leaders of religious groups.

6. This Report considers the scientific basis for research with human-animal combinations, and outlines the ethical, legal and social issues arising from such research. It also describes the public consultation process conducted by the BAC on this subject and includes the written responses received. The Report focuses on cytoplasmic hybrids, and animal chimeras in which human stem cells have been introduced at various stages of development. The BAC considers these two main types of human-animal combination to be of potential scientific value and likely to be important to Singapore now or in the near future. Other possible types of human-animal combination would require more specific and detailed evaluation.

7. The Report concludes that cytoplasmic hybrids and animal chimeras as described above should be allowed on grounds of scientific merit, provided a regulatory framework is in place, and ethical requirements or limits are properly observed. Five recommendations consistent with current international practices and guidelines have been proposed to ensure that there is adequate and proper oversight, and to allay any fear that undesired living creatures may be created.

LIST OF RECOMMENDATIONS

Recommendation 1
A single national body, which must include lay members of the public, should be established to review and monitor all stem cell research involving human pluripotent stem cells or human-animal combinations conducted in Singapore. This body should also be empowered to determine the kinds of research that need not undergo its review.

Recommendation 2
The creation of cytoplasmic hybrid embryos should be permitted only where there is strong scientific merit in, and potential medical benefit from, such research. These embryos should not be allowed to develop beyond 14 days or the appearance of the primitive streak, whichever is earlier, nor be implanted into any human or animal uterus.

Recommendation 3
Where human embryonic stem cells, induced pluripotent stem cells, or any other kind of pluripotent stem cells are introduced into non-human animals at any stage of development, particular attention should be paid to the need to avoid the creation of entities in which human sentience or consciousness might be expected to occur.

Recommendation 4
Animals into which human embryonic stem cells, induced pluripotent stem cells, or any other kind of pluripotent stem cells have been introduced should not be allowed to breed.

Recommendation 5
No clinical or research personnel should be under a duty to conduct or assist in stem cell research involving human-animal combinations, to which they have a conscientious objection.

HUMAN-ANIMAL COMBINATIONS IN STEM CELL RESEARCH

I. Introduction

1.1 In 2002, the Bioethics Advisory Committee (BAC) published a report on the ethical, legal and social issues in human cloning and stem cell research.[1] This report established an ethical framework for human stem cell research, including the derivation of embryonic stem cells through the process of somatic cell[2] nuclear transfer (SCNT).[3] Under this framework, existing embryos or embryos created by SCNT could be used to derive stem cells, provided the embryos were less than 14 days old, and such research was carefully regulated.

1.2 Stem cell research has advanced significantly in recent years, and evaluation of therapies based on stem cells is beginning to occur. The BAC has already considered the issues related to the donation of human eggs (required in SCNT) for research, and published its recommendations in a report in 2008.[4] Given the difficulties in obtaining human eggs for research and their limited availability, some scientists have started using animal eggs as an alternative means of deriving stem cells. As part of stem cell research, scientists also introduce human stem cells into animals, animal embryos or animal foetuses to study the nature and potential of these cells. In the present Report, the BAC considers the issues related to human-animal combinations used in stem cell research.

1.3 The term 'human-animal combination' is a broad one, and refers to any kind of living organism in which there is some mixing of human and animal material. Although certain types of human-animal combination have been used for several decades in biomedical research, for example human-mouse chimeras have been used in the production of monoclonal antibodies of the kind administered in cancer therapy, their use has increased significantly in recent years, especially in the field of stem cell research, and new types of combination are also being envisaged. As animals at various stages of development, from embryos to fully developed animals, are used for research, and as they may be non-human primates, ethical concerns have arisen. Where human stem cells are introduced into the nervous system of animals, uncertainty over the extent of human contribution to the resulting animal's behaviour has contributed to a concern that living creatures with both human and animal features, in particular animals with human consciousness or mental characteristics, might be created.

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1 Bioethics Advisory Committee, Singapore. *Ethical, Legal and Social Issues in Human Stem Cell Research, Reproductive and Therapeutic Cloning*. 2002.

2 A somatic cell is any mature (or differentiated) cell in the body that is not a sperm or an egg.

3 SCNT, also referred to as therapeutic cloning or research cloning, involves the transfer of the nucleus of a somatic cell into an egg from which the nucleus has been removed.

4 Bioethics Advisory Committee, Singapore. *Donation of Human Eggs for Research*. 2008.

1.4 The increasing ethical debate on this subject internationally led the BAC to form a working group in 2006, to consider in detail and with respect to Singapore, the ethical, legal and social issues that arise from such research. Various types of human-animal combinations that have been created for research, together with the scientific rationale behind such creations were studied, and the ethical issues and regulatory policies in the major scientific jurisdictions were examined. The BAC also sought the views of its International Panel of Experts. In addition two background submissions on this subject were received and are provided at Annex E.

1.5 A public consultation was conducted between 8 January and 10 March 2008, to ascertain and understand the concerns of the Singaporean public. Seventy-one research, governmental and healthcare institutions, and professional and religious organisations were invited to give their comments on a Consultation Paper entitled "Human-Animal Combinations for Biomedical Research". The Consultation Paper is provided in Annex A and the distribution list in Annex B. Members of the public were invited to give their views via email or the REACH[5] e-Consultation Paper portal, and to participate in a discussion forum on the REACH website. The written responses received, together with a summary of the responses from the REACH e-Consultation and Online Discussion Forum are set out in Annexes C and D respectively. The BAC also conducted a survey of stem cell researchers and met representatives of the stem cell research community, regulatory bodies, leaders of religious groups and institutional review board (IRB) members to obtain their views. In addition, two public fora were held on 19 January 2008 and 16 August 2008.

1.6 The objectives of this Report are:

(a) to consider the ethical, legal and social issues arising from the use of human-animal combinations in stem cell research, and review best practice that has been adopted in major scientific jurisdictions;

(b) to dispel some misconceptions and address concerns about research using human-animal combinations as revealed in the consultations; and

(c) to make recommendations for the conduct of stem cell research involving human-animal combinations in Singapore.

1.7 The Report focuses on the following two types of human-animal combinations that the BAC considers as important for stem cell research in Singapore:

(a) *Animal chimeras* in which human stem cells have been introduced into animals at various stages of development, from embryo to adult; and

[5] REACH (Reaching Everyone for Active Citizenry @ Home) was set up by the Feedback Unit in 2006 to engage and reach out to as many Singaporean and permanent residents as possible to develop and promote an active citizenry through citizen participation and involvement.

(b) *Cytoplasmic hybrid embryos* in which human somatic cell nuclei are combined with enucleated animal eggs.[6]

1.8 Other possible types of human-animal combination are either not of scientific interest (e.g. true hybrids created by fusing human gametes with that of a different species) or would require a more specific and detailed evaluation (e.g. transgenic non-human primates[7]). This Report does not extend to consideration of these or other more speculative combinations.

1.9 The Report considers the basic science and potential value of these two types of human-animal combinations, of research using them, and the discussions and conclusions of other major jurisdictions. It reviews the ethical principles that the BAC has followed in its recommendations since its first report in 2002, and applies them to make recommendations regarding stem cell research that involves human-animal combinations. These recommendations were made after reviewing the scientific literature, international and national policies on stem cell research and human-animal combinations, and careful consideration of feedback received from the public consultations.

6 An enucleated egg is one from which the nucleus has been removed.

7 A transgenic animal is an animal whose genome contains genes from another species. Transgenic mice with human genes are frequently used in laboratory research.

II. Background Information

Chimeras and Hybrids

2.1 Genes, cells or tissues from humans may be incorporated into animals (and *vice versa*) for the purposes of treatment or research. The term 'human-animal combination' is a general term used to describe any instance of living combinations of human and animal tissue, cells, or genetic material. There is a wide range of possible combinations, some of which are of no foreseeable value for research, while others have already been in use for some time without raising ethical concerns.

2.2 The terms 'chimera' and 'hybrid' have been used to describe certain inter-species combinations. Traditionally, chimeras are imaginary creatures made up of parts from two or more different species, e.g. a Centaur, with the body of a horse and a human head and torso, or the original Chimera of Greek mythology, a fire-breathing monster with a lion's head, a goat's body and a serpent's tail. The Merlion, familiar to Singaporeans, is another example of a chimera. Hybrids, on the other hand, are the result of a mating between two different species. Whether chimeras or hybrids, inter-species combinations with humans might be viewed with much apprehension if thought of in these terms. However, such creatures are not what scientists are planning to create for research or have used in research.

2.3 Scientifically, a *chimera* is an organism whose body contains cells from another organism of the same or a different species. As such, a person whose diseased heart valve has been replaced with a pig heart valve (a xenotransplant) is a chimera. Even a person who has undergone a blood transfusion or any kind of human organ transplant is by definition a chimera, as his or her body would contain cells from the donor. This Report will not be considering such chimeras because they are consequences of already established clinical treatments. Ethical concerns in xenotransplants generally are related to clinical effectiveness and safety concerns, such as the prevention of cross-species infections. This Report will only consider those chimeras specifically created by the transplantation of human stem cells into non-human animals, animal foetuses or animal embryos.

2.4 A *hybrid* is an organism whose cells contain genetic material from organisms of different species. A *true hybrid* is an organism that results from the fertilisation of an egg from one species by a sperm from another species. Any cell of such an organism would contain genetic material from both species. The mule, which is the offspring of a horse and a donkey, and the liger, which is a cross between a lion and a tiger, are examples of true hybrids. True hybrids can be produced only when the species are genetically similar, and such hybrids are usually infertile. True human-animal hybrids of this kind have not been contemplated

for research, as they would patently be unethical, nor do they appear to offer unique answers to questions of sufficient importance to warrant research on hybrid embryos *in vitro*.

Cytoplasmic Hybrid Embryos

2.5 Scientists are, however, interested in creating another kind of hybrid, called a *cytoplasmic hybrid embryo*, for the purpose of deriving stem cells. Using SCNT technology to overcome the shortage of human eggs, some scientists have combined enucleated animal eggs with the nuclei of human somatic cells to create embryo-like entities called cytoplasmic hybrid embryos, from which stem cells can be derived. A cytoplasmic hybrid embryo is considered a 'hybrid' because its genetic material, though more than 99% human, originated from two species – human and animal. The human component comes from the nucleus of the human somatic cell and the animal component comes from the mitochondria,[8] present in the cytoplasm,[9] of the animal egg. Figure 1 shows how a cytoplasmic hybrid embryo is created.

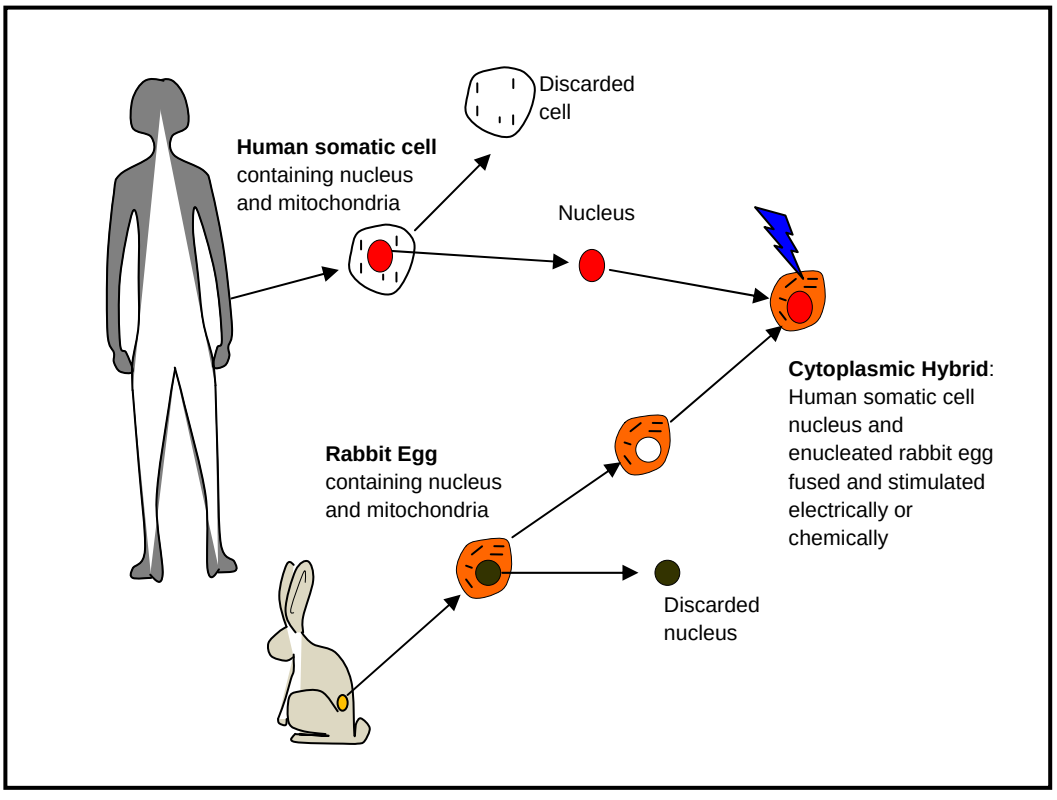

Figure 1. The creation of a cytoplasmic hybrid embryo by SCNT

8 Mitochondria are minute structures in the cytoplasm of a cell that produce energy and contain some genetic material.

9 Cytoplasm is the cellular substance outside the nucleus.

2.6 Cytoplasmic hybrid embryos can be used to study nuclear reprogramming,[10] which may lead to finding methods of direct reprogramming that do not involve the use of human eggs or the need to create human embryos. Cytoplasmic hybrid embryos can also be used to derive disease-specific stem cells or patient-specific stem cells, as stem cells derived from cytoplasmic hybrid embryos created using somatic cells from a patient with a specific genetic disorder would carry the genes responsible for that disorder (disease-specific stem cells). They would thus be useful for studying such disorders. Understanding the development and progression of the disorder may lead to the discovery of better treatments or ways to reverse or prevent further progression of the condition. As these stem cells are also genetically identical to the patient (patient-specific stem cells), they may help overcome the problem of tissue rejection when used for therapy, although other therapeutic problems, such as safety issues, will need to be addressed as well.

2.7 In 2003, a team of researchers from China reported deriving stem cells with many properties of human embryonic stem cells from cytoplasmic hybrid embryos created by the transfer of human somatic cell nuclei into enucleated rabbit eggs.[11] In 2008, the UK Human Fertilisation and Embryology Authority (HFEA) granted licences to three research teams to create cytoplasmic hybrid embryos. The team from the University of Newcastle had created 270 cytoplasmic hybrid embryos by introducing human somatic nuclear material into enucleated cow eggs.[12] They attributed the success to the large number (200) of cow eggs available per day compared to the number (10) of human eggs available per month. However, the embryos stopped growing at the 32 cell-stage. Another team, from King's College London, planned to derive disease-specific stem cell lines from cytoplasmic hybrid embryos using eggs from domestic livestock species (e.g. cows, rabbits, sheep and goats) to study neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Spinal Muscular Atrophy. The third team, from the University of Warwick, planned to create human-pig embryos to study heart diseases.

2.8 Some researchers have shown that human somatic cells are not fully reprogrammed when animal eggs are used to create cytoplasmic hybrid embryos. Although their findings suggest that it may not be practicable to produce patient-specific stem cells using cytoplasmic hybrid embryos,[13] more research is required before any definitive conclusions can be made on the usefulness of such embryos for clinical purposes.

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10 Nuclear reprogramming is the process whereby the nucleus of a somatic cell is transformed to acquire the characteristics and potential of an embryonic cell nucleus.

11 Chen Y *et al.* Embryonic stem cells generated by nuclear transfer of human somatic nuclei into rabbit oocytes. *Cell Research*. 13 (2003): 251-263.

12 Newcastle University. *Hybrid embryos statement*, Press Release. UK, 1 Apr 2008; BioNews. *UK team creates human hybrid embryos.* UK, 7 April 2008; and BioNews. *Human/animal hybrid embryos are 'easy' to make.* UK, 23 June 2008.

13 Chung Y *et al.* Reprogramming of Human Somatic Cells Using Human and Animal Oocytes. *Cloning and Stem Cells.* 11 (2009): 213-223.

2.9 Following recent reports of success in deriving pluripotent cells[14] from human somatic cells, some people have questioned the need to create cytoplasmic hybrid embryos for the purpose of obtaining pluripotent stem cells. Several research groups have demonstrated that human skin cells can be transformed into cells with properties similar to that of embryonic stem cells through the introduction of specific genes into the skin cells.[15] The transformed cells are called induced pluripotent stem (iPS) cells. The technology avoids the controversial use of human eggs and embryos, and could lead to the creation of patient-specific and disease-specific stem cells. However, the differences between iPS cells and other pluripotent cells remain to be clarified, and continuing to work on multiple fronts is a sound approach. The BAC feels that it would be premature to assume that iPS cell technology can replace SCNT in producing disease-specific and patient-specific cells.

Animal Chimeras

2.10 Researchers have produced animal chimeras by injecting human stem cells, including embryonic stem cells, into animals at various stages of development, for one or more of the following reasons:

a. to study stem cell integration and differentiation;

b. to test the developmental potential of human stem cells or their derivatives;

c. to evaluate the potential usefulness and safety of transplanting human stem cells for clinical treatment; or

d. to study the possibility of growing human tissues and organs in animals for transplantation into humans.

2.11 Animal chimeras can be used to study stem cell integration and differentiation. A team of American and Japanese researchers reported in 2005 that mice with brains containing less than 0.1 percent of human brain cells had been created by implanting human embryonic stem cells into the brains of embryonic mice.[16] The results revealed that the stem cells developed into cells with the form, structure and characteristics of mouse brain cells, and functioned accordingly. In other words, the human embryonic stem cells differentiated into brain cells, which integrated into the mouse brains physically and functionally.

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14 Pluripotent cells are unspecialised cells capable of differentiating into the range of specialised cells that make up the various tissues and organs of the body.

15 Takahashi K *et al.* Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors. *Cell*. 131 (2007): 1-12; and Yu J *et al*. Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells. *Science*. 318 (2007): 1917-1920.

16 Muotri AR *et al.* Development of functional human embryonic stem cell-derived neurons in mouse brain. *Proceedings of the National Academy of Sciences of the United States of America*. 102 (2005): 18644-18648.

2.12 Animal chimeras are routinely created in the laboratory when human cells are introduced into immune-deficient mice to ascertain the pluripotency of the injected cells. Creating such animal chimeras is common practice, and does not raise significant ethical concerns, as the risk of these animals developing human function or capability is non-existent.

2.13 Scientists also create animal chimeras to test the therapeutic potential of stem cells. For instance, scientists have used adult stem cells from human umbilical cord blood to test their effects on rat disease models, and in the process created animal chimeras. Such research has demonstrated the therapeutic potential of cord blood stem cells in healing neurological defects in rats with spinal cord injury[17] and neurological deficits in rat models of stroke.[18] In another example, rats with induced heart failure showed improved heart function when heart cells derived from human embryonic stem cells were transplanted into them.[19] These demonstrations of the therapeutic effects of human stem cells and their derivatives in animals are important, and required, before these cells may be considered for human therapy. In addition, it is necessary to test the cells for efficacy and any adverse effects in animals prior to testing them in humans. The rationale is similar to that of pre-clinical testing of a drug or a medical device before clinical trials in humans.

2.14 As earlier mentioned, the essential concept of xenotransplantation is not seen as ethically controversial and is not addressed in this report. However, the creation of organs from human stem cells in an animal for the purpose of transplantation, is a matter that does require consideration. There is always a shortage of human tissues and organs to replace diseased and damaged ones, and researchers are attempting to create or grow them using various methods, including trying to grow them in animals. They have tried transplanting human stem cells into animal embryos and foetuses, in the hope of growing human cells and tissues for transplantation. Fully-grown chimeric sheep with organs that are about 15 percent human were created by researchers at the University of Nevada in the USA. These chimeric sheep were created by implanting human adult stem cells into sheep foetuses.[20] The researchers hoped to use such sheep as a way of developing 'humanised' sheep organs that may one day be used for transplantation into patients.

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17 Saporta S *et al.* Human umbilical cord blood stem cells infusion in spinal cord injury: engraftment and beneficial influence on behavior. *Journal of Hematotherapy & Stem Cell Research*. 12 (2003): 271-278.

18 Xiao J *et al.* Transplantation of a novel cell line population of umbilical cord blood stem cells ameliorates neurological deficits associated with ischemic brain injury. *Stem Cells and Development*. 14 (2005): 722-733.

19 Laflamme MA *et al.* Cardiomyocytes derived from human embryonic stem cells in pro-survival factors enhance function of infarcted rat hearts. *Nature Biotechnology*. 25 (2007): 1015-1024.

20 Almeida-Porada G *et al.* Formation of human hepatocytes by human hematopoietic stem cells in sheep. *Blood*. 104 (2004): 2582-2590.

2.15 In 2005, a team of Japanese researchers showed that human stem cells from the bone marrow, when placed in a rat embryo, integrated into the developing rat kidney.[21] The integrated cells were shown to have differentiated into complex functional kidney structures. Some researchers have suggested that tissue destined for a specific person might be grown in an animal foetus from stem cells obtained by SCNT, using the nucleus of a somatic cell from that person. Such stem cells would be compatible with the person, thus avoiding the problem of tissue rejection when used for treatment, and the animal would be a means of growing the human organ. The animal is a chimera in consequence of its status as host to the human stem cells and subsequent differentiated cells and tissues. This scenario is shown in Figure 2 below. However, producing chimera-based patient-specific tissues or organs that are safe for transplantation into humans is still in its preliminary stage and much more research has to be done.

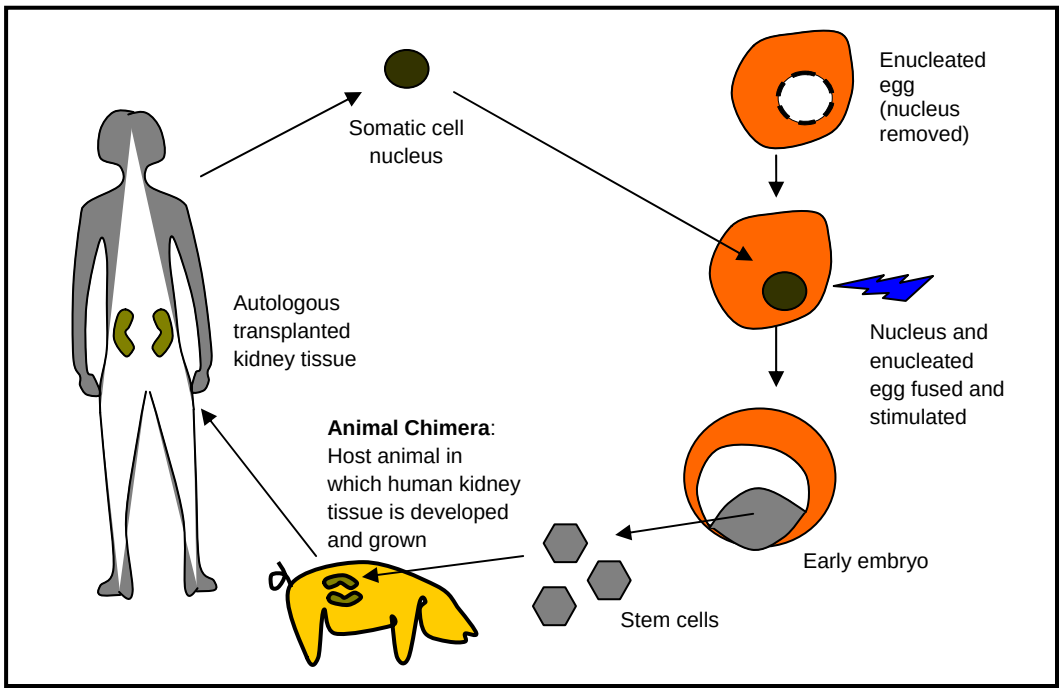

Figure 2. Schematic possible use of an animal host in the growth of organs (e.g. kidneys) derived from cloned human stem cells by SCNT.[22]

[21] Yokoo T *et al.* Human mesenchymal stem cells in rodent whole-embryo culture are re-programmed to contribute to kidney tissues. *Proceedings of the National Academy of Sciences of the United States of America*. 102 (2005): 3296–3300.

[22] Adapted from Cascalho M and Platt JL. New Technologies for Organ Replacement and Augmentation. *Mayo Clinic Proceedings*. 80 (2005): 370-378.

III. Ethical and Social Considerations

General Ethical Principles

3.1 The BAC has observed the following ethical principles in its various reports:

(a) *Respect for individuals*. The autonomy of individuals is to be respected, and they or their interests protected, even if their ability to exercise their autonomy is impaired or lacking. This principle justifies the importance of informed consent, respect for privacy, safeguarding confidentiality, and it is the foundation of a proper regard for religious and cultural diversity. It is also the basis for the protection of vulnerable persons from exploitation and for ensuring that their interests are properly represented in any proposed research participation involving them;

(b) *Reciprocity*. The BAC has interpreted the idea of reciprocity to refer to the mutual obligation that regulates the relationship between the individual and the society, resulting in the need for a balance to be struck between the public interest and the rights of individuals;

(c) *Proportionality*. The regulation, and implicitly the restriction, of research should be in proportion to the possible threats to autonomy, welfare or public good incurred. Proper regulation needs to be exercised in research that does pose real risks, but on the other hand, research should not, in general, be treated as if it were something to be guarded against;

(d) *Justice.* The idea of justice as applied to research implies that access to the benefits of publicly funded research, and the burden of supporting it, should be equitably shared in society; and

(e) *Sustainability*. The research process and outcome should be sustainable, in the sense that it should not jeopardise or prejudice the welfare of later generations.

The BAC's Position on Human Embryonic Stem Cell Research

3.2 The BAC has previously considered arguments for human embryonic stem cell research, and the creation or sacrifice of embryos in that connection. We summarise our position as follows, since it is relevant to considering our views on the ethics of human-animal combinations in research:

(a) The BAC accepts that a human embryo has a unique potential for development, but feels that it is not of the same moral status as a living child or adult. Its future individual interest need not always prevail to

prevent potential benefits of stem cell research through the use of human embryonic stem cells. Consequently, the BAC does not feel the potential interests of insentient (or pre-sentient) embryos can properly enjoy a relation of equality with the actual interests of sentient persons;

(b) Sacrificing a human embryo may be acceptable if it offers a prospect of furthering research that would eventually yield medical benefits, and especially if the embryo is not destined for fertility treatment and has thus no prospect of implantation and development; and

(c) The BAC also recommended allowing cloned human embryos for desirable research, but with stringent regulation to avoid the possibility of cloning technology being used for reproduction. Human reproductive cloning was made illegal in Singapore in 2004.[23]

Human-Animal Combinations - Considerations Arising from the Views of the Public

Public Reaction in Singapore

3.3 The BAC consultations revealed various concerns about human-animal combinations. Opposition to the creation of human-animal combinations came from those concerned that such combinations would not be confined to a laboratory environment, and from many with religious concerns. Of four religious bodies that responded, all except MUIS[24] (the Islamic Religious Council of Singapore), were either opposed to or offered very limited support for human-animal combinations. MUIS did not object in principle, provided a number of regulatory provisions to avoid possible harms were in place. In addition, not all scientists expressed support for the creation and use of cytoplasmic hybrids, due to concern over feasibility and lack of justification. iPS cell technology was proposed by a number of respondents as a viable alternative, although most respondents also agreed with the BAC's view that a multi-fronted approach is preferable. A relatively large number of respondents did not explicitly express either support for or opposition to the research. Those respondents who gave support to the research, did so only if certain requirements could be met. Many highlighted the importance of an effective legal and/or ethical regulatory regime. They often expressed concerns relating to safety, public acceptance, the suitability of the animals used, and the effectiveness of controls.

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23 Singapore. *Human Cloning and Other Prohibited Practices Act* (Chapter 131B). Revised 2005. See Section 5.

24 Majlis Ugama Islam Singapura.

3.4 Respondents raising objections variously mentioned an eroding of the moral boundary between human and animal, the violation of human dignity and the concern with producing creatures with both human and animal features, or creatures with human consciousness or mental characteristics. In some cases, there were misconceptions that scientists are trying to create undesirable live creatures with mixed human and animal characteristics. These are valid concerns, which the BAC seeks to address in this Report.

Public Reaction in Other Countries

3.5 Apart from Singapore, Denmark, Germany, New Zealand and the UK have systematically engaged with their citizenry in dialogue on the subject. Of these countries, the UK seems to have the longest history of public engagement, mainly focused on cytoplasmic hybrid embryos. In the UK, human-animal combinations in research became a public issue when a Department of Health expert advisory group in 2000 recommended that the creation of cytoplasmic hybrid embryos should be prohibited.[25] However, from the various polls and public consultations conducted subsequently, it was observed that on the whole, support for such research tended to be higher when a possible benefit could be seen, and lower otherwise.[26] In 2008, the concerted effort of scientific bodies and medical charities in the UK culminated in the passage through Parliament of comprehensive legislation allowing and regulating human-animal embryos.[27]

3.6 On 5 November 2008, the Danish Council of Ethics, the Danish Ethical Council for Animals and the Nordic Committee on Bioethics for the Parliamentary Committee on the Council of Ethics and the Health Committee organised a conference entitled "Chimera Research – Ethical and Legal Aspects" at the request of Parliamentary Committees. The intent was to gather public reaction on a report on chimera research jointly published by the Danish Council of Ethics and the Danish Ethical Council for Animals in 2007.[28] In that report, both councils concluded that there were no convincing arguments to prohibit chimera research completely, but they agreed that clear limits on such research should be drawn up. Politicians were urged to take legislative steps to prevent the creation of chimeras that are difficult to identify as human or as animal biologically, ethically or legally. The conference was also intended to enable a debate on the ways in which legislation could be adjusted to take into account the latest research into chimeras and hybrids.

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25 Department of Health, UK. *Stem cell research: medical progress with responsibility.* June 2000. See Recommendation 6, at page 47.

26 Jones DA. What does the British public think about human-animal hybrid embryos? *Journal of Medical Ethics.* 35 (2009): 168-170, at page 169.

27 The *Human Fertilisation and Embryology Act 2008* received Royal Assent on 13 November 2008.

28 Danish Council of Ethics and the Danish Ethical Council for Animals. *Man or Mouse? Ethical aspects of chimera research*. 2007.

3.7 The Bioethics Council of New Zealand conducted public consultations in 2004 on the use of human genes in other organisms. The Council reported opposition to genetic modifications that would risk conferring on animals the capacity for human language and associated powers of reason, or that would cause animals to look human.[29] This objection surfaced in the UK and Denmark as well, and appears to reflect the recurrent issue of most concern that surfaces whenever human-animal combinations are mooted.

3.8 More recently, the German Ethics Council held a public hearing on 25 February 2010 to gather feedback on the creation of human-animal entities in research. Experts from the US, the UK and Austria spoke at the public event, and interested members of the public were invited to express their views on the creation of such entities through a written survey. The working group of the German Ethics Council responsible for drafting an opinion on the subject will deliberate further on how far qualitative modification of an animal's characteristics and behaviour is permissible.[30]

Ethical Considerations Specific to Human-Animal Combinations

3.9 The issues raised by the public, and considered by bioethicists and the various bodies concerned with the oversight of research, are not confined to research with human embryonic stem cells. They apply also to adult stem cells and iPS cells, because these cells will almost certainly require testing with animals before they can be used clinically, or to answer certain questions about the nature of cellular differentiation. It is unavoidable that stem cells intended for therapeutic use will need to be tested, as well as researched, by the injection of these cells into animals. Such tests are likely to be necessary components of cell therapy research, where animal models and trials are needed before clinical interventions with humans are properly contemplated, just as in the normal development of drug treatments. Below is a systematic consideration of the various issues and objections that appear salient.

Repugnance

3.10 Many people express repugnance or disgust at the idea of human-animal combinations, as human and animal tissues are not normally thought of as something that can or should be mixed. It is seen as unnatural. The idea of combining human and animal tissues or cellular components whether as cytoplasmic hybrid embryos or as animal chimeras, can raise disquiet, or even repugnance. Some of this repugnance may derive from strong social taboos on the idea of sexual intercourse with animals, or other forms of bodily intimacy. Although some animals enjoy a privileged status as pets, most do not, and we

[29] Bioethics Council, New Zealand. *The Cultural, Ethical and Spiritual Dimensions of the Use of Human Genes in Other Organisms*. 2004.

[30] German Ethics Council. *The German Ethics Council invites international experts to a hearing on human-animal mixed-species entities*, Press Release. 26 February 2010.

are usually careful to observe hygiene precautions in handling or dealing with animals. Some, such as rats or cockroaches are considered vermin, either because they carry disease, or because they are destructive. Some religions have constraints on the eating of animals deemed unclean, and a few discourage the eating of meat entirely.

3.11 Some bioethicists have argued that natural feelings of repugnance should be taken as a reliable guide to ethics, and that we should not presume to disregard them.[31] Others take the view that it risks a fallacy to assume that natural feelings are always a sound guide to the ethics of actions, because feelings do change on many issues and can be a product of custom and practice.[32] This does not, of course, render feelings unimportant or irrelevant, but it does mean that they cannot be taken as fixed or infallible guides to ethical practice.

3.12 The BAC's position is that while feelings of repugnance cannot be ignored, the process of paying heed to them should involve an evaluation of actual likely harms and benefits. A sense of repugnance in itself is not a sufficient reason to prohibit research – there needs to be good reason for the repugnance. A general appeal to repugnance or the wisdom of nature would exclude viable treatments such as vaccination or the use of transgenic or other animals in routine laboratory tests relevant to disease research and prevention. Attitudes change over time, and feelings alone are not a sufficient basis for a long term view of what ought to be allowed.

Slippery Slope Arguments

3.13 A concern is sometimes expressed that research with human-animal combinations risks a 'slippery slope' that will open the way to unacceptable research or applications. This was a major reason for public concern over the possibility of human reproductive cloning occurring in the context of reproductive or research cloning using SCNT.

3.14 The BAC's view is that cases should be considered on their merits, and any danger of this kind should be considered when a case is reviewed. Just as with cloning technology, human-animal combinations do not appear to create risks that cannot be removed by proper regulation and, if necessary, legal prohibition.

Human Dignity - Maintaining a distinction between humans and animals

3.15 There is and should be no intention, in research, to try and produce animals that have been rendered human in some important and essential mental or existential characteristic. Human consciousness is the most fundamental of such

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31 See e.g. Kass LR. The Wisdom of Repugnance. *New Republic*. 216 (1997): 17-26.

32 See e.g. Harris J. *Enhancing Evolution: The Ethical Case for Making Better People*. Princeton: Princeton University Press, 2007, pages 129-131; and the background submission by Nuyen Anh Tuan entitled *Stem Cell Research and Interspecies Fusion* (Annex E2).

characteristics. The BAC is of the view that acceptable research must preclude procedures that risk this consequence, and should certainly never have it as an explicit aim. The BAC has no hesitation in accepting the need to prohibit the creation of any animal with human mental attributes, while at the same time not rejecting, without good reason, research that does not risk such an outcome.

The Risk of Hubris and 'Playing God'

3.16 The expression 'playing God' is often heard in connection with research or practice at the boundaries of medicine, and the exact meaning to be read into it may depend on the speaker. Religious critics may mean by it that interference with the process of creating life is interference with divine prerogative. In its secular form, this criticism can imply that we may suffer from scientific or ethical hubris, a pride in power that blinds us to limitations or unforeseen risks, and leads us as a society or as individuals to undertake things that wiser and more modest counsel might not have led us to.

3.17 Such concerns are not to be lightly dismissed, but they are not without answers. Whatever we do will affect the future. Future generations are inevitably affected by what we do now. It is also 'playing God' if we prohibit research that might help patients. The problem of slippery slopes, hubris, and other ethical concerns discussed above cannot be lightly dismissed. They arguably present a powerful case for ethical and legal regulation. Regulation is an assurance that change will be introduced without abrupt and radical challenge to the fundamental values, beliefs and practices that underlie society, and only when the key ethical issues arising from research involving human-animal combinations have been considered in each case.

The Possibility of Creating Humanised Animals

3.18 Most of the concerns just discussed are related to the possibility of allowing actual independent living entities to develop from human-animal combinations. It seems to the BAC that the main ethical hazard lies in the possibility of inadvertently creating an animal with human characteristics, especially mental attributes. In this sense, we could call such an animal humanised. In particular, whenever considering the use of animals into which human stem cells could be introduced, there are a number of relevant considerations. These can be seen most clearly in the specific case of human neural stem cells grafted into the brains of non-human primate foetuses[33], which offers an in-principle possibility of a degree of humanisation of the resulting brain. In this case, six relevant factors have been suggested[34] for the guidance of ethics committees, namely:

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33 Ourednik V *et al.* Segregation of Human Neural Stem Cells in the Developing Primate Forebrain. *Science*. 293 (2001): 1820-1824.

34 Greene M *et al.* Moral Issues of Human-Non-Human Primate Neural Grafting. *Science*. 309 (2005): 385-386.

(a) *The proportion or ratio of human to animal cells in the animal's brain*: When the amount of human material is low, the likelihood of the animal acquiring something like human awareness as a result is correspondingly remote;

(b) *The age of the animal*: The earlier in development, the greater the likely integration of transplanted cells, so human cells transplanted into animal embryos will probably result in greater likelihood of humanisation of the host animal's brain;

(c) *The recipient species*: Species with a closer approximation to human neural organisation are more problematic, because the likelihood of human attributes occurring in another species is increased when the other species is biologically close;

(d) *The brain size of the animal involved*: It is reasonable to suppose that animals with larger brains are more likely to be capable of an approximation to human consciousness in the event that they incorporate human neural cells;

(e) *The site of integration of the human neural cells*: Integration into the parts of the brain which control cognitive functions, is more likely to affect cognitive abilities than integration into other parts of the brain; and

(f) *The presence of pathologies in the host animal*: It is possible that the humanising effect of transplanted human stem cells in an animal with a pathological condition might be greater than would be the case in a robust healthy organism. This is relevant if animal models of disease processes are used as a basis for trial approaches to treatment.

These factors and others need to be considered together and not in isolation, as they may combine or interact. The BAC is of the view that these or similar considerations should guide the deliberations of bodies in a position to permit or regulate research with human-animal combinations.

IV. Regulatory Considerations

4.1 Public reaction to ethical concerns presents a powerful argument for regulation to ensure that the fundamental values, beliefs and practices of society are not disrupted, and to balance a wide spectrum of interests and values that are implicated in research involving human-animal combinations. Regulatory regimes have already been established or are actively being debated in a number of countries with an interest in such research, notably Australia, Canada, China, Denmark, India, Japan, New Zealand, South Korea, the UK and the US, together with the countries of the European Union. Table 1 (at page 27) shows the regulatory approaches in these countries.

4.2 The UK has decided to regulate research involving human embryos with some animal component by revising its 1990 Human Fertilisation and Embryology Act. In November 2008, this legislation was amended to empower the HFEA to regulate research involving 'human admixed embryos', which term includes cytoplasmic hybrid embryos.[35] In addition, the legislation prohibits placing a 'human admixed embryo' in a woman or an animal, and keeping or using such an embryo after the appearance of the primitive streak or after a period of 14 days development, whichever is earlier.[36]

4.3 While the US lacks federal laws that address human-animal combinations directly, the guidelines of the National Institutes of Health (NIH)[37] and the National Academy of Sciences (NAS) that relate to human embryonic stem cell research are relevant. Some states, such as California, have modelled their regulatory regimes after the NAS guidelines.[38] In relation to human pluripotent stem cell research involving animal chimeras or cytoplasmic hybrid embryos, the guidelines recommend additional review and approval by a specially constituted Embryonic Stem Cell Research Oversight (ESCRO) Committee. The Committee is expected to pay particular attention to the probable pattern and effects of differentiation and integration of the human stem cells that are introduced into animals. As in the UK legislation, the NAS guidelines disallow the development of SCNT embryos or cytoplasmic hybrid embryos for longer than 14 days or until formation of the primitive streak begins, whichever occurs first, or their implantation into a human or animal uterus. The NAS guidelines further stipulate that the breeding of any animal into which human pluripotent stem cells have been introduced such that they could contribute to the germ line should be prohibited.

35 UK. *Human Fertilisation and Embryology Act 2008*, Section 4(2).

36 *Ibid*. Section 4(2)-(3).

37 National Institutes of Health, USA. *Guidelines on Human Stem Cell Research*. 7 July 2009.

38 National Academy of Sciences, USA. *Guidelines for Human Embryonic Stem Cell Research*. Amended 2010.

4.4 The NAS did not think that experiments involving the introduction of human pluripotent stem cells into non-human primate embryos, or any embryonic stem cell into human embryos, should be allowed at this point of time. The position adopted by the International Society for Stem Cell Research (ISSCR) is on many points similar to that of the NAS, but it does not prohibit the introduction of human pluripotent stem cells into human embryos and non-human primate embryos.[39]

4.5 In the European Union sponsored 'CHIMBRIDS' project, the project group similarly recommends that the implantation of a cytoplasmic hybrid embryo into a human or animal uterus should be prohibited, as this is considered to be a type of reproductive cloning.[40] In relation to animal chimeras, it recommends that the greater the possibility of "humanisation" of the existing or future animal, the stronger the need for restrictions. Precaution should be exercised where the relevant knowledge is not available.[41] It adds that: "Careful monitoring is required for projects in which the incorporation of human material into animal embryos, foetuses or post-natal beings is likely to affect the animal's germline because of the potential risks to, for example, human health and the environment, and the specific risk of a possible development of human gametes in an animal."[42]

4.6 Considering the above and the countries in Table 1 (at page 27), there appear to be certain salient features to the various regulatory approaches to research with human-animal combinations. First, such research would usually be subject to supervision within a specialised and more intensive oversight mechanism. The 'CHIMBRIDS' project group recommends legal oversight, given what it sees as the gravity of the ethical and legal issues involved.[43] It proposes that special consideration be given to research involving human-animal combinations such as incorporation of human pluripotent cells into an animal blastocyst or into its preliminary embryonic stages, and mixing of animal and human totipotent cells[44] or embryos.

4.7 A second salient generalisation is that embryos with some degree of human-animal combination are not to be implanted into a human uterus. Chimeric animal embryos may sometimes be implanted into an animal depending on a number of factors including the type of animal concerned, and the type and amount of human cells introduced into the animal embryo.

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39 International Society for Stem Cell Research. *Guidelines for the Conduct of Human Embryonic Stem Cell Research.* 21 December 2006; and Ethical Standards for Human-to-Animal Chimera Experiments in Stem Cell Research. *Cell Stem Cell*. 1 (2007): 159-163.

40 Taupitz J and Weschka M (eds). *CHIMBRIDS – Chimeras and Hybrids in Comparative European and International Research.* Heidelberg: Springer, 2009. Recommendation 16, page 457.

41 *Ibid*. Recommendation 8, page 456.

42 *Ibid.* Recommendation 14, page 457.

43 *Ibid.* Pages 456 and 457.

44 Totipotent cells are cells with the capability to develop into a complete organism.

4.8 It is generally considered inappropriate to perpetuate offspring with unknown combinations of human and animal characteristics. It follows that animals into which human embryonic stem cells, induced pluripotent stem cells, or any other kind of pluripotent stem cells have been introduced should normally not be allowed to breed.

4.9 Currently, no governmental body in Singapore has explicit statutory power to regulate human stem cell research involving human-animal combinations. The Ministry of Health (MOH) regulates research involving human eggs or embryos in healthcare institutions and assisted reproduction clinics.[45] However, such research does not come under the purview of the MOH if it is not conducted within such establishments. The MOH also administers the Human Cloning and Other Prohibited Practices Act, 2004. It is unclear whether a cytoplasmic hybrid embryo would be interpreted as being a prohibited embryo under the terms of the Act.

4.10 It is in the public interest to provide clear and comprehensive legal guidance that explicitly addresses the subject of research involving human-animal combinations. From the BAC's consultations with IRB members and researchers, it appears that IRBs may not be comfortable with or capable of reviewing research involving human-animal combinations, given the ethical and scientific challenges entailed. In addition, researchers are concerned with further bureaucratisation of the ethics review process if the research is to undergo several stages of ethics review. Currently, IRBs review all stem cell research proposals. It may be more cost-effective and a better use of resources for Singapore to have a national stem cell ethics review body that can handle all human stem cell research, including research involving human-animal combinations.

4.11 As in almost all major scientific jurisdictions (see Table 1 at page 27), there are guidelines relating to the welfare of laboratory animals. In Singapore, any research facility that uses animals for scientific purposes would be regulated by the Agri-Food and Veterinary Authority (AVA) under the Animal & Birds (Care and Use of Animals for Scientific Purposes) Rules.[46] These regulatory requirements pertain essentially to the facility and the care of the animals, rather than the ethics of the research in relation to humans. Research involving human-animal combinations may be subject to ethics review by an IRB or an Institutional Animal Care and Use Committee, or both. The BAC is of the view that no major change in existing procedure is needed, and that the foci of the respective reviews do not overlap. Stem cell research proposals involving any live animals, or animal embryos and foetuses that are likely to be brought to

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45 Ministry of Health, Singapore. *Directives for Private Healthcare Institutions Providing Assisted Reproductive Services: Regulation 4 of the Private Hospitals and Medical Clinics Regulations* (Cap 248, Reg 1). March 2006, paragraph 8.1.

46 Ministry of National Development, Singapore. *Animal & Birds* (*Care and Use of Animals for Scientific Purposes*) *Rules*. 2004.

term, should be approved by an Institutional Animal Care and Use Committee in the same way as would apply to animal research not involving stem cells.

V. Conclusion and Recommendations

5.1 Research with human-animal combination is a scientific practice of long standing and is likely to remain an important and necessary part of future progress in biomedical sciences. The BAC is not in principle opposed to the creation of human-animal combinations in stem cell research, provided that appropriate regulation is in place. The BAC agrees with the view of the majority of the public and scientific community supportive of such research, that close monitoring is required within an effective regulatory regime.

5.2 Many of the concerns raised in respect of human-animal combinations are related to the possibility of developing actual independent living creatures with both human and animal features, or animals with human consciousness or mental characteristics, as an inadvertent result of biomedical research. For cytoplasmic hybrids, it is clear that these concerns could be alleviated by prohibiting embryonic development beyond 14 days or the emergence of the primitive streak, whichever is earlier, or any implantation into a human or animal uterus. As for animal chimeras created with human embryonic stem cells, induced pluripotent stem cells, or any other kind of pluripotent stem cells, they should not be allowed to breed.

5.3 Currently in Singapore, the Ministry of Health regulates certain types of research such as clinical research and research using human embryos under the Private Hospitals and Medical Clinics Act. However, research institutes, other than those that provide healthcare, are not under the jurisdiction of the MOH. In 2002, the BAC recommended a single body with oversight powers for human stem cell research,[47] and in 2004, it recommended that all biomedical research (with certain exceptions) be the subject of ethics review by IRBs accredited with the MOH.[48] As a significant amount of research involving human-animal combinations relates to stem cell research, the BAC proposes that all human stem cell research, including research with human-animal combinations, be the responsibility of a national stem cell ethics review body. This body, which should include lay members of the public, could appropriately be under the jurisdiction of the Ministry of Health.

5.4 Human-animal combination research should be permitted only where there is strong scientific merit and potential medical benefit, and there is no satisfactory alternative way of pursuing the same research. Such research proposals should be reviewed by the proposed national stem cell ethics review body. However,

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47 Recommendation 8 of the Bioethics Advisory Committee's 2002 Report on *Ethical, Legal and Social Issues in Human Stem Cell Research, Reproductive and Therapeutic Cloning*: "There should be a statutory body to license, control and monitor all human stem cell research conducted in Singapore, together with a comprehensive legislative framework and guidelines."

48 Bioethics Advisory Committee, Singapore. *Research Involving Human Subjects: Guidelines for IRBs*. 2004. Paragraphs 3.9 to 3.30 and 8.6.

research that is ethically uncontentious should be exempted from review by this body. Such research could include: (a) research using established pluripotent stem cell lines and confined to cell culture; and (b) research that involves routine and standard research practice with laboratory animals. However, researchers should have to notify the national stem cell ethics review body and submit documentation confirming that any stem cells used have been acceptably derived. The national stem cell ethics review body should be empowered to determine the kinds of research that need not undergo its review.

5.5 The responsibilities of the national stem cell ethics review body would be those of any IRB as set out in the BAC's report on Research Involving Human Subjects,[49] but with particular attention to:

a) ensuring that all proposals have been reviewed by a scientific committee and have scientific merit, and that the intending researchers and their institutions have or can provide the appropriate expertise. Where required, researchers must also have obtained approval from an animal ethics review committee;

b) reviewing the procurement process of biological materials for the research, including recruitment and consent procedures for research participants or donors of biological materials, to ensure that likely concerns and sensitivities relating to intended research on human-animal combination are properly addressed and adequate information given, that vulnerable people and people in dependent positions are not exploited and that there are no inducements for the provision of the materials;

c) considering any possible conflicts of interest arising in the research and ensuring they are avoided or managed appropriately; and

d) the probable pattern and effects of differentiation and integration of the human stem cells that are introduced into animals at various stages of development.

5.6 To ensure that there is adequate and proper oversight of stem cell research involving human-animal combinations, and to allay any fear that undesired living creatures may be created, the BAC has proposed five recommendations. As in the case of human embryonic stem cells, one of these recommendations embodies a conscience clause, given that there may be opposition to human-animal combinations, especially cytoplasmic hybrid embryos, that arise from similar deeply felt convictions.

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[49] *Ibid.* Paragraphs 5.18 to 5.29.

List of Recommendations

Recommendation 1
A single national body, which must include lay members of the public, should be established to review and monitor all stem cell research involving human pluripotent stem cells or human-animal combinations conducted in Singapore. This body should also be empowered to determine the kinds of research that need not undergo its review.

Recommendation 2
The creation of cytoplasmic hybrid embryos should be permitted only where there is strong scientific merit in, and potential medical benefit from, such research. These embryos should not be allowed to develop beyond 14 days or the appearance of the primitive streak, whichever is earlier, nor be implanted into any human or animal uterus.

Recommendation 3
Where human embryonic stem cells, induced pluripotent stem cells, or any other kind of pluripotent stem cells are introduced into non-human animals at any stage of development, particular attention should be paid to the need to avoid the creation of entities in which human sentience or consciousness might be expected to occur.

Recommendation 4
Animals into which human embryonic stem cells, induced pluripotent stem cells, or any other kind of pluripotent stem cells have been introduced should not be allowed to breed.

Recommendation 5
No clinical or research personnel should be under a duty to conduct or assist in stem cell research involving human-animal combinations, to which they have a conscientious objection.

TABLE 1: REGULATORY APPROACHES OF SELECTED COUNTRIES ON THE CREATION OF ANIMAL CHIMERAS AND CYTOPLASMIC HYBRID EMBRYOS

Country[50]	Animal Chimeras	Cytoplasmic Hybrid Embryos
Australia *Prohibition of Human Cloning Act*, 2002 *Prohibition of Human Cloning for Reproduction and the Regulation of Human Embryo Research Amendment Act*, 2006 National Health and Medical Research Council, *Australian code of practice for the care and use of animals for scientific purposes*, 2004	There are no specific regulations or guidelines on the creation of animal chimeras in research, although there are guidelines relating to the welfare of laboratory animals (which have legal standing in some states).	The creation of cytoplasmic hybrid embryos is allowed under licence and the hybrid embryos are not to be developed for a period longer than 14 days (Section 23B(3) of the 2006 Amendment Act).
Canada *Assisted Human Reproduction Act*, 2004 (AHRA)	The creation of animal chimeric embryos and foetuses using human pluripotent cells is prohibited for publicly funded research (Section 8.2.6 – 8.2.7 of the Updated Guidelines).	There is no provision for the creation of cytoplasmic hybrid embryos for research in the AHRA. However, the creation of cytoplasmic hybrid embryos for reproduction or transplantation into a human being or a non-human life form is

[50] Many countries do not have specific legislation or regulatory policy to govern the creation and use of human-animal combinations. Countries are selected based on several factors including availability of information (in the English language), availability of legislation and regulatory guidelines (both legally binding and non-binding), and the extent that these issues have been deliberated on and debated in these countries.

TABLE 1: REGULATORY APPROACHES OF SELECTED COUNTRIES ON THE CREATION OF ANIMAL CHIMERAS AND CYTOPLASMIC HYBRID EMBRYOS

Country[50]	Animal Chimeras	Cytoplasmic Hybrid Embryos
Canadian Institutes of Health Research, *Updated Guidelines for Human Pluripotent Stem Cell Research*, 30 June 2010 Canadian Council on Animal Care, *Guide to the Care and Use of Experimental Animals*, May 1999 (year of adoption)	The creation of post-natal animal chimeras is allowed provided that the research aims to produce pre-clinical models of specific tissue or organ, or to determine the pluripotency of cells (e.g. teratoma formation), and that such non-human animals will not be used for reproductive purposes (Section 8.1.6 of the Updated Guidelines). There are guidelines relating to the welfare of laboratory animals.	prohibited (Section 5(1)(j) of the AHRA).
China *Ethical Guidelines for Human Embryonic Stem Cell Research* (promulgated by the Ministry of Science and Technology and the Ministry of Health of the People's Republic of China on 24 December 2003)	There are no specific regulations or guidelines on the creation of animal chimeras in research, but ethics review is required for all research involving human embryonic stem cells (Section 9 of the Ethical Guidelines).	There are no specific regulations or guidelines relating to the creation of cytoplasmic hybrids embryos. However, embryos created through human somatic cell nuclear transfer are not allowed to develop beyond 14 days or to be implanted into a human being or animal (under Sections 6(1) and 6(2) of the Ethical Guidelines).

TABLE 1: REGULATORY APPROACHES OF SELECTED COUNTRIES ON THE CREATION OF ANIMAL CHIMERAS AND CYTOPLASMIC HYBRID EMBRYOS

Country[50]	Animal Chimeras	Cytoplasmic Hybrid Embryos
Denmark *Act on a Scientific-Ethical Committee System and Handling of Biomedical Research Projects*, 2003 (as amended, and interpreted by the Danish Council of Ethics and the Danish Ethical Council for Animals in their 2007 report entitled "Man or Mouse?") *Act on Assisted Reproduction*, 2003 (as amended, and interpreted by the Danish Council of Ethics and the Danish Ethical Council for Animals in their 2007 report entitled "Man or Mouse?")	The creation of animal chimeras to advance knowledge on medical therapy is allowed but the research must be approved by both a scientific-ethical committee and the Animal Experiments Inspectorate (see pages 37 to 40 of the 2007 report).	There are no specific regulations or guidelines relating to the creation of cytoplasmic hybrid embryos, but the Act on Assisted Reproduction could be interpreted as prohibiting the creation of such hybrid embryos if they are taken to be human embryos (see pages 27 to 29 of the 2007 report).
India *Guidelines for Stem Cell Research and Therapy*, Department of Biotechnology & Indian Council of Medical Research, 2007	The creation of animal chimeras at all stages of development is allowed with prior approval from institutional and national level ethics review and animal review committees, provided such animals are not allowed to breed (Paragraphs 6.1.2, 6.2.3 and 6.2.4 of the 2007 Guidelines).	There are no specific regulations or guidelines relating to the creation of cytoplasmic hybrid embryos. However, the development of human embryos, regardless of the method of derivation, beyond 14 day or the formation of the primitive streak, whichever is earlier, and implantation into a human or non-human uterus are prohibited

TABLE 1: REGULATORY APPROACHES OF SELECTED COUNTRIES ON THE CREATION OF ANIMAL CHIMERAS AND CYTOPLASMIC HYBRID EMBRYOS

Country[50]	Animal Chimeras	Cytoplasmic Hybrid Embryos
Ministry of Environment and Forests, Animal Welfare Division, *Standard Operating Procedures for Institutional Animal Ethics Committee*, January 2010	There are guidelines relating to the use of laboratory animals.	(Paragraphs 6.3.2 and 6.3.3 of the 2007 Guidelines).
Japan *The Law Concerning Regulation Relating to Human Cloning Techniques and Other Similar Techniques*, 2001 *Guidelines for the Handling of a Specified Embryo*, 2001 *Guidelines for the derivation and distribution of human embryonic stem cells*, 2009 (drawn from Caulfield T *et al*, "Stem cell research policy and iPS cells", *Nature Methods*, 7(2010): 28-33)	The creation of animal chimeric embryos is allowed, with approval from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) is required (Article 2(1) of the 2001 Guidelines, and Article 6 of the 2001 Law). The transfer of such embryos into a human or non-human uterus is prohibited (Article 3 of the 2001 Law). Research involving the production of germ cells from pluripotent stem cells (whether from human embryonic stem cells or iPS cells) should be allowed under strict oversight, but fertilisation using these derived gametes should be prohibited. In addition, research involving the grafting of human iPS cells into animal embryos is allowed, although implantation of such embryos into an	The creation of cytoplasmic hybrid embryos is prohibited (Article 2(1) of the 2001 Guidelines, and Article 2(1)14 of the 2001 Law). (Further reference: Taupitz J and Weschka M (eds). *CHIMBRIDS – Chimeras and Hybrids in Comparative European and International Research*. Heidelberg: Springer, 2009. Page 1029.)

TABLE 1: REGULATORY APPROACHES OF SELECTED COUNTRIES ON THE CREATION OF ANIMAL CHIMERAS AND CYTOPLASMIC HYBRID EMBRYOS

Country[50]	Animal Chimeras	Cytoplasmic Hybrid Embryos
Guidelines for the utilization of human embryonic stem cells, 2009 (drawn from Caulfield T *et al*, "Stem cell research policy and iPS cells", *Nature Methods*, 7(2010): 28-33) Science Council of Japan, *Guidelines for Proper Conduct of Animal Experiments*, 1 June 2006	animal uterus is prohibited (2009 Guidelines). There are no specific regulations or guidelines on the creation of animal chimeric foetuses or post-natal human chimeras for research. There are guidelines on the use of animals in research.	
New Zealand *Human Assisted Reproductive Technology Act*, 2004 Ministry of Health, *Guidelines for Using Cells from Established Human Embryonic Stem Cell Lines for Research*, 2006 *Animal Welfare Act*, 1999	The creation of animal chimeras is allowed but must be ethically reviewed and approved by the Ethics Committee on Assisted Reproductive Technology and also by an animal ethics committee (Paragraph 2, Page 5 of the Guidelines). Use of animals in research, testing and teaching is regulated under the Animal Welfare Act, 1999.	The creation of cytoplasmic hybrid embryos is permitted, but they are not allowed to develop beyond 14 days or after the primitive streak appears, whichever is earlier (Sections 9 read with definition of "hybrid embryo" in Section 5 of the Act).

TABLE 1: REGULATORY APPROACHES OF SELECTED COUNTRIES ON THE CREATION OF ANIMAL CHIMERAS AND CYTOPLASMIC HYBRID EMBRYOS

Country[50]	Animal Chimeras	Cytoplasmic Hybrid Embryos
South Korea *Bioethics and Biosafety Act*, revised 2008 *Animal Protection Law*, 2007	There are no specific regulations or guidelines on the creation of animal chimeras for research, but fusing a human embryo with an animal embryo is prohibited (Article 12 (2) (3) of the Act). The use of animals in research is regulated by law.	The creation of cytoplasmic hybrid embryos or the transfer of such embryos into the uterus of a human being or an animal are prohibited (Articles 12 (2) (2) and 12 (3) of the Act).
Singapore *Human Cloning and Other Prohibited Practices Act*, 2004 *Animal & Birds (Care and Use of Animals for Scientific Purposes) Rules*, 2004 National Advisory Committee for Laboratory Animal Research, *Guidelines on the Care and Use of Animals for Scientific Purposes*, 2004	There are no specific regulations or guidelines on the creation of animal chimeras for research. There are guidelines on the use of animals in research.	It is unclear if the creation of cytoplasmic hybrid embryos is regulated under the Act.

TABLE 1: REGULATORY APPROACHES OF SELECTED COUNTRIES ON THE CREATION OF ANIMAL CHIMERAS AND CYTOPLASMIC HYBRID EMBRYOS

Country[50]	Animal Chimeras	Cytoplasmic Hybrid Embryos
United Kingdom *Human Fertilisation and Embryology Act* 2008 *Animals (Scientific Procedures) Act*, 1986	There are no specific regulations or guidelines on the creation of animal chimeras for research, apart from those that relate to the welfare of laboratory animals.	The creation of cytoplasmic hybrid embryos is allowed only if under licence from the HFEA. (Sections 1(2) and 4(2) of the Act). Development of such embryos beyond 14 days or after appearance of the primitive streak, whichever is earlier, and implantation into a woman or an animal, are prohibited (Sections 4(2)(1), 4(3) and 4(4) of the Act).
United States of America National Academy of Sciences (NAS), *Guidelines for Human Embryonic Stem Cell Research*, 2005, amended 26 May 2010 National Institutes of Health (NIH), *Guidelines for Research Using Human Stem Cells*, 2009 *Animal Welfare Act*, amended 1990	There is no provision under Federal law for the creation of animal chimeras for research, although the use of certain animals in research is regulated by law. Under the NAS Guidelines, the creation of animal chimeras for research is allowed, after additional review and approval by an Embryonic Stem Cell Research Oversight (ESCRO) committee (Paragraphs 1.3(a), 1.3(b)(ii) and 1.3(b)(iii)).	There is no provision under Federal law for the creation of cytoplasmic hybrid embryos for research. Under the NAS Guidelines, the creation of cytoplasmic hybrid embryos is allowed. Development of such embryos beyond 14 days or appearance of the primitive streak, whichever is earlier, and implantation into a human or non-human uterus are prohibited (Paragraph 4.5).

TABLE 1: REGULATORY APPROACHES OF SELECTED COUNTRIES ON THE CREATION OF ANIMAL CHIMERAS AND CYTOPLASMIC HYBRID EMBRYOS

Country[50]	Animal Chimeras	Cytoplasmic Hybrid Embryos
State law varies significantly, with a number of states that allow nuclear transfer research and a number that do not.	Animals into which human embryonic stem cells have been introduced such that they could contribute to the germ line should not be allowed to breed (Paragraph 1.3(c)(iii), NAS Guidelines; Part IV (B), NIH Guidelines). However, the introduction of human embryonic stem cells into non-human primate embryos should not be conducted at this time (Paragraph 1.3(c)(ii), NAS Guidelines) / is ineligible for funding (Part IV (A), NIH Guidelines).	When hES cell lines are to be derived from cytoplasmic hybrid embryos, the approval of an ESCRO will have to be obtained (Paragraph 4.4, NAS Guidelines).

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