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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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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Human-Animal Combinations for Biomedical Research

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1. An Argument for Transplanting Human Stem Cells into Non-Human Embryos
   - *Mr Kyle Loh and Dr Lim Bing*
     Genome Institute of Singapore

2. Stem Cell Research and Interspecies Fusion: Some Philosophical Issues
   - *Associate Professor Nuyen Anh Tuan*
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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.

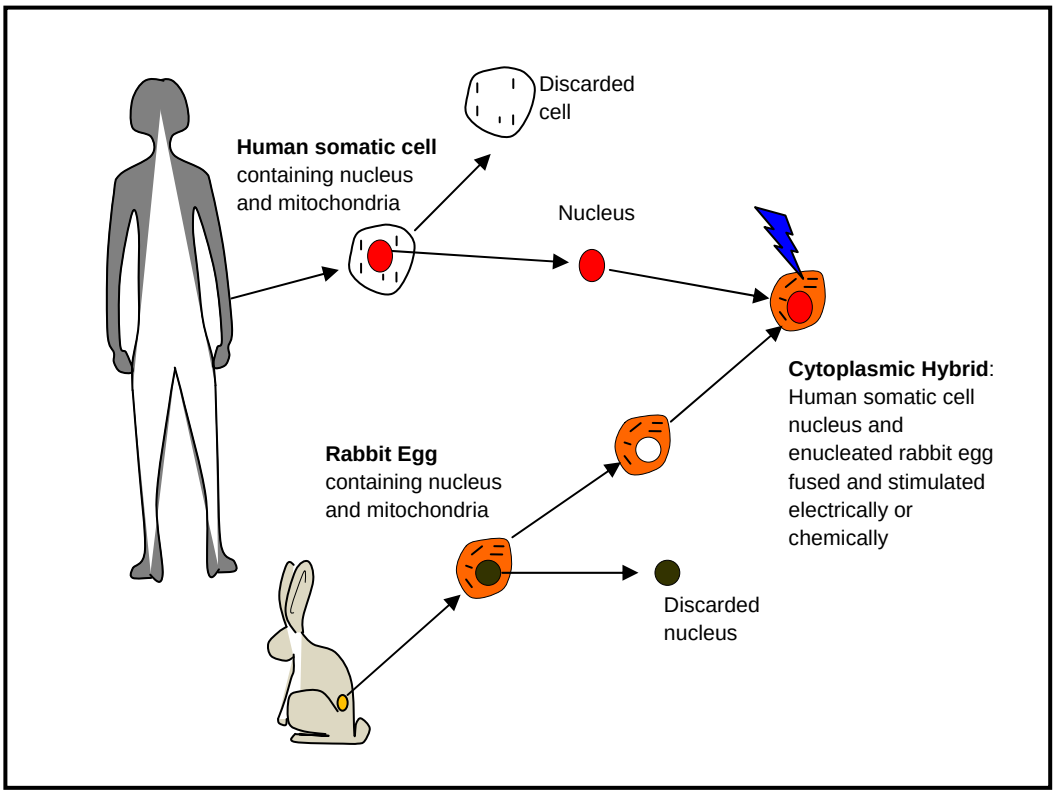

Figure 1. The creation of a cytoplasmic hybrid embryo by SCNT

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.

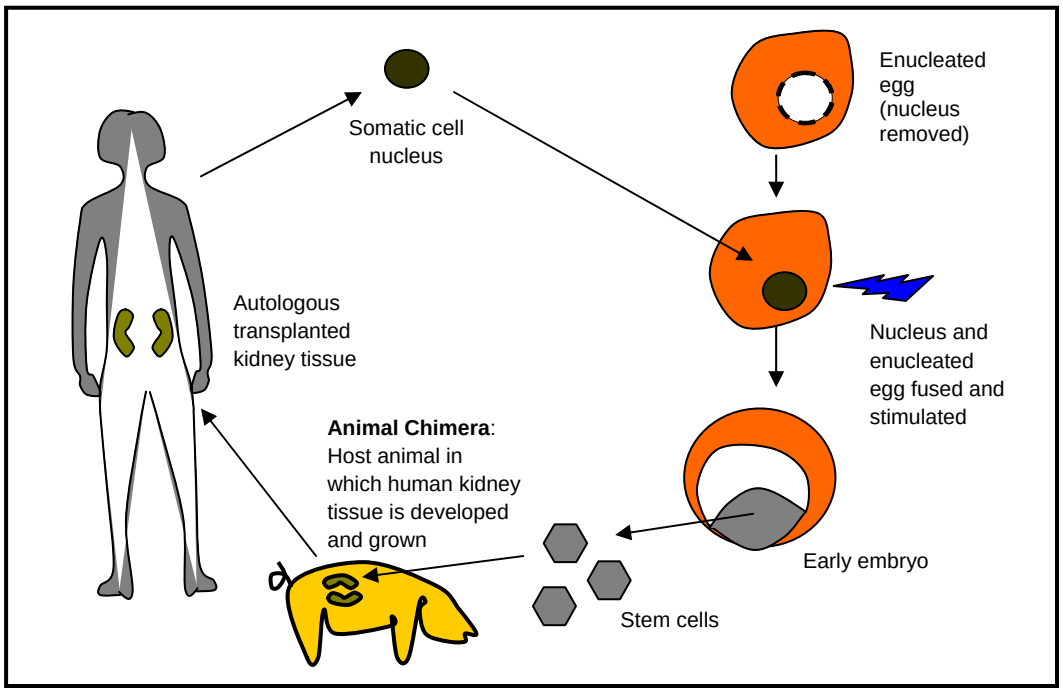

Figure 2. Schematic possible use of an animal host in the growth of organs (e.g. kidneys) derived from cloned human stem cells by SCNT.[22]

[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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ANNEX A

CONSULTATION PAPER:
HUMAN-ANIMAL COMBINATIONS FOR BIOMEDICAL RESEARCH

HUMAN-ANIMAL COMBINATIONS FOR BIOMEDICAL RESEARCH

A CONSULTATION PAPER

BIOETHICS ADVISORY COMMITTEE

SINGAPORE

8 January 2008

HUMAN-ANIMAL COMBINATIONS FOR BIOMEDICAL RESEARCH

SUMMARY

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 (the Stem Cell Report).[1] Since then, significant advances have been made in stem cell science and technology and ethical issues have arisen as a result of the shortage of human eggs and the need to create human-animal combinations to further stem cell research.

2. This Consultation Paper highlights some recent developments and explains why researchers wish to conduct this kind of research. It also seeks public feedback on these issues, which will be of great value in preparing a revised Stem Cell Report.

3. Human-animal combinations are created through certain research techniques in which genes, cells or tissues from humans may be incorporated into animals (and *vice versa*) for the purposes of research. The terms *chimera* and *hybrid* have been used to describe such inter-species combinations.

4. Traditionally a chimera is an imaginary creature, made up of parts from two or more different species, for example a centaur, with the body of a horse and a human head and torso. To Singaporeans, the Merlion is a familiar chimera.

5. However, when scientists talk about human-animal combinations in research, they do not plan the creation of such monsters. In science, a chimera is an animal or a human whose body contains cells or tissues from another animal or human. Any person who has undergone a blood transfusion or any kind of transplant is by definition a chimera, because his or her body would contain cells or tissue from the donor. Thus a person with a pig heart valve transplant is, scientifically speaking, a chimera. Putting animal and human tissues or cells together, for scientific purposes or for treatment has been happening for some time. Chimeras are usually created in research by introducing human cells such as stem cells into an animal, or an animal embryo or foetus, and this process does not involve creating bizarre creatures.

6. A *hybrid*, on the other hand, is the result of the fertilisation of an egg of one species by a sperm of another species. A well known animal hybrid is the mule, which is the product of crossing a horse and a donkey. Such hybrids are called *true hybrids*.

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

7. Scientists have little interest in creating true human-animal hybrids. However, owing to the limited availability of human eggs for research, scientists are interested in creating another type of hybrid, called a *cytoplasmic hybrid*, by transferring the nucleus of a human body cell into an animal egg from which the nucleus has been removed.

8. Chimeras and cytoplasmic hybrids are examples of human-animal combinations. There are several reasons for creating human-animal combinations, such as:

   (a) to study specific disease mechanisms and methods of treatment;

   (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;

   (d) to study the possibility of growing human tissues and organs in animals for the purpose of transplantation into humans; and

   (e) to study the processes involved in nuclear reprogramming (how the nucleus of an adult specialised cell can be induced to regain its potential to develop into other types of cell).

9. Biomedical research advances scientific knowledge and could lead to new or improved medical treatments. However, people might have concerns about the use of human-animal combinations in research. Some concerns relate to ensuring the safety of treatments, or that these treatments be available generally and fairly. Other concerns may be based on religious beliefs.

10. In addition, some people feel that human-animal combinations are repugnant, because they are unnatural. Some would say that scientists are ‘playing God’ and creating new life forms. Others worry that we might slide down a slippery slope and end up producing something like an animal with human consciousness, or worse, that these might breed and produce a kind of sub-human or part-human creature, with doubtful legal and moral status. These critics usually see a need to keep a clear distinction between humans and animals.

11. Such concerns are not to be lightly dismissed, but they are not without answers. Many existing treatments, like vaccination, are in the same sense unnatural. Moreover it is also ‘playing God’ if we prohibit research that might help patients. In any case, researchers should not, as a matter of ethics, create or breed creatures with human consciousness, and it is probably not a realistic scientific possibility.

12. Regardless of scientific possibility, a number of countries such as Australia and Canada, have prohibited the development of hybrid or chimeric embryos beyond 14 days or their implantation into the womb of a human or animal. A summary of the regulatory approaches of select countries is given in this Consultation Paper. In the UK, for example, legislation is proposed that would limit research to scientifically useful work that minimises risks of undesirable consequences.

13. The public is invited to comment on whether human-animal combinations should be created and used for research in Singapore, and if so under what kinds of restrictions and regulation. Other comments on this subject are also welcome.

HUMAN-ANIMAL COMBINATIONS FOR BIOMEDICAL RESEARCH

CONSULTATION PAPER

INTRODUCTION

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.[2] This Report established an ethical framework for human stem cell research, including the derivation of embryonic stem cells through the process of somatic cell[3] nuclear transfer (SCNT).[4] Under this framework, embryos could be created and used to derive embryonic stem cells, provided they were less than 14 days old, and such research would be carefully regulated.

2. Stem cell research has advanced significantly in recent years and it is believed that this area of research could lead to new treatments for debilitating and currently incurable illnesses, such as diabetes, Alzheimer's disease and Parkinson's disease. However, as such research progressed, ethical concerns relating to the availability of human eggs for research became increasingly pressing. These issues were discussed by the BAC in a Consultation Paper, which was released on 7 November 2007.[5]

3. Given the difficulties in obtaining human eggs for stem cell research and their limited availability, scientists have proposed using animal eggs as an alternative means of deriving stem cells. To further stem cell research, scientists are also introducing human stem cells into animals, animal embryos or animal foetuses to study the nature and potential of these cells. In addition, human genes are being introduced into animals to facilitate the study of specific diseases. However, such combination of human and animal materials (whether genes, cells or tissues) raises ethical concerns. Should such research be prohibited? If not, what are the limits and how should it be monitored?

4. This Consultation Paper highlights some recent developments in biomedical research involving the creation of human-animal combinations, explains the reasons for such research, and discusses the related ethical, legal and social issues. Prior to making recommendations on this area of research to the Steering

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2 BAC. *Ethical, Legal and Social Issues in Human Stem Cell Research, Reproductive and Therapeutic Cloning*. Singapore, 2002.

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

4 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.

5 BAC. *Donation of Human Eggs for Research: A Consultation Paper*. Singapore, 2007.

Committee on Life Sciences, the BAC would like to seek the views of the public, as well as those involved directly or indirectly in research on:

(a) the creation and use of human-animal combinations for research;

(b) the prohibitions, limits and regulatory mechanisms that will be needed for such research in Singapore; and

(c) any other matters related to human-animal combinations for biomedical research.

BACKGROUND INFORMATION

Stem Cells and Nuclear Reprogramming

5. Stem cells are unspecialised (undifferentiated) cells that are able to replicate themselves and become specialised (differentiated) cells.[6] There are primarily two types of stem cell that scientists work with – adult stem cells and embryonic stem cells. Adult stem cells are present in a tissue or organ and are able to develop into specialised cell types of that tissue or organ, and some other cell types. Embryonic stem cells are derived from early embryos and they are able to replicate themselves indefinitely and develop into all types of cell. This ability is termed pluripotence. There is currently little evidence that adult stem cells are similarly pluripotent.

6. Embryonic stem cells can be derived through the technique of SCNT, which involves the transfer of the nucleus of a somatic cell into an egg, from which the nucleus has been removed. This is followed by stimulation of the egg to start dividing. After three to five days, pluripotent stem cells can be extracted from the resulting embryo. Thus, SCNT converts the somatic cell nucleus into one with the characteristics of an embryonic cell nucleus. This process is called nuclear reprogramming. Figure 1 shows the derivation of stem cells using SCNT.

7. Scientists are finding ways to direct the development of embryonic stem cells into various desired cell types that are useful for therapy. Embryonic stem cells derived through SCNT are genetically identical to the person who contributed the somatic cell. Thus when transplanted into the person as a form of therapy, they would not be rejected. When the somatic cell from a person with a genetic disorder is used, the resulting stem cells carry the genes responsible for the disorder and are thus useful tools for studying that disorder.

6 Specialised cells are mature cells with specific functions, for example, skin cells and liver cells.

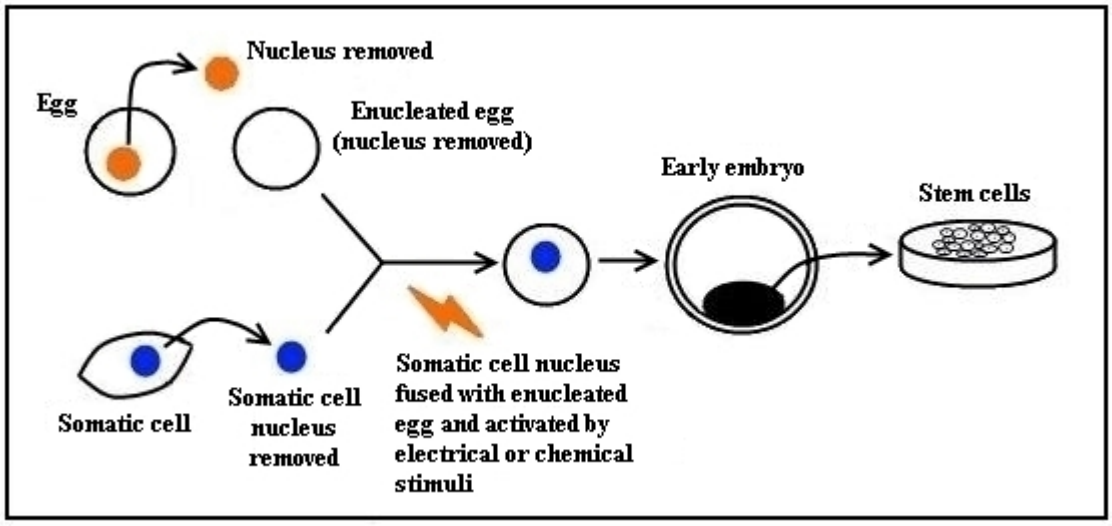

Figure 1. Derivation of stem cells using SCNT

8. Nuclear reprogramming of somatic cell nuclei without the use of SCNT, and thus without requiring human eggs, has recently been reported. Research groups 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.[7] The transformed cells are called induced pluripotent stem cells. This technology could lead to the creation of patient-specific and disease-specific pluripotent stem cells and is a welcome development, although it remains to be seen to what extent it will lead to reduced SCNT research.

Chimeras and Hybrids

9. Genes, cells or tissues from humans may be incorporated into animals (and *vice versa*) for the purposes of treatment or research. 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, such as a centaur, with the body of a horse and a human head and torso, or a fire-breathing monster with a lion's head, a goat's body and a serpent's tail. The Merlion, familiar to Singaporeans, is an example of a chimera. Hybrids, on the other hand, are simply the result of a mating between two different species. Whether chimeras or hybrids, such 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.

10. Technically, a *chimera* is an organism whose body contains cells from another different organism of the same or different species. As such, a person whose

7 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.

diseased heart value 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 as well as his or her own cells. This Consultation Paper will not be considering such chimeras because they are consequences of already established clinical treatments. Moreover in the case of xeno-transplantation, few ethical issues arise since any transplanted tissue does not develop further but simply serves the function for which it was transplanted.

11. This Consultation Paper considers chimeras created by introducing human cells into animals, animal foetuses or animal embryos, and refers to them as *animal chimeras*. These chimeras are useful for research, such as the study of the developmental potential of human embryonic stem cells or their derivatives. In contrast, chimeras created by injecting animal cells into human embryos (*human chimeras*) are not currently used or planned for research.

12. 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. A true human-animal hybrid of this kind has not been contemplated for research, and it is illegal to create such hybrids in many jurisdictions, including Singapore.[8]

13. Scientists are, however, interested in creating another kind of hybrid, called a *cytoplasmic hybrid embryo*, for the purpose of deriving stem cells. These embryos are created by SCNT in which the nucleus of a human somatic cell is transferred into an animal egg from which the nucleus has been removed. A cytoplasmic hybrid embryo is considered a 'hybrid' because its genetic material, which is 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,[9] present in the cytoplasm[10] of the animal egg. Figure 2 shows how a cytoplasmic hybrid embryo is created.

8 Ministry of Health. *Directives for Private Healthcare Institutions Providing Assisted Reproduction Services: Regulation 4 of the Private Hospitals and Medical Clinics Regulations* (Cap 248, Reg 1). March 2006, paragraph 8.7.

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

10 Cytoplasm is the cellular substance outside the nucleus.

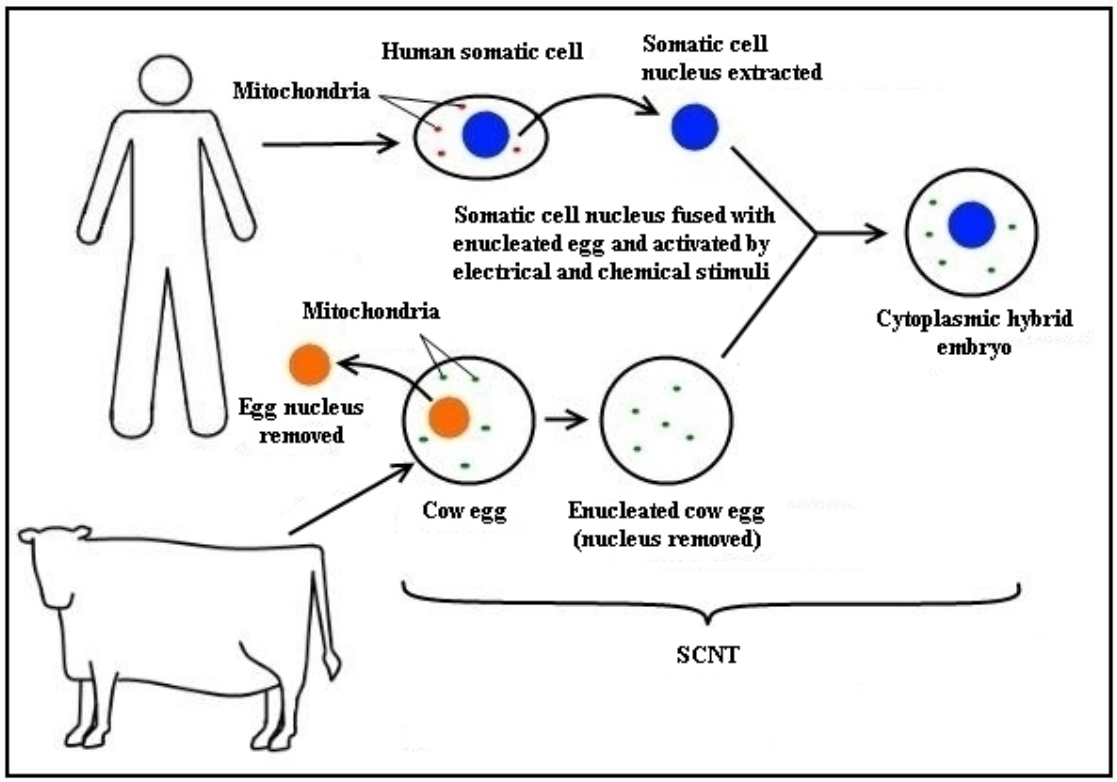

Figure 2. The creation of a cytoplasmic hybrid embryo by SCNT

14. Another human-animal combination of interest is the transgenic animal, which is an animal that has a genome containing genes from another species. Transgenic animals with genomes that incorporate human genes are useful experimental models of human diseases. For example, transgenic mice expressing the human gene for the polio receptor have been created as a 'disease model' for studying poliomyelitis. These mice can be infected by the polio virus and manifest the disease in much the same way as humans can, and studying them can shed light on the disease process in humans. Another example is the 'oncomouse', a transgenic mouse with an increased susceptibility to developing cancer, created by inserting a human oncogene (a gene associated with cancer development) into an early mouse embryo. It is a valuable model for studying human cancers. Transgenic animals are already widely used in research. Besides enabling scientists to understand the cause of diseases, and to develop more effective treatment for these diseases, they have also been used to test the safety of new products and vaccines and to study the possibility of producing organs for transplantation that will not be rejected. As transgenic animals are not thought to raise any new ethical difficulties, they are not considered further in this Consultation Paper.

REASONS FOR EXPERIMENTS WITH HUMAN-ANIMAL COMBINATIONS

15. The ultimate reason for SCNT and stem cell research is the potential that such research holds in finding new treatments for serious and currently incurable diseases. Ideally, SCNT and stem cell research should be done using human eggs and embryos. However, due to ethical concerns and the limited availability of these resources, scientists are turning to using animal eggs and embryos, and creating human-animal combinations for research. They consider human-animal combinations to be powerful tools for gaining better understanding of stem cells and their possible clinical applications, as well as of development biology. Table 1 summarises the reasons for research interest in the types of human-animal combinations considered in this Consultation Paper.

Animal Chimeras

16. An important test of human stem cell pluripotence is the injection of stem cells into immuno-deficient mice. This test is a common practice, and human-mouse chimeras are produced in the process. If the stem cells are pluripotent, they will form tumours, called teratomas, which consist of many differentiated cell types and tissues from the three basic cell layers, i.e. the layers that are the foundation of all subsequent tissue and organ development. The ability to form teratomas is considered to be an established test of pluripotence.

17. Animal chimeras can be used to study stem cell integration and differentiation. It was announced in 2005 that mice with brains containing less than 0.1 percent of human cells had been created by implanting human embryonic stem cells into the brains of adult mice. The mice were created to study the effects of stem cells when implanted into mouse brains.[11] The results revealed that the stem cells developed into cells with the form, structure and characteristics of mouse cells, and functioned accordingly. In other words, there were cells in the mouse brains, with the structure and functions of mouse brain cells, that were of human origin. Following this, it has been suggested that transplanting human embryonic stem cells, modified to represent human neurological disease, into adult mice, could create models for research into the development and progression of the disease, and new methods of treatment.

11 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.

Table 1. Types of Human-Animal Combinations Used in Research

Human-Animal Combination	**How they are created**	**Examples of use in research**
Animal chimeras	By introducing human cells, usually stem cells, into an animal or an early animal embryo or an animal foetus.	Testing the developmental potential of human stem cells or their derivatives. Evaluating the potential usefulness and safety of transplanting human stem cells for clinical treatment. *In vivo* drug testing giving an approximation to human responses. Studying the possibility of growing human tissues and organs in animals for the purpose of transplantation into humans.
Cytoplasmic hybrid embryos	By the transfer of the nucleus of a human somatic cell into an animal egg from which the nucleus has been removed (see Figure 2).	A source of pluripotent stem cells for research. Studying the processes involved in nuclear reprogramming. A source of disease-specific stem cells for the study of specific disease processes and methods of treatment.
Transgenic animals	By introducing human genes into an animal embryo.	Routinely used in research to understand the cause of diseases, to develop more effective treatment for these diseases, to test the safety of new products and vaccines, and to study the possibility of producing organs for transplantation that will not be rejected.

18. Animal chimeras can also be used as models for drug testing, giving an approximation to human responses. The SCID-hu mouse[12] created in the late 1980's is an example of a research model for drug testing. SCID or Severe Combined Immunodeficiency is a genetic disorder that results in a dysfunctional immune system and hence mice suffering from SCID will be unable to fight infection or reject transplanted tissue. By transplanting human

12 McCune JM et al. The SCID-hu mouse: murine model for the analysis of human hematolymphoid differentiation and function. *Science*. 241 (1988):1632-1639.

foetal immune cells or tissues into SCID mice, chimeric mice with the immune system of humans are created and have served as successful research models. For example, unlike normal mice, they can be infected with HIV and thus used to test the efficacy of antiviral compounds.[13]

19. Scientists also create animal chimeras in testing the therapeutic potential of stem cells. For instance, scientists have used adult stem cells from human umbilical cord blood to test their effect 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[14] and neurological deficits in rat models of stroke.[15] In a more recent example, rats with induced heart failure showed improved heart function when heart cells derived from human embryonic stem cells were transplanted into them.[16] These are important demonstrations of therapeutic effects in animals that are needed before stem cells may be used for human therapy. In addition, it is necessary to test for efficacy and any adverse effects. These tests should be conducted in animals prior to humans. The rationale is similar to pre-clinical testing of a drug or a medical device before clinical trials in humans, and human-animal chimeras are created in the process.

20. As there is always a shortage of human tissues and organs to replace diseased and damaged ones, 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 have been created.[17] Researcher Esmail Zanjani and his team at the University of Nevada in the USA have created these sheep by implanting human adult stem cells into sheep foetuses. They hope to use the sheep as a way of developing 'humanised' sheep organs that may one day be used for transplantation into patients.

21. In 2005, researchers were able to show that human adult stem cells from bone marrow, when placed in a rat embryo, integrated into the developing rat

13 Namikawa R et al. Infection of the SCID-hu mouse by HIV-1. *Science*. 242 (1988):1684-1686; and McCune JM et al. Suppression of HIV infection in AZT-treated SCID-hu mice. *Science*. 247 (1990):564-566.

14 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.

15 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.

16 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.

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

kidney.[18] The integrated cells were shown to have differentiated into complex functional kidney structures. Some researchers have also suggested that tissue destined for a specific person might be grown in an animal foetus from stem cells obtained by SCNT, using 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 3 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.

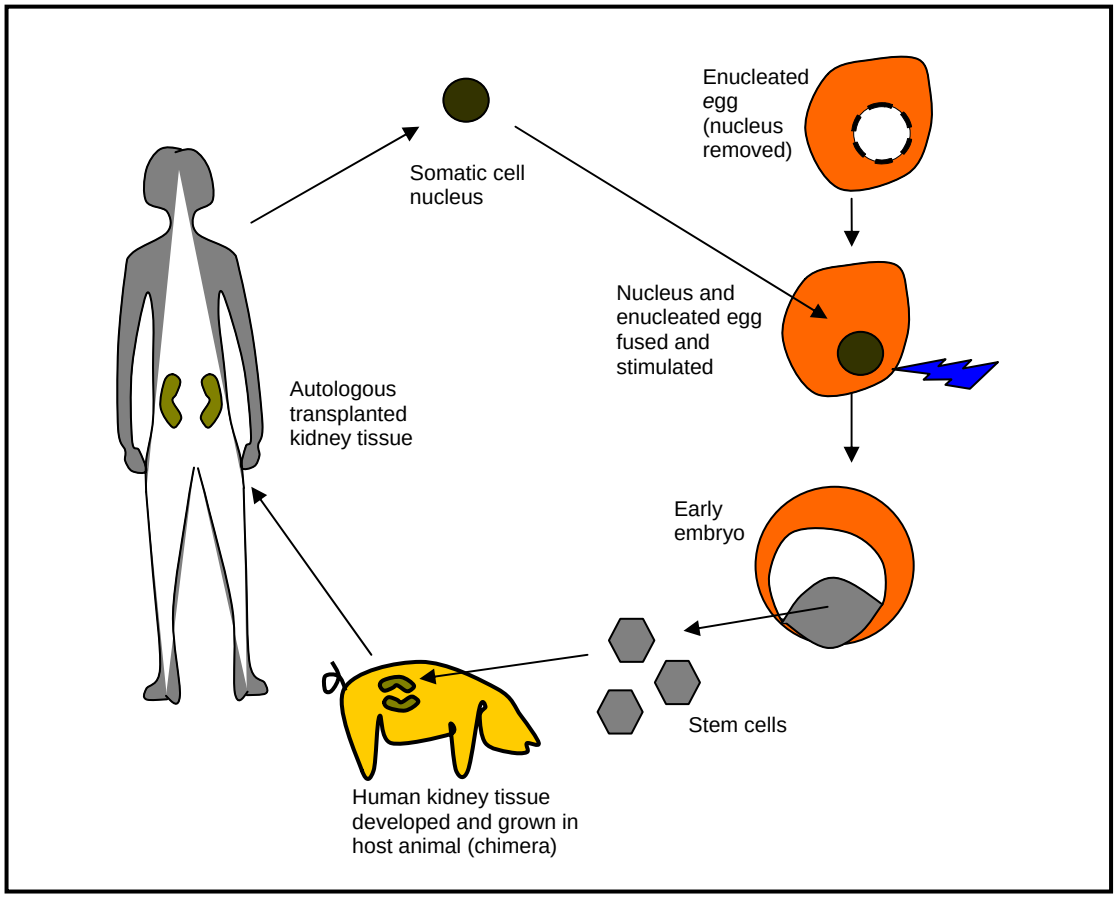

Figure 3. Schematic possible use of an animal host in the growth of organs (e.g. kidneys) derived from cloned human stem cells by SCNT.[19]

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

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

Cytoplasmic Hybrid Embryos

22. Stem cells derived from a cytoplasmic hybrid embryo created using a somatic cell from a patient with a genetic disorder, would carry the genes responsible for the disorder and thus are valuable research tools for studying that disorder. 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.

23. Cytoplasmic hybrid embryos can also be used to study nuclear reprogramming. This may lead to finding methods of direct reprogramming, which do not involve the use of eggs or the need to create embryos and thus help solve the problem of a limited supply of human eggs for research.

24. Embryonic stem cells are a potential source of cells to replace diseased or damaged tissues, as they can differentiate into all types of cells. To prevent the cells from being rejected by the body when used for treatment, these cells would have to be compatible with the patient. One way of achieving such customised cell or tissue therapy is by SCNT. Although embryonic stem cells can potentially be derived from cytoplasmic hybrid embryos, several challenges, such as the possible transmission of infectious diseases and harmful physiological and immunological effects on the patient, need to be overcome before they are used for treatment.

25. In 2003, a team of researchers from China reported success in 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 rabbit eggs from which the nuclei had been removed.[20]

26. Two teams of researchers in the UK have recently requested permission from the regulating authority, the Human Fertilisation and Embryology Authority (HFEA), to create cytoplasmic hybrid embryos from human somatic cells and cow or rabbit eggs.[21] They hope to derive disease-specific stem cell lines from people who have genetic forms of degenerative nervous disorders such as Parkinson's disease, spinal muscular atrophy or Alzheimer's disease, to further understanding of these disorders. The HFEA has indicated qualified support for such research,[22] which is strongly favoured by a large group of scientists and medical research organisations.[23]

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

21 HFEA. *Research applications*. UK, September 06, 2007. http://www.hfea.gov.uk/en/375.html (Accessed Jan 04, 2008).

22 HFEA. *HFEA statement on its decision regarding hybrid embryos*. UK, September 05, 2007. http://www.hfea.gov.uk/en/1581.html (Accessed Jan 04, 2008).

23 Pincock S. *Groups unite to oppose UK hybrid ban*. The Scientist.com, April 05, 2007. http://www.the-scientist.com/news/display/53055/# (Accessed Jan 04, 2008).

ETHICAL CONSIDERATIONS IN RESEARCH WITH HUMAN-ANIMAL COMBINATIONS[24]

27. The BAC has taken the view that an embryo and a sentient human do not stand in a relation of moral equivalence. It does recognise that this is not a position that commands universal agreement, but it is not re-evaluating the wider issue of whether human embryonic stem cell research should be done at all. It is concerned, rather, to explore the added ethical issues that arise when considering research with human-animal combinations of the kind just discussed. This part of the Consultation Paper considers these issues.

28. Is the research something that might yield a benefit that people want and should be able to get, such as basic knowledge of how cells work, or relief from a disease, or from the threat of an early death? We need some assurance that there is something good to be achieved by research in the first place. However, as can be seen from the examples given earlier, research with human-animal combinations is already regarded as important in basic biomedicine, and is likely to become more important with the shift of emphasis to translational medicine, that is, the translation of basic laboratory findings into prospective clinical treatments. Therefore, we would accept as a premise that there is likely benefit in the research, and the issue is rather whether there are ethical objections or drawbacks that might render it unacceptable despite the likely benefit.

Health Risk

29. Some are concerned about possible health risks in allowing research with human-animal combinations, as the crossing of species boundaries may lead to the transfer of diseases between humans and non-humans. In fact, research with human-animal combinations has been conducted for many years and the risk has proved to be minimal when the research takes place under standard laboratory conditions.

30. In research, there is an ethical responsibility on the part of scientists to discover as much as possible about health risks and to minimise them (just as there is an ethical responsibility to produce safer vaccines and other drugs). Moreover, it is through basic research that the health risk in new treatments is evaluated, as part of the development of such treatments. It is always essential to evaluate and investigate the risk, but the mere possibility of risk is not, in itself, a reason to preclude research.

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24 The background paper, Stem Cell Research and Interspecies Fusion: Some Philosophical Issues, 2006, by Nuyen AT has addressed the ethical issues surrounding research with human-animal combinations in depth, and this paper has formed the basis for much of the discussion here. The paper is available at http://www.bioethics-singapore.org.

31. Nevertheless, given some risk, one approach is to weigh the health risk against the benefit. For instance, in deciding whether or not to immunise one's children against potentially fatal childhood diseases, the benefit needs to be weighed against the risk of adverse effects of vaccines.

32. What benefit we can expect from research involving human-animal combinations is largely a scientific question. But if it proves impossible to develop treatments that are safe, the treatments will not be offered to patients. This is a very basic premise of medical treatment and a fundamental aspect of research into clinical applications.

Human-Animal Combinations are Repugnant (the 'Yuk' Factor)

33. It is likely that many people find the idea of combining or mixing species distasteful, repugnant, or even disgusting. The obvious point to make here is that repugnance[25] is an emotional response. What role it plays in moral judgments is not clear. It may be argued that it should play no role at all. On the other hand, it may be that we 'naturally' feel repugnant about something so as to avoid it for our own good. For instance, we find that incest is repugnant, and in this case, it also turns out that there are scientific reasons (i.e. the risks of inbreeding) to support this feeling. However, the case of incest also suggests that we should not object to something just because it is repugnant. We need to ask if there are sound reasons for the objection. The 'repugnance argument' is a signal of the need to find out whether there really are reasons for objecting to research involving human-animal combinations.

34. Perhaps less weight should be given to negative reactions that are not supported by sound reasons, although they should not be lightly dismissed. Clearly, it is unreasonable to suggest that a research activity should be stopped just because some people strongly object to it but cannot offer good reasons for the objection. After all, many people once strongly objected to inter-racial relations, or to kissing or holding hands in public, and some still do. Even then, it has to be acknowledged that if a large number of people turned out to feel that something is objectionable, it would be morally problematic at least. Any claimed benefits of research involving human-animal combinations need to be evaluated against the ethical costs expressed in the preferences of those who object strongly.

35. A further difficulty with too ready an acceptance of feelings as a guide to ethics, is that many things we now accept as good, were originally seen as repugnant. For example, vaccination was once seen in this light, and eminent people[26]

25 In the context of bioethics, the term "repugnance" was first used by Leon Kass against cloning. See Kass LR. The Wisdom of Repugnance. *The New Republic*. 216 (1997):17-26. and Kass LR & Wilson JQ. *The Ethics of Human Cloning*. Washington DC: AEI Press, 1998, pages 3-59.

26 Famously, George Bernard Shaw, for example; "At present, intelligent people do not have their children vaccinated, nor does the law now compel them to. The result is not, as the Jennerians

campaigned against it as contrary to nature. However, this should not be seen as a justification for embracing any change without a careful examination of the reasons behind any feelings of repugnance.

The View that Human-Animal Combinations are Against Nature and Concern with 'Playing God'

36. A cluster of issues comes under this heading. One is that a human-animal combination is a life form artificially created and any such creation may be wrong, as it may be thought that the creation of life should be left to God or nature. Another is that, left alone, human and non-human tissues have their own natural ways of developing, which will be frustrated if they are merged. Also, it is often said that each species has its own natural integrity (and some say, dignity as well), and it is wrong to destroy it through research. Thus, the creation of human-animal combinations for research is objectionable as the integrity of the species (human or animal) is compromised.

37. The concern about 'playing God', and other religious objections, applies to a whole range of biomedical issues, from *in vitro* fertilisation (IVF) to gene therapy. In non-religious terms, the claim is that anything unnatural is wrong. A number of things can be said about this claim. One is that nothing people do can be unnatural in the sense of going against the laws of nature. Scientific experiments, like everything else, must conform to the laws of nature. If 'unnatural' is taken in this sense then there is no objection. If on the other hand by 'unnatural' is meant 'not how things occur or behave in nature', then taking medication for an illness is also unnatural (as this is not how a body heals itself in nature), and a similar objection would apply to surgery or other medical interventions.

38. In the case of research involving human-animal combinations, the objection is more that scientists should not be 'playing God' in compromising species integrity and in creating new life forms. As for creating new life forms and other ways of 'playing God', a number of things should be borne in mind:

    (a) Scientists do not create life as such; they just 'rearrange' the ways life manifests itself. Similarly, many standard medical procedures are just 'rearranging' how life manifests itself, typically from a diseased state to a healthy state.

    (b) How do we know what divine plans are when it comes to scientific knowledge and practice? Is it not possible that stem cell research is part of those plans?

prophesied, the extermination of the human race by smallpox; on the contrary more people are now killed by vaccination than by smallpox." The Irish Times, August 09, 1944. http://www.whale.to/v/shaw1.html (Accessed Jan 04, 2008).

(c) The 'playing God' argument cuts both ways. If research involving human-animal combinations can save life, then to stop the research is to 'play God' with respect to those whose lives could be saved.

39. Noting the points above does not mean that the religious aspect of the 'playing God' argument can simply be ignored. The underlying religious convictions are strongly held, and a society, particularly a multi-religious one, has the responsibility to respect individual preference and sensibility while considering how good science can best be done.

Concern with Producing Creatures with Human Consciousness or Mental Characteristics

40. If research involving human-animal combinations is allowed, there is concern that uncontrollable monsters could be created. The harm may be great, though on available evidence the probability of this occurring is low. However, a 'better safe than sorry' argument has some force here. One especially worrying kind of monster would be a non-human animal with human cognitive functions.

41. There is little likelihood of such a monster being created if only individual human neural cells are used, and none if non-neural cells, such as human retinal stem cells, are used. Indeed, as long as the number of cells transferred is small enough, the host will retain its own characteristics. Even if the number is large, the anatomical constraints of the host are such that the development of human characteristics is unlikely. Still, it may be wise for society to adopt precautionary measures even if the probability of producing creatures with human consciousness or mental characteristics is low. Such measures may include rules regulating the number and kind of human cells transferred, and the selection of host animals, if indeed such research is to be allowed at all.

42. A concern that these characteristics could arise from mixing human and animal genetic material can be seen as misplaced, since genetic material is shared in nature across many different species, including humans. It is in the combination of genetic material and the details of the interactions of such material that any species is defined, rather than merely the possession of some small proportion of unique genes. Nevertheless, there would be grounds for concern if a human-animal combination containing a substantial proportion of human material developed to become a living creature. This concern arises particularly when neural tissue is used, as it is the prerequisite for consciousness, or even for basic sentience,[27] and this concern becomes greater as the animal species involved appears closer to humans. Work with mice occasions less concern in this field than work with monkeys or apes. Nevertheless, concerns about the potential for

27 Feeling or sensation should be distinguished from perception and thought. A sentient creature or person is responsive to stimulation, without necessarily having what we would regard as conscious awareness, though whether or not sentience is accompanied by consciousness is impossible to determine with certainty.

human consciousness in chimeras have persistently been mentioned as one of the main concerns voiced by those objecting to such research.

43. In the specific case of human neural tissue grafted into non-human primates, the issue has attracted expert attention.[28] Recommendations have been proposed for ethics committees to oversee the creation of human-non-human primate neural tissue chimeras via the implantation of human neural stem cells into an animal, having regard to five factors, namely:

(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 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;

(c) *The recipient species*: Species with a closer approximation to human neural organisation are more problematic, because in general we like to think of ourselves as uniquely possessed of human attributes, and the likelihood of such attributes occurring in another species is increased when the other species is biologically close; and

(d) *The brain size of the animal involved*: This is a similar argument to (c). 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 tissue.

Eroding the Moral Boundary between Human and Animals

44. Current social institutions and practices are based on long established and fairly entrenched views about what counts as human and animal, and these have contributed to some form of moral demarcation between the two groups. Human-animal combinations can blur this boundary and thus potentially lead to moral and social confusion. Some are concerned that new rights and obligations that emerge may be difficult to enforce. What would happen to meat-eating practices in a world in which many animals had human tissues in them? How would we treat, say, monkeys that had human blood running through their veins?

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

45. Some may argue that the moral 'status quo' that separates humans from animals should not be disturbed. Such an argument may be grounded in a preference for certainty, and perhaps even an innate fear of or wariness towards the unknown. However, confusion or change due to departure from a generally accepted 'status quo' or social norms may not be a bad thing in the long run. The emancipation of slaves in the United States, the women's liberation movement and the civil rights movement are all instances of important changes to the moral and social 'status quo' of the time.

46. At a deeper level, it may be necessary to rethink the integrity and dignity of species in the context of our time, in perhaps the same way that moral and social phenomena such as the role of women, race relations and the family unit have seen fundamental changes in recent decades. The point to be made here is that a moral 'status quo' or well accepted social norm should not lead to a presumption that any change from that position is bad or harmful.

Identity Problems and the Moral Status of Human-Animal Combinations

47. Many of the concerns above are grounded in more deep-seated issues about the identity and the moral status of human-animal combinations. As noted, many ethical concerns arise from the fear that stem cell research, in creating inter-species organisms, will undermine the boundaries that now separate the species. In part, the 'playing God' argument says that crossing species boundaries will harm the integrity and dignity of species. Another concern is that blurring the species boundaries will cause moral confusion insofar as there is an established moral order based on the hierarchy of species. On the assumption that the moral status of something can only be determined if we know what kind of a thing it is (i.e. its identity), we need to settle questions such as: What kind of a thing is a chimera? Is it human or non-human? When is a chimera human enough for certain moral standards to apply (such as being respected, not being used solely as a means to an end, etc)? In particular, many people find the prospect of unintentionally transferring cognitive capacities to non-humans alarming.

48. Some of the concerns above appear to be based on the notion that there are rigidly fixed species boundaries. However, many biologists have dismissed such a notion: "The biological categorization of species is empirical and pragmatic," which means that "species categories are never real…"[29] Indeed, there are many different concepts of species.[30] On the other hand, it may be said that this scientific view is irrelevant and that the concerns have to do with the kinds of things that we are perfectly familiar with. In our ordinary conceptual scheme, there is such a thing as the humankind, members of which we can easily

29 Karpowicz P et al. It is Ethical to Transplant Human Stem Cells into Nonhuman Embryos. *Nature Medicine*. 10 (2004):331-335; page 333.

30 Mayden R. A Hierarchy of Species Concepts: The Denouement in the Saga of the Species Problem, in M. Claridge, H. Dawah and M. Wilson (eds.), *Species: The Units of Biodiversity*. London: Chapman and Hall, 1997, pages 381-424.

identify and pick out, and distinguish from members of other kinds, such as cats or insects. Mapped onto this conceptual scheme is a moral hierarchy in which the humankind occupies the top rung while other species occupy the lower rungs according to how close they are to us in terms of anatomical and psychological development. For instance, we typically regard killing an insect to be less serious than killing a cat, which in turn is not as serious as killing a monkey, a chimpanzee and a human being, in that order. It is likely that the objection to stem cell research and the use of human-animal combinations is really based on this ordinary conceptual and moral framework.

49. There are two concerns here. One is that human-animal combinations invalidate how we classify things, and as a result cause moral confusion. We may no longer be sure about what defines a member of a certain kind. However, the introduction of inter-species entities such as 'ligers' and 'geep' does not destroy lions and tigers, and goats and sheep, as we know them. Our ordinary conceptual scheme still applies to ordinary human beings and ordinary animals, and the only difficulty is that there are now additional kinds to consider as well. Against this, it may be said that our ordinary conceptual scheme will be undermined if there are more and more entities that do not fit in any existing kind. However, if we can cope with mules as a kind, and assimilate them into our thinking, then there is no obvious reason why we cannot cope with human-animal combinations, such as sheep with humanised livers or mice with human neurons. We would have new kinds, new entities, but the existing ones remain. That leads to the second concern, namely how we are to treat the individual new entities, or decide what moral status they possess.

50. Biological properties characteristic of one biological kind tend to preclude the development of biological properties characteristic of another kind. For instance, it is "highly unlikely that even a monkey chimera whose entire thalamocortical system was human-derived could possess human consciousness, as its neurons would lie in anatomically different networks."[31] This means that even if we take the capacity for human consciousness as sufficient for being a member of the humankind, it is still highly unlikely that there can be an entity that is both wholly human in its consciousness and wholly monkey or wholly something else in other aspects.

51. Another way of expressing this point is to refer to the function rather than to the structure of the animal, or human, or chimera being discussed. It can be argued that the essential nature of a human being or an animal is not defined just by virtue of the tissue they possess. Blood, for example, circulates oxygen to the body. A monkey with human blood is not thereby any less a monkey, since the function of blood with respect to body tissues is the same in monkeys and humans. In the case of the brain, it may be how the component tissues are organised that determines its properties, including its consciousness.

31 Karpowicz P et al. It is Ethical to Transplant Human Stem Cells into Nonhuman Embryos. *Nature Medicine*. 10 (2004):331-335; page 334.

52. An entity that does not fit any existing category may present conceptual difficulties but still, at the minimum, it can be said that if something is neither a human nor a monkey, then it does not have the status of either. How this entity may come to be understood will depend on where it fits within an existing moral order. There is little problem if this entity comes from different kinds of animals of the same moral status. Thus, insofar as the goat and the sheep have the same moral status, the hybrid geep takes on that same moral status. As for combinations with humans, the moral position of the entity becomes more challenging. We might decide to place the 'humouse' higher than the mouse, in which case we would give a 'humouse' greater moral status than we would a mouse. However, it may be said that only if and when there are enough entities of this type proliferating as naturally living entities will we have to start thinking about the practical implications of their moral status, not when they are merely laboratory specimens. On the other hand, this could be regarded as an invitation to a 'slippery slope', and the objections from slippery slope arguments therefore also need to be considered.

Human-Animal Combinations set us on a 'Slippery Slope'

53. Much of the defence raised by advocates of human-animal combinations, and indeed of embryonic stem cell research, relies on the idea that the benefits of research can justify a limited and regulated use of embryos or human-animal combinations as a useful means to an end. Yet, many objectors feel that while there may be benefits, the promise of them does not justify breaking absolute taboos that should preclude such research, because once the techniques and knowledge are developed, they may be misapplied. In short, once on a slippery slope, the very things that are now said to be improbable or should be prevented by regulation would inevitably materialise. This argument is exemplified in the claim that research cloning, or cloning technology, ought to be banned because it will sooner or later be used for reproductive cloning, whatever the law may say now. Similarly, a slippery slope argument will maintain that once research involving human-animal combinations becomes allowable, it will sooner or later lead to the creation of undesirable 'monsters' because not all scientific activity is controllable, and scientists are human and can be influenced or 'bought' like anyone else. Moreover, and more subtly, such critics maintain that our moral or ethical standards shift as we become accustomed to what was once considered objectionable. When women have a legal right to request an abortion on social grounds, it results in a shift of emphasis away from any rights an aborted foetus, or unborn child, might once have been deemed to have, say such critics. Why then should we not entertain similar fears about research involving human-animal combinations?

54. The main limitation of 'slippery slope' arguments is that they easily become an argument against change regardless of merit. It is a weak argument to suppose that one should not allow a potentially beneficial action for fear of others who might misapply such action towards harmful ends. If research involving human-

animal combinations is desirable in some respects, should it be avoided merely because we might get used to the idea and then do other things that we now think would be bad? As earlier discussed, the change of ethical standards and ideals over time, in response to changing circumstances, is not necessarily a harmful thing. The ethics of research, as with everything else, need to be considered at the time decisions have to be made, and to also take into account what is morally, politically and socially possible at that time. Otherwise, many reforms that we now appreciate and value, such as the Women's Charter, would never have been enacted, because they required a fresh ethical perspective.

LEGAL AND REGULATORY CONSIDERATIONS

55. The problem of slippery slopes and other ethical concerns discussed above cannot be lightly dismissed. They present a powerful argument for regulation, which has in many ways been an assurance that beneficial change would be introduced without abrupt and radical change to the fundamental values, beliefs and practices that underlie many of the key ethical issues arising from research involving human-animal combinations. Thus, there is a need for careful review of these concerns to determine whether, singly or in combination, they amount to an ethical barrier against some or all stem cell research involving human-animal combinations. Intrinsic to the review is an evaluation as to whether legal and regulatory responses could bring about beneficial change, while averting or mitigating any deleterious effect. If any of the ethical objections outlined above, or others, are found to be so overwhelming as to be inadequately addressed by legal and regulatory control, they might justify the outright prohibition of research using human-animal combinations. In considering the effectiveness of legal and regulatory responses to ethical concerns, there are useful precedents at hand.

56. Most if not all forms of biomedical research involving human subjects pose a threat to the dignity and integrity of human beings at some level. However, such research is not the subject of a comprehensive ban because the risk of serious harm can be mitigated by an effective legal and regulatory regime. In addition, this regime is increasingly supported by a more pervasive ethical infrastructure, within which research is also reviewed by research ethics committees or Institutional Review Boards (IRBs). An example of what such an ethical infrastructure attempts to achieve is encapsulated in the recommendations of the International Society for Stem Cell Research (ISSCR). These recommendations seek to ensure that all human embryonic stem cell research, whether or not human-animal combinations are used, meets certain requirements. They include scientific merit, being directed to the increase of knowledge and potential public

benefit, taking place in appropriate facilities with properly trained and supported scientists and staff, and having been peer reviewed.[32]

57. The proportion and nature of the human material in animal chimeras are generally not such as to risk creating human awareness or cognitive process, and the use of such animals is confined to research settings. The ISSCR argues for the need to avoid unwarranted stem cell exceptionalism in assessing the permissibility of animal chimera studies in stem cell research. By unwarranted exceptionalism it means the tendency to make the mere fact that the research entails stem cells, or chimeras for that matter, a basis for requiring a restrictive approach. When human embryonic stem cells are introduced into an animal in order to test the pluripotence of the stem cells, the risk of the animal developing human function or capability is negligible. For this reason, it has been argued that creating animal chimeras for such a purpose does not raise significant moral concerns and thus need not be subjected to the formal review of a stem cell research oversight committee but could be routinely approved by an animal care and use committee.[33] The relevant principle is that the degree of oversight should reflect the actual level of likely risk, not the category of research as such.

58. Following this principle, greater caution (and regulatory oversight) is needed when human stem cells or tissues are introduced into closely related, developing or injured organisms. Hence research with higher primates (such as monkeys and apes) is allowed only for very particular reasons (for example, the testing on primates of stem cell treatments targeting neurodegenerative diseases) and is properly subject to close ethical and regulatory scrutiny.

59. When considering any possible regulatory framework for research with human-animal combinations, it is of interest to consider legal and regulatory regimes for reproductive technologies. Although such technologies do not entail human animal combinations, the regimes regulating them present analogous problems, in that reproductive technologies have been the subject of objections similar to the ones discussed above and directed at human-animal combinations. Moreover, in many of the jurisdictions considered, the regulatory regimes for reproductive technologies have been extended to include within their ambit human stem cell research. Human reproductive cloning is explicitly prohibited and human embryonic stem cell research may be conducted under close regulatory scrutiny. Research with human-animal combinations falls within the ambit of such a regime as such research is generally considered as closely related to human embryonic stem cell research.

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32 ISSCR. Ethical Standards for Human-to-Animal Chimera Experiments in Stem Cell Research. *Cell Stem Cell*. 1 (2007):159-163, page 161, Recommendation 1; and ISSCR. Guidelines for the Conduct of Human Embryonic Stem Cell Research. 2006.

33 Lensch MW et al. Teratoma Formation Assays with Human Embryonic Stem Cells: A Rationale for One Type of Human-Animal Chimera. *Cell Stem Cell*. 1 (2007):1-6; and ISSCR. Ethical Standards for Human-to-Animal Chimera Experiments in Stem Cell Research. *Cell Stem Cell*. 1 (2007):59-163, Recommendation 3.

60. The UK is a country with one of the longest experiences with such a regime, first established under the Human Fertilisation and Embryology Act in 1990. This regime was in turn the result of a decade long process of deliberation and consultation since the publication of the Warnock Report.[34] During the periods prior to and even after this regime has been established, there was concern that reproductive technologies may be misused for purposes such as eugenics. The 'slippery slope' argument was often raised as a basis for this concern. But for almost twenty years since its enactment, this legal and regulatory regime appears to have been effective in keeping reproductive technologies within acceptable ethical limits.[35] This regime has allowed the control of extremes, as well as flexibility in dealing with new issues, although it should be noted that a moderated approach may not be practicable in every country.[36]

61. In a number of countries, regulatory oversight has been established for experimentation with human-animal combinations, particularly over the use of various experimental methods, and kinds of combinations that could be created. A summary of the regulatory approaches of select jurisdictions is set out in Table 2. It can be seen that in some jurisdictions, for at least some kinds of chimera or cytoplasmic hybrid, the benefits of research carried out in a carefully monitored environment have been held to justify the procedures. The extent to which this view should also prevail in Singapore is still to be decided.

62. There appear to be some especially salient features to regulatory regimes on research with human-animal combinations. In general, where creation of a cytoplasmic hybrid embryo is allowed for research, its development is limited to some early stage. Furthermore, the implantation of such an embryo into a woman or animal is generally prohibited. Research does not foreseeably require the creation of true human-animal hybrids or chimeras through injecting animal cells into human embryos. Moreover, it is illegal to create these entities in many countries.

63. In addition, as it is generally considered inappropriate to perpetuate offspring with unknown combinations of human and animal characteristics, it follows that animal chimeras with some human cells in the germline should not be allowed to breed.

34 Warnock M (1984). *Report of the Committee of Enquiry into Human Fertilisation and Embryology*. Great Britain, HMSO, Cmnd 9314.

35 Franklin S and Roberts C. *Born and Made: An Ethnography of Preimplantation Genetic Diagnosis*. Princeton University Press, 2006.

36 Campbell AV. Public Policy and the Future of Bioethics. *Genomics, Society and Policy*. 1 (2005):86-91, page 87.

CONCLUSION

64. It is clear that there are many ways in which research with human-animal combinations is likely to be an important part of future progress in biomedical science. It is also clear that to proceed with such research raises ethical and regulatory issues that require careful consideration. However, none of the issues discussed in this paper are settled as yet, and a major purpose of this Consultation Paper is to solicit public feedback, so as to gauge the nature of any public concerns, and consider whether and how they might best be addressed.

Table 2. Regulatory Approaches of Select Countries on Human-Animal Chimeras and Hybrids[37]

Country[38]	Human-Animal Chimeras	Human-Animal Hybrids	
		True Hybrids	Cytoplasmic Hybrids
Australia Prohibition of Human Cloning Act, 2002 Prohibition of Human Cloning for Reproduction and the Regulation of Human Embryo Research Amendment Act 2006	The intentional creation of a chimeric embryo is prohibited (Section 17 of the 2006 Amendment Act). A chimeric embryo is defined as "a human embryo into which a cell, or any component part of a cell, of an animal has been introduced" or a thing declared as such by regulation (Section 8 of the 2002 Act).	The intentional creation and development of a hybrid embryo is prohibited, except when it is created under licence for the purpose of testing sperm quality in an accredited ART centre (Section 23B(1) and (2) of the 2006 Amendment Act).	The creation of a cytoplasmic hybrid embryo, whereby a human somatic cell and an animal egg are used, is allowed under licence and the hybrid embryo is 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) Canadian Institutes of Health Research, Updated Guidelines for	The creation or transplantation of a chimera into a human or a non-human life form is prohibited (Section 5(1)(i) the AHRA). In the AHRA, a chimera is "(a) an embryo into which a cell of any non-	The creation of hybrid individuals by "mixing human and animal gametes" is not ethically acceptable under the Tri-Council Policy Statement (Articles 9.3 and 9.5).	The creation of a cytoplasmic hybrid for reproduction or transplantation into a human being or a non-human life form is prohibited (Section 5(1)(j) of the AHRA.

37 The information set out in the table is indicative and need not necessarily be a complete representation of the regulatory approach of the specified country. In particular, the regulatory approach of the country presented has been interpreted in relation to human-animal combinations as they are defined in this Consultation Paper and for the purposes set out in the Introduction.

38 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.

Country[38]	**Human-Animal Chimeras**	**Human-Animal Hybrids**	
		True Hybrids	**Cytoplasmic Hybrids**
Human Pluripotent Stem Cell Research, 29 June 2007 (Updated Guidelines) Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (1998, with 2000, 2002 and 2005 amendments)	human life form has been introduced; or (b) an embryo that consists of cells of more than one embryo, foetus or human being" and an embryo refers to a human embryo. The AHRA does not prohibit the creation of chimeras that combines any cell of a human with an animal embryo (i.e. animal chimera). Notwithstanding the AHRA, the creation of a chimera using any cells likely to be pluripotent in a human or non-human embryo, or grafting such cells onto human or non-human foetuses is prohibited for publicly funded research (Section 8.2.4 – 8.2.7 of the Updated Guidelines). Research involving the grafting of human pluripotent cells into developed non-human animals (i.e. animal chimeras are created in the process), are allowed provided that the research aims to produce pre-clinical models of specific	The creation of a true human-animal hybrid for reproduction or transplantation into a human being or a non-human life form is prohibited (Section 5(1)(j) of the AHRA).	

Country[38]	Human-Animal Chimeras	Human-Animal Hybrids	
		True Hybrids	**Cytoplasmic Hybrids**
	tissue or organ and that such non-human animals used for research will not be used for reproductive purposes (Section 8.1.6 of the Updated Guidelines).		
China Guidelines on Assisted Reproductive Technology (ART Guidelines, 2003) Ethical Guiding Principles on Human Embryonic Stem Cell Research, 2003, (HESCR Principles)	Research on embryos that are more than 14 days from the time of fertilisation or nuclear transfer is prohibited (Principle 6(1) of the HESCR Principles). Mixing of human material with non-human material is prohibited (Chapter 3 Paragraph 2 of the ART Guidelines).	Mixing or combining human and non-human gametes is prohibited (Chapter 3 Paragraph 2 of the ART Guidelines and Principle 6(3) of the HESCR Principles).	The creation of cytoplasmic hybrids is not explicitly prohibited in the HESCR Principles.
India National Guidelines for Accreditation, Supervision and Regulation of ART Clinics in India, Indian Council of Medical Research (ICMR) and the National Academy of Medical Sciences, 2005 Guidelines for Stem Cell Research and Therapy, ICMR,2006	*In-vivo* studies with established stem cell lines on animals are allowed with prior approval of institutional and national level committee, provided such animals are not allowed to breed (Paragraph 6.1.2 of 2006 Guidelines). Research involving the introduction of human embryonic stem cell into animals at the embryonic or foetal stage, and studies on chimeras where stem cells from two or more species are mixed and	The creation of a true hybrid is prohibited (Paragraph 3.5.16 of the 2005 National Guidelines).	There is no specific regulation relating to the creation or use of cytoplasmic hybrids.

Country[38]	Human-Animal Chimeras	Human-Animal Hybrids	
		True Hybrids	**Cytoplasmic Hybrids**
	introduced into animals at any stage of development, must be monitored institutionally and by a national level committee (Paragraphs 6.2.3 and 6.2.4 of the 2006 Guidelines).		
Japan The Law Concerning Regulation Relating to Human Cloning Techniques and Other Similar Techniques (2001)	The transfer of a human-animal chimeric embryo into the uterus of a human or an animal is prohibited (Article 3 of the Law). Approval of the Ministry of Education, Culture, Sports, Science and Technology (MEXT) is required for the production of a chimera (Article 6 of the Law).	The transfer of a true hybrid (referred to as a human-animal amphimictic embryo) into the uterus of a human or an animal is prohibited (Article 3 of the Law). Approval of the MEXT is required for the production of a true hybrid (Article 6 of the Law).	Transfer of a cytoplasmic hybrid (referred to as a human-animal hybrid embryo) into a uterus of a human or an animal is prohibited (Article 3 of the Law). Approval of the MEXT is required for the production of a cytoplasmic hybrid (Article 6 of the Law).
South Korea Bioethics and Biosafety Act (2004)	Fusing a human embryo with an animal embryo is prohibited (Article 12(2)(3) of the Act). Research on embryos is regulated by the Ministry of Health and Welfare (Articles 18 and 19 of the Act).	The creation of a true hybrid is prohibited, except for the purpose of testing human sperm cells (Article 12(2)(1) of the Act).	The creation of a cytoplasmic hybrid for research, whereby a human somatic cell and an animal egg are used, is allowed, subject to requirements set out in the Act, including the requirement for such research to be aimed at

Country[38]	Human-Animal Chimeras	Human-Animal Hybrids	
		True Hybrids	**Cytoplasmic Hybrids**
			curing rare and incurable diseases as decreed by the President (Articles 17 and 22 of the Act). The creation of a cytoplasmic hybrid, whereby an animal somatic cell and a human egg are used is prohibited. The implantation of such a hybrid into the uterus of an animal or a human is also prohibited (Articles 12(2)(2) and 12(2)(3)). Production of and research on cytoplasmic hybrid are regulated by the Ministry of Health and Welfare. However, the implantation of an animal's somatic cell nucleus into an enucleated human egg is prohibited (Article 12).
Singapore Private Hospitals and Medical	All research on human eggs or embryos to be carried out only after written approval of the Ministry of Health has	Trans-species fertilisation for the purpose of reproduction is not allowed. However, trans-	It is unclear if the creation of a cytoplasmic hybrid is a regulated activity under the

Country[38]	Human-Animal Chimeras	Human-Animal Hybrids	
		True Hybrids	**Cytoplasmic Hybrids**
Clinics Act (2004, amended) Directives for Private Healthcare Institutions Providing Assisted Reproduction Services: Regulation 4 of the Private Hospitals and Medical Clinics Regulations (Cap 248, Reg 1), March 2006	been obtained (Paragraph 8.1 of the Directives). Research on or using human embryos which are more than 14 days old from the time of creation is prohibited (Paragraph 8.4 of the Directives).	species fertilisation to assess or diagnose sub-fertility is allowed, although the resulting hybrid must be terminated at the two-cell stage (Paragraph 8.7 of the Directives).	existing regulatory regime.
United Kingdom Human Fertilisation and Embryology Act 1990 Human Fertilisation and Embryology Bill (2007)	Under the current (1990) legislation, it is unclear whether the creation of a human-animal chimera is permitted. The creation of an inter-species embryo, as well as its storage and use, will be permitted under licence if the Bill is enacted (Section 4(2) of the published Bill). An "inter-species embryo" includes a human embryo altered by the introduction of one or more animal cells. The Bill stipulates that a licence cannot authorise placing an inter-species embryo in a woman or in an animal, and keeping or using of such an embryo after the appearance of the primitive streak or after	The mixing of human and animal gametes is prohibited unless pursuant to a licence (Section 4(c) of the Act). The current scope of a licence (under Schedule 2 of the Act) covers only the mixing of sperm with the egg of a hamster (or such other approved animal) for the purpose of testing the fertility or normality of the sperm, and in no event shall the growth of such a combination extend beyond the two-cell stage. The creation of an inter-	It is unclear if the creation of a cytoplasmic hybrid embryo may be licensed under the current (1990) legislation. The House of Lords (the highest court in Britain) has ruled that therapeutic cloning falls within the regulatory ambit of the legislation, although this was in relation to human embryos (*R v Secretary of State for Health* [2003] 2 All ER 113). An "inter-species embryo" created by replacing the nucleus of an animal egg or of an animal cell, or two animal

Country[38]	Human-Animal Chimeras	Human-Animal Hybrids	
		True Hybrids	**Cytoplasmic Hybrids**
	a period 14 days from when the embryo was created, which ever is earlier.	species embryo, as well as its storage and use, will be permitted under licence if the Bill is enacted (Section 4(2) of the published Bill). An "inter-species embryo" includes an embryo created by using human gametes and animal gametes, or one human pronucleus and one animal pronucleus. The Bill stipulates that a licence cannot authorise placing an inter-species embryo in a woman or in an animal, or keeping or using of such an embryo after the appearance of the primitive streak or after a period 14 days from when the embryo was created, which ever is earlier.	pronuclei with two human pronuclei, one nucleus of a human cell or one human cell, would be permitted pursuant to licence if the Bill is enacted (Section 4(2) of the published Bill). The Bill stipulates that a licence cannot authorise placing an inter-species embryo in a woman or in an animal, and keeping or using of such an embryo after the appearance of the primitive streak or after a period 14 days from when the embryo was created, which ever is earlier.
United States of America Federal Law	US Federal law does not prohibit the creation and use of a human-animal chimera for research.	US Federal law does not prohibit the creation and use of a true hybrid for research.	US Federal law does not prohibit the creation and use of a cytoplasmic hybrid for

Country[38]	Human-Animal Chimeras	Human-Animal Hybrids	
		True Hybrids	**Cytoplasmic Hybrids**
National Academy of Sciences, Guidelines for Human Embryonic Stem Cell Research (2005, amended February 2007) State law varies significantly, with a number of states that allow nuclear transfer research (such as the states of California and Massachusetts) and a number that do not (such as the states of Florida and Louisiana). A general survey of US State laws regarding embryo and foetal research is available at this webpage of the National Conference of State Legislatures: http://www.ncsl.org/programs/health/genetics/embfet.htm (last visited November 2007).	The National Academy of Sciences (NAS) recommended that: (i) Research where human embryonic stem (hES) cells are introduced into nonhuman primate blastocysts or where any embryonic stem cells are introduced into human blastocysts should not be conducted at this time (Paragraph 1.2(c)(2) of the 2007 Guidelines); (ii) No animal into which hES cells have been introduced at any stage of development should be allowed to breed (Paragraph 1.2(c)(3) of the 2007 Guidelines); (iii) Research involving the introduction of hES cells into non-human animals at any stage of development will require additional review and approval by an Embryonic Stem Cell Research Oversight (ESCRO) committee. Particular attention should		research. The NAS Guidelines regarded a cytoplasmic hybrid (referred to as an "interspecies combination" or "interspecies construct") as a product similar to that of human nuclear transfer and would thereby be subject to similar guidelines prohibiting implantation or culture beyond 14 days or the primitive streak stage (Page 41 of the NAS Guidelines, 2005 edition). When hES cell lines are to be derived from a cytoplasmic hybrid, the approval of an ESCRO will have to be obtained (Paragraph 4 of the 2007 Guidelines).

Country[38]	Human-Animal Chimeras	Human-Animal Hybrids	
		True Hybrids	**Cytoplasmic Hybrids**
	be paid to the probable pattern and effects of differentiation and integration of the human cells into the non-human animal tissues (Paragraph 1.2(b)(2) of the 2007 Guidelines); (iv) Introduction of hES cells, their derivatives or other pluripotent cells into non-human foetuses and allowed to develop into adult chimeras need more careful consideration. Consideration of any major functional contributions to the brain should be a main focus of review (Paragraph 6.6 of the 2007 Guidelines); and (v) Introduction of hES cells into non-human mammalian blastocysts should be considered only under circumstances in which no other experiment can provide the information needed (Paragraph 6.7 of the 2007 Guidelines).		

Glossary

Adult stem cell – An unspecialised cell, present in a tissue or organ, that is able to replicate itself and develop into specialised cell types of that tissue or organ, or into some other cell types.

Alzheimer's disease – A degenerative brain disorder common in the elderly, characterised by progressive deterioration of mental functions leading to impaired memory, thinking, judgment and ability to concentrate, emotional instability and increased reliance on others for daily activities.

Bone marrow – Tissue found in the interior cavities of bone and which is capable of producing blood cells.

Chimera – An organism whose body contains cells from another organism of the same or a different species. Sometimes spelled 'Chimaera'.

Cytoplasmic hybrid embryo – An embryo created by the transfer of the nucleus of a somatic cell from one species into an egg of another species from which the nucleus has been removed.

Differentiation – The process whereby an unspecialised cell become a specialised cell.

Disease-specific stem cells – Stem cells that contain genes associated with a specific disease.

Embryo – The earliest stage of development of an organism.

Embryonic stem cell – An unspecialised cell derived from an embryo, that is able to replicate itself indefinitely and develop into all types of cells, for example, skin, nerve or heart cells.

Foetus (Fetus) – The stage of development of an organism beyond the embryo and before birth, when tissues and organs have started to differentiate.

Gamete – Sperm or egg.

Gene therapy – Treatment of a genetic disorder by the insertion of functional genes to replace, supplement or manipulate the expression (the working) of non-functional or abnormal genes.

Genome – The complete set of genetic information in an organism.

Hybrid – An organism whose cells contain genetic material from organisms of different species.

Immuno-deficient – A state in which the body's immune system is weakened or not functioning normally.

Immune system – The body's protective mechanism against disease and foreign tissue or substances.

In vitro fertilisation (IVF) – A clinical and laboratory procedure whereby eggs and sperms from a couple are extracted and fertilised outside their bodies. Such a procedure is a kind of assisted reproduction aimed at increasing the chances of a couple conceiving a baby.

In vivo – In a living organism.

Nuclear reprogramming – The process whereby the nucleus of a somatic cell is converted into one with the characteristics and potential of an embryonic cell nucleus.

Nucleus – The part of a cell that carries most of the cell's genetic material.

Oncogene – A gene associated with cancer development.

Oncomouse – A transgenic mouse with an increased susceptibility to developing cancer, created by inserting a human oncogene into an early mouse embryo.

Parkinson's disease – A disorder characterised by progressive degeneration of certain nerve cells in the brain, resulting in muscular tremors, rigid movement, stooped posture, and mask-like face.

Pluripotent – Able to develop into all types of specialised cell.

Poliomyelitis – An infectious viral disease of the central nervous system, which can lead to muscle weakness and paralysis.

Post-natal – After birth.

Receptor - A protein on the outermost layer (membrane) of a cell, capable of binding specific molecules.

Research cloning (also known as therapeutic cloning) – The use of cloning technology for research and therapeutic purposes in ways that that do not result in the creation of a complete animal or human being.

SCID-hu mouse – A mouse with a human immune system. It is used as a research model and is created by transplanting human foetal immune cells or tissue into a mouse with severe combined immunodeficiency (SCID).

Severe combined immunodeficiency (SCID) – A genetic disorder that results in a dysfunctional immune system.

Somatic cell – Any mature (or differentiated) cell in the body that is not a sperm or an egg.

Somatic cell nuclear transfer (SCNT) – The process whereby the nucleus of a somatic cell is transferred into an egg from which the nucleus has been removed.

Spinal muscular atrophy – A genetic disorder where cells of the spinal cord die, resulting in progressively weaker muscles.

Stem cell – An unspecialised cell that is able to replicate itself and develop into specialised cell types (such as a skin, nerve, or heart cell).

Specialised (differentiated) cell – A mature cell with a specific function, for example, skin cells and liver cells.

Teratoma – A tumour that consists of different cell types and tissues from the three basic cell layers, i.e. the layers that are the foundation of all subsequent tissue and organ development.

Thalamocortical system – The system of connections in the brain, whereby information is processed and transmitted.

Therapeutic cloning – See Research cloning.

Tissue – An aggregation of similar cells that perform a particular function.

Transgenic animal – An animal that has a genome containing genes from another species.

True hybrid – An organism that results from the fertilisation of an egg from one species by a sperm from another species.

Xenotransplant – The transplantation of an organ or tissue from one species to another.

List of Useful Documents

Bioethics Advisory Committee. *Ethical, Legal and Social Issues in Human Stem Cell Research, Reproductive and Therapeutic Cloning*. Singapore, June 2002. http://www.bioethics-singapore.org/uploadfile/60517 PMHSC Research.pdf.

Bioethics Advisory Committee. *Donation of Human Eggs for Research: A Consultation Paper*. Singapore, 7 November 2007. http://www.bioethics-singapore.org/uploadfile/52533 PMEgg Donation Consultation Paper.pdf.

California Institute for Regenerative Medicine. *The CIRM Medical and Ethical Standards Regulations*. US, January 2007. www.cirm.ca.gov/reg/pdf/Reg100010_CompRegs.pdf (accessed 4 January 2008).

Human Fertilisation and Embryology Authority. *Hybrids and Chimeras: A consultation on the ethical and social implications of creating human/animal embryos in research*. UK, April 2007. http://www.hfea.gov.uk/docs/HFEA_Final.pdf (accessed 4 January 2008).

Human Fertilisation and Embryology Authority. *Hybrids and Chimeras: A report on the findings of the consultation*. UK, October 2007. http://www.hfea.gov.uk/docs/Hybrids_Report.pdf (accessed 4 January 2008)

Human Fertilisation and Embryology Authority. *HFEA statement on its decision regarding hybrid embryos*. UK, 5 September 2007. http://www.hfea.gov.uk/en/1581.html (accessed 4 January 2008).

Indian Council of Medical Research. *National Guidelines for Stem Cell Research and Therapy*. 2006. http://www.icmr.nic.in/stem_cell/stem_cell_guidelines.pdf (accessed 4 January 2008).

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Ministry of Health. *Directives for Private Healthcare Institutions providing Assisted Reproduction Services: Regulation 4 of the Private Hospitals and Medical Clinics Regulations (Cap 248, Reg1).* Singapore, revised March 2006. https://www.moh-ela.gov.sg/ela/docroot/html/assisted_reproduction_services_directives.pdf (accessed 4 January 2008).

National Health and Medical Research Council. *Ethical Guidelines on the Use of Assisted Reproductive Technology in Clinical Practice and Research*. Australia, 2004, revised 2007.
http://www.nhmrc.gov.au/publications/synopses/_files/e78.pdf (accessed 4 January 2008).

The Academy of Medical Sciences. *Inter-species embryos*. UK, June 2007.
http://www.acmedsci.ac.uk/download.php?file=/images/project/interspe.pdf (accessed 4 January 2008)

The National Academy of Sciences. *Guidelines for Human Embryonic Stem Cell Research*. USA, 2005, amended 2007.
http://www.nap.edu/catalog.php?record_id=11278#toc (accessed 4 January 2008).

Nuyen AT. *Stem Cell Research and Interspecies Fusion: Some Philosophical Issues*. A background paper for the Bioethics Advisory Committee, Singapore. 2006.
http://www.bioethics-singapore.org

ANNEX B

CONSULTATION PAPER DISTRIBUTION LIST

Distribution List for Consultation Paper on
"Human-Animal Combinations for Biomedical Research"
(Public Consultation Period: 8 January to 10 March 2008)

1. Academy of Medicine, Singapore
2. Alexandra Hospital
3. Bioinformatics Institute
4. Bioprocessing Technology Institute
5. Buddhist Fellowship
6. The Catholic Medical Guild of Singapore
7. Centre for Research on Islamic and Malay Affairs, Association of Muslim Professionals
8. Changi General Hospital
9. College of Family Physicians Singapore
10. Duke-NUS Graduate Medical School
11. ES Cell International
12. Faculty of Arts and Social Science, National University of Singapore
13. Faculty of Dentistry, National University of Singapore
14. Faculty of Law, National University of Singapore
15. Faculty of Science, National University of Singapore
16. Genetic Modification Advisory Committee
17. Genome Institute of Singapore
18. Graduates' Christian Fellowship
19. Hindu Advisory Board
20. Institute of Bioengineering and Nanotechnology
21. Institute of Medical Biology
22. Institute of Mental Health/Woodbridge Hospital
23. Institute of Molecular and Cell Biology
24. Jewish Welfare Board
25. Johns Hopkins Singapore International Medical Centre
26. KK Women's and Children's Hospital
27. Law Reform Committee, Singapore Academy of Law
28. Lee Kuan Yew School of Public Policy, National University of Singapore
29. The Law Society of Singapore
30. Majlis Ugama Islam Singapura (Islamic Religious Council of Singapore)
31. Mount Alvernia Hospital
32. National Advisory Committee for Laboratory Animal Research
33. National Cancer Centre
34. National Council of Churches of Singapore

35. National Dental Centre
36. National Heart Centre
37. National Medical Ethics Committee, Ministry of Health, Singapore
38. National Neuroscience Institute
39. National Skin Centre
40. National University Hospital
41. Natural Sciences and Science Education Academic Group, National Institute of Education
42. NUH-NUS Tissue Repository
43. Obstetrical and Gynaecological Society of Singapore
44. Office of Life Sciences, National University of Singapore
45. Parkway Hospitals Singapore Pte Ltd
46. Raffles Hospital
47. School of Arts and Social Science, SIM University
48. School of Biological Sciences, Nanyang Technological University
49. School of Human Development and Social Science, SIM University
50. School of Humanities and Social Science, Nanyang Technological University
51. School of Law, Singapore Management University
52. School of Science and Technology, SIM University
53. School of Social Sciences, Singapore Management University
54. Sikh Advisory Board
55. Singapore Buddhist Federation
56. Singapore Chinese Buddhist Association
57. Singapore General Hospital
58. Singapore Institute for Clinical Sciences
59. Singapore Medical Association
60. Singapore Medical Council
61. Singapore National Academy of Science
62. Singapore National Eye Centre
63. Singapore Nurses Association
64. Singapore Nursing Board
65. Singapore Psychological Society
66. Society of Bioscience & Technology
67. The Spiritual Assembly of the Bahá'is of Singapore
68. Tan Tock Seng Hospital
69. Taoist Mission (Singapore)
70. Thomson Medical Centre
71. Yong Loo Lin School of Medicine, National University of Singapore

ANNEX C

WRITTEN RESPONSES RECEIVED DURING THE PUBLIC CONSULTATION

Written Responses Received During the Public Consultation on Human-Animal Combinations for Biomedical Research

Organisations / Institutions

C1 The Catholic Medical Guild of Singapore
C2 Centre for Research on Islamic and Malay Affairs (RIMA)
C3 Institute of Bioengineering and Nanotechnology
C4 Institute of Medical Biology
C5 Institute of Molecular and Cell Biology
C6 KK Women's and Children's Hospital
C7 The Law Society of Singapore
C8 Majlis Ugama Islam Singapura (Islamic Religious Council of Singapore)
C9 National Council of Churches of Singapore
C10 National Dental Centre Institutional Review Board
C11 National Medical Ethics Committee, Ministry of Health, Singapore
C12 National University Hospital
C13 Office of Life Sciences, National University of Singapore (renamed Life Sciences Institute since 1 April 2008)
C14 Parkway Independent Ethics Committee
C15 Raffles Hospital
C16 Singapore Medical Council
C17 Singapore Nursing Board
C18 Society of Bioscience and Technology
C19 Taoist Mission (Singapore)

Individuals

C20 Gordon Carson
C21 Nicole Cheng
C22 Dr Chuah Khoon Leong
C23 Dr Hannes Hentze
C24 Dr Steven Ho
C25 Dr Matiullah Khan
C26 Dr Khoo Lock Nah
C27 Dr Prasanna Ratnakar Kolatkar
C28 A/Prof Li Guodong
C29 Dr Lim Sai Kiang
C30 Cognose Lim Swee Keng
C31 Dr Steve Oh

C32 Dr Gabriel Oon Chong Jin
C33 Evelyn Quek
C34 Prof Davor Solter
C35 Dr Uttam Surana
C36 Member of the Public 1
C37 Member of the Public 2
C38 Member of the Public 3
C39 Member of the Public 4

In addition to the comments from the above organisations and individuals, several confidential comments were also received and considered.

Comments from The Catholic Medical Guild of Singapore

27 March 2008

Dear Sirs

We are grateful for this opportunity to provide feedback on the above issue.
We shall like to begin with a review of principles on which we base our feedback.

PRINCIPLES:

1. We fully encourage the pursuit of science as a means to improve the human condition, to treat disease, and to save human life.

2. Yet we recognize that not everything that is scientifically possible is for that reason morally permissible. Ethics committees exist because we recognize the fact that the pursuit of science without conscience can only lead to humanity's ruin.[1]

3. The life of every human being must be respected from the very first instance of his existence. From that same moment his or her rights as a person must be recognized, among which in the first place is the inviolable right of every innocent human being to life.[2]

4. Every human being is to be respected for himself or herself and cannot be reduced in worth to an instrument for the advantage of others.[3]

5. In stem cell research and therapy, human embryos should be treated with the respect proper to all human beings and should be protected. It is ethically unacceptable to:

    - Deliberately destroy human embryos at any stage of development;
    - Risk causing harm to a developing human embryo for research;
    - Intentionally use reproductive technology to produce a human embryo, by fertilization or other means such as cloning, for the purpose of growing tissues or organs, or of obtaining stem cells.

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1 Donum Vitae, I.2
2 Donum Vitae, I.1
3 Donum Vitae, I.5

We will give our feedback with a discussion on the scientific aspects of human-animal chimera research, which appears to be a major part of the BAC paper, and then discuss some philosophical aspects brought up in the paper as well.

Problems with formation of cybrids from a scientific point of view

In research involving cybrids, scientists remove the nucleus of the egg cell of an animal (e.g. cow) and replace it with the nucleus of a body cell (e.g. skin cell) of a human. The resulting embryo, a hybrid made of the cytoplasm of the animal egg cell and the nucleus of the human cell, is called a "cybrid" (short for cytoplasmic hybrid).

The human cybrid is essentially a human clone in animal egg. It is made of 99% human genes and 1% animal genes.

The animal genes come from the mitochondria (structures which provide energy for a cell's activity). The cybrids are then made to divide until they are about 4 to 5 days old when they reach the blastocyst stage. At this stage, the embryos are killed and their stem cells harvested in the hope that they can be used to treat certain diseases like stroke, Parkinson's disease, and diabetes.

Despite all the excitement generated in the scientific community, to date there has been only ***one*** published record of success in obtaining embryonic stem cells from cybrids. (Chen et al[4] in 2003). Interestingly, since then, even this team had been unable to repeat their feat.

It is also significant that the eminent embryonic stem-cell researcher Robert Lanza,[5] of Advanced Cell Technology disclosed that his company had failed despite many attempts at producing embryonic stem cells derived from cybrids. He observed that the artificially created cells were somehow just unable to progress beyond the 16-cell stage (i.e. just short of the blastocyst stage from which stems cells may be derived).

Lanza attributed this blockage in growth to the incompatibility of the animal mitochondrial genes and the human genes.

Moreover, there are certain serious diseases that are transmitted specifically by mitochondrial genes. Mitochondria contain genetic material, and are responsible for the production of energy that help power the cell's life processes. Any defect in their make-up, or the way they interact with the rest of the cell, could result in a number of serious diseases, such as fatal liver failure, blindness, mental retardation with intractable epilepsy, muscle weakness, diabetes and deafness.[6]

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

5 Andy Coghlan. Human-animal cybrids may not be possible. New Scientist 14 September 2007; 2621: 15

6 Roger Highfield, "Transplant creates embryos with three parents", The Telegraph, 05.02.2008.

Since embryonic stem cells derived from cybrids are likely to retain the mitochondrial genes of the animal cell involved, there exists the strong possibility that animal related mitochondrial disease may be transmitted to humans through the cell lines created.

Therefore, formation of cybrids with the intention of harvesting the stem cells poses the following problems:

1. the potential for transmission of animal-related mitochondrial disease.

2. in the field of human embryonic research, there remains the unresolved problem of possible tumour (cancer) formation. Embryonic cells obtained from cybrids are likely to face a similar if not greater obstacle.

3. In some experiments, scientists have noted significant changes in the genes (i.e. mutations) of the cultured human embryonic stem cells.[7] Some of these mutations play a role in transforming normal cells into cancer cells. Transplanting such cells into a patient could cause more medical problems than they would be likely to solve.

4. There is also the risk of transmission of retroviruses and other forms of serious infections initially confined to the animal kingdom. The genes of such viruses existing within the mitochondria or cytoplasm of the egg, may integrate themselves with the genes of the cybrid and cause illnesses, including the formation of tumors. Presently, there is no way to guarantee that such mixed stem-cell lines are free from animal retroviral contamination. It is thus highly questionable if such cell lines can be safely used on humans.

Considering the above problems, one might reasonably question the wisdom of draining vast resources on a project which offers little guarantee of success when there are already viable alternatives, such as adult stem cells. Obtained from sources such as bone marrow, umbilical cord, and the placenta, adult stem cells do not involve the destruction of any human embryo and are free of ethical and legal concerns, Adult stem cell lines have been used to treat diseases successfully. There have been at least 65 proven reports of successful adult stem cell therapy whereas none had so far been recorded for embryonic stem cells.[8]

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7 Maitra A et al. Genomic alterations in cultured human embryonic stem cells. Nat Genet 2005; 37(10): 1099-1103

8 Prentice D, Tarne G. Adult versus embryonic stem cells : treatments. Science 2007 Jun 8;316(5830): author reply 1422-3

A Philosophical Viewpoint

The Status of the Cybrid Embryo

It has been argued that the human-animal cybrid embryos are not technically humans because they do not come from a human egg and human sperm. The question therefore arises: should the ethical rule of absolute respect for human embryos also apply to embryonic human cybrids?

Let us imagine, for the sake of discussion, that, one day, a group of anthropologists discovers in a remote island a strange creature which they have never seen before. They observe that this creature looks quite human. In fact, it shows all the human traits we have. What puzzles scientists is that this creature is not born from other female members of the species but surprisingly and inexplicably, grows from trees. A human-like bud develops in a tree, the bud blooms into a flower, and after 9 months, a human-like creature is born. The whole world is confused and mesmerized about this human-like creature. Soon some scientists decide that the scientific thing to do is to retrieve a few specimens, kill them and dissect them for experimentation. Would that be reasonable?

No, it would not. There is a basic ethical rule that forbids acting in the face of doubt as to what we are doing. If during hunting season, someone notices some movement behind the bushes, but is not sure if that is due to a human or an animal that is moving behind those bushes, is he allowed to shoot? No, it is not permissible since what is moving behind the bushes could either be a person or an animal. It would not be a responsible thing to shoot before confirming that what is moving is indeed an animal and not a person.

We cannot act responsibly and therefore ethically before we resolve the doubt or ignorance as to what we are really doing — in our case, shooting an animal or a person. When in doubt, one should never shoot. This is common sense. The same rule would apply for this “strange new creature”. Until we know, beyond any reasonable doubt, that what we are dissecting is not a human creature, scientists should refrain from harming this creature in any way.

The human cybrid would be such a creature. For all we know, it is more likely to be human than non-human.

We know this because previous clones resemble the donor of the cellular nucleus –in fact they are almost genetically identical– more than they resemble the donor of the egg, in our case, the animal. So as far as science can tell us today, this embryo is genetically mainly human.

Therefore the only consistent conclusion is that if human embryos should be absolutely respected, so should be the embryonic human cybrids. They should be respected

regardless of our doubts about their real nature. They should still be respected, and all the more, since we scientifically know that they are "genetically" mainly human. The only reasonable thing to do is to give them the benefit of the doubt and protect them with the same respect the normal human embryos deserve.

'Playing God'

The BAC had noted in its paper that:

"The 'playing God' argument cuts both ways. If research involving human-animal combinations can save life, then to stop the research is to 'play God' with respect to those whose lives could be saved" (*Ethical Considerations in Research with Human-Animal Combinations*, # 38).

The 'playing God' argument needs to be understood more precisely before it can be honestly used. There is nothing wrong with using science and technology to have some control over nature and animals. We harness the power of rivers, breed cattle, cultivate deserts, transplant hearts, and attempt to master the global climate. Control over nature however must not be despotic and capricious. We are not absolute lords of the universe, only "stewards" of God's creation. How to know when we have trespassed into forbidden territory?

Playing God is not creation husbandry; it is stepping where God alone can step in: dominion over the human person. The human person can never be used as a means to an end and must always be respected and considered an end in himself (Kant). This is not a religious conclusion but the most basic ethical concept without which civilization itself collapses. All humans are equal in dignity. When a person controls the destiny of another human being, he breaches this fundamental ethical norm and erects himself as superior to his equals. He plays a forbidden game, not only because he usurps God's prerogative, but also because he creates a divide of masters and slaves.

Hitler did not play God because he spent his life in a laboratory. He played God when he made himself god unto others by deciding to terminate people's lives. If all humans deserve absolute respect, this means that no one has any right whatsoever to decide when a person should stop living. When someone does, we call it murder.

But it also means that no one has the right to decide when, how or for what purpose a person is created. Human cloning is an example of such 'technological dominion" over the human person. Not even parents should exert their dominion over their children. They are called to be stewards of the human life that has been entrusted to them, not tyrants. In other words, no one, no parent, no ruler, no religious or political leader has the right to be superior in dignity to others by deciding their destiny.

When it comes to dealing with human beings (embryos or not), other humans (scientists or not) may not destroy them, experiment on them without informed consent,

manipulate their genetic identity or transfer inside or outside them biological material that affects their identity.

Making cybrids is "playing God", not because it is an artificial research project but because when scientists fabricate, use and dispose of human cybrids, they take a position of dominion, and not one of respect, over the lives of human beings. The "playing God" argument does not cut both ways when we understand that God has taken the human cause seriously. Even if the providence of God is not accepted, we must never justify the dominion of some individuals over others. We are supposed to be past the age of totalitarianism.

Making cybrids is not wrong because it could start a dangerous slippery slope that ends up in creating human monsters. It is wrong because it is one more step down the wrong path that had begun with research on human embryos for their stem cells.

Conclusion

Examples do exist where debilitating human diseases have arisen as a result of the crossing of the human-animal barrier, such as HIV[9], the virus that causes AIDS, and which is known to have originated in primates. These are sober reminders that there exists a distinct boundary between man and the rest of the animal kingdom; a boundary that we may cross at our peril.

It is prudent for us to remember this wise saying:
"God always forgives, Man sometimes, but Nature never."

[9] Keele BF et al. Chimpanzee reservoirs of pandemic and nonpandemic HIV-1. Science. 2006;313(5786):523-526

AMP-243-08

25th March 2008

Professor Lee Eng Hin
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Human Embryo and Chimera Research Working Group
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Dear Professor Lee,

CONSULTATION PAPER ON HUMAN-ANIMAL COMBINATIONS FOR BIOMEDICAL RESEARCH – A FEEDBACK

We refer to the above.

First of all, we would like to commend BAC for the very comprehensive paper covering many of the ethical issues associated with human-animal combinations research.

We raise the following as additional feedback that BAC may want to look into when drafting future recommendations.

A human-animal hybrid will raise many ethical issues especially with regards to whether such a chimera should be considered half-human or partially human and therefore be subjected to different moral standards as compared to what we do with animals. If there are indications that the embryo is developing partially human forms, we believe it should be destroyed and not be allowed to proceed. When it develops partial human forms and when to destroy it might be a difficult issue to settle. Also, there is a problem of defining what is partially human. In fact, BAC seems to suggest in the paper that an essentialist concept of what is human can even be challenged.

BAC already accepts that embryonic stem cells can be used for research provided they are destroyed within 14 days. Some of these embryos are created from donated sperm and eggs specifically for research with much ethical ramifications. One of which is that the same principle allowing human embryonic stem cell research may be extended to human-animal hybrids (and beyond two-cell stage). Granted, the creation of human-animal hybrids may bring many risks beyond human embryonic stem cells, yet BAC may need to reconcile existing guidelines with new ones on human-animal hybrids.

The consultation paper focuses on the issue of neural tissues and its relation to the controversy of creating animals with human cognitive functions. However, it is likely that more sophisticated genetic engineering in the future can be implemented in addition to grafting of neural stem cells. For example, certain genes have been identified and inserted into transgenic animals to produce enlarged cerebral cortex (believed to be where higher cognitive functions reside) and one can couple this with grafting of human neural stem cells into the animals. We believe such a factor of whether any genetic engineering is done on top of tissue transfer needs to be considered in addition to the five factors already identified on page 23.

Although the ethical issue of creating animal chimeras with human cognitive functions seems particularly important given the public's interest in such a possibility, other areas of risky human-animal chimera research should also be rigorously reviewed. For example, in infectious diseases research, transferring human tissues into animals carrying unknown pathogens may inadvertently allow the latter to mutate into forms suitable for survival in human cells, posing future health risks for humans.

The current consultation focuses on animal-human chimeras. However, there have been recent advances in creating a three-parent zygote where gametes from a male, a female and cytoplasm from a third individual of the same species (with cytoplasmic genome such as mitochondrial) are used. Although such techniques may currently be focused on fertility treatments, it has wider biomedical application. The advancement if applied to humans may bring up new ethical questions, particularly from the religious point of view and might warrant attention by BAC in the future.

Finally, any future recommendations by BAC that allow human-animal chimera research should not preclude the need for a thorough review by relevant institutional review boards or ethics committee. We feel that only research with clear and genuine biomedical aims and benefits should be allowed, particularly very risky human-animal chimera research and that any position taken by BAC (e.g., on human-animal hybrids) should not be taken as the default position.

Prepared by : Farhan Ali
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: Dr Abdul Razak Chanbasha
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With inputs from : Jameelah Sheikh Mohamed
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March 8, 2008

Professor Lee Eng Hin
Chairman
Human Embryo and Chimera Research Working Group
Bioethics Advisory Committee

Dear Professor Lee:

I am writing in response to your letter, dated on 8 January, 2008 to Professor Jackie Ying, Executive Director of Institute of Bioengineering and Nanotechnology (IBN), inviting to comment on the consultation paper on "Human-Animal Combinations for Research". Being a group leader in IBN working in the area of human embryonic stem (hES) cell bioengineering, I am glad to be given this opportunity to share with you our thoughts. My Comments on the consultation paper are listed below.

Page 11: Chimeras and Hybrids

13. Cytoplasmic hybrid embryo: The obtained cells can described as human cells as assessed by in situ hybridization, PCR and immunocytochemistry with specific human probes, especially karyotype is the same as the person who provides the somatic cell.

Page 27: Legal and Regulatory Consideration:

56. "Biomedical research involving human subjects pose a threat to the dignity and integrity of human beings at some level."
Comments: Biomedical research involving human subjects can also be viewed a way to protect and affirm the dignity and integrity of human being by providing decent life. To protect and promote a health life is consistent with the theme of respect for human life.

57. When human embryonic stem cells are introduced into an animal in order to test the pluripotence of the stem cells, ***the genetic materials of the human stem cells will not pass down to the next generation of the animal,*** thus the risk of the animal developing human function or capability is negligible. The same is true for almost all other animal experiments that are testing human cells.

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58. Even human embryonic stem cells are introduced into closely related, developing organisms, such as higher primates (monkeys or apes), the genetic materials of human stem cells will not be stably present in animal cells and pass down to the next generation of the tested primates. Hence, the risk of the animal developing human function or capability is negligible.

59. Human reproductive cloning is explicitly prohibited, as stated in a previous report on "Ethical, Legal and Social Issues in Human Stem Cell Research, Reproductive and Therapeutic Cloning."

General comment:

Somatic cell nuclear transfer (SCNT) has been proposed to produce genetically personalized hES cell lines, in which the nucleus of an unfertilized egg is replaced with the nucleus from a somatic cell. The method holds great promise both for understanding human developmental biology and disease development/progression, and for regenerative medicine with organ and tissue replacement. However, the efficiency of deriving hES cell lines in this way is estimated to be extremely low, requiring about 100 human eggs to generate a customized hES cell line for a single individual. This is why human eggs become highly sought after, which further triggers the concern in compensating egg donors. Fortunately, recent progress in the area of stem cell research has totally changed the landscape. The new method has been established to create pluripotent human stem cells by gene delivery of 4 functional genes to reprogram human somatic cells, eliminating the use of human eggs. The advance overcomes ethical, political and practical obstacles in the generation and use of hES cells. Facing this successful breakthrough, even the British creator of the cloned sheep Dolly, Dr. Ian Wilmut, has voiced to abandon SCNT technique for cloning human cells. In view of this change, I would suggest placing more emphasis on issues related to the recent progress in human stem cells.

Sincerely yours,

WANG Shu, PhD
Group Leader
Institute of Bioengineering and Nanotechnology

cc: Prof Jackie Y. Ying, Executive Director
Noreena AbuBakar, Director, Administration

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3 March 2008

Dear Committee

I must commend the wonderful work of this committee in preparing a comprehensive consultation paper on human-animal combinations for biomedical research. The information presented is balanced and provides a succinct overview of the current status of this field of research in the world. Although I am a scientist and do understand a lot of the technicalities described in this paper, I have had a deep review of this topic as a lay person along with non scientist members in my family and friends. There are two clear views that I as a scientist have. One is that this field is in very early stages of infancy and the second that Singapore is well poised to contribute in this area. Finally, I along with my non scientist colleagues do concur (based on the very nice examples laid out in the paper), that even though there are moral, ethical and health risks involved in this research, a balanced set of guidelines and their strict adherence would be instrumental in perusing this area such that we derive the wealth of benefits it offers without getting entangled in the ugly side of it.

I wish the committee and all the scientists undertaking this research a very successful journey.

Vinay Tergaonkar

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10 March 2008

Re Consultation Paper on Human-Animal Combinations for Research.

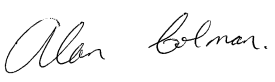
1 First I would like to commend the efforts of the Committee in producing such an informative, well written, and balanced account of the technology, objectives, concerns and regulation of human-animal chimeras. It was a pleasure to read.

2 I have little to say about the accuracy of the content, save that I would correct the definition of 'chimera" by referring only to **living** cells. I would therefore drop reference in future to the "fixed" pig valve as an example. This will confuse people.

3 Although quite comprehensive in its coverage of the types of research involving human-animal, I feel the committee catered perhaps too much to stem cell examples. Tumorogenicity tests are a major consumer of human-rodent chimeras. I assume the focus on human stem cell-animal combinations reflects the Committee's views of where the major public concerns lie?.

4 I would ask that in going forward to making recommendations to the Life Sciences Steering Committee, the BAC is very careful to avoid a situation where oversight becomes stifling to pioneering research. I believe the emergence in the US of ESCRO committees to look at all uses of hES cells is an example of this over reaction. I agree with this report's clear sightedness in suggesting (section 57) that such oversight might be the province of the IACUC committees. Perhaps such committees could co-opt a relevant expert for stem cell related reviews? I would further suggest that they might take time to review the current situation re: IRB oversight on use of human cell lines in particular, which I believe can be unnecessary, where well characterized cells whose provenance is well established and accepted. I do note however that this may be judged outside the current brief. Nevertheless, this is an area needing immediate attention as we are going to need guidelines as to how to deal with the (non)-donor consent issues for established frozen disease-specific tissue banks, particularly since we can predict a large increase in requests for this source of tissue in the establishment of iPS cell lines.

5 I note that the Committee welcomes the arrival of iPS cells (Section 8) but only mentions them in the context of possibly superceding a need for SCNT. However, do they think that in terms of **regulation** of their experimental use (and I am not thinking here of clinical use where iPS research clearly has some way to go), they should (on a precautionary principle) be regarded as ES cells?



Alan Colman MA PhD
Executive Director
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11 February 2008

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Bioethics Advisory Committee
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Dear Eng Hin

CONSULTATION PAPER ON HUMAN-ANIMAL COMBINATIONS FOR RESEARCH

I refer to your letter dated 8 January 2008.

At KK Hospital, we have discussed this paper at our Medical Board and members of the Board have shared their opinions.

1. In general everyone is supportive that there is a need to find an alternative way for the progress of human stem cell research.

2. Should there be any such research, there is an obvious vulnerability for abuse and creation of human-animal organism that will attract both social and religious controversies. That left alone, such risk is substantial and open to individual misinterpretation and self-directed use and abuse.

3. A few members did not support this research direction.

4. Majority of the members supported the research but provided strict governance with meticulous audits are performed on such research whereby all researchers must be transparent and must avoid the creation of human-animal organisms.

5. 1 member supported the research provided any resultant human-animal combination embryo cannot be allowed to grow beyond 14 days of life.

Eng Hin, personally, I feel that this borders on the creation of new life (organism) and for those who do not believe in the sanctity of the Creator, it will not be a major controversy and hence will not have great difficulty in accepting to such human-animal combinations for research. Whereas for those who believe in the Creator of life will shun away and struggle with condoning such a research, albeit for the progress of science and medicine

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for mankind. Research involving somatic cells whereby the purpose is to use the somatic cells cytological organelles, to create tissues and organs that is of benefit to mankind, without the risk of growing into an organism should not cause much controversies. In other words, should there be any human-animal combinations, it must be such that these combinations will not have the potential to form a human-animal organism which is not meant to be in natural forms.

Eng Hin, thank you once again for seeking our views for this paper.

With warmest regards

Yours sincerely

A/Prof Tay Eng Hseon
Chairman Medical Board

Comments from the Institutional Review Board of KK Women's and Children's Hospital

4 March 2008

Consultation Paper on Human-Animal Combinations for Research

KKH IRB comments:

Although some good may come out of this research benefiting mankind, tight governance must be in place with clear guidelines on what is acceptable and what is not acceptable. Chimera research must limit the cytoplasmic hybrid to an early stage.

However, a few members have strong reservation and would definitely draw a line at research leading to 'hybrid' and reproductive cloning

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10 March 2008

BY FAX AND POST
Fax No. 6478 9956
No. of Pages: 6
(including this page)

Professor Lee Eng Hin
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Bioethics Advisory Committee
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Singapore 138667

Dear Sir

INVITATION TO COMMENT ON CONSULTATION PAPER

We refer to your letter dated 8 January 2008 inviting the Law Society to provide its comments on the issues set out in the consultation paper entitled "Human-Animal combinations for Biomedical Research".

The Society appointed an ad hoc committee to review the consultation paper.

We are pleased to enclose our ad hoc committee's feedback on the matter for your consideration.

Thank you for giving the Society the opportunity to give our views on the matter.

Yours faithfully

Alvin Chen
Director, Representation and Law Reform

Enc.

THE LAW SOCIETY OF SINGAPORE

AD HOC COMMITTEE'S FEEDBACK ON THE BIOETHICS ADVISORY COMMITTEE'S CONSULTATION PAPER ON HUMAN-ANIMAL COMBINATIONS FOR BIOMEDICAL RESEARCH

THE LAW SOCIETY
OF SINGAPORE

COMMENTS ON THE BIOETHICS ADVISORY COMMITTEE'S CONSULTATION PAPER ON HUMAN-ANIMAL COMBINATIONS FOR BIOMEDICAL RESEARCH

1. We have been appointed by the Law Society of Singapore to provide our comments on the Consultation Paper by the Bioethics Advisory Committee ("BAC") on Human-Animal Combinations for Biomedical Research.

2. All members of this ad-hoc committee are involved in advising and representing individuals and organisations in the health care industry as part of their legal work.

Background

3. The Committee notes that presently, human-animal combinations in biomedical research are already an existing feature of various ongoing animal research activities being conducted in Singapore. For example, animals such as SCID (Severe Combined Immunodeficiency) mice are often used in research protocols entailing for example, the transplantation of human cancer tissue or injection of stem cells, so as to test new drugs and novel therapies intended for eventual use in the clinical treatment of human diseases.

4. In Singapore, healthcare institutions that use animals in research must be licensed under the Agri-Food and Veterinary and Birds (Care and Use of Animals for Scientific Purposes) Rules, and are expected to comply with the NACLAR (National Advisory Committee on Laboratory Animal Research) Guidelines. Our NACLAR Guidelines aims to promote the humane and responsible care and use of animals in research, and these Guidelines have been drawn up to ensure that the principles and standards of research in Singapore involving the use of animals are in accordance with accepted legal and ethical standards. The Guidelines exhort researchers to ensure there is no unnecessary or unjustified experimentation on animals, and that animals used in research are also not unnecessarily subjected to pain suffering and discomfort.

5. As far as the Committee is aware, the present NACLAR Guidelines do not bar the use of human-animal combinations in research involving laboratory animals. However, the general theme of the NACLAR Guidelines in underscoring the importance of having a proper scientific basis in animal research, would mean that the use of human-animal combinations in research involving laboratory animals should first and foremost be considered only there is a sound basis to believe that the study is of scientific value, and can be designed to produce data that can be meaningfully interpreted. The Committee notes that while the BAC Paper gives an interesting account of how some of these human-animal research techniques may hold great potential and promise for the future, until such time when there is evidence that the techniques are actually effective or workable, there should be great care and caution exercised before such *in vivo* animal experimentation is allowed.

6. Animal experimentation that does not have a good scientific basis may also be deemed contrary to Section 42 of the Animals and Birds Act, as it may unnecessarily subject the research animal to the pain, suffering and stress of the experiment. This is true whether the research involves human-animal combinations, or not. However the Committee believes that if the implications of human-animal combinations are such as may (1) conceivably lead to additional consequences for the animal especially as a sentient being, (2) result in any additional risks to humans, and (3) give rise to deeply held moral and religious objections from the community, then in some circumstances the potential benefits of the research may be outweighed by these undesirable consequences.

Additional Consequences to the Animal

7. Potential concerns outlined in the BAC Paper that fall into this category would include the issues raised under "Concern with Producing Creatures with Human Consciousness or Mental Characteristics" at page 22-23. We agree with the BAC that precautionary measures should be taken and recommendations proposed to minimize the risks of producing new or altering existing animal species with potential human consciousness, and we feel that issuing formal guidance to researchers would be a welcome development.

Additional Risks to Humans

8. The BAC has also alluded to the risk of health risks for eg the potential transfer of diseases between humans and non-humans as a serious unintended consequence of human-animal combinations. Although the BAC reports that over the years this risk has proven to be minimal, in recent times the scourge of infectious diseases such as SARS and bird flu means that the risk of possible animal to human transmission must be viewed as a serious health threat. The Committee is of the view that such health risks should be further studied with the aim of adopting safeguards in prevention and identification of zoonoses, including the issue of whether human-animal combinations in animal research may lead to an increased risk of zoonoses.

Moral and Religious Objections

9. The Committee acknowledges that there are potential moral and religious objections to the use of human-animal combinations in research and hence there is a need to consult with appropriate bodies for their feedback.

10. Apart from seeking such general feedback, we wish to point out that where an individual has donated his or her tissues/cells/eggs/embryos to research, and in cases where the donated material is being contemplated for use in such human-animal combinations in research, these individuals must be given an opportunity to consent to or refuse such proposed use in animal research. This is because these original donors may not have contemplated at the time of the donation that their donated material may end up being used in such human-animal combinations. With the knowledge that people have their own individual viewpoints on moral, religious and other grounds, the Committee is of the view that their donated material should not be used unless their consent to such use has been expressly sought beforehand.

Regulatory Regimes

11. The Committee notes that in some other jurisdictions, regulatory regimes have been adopted that govern research involving human-animal combinations. We

feel that as such types of research activities increase in Singapore, this would be a welcome development here as well. Guidelines such as those issued by the National Academy of Sciences in the US appear to introduce sound and sensible guidance for researchers and research institutions to follow. No doubt our BAC in consultation with the experts in the relevant fields, would be well placed to devise guidelines and recommendations that would best serve the biomedical research community in Singapore.

Dated this 5th day of March 2008

Ad Hoc Committee Members: Kuah Boon Theng
Mak Wei Munn
Audrey Chiang
Charles Lin

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21 May 2008

Dr John Elliott
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Dear Dr Elliott,

REQUEST FOR FEEDBACK ON CONSULTATION PAPER "HUMAN-ANIMAL COMBINATIONS FOR BIOMEDICAL RESEARCH"

Please find the enclosed attachment for our comments on the consultation paper entitled "Human-Animal Combinations for Biomedical Research".

2 We hope the comments are helpful in the BAC's deliberations on the ethical perspectives of the issue.

Thank you.

Yours sincerely,

Nazirudin Mohd Nasir
Assistant Director
Office of the Mufti
Majlis Ugama Islam Singapura

Feedback from Majlis Ugama Islam Singapura (MUIS)
BAC Consultation Paper
Human-Animal Combinations for Biomedical Research

Introduction

The Majlis Ugama Islam Singapura (MUIS) has been invited to comment on the issues and recommendations contained within the Bioethics Advisory Committee's (BAC) consultation paper entitled "Human-Animal Combinations for Biomedical Research". The comments are provided on the following points:

i. The creation and use of human-animal combinations for research
ii. The prohibitions, limits and regulatory mechanisms that will be needed for such research in Singapore

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I. The creation and use of human-animal combinations for research

2 The consultation paper indicates clearly the objectives of research involving human-animal combinations. As stated in para. 15 of the paper, this type of research appears to be the better current alternative to finding longer term cures for diseases. We find no religious objection to the purposes and objectives of this kind of research. In fact, Islam encourages research that advances the welfare of human beings and removes all forms of harm and difficulties. It falls in neatly with the objective of the *Syariah* (Islamic jurisprudence) which is to promote the well-being of mankind and to enhance human life. Achieving these goals by way of scientific research is recognised as an objective of the Syariah and is a form of public utility (*maslahah*) that should be secured.

3 In the pursuit of public utility, the *Syariah* makes it clear that harm must be avoided at all costs. As such, where there is a certainty that a research will be harmful to those involved in it, or will bring about greater harm in general, then the research shall not be allowed to take place. This is in accordance with the Islamic legal maxim

that states "removal of harm takes precedence over pursuing welfare/interest (*maslahah*)". However, if both benefits and harm are probable and not certain, then the potential benefits must outweigh the potential harm, in order to warrant the pursuit of such research work.

4 There are some concerns which are already raised in the consultation paper which qualify to be potential harm that may arise from such research work. These include risks to health (para.s 29 – 32) and the possibility, albeit minute, of producing creatures with human-type consciousness and cognitive features (para.s 40 – 43). From an Islamic perspective, risks such as health and pain apply not only to human beings, but also to animals, as the Prophet (peace be upon him) showed great compassion and mercy to animals. The probability of such harm occurring has to be weighed against the potential benefits of such research. Thus, the relevant steps to minimise such harm, where possible, is in order, so as to strengthen the case for supporting such research. As such, we see the role of regulatory mechanisms as highly critical, and the imposition of the appropriate and adequate prohibitions and limits on such research as mandatory. We explain some of these recommendations in the next section.

II. The prohibitions, limits and regulatory mechanisms that will be needed for such research in Singapore

5 In light of the above, we feel that much focus has to be paid to the regulations that are specifically required to allow such research to take place, which from the onset represent research with compelling scientific rationale that should only be considered under circumstances where no other experiment can provide the information needed.

6 For now, such regulation should prohibit any transfer to a human or nonhuman uterus, as well as in vitro culture of human-animal embryos (be they true or cytoplasmic hybrids) beyond the 14-day limit. This limit is being taken since such products are similar to those of human nuclear transfer, and should thereby be subject to similar current guidelines on human embryonic stem cell research such as those of

the International Society for Stem Cell Research.

7 Meanwhile, the transfer of human cells into animal hosts and vice versa will need more detailed analysis to generate some general guidelines (such as the types of cells transferred, the ratio of human:animal cells involved, the site of transfer, the biological processes impacted, etc), but specific approvals should only be granted on a case by case basis, by the relevant ethical review boards after determining individual research methodology, scientific merit and ethical propriety.

8 A specialised, additional oversight process by a stem cell research oversight committee, either at the institutional or national level, should also be carried out to complement the work of the ethical review boards when dealing with human-animal combinations in biomedicine research involving stem cells.

9 Additionally, strict containment procedures already in place in most research set-ups, which include humane destruction and careful disposal of unused and unwanted human-animal hybrids, as well as restrictions on breeding and release, should be further enforced.

10 Lastly, in the future, once such regulated research has "matured" and yielded further information and results, it may be prudent to revisit this issue to determine whether existing guidelines are indeed adequate or will need further revision in light of new knowledge uncovered.

Co. Reg No. ROS 146/51/REL

National Council of Churches of Singapore
新加坡基督教會協會
சிங்கப்பூர் திருச்சபைகளின் தேசிய மன்றம்

3 March 2008

Professor Lee Eng Hin
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Dear Prof Lee

'HUMAN-ANIMAL COMBINATIONS FOR BIOMEDICAL RESEARCH'

Thank you for seeking feedback from the National Council of Churches of Singapore on the above subject.

We enclose herewith our response to the Consultation Paper on **'HUMAN-ANIMAL COMBINATIONS FOR BIOMEDICAL RESEARCH'**

We trust that this feedback will receive careful and serious consideration.

Thank you.

Yours sincerely

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"Many members... One Body... with Christ." 1 Cor 12:12

RESPONSE TO THE BIOETHICS ADVISORY COMMITTEE'S CONSULTATION PAPER ENTITLED, 'HUMAN-ANIMAL COMBINATIONS FOR BIOMEDICAL RESEARCH' BY THE NATIONAL COUNCIL OF CHURCHES IN SINGAPORE

INTRODUCTION

The National Council of Churches (NCCS) appreciates the invitation by the Bioethics Advisory Committee (BAC) to respond to its consultation paper entitled, 'Human-Animal Combinations for Biomedical Research'. The NCCS is also appreciative of the care and sensitivity with which the BAC has presented its position on this complex and controversial topic, and the extended time that it has given for the public to debate the issue.

This paper is divided into three parts. In Part One, we briefly respond to some of the points raised in the BAC consultation paper. As many of the issues raised by the consultation paper will be addressed in the main body of this paper (i.e., Parts Two and Three), the first part of the paper is necessarily brief. In Part Two, we present some general ethical concerns concerning some forms of chimera research from the standpoint of the Christian Faith. These concerns have to do mainly with human uniqueness and dignity and with the integrity of the created order that certain forms of research involving human-animal mixtures may violate. Part Two examines the ethical concerns of the different forms of research involving human-animal mixtures. This approach is necessary for two reasons. The first is that not every type of chimera research poses the same ethical concerns from the Christian standpoint. The second reason for this approach is to address what we perceive to be a weakness in the BAC's presentation. While the consultation paper is very lucid and tightly argued, at the same time it suffers the disadvantage of being too general. Because there are many different types of chimera research, it is not only profitable but it is indeed necessary to evaluate the ethics of each. Only when this is done will a clearer and fairer picture emerge.

At the outset, it is important to state that the NCCS is not opposed to all forms of induced chimeras or biomedical research involving human-animal mixtures. For example, the NCCS maintains that there are no strong ethical objections to xenografts where the heart valve of a pig is transplanted to a human patient. Neither do we object to the transfer of most types of differentiated human stem cells into the hearts or kidneys of mice, pigs or even non-human primates for the purpose of research because this is not likely to result in the emergence of chimeric beings with the capacity to think, feel and act like humans. In this sense, we agree with the view forwarded by the BAC that the contrary to nature argument does not succeed. If it were to succeed, then we would have to stop all interspecies procedures like xenotransplantation, and the manufacture of insulin and erythropoietin. But there are many forms of chimera research, for example the transferring of human neural stem cells into prenatal non-human hosts (especially primates), which we maintain are ethically questionable and should therefore be prohibited.

In many ways, this paper goes beyond a point-by-point response to the BAC's consultation paper. It also aims to present the positions of the NCCS on the different forms of human-animal combinations. Some of the procedures addressed in this paper have not been actually carried out, and are already prohibited by many significant international bodies. For other procedures addressed in this paper, experiments have already been undertaken, although assessments on the ethical

problems or concerns they pose have been varied. The NCCS would like to present its views on these procedures as well as the reasons that informed and shaped these views. This paper therefore addresses many issues that are not specifically discussed in the BAC consultation.

PART ONE: GENERAL COMMENTS ON CONSULTATION PAPER

The purpose of the first part of this paper is to interact directly with the consultation paper presented by the BAC. In particular, attention will be directed at those points or issues raised by the consultation paper that will not be addressed in parts two and three of this paper. The discussion in Part One will include general observations and comments about the consultation paper as well as some of the specific issues it raises. Because most of the main issues will be taken up in Parts Two and Three of this paper, the discussion here will be brief.

As we have mentioned in the introduction, while the consultation paper is well-written and lucid, it suffers from being too sweeping and in some sense abstract. While the paper has done a fine job in defining chimera and hybrids and describing some of the potential benefits of such research, it fails to examine the different types of chimera research, especially those involving human-animal mixtures. This approach in our opinion has compromised the discussion because it implies that all forms of research involving human-animal mixtures present the same ethical concerns when this in fact is not the case. This approach also can potentially lead the reader who is unfamiliar with the ethical issues surrounding such research to think that once the ethical objections (discussed in pages 19-27) are examined and rebutted, all chimera research should be allowed. But in reality this is not the case at all. For a clearer, comprehensive and fairer discussion of research involving human-animal mixtures it is imperative that the different types of research are discussed and the ethical concerns that attend to each of them are assessed.

While the BAC is generally correct when it states that a person who has received a pig heart valve through xenotransplantation and a person who has had blood transfusion are technically speaking chimeras, its failure to differentiate such examples from the chimeras that scientists have produce or intend to produce can be misleading. This presentation may lead the reader to conclude that since there are no strong ethical objections to the 'creation' of such chimeras (e.g., through transplantation) there should also be no strong objections to the 'creation' of other forms of chimera in the laboratory. But using a pig's valve to replace the diseased heart valve of a human patient is very different from injecting undifferentiated human stem cells into a nonhuman zygote. If discussion on the ethical implications of human-animal chimera research is to be conducted in such a way that members of the public are able to make a reasoned evaluation, this distinction must be discussed and even emphasised. This is especially when people with no background in biological science or ethics are invited to participate in the consultation.

In its discussion on the concept of 'Playing God' forwarded by some Christians, the consultation paper asks, 'How do we know what divine plans are when it comes to scientific knowledge and practice? Is it not possible that stem cell research is part of those plans?' A fuller response to the BAC's interpretation of this concept is given below (See section entitled, 'Playing God' in Part Two). Briefly, the concept 'Playing God' should not be abstracted from its original theological framework in the Judeo-Christian tradition. According to that tradition, God has called human beings to serve as stewards of his creation. When Christians say that human beings should not 'play God' they mean that they should not act in ways that transgress the will of God and

his intentions for humankind and the created order. One of the ways in which scientists 'play God' is when they see human lives as having only instrumental and not intrinsic worth. Such an approach would violate the dignity that God himself has accorded to human beings. Not all stem cell research is a violation of human dignity. In the view of the NCCS, human embryonic stem cell research, which results in the destruction of the human embryo, is a violation of human dignity because the early embryo is a human being worthy of respect. Thus, we know that certain forms of embryonic stem cell research is not part of the divine plan because it results in the destruction of human beings created to be bearers of God's image.

The question of the moral status quo that separates humans from animals is important for Christians. The BAC has argued that change in this moral status quo is not necessarily a 'bad thing in the long run' (p. 24). It provides as examples the emancipation of slaves and the women's liberation movement to substantiate its point. The NCCS maintains that changes in perception of the moral status of humans and animals should not be confused with the changing social norms concerning women or slaves. For the Christian, the special moral status of human beings is not a social construct that may be subjected to deconstruction. The distinction between human beings and animals is deeply rooted in our understanding of ourselves and the other animal species. It is from this profound self-understanding that human beings develop their attitude to the world and the other animal species. No civilised society would countenance a shift in social norms in which farm animals, for instance, are valued more highly than human infants because of their economic worth and potential. Such a change in the moral status quo or social norm is profoundly harmful to human society. The moral status of human beings is discussed at greater depth in Part Two of this paper.

Finally, we wish to comment briefly on the 'wisdom of repugnance' and the slippery slope argument which in our opinion the BAC paper dismisses too quickly. The NCCS agrees that the feeling of repugnance towards a particular research should not be the sole reason for rejecting it. The feeling of repugnance does not constitute an ethical argument, and those who appeal to it have never presented it as such. But repugnance (i.e., things that one finds 'repulsive', 'distasteful' and 'offensive') should not be dismissed simply because it is not a reasoned ethical argument because such reactions often point to deeper realities. Leon Kass explains:

> In this age in which everything is held to be permissible so long as it is freely done, in which our given human nature no longer commands respect, in which our bodies are regarded as mere instruments of our autonomous rational wills, repugnance may be the only voice left that speaks up to defend the central core of our humanity. Shallow are the souls that have forgotten how to shudder.[1]

Those who see repugnance only as irrational emotion fail to understand that human emotions are complex, laced through and through with thought. This is especially so when it is the collective response of members of a community. Repugnance, of course, is not the end of the matter but simply the beginning. The point is that we must take these reactions seriously enough to submit them to rigorous reflection. In similar vein, although it is true that the 'slippery slope' argument cannot be the sole or main factor in ethics, it is nonetheless important because it alerts us to the fact that our actions have consequences and it compels us to pause and reflect deeply on these consequences.

[1] Leon R. Kass, 'The Wisdom of Repugnance', *New Republic*, Vol.216, Issue 22 (June 2, 1997).

PART TWO: THEOLOGICAL AND MORAL FRAMEWORK

Research involving the combination of human and animals present serious and complex ethical concerns not just for the Christian community but also for society in general. The novel situation that results from the creation of animal-human mixtures presents such an immense challenge to society that the responses have often been visceral and mixed. Some would support such research because of their therapeutic potentials while others would find such research, which unnaturally induce interspecies genetic combinations that causes the emergence of chimeric entities, repugnant and repulsive.

While the Christian scriptures have very little to say directly about such research, it does provide a broad theological framework within which members of the Christian community could reflect responsibly on their ethical implications. For instance, because such research involves genetic and other materials that are taken from humans and combined with that of animals, the question of the uniqueness and dignity of the human being becomes a pressing one. This question also relates to the status of the early embryo, which is often used in such research. Questions concerning the use of animals for research and the biomedical risks associated with such research must also be addressed. The ability to create chimeric entities through genetic engineering and other forms of biotechnology has fascinated scientists. But the technological imperative which silently albeit powerfully drives such research must be critiqued. This is where the notion of 'Playing God', which has been variously utilised by theologians, ethicists and scientists, must be examined more closely.

A. Human Uniqueness

The Christian faith teaches that human beings are created in the image of God and therefore must be distinguished from the other species in the animal kingdom. There are many ways in which the concept of the divine image has been interpreted in the Christian tradition. All these various interpretations point to the general idea that because human beings are created sufficiently like God they have the capacity to relate to him. In other words, the communion between God and human beings is made possible by the fact that human beings bear the divine image. Human beings therefore are accorded a special moral status among God's creatures. This of course does not imply that other animal species are denied moral standing. But as bearers of the divine image, human beings are conferred a special place in the moral universe.

The view that human beings enjoy a special moral status and must therefore be treated differently from other animal species is not exclusively a Christian one but is shared by many. This is seen in a number of cultural and ethical conventions. For example, in most societies, killing a human being requires a quite different moral justification than taking the lives of other animal species. Many would also find the suggestion to use members of our own species to serve our own ends morally unjustifiable. The restrictions to the use of animals are not as stringent as those that apply to our treatment and use of human. And finally, human flourishing is deemed as more important than animal flourishing, and consequently the lives of humans are worth greater sacrifices to protect and support than the lives of animals.

Different attempts have been made to point to that which distinguishes humans and other animals. It is important to note that because the human being is such a rich and complex arrangement of powers and qualities it is impossible to isolate a single property or *differentia* that distinguishes it from the other animal species. There are, however, a number of qualities that make human beings different from the other

animal species. Some of these qualities are language, conceptual thought, moral understanding, morally responsible behaviour, and second-order beliefs (i.e., beliefs about one's beliefs). The list can be expanded. Some thinkers have argued that humans are different from animals because they have 'meaning-producing abilities'. That is to say, humans, unlike the animals do not simply live their lives. They seek to interpret their lives, make sense of it, and search for the ultimate meaning of their existence.

This account of what it means to be human calls to question all anthropological reductionism, whether they are inspired by Darwinian evolutionism or genetic determinism. Although the human being is profoundly related to other animal species it cannot be simply reduced to them. And although the genotype of the human being does contribute to its phenotype, human abilities and behaviour cannot be reduced to genetics as some philosophers and scientists have suggested. The biblical image of Adam being formed from the soil and then given vitality through the spirit points to the irreducible complexity of what it means to be human. The language of *soil* and *spirit* helps us to understand the true nature of humankind, which is at once similar and dissimilar with that of the other animals.

The special status that human beings enjoy is accompanied with special responsibilities. Chief among these responsibilities are caring for God's creation, respecting the *telos* of animal and plants, and the humane treatment of fellow human beings. Some philosophers and theologians have rightly described humankind as the 'servant species' that is commissioned to exercise self-sacrificial priesthood for members of its own species and for all sentient creatures. As God's special creatures and bearers of God's image human beings must not only care for their own kind but also for the whole creation, including the preservation of the delicate order of nature. Needless to say, this insight has profound implications on our scientific activities.

B. Human Dignity

Discussion on the special moral status of the human being would not be complete without reference to human dignity. This concept is undoubtedly very prominent in the discussion of bioethical issues and has played a key role in the constitutions of countries as politically diverse as Afghanistan, Germany, Italy Nicaragua, Peru and Korea – to name just a few. Human dignity is also prominent in many international documents like the United Nations' Universal Declaration of Human Rights in 1948 and the so-called International Bill of Rights of 1966. Much of the modern discourse in human dignity has become *decontextualised*: whereas such discourse used to be a part of the Christian understanding of what it means to be human, this context is now largely ignored.

In many ways the modern secular understanding of human dignity is beholden to the Enlightenment philosopher Immanuel Kant, who locates human dignity in morality and autonomy. In *Groundwork of the Metaphysics of Morals* Kant famously asserted that 'morality, and humanity so far as it is capable of morality, is the only dignity'.[2] And since, for Kant, morality is not possible without the autonomous will, he is led to the conclusion that 'autonomy is therefore the ground of the dignity of human nature'.[3] This means that human beings are accorded dignity not because they are human beings but because they have the capacity for morality and autonomy. This view of human dignity suffers from a profound weakness. Because dignity is rooted in

[2] Immanuel Kant, *Groundwork of the Metaphysics of Morals*, trans. H.J. Paton (New York: Harper and Row, 1964 [1785]), 102.
[3] Kant, *Groundwork*, 107.

human rationality and freedom, it cannot be comprehensively applied to all human beings. In other words, if having human dignity requires the ability to exercise autonomy, then those who are unable to do this – people with mental disabilities, the comatose and the human foetus – do not have human dignity even though they are recognised as humans.

Understanding human dignity in light of human characteristics, however, is not an entirely misdirected approach. The Judeo-Christian tradition also refers to certain characteristics, especially mental capacities, when it discusses human dignity.[4] There are, however, profound differences between the Judeo-Christian and secular accounts. Firstly, the Judeo-Christian tradition does not privilege particular characteristics like autonomy and root human dignity in them. Rather it considers the whole complex of characteristics and human capabilities as an inseparable whole that provides the basis for human dignity. But the most important difference between the Christian understanding of human dignity and secular accounts is that according to the former human dignity belongs inalienably to human beings because of the sort of creatures they are. Put differently, dignity is not accorded only to human beings who display certain characteristics like sentience or moral judgement. Human dignity belongs to human beings *qua* human beings.[5] Thus people with severe mental disabilities, the comatose and the human embryo must be accorded the dignity that belongs to all human beings.

Human dignity is undermined when human worth is called to question when human beings are inappropriately *used, forced* or *injured.* Human dignity requires that human beings be treated as having intrinsic and not just instrumental worth. Human beings should not be used. In the same way, they should not be forced because dignity demands that their wills should be respected. And finally, human beings should not be injured because their wellbeing should be preserved. In bioethics, it is generally agreed that respect for human dignity must be given priority. In human experimentation for instance, it is imperative that participants give their informed consent, lest their dignity is violated when something is done to them against their wishes. With regard to embryonic stem cell research, if the embryo is seen as a human being worthy of respect, its use for research and its subsequent destruction would tantamount to the grave violation of its human dignity. This would also include the cytoplasmic hybrid embryo that is 99% human.

When it comes to the production of animal-human chimeras, the core concerns raised by the human dignity argument have to do with the diminution or destruction of human dignity-related capacities like rationality. Cynthia Cohen explains:

> ... it would be wrong to encase within an animal's body those physical components of human that are necessary for exercising the cluster of capacities associated with human dignity because this would eliminate or diminish those very capacities. The torturer or enslaver of human beings wrongs them, not only because he or she harms them but also

[4] These include: the ability to feel pleasure or pain; the use of language; rationality; the possibility of forming rich and meaningful relationships; the potential to have complex emotions, and unparalleled ability to imagine a future and remember the past.

[5] In addition, it must be pointed out that according to the theological anthropology that we have been developing, there can be no distinction between being a human and being a person. Personhood is intrinsically bound up with our humanity. We would therefore reject the view that makes a distinction between being a person and being a human proposed by thinkers such as Peter Singer, where personhood is tied to certain characteristics like rationality and consciousness. This approach has led Singer to conclude that the gorilla Koko is a person, although she is not human. See Peter Singer, *Rethinking Life and Death: The Collapse of Our Traditional Ethics* (Oxford: Oxford University Press, 1995), 181.

> because he or she denies them the option of exercising many of the capacities associated with human dignity. The creator of the human-non-human chimera would do even worse – he or she would obliterate or enfeeble those very capacities.[6]

For example, it would be wrong to introduce substantial numbers of specialised human neural stem cells into a nonhuman host in which the stem cells could form functional connectivity within the host brain and modulate its functions. Such an experiment would violate human dignity because the resulting chimera would not be able to exercise its distinctively human capacities as its brain is imprisoned in an animal-like body. In the same way, it would be wrong to insert undifferentiated human embryonic stem cells into an animal embryo. The pluripotent human stem cells may integrate into the brain of the animal embryo resulting in a human-animal chimera acquiring human-like brain functions.

In their article entitled, 'Chimeras and "Human Dignity"', Josephine Johnston and Christopher Eliot argue that the creation of chimeras that possess compromised humanness can be said to be ethically problematic:

1. Intentionally creating compromised human beings or part-human beings is cruel to the creature. For example, it is cruel to create a laboratory subject for the purposes of experimentation, which is able to exercise only compromised human faculties, likely to be kept in a cage, and perhaps not able to fend for itself.
2. Intentionally creating compromised human beings or part-human beings reflects badly both on those who create the chimera and on those societies or governments allowing its creation. What kind of an institutional intention do we exhibit when we create compromised human beings or part-human beings for laboratory use?
3. Finally intentionally creating compromised human beings or part-human beings might appear to "all the world" to be using another human or part-human, as a means to an end rather than as an end in itself, a use that has been confirmed as morally unacceptable since at least the Declaration of Helsinki.[7]

C. Moral Status of the Human Embryo

Discussion on research involving the creation of human-animal hybrid embryos cannot avoid the issue of the moral status of the human embryo. Here, the NCCS must reiterate its position that human life begins at conception and that the early embryo is a human being worthy of special respect. This means that the NCCS is opposed to all research that would inflict harm to or cause the destruction of human embryos. In light of the discussion on human dignity, the NCCS would also oppose all research and experimentation that uses the human embryo merely as a means to achieve an end, regardless how noble that end may be. Because the human embryo is a human being worthy of special respect, it should never be treated this way. This would include the cytoplasmic hybrid embryo which is 99% human.

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[6] Cynthia Cohen, *Renewing the Stuff of Life: Stem Cells, Ethics and Public Policy* (Oxford: Oxford University Press, 2007), 126.
[7] Josephine Johnston and Christopher Eliot, 'Chimeras and "Human Dignity"', *American Journal of Law and Medicine*, Summer 2003, 3 (3): W7.

Theologically, the view that the human embryo, from the time of conception, is a human being worthy of respect is based on the premise that in Scripture achievement and potential are placed in one unbroken continuum. This means that Scripture prevents us from concluding that the early embryo is only a potential human being and therefore should not be accorded the same kind of respect and protection that an adult human being deserves. Various passages in Scripture allude to this (e.g., Psalm 139:13-16; Jeremiah 1:5). It is in the doctrine of the incarnation that this view receives it most profound theological justification. The incarnate Son of God did not take on human flesh at birth, but at the moment of conception. In the incarnation, therefore, the Son of God identified with and redeemed all of human life, from the darkness of the womb to the darkness of the tomb.

Philosophically, we argue that the zygote of human parentage bears the nature of its parents. The zygote of human parentage cannot articulate itself into another animal. To those who argue that the zygote does not look like a human being, we answer that that is exactly what we look like – what you and I look like – at that stage of development. Put differently, at fertilisation the zygote is an individual identity[8] whose genome directs the multiplication of its cells and the direction of the development of its tissues. The zygote and its newly constituted genome organises itself into an embryo, foetus, infant, child and adult without ceasing to be one and the same living being.

There are many established embryologists and scientists who hold that human life begins at conception. 'Development of the embryo begins at Stage 1', writes Marjorie England, 'when a sperm fertilises an oocyte and together they form a zygote'.[9] In similar vein Keith Moore maintains that 'human development begins after the union of male and female gametes or germ cells during a process known as fertilisation (conception)'.[10] In *Cloning Human Beings*, a report of the National Bioethics Advisory Commission, an embryo is defined as 'the developing organism from the time of fertilisation until significant differentiation has occurred, when the organism becomes known as a fetus'.[11]

William Larsen describes the zero point of embryonic development thus: 'The chromosomes of the oocyte and sperm are ... respectively enclosed within female and male pronuclei. These pronuclei fuse with each other to produce the single, diploid, 2N nucleus of the fertilised zygote. This moment of zygote formation may be taken as the beginning or zero time point of embryonic development'.[12] 'If it's not an embryo', Jonathan Van Blerkom, the embryologist at University of Colorado asks with reference to the early embryo, 'what is it?'[13] And finally, in *Human Embryology & Teratology*, Ronan O'Rahilly and Fabiola Müller contend that 'although life is a continuous process, fertilisation is a critical landmark because, under ordinary circumstances, a new genetically human organism is thereby formed ... The combination of 23 chromosomes present in each pronucleus results in 46 chromosomes in the zygote. Thus the diploid number is restored and the embryonic genome is formed. The embryo now exists as a genetic unity'[14]. This textbook

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[8] In the case of twinning which takes place in the initial fourteenth day period, it must be stated that before this time it is possible that the early embryo is a being that is not confined to only *one* individual.

[9] Marjorie England, *A Life Before Birth*. (England: Mosby-Wolf, 1996), 31.

[10] Keith Moore, *Essentials of Human Embryology*. (Toronto: B.C. Decker Inc., 1988), 2.

[11] *Cloning Human Beings*. Report and Recommendations of the National Bioethics Advisory Commission, (Rockville, MD: GOP, 1992), Appendic 2.

[12] William J. Larsen, *Human Embryology*. 2nd Edition. (New York: Churchill Livingstone, 1997), 17.

[13] *American Medical News*, February 23, 1998, 32.

[14] Ronan O'Rahilly and Fabiola Müller, *Human Embryology & Teratology*. 2nd Edition. (New York: Wiley-Liss, 1999), 8, 29.

describes 'pre-embryo' as 'ill-defined and inaccurate' and lists it among 'discarded and replaced terms'.[15]

The members of the President's Council on Bioethics have also expressed this view with eloquence and force:

> The fertilised egg is human organism in its germinal stage. It is not just a 'clump of cells' but an integrated, self-developing whole, capable (if all goes well) of the continued organic development characteristic of human beings. To be sure, the embryo does not yet have, except in potential, the full range of characteristics that distinguish the human species from others, but one need not have those characteristics in evidence in order to belong to the species ... The embryo is in fact fully 'one of us': a human life in process, and equal member of the species *Homo sapiens* in the embryonic stage of his or her natural development.[16]

This is not the place to respond to the objections raised by those who advocate the fourteenth day view. The purpose of this brief sub-section is to state again the view of the NCCS and to show that although this view is informed by a certain reading of Scripture, it can be defended philosophically and has received support from some texts on human embryology and a panel of experts. This chorus of voices should at least caution against regarding too hastily what appears to be an abstract and arbitrary distinction (i.e., between 'pre-embryo' and 'embryo') as a dogma that has achieved widespread consensus among members of the scientific community.

D. The Moral Status of the Human-Animal Chimera

One of the challenges confronting the ethicist is to ascertain the moral status of animal-human mixtures created for research. Those who work within the evolutionary framework may argue that species distinctions are arbitrary constructs and therefore the emergence of animal-human mixtures pose no serious moral problems. For Christians, however, the concept of the uniqueness of the human being implies that animal-human mixtures that either compromise the humanness of the human subject or 'humanise' the animal subject poses serious ethical problems. It is impossible, then, for Christians to sidestep the issue of the moral status of the human-animal chimera. The view that 'only if and when there are enough entities of this type [referring to the 'humouse'] proliferating as naturally living entities will we have to start thinking about the practical implications of their moral status, not when they are merely laboratory specimens'[17] is simply unacceptable.

A possible approach in addressing the problem of the moral status of the human-animal chimera has in a sense already been alluded to in the preceding sub-section. The crucial issue here has to do with the change of identity of the chimeric creature that is produced through the introduction of human stem cells or other human genetic material. This is clearly spelt out by the Pontifical Academy for Life in their document concerning xenotransplantation:

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[15] O'Rahilly, *Human Embryology and Teratology*, 12.
[16] President's Council on Bioethics, *Human Cloning and Human Dignity* (New York: Public Affairs, 2002), 173-175.
[17] BAC, *Human-Animal Combinations for Biomedical Research*, 26.

> ...in general, the implantation of a foreign organ into a human body finds an ethical limit in the degree of change that it may entail in the identity of the person who receives it.[18]

By 'personal identity' the Pontifical Academy of Life means the essential core of the being of a person, his 'unrepeatability'. It also refers to the being of the person (ontological level) and the feeling that he is a person (psychological level).

Once the recipient animal into which human pluripotent cells are inserted begins to acquire or display human capacities like thought and feeling, there is a change in the identity of the recipient animal. This must result in the corresponding change in its moral status. Whereas before the emergence of these capacities the animal in question enjoys the moral status accorded to animals, after these abilities appear it must be accorded the moral status of humans, even if these capacities are severely compromised in the developing creature. It is the view of some scientists and ethicists that some organs in the human or mammalian body (especially that of primates) like the encephalon (brain) and the gonads (ovaries and testes) are linked to the identities of the creature because of their specific function.

Although this general guideline is to some extent helpful, it is difficult to ascertain if and when the change in the identity of the animal has taken place. As we shall see below, although scientists maintain that inserting certain amounts of dissociated human neural stem cells in the brains of prenatal animals have not resulted in the changes in the brains of those animals as to warrant the belief that they have developed human capacities, it is extremely difficult to be certain where to draw the line. In addition, these capacities may not be evident in the duration of the experiment. The absence of evidence, however, does not mean that there has not been a significant change in the chimera that warrants special respect to be shown to it.[19]

E. Playing God

We turn finally to the questions whether in the utilisation of certain technologies for research and whether in the pursuit of those research themselves human beings are 'playing God'. Although some ethicists maintain that this idea is too ambiguous to be helpful, we maintain that if understood clearly it provides the broad parameters that would govern our scientific pursuits. This idea is grounded in the Judeo-Christian tradition that sees the specific role of human beings as God's stewards, taking care of and tending the creation. At its most basic level, this idea alerts us to the fact that we must learn and respect our roles as creatures and to bear in mind that science and medicine are meant to serve human life. Far from being Luddites, those who speak

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[18] Pontifical Academy for Life, *Prospects for Xenotransplantation: Scientific Aspects and Ethical Considerations* (September 26, 2001), n. 10.

[19] The question concerning the use of animals for the good of human beings must be briefly addressed. The Christian tradition maintains that animals as God creatures have their own specific values which human beings must recognise and respect. However, human beings enjoy a unique and higher dignity since they are created in the image of God. Animals are given for the service of human beings in order that they may achieve their fullest potential. Human beings have always used animals for their good, either to provide food, clothing or transport. With the advances in technology, the 'service' that animals can render to human beings takes a different form. In the biomedical field, animals perform a special service to human beings through xenotransplantation. We therefore agree with the Pontifical Academy for Life in its statement that the sacrifice of animals can be justified if it is required 'to achieve an important benefit for man, as is the case with xenotransplantation of organs or tissues to man, even when this involves experiments on animals and/or genetically modifying them'.

against playing God maintain that science would achieve its noblest goals only when it is directed at human flourishing.

Some thinkers have extracted this phrase from its proper theological context and grafted it onto a fundamentally utilitarian understanding of science and medicine. The ethicist Joseph Fletcher presents this form of utilitarianism in his book *The Ethics of Genetic Control*[20] where he boldly suggests that we must 'play God'.[21] Fletcher's secularism is unmistakably wedded to his utilitarianism. Since for him 'the old God'[22] is dead, and since the world is no longer 'run from outside by God's will',[23] we must steal the 'powers from the gods'[24] by invading God's privileges and prerogatives'[25] and take control of the world. Fletcher could therefore write: 'As we learn to direct mutations medically we should do so. Not to control when we can is immoral'.[26] Thus, Fletcher's enthusiasm for the creation of human-nonhuman chimeras could hardly be concealed when he wrote:

> Chimeras or parahumans might legitimately be fashioned to do dangerous or demeaning jobs. As it is now, low-grade work is shoved off on moronic ... individuals, the victims of uncontrolled reproduction. Should we not 'program' such workers thoughtfully instead of accidentally, by means of hybridisation?[27]

In our view there are echoes of this form of utilitarianism in the argument that is so well formulated in the BAC Consultation paper that 'If research involving human-animal combinations can save life, then to stop the research is to "play God" with respect to those whose lives could be saved'. To argue in this way is to miss the theological assumptions behind the idea of 'playing God'. These assumptions must be given serious consideration if we are to understand how the concept of 'playing God' serves as a check even to some forms of humanitarianism.

For Paul Ramsey, who used this phrase in the context of his discussion on procreation, 'playing God' serves as a critique of modern science and medicine in two ways. Firstly, it reminds us that there are things which we can do but which we ought not do. In order words, 'playing God' puts a check on our technological and scientific prowess by insisting that our scientific initiatives must be governed by ethics. Thus with eloquence and force Ramsay wrote: 'I do not believe men should enslave themselves to an acknowledged minority of scientific saviours, or any man himself willing to reduce another fellow man to a "thing in the world" over whom benefits are to be "wrought", while unfurling the banner of man's triumph over natural forces'.[28] An example of the commodification of human beings, i.e., of treating a fellow human being as a 'thing in the world' is the creation, use and destruction of the human embryo or the human-bovine cytoplasmic hybrid embryo.

Secondly, this phrase calls us to resist the march of blind technology. The Dutch philosopher Egbert Schuurman describes the pervasive 'technicism' in our culture well.

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[20] Joseph Fletcher, *The Ethics of Genetics Control: Ending Reproductive Roulette* (Garden City, N.Y.: Anchor Books, 1974).
[21] Ibid., 126.
[22] Ibid., 200.
[23] Ibid., 127.
[24] Ibid., 6.
[25] Ibid., 200.
[26] Ibid., 158.
[27] Ibid., 173.
[28] Paul Ramsey, *Fabricated Man* (New Haven, Conn.: Yale University Press, 1970), 151.

> Technicism entails the pretension of human autonomy to control the whole of reality: man as master seeks victory over the future; he is to have everything his way; he is to solve all problems, including the new problems caused by technicism; and to guarantee ... material progress ... One can argue that ... the main trend of Western philosophical thought is best characterised as thinking through technology. This means that science and rationality in general are distorted because they have been used as technical instruments in the service of technological powers.[29]

Philosophers and even theologians – not just scientists – have championed what has been described as the Baconian project. But such unbridled optimism towards (faith in?) blind technology has quite serious consequences and repercussions. The caution against 'playing God' reminds us that ethics must always inform our scientific enterprises. It also calls to question the technological imperative that drives those enterprises. It is in this sense of the phrase 'playing God' that we are to understand Ramsey's refrain: 'Men ought not to play God before they learn to be men, and after they have learned to be men they will not play God'.[30]

But the caution against 'playing God' in this sense is at the same time an injunction to play God in another sense – to play God in the correct way! Ramsey's admonishment that we should not 'play God' presents some prohibitions. We are not to be the substitute for the absent God and try to 'be' God (Fletcher). But we are called to 'imitate' God, to follow his ways, to 'be like' God. To 'play God' the way God plays God is to promote life and its flourishing and never death and human suffering. It is to embrace the gift of wisdom that has allowed science and technology to be used to alleviate human suffering and treat diseases. It is to affirm the different forms of biomedical research that hold therapeutic potentials.

To play God the way God plays God, however, also means that certain enterprises cannot be countenanced.[31] It means that experiments that make use of human beings in such a way that their dignity is violated cannot be countenanced. It means that the commodification of human beings must be resisted. It means that the ethic that sanctions the exploitation of the vulnerable, the minority, the poor or the voiceless for the sake of the majority and in the name of the 'common good' must be called to question and rejected. To play God the way God plays God means that ethics – the question whether certain researches ought to be pursued – must guide our decisions, and not simply scientific knowledge and technological capability. To play God the way God plays God is to conduct our scientific and therapeutic activities in concert with the intentions of the Creator. Abstracted from this theological context, 'playing God' becomes a vacuous phrase that can be easily exploited.

Allen Verhey summarises the discussion well:

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[29] Egbert Schuurman, *Perspectives on Technology and Culture* (Sioux Center, Iowa: Dordt College Press, 1995), 139-140.

[30] Ramsey, *Fabricated Man*, 138.

[31] For the Christian the concept of 'Playing God' provokes the following questions in relation to our use of technology:

a. Does the technology assist humankind in fulfilling its stewardship responsibilities?
b. Does the technology result in the commodification or destruction of human life?
c. Does the technology degrade, demean or debase individuals?
d. Does the technology serve primarily to promote our narcissistic self-absorption?
e. Does the technology promote technological or economic imperatives?
f. Must we adapt to the technology or is the technology designed to adapt to human nature and human needs?

> We must, in stewardship and service, resist the power of the Baconian perspective in the culture and in the academy. We must, in stewardship and in service, resist the temptation to worship some God of the Gaps instead of the God of Scripture and creation. We must, in faith, refuse to pretend to substitute for an absent God – *etsi dues non daretur*. We must, in faithfulness, respond with all our powers and with all human powers to the cause of God made known in Christ. We must 'play God' as God plays God. God is God, and not us, but God has called us to follow where God leads, to imitate God's works, to serve God's cause.[32]

PART THREE: ETHICAL CONCERNS RELATED TO SPECIFIC RESEARCH INVOLVING HUMAN-ANIMAL MIXTURES

A. General Comments

As mentioned above, the NCCS does not object to some forms of chimeric research, for example, those involving the transfer of differentiated human stem cells into the kidneys or hearts of pigs, mice or even monkeys. Such experiments would not result in chimeric creatures with the human capacity to think and feel. But the NCCS maintains that research involving the transplant of human neural stem cells, human germinal cells, or undifferentiated human stem cells to prenatal nonhumans must be prohibited. Such experiments may produce human-animal creatures with human features and capacities.

Whether research involving the introduction of human stem cells into nonhuman hosts should be approved or not therefore depends on the following factors:

a. the sort of human stem cells being studied;
b. whether these stem cells are specialised or unspecialised;
c. the number of human stem cells to be implanted into non-human hosts;
d. the pluripotency of the implanted cells
e. where in the animal hosts these stem cells are inserted;
f. how closely related is the animal to the human;
g. when a prenatal animal is used as host, i.e., at what stage of development is the animal;
h. what sort of outcome is expected;
i. measures to regulate or limit the proliferation and development of planted cells in the recipient animal;
j. experimental data from implantation of non-human stem cells on all the outcomes (likely and rare).[33]

In Section B of this part, we examine the different types of research involving human-animal mixtures.[34] While many of these experiments involve the use of stem cells, others do not. Some of the procedures examined here have not been carried out and are currently prohibited in most parts of the world. These procedures are discussed nonetheless because the fact that they are currently prohibited does not preclude

[32] Allen Verhey, 'Playing God', *Genetic Ethics: Do the Ends Justify the Genes?* Edited by John F. Kilner, Rebecca D. Pentz ad Frank E. Young (Grand Rapids, Michigan: Eerdmans, 1997), 72.
[33] Cohen, *Renewing the Stuff of Life*, 129.
[34] Section B of this Part is in many ways indebted to the Scottish Council on Human Bioethics' Report entitled, 'Embryonic, Fetal and Post-natal Anima-Human Mixtures: An Ethical Discussion', published on 1 September 2005.

them from being carried out in the future. Furthermore, in this paper, the NCCS aims to provide its clear position on as many variations of research involving human-animal combinations as possible.

B. Animal and Human Gestation

The first group of experiments involving animal-human mixtures that we would like to discuss is animal and human gestation. There are four possible ways in which such experiments can be conducted:

(1) By inserting *ex vivo* human embryos into the bodies of animals
(2) By inserting an animal embryo in a human
(3) By placing human sperm into an animal
(4) By placing animal sperm into a woman

To date, none of the above experiments have been conducted and there is a clear international consensus that they should be prohibited. However, in its 2005 report entitled, 'Human Reproductive Technologies and the Law' the UK House of Commons Science and Technology Committee suggested that research involving the incubation of a human embryo in an animal could help scientists better understand the causes of infertility and miscarriage. If this is indeed the case, the report maintains that this is an appropriate use for the embryo and that it is also consistent to its status.

These experiments, however, pose serious ethical problems. Inserting a human embryo into the body of an animal (1) would violate the dignity of the embryo that must be regarded as a human being worthy of respect and protection. Such a procedure would result in possible moral confusion in that the human embryo in an animal will be accorded the status of an animal. Similar ethical problems would arise when an animal embryo is placed in the womb of a human being (2). In light of these ethical problems the President's Council on Bioethics states in its report entitled *Reproduction and Responsibility: The Regulation of New Biotechnologies* that a bright line must be drawn at the 'insertion of *ex vivo* human embryos into the bodies of animals: an *ex vivo* human embryo entering a uterus belongs *only* in a human uterus'.[35] In similar vein, the UK Human Fertilisation and Embryology Acts (1990) states that 'No person shall place in a woman a live embryo other than a human embryo' (Section 3[2]).[36]

Experiments (3) and (4) also pose serious ethical problems. Judeo-Christian ethics is unequivocal on the question of bestiality. Prohibition against the act is clearly expressed in Leviticus 18:23: 'Do not have sexual relations with an animal and defile yourself with it. A woman must not present herself to an animal to have sexual relations with it; that is a perversion'.[37] Many countries prohibit human-animal sexual activity. In the UK, the Sexual Offences Act 2003 states in Section 69, paragraph (1) that a man commits an offence if he has sexual intercourse with an animal. The same revulsion must be expressed for experiments that involve the

[35] The President's Council on Bioethics, *Reproduction and Responsibility: The Regulations of New Biotechnologies*, Washington D.C., March 2004, http://bioethics.gov/reports/reproductionandresponsibility/chapter10.html.
[36] House of Commons science and Technology Committee, *Human Reproductive Technologies and the Law*, Fifth Reportof Session 2004-5, Vol. 1, 30-32. http://www.publications.parliament.uk/pa/cm200405/cmselect/cmsctech/7/702.htm.
[37] See also Exodus 22:19: 'Anyone who has sexual relations with an animal must be put to death'.

biological insertion of animal sperm into a woman or human sperm into a female animal that may result in human-animal mixtures.

The NCCS maintains that because of the grave ethical problems they pose the above experiments should be prohibited.

C. Animal-Human Hybrid Embryos

The next group of experiments aim to produce animal-human hybrid embryos for research. Unlike the experiments discussed in the last sub-section, the experiments below have been conducted and the ethical responses to them are varied.

The insertion of human nuclei into non-human eggs

Dr Orly Lacham-Kaplan and her colleagues at the Monash Institute of Reproduction and Development in Australia have developed a way of 'fertilising' non-nucleated mouse oocytes by injecting somatic cell nuclei taken from adult male mice. Embryos with two sets of chromosomes were then formed after the chemical activation of the 'fertilised' oocytes and the extrusion of two secondary polar bodies.[38] In 2003, a team of scientists from Cambridge University fused frog eggs with nuclei from adult human cells. The purpose of this procedure was to produce rejuvenated master cells that could be developed into replacement tissues for treating certain diseases.[39]

Serious and complex ethical problems would arise if such experiments result in human-animal entities (i.e., human-frog embryos). If the purpose of such experiments and research is to better understand the mechanism of nuclear reprogramming, the nuclei of other mammalian species should be used instead of the nuclei from a human donor. There is the possibility of cross infection or even of creating new diseases through such animal-human mixtures. The benefits versus risks of such research are ambiguous and therefore caution must be exercised.

The NCCS maintains that experiments involving the insertion of human nuclei into non-human eggs should be prohibited.

The insertion of human nuclei into non-human eggs stripped of their chromosomes

Hui Zhen Sheng of Shanghai Second Medical University, China, announced in August 2003 that they had succeeded in creating rabbit-human embryos by fusing adult human stem cells with rabbit eggs stripped of chromosomes (nuclei). The rabbit-human hybrid embryos, which were created by using donor cells from the foreskins of a five-year old boy, two men and facial tissue from a woman, developed to the approximately 100 cell-stage that forms about four days of development.[40] Gametal cow-human hybrid embryos have also been created using this method.[41,42] By

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[38] Lachm-Kaplan, O. Daniels, R. & Trouson A. *Reprod. Biomed. Online* 3, 205-211(2001). http://www.ncbi.nim.nih.gov/entrez/query.fcgi?holding=npg&cmd=Retrieve&db=PubMed&list_uids=12513856&dopt=Abstract.

[39] Byrne, J.A. Simonsson, S., Western, P.S. & Gurdon, J.B. entitled *Nuclei of adult mammalian somatic cells are directly reprogrammed to oct-4 stem cells gene expression by amphibian occytes. Current Biology*, 13, 1206-1213 (2003).

[40] Hui Zheng Sheng et al., 'Embryonic stem cells generated by nuclear transfer of human somatic nuclei into rabbit oocytes', *Cell Research* (2003) 13 (4): 251-264, http://www.cell-research.com/20034/2003-116/2003-4-05-ShengHZ.htm.

[41] BBC News -18 June 1999, 'Company 'cloned human cells', http://news.bbc.co.uk/1/hi/sci/tech/213663.stm.

generating human embryonic stem cell lines through the creation of cytoplasmic hybrid embryos scientists hope to address the problem of the limited supply of human eggs. Scientists also hope that interspecies hybrid embryos would provide valuable tools to study the reprogramming of somatic nuclei that could provide long-term solutions to the problem of tissue rejections.

There are, however, a number of serious and complex ethical problems associated with such research. Because the hybrid embryos created by this method are 99% human, the ethical objection surrounding the use of human embryos for research must be answered. These interspecies embryos that are 99% human must be accorded the dignity and protection they deserve. They should not be used for research or for obtaining cell-lines and then destroyed.

It is important to note that oocytes are not totally devoid of genetic material, and the mammalian ooctye cytoplasm is rich in mitochondrial DNA. According to M.H. Pineda, 'the cytoplasmic inheritance of mitochondrial DNA is an important component of the eukaryotic inheritance'.[43] There is evidence that there can be interaction between mitochondrial DNA and nuclear DNA. This means that in experiments where the human nuclei is inserted into an animal egg, there may be interaction between the human and animal DNA even though the egg in question has been enucleated.

Due to the presence of different degrees of interspecies incompatibility between mitochondrial and nuclear function, there are therefore considerable medical risks in implanting cells that contain a mixture of animal mitochondrial DNA and human nuclear DNA. In addition, the some of the diseases for which therapeutic cloning are supposed to provide treatment are neurodegenerative diseases. Since mitochondrial dysfunction is the key to many neurodegenerative diseases, their treatment using enucleated animal eggs for somatic nuclear transfer (SCNT) is liable to result in serious medical risks. There is also the possibility of the transmission of animal diseases to humans and / or the creation of new diseases. Furthermore, the risks involved are unknown and the benefits of such research are largely speculative.

Finally, there are so many serious and profound genetic and epigenetic flaws in cloned embryos even when the eggs of the same species are used. The use of interspecies hybrid embryos created through SCNT involving enucleated animal eggs for research into diseases could be so problematic that such research would become a study of artefacts: the results of such studies would be very difficult to interpret.

The NCCS maintains that experiments involving the insertion of human nuclei into animal eggs stripped of their chromosomes should be prohibited.

Mixing human and animal gametes to form human-animal entities

In the UK, the 'Hamster Egg Penetration Test' (HEPT) in which human sperm is mixed with the egg of a hamster stripped of its outer membrane (zona pellucida) was used to test the viability of some patient's sperm. The resulting human-hamster chimera was sometimes allowed to develop to the two-cell stage for observation before it was destroyed. With the introduction of Intra Cytoplasmic Sperm Injection (ICSI) and other treatments HEPT was effectively rendered obsolete.

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[42] Coghian, A., NewScientist.com – 15 September 2003, 'First human clone embryo ready for implantation', http://uk.news.yahoo.com/030916/12/e8k6h.html.
[43] M.H. Pineda, 'The Biology of Sex' in *McDonald's Veterinary Endocrinology and Reproduction* (5th Edition), Edited, M.H. Pineda (Ames, IA: Iowa State Press, 2003), 229.

A number of countries like Denmark, Germany, and France[44] have prohibited such procedures, which are deemed to have no scientific benefits. The creation of human-hamster chimera as a result of such procedures poses serious and complex ethical problems that have to do with the moral status of such entities and the question of human dignity.

The NCCS maintains that the mixing of human and animal gametes to form human-animal entities should be prohibited.

D. Animal-Human Chimeras

While the hybrid is 'an organism whose cells contain genetic material from organisms of different species', a chimera is an organism 'whose body contains cells from another different organism of the same or different species'.[45] In this section, we examine research that requires the creation of embryonic, foetal and post-natal animal-human chimeras.

Transplanting (1) human pluripotent stem cells into a non-human blastocyst or early embryo (2) non-human pluripotent stem cells into a human blastocyst or early embryo

It was reported that scientists at the South Korean firm Maria Biotech injected human embryonic stem cells labelled with fluorescent protein into 11 mouse blastocysts in an experiment conducted in 2003.[46] Foster mice were used to carry the embryos. Five offspring with fluorescence in tissues including heart, bone, kidney and liver were eventually born. But 'severe protests' from the public forced these scientists to terminate the project.

Such research would create serious and complex ethical difficulties because the developing inner cell mass of the non-human blastocyst or early embryo – the progenitor of the foetus – into which human pluripotent stem cells are incorporated, would then consist of a mixture of human and animal cells. It is not clear how great the human contribution to the resulting chimera would be. Most scientists would agree that the closer the animal whose embryo is the recipient of these stem cells is biologically to the human, the greater the potential for human contributions. The moral status of such creatures would at best be ambiguous.

In its guidelines on research involving the insertion of undifferentiated human embryonic stem cells into nonhuman host, the National Academies of Sciences (NAS) highlights the following considerations:

> The number of hES cells to be transferred, what areas of the animal body would be involved, and whether the cells might migrate through the animal's body. The hES cells might affect some animal organs rather than others, raising questions about the number of organs affected, how the animal's functioning would be affected, and whether

[44] Calum MacKellar, 'Reproductive Medicine and Embryological Research – A European Handbook of Bioethical Legislation', *European Bioethical Research*, 1997.
[45] BAC, 'Human-Animal Combinations for Biomedical Research: A Consultation Paper', 8 January 2008, 11-12.
[46] Neil Boyce, 'Mixing species – and crossing a line?', 27 October 2003, usnews.com, http://www.usnews.com/usnews/issue/031027/misc/27chimeras.htm?track=rss.

> some valued human characteristics might be exhibited in the animal, including physical appearance.[47]

In its discussion on the insertion of human embryonic stem cells into the blastocyst of the mouse, the NAS document again expressed profound concerns. Its recommendation is that such research is not justified at this time.

> [when hES cells are incorporated into a mouse blastocyst] the human cells [could] contribute extensively to any mouse that arises from the implantation of such a chimeric blastocyst ... Potentially the inner cell mass, the progenitor of the foetus, would consist of a mixture of human and mouse cells. It is not now possible to predict the extent of human contributions to such chimeras. If the recipient blastocyst were from an animal that is evolutionarily close to a human the potential for human contributions would appear to be greater. For these reasons, research that involves the production of such chimeras should be performed first using nonhuman primate ES cells in mouse blastocysts before proceeding to the use of hES cells. The need for the use of blastocysts from larger mammals would need to be very clearly justified and nonhuman primate blastocysts should not be used at this time.[48]

The NCCS maintains that the transplantation of (1) human pluripotent stem cells into a non-human blastocyst or early embryo and (2) non-human pluripotent stem cells into a human blastocyst or early embryo should be prohibited.

Transplanting human pluripotent stem cells into post-blastocyst stages of animal embryo

In December 2003, scientists injected human stem cells into the foetuses of sheep, which produced a high proportion of human cells in some of the organs of these animals. In some cases 40% of the cells in these sheep were human. Although the animals looked normal scientists are unsure whether these sheep foetuses had human brain cells.[49]

This sort of research would raise the same ethical problems as above. The degree of human participation in the resulting chimera is largely unknown. The moral status of the resulting creature would be ambiguous. More research should be done using other mammalian pluripotent stem cells before employing human stem cells.

The NCCS maintains that transplanting (1) human pluripotent stem cells into post-blastocyst stages of animal embryo and (2) non-human pluripotent cells into post-blastocyst of human embryos should be prohibited

Transferring human neural stem cells into prenatal nonhuman animals

The experiment conducted by Ourednik and colleagues in which human neural progenitor cells are transferred into the forebrain of foetal monkeys has indicated that the human neural cells became an integral part of the monkey brain. In other words, the human neural cells developed along the same pathways as the

[47] National Research Council and the Institute of Medicine of the National Academies, *Stem Cells and the Future of Regenerative Medicine* (Washington, D.C.: National Academies, 2002), 50.
[48] Ibid. 40-41.
[49] '"Humanised" organs can be grown in animals', 17 December 2003, *New Scientist*, http://www.newscientist.com/news/news.jsp?id=n99994558.

surrounding monkey cells, and no adult human-monkey chimera had resulted.[50] In the same way, the study conducted by Weissman showed that when human foetal neural stem cells are inserted into the brains of newborn mice, the human cells migrated to various regions of the brains of the mice and became integrated with the mouse neural cells.[51] However, in a famous experiment conducted more than a decade ago in which small sections of the brains from developing quails were transplanted into the developing brains of chickens, the recipient chickens exhibited vocal trills and head bobs unique to quails.[52]

This led scientists to conclude that only when whole masses of associated neural stem cells are introduced into nonhuman embryos would there be a risk of the nonhuman host developing a human-like brain.

This conclusion does not satisfy some ethicists simply because not enough is known about the behaviour of human neural stem cells in prenatal nonhuman hosts. The suggestion, forwarded by some scientists that the number of human stem cells introduced to the nonhuman host should be reduced to the smallest number fails to satisfy ethicists and scientists alike. For reasons already cited, the suggestion that such experiments should be conducted only by transferring dissociated neural stem cells and not whole masses of organised tissue into the host does not fully address the ethical concerns. The limitations introduced to these procedures are purposed to prevent the emergence of chimeric creatures with the capacities and characteristics that are associated with human dignity. But such limitations are theoretical because scientists are unsure about how much human stem cells in the brains of nonhuman hosts would bring about these characteristics. Not enough research is done using animal neural stems cells to justify the use of human neural stems cells.

The NCCS maintains that transferring human neural stem cells into nonhuman animals should be prohibited until scientists are sure that such procedures will not result in 'higher order' brain functions in the nonhuman hosts.

Human and animal chimeras through xenotransplantation

Xenotransplantation technology is not new, as inert heart valves of pigs are already used in heart valve replacement operations. Xenotransplantation promises to surmount some of the issues that we have examined above attending allotransplantation from the availability of organs to the problems associated with living donors. Xenotransplantation chimeras are widely used in research and medicine. Some examples include the transplantation of human skin onto mice, human tumours onto mice, and human bone marrow into mice. These experiments are used to provide models for biomedical examinations.

One of the most serious issues surrounding this procedure is the threat of Porcine Endogenous Retro Viruses (PERVs), the spread of animal diseases to humans. The dangers include the spread of Bovine Spongiform Encephalopathy (BSE or 'Mad Cow Disease'), HIV and AIDS from animals to humans. Another major issue has to do with the emotional response related to xenotransplantation. Some have expressed

[50] V. Ourednik, J. Ourednik, J.D. Flax, W.M. Zawada, C. Hutt, C. Yang, K.I. Park, S.U. Kim, R.I. Sidman, E.Y. Snyder, 'Segregation of Human Neural Stem Cells in the Developing Primate Forebrain', *Science* 293 (2001): 998-999.
[51] N. Uchida, D.W. Buck, D. He, M.J. Reitsma, M. Masek, T.V. Phan, A.S. Tsukamoto, F.H. Gage, I.L. Weissman, 'Direct Isolation of Human Central Nervous System Stem Cells', *Proceedings of the National Academy of Sciences USA* 97 (2000): 14720-14725.
[52] E. Balaban, M.A. Teillet, N. Le Douarin, 'Application of the Quail-Chick Chimera System to the Study of Brain Development and Behaviour', *Science* 241 (1988): 1339-1342.

repugnance over the idea of humans receiving animal organ transplants. The final issue has to do with concerns about the abuse of animals.[53]

For the NCCS, however, xenotransplantation does not pose serious theological or ethical problems so long as the procedure itself does not cause any physical and psychological harm to the recipient. The question of whether the introduction of an organ from an animal into a human body will significantly change or affect the genetic or psychological identity of the person has been raised. As we have already seen, from the standpoint of theological anthropology, the identity of a person is established firstly in God's knowledge of the person, and secondarily on the being of his person, his embodied individuality. We have seen that it is our duty to protect the integrity and dignity of the whole person. Xenotransplantation is permissible only if it does not affect the psychological and genetic identity of the person who receives it. We concur with the conclusion of the Pontifical Academy for Life in a paper entitled *Prospects for Xenotransplantation: Scientific Aspects and Ethical Considerations* that 'the implantation of a foreign organ into a human body finds an ethical limit in the degree of change that it may entail in the identity of the person who receives it'.[54]

The NCCS maintains that research involving xenotransplantation chimera is permissible as long as the proper guidelines and international laws governing such research are strictly observed.

SUMMARY

Here is the summary of the positions of the NCCS on the various forms of research involving human-animal chimeras or hybrids:

- The insertion ex vivo human embryos into the bodies of animals should be prohibited.
- The insertion of an animal into a human should be prohibited.
- The insertion of human sperm into an animal should be prohibited.
- The insertion of an animal sperm into a woman should be prohibited.
- The insertions of human nuclei into non-human eggs should be prohibited.
- The insertion of human nuclei into animal eggs stripped of their chromosomes should be prohibited.
- The mixing of human and animal gametes to form human-animal entities should be prohibited.
- The transplantation of (1) human pluripotent stem cells into a non-human blastocyst or early embryo (2) non-human pluripotent stem cells into a human blastocyst or early embryo should be prohibited.

[53] The question concerning the use of animals for the good of human beings must be briefly addressed. The Christian tradition maintains that animals as God creatures have their own specific values which human beings must recognise and respect. However, human beings enjoy a unique and higher dignity since they are created in the image of God. Animals are given for the service of human beings in order that they may achieve their fullest potential. Human beings have always used animals for their good, either to provide food, clothing or transport. With the advances in technology, the 'service' that animals can render to human beings takes a different form. In the biomedical field, animals perform a special service to human beings through xenotransplantation. We therefore agree with the Pontifical Academy for Life in its statement that the sacrifice of animals can be justified if it is required 'to achieve an important benefit for man, as is the case with xenotransplantation of organs or tissues to man, even when this involves experiments on animals and/or genetically modifying them'.

[54] https://www. Vatican.va/roman_ curia/pont...ife_doc_20010926_xenotrapianti_en.html.

- The transplantation of (1) human pluripotent cells into post-blastocyst stages of animal embryo and (2) non-human pluripotent cells into post-blastocyst of human embryos should be prohibited.
- The transference of human neural stem cells into nonhuman animals should be prohibited until scientists are sure that such procedures will not result in 'higher order' brain functions in the nonhuman hosts.
- The creation of human and animal chimeras through xenotransplantation should proceed with caution and should abide by established international laws.

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3 March 2008

Professor Lee Eng Hin
Chairman, Human Embryo and Chimera Research Working Group
Bioethics Advisory Committee (BAC)

Dear Prof Lee

Consultation Paper on Human-Animal Combinations for Research

I refer to your letter to Dr Yuen Kwong Wing, Clinical Advisor, NDC, requesting for views of NDC on the issues discussed. I have been tasked to provide feedback on the above.

In summary, the BAC would like to seek our views on:
(a) the creation and use of human-animal combinations for research;
(b) the prohibitions, limits and regulatory mechanisms that will be needed for such research in Singapore; and
(c) any other matters related to human-animal combinations for biomedical research.

My comments in relation to the issues raised in the paper are as follows:

I am convinced that biomedical research using human-animal combinations is the way forward to increase further medical knowledge and improve treatment modalities and such research will benefit mankind. A large part of the exciting promise of using stem cells for treatment of diseases such as Alzheimer's disease and neurological defects, and growing organs for transplant are from past and on-going studies using such combinations like animal chimeras and cytoplasmic hybrid embryos. These research using human-animal combinations will also help to offset the shortage of human eggs to further stem cell research.

Nevertheless, I am not without reservations on the use of human-animal combinations for research and the contents from the consultation paper suggest that there are some real non-emotive concerns:

i) The possibility of transfer of diseases between humans and non-humans though minimal, is not improbable (pg 19 para 29).
ii) While the evidence suggests the probability of producing uncontrollable monsters or creatures with human consciousness or mental characteristics is low, (pg 22 para 40), or that it is still highly unlikely that there can be an entity that is both wholly human in its consciousness and wholly monkey or wholly something else in other aspects (pg 25 para 50), there is no absolute certainty that this may not happen.
iii) There is the possibility that once the techniques and knowledge are developed, they may be abused, because not all scientific activity is controllable, and scientists can be influenced adversely or 'bought'.

Definitely, a true hybrid between a human and an animal is a no-no. Although there may be the possibility of "growing" organs in an animal for human use, implantation of any human-animal combinations into a human or animal womb should be absolutely disallowed.

Thus, for mankind to benefit from these promising research using human-animal combinations, and yet not suffer any indignity or potential harm, the best option is to implement very clear-cut and strict regulations, with highly deterrent punitive action when contravened. The legislation with regard to this, adopted in Canada and United Kingdom; seems the most comprehensive, and I think Singapore could adopt the same and more.

The above are my personal views. I have further included the comments of my IRB members. They are as follows:

View 1:
I have difficulty accepting human-animal combinations (especially the animal chimeras and cytoplasmic hybrid embryos). I understand that the use of human-animal combinations will help to advance scientific research and to do this; we will need fresh ethical perspectives. (Quote from the consultation paper para 46: "The point to be made here is that a moral 'status quo' or well accepted social norm should not lead to a presumption that change from that position is bad or harmful.") As further mentioned in the paper, the emancipation of slaves in United States, woman's liberation movement and civil rights movement happened even when they were against the 'status quo' during their times. However, I am of the opinion that the 'use of human-animal combinations in research' issue is very different because human-animal combinations have the possibility of creating a creature that is 'half human' (e.g. in human consciousness, mental characteristics and may even exhibit physical semblance).

Besides, the use of human-animal combinations in research may set us up on a "slippery slope", because one of the human weaknesses is greed. Hence, there will always be a 'knowledge thirst' to want to know more. And even with all the legal and regulatory oversight in place, there is a possibility of a scientist being influenced and 'bought'; and ultimately will this benefit the powerful and wealthy in our society?

View 2:
My concern with the use of human-animal combinations in research is the transference of inter-species material, genetic as well as cytoplasmic, and creating a human-hybrid organism. In the interest of generating new knowledge, to advance medical treatment to save lives or to prolong meaningful living, breeding of hybrids using genetic or cytoplasmic material should be allowed, but only *in vitro* and not *in vivo*. The development of the hybrid embryo should be terminated by the 14th day while it is still in the primitive stage - it's kinder to the developing hybrid embryo, which deserves the respect, that it is a life-form.

View 3:
- legislation is required to strictly limit the research to scientifically useful work only.

- the creation of chimeric embryo, cytoplamic hybrid or transgenic animal that will lead to reproduction or breed into a kind of sub-human or part-human creature should be strictly prohibited.

View 4:
Biomedical research with animal-human combinations should be allowed for the advancement of scientific knowledge that could lead to new or improved medical treatments. The benefits for mankind from such research could outweigh the ethical concerns that are often emotional in nature. Nevertheless, there must be strict guidelines to regulate the research and severe punitive actions if contravened.

View 5:
Comments on BAC's Consultation Paper on Human-Animal Combinations for Biomedical Research

1. *Background Information*
I found this factually educational and succinctly written. Thank you.

2. *Ethical Considerations in Research with Human-Animal Combinations*

2.1 I acknowledge the BAC's view on the lack of moral equivalence between an embryo and a sentient human, but it is not a view I personally accept. I am now invited to comment on the *added* ethical issues that arise from human-animal combinations.

2.2 We are told that the *basic premise* is that there is likely benefit in the bio-medical research into human-animal combinations in the form of translational medicine and that the *issue* is whether there are ethical objections or drawbacks that might render it unacceptable despite the likely benefit.

2.3 Before looking at the ethical considerations listed by the BAC, I would like to mention that, in my opinion, the Consultation Paper, at this point, fails to present a balanced and objective platform to enable members of the public to fully appreciate the ethics of the proposed research. The Paper tends to briefly introduce known objections and then proceeds to demolish the stated objections with specific examples leading to a conclusion that appears to justify change in the name of scientific advancement. The supporting examples for the known objections were not similarly shared as with the counter-objections.

2.4 Having said that, I set out below my comments on the listed ethical considerations.

2.5 Health Risk
Medical research of any kind with clinical applications must be conducted under stringent research & laboratory protocol. I think that this is a 'given' and should not pose too much of an ethical issue, as such.

2.6 Repugnancy Factor
In law, there is the concept of "natural justice", "due process", upholding the "spirit of the law" as opposed to the literal interpretation of text and in refusing to accept arguments that are repugnant to public policy and the common good. As you can see, we are dealing with 'concepts' and 'principles', but it is these very concepts and principles, which have created social cohesion and allowed for comparatively peaceful human co-existence since time immemorial. It is not an 'emotive factor' – it is an underlying premise of what is acceptable to society as a whole. It ought not to be dismissed as a 'whim'. It is also not 'an obvious point'.

2.7 Playing God & Acting against Nature
BAC is playing with semantics when claiming that 'scientists do not create life; they just rearrange the ways life manifests itself' – it begs the question, at which point in time does creative rearrangement become a new life form? The discernment of divine plans is not, as far as I am aware, within the realm of scientists – it is a contradiction in terms. Respecting the true Creator of 'life' as we know it today is very different from the political agenda of maintaining harmony in a multi-religious society – the 2 issues ought not to be confused.

2.8 Concerns with Producing Creatures with Human Consciousness or Mental Characteristics
Eroding the Moral Boundary between Human and Animals
Identity Problems & the Moral Status of Human-Animal Combinations
Human-Animal Combinations set us on a "Slippery Slope'
My comments on the above 4 areas are similar:-

(a) The area of research deals with 'probabilities' and 'likelihoods' of stem cell research involving human-animal combinations. Hence the chances of success are evenly shared with the chances of undetermined outcomes. Humans, especially scientists, are constantly pushing boundaries, even where boundaries are cast in stone. It is a fact that laws will be contravened or circumvented in the feverish anticipation of new discoveries.

(b) The example of the 'mule' is oft cited – but the mule & its characteristics (both scientific & non-scientific) have been allowed the benefit of time to conclude that they not harmful to mankind.

(c) Society's consent is being sought not for the human-animal combination per se, as this has taken place already in the form of the 'mule' and laboratory mice, but for the expedited production of such chimeras & cytoplasmic hybrids to aid scientific development in the forecasted hope of alleviating human suffering as soon as possible.

(d) This expedited production chain does not have the benefit of time unlike the development of the mule. The pace at which all these new scientific discoveries have taken place recently is astounding as is the fact that we are still simultaneously discovering the downsides.

(e) The speed at which we desire results and our increasing incapacity for patience is my greatest fear in biomedical research. It is our greed and insatiable thirst for knowledge that could also be our nemesis.

2.9 Legal and Regulatory Compliance
Legislation is only as good as one's respect of the law stands. Enforcement is a post-event action – damage done & damage control. Outright prohibition in Singapore only means that the scientific research will move to jurisdictions which support such research, which jurisdictions may have no regard for ethics of any form whatsoever.

2.10 Conclusion
I am unable to support the bio-medical stem cell research involving human-animal combinations for the reasons stated above. However, in the event, that such research is permitted in Singapore for whatever reason, I would strongly urge that:-

(a) Stringent legislation and regulatory compliance for scientific safe-guards be enacted and enforced;

(b) Adequate time be allocated for studying the results of such human-animal combinations, before proceeding onto the next research phase.

(c) To ensure sufficient safeguards against scientists who push boundaries to achieve personal acclaim or for any other reason.

(d) To train doctors and scientists at the very start of their secondary/tertiary education on the importance of ethics and the dignity of the human person. Such ethical studies and respect for human life (as we know it today) must be ingrained in our students from the moment they enter the profession, and not treated as an incidental non-examinable subject.

View 6:
Agree with and endorse View 5.

View 7:
There are certainly some benefits from research using human-animal combinations. However, there are also concerns of the probability of producing uncontrollable monsters or creatures with human consciousness or mental characteristics, possible abuse of the knowledge, etc. Thus, there has to be strict regulations and stiff penalties for individuals / organizations who flout these regulations.

I am of the opinion that the research should remain in vitro and in the laboratory. Crossing this line would certainly pull us down the already slippery slope.

View 8:
I have no objections to this aspect of medical research, which I think will be the way forward.

My other comments are:
1. Report of any untoward effects or outcome that may directly or indirectly affect humankind adversely must be made mandatory (legislated) and must be immediately announced to the scientific community. The fear of any negative and unexpected genetic expression in human-animal combinations whilst minimal at this juncture, is real, given that genetic evolution is continuous and not within our control.

2. Commercialization of research: I have lots of reservation about researchers not sharing scientific findings; hoping to make big bucks out of patents. This is the reality today and in this aspect of human-animal research, it is vital that any new findings, good or bad should be shared openly.

I hope the above feedback is useful to the Bioethics Advisory Committee.

Yours Sincerely

Dr Teh Luan Yook
Chairman, Institutional Review Board,
National Dental Centre

Cc. Dr Yuen Kwong Wing, Clinical Advisor, National Dental Centre

Dr Kwa Chong Teck, Executive Director, National Dental Centre

Members, NDC IRB

MINISTRY OF HEALTH
SINGAPORE

MH 24:63/1-25

20 Feb 2008

Professor Lee Eng Hin
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Dear Prof Lee

INVITATION TO COMMENT ON CONSULTATION PAPER

Thank you for your letter, dated 8 Jan 08, inviting the National Medical Ethics Committee (NMEC) to provide its comments on the Bioethics Advisory Committee (BAC) consultation paper on human-animal combinations for biomedical research.

2 The NMEC acknowledges the potential scientific advancements that may result from the use of human-animal combinations for biomedical research. However, in the absence of strong evidence for its benefits, and the multitude of safety and ethical concerns, such as were discussed in the consultation paper, it is the NMEC's opinion that research involving the use of human-animal combinations should be cautiously advanced in measured, incremental steps. For example, consideration could first be given to study animal-animal combinations further before moving on to human-animal combinations.

3 It could be more timely to explore the ethical issues involved in the use of human-animal combinations for biomedical research when there is sufficient evidence that their use for research is safe and of certain benefit.

Thank you.

Yours sincerely,

DR LEE SUAN YEW
CHAIRMAN
NATIONAL MEDICAL ETHICS COMMITTEE

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13 February 2008

Professor Lee Eng Hin
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Dear Eng Hin

CONSULTATION PAPER ON HUMAN-ANIMAL COMBINATIONS FOR RESEARCH

Thank you for your letter dated 8 January 2008 seeking our views on the above.

I have asked our Ethics Committee for their views and would like to reflect their comments.

In Singapore, the current position is as follows:

Human –Animal Chimeras

1. All research on human eggs or embryos are to be carried out only after written approval of the Ministry of Health has been obtained.

2. Research on or using human embryos which are more than 14 days old from the time of creation is prohibited.

True Hybrids

3. Trans species fertilization for the purpose of reproduction is not allowed.

4. It is however allowed to assess or diagnose subfertility, with the restriction that the resulting true hybrid must be terminated at the two cell stage.

Cytoplasmic Hybrids

5. It is unclear if the creation of a cytoplasmic hybrid is a regulated activity.

The Committee is of the opinion that the regulations and restrictions that govern research on Human–animal chimeras and on true hybrids are adequate and ethically acceptable. In the case of research on cytoplasmic hybrids, there is a need for additional regulations that will allow only hypothesis driven and IRB approved research to be conducted; there is a need for experts and researchers to agree on an age by which the hybrid will be terminated.

They are also of the opinion that all research using human animal chimeras and true hybrids should demonstrate no ability to pose a health risk, i.e. either increasing transfer of diseases between humans and non humans or increasing resistance of human disease (especially) and non human disease (to a lesser extent) to available treatments. Where such risks exist, the research should not be allowed unless the benefits outweigh such risks and suitable prohibitions can be put in place to mitigate the risks.

It would be helpful for the BAC to describe details of the research on human animal combinations (chimeras, true hybrids, and cytoplasmic hybrid) that have been carried out in Singapore to date and the benefits (if any) and problems encountered so that the public, ethical and scientific reviewers, can make informed and ongoing decisions to better guide research in this area.

Yours faithfully

Assoc Professor Benjamin Ong
Chairman
NUH Medical Board

Office of Life Sciences

NUS National University of Singapore

07 March, 2008

Professor Lee Eng Hin
Chairman
Human Embryo and Chimera Research Working Group
Bioethics Advisory Committee

Dear Prof Lee,

RE: Consultation Paper on Human-Animal Combinations for Research

This is with regards to the request for comments on the consultation paper on human- animal combinations for research.

Attached, please find the comments from Dr Patrick and Prof Lam Toong Jin for your information.

Thank you.

Yours sincerely

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LAC (Laboratory Animal Centre) & IACUC (Institutional Animal Care and Use Committee) RESPONSE

HUMAN & ANIMAL COMBINATIONS IN RESEARCH

IACUC's concerns about human-animal combinations in research lie in the possibility of pain and distress to the animals receiving human gene, cells or tissues and developing human tissue or organs (for example, human teratoma or tumour), and in health and safety issues for personnel and animals as well as religious considerations.

If pain and distress are manifested during the experimental process, according to the established criteria of pain and distress, the animals would have to be euthanized even before the experimental endpoint is reached. In any case, the animals would have to be euthanized at the end of the experiment. Exceptions are rarely granted and that only upon full scientific justification.

The health and safety concerns relate to adventitious agents in cell lines and tissues and food chain issues, and religious considerations concern religious sensitivities of investigators and animal handlers.

These concerns are elaborated below and contributed by Dr Patrick Sharp of LAC (the NUS Attending Veterinarian).

Pre-mature termination of experiment

Many scientific advisory groups and journals have developed a brief statement outlining the importance of clearly defining experimental endpoints and criteria for premature termination from a scientific study (e.g. euthanasia). Frequently investigators will cite that a given procedure must use death as an endpoint when this is discouraged in both Europe and North America, in fact strongly discouraged is perhaps more accurate. Not only does this (death as endpoint) add to the animal's pain and suffering, but it adds to the cost of the research project by maintaining the animals much more intensely than otherwise would be expected, holds the institution up to additional scrutiny both nationally and internationally, and at the end of the day answers few (if any) additional scientific questions. Many journals realize this and make this particularly clear to those who submit for publication. In an area that is already emotionally charged, it may be best for the Committee to address this important matter and strongly encourage researchers to not only search for alternatives to painful procedures (this is already required by the Agri-food and Veterinary Authority), but also work to develop endpoints and criteria for premature termination that rival those of Europe and North America. An example of this would be hu-SCID mice contracting *Pneumocystis.* The best plan is to first prevent the animals from being infected; however, now that this has happened serious consideration should be given to euthanizing the animals because this is an undesired event that in all likelihood will result in research interference whether the animals are treated or not; furthermore if they are treated, what about the research variable of antibiotic treatment?

Cell lines and tissues

Cell lines and tissues used for human-animal combination run the risk of contamination by deleterious agents of humans, animals, and occasionally both. Whenever cell lines and tissues are used they should be appropriately tested for human and animal pathogens. The reason for human pathogen testing should be clear. Testing for animal pathogens should occur because of the existence of zoonotic agents, research interference with the research project where the animals are enrolled, and risk to neighboring research projects, as more than one researcher will occupy a room. It is the belief of many researches that organizations, such as the American Type Culture Collection (ATCC), test their cell cultures for agents which may interfere with research (e.g., viral agents); however, they do not. They do check for bacterial and *Mycoplasma* contamination, but once they leave ATCC there is no control on how these samples are handled. Therefore, it is important for the Committee to make a statement which reinforces the importance of this testing to ensure the reported results are not confounded by contamination of the cell lines and tissues used in contemporary biomedical research.

Food Chain

Every effort should be made to preclude these animals from entering the food chain. The United States Food and Drug Administration has expected such practices on genetically modified animals and something should be added to address these concerns, too. Although this seems like a simple process, it was not followed at one institution where genetically modified animals entered the food chain. To clarify the matter, this can happen directly, by the animal itself entering the food chain, or indirectly, by animal by-products from genetically modified animals entering the food chain.

Religious sensitivities

As a multi-ethnic society it may be worthwhile to address matters involving religion considering that benefits of the research may be derived from animals such as pigs and cattle. How will this be perceived by individuals who practice these religions?

It would seem important for the Committee to reinforce the importance of the Institutional Animal Care and Use Committee (IACUC) and the Institutional Review Board (IRB) to evaluate these protocols. In fact in may be necessary for *both* the IACUC and IRB to review some research proposals. Once again, this is an emotionally charged issue and it seems important for the community at general to understand that there are lay people on these Committees (e.g., IACUC, IRB) and they playa role in the research protocol evaluation.

Dr Sharp has also the following specifics:
#14, page13: With the generation of transgenic animals there is a potential for these animals to develop pathologic susceptibilities; these susceptibilities occur with some frequency and are frequently outside the clinical disease manifestations seen in the

human disease. Therefore, it is important that criteria for premature termination from the study be developed between the IACUC, the researcher, and the institutional veterinarian (or their designee). Special consideration should be given to 'side effects' of a genetically modified animal and the potential to develop a pathogen because of an animal's unique susceptibility.

#41, page22: The statement is made, "There is little likelihood of such a monster being created if only individual human neural cells are used, and none if non-neural cells, such as human retinal stem cells, are used." Although the statement is truthful, it is confusing. It may be better to use something other than 'human retinal stem cells' considering the retina has a sizeable neural component.

#56, page27: Regarding the statement, "These recommendations seek to ensure that all human embryonic stem cell research, whether or not human-animal combinations are used, meets certain requirements." It would seem prudent to for the Committee to adopt the statement, "".meets or exceeds certain requirements."

#59 page28: Regarding the statement, "Human reproductive cloning is explicitly prohibited and human embryonic stem cell research may be conducted under close regulatory scrutiny." It seems that there should be a reference cited here.

Feedback/Concerns Regarding "Human-Animal Combinations for Biomedical Research – A Consultation Paper by Bioethics Advisory Committee of Singapore dated January, 2008"

From: Dr Khoo Chong Yew, Dr Foong Weng Cheong
Parkway Independent Ethics Committee, Gleneagles Clinical Research Centre, 111 Somerset Road #11-02, Singapore Power Building

1) This is very controversial, very sensitive and very new. BAC is right that public opinion should be sought. Besides holding public forums, it is important that BAC should have a Dialogue with the various religious bodies, when there is so much talk that such kind of work is like "playing God".

2) There are many possible human-animal combinations. It is important to point out to all concerned that this paper concerns only these two types:

   a) "Animal Chimera", where human cells are injected into animals.
   b) "Cytoplasmic Hybrid Embryo", where the nucleus of a human somatic cell is transferred into an enucleated animal egg. (A true human-animal Hybrid, like a mule, results from fertilisation of an egg by a sperm from another species. This is prohibited in Singapore.)

3) To help us make a decision, it is necessary to state what precautions, restrictions, regulations, prohibitions and limits will be in place if this kind of research is allowed to be done. E.g. will there be regulations for the number and kind of human cells to be transferred, the selection of host animals, and the sites of integration? Will such combinations be prohibited from developing beyond 14 days?

4) Would such studies be reviewed by an IRB, or an ACUC (Animal Care and Use Committee) or an SCROC (Stem Cell Research Oversight Committee)? The recommendations of the ISSCR (International Society for Stem Cell Research) seek to ensure the scientific merit, the appropriate facilities and the proper qualifications of the investigators.

5) Will there be a Registry of every chimera and hybrid developed? It would be easier to decide if we are sure that the necessary rules and regulations are going to be in place, and that there will be strict monitoring and auditing of compliance.

Feedback/Concerns Regarding "Human-Animal Combinations for Biomedical Research – A Consultation Paper by Bioethics Advisory Committee of Singapore dated January, 2008"

From: Fr. Philip Heng, S.J. , Dr. Anthony Heng, Dr Chan Siew Chee, Dr Akira Wu
Parkway Independent Ethics Committee, Gleneagles Clinical Research Centre, 111 Somerset Road #11-02, Singapore Power Building

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Introduction:

First, we would like to commend the Bioethics Advisory Committee (BAC) for opening the above Consultation Paper for public feedback before making recommendations to the Steering Committee on Life Sciences (para 4). It is laudible that BAC assures the public that "none of the issues in this paper are settled as yet" (para. 64) and more importantly, that "if any of the ethical objections outlined . . . are found to be overwhelming as to be inadequately addressed by legal and regulatory control, they might justify the outright prohibition of research using human-animal combinations" (para. 55).

Second, at the outset, we would agree with BAC that any objections raised should be based on "sound reasons" and not based solely on an emotional response and mere assertions that "mixing species is distasteful, repugnant, or even disgusting." (para. 33).

Third, we should support scientific researches that promote human flourishing of the common/universal good of humankind. Thus, while many scientific researches are ethically sound, not all of them are free from serious ethical concerns. As such, if objections have to be registered to assert an "outright prohibition, of certain scientific researches, then they should be done so with the sole objective of protecting the common good, the lives of human beings and the dignity of the human person.

Fourth, we note that in this consultation paper, BAC discusses the "Animal Chimera" briefly (para 16 etc.) and is primarily grappling with the issue of the scientific research on "Cytoplasmic Hybrid Embryo" where the nucleus of a human somatic cell is transferred into an enucleated animal egg. We also understand that the main reason for exploring such an option is that there has been great difficulties in obtaining human eggs due to the risks involved and their limited availability" for stem cell research (para. 3.)

Position:

1. **Main Objection – Inter-Species Combination:**

While we see the basic problem of the shortage of human eggs for stem cell research, our main objection to BAC's Consultation Paper above on "Cytoplasmic Hybrid Embryo" is that this "Cybrid embryo" method involves the creation of "new" species from the inter-species of the human and the animal.

2. **Main Concern – Infinite Wisdom innate in the Laws of Nature":**

We would like to affirm BAC's stand that "Scientific experiments, like everything else must conform to the laws of nature."(para.37). We would like to underline this by asserting that scientific experiments and researches should never over look but on the contrary respect the law of nature i.e. the infinite Wisdom, that is innate in all human beings let alone in animals, plants and the indeed the universe. Our human knowledge regardless of how much the sciences have progressed and discovered is but a drop of water in the ocean to this infinite innate Wisdom in nature.

3. The Laws of Nature - Grave Evidences of Violations

Our scientific experiments and researches must respect and work within the framework and reality of the laws of nature; otherwise, we will be "playing God." If we ignore this innate reality in nature i.e. by crossing species i.e. creating cybrid embryos of the human-animal combinations, we will be disrupting and violating a laws of nature and would have to face the destructive consequences that may be uncontrollable.

Do we not have the grave and glaring evidences from science that HIV and hepatitis B viruses have their origins in chimpanzee species that have crossed over to the human species? Hundreds of millions of innocent lives have been lost through such diseases, and thousands continue to die every hour. Science is no where near in finding any solutions even after fifty years of research and after having spent billions of dollars on such researches. Are we still bold enough to pursue inter-species combination approach? Are we tampering with a similar "time bomb" that has similar effects like HIV virus?

What about the avian Flu which are confined to birds, chickens and poultry, the napa virus in pigs, the ebola virus from bats and the like?

4. The Laws of Nature – Universal and Consistent:

The argument of BAC (para 48) that biologists are dismissing the reality of rigidly fixed species and the assertion that biological categorization of species is empirical and pragmatic accordingly does not support the overwhelming and all pervading evidence we see in nature. All species in the world reveal one common truth. Species do not mix

or cross-over to other species naturally; only artificially in laboratories through the interventions of scientific experiments and researches.

Moreover, in the whole history of the animal kingdom, NO natural intermediate species have been found e.g. a half dog and a half cat, a tiger with horns, a frog with scales and the like. To date not a single paleontologist has discovered any natural intermediate fossil/species. The hybrids of mule, ligers, geep and the like are all unnatural scientific human creations. Again, the problem of classification (para 49) is not our main concern, BAC has demonstrated that there is no real problem in introducing a new category.
The Law of Nature is "protesting" against our human experiments in inter-species combinations of producing mules that are infertile. What is produced "artificially" in such inter-species will remain artificial. The Law of Nature has a "Wisdom" that must be respected not violated.

5. Other Risks – Spread of Diseases from Animals to Human Beings:

Our strong objections to the crossing of species experimentation in scientific researches are clearly not simply an emotional assertion that is baseless (para.35). The dangers of disease being transmitted from animals to human beings cannot be under estimated when we have human-animal cybrid embroys. The risks at stake are too high. The lives of millions of people cannot be at the mercy of science. Science should serve the greater common good of all humankind without exposing us to high risks. Scientific reports that assert the threats of Avian flu that if transmitted to human beings is unstoppable and is capable of wiping out 200 million people in the world. Our threat of SARS in recent years that shook the world especially Asia should also not be forgotten. These risks to human lives are what we are most concerned about. Thus, in this context, we would like to assert that the reason given in favour of carrying out the cybrid embryos experiment in paragraph 57 of the BAC's consultation paper that the "risk of the animal developing human function or capability is negligible" is not acceptable.

Proposals:

6. Leave Species to their own Natural Integrity:
We would like to affirm the contention that BAC has highlighted in paragraphs 36 and 37. That is "a human-animal combination is a life form that is artificially created." That "left alone, human and non-human tissues have their own natural ways of developing, which will be frustrated if merged . . . each species has its own natural integrity/dignity, and it is wrong to destroy it through research. Thus, the creation of human-animal combinations for research is objectionable as the integrity of the species of (human or animal) is compromised."

We would also like BAC to note that the "chimeras" in treatments like vaccination, are ethically acceptable as established clinical treatments (para. 10) because there are precisely no crossings of species. However, the "animal chimeras" of the proposed Cybrid embryos created by SCNT are clearly different (para. 6). The implication that

both of these "chimeras" are similar because they are both "unnatural" as presented in paragraph 11 is not acceptable.

7. Conform to the Laws of Nature – within each species:

In paragraph 38(a) of BAC's Consultation paper, it contends that "scientists do not create life as such; they just 'rearrange' the ways life manifests itself. This position is acceptable only if such scientific researches confined within one species i.e. solely within the human species, or solely within the animal species, without any cross-species combinations like the cybrid embryos.

However, we know that a cybrid embryo is more than just "rearranging" ways of life." A cybrid embryo is "considered a 'hybrid' because its genetic material, which is 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 mitocondria, present in the cytoplasm of the animal egg." (para 13.) As such, BAC's contentions of para 38 (b) and (c) are untenable.

The cytoplasmic hybrid do create "new life forms" that leads down a "slippery slope that ends up producing something like an animal with human consciousness, or worse . . . as sub-human or part-human creature, with doubtful legal and moral status (para 10). Again, these "monsters" are to be measured in the context of the "risks/grave dangers to humankind" mentioned sections (3) to (5) above.

8. Compare light with light – "Status Quo and Certainty":

BAC's argument in paragraphs 44 to 46 that "departure from the generally accepted 'status quo' or social norms" instead of preserving the preference of a clear cut distinction between 'humans' and 'animals' may not be a bad thing in the long run as social norms and our views can be changed as in the "emancipation of slaves in United States, and women's liberation movement" and the like cannot be accepted.

To such views, we would like to state clearly that our main contention in this paper is not about the resistance to change of perceptions of people, whether slaves or women right, but the reality of the destructive consequences of crossing species. The inevitable "moral and social confusion" that will result from the existence of such Cybrid embryos are the additional negative effects of such proposed cross species combination experiments. Such confusions are relatively less serious than the human destruction and monsters that may be produced from such researches.

9. Limited Cytoplasmic hybrid Embryos – Legal Guarantee?

The proposed limitation by legal and regulatory means to some early stage e.g. 14 days of the "creation of cytoplasmic hybrid embryo for research is also not acceptable as the risks of serious harm to humankind (discussed above in sections (3 to 5) are too high.

Thus, we fully support the views expressed in para 53 that "once the techniques and knowledge of such cybrid embryos are developed, they may be misapplied. Once research involving human-animal combinations become available, it will sooner or later lead to the creation of undesirable 'monsters' because not all scientific activity is controllable, and scientists are human and can be influenced or 'bought' like anyone else. . . Moreover, our moral or ethical standards shift as we become accustomed to what was once considered objectionable e.g. the once rights of the unborn child to live has developed into today's women's legal right to request an abortion on social grounds."

Again, our support of paragraph 53 of BAC Consultation Paper is not because we are preserving the distinction between human from animals rigidly, but that the inherent destructive dangers of "playing God" are too high, and moreover there are other ethically acceptable approaches that respect and preserve the boundaries between species.

Conclusion:

10. Cytoplasmic Hybrid Embryo Researches - Unethical, Unproductive & Unsafe Scientific Efforts:

i. To pursue the path of this cybrid embryo experiment and research is ethically objectionable. Primarily, such human-animal combinations produce "new creatures" which is unacceptable and unethical.

ii. Should our precious limited human and financial resources be invested in a project that presents infinitesimally negligible potential gains to humankind in contrast to the grave and real risks of transmitting animal diseases to humankind?

iii. Would it not be more strategic to invest our attention, time and money on "intra species" scientific experiments and researches which are not only ethically acceptable e.g. using adult stem cells from bone marrow, umbilical cord, placenta and the like, but are also showing promising results in many treatments for disease like leukaemia and other blood disorders?

iv. It is an essential principle that we respect the Laws of Nature and not violate them. In doing so, we are "playing God" as our human scientific knowledge is but a drop of water in the ocean of the unknown. The grave and destructive consequences of inter-species combinations may not be known in the near future, but once known it may be too late and unstoppable. The fact that BAC in Singapore and other countries are suggesting that there be cautious and stringent "Legal and Regulatory Considerations" in themselves are indications that there is something seriously wrong about such cybrid embryo experiments and researches.

Feedback/Concerns Regarding "Human-Animal Combinations for Biomedical Research – A Consultation Paper by Bioethics Advisory Committee of Singapore dated January, 2008"

From: Ms Azizah Mohammed
Parkway Independent Ethics Committee, Gleneagles Clinical Research Centre, 111 Somerset Road #11-02, Singapore Power Building

This is necessary for advancement in Biomedical Research and discovery of New of or improved medical treatment. It is critical that maximum safety on all subjects are addressed. When applicable, all the important and relevant information must be made known to all party who are involved in the research.

RafflesHospital

11 March 2008

Professor Lee Eng Hin
Chairman
Human Embryo and Chimera Research Working Group
Bioethics Advisory Committee
11 Biopolis Way
#10-12 Helios
Singapore 138667

Dear Prof Lee

CONSULTATION PAPER ON HUMAN-ANIMAL COMBINATIONS FOR RESEARCH

Thank you for your invitation to comment on the Bioethics Advisory Committee's consultation paper entitled "Human-Animal Combinations for Biomedical Research".

The Ethics Committee of Raffles Hospital has met on 11 March 2008 to discuss the abovementioned consultation paper. After careful thought, the Ethics Committee has decided that it cannot support the case for human-animal combinations for biomedical research on moral and ethical grounds.

Yours sincerely

DR JJ MURUGASU
Chairman
RH Ethics Committee

DR ALFRED LOH
Member
RH Ethics Committee

DR CHEW CHIN HIN
Member
RH Ethics Committee

PROF EDWARD TOCK
Member
RH Ethics Committee

585 North Bridge Road Raffles Hospital Singapore 188770 Tel: 6311 1111 Fax: 6311 2390 Website: www.raffleshospital.com Registration No. 199303258D

Comments from Singapore Medical Council

Received via email on10 March 2008

Dear Jaz,

I refer to your email below and Prof Lee Eng Hin's letter of 8 Jan 2008 addressed to the President of the Singapore Medical Council (SMC).

We wish to inform that the SMC has noted this consultation paper on Human-Animal Combinations for Biomedical Research. The Council agrees in principle with the paper and support the initiatives to promote biomedical research in Singapore.

Thank you.

Yours sincerely,

Ms Serene WONG
Manager (Legal / Education), Singapore Medical Council

SINGAPORE NURSING BOARD

6 March 2008

Professor Lee Eng Hin
Chairman
Human Embryo and Chimera Research Working Group
Bioethics Advisory Committee
11 Biopolis Way
#10-12 Helios
Singapore 138667

Dear Prof Lee

CONSULTATION PAPER ON HUMAN-ANIMAL COMBINATIONS FOR RESEARCH

Thank you for inviting the Singapore Nursing Board to comment on the consultation paper on Human-Animal Combinations for Research.

We are not averse to human-animal combinations for research to understand causalities of diseases and derive consequential treatment modalities. There should be stringent oversight on scientists engaged in this area of research to ensure that it does not lead to the formation of human germlines in animals. Similarly, non-human cells transplantation into humans should not result in changes that affect cognitive and moral identity of the human.

We would like to comment the Human Embryo and Chimera Research Working Group for a comprehensive coverage of the underlying issues.

Yours sincerely

NELLIE TANG MK (MRS)
CHAIRMAN

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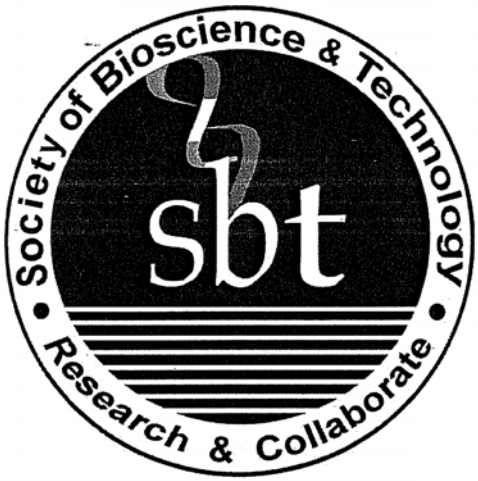

Feedback on Human – Animal Combinations for Biomedical Research

Human - Animal Combinations for Biomedical Research

CONSULTATION PAPER

The creation and use of human-animal combinations for research.

We appreciate the conundrum encountered by scientific communities worldwide involving stem cell research as present supplies of human embryonic stem cells (hES) are limited and subject to stringent bioethical and regulatory jurisdictions. Hence, scientists have discovered alternative routes to generate hES cells that are believed to be quintessential for disease treatment, tissue and organ transplantation.

However, we are of the opinion, that the combined use of human and animal materials (genes, cells or tissues) to develop animal chimeras and cytoplasmic hybrids should for the present, be limited and subject to continuous reviews. This should be so, even if it is to improve the etiology of diseases and develop medical treatments associated with alleviating debilitating and life-threatening diseases.

Fundamentally, it is vital that the outcome of developing chimeras or cytoplasmic hybrids must not ultimately result in any adverse alteration of the nature and intrinsic genomic integrity of species involved that would result in aberrant evolution of *de noveau* species arising from deleterious genetic mutation or crossing. This caveat should irrevocably apply to the use of materials obtained from species other than that of the human kind.

Our concerns in the development of hES cells through the use of techniques to form animal chimeras and cytoplasmic hybrids lie in the possible outcome that will trivialise the sanctity of human life since therein lies a controversy where, despite the limited availability of naturally-derived embryonic stem cells, scientists still seek to invest such a limited and guarded resource in exploratory techniques that would involve "wastage" in the experimental stages. It should instead, be clinically employed to treat patients whose treatable diseases involve current established procedures that require hES.

We believe that there are alternative methods that have already been used by scientific communities to achieve similar goals in studying the nature and potential of stem cells, genes and tissues using combinatorial species. Scientists should continue using such techniques until the science becomes "confident" that there is clearly none or minimal deviance to the positive results prior to resorting to the use of highly pluripotent hES. For instance, it is possible to use other animal – animal combinatorial species to study the plausible application of combinatorial species in ameliorating the outcome of treating specific diseases without using human species as an immediate recourse. We propose therefore, to err on the side of caution rather than to open Pandora's Box that could consequently lead to

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immeasurable complexities opposed to benefits.

We also propose that human adult stem cells instead of hES cells are to be used for human – animal combinations as they have scientifically demonstrated that there is an innate degree of pluripotence in them, although lacking behind the more superior hES cells. It is our view that human adult stem cells should be used to investigate the potential viability of developing animal chimeras and cytoplasmic hybrids for the purpose of studying complications in transplantation and forming a research resource to study genetic disorders. With the research outcome using human adult stem cells, it is therefore possible to obtain a good assessment should hES cells be subsequently used.

The prohibitions, limits and regulatory mechanisms that will be needed for such research in Singapore.

In considering the stipulated reasons to develop animal chimeras and cytoplasmic hybrids as listed in Para 8a) – 8e), we are in agreement for their use and objectives only when there is a regulatory and legal framework in place to govern their bioethical use.

8. Chimeras and cytoplasmic hybrids are examples of human-animal combinations. There are several reasons for creating human-animal combinations, such as:

   (a) to study specific disease mechanisms and methods of treatment;
   (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;
   (d) to study the possibility of growing human tissues and organs in animals for the purpose of transplantation into humans; and
   (e) to study the processes involved in nuclear reprogramming (how the nucleus of an adult specialised cell can be induced to regain its potential to develop into other types of cell).

We firmly believe that it is highly important to implement and enforce such a framework to protect and control access in the use of human-animal combinatorial techniques that can adversely become precursors for acquiring "embryonic stem cells on demand". This would not only trivialize the intrinsic value of hES and the sanctity of life, but also form pathways for errant commercial and profitable exploitations. These exploitations would likely segment society, such that only the rich would have an exclusive benefit and access to the technology rather than rendering equal benefits of the technology to all.

Also, such an advanced technology if unprotected or controlled, could easily be misused by errant scientists, terrorists or clandestine groups with inappropriate, warped and unacceptable research agenda. These clandestine experiments may become aberrant and result in the illegal development of *de noveau* hybrids that are universally illegal (For instance, to develop an indestructible or invincible being

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for the purpose of creating terror and mayhem). Additionally, in the event of such aberrant incidence and should the resultant hybrids exhibit a dangerous nature to mankind, the course of action to contain and destroy the hybrid, may possibly infringe other areas of human and animal bioethics since it contains part human and part animal materials. Hence, we reiterate the importance of establishing appropriate and adequate control measures with legal restrictions to prevent undue bioethical and safety implications from occurring.

Engaging the application of such advanced combinatorial techniques to further the research of pluripotent stem cells should however, be prudently adopted in a stepwise approach without the necessity of halting the research. Continuous close monitoring of scientific prerequisites, procedures and approaches employed should be conducted to review the relevance and efficacy versus the plausible hazards or implications that could inadvertently evolve as the science is progressively unraveled.

The aforementioned proposed limited and bioethical use of combinatorial techniques involving human and animal materials must instead, be subjected to the approval by a tripartite authority. Such an authority should comprise of an appointed panel of bioethicists of reliable international repute, together with government officials and representatives of bioscience NGOs (Non-Government Organisations).

In a multi-religious country such as Singapore, where Christians, Muslims, Hindus and Buddhists constitute the population of Singapore, it is necessary to be sensitive and respectful of the religious sentiments pertinent to the sanctity of life and the use of materials derived from Human – Animal Combinations for medical treatment. It has been observed that devout Muslims have negative sentiments concerning the use of allografts or xenografts as bone graft materials used in orthopaedic reconstructive surgery but do not however, oppose the use of synthetic bone graft materials.

In order to exercise religious sensitivity, the panel of bioethicists that constitutes the authority, should comprise of religious theologians for the respective religious groups. Therefore, akin to the elective use of allografts and xenografts, we believe that there is no "one size fits all" scenario; we propose that the limited and panel-approved use of materials derived from human-animal or other combinations of species, should also be made elective to an individual.

- THE END -

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勿以善小無益而不為　勿以惡小無損而為之

4 April 2008

Human-Animal Combinations Research Working Group
The Bioethics Adivsory Committee
11 Biopolis Way, #10-12 Helios
Singapore 138667

Dear Esteemed Members of the BAC,

[The Quest for Immortality - The Taoist Experience]

"Fu Sheng Wu Liang Tian Zun" May Heavenly Blessings Be Upon You.

Thank you for inviting us to the forum. It has been an informative one to hear experts of various fields presenting their viewpoints. The present topic is not new to the Taoists. It reminds of the ancient quest for immortality - to be free from illnesses and diseases. The Taoists have been the quasi-scientists in ancient's times. We are involved in alchemy and herbology that led to the discovery of gunpowder. The Taoists contributed much to traditional Chinese medicine and hygiene through the centuries. This is not a purely positive state of development. Unscrupulous practitioners have abused such techniques for their own means as well. The rich and wealthy have abused it to create drugs for recreation. Emperors obsessed with power have spent much time and resources on it so that they can rule the empire forever.

One speaker has doubted the slippery road downwards argument to be a credible opposition to the current issue. I beg to differ as time and again man succumbed to unethical acts for personal gains. Can any committee vouch for the ethics of all researchers and scientists involved in such research?

As a Taoist, we are always in favour of any advancement that brings about more good to mankind, but it should be carefully thought through and safeguards should be in place. Avoiding or shunning such issues is not the way to go as such experiments might be carried out illegally, away from the eyes of any watchdog.

It is not so long ago that the Taoist community is consulted upon regarding the research of human stem cells and human embryo and chimera. Within such a short span of time, the target has been shifted to the human-animal experiments. Has the research on human stem cells been thoroughly exhausted or is it inevitable that stem cell research will lead to human-animal experiment? If it is inevitable, it worries us what it will next lead to?

It is also true that Taoists worship Divine beings who are in human-animal forms, but that is not to say, we are ready to accept human-animal beings in the mortal realm. We seriously beg proponents of such reasoning not to confuse the public with such arguments.

We do not support this research.

Lastly, we like to thank the BAC for your invitation again.

"Wu Liang Shou Fu" With Blessings Always

Rev Master LEE Zhiwang
President
Taoist Mission (Singapore)

tm/mizw/thy:pa

Comments from Gordon Carson

13 January 2008

Hello,

The concept of creating human-animal hybrids for any purpose whatsoever is not only morally disgusting but also quite dangerous. Imagine a race of beings created with the physical power of tigers and the intellectual power of humans. Such technology will be impossible to control, once the genii is released from the bottle. A good example of such powerful technology going awry is nuclear weaponry. Years ago, only a select few countries, the US, Russia and maybe France, had nuclear weapons. Now, almost every country on Earth has the ability to wipe out another country with a nuclear strike.

What would it be like if, instead of nukes, you had countries with squadrons of eagle-like creatures with human brains, able to fly into the airspace of another country, undetected by radar because they could fly just above the tree-tops?

I firmly believe all research into human-animal hybrid creation be halted and made illegal immediately, for all our sakes.

Sincerely,
Gordon Carson
Canada

Comments from Nicole Cheng

25 January 2008

Dear Sir/ Madam,

I am a student from Nanyang Polytechnic completing my Diploma in Molecular Biotechnology. First and foremost, I would like to thank the speakers for the excellent presentations at today's (19 January 2007) public forum regarding Human-Animal Combinations for Biomedical Research.

Firstly, I would like to state that as a student studying in this field, I have no objections regarding the use of animal eggs as a proliferation vector for human somatic cells. However, I would like to make a few suggestions regarding future presentations targeted towards the general public.

1: Biological terms such a somatic cells should be explained in a very general manner. 2: If i am not wrong, Clarifications such as animals are not harmed during the process of harvesting the eggs, should be told to the public in a layman's version e.g. chicken lays an egg and we harvest the egg. 3: From my point of view, the ethical reasons and the questions and feedback from the forum, indicate that the general public view Chimeras as part-human, part-animal like a Centaur or flying pigs. however from my point of view, i see it as a human or animal with parts not from the same entity, e.g. a human with a shark cornea as an implant. this should be clearly explained, as i found it quite annoying that people kept seeing Chimeras as potential X-men like creatures or pigs that fly.
4: As long as boundaries and GCP are kept there should be no problem arising from this Human- Animal Combinations. Frankly speaking this Human-- Animal combi has been going on for years in the drug discovery area. If people were to make such a fuss regarding this, then they might as well be against vaccines as they are ultimately from bacteria-non-human.However, there is a potential risk of having one crazed scientist that would be in secret creating chimeras and reinserting them into organisms trying to find out what it would grow up to be. this, to me, is a reason for concern.
5: As a student and from my understanding, when human somatic cells are fused with animal egg cells without nucleus, the resulting cells from proliferation are of human origin. this is because the cells would contain the genome of the human and not the animal. Also, mitochondria DNA should not affect the cells and thus the function. this is because the mitochodria itself is a separate organelle with its own nucleus containing its down DNA. DNA, from my understanding, is unable to go through the nucleus and integrate itself into the host's (human) genome as it's own DNA encodes for it's own function. Which brings me back to saying that, if people are so worried about Chimeras, then they should technically be afraid of themselves. Human have mitochondria- of non-human origin in them.

even worse, is that we don't know how such a 'bacteria'- like creature got into us. Thus to me, it is completely illogical to be worried over chimeras as long as scientist keep within the boundaries set by the authorities.

These are some of the items that I want to point out.
I, as an individual, A Christian- if you want to pull in the religious factor, feel that this poses no necessary threat to the human society. At this current point of time, I believe that there is a certain percentage of human- chimera's walking around as well as bionics. People accept them as humans, no more no less. So what if some part of them has been replaced by something not human? Are you going to treat that person any different from the way he/she was before? No. As a scientist, I feel that if this Human-Animal combi benefits others, then why not? Science itself is not a beneficial occupation or field to go into. But to me, as long as i am able to help someone with what i do, that I enough payment for me. However, if transgenic mutants such as flying pigs occur, then i am not for it. because in the first place, this is not of natural occurance. secondly, it is beyond my personal principles and religious belief to accept such a thing. thirdly, if i was the animal, i would not know where in the animal world i stand in. i would be neither animal nor fowl.

Thus i would like to conclude that, as long as people understand the situation in a very clear and layman's term, then this experiment would, in any degree, be widely accepted by the general public.

As long as the public is fully aware and understand the terms, there should not be any major ethical objections or any objections of that sort arising regarding this form of cell proliferation. As mentioned previously, we need to make the public understand that Chimeras are not creatures like flying pigs, so as to rid of the controversy issues posed as heard at today's forum. Also, i feel that absolute restrictions and prohibition of reinserting Human-Animal combi cells into a surrogate mother resulting in mutants, should be enforced so that the tampering of life would be prohibited thus eliminating the playing GOD argument. However, this is on a different level of understanding as it deals also with the genetic make up of the organisms in question.

Anyway, this ends my comments for the public forum held today.
Thank you for your time for reading my comments.

Regards
Nicole Cheng

Comments from Dr Chuah Khoon Leong

7 March 2008

The Chairman
Bioethics Advisory Committee
11 Biopolis Way
#10-12, Helios
Singapore 138667

7 March 2008

Dear Sir

Re : Human-Animal Combinations for Biomedical Research

I am writing in response to the Bioethics Advisory Committee request for an opinion with regards to human-animal combinations for biomedical research. I will highlight the problems from both a scientific as well as ethical point of view. References are appended at the end of this letter.

Problems from a Scientific Point of View

The production of human-animal cytoplasmic hybrids or cybrids involves the transfer of human nuclear material from somatic cells into enucleated oocytes of animal origin via somatic cell nuclear transfer. The new organism is a non-existent entity in nature with predominant human genetic patrimony (due to the nuclear DNA) and with a minor animal genetic patrimony (through the mitochondrial DNA). Basically, it is an attempt to clone human in animal eggs.

So far, only Chen et al[1] had claimed success in extracting embryonic stem cells from cybrids and this success had not been repeated. Robert Lanza,[2] an eminent embryonic stem cell researcher, of Advanced Cell Technology had indicated that his company had been unsuccessful in procuring embryonic stem cells from cybrids because the development of such artificially created cells stopped at the 16-cell stage immediately prior to the blastocyte stage. He attributed the cessation of growth and development as a consequence of incompatibility of the animal mitochondrial genome and the human genome.

Recently,[3] British scientists had successfully produced embryos from the DNA of 2 women and a man to avoid the transmission of mitochondrial related disease of one of the women. This implies that embryonic stem cells obtained from cybrids are likely to retain the mitochondrial characteristics of the animal oocytes and therefore there

remains a distinct likelihood of transmitting animal related mitochondrial disease into the cell lines created, resulting in dire consequences.

Hence, the creation of human-animal cybrids with the intention of harvesting the stem cells faces the following:

1. the likely failure in developing beyond the blastocyte stage for reason stated above

2. the risk of transmitting animal related mitochondrial disease

3. even in the event of successful procurement of embryonic stem cells from cybrids, the problem of unrestrained growth resulting in tumour formation e.g. teratoma has to be resolved. The problem of unrestrained growth and inability to direct cell differentiation remains a major issue in the realm of embryonic stem cell research[4] and embryonic stem cells derived from cybrids are unlikely to be spared of this problem either. This casts doubts on the possibility of success.

4. genomic alterations are documented in cultured human embryonic stem cells.[5] These genetic alterations were so significant in some cells, rendering those affected cells unsuitable for therapeutic purposes since these mutations play a role in carcinogenesis associated with growth advantage over non-cancerous cells. It will be impossible to use these malignant cells for therapeutic purposes. If human embryonic stem cells do not remain ageless and perpetually unblemished, this problem will also apply to embryonic stem cells derived from cybrids.

5. if the usage of animal oocytes is needed to ensure greater success in the process of cloning (and therefore the creation of cybrids) because animals eggs are more abundant, one questions why such improvement has not happened to date in animal cloning. As a matter of fact, in the cloning of monkey embryonic stem cell, 304 eggs were used for the production of 2 cell lines of which one was genetically defective.[6]

6. transmission of retroviruses and other forms of serious infections initially confined to the animal kingdom. Endogenous retroviruses form a significant part of the host genetic heritage in animals and are transmitted to the next generation during reproduction.[7] There is no guarantee that such viruses, existing within the mitochondria or cytoplasm of the oocyte, are not re-integrated into the transferred human nucleus during the formation of cybrids, resulting in illnesses which may include tumour formation. Contamination of cybrid derived mixed stem cell lines with biological materials of animal origin remains real, prompting doubt whether such cell lines could be used clinically.

Vast resources will be used in human-animal cybrid research and there is no guarantee of success given the above problems. It is better that such resources be used for other more promising research such as adult stem cell research where ethical and/or legal concerns shrouding embryonic stem cell research do not arise. Adult stem cells display significant capabilities for growth, repair and regeneration of damaged cells and tissues in the body and there are at least 70 scientific publications alluding the benefits of adult stem cell therapy in patient therapy whereas none had so far been recorded for embryonic stem cells.[8]

These problems should be addressed and clarified even before the problems on bioethics are tackled. Prudence beholds that a distinct boundary between the animal and human kingdom be maintained with regards to certain issues and the creation of cybrids is one of them. After all, HIV[9] and hepatitis B[10] are shown to have their origins in the animal primates such as chimpanzees and it is obvious that the boundary had been transgressed, resulting in the dire consequences that we face today.

Problems from an Ethical Point of View

The purpose of human-animal combination research is to clone humans in animal eggs so that embryonic stem cells can be obtained. The human-animal combination is likely to retain an overwhelming human characteristics given the experience with Dolly, the first cloned sheep. Dolly was created using Scottish blackface enucleated oocyte following which nuclear material from the mammary cell of Finn Dorset breed of sheep was introduced. Dolly resembled a Finn Dorset sheep and not a Scottish blackface sheep.

Given the above fact, it is likely that cybrids will bear an extreme resemblance to a human person and therefore will share the same ethical concerns as human clones. Human life is sacred and must not be destroyed. Therefore cloning human in animal eggs only serves to underscore the serious ethical problem associated with cloning in the first place.

Conclusion

In summary, alternate ethically sound methods of obtaining stem cells should be looked into. Interestingly,[11] the creator of the cloned sheep Dolly, Professor Ian Wilmut, had abandoned the cloning method via 'nuclear transfer' in pursuit of other means of obtaining stem cells. His experience should serve as an indicator that in cloning, vast amount of resources may be wasted in the pursuit of a science that is unlikely to yield any therapeutic benefits.

Thank you.

Yours sincerely
Dr Chuah Khoon Leong, MBBS, FRCPA, FAMS (Pathology)

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Comments from Dr Hannes Hentze

6 March 2008

To the BIOETHICS ADVISORY COMMITTEE
11 Biopolis Way, #10-12 Helios
Singapore 138667

Dear Alvin Chew,

As requested in your letter dated 4th Feb, here are some comments on the abovementioned paper.

Firstly, I answered in a similar a questionnaire in November 2007. As this seems to be another round of consultation, I do wonder how long it will take to come to clear guidelines or even a legislation in Singapore. This is a long overdue, urgent matter in certain areas of research.

1) Firstly and most importantly, I find that the discussion is too broad and overregulates one very common area of research, I cite from the paper:

"This Consultation Paper considers chimeras created by *introducing human cells into animals*, animal foetuses or animal embryos, and refers to them as *animal chimeras*. These chimeras are useful for research, such as the study of the developmental potential of human embryonic stem cells or their derivatives."

What is left unconsidered here are very common xenograft models used in oncology research, where either established tumor cell lines (which can be ordered from suppliers such as ATCC) or primary human tumor tissue is transplanted into immune-deficient mice, typically subcutaneously for solid tumor models or intravenously for leukemic models. These models are very common in drug companies like ours, and the necessity to have to apply for IRB approval for each of these experiments provides a totally unnecessary hurdle since these type of chimeras pose absolutely no ethical concern and are used since decades as standard assays.

My question here would be: **Why are these kind of experiments with DIFFERENTIATED SOMATIC CELLS not explicitly excluded from IRB review?**

Again in this consultation paper (as in the last document), these very unquestionable research areas are mixed with very questionable ones such as cytoplamatic hybrids.

To go one step further, I would similarly tend to deregulate standard human embryonic stem cell experiments in mice with established lines, there is no ethical reason to have

an IRB review for each experimental set as they are pure repeats of previous conditions (ie, with EXISTING hESC lines).

2) "Scientists are, however, interested in creating another kind of hybrid, called a *cytoplasmic hybrid embryo*, for the purpose of deriving stem cells."

I agree that this area has a lot of ethical conflict potential, and personally I do not see the necessity to allow such research in Singapore. Especially recently, and not mentioned in this document, iPS cells created from somatic cells may be replacing these approaches soon. The field moves too fast here to follow by this kind of slow review process, and the particular use of this particular method is questionable for our small research community here. Rather we should make an effort to de-regulate common, ethically unquestionable areas (like above, tumor xenograft experiment do NOT need IRB review in other countries).

3) "For instance, scientists have used adult stem cells from human umbilical cord blood to test their effect on rat disease models, and in the process created animal chimeras."

Again since these are adult stem cells, I would tend to not overregulate this area.

4) "There are two concerns here. One is that human-animal combinations invalidate how we classify things, and as a result cause moral confusion."

I have one possibly important notion here: in contrast to for instance transgenic plants that are later on consumed by the population and are able to spread into nature, these kind of "new entities" are very different from this angle: (i) these new entities are short-lived; (ii) they will not be allowed to reproduce; (iii) they will confined physically in appropriate laboratory spaces; (iv) they will not be seen, come in contact or be consumed by the population.

I think these practical limitations are important considerations when talking about the impact of such chimeras on the society as such, and I do see a great difference here to other areas which can have a direct contact/impact on the society at large (such as transgenic plants or pigs).

I possibly repeat myself but my sentiment is that before spending time to allow or disallow this rather boutique/exotic methods that are anyway done in UK now, we should first de-regulate other areas. Still, we have no stem cell legislation in Singapore, which poses great bureaucratic obstacles for many researchers. For instance, any cell line we want to use for a standard mouse tumor assay requires an IRB exemption, a practice unheard of in UK, Europe or US. If we intend to use human stem cells of any kind we need to get a full IRB review, which is costly (2,000 S$/review), cumbersome to prepare, and sometimes the review process is slow. Even the form that has to be filled out for a standard IRB (like NUS) is not at all designed for basic research purpose, and the whole process is just unbelievably complicated – although I have to

say that the IRB I worked with tries to be really helpful and fast. These practices of overregulation SERIOUSLY slow down research in Singapore. This issue has to be resolved ASAP, before we venture into such esoteric research areas that have no immediate effect on applied research in Singapore.

I would truly welcome any step into the direction of deregulating research areas that do not need any IRB.

With best regards,
Hannes Hentze, PhD
Senior Scientist
S*BIO Pte Ltd

Comments from Dr Steven Ho

13 August 2008

We support whatever decision the government made, because the government will have scientific evidence to support it.

We generally agreed if it is to save live.

We do not agree if it is for purely commercial exploit.

Take for example; we saw a documentary on how shark fins are harvested from shark. A shark is hauled up onto the ship. Only its fins are cut-off and taken. The shark still alive is thrown back into the water. It cannot swim anymore. It died by drowning gradually on its way down. Along the way down other fish eats it. This is quite inhumane.

Comments from Dr Matiullah Khan

24 March 2008

I have carefully read the current consultation paper on Human-Animal combination for biomedical research prepared by Singapore Bioethics advisory committee. This is an exceptionally well prepared document; most of the ethical and scientific issues related to research in human animal combination have been addressed comprehensively in this consultation paper. Therefore, I think there is very little that one can suggest to improve it at this point of time. The comprehensiveness of the consultation paper notwithstanding, I would like to make following suggestions:

1). All research involving human stem cell and human animal combination should be strictly regulated and monitored by relevant regulatory authority. Proposals that seek to create human-animal combination in any form should be reviewed by a committee comprising of scientific and legal experts.

2). Meaningful research on human animal combination should be encouraged under the watchful eyes of appropriate regulatory authority and the progress as well as lack of progress, or any adverse or unexpected outcomes, should be strictly monitored.

3). Research on human animal combination should be based strictly on well defined and clearly identified objectives and goals. There should be strong disincentive for any fantasy science.

4). Even if the research involving the human animal combination is performed within acceptable norms of ethical and scientific guidelines, it is still possible that such research may go awry and produce something totally unexpected and unacceptable. Under these circumstances, there should be adequate legal protection for scientists who started the research with good intention. Moreover, there should be adequate guide lines how to deal with the "outcome" of such experiments.

5). Scientific priorities in biomedical research must be adjusted with the realities of time and space. Today, obtaining therapeutic benefits are the prime objectives for such research. However, with the emergence of new challenges due to changes in the environment and natural habitat of our planet, the regulatory authority must be prepared ethically and scientifically to adopt and implement futuristic objectives in biomedical research related to human-animal combination.

Matiullah Khan, MBBS, MPH, PhD
Oncology Research Institute
National University of Singapore

Comments from Dr Khoo Lock Nah

18 January 2008

I am concerned about the chimera from the perspective of the creature.
We might be 'playing God' but we ARE NOT God. We do not necessarily reflect the goodness of God in whatever we do as humans with self-serving motivations.

There must be some protection in place for the chimera.
As a living creature, it is NOT a THING for us to do whatever we like with it - causing it suffering without pain killers etc.

I believe STRONGLY that we must have
1. some guidelines in place if we should go ahead with the research so that chimeras will be treated with respect and care and not abused in the name of science and research.

2. There must be outside bodies (eg Humane Societies like SPCA NOT govt groups like AVA) monitoring this. Of course the local SPCA cannot do such a job (they already failed to preserve lives of about 80 per cent of all animals surrendered to them in the past year) but since we are supposed to be a world-class society with world class research, it would be important to get world class humane societies who are concerned about animals/creatures- to monitor this...This is very important if we are to be transparent, accountable and truly world class.

KHOO LOCK NAH (Dr)

Comments from Dr Prasanna Ratnakar Kolatkar

10 March 2008

After reviewing the doc you had sent me as well as looking at other related works I have the following opinion.

I think that we should adhere to well-practiced laws that have been applied to the cytoplasmic hybrid embryos. Specifically to terminate any such embryos within the 14 day period as has been done for some time. They could be very useful for creation of pluripotent stem cells as well as other studies mentioned in the consultation paper and pose little or no problems in terms of ethics such an any sort of developed offspring. Considering there is a large shortage of available human eggs, this appears to be the best route possible until methods such as iPS are more mature and proven.

It is possible that in the more distant future we could look at potentially extending the type of experiments as more information becomes available but I think based on the information that is available, the 14 day SCNT embryo period is logical and reasonable.

Comments from Associate Professor Li GuoDong

National University Medical Institutes, National University of Singapore

10 March 2008

I would principally support the generation of stem cells by cytoplasmic hybrids (human nucleus into animal oocyte but not vice versa) for basic research. Derived embryo should not be kept beyond 2 weeks and transplantation of such embryo should be forbidden.

The research on human-animal chimeras needs more strictly regulated and carefully reviewed, in particular, when neurons or brain tissues are involved. Breeding should be not allowed in any case.

Comments from Dr Lim Sai Kiang

Principal Investigator
Institute of Medical Biology, Agency for Science, Technology and Research

8 March 2008

The consultation paper is a balanced and accurate presentation. It recognizes the importance of providing room for scientists to push the frontier of science and at the same time, remaining sensitive to the ethical and religious concerns of the society at large. While keeping legislative guidelines in pace with scientific advances is important for the health of the local scientific community, it is essential and prudent for this pace not to exceed or lag behind scientific advances.'

bio-research- necessary fundamental understanding 生物研究–必要的领悟
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Bio-Research – Necessary Fundamental Understanding
Thursday, January 24, 2008
Cognose Lim Swee Keng SM(MIT),
Engineer, Inventor, Philosopher
699 words
http://cognose.blogspot.com

The west, occidental intelligentsias were subjected to the most brutal oppression, scrutiny of ideas, of inventions, of findings during the dark ages, medieval eras.

Scientists, many of them were brutally punished. Only those passionately pursuing, supported by useful facts that can be repeatedly sensed, measured, produced, reproduced, mass reproduced survived these rigors and become sciences.

This has led to such magical number of 6.023×10^{24} as the consistent number of atoms, molecules in one standard measure. How rigorous they became!

This tradition passed down many generations till recently.

Only through this rigor, that we can make heavy jet flying like a bird, train faster than bullet, voice, photos, even movies zoom across oceans in split seconds, without distortions. And all are made efficient, that even children around the world can enjoy them a plenty.

The same is made to medicine, surgery. Even tying a knot of threads, has name, even which pincer to do which twisting at which moment. This made doctors can be trained by thousands, millions saved each years.

Human, when given more power, is detached from the immense order of nature, and yearning to be free, yearning to accomplish more, faster, more comforts, even at all cost.

So asbestos, tobaccos, DDT, Lead added into gasoline, CFC in hair spray, refrigerants, coating cooking utensils, were accepted as good solutions, great solutions. Even though they merely bring some marginal improvement, luxury, comforts, aesthetics.

These inventions have no real needs, pressing needs.

However their damages were proliferated, multiplied quietly. Damages that would take many decades to discover, confirm, before law enacted, before counter measures are devised. And whether such counter measures are effective, are harmless, would open up new cycles of labors, complex labors, endless labors, shrouded by interested parties uttering in newly created terminology.

So when the effect of some newly formulated medicines have yet to be proven harmless, stem cells research yet to create windfalls, human-animal crossing is now a hot pursuit.

i am an inventor, i support innovative quest, creative ideas.
Creative ideas are more easily done for physical systems. Physical systems are so much simpler, predictable compared to biological forms.

Physical systems are also so profitable for one can have many, can upgrade frequently, like auto-car, phones, computers, travels. In fact these are biggest industries, consistently be the locomotive for economic growth, throughout history.

But Medicines, Pharmaceutical research, Gene Modifications, Stem Cells, Human-Animal crossing of gene even can be proven important, even found to be critical to the well beings of good quality living, they cannot, and will never be pillar of economy.

For any Industry to be pillar of economy, it has to have substantial consumptions by whole populations, without upper bound. It will require a person, every person consume daily a few hundred gram of drugs, like making phone calls. It will require a person to change a few organs in their life spans, like buying computers, auto cars.

Even this can be manipulated to become a norm.
is this healthy society?
is this quality living?

From history of beasts to civilized world, no community prospers because of medicines, even though no prosperous community can live without good health care. The needs and wants, the profit and magnitude, we must be very clear about.

i am not against such exoteric research, but such research must not be driven by economic forces, else doctors become butchers, else lawyers become crooks. When it is so, many forgery of research will be given high prizes, many powerful procedures, very harmful one, would become hot sells.

Biological research is in different league from physical sciences.
Engineers made airplanes, mobile phones that work the same way every time, that connected the world together, that integrate civilization into one with greater wisdom, that enriched thousands of college boys, like Bill Gates, Jobs, into billionaires.

Only by placing bio research into this right perspective, progressing slowly without pressure for profits, subjected to tightest, longest durations of verification, can Bio research really serve the greater good of civilization, inspired gifted researchers, formed greatly profitable enterprises, hospitals a few, less than a handful.

There is no pressing need to catapult such research, for there is no epidemic that is killing even a few hundreds today.

Much simpler inventions are common examples, spanning from tobaccos, DDT, Tetra-ethyl lead, transfats, CFC. They can be precisely formulated and created big enterprises. These enterprises have their strong muscles, determined hearts and therefore are well capable of deciding what is legal, marketable.
The less obvious long term impacts to the welfare of human life were never considered.
Therefore, there is no justification to say more complex biological research can be effectively regulated.

This goes back to the contribution of the occidental thoughts.
Their long suffering journey that demand the highest discipline, precision is absolutely needed to bring us forward, to bring wealth overflowing.

For the world to prosper long, progress well, the west cannot be set free.
if they are set free, the wealth created is small, the harm induced have been demonstrated for many generations to suffer.

Comments from Dr Steve Oh

Associate Director & Principal Scientist, MEng CEng CSci MIChemE
Stem Cell & Fermentation Groups, Bioprocessing Technology Institute
Agency for Science, Technology and Research

23 January 2008

Firstly, I would say that the Key reason for proposing the study of human animal combinations is the scientific enquiry to understand nuclear reprogramming (how the nucleus of an adult specialized cell can be induced to regain its potential to develop into other cell types).

This research would 'ideally' have been carried out by somatic nuclear transfer of nuclei from adult human cells into donated human eggs. However, due to the shortage of these eggs and the potential adverse events that might result from obtaining them from women in Singapore through induced ovulation, investigators are exploring as an alternative, eggs from animals which has resulted in the consultation paper on "Human animal combinations (or animal chimeras) for research".

My Views

I personally feel that Singapore should try to focus her research efforts on human embryonic stem cells, where she has developed a certain amount of leadership already. As venturing into too many stem cell research options may dilute our research capabilities. It is interesting that the consultation paper highlighted that true hybrids such as the liger and mule are infertile (page 12, paragraph 12). What can we already learn from these lessons? If hybrids within the same species that are created turn out to be infertile, then interspecies hybrids have a high possibility to develop 'abnormally'. Thus my own 'gut feel' is that this avenue of pursuit is likely to reveal little insight into reprogramming as the likelihood of success in experiments will be very low.

The landmark work by Yamanaka in reprogramming adult cells to become induced pluripotent stem cells had a success rate of < 1% even with targeted gene expression. Therefore, I do not expect the success rate with inter-species hybrids to be any higher. To put it in perspective, it could take between 100 to 1000 animal eggs to be implanted with human nuclei to possible get one successful hybrid embryo. So each individual experiment minimally would require hundreds of rabbit or cow eggs. And where would Singapore researchers get these from???

Another scientific error of this avenue of investigation is that even if these hybrids cells were successfully created, when they are implanted into animals, they would take on the characteristics of the host animal (see page 14 and paragraph 17 and page 25, paragraph 50 of the consultation document). If this is the case, why then go through the immense trouble of make these hybrid cells, when the implanted phenotype would end

up being that of the animal rather than a hybrid human cell? My understanding is that the purpose of this research is to create human cells which behave like human cells to study their behaviour. If these cells upon implantation into animals display animal characteristics, then the benefit of this complex creation has been lost!

Another study that was cited was the creation of chimaeric sheep with organs that are 15% human and these researchers hope that the 'humanised' sheep organs would be used for transplantation into patients one day (page 16, paragraph 20). As a matter of fact, the biomedical industry is moving away from animal derived products. Putting cells back into animals and creating 'humanised' organs from animals for implantation will need to overcome some very high safety hurdles to get past the regulatory authorities! My view would be that this approach would be both impossible scientifically, and significantly difficult from a regulatory perspective. Some significant health issues to be addressed would be animal derived viruses, both known and unknown which will have to be tested for in such animal hybrids to prevent transfer of diseases from animals to humans. I would predict that it would require 30 to 50 years from the demonstration of scientific proof of concept to application, based on the historical cycles of the biomedical industry in bringing any therapeutic to the market, e.g. vaccines, monoclonal antibodies, and in the case of failures: gene therapy.

Finally from the ethical view point, my own view is that there is indeed an innate species barrier and that each species has its own natural integrity that cannot be crossed without some significant global changes to their genome or proteome. And for the foreseeable future, we do not have the knowledge to make these global changes, merely by using another animal's eggs to do this reprogramming. One might perhaps have more success trying to extract the contents of 100's of eggs, to profile the proteome and characterize potential reprogramming factors.

Recently, I have mentioned in another forum on the *"Use of donated women eggs for stem cell research"* that the breakthrough by Yamanaka's group in Kyoto University in reprogramming with 4 genes should be pursued rather than the approach of using human eggs for reprogramming since this is more facile, and has been proven time and time again by 6 different groups in the last 6 months, that these genes can reprogramme adult cells into cells with embryonic like characteristics.

Therefore, I will again state my opinion that the use of animal eggs is likely to be a scientific "cul de sac" similar to the use of women's eggs and it would be more fruitful to pursue reprogramming with individual genes such as the "Yamanaka factors or genes" than creating animal human hybrids.

Thank you for listening, and I hope that these views are useful to the Bioethics Advisory Committee in making your decisions.

Comments from Dr Gabriel Oon Chong Jin

23 January 2008

Professor Lim Pin
Chairman
Bioethics Advisory Committee
Singapore

Dear Professor Lim

Re: PUBLIC FORUM ON HUMAN-ANIMAL COMBINATIONS FOR RESEARCH, Breakthrough Theatre, Matrix, Bipolis, Singapore
Feed back

Thank you for inviting me to listen to the proposal and to provide a feedback on the new exciting area of tissue engineering to raise eventually suitable tissues for human repair of diseases. I received this invitation from our Academy of Medicine.

At the request of your Committee to submit public feedback, I have put some of my comments which I had mentioned at the Public Forum.

My comments are made from the angle of a past researcher with five industrial patents and familiar with the problems of requirements of secrecy, intellectual property rights, industrial research and the difficulties of bringing a research product to fruition and commercialization.

1. PUBLICITY

Unlike the first Public Forum on Human Female Egg donation, which had a few people, this was better advertised and attended. The invitation was extended to our specialists in the Academy of Medicine, and other tertiary Institutions and hospitals. It was good to see the laity contribute their concerns, even though the medical information was probably too advanced for them. The ethical issues effecting the ordinary man in the street was well discussed and this should continue. No matter how simple or 'naïve' the questions appeared, the public, like us, are anxious, and concerned, as a lot of public funds are being channeled into this Stem Cell Research area, with big financial losses reported by ES Stem Cell International and other companies.

2. SOMATIC CELL NUCLEAR TRANSFER (SCNT)

(i) The use of fertilized human embryos for SCNT experiments to create clones to be 'dismembered' and then used for tissue engineering is abhorrent, as it would involve the destruction of an innocent human life. Why is this abhorrent?

(a) 90% of the world's religious population have a religious belief. These believers share common moral values such as, "The respect of human dignity, human life, human individual rights, love, compassion, do not steal, respect for father and mother; care for the handicap, do not kill". These are fundamental beliefs.

(b) Where these beliefs are strong and products which have serious ethical or religious moral objections would be a liability risk for the investor(s)

(c) If the product is sold to a small market for only those who are in desperate need, manufacturing costs can't be sustained or viable.

(d) **fear** that if these unwanted humans are considered dispensable and their organs can be removed from them. "If they can do it to these innocent 'baby humans' (who can't complain), why can't they do it to us too one day.

(ii) The use of **adult sources of Stem Cells, converted experimentally into embryonic properties is exciting news, as it means that the serious ethical objections of using living human embryos can now be averted using fresh approaches.**

3. ANIMAL CHIMERAS

(a) The use of somatic tissue from humans to animals or vice versa from animals to humans is not new. Human cancer tissues, e.g sarcoma or leukaemia tissues/cells have been injected into experimental animals to raise immune xenografts for treating some human diseases since the early 1950s. On a larger scale, some animal livers, e.g. baboons have been used in human xenografts, but major obstacle has been rejection and the anxiety of animal transmitted disease. e.g. There is some evidence that the human immunodeficiency virus (HIV) was transmitted in the 1950s from chimpanzees to humans and spread from Africa, as there were no human HIV before then.

(b) Pig valves for replacement of diseased human heart valves have been more successful.

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(c) Animals have always being used for the testing of orphan drugs and vaccines, before humans are finally used. These animals are mice, rabbits, and going on to bigger animals like chimpanzees for human hepatitis viruses, like hepatitis B.

The use of animal chimeras for testing of drugs is a useful in vitro screening test for potential toxicity.

(i) **The more serious question would be, can remnant product (protein, or DNA sequence, or gene of an 'enucleated animal egg', either in its natural or altered state cause harm in a recipient human?** Would it be capable of producing some disease unknown to humans now, but appearing later because of the 'slow expression' of the gene or protein?

Some cancers, like liver cancer takes 20-40 years to develop in humans after the primary infection becomes a chronic infection. In the Thalidomide disaster in the early 1950s, many children were born with deformed limbs. In another accident in that time, during the manufacture of polio vaccine some SV 40 sarcoma virus entered accidentally into the manufacturing vats and not detected, after vaccination.

Thus transmission of animal diseases is a serious concern, and when disease would appear may not be answerable now, except in human long term trials and follow ups

(ii) Also would zoonosis, of animal viruses, in which the animal is the natural reservoir and confined to the animal kingdom, spread into humans and cause human diseases. Some examples are the avian Flu, which is confined to birds, chickens and poultry, napa virus in pigs, ebola virus from bats, murine leukaemia virus to humans, and HIV as mentioned above. Slow viruses (like Kuru) take many years to develop into brain atrophy and Alzheimer's Disease.

(iii) PLAYING GOD

(a) Professor Nuyen, who admitted that he has no religion and a non Christian was too outspoken on the subject of "Playing God". His views of no religion and 'no God' should be confined to his own personal views and not included into a 'policy document of BAC. From the World Directory of Religions (mid 2006 census) 75% are Christians. If the believers of the one God of Abraham are included (i.e. Christianity, Islam and Judaism this would make up to about 80% of the world population, the remaining 10% is composed of Buddhism, Taosim, Hinduism, Sikhs Baathists, Shintoism and tribals. Only a small 10% are anti-religion, antiGod.

The small minority of anti-Gods in your BAC should not impose their own idea of no God on some 90 % of the religious in the population. Many of us with a religion, are very disturbed and concerned by these views.

On your esteemed Committee are men of God, and it is good that they are there. In societies which is God center, there is social order, compared to those with none, when there is disorder and chaos.

(b) Is there God in Science?

Many great scientists have been men of God, and one should not discredit Godly persons doing science or their views of God and science.

In the 1820s in Paris, a young scientist got into a horse carriage. Noticing an old man praying quietly at one corner, this young man told the old man, "Forget about praying. It is science and technology today. Look at inventions in electricity, telegraphy, the steam engines… .this is science and progress and the future." Later the carriage stopped, and the old man started to get out. Before he alighted, he turned to the young man and said. "Without seeing God in Science, there is no discovery." Who was this old man? He was Louis Pasteur, Father of sterilization, vaccination and discoverer of rabies vaccine. He was praying the Rosary. This is a true story.

(iii) Professor Hoyle, Nobel laureate in Astrophysics from Cambridge University once said "Take a jumbo jet. Blow it up. Try and put the pieces together. No human can put them together, except God" (From Scientists who converted into Christianity publication)

(iv) In human molecular science, we see the trillions of atoms assembled together in an orderly manner in the human body, to form organized cells, and organs. They are coordinated and function like an orchestra with a conductor. Man can synthesis and put chemicals together and make DNA sequences. We can chop and splice genes and reassemble them to make pharmaceutical products, but does that product have feelings, emotions, liveliness, or spirit? Man can make robots to do whatever we want it to do, but do the robots have human feelings and emotions? Can Man make water from hydrogen and oxygen atoms and in the abundance in nature? Starting from nothingness where is the origin of ATP, the source of energy to start all metabolic activity to make proteins, cells?

Sharing my personal experiences in research into discoveries, inventions and patent protection.

After some 20 years of research on hepatitis B and liver cancer, we were able to develop 5 products from our research to be able to patent them, and have these patents awarded globally, e.g in the USA, EEC, Asia, and Australia. We did not retain these for our financial gain, but gave them to

the Government so, that from the profits, our people would benefit from them.

Was it easy to reach this seemingly impossible high hurdle? **No**. There were serious and fierce competition between us and rival groups.
We prayed together as a team, so that the benefit of our research would go to humanity. When we were awarded these patents from 2005-7, we knew we were the best team in the world "Praise the Lord".

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(v) Were there pitfalls?

When one is at the forefront of research the away ahead is darkness, because no one is in front. Would that darkness be a crevasse and we fall, or would it be glory and a major discovery.
So, I view the proposed research on animal human chimeras as a journey into darkness ahead, with many difficulties. It is not easy. The journey would likely take many years. Seldom are discoveries made in a few years, but long years of patient research

3. **ETHICS IN REGULATION**

The public perceives that BAC is not just an Bioethics Advisory Body on Stem Cells, but also the promoter, the financier, regulator, licensor and a potential manufacturer
W. H.O. requirements for Biological products for human usage, had strongly emphasized that the regulator should not also be a member of the committee, as this would indicate vested or conflict of interest.

One possible way to overcome these objections is to have an independent Scientific Body comprising eminent senior/elder statesmen in Science and Medicine, perhaps appointed by the Prime Minister to oversee the sensitive Bioethics projects, such as Stem Cell Research, where there is so much ethical difficulties.
This would give public assurance, transparency and accountability, because a lot of public money is needed and the research can be very long and there can be many failures before there is success.

As a note, the US President has a Council of top scientists, consisting of Nobel prize winners to advise him, besides having his own Bioethics Committee, headed by Leon Kass.

Dr. Gabriel Oon Chong Jin, MD Cantab,
FRCP London, FAMS, DCH London.

23/1/08

Comments from Evelyn Quek

23 January 2008

Should research on human animal combinations be allowed?

Can no longer be disallowed as it has already started but it should be highly regulated to ensure:

Researchers do not get carried away with playing 'God'. Although many arguments exist why such research should be allowed, primarily its benefits is to aid human life and suffering, therefore, the following safeguards should be put in place to ensure that scientists sidetracked do not get into the excitement of new discovery, pushing frontiers with no ethical considerations.

1) There must be clear medical benefits for the research outweighing the cons, not just one based on the numbers game or being in the forefront of 'chimera hub'.

2) There should be several ethical bodies comprised not just of scientists but predominated by futurists with strong moral codes of human decency, religious thinkers who are forward looking, lay people, strong in the community who can provide a strong counter balance with no vested interest.

3) Research should be conducted with no cruelty to any animal or being (chimera). Getting used to cruelty in the name of research is the beginning of the slippery slope. When the example in the paper cites incest, I can only say that difference between human sex and rape is one of violence and cruelty as opposed to a natural act. And if our courts now admit rape by husbands, it is a measure of how the law itself has progressed from its own narrow minded thinking about marital rights of husbands to acknowledging the rights of wives as individuals.

4) If doubts exist about the 'yuk' factor, whether we are about to create monsters (foreseeable if research boundaries are pushed) there must be strong legislation to ensure that the issue is open to discussion and the majority views of the ethical bodies taken into consideration. After all, human compassion and decency can hardly be dissected at just the analytical and intellectual level. It is primarily a fundamental sense of wrong doing that has stopped human societies from going of the tracks while 'playing God' - genocide (Hitler, Mao, Pol Pot, sterilisation) always produce widespread undesirable consequences.

5) There has to be an acknowledgement that not everyone wants a transplanted pig's heart etc. The right to refuse chimera stem cells or transplants must be an inviolable right of each citizen.

6) Heads of research must show proof of human compassion and be well balanced individuals. They should be encouraged to spend time in the natural outdoors or do a stint in animal care e.g. the zoo, dolphin training, train dogs, or go on yearly meditation retreats etc. This will ensure that they do not get overwhelmed by human pride and forget the possible consequences of what they do.

Comments from Professor Davor Solter

Senior Principal Investigator
Institute of Medical Biology, Agency for Science, Technology and Research

10 March 2008

I actually read the consultation paper several times since I was involved in similar projects. I find it very well written and in contrast to many similar papers, completely free of bias. They have correctly presented the issues and possible solutions without trying to push any special agenda. The paper will be a good basis for any subsequent legislative decision.'

Comments from Dr Uttam Surana

17 March 2008

Dear Jaz

I have now gone through the Consultation Paper on Human-Animal Combination for Biomedical Research. It is a well written document which covers carefully almost all immediately-relevant grounds without succumbing to the traps of controversial issues. Of course, there other multitudes of other related nuances; however, dealing with all them will take away the sharpness of this paper. They are, therefore, beyond the scope of a document such as this.

I really do not have any major comment which will add significantly to this already well written document.

Best regards

Uttam

Institute of Molecular and Cell Biology
Agency for Science, Technology and Research

Comments from a member of the public (1)

9 January 2008

Please don't try this experiment. This will causes a lot of problem...

Imagine this animals called "chimera" became a creatures which kill the human race. How are the human race going to stop this disaster? There's some movie topic on this thing. Like, "Black sheep" and an animation "Fullmetal alchemist". This have shown the problem after the creature is created. Let's not talk about animals. If this method is use on human? Use of animal tissue on the human... If that human used were your child? And your child became a creature that everyone outcast. Put yourself in their shoes. How would you feel? Will you be mad with the people who is normal?

Will you be mad with the scientist? Will you begin to kill the human race due to anger? The natural resource on the earth is depleting, why don't you all go research on this, other than this making of chimera?

I hope you will look at my e-mail. And give me a reply as soon as possible.

Thank you.

Comments from a member of the public (2)

13 February 2008

My humble views are:

1. Prohibit introduction of animal genes or cells into human embryos.

2. Allow introduction of human genes or cells into animals for medical research only. Such organisms must not be allowed to breed.

3. All such research must be legally regulated by the Bioethics Advisory Committee or an IRB which includes at least 3 eminently qualified members with the relevant scientific expertise but without any conflict of interest.

Comments from a member of the public (3)

7 March 2008

Chimera research

Is the term "animal chimera" a misnomer?

When we insert human nuclei into animal eggs, we create embryos that are 99.9% human and 0.01 % animal. It thus seems more correct to call them "human chimeras". Using the misnomer "animal chimeras", however, seems to be a convenient nomological sleight of mind - it makes them intuitively less objectionable. (In what follows, I will continue to use the phrase "animal chimera".)

Should we create human-animal combinations for research?

The positive argument seems to be the following.

Stem cell research may produce cures for various diseases e.g. diabetes, Alzheimer's disease, Parkinson's disease. Stem cell research requires eggs, ideally human ones. Human eggs are in short supply. Hence, we turn to using animal eggs. The proposed technique is to insert human nuclei into enucleated animal eggs. This creates cytoplasmic hybrid embryos, also called animal chimeras.

I shall now assess this argument.

There is no clear indication that chimera research will yield cures for thus far incurable diseases. All we are offered is a possibility. This is a weak argument.

Medical science has made amazing progress with animal research, in particular using laboratory rats. Applicability to humans is established via clinical trials. Induction suggests that this mode of research can also be used to investigate diabetes, Alzheimers' Disease, Parkinson's Disease etc.

There is a long history of studying animal biology, then extending that knowledge to human biology. Induction again suggests that stem cell behaviour can also be studied using animal stem cells, and then extending that knowledge to human biology.

We should also consider the possibility that we are facing a case of "we can do genetic manipulation, therefore we should do genetic manipulation, and therefore we must do genetic manipulation". That is, we are curious, so let's scratch the itch. Well, some itches, when scratched, can turn septic. We need to beware of this danger.

What restrictions would be applicable?

It seems to me that the aversion, hesitation and reluctance is entirely anthropomorphic. There is no problem with human-animal combinations so long we can see them as merely multiplications of biological cells. The problem arises only if the result looks human.

It is suggested that sentience will also pose a problem. I agree. However, I suspect that non-sentience will also pose a problem. We do regard killing a vegetative human as murder. It is physical resemblance that is the tipping factor.

The proposed technique will produce embryos that are genetically 99.9% human and 0.01 % animal. Can we be sure the final 0.01 % will not somehow be crossed?

We are told that if non-neural cells are used, there is no possibility of creating “monsters". This is, of course, one restriction that could be set. However, this seems to prevent the creation of whole creatures, but not body parts. Will the problem arise with only body parts?

I doubt we will have any trouble if we grow human hearts, kidneys and livers in pigs. This is because laymen do not know what human hearts, kidneys, and livers look like. But what if we grow human ears, noses, eyes, teeth, fingers etc. on rats? It is but a slippery slope to "hey, that looks human!" Can we maintain public equanimity then?

I think we must certainly prohibit the growing of an entire human face. That will surely attract the problematic "Hey! That looks human!" response. If necessary, say for transplant purposes, the facial parts should be separately grown, and then surgically assembled.

Assuming sentience to be also a tipping factor, do we currently know precisely what creates or prevents sentience? If it is sheer genetic complexity, then at 99.9% human we will be almost there. If it is response to stimuli, what is the threshold? People are ecstatic when their comatose loved ones so much as twitches an eyelid. Computers, which are capable of only yes-no responses, are described as possessing artificial intelligence. The threshold will be difficult to set, and hence to avoid crossing.

Let us conduct a thought experiment here. Let us suppose that, despite all precautions and against all odds, an animal chimera that we create somehow resembles humans and is sentient. Will we be able to blithely say "this is merely an animal chimera", then calmly discard it as biological waste? Can we do this even in the face of public, and possibly globally public, opinion? Intuitively, I think we will experience some difficulty here.

This, I think, is the acid test. If we are not able to do the dirty deed, then let us run absolutely no risk (not just a negligible risk) of producing a sentient animal chimera.

What is the ultimate objective?

If we are proposing to do research at so basic a level as genes and stem cells, perhaps it is also appropriate to ask a basic philosophical question. What is the ultimate objective of medical research? Is it to cure all diseases, and remedy all disabilities? Is it, finally, to achieve human immortality?

As far as I understand it, both science and philosophy agree that death is a part of life. Just as there is a water cycle, there is also a life cycle (at least at the physical level). Living things need to die. What will be the environmental, social, and political ramifications if human beings become the exception? Indeed, what will be the religious ramifications if human beings no longer die? How will we go to Heaven? How will we be reincarnated? Can we afford to achieve immortality?

Should medical research stop somewhere? If so, what should we allow people to die of?

Comments from a member of the public (4)

30 May 2008

Thank you for inviting the public feedback on the above topic.

I wish to express my disapproval on the creation of cybrid and its use for research.

As cybrid is 99.9% human, using its stem cell involves killing of a 'human' embryo.

There is also a high risk of transmission of diseases from animal to human. The serious consequences of such possibilities outweigh the uncertain benefits.

I do hope more publicity & information is given to the public before a decision is made.

Thank you.

ANNEX D

SUMMARY OF RESPONSES FROM REACH ONLINE DISCUSSION FORUM AND E-CONSULTATION

Summary of Responses from the REACH Online Discussion Forum and e-Consultation Paper on "Human-Animal Combinations for Biomedical Research"

On 8 January 2008, the BAC released a public consultation paper on "Human-Animal Combinations for Biomedical Research". The public was invited to provide views on:

(a) the creation and use of human-animal combinations for research;

(b) the prohibitions, limits and regulatory mechanisms that will be needed for such research in Singapore; and

(c) any other matters related to human-animal combinations for biomedical research.

Fifty-eight entries were made on the REACH Discussion Forum by at least 43 individuals. Of the 43 individuals, 18 expressed some support for research using human-animal combinations, while 6 opposed such research. The comments of the remaining 19 did not show any clear views as to whether they supported or opposed the research.

Six entries were made on the REACH e-Consultation Paper. Of the 6 entries, 5 expressed opposition to the research.

These numbers are in themselves far from conclusive. The intention was not to conduct a survey but to discover if the discussions raised issues not covered in the consultation paper that needed to be addressed.

It transpired that the online debate was largely centred around the question of whether scientists can be trusted to regulate themselves. There also appears to be significant concern over effective supervision and control.

Possible implications of the research on relationship between human and non-human animal remain unsettling, especially among animal rights advocates and religious groups.

Human form clearly matters since a number of respondents expressed strong disapproval against the research where the form of a human ear was developed on the back of a mouse.

ANNEX E

BACKGROUND SUBMISSIONS

Background Submissions

1. An Argument for Transplanting Human Stem Cells into Non-Human Embryos
   - *Mr Kyle Loh and Dr Lim Bing*
   Genome Institute of Singapore

2. Stem Cell Research and Interspecies Fusion: Some Philosophical Issues
   - *Associate Professor Nuyen Anh Tuan*
   Department of Philosophy, Faculty of Arts and Social Sciences, National University of Singapore

AN ARGUMENT FOR TRANSPLANTING HUMAN STEM CELLS INTO NON-HUMAN EMBRYOS

Mr Kyle Loh and Dr Lim Bing
Genome Institute of Singapore

Characteristics of Embryonic Stem Cells

The defining characteristic of an embryonic stem cell is that it is "*pluripotent*"—capable of differentiating into every cell type present within the foetus.

This unique property of embryonic stem cells has ignited aspirations that one day, embryonic stem cells will be able to ameliorate diverse human diseases. Why? Many human diseases (e.g. diabetes, deafness) are due to the deficiency of a specific cell type from the patient's body—such as the pancreatic β-cell or the inner hair cell, respectively[1]. Such diseases should be curable by restoration of normal or near-normal numbers of the missing cell type.

Given the pluripotentiality of embryonic stem cells to differentiate into any cell type within the body, one could differentiate embryonic stem cells into the "missing" cell type, and then transplant these stem cell-derived cells into the patient's body, thus renewing near-normal numbers of the missing cell and ameliorating the disease. Indeed, such an embryonic stem cell-based approach shows great therapeutic promise, as embryonic stem cells have been successfully used to ameliorate a spectrum of conditions within animal models, such as blindness, cardiac infarction, diabetes, immunodeficiency, Parkinson's Disease, and spinal cord injury[2-8].

Limitations of Human Embryonic Stem Cells

Nevertheless, our exploitation of human embryonic stem cells for clinical and scientific applications remains restrained by certain present-day limitations.

Above, we have stated that embryonic stem cells are pluripotent—capable of differentiating into any cell type. However, we note that this is only true for mouse embryonic stem cells and may not apply for human embryonic stem cells (hESCs). Thus, the question remains whether or not hESCs can indeed differentiate into any cell type that is desired by a patient or a researcher. Although hESCs have a capacity to differentiate into specific clinically-relevant cell types (such as pancreatic β-cells[9]), it remains uncertain whether or not hESCs can differentiate into all cell types within the human body. Disturbingly, certain hESC cell lines differentiate into certain lineages thousands of times more inefficiently than other hESC lines[10]. Furthermore, hESCs display gene expression patterns and molecular characteristics unbecoming of

pluripotent cells—for example, hESCs exhibit X chromosome inactivation[11], which is diagnostic of differentiated cells[12]. Such observations have elicited allegations that hESCs indeed are not entirely pluripotent[13,14] and that they may be incapable of differentiating into all human cell types; if this were to be true, this might invalidate the utility of hESCs for therapeutic and academic applications.

In contrast, mouse embryonic stem cells are unequivocally pluripotent and have been shown to be able to differentiate into every cell type present within the mouse foetus[15,16]. Within the early embryo (the "blastocyst"), pluripotent embryonic cells (known as "epiblast" cells) are responsible for constructing the entire foetus proper[17]. When mouse embryonic stem cells are transplanted into blastocyst-stage embryos, they synergize with the native epiblast cells and contribute to normal foetal development, generating many foetal cell types[18]. Thus, transplantation of embryonic stem cells to early embryos undergoing foetal development serves as a test of whether or not these embryonic stem cells are truly pluripotent and are competent to generate many different foetal lineages.

Rationale For A Physiological Test to Assess hESC Pluripotency

Thus, it is imperative to resolve whether or not hESCs are authentic pluripotent cells. Validation or invalidation of such a statement will be necessary to determine the extent of the clinical and academic utility of hESCs. Our current assessments thus far of the pluripotentiality of hESCs have largely been restricted to: (1) trying to differentiate hESCs into specific lineages of interest and seeing whether or not it is possible for hESCs to differentiate into that lineage or (2) subjecting hESCs to conditions that favour promiscuous differentiation into multiple lineages simultaneously, thus allowing for the assessment of whether or not hESCs can differentiate into those lineages. However, as one could imagine, such *in vitro* approaches are unsatisfactory in determining the pluripotency of hESCs, for the following reason: *in vitro* differentiation of hESCs is an imperfect recreation of *in vivo* differentiation of human epiblast cells during foetal development. hESCs differentiated *in vitro* are not subject to the complex organisation of cells in a developing embryo and all *in vitro* culture methods essentially are differentiation and embryonic development progressing under an unnatural environment[19,20]. Therefore what we can learn from *in vitro* hESC differentiation is limited and may even be misleading.

Ultimately, we conclude that verification of the pluripotentiality of hESCs to differentiate into every human cell type can only be attained through testing whether or not hESCs can contribute to foetal development within the early embryo[21]. Here, we argue for the development of an assay whereby hESCs are transplanted into non-human embryos to determine the capacity of hESCs to respond to developmental signals and to differentiate into the entire repertoire of cells present within the body. The resultant embryos would be "chimeras" —embryos comprised of human cells generated from the hESCs as well as non-human cells from the host embryo.

Background to Chimerism

The word chimera means different things in different disciplines:

1. Molecular biologist: Chimeric DNA sequences (genetic material) from 2 sources (i.e. cells from 2 individuals) are combined into one.

2. Cell biologist: Somatic nuclear transfer into oocyte cytoplasm, intra-species or inter-species (i.e. transferring a nucleus from a body cell into an egg, replacing the egg nucleus; the egg can be from the same or a different species).

3. Embryologist: Prenatal combinations of cells with zygotes (fertilized eggs) or early embryos, intra-species or inter-species.

4. Stem cell biologist: Grafting tissue into a prenatal host of a different species (a xenograft).

In this paper, "chimerism" refers to the embryos resultant after the transplantation of hESCs into early non-human embryos—such embryos would be comprised of both human and non-human cells.

Why Studies With Such Chimeras Are Useful

We reify again the decisive benefits that can be attained by transplanting hESCs into non-human embryos—

1. *In vivo* experiments (literally, 'in life'; experiments with live organisms) are more physiological and yield more accurate data than *in vitro* studies (literally 'in glass'; experiments with artificially maintained tissues). *In vitro* studies with hESCs are an unsatisfactory surrogate for *in vivo* studies[19-21].

2. hESCs cannot be proven to be authentic pluripotent cells without testing whether or not they can contribute to foetal development[21].

3. To regenerate human tissue for cell replacement therapies, we first need proof of human cell contribution in corresponding animal models.

4. Examination of how hESCs differentiate into the early embryonic lineages within the nascent foetus is key to understanding how we can control hESC differentiation *in vitro*. Present attempts to recreate developmental differentiation signals *in vitro* to control hESC differentiation thus far have been largely unsatisfactory[19,20] and the resultant cells may be aberrant and partially non-functional[2,9,22].

We highlight a recent landmark publication wherein rat pluripotent stem cells (the rat equivalent of hESCs) were transplanted into mouse embryos that were unable to

generate a pancreas (due to a genetic mutation; *Pdx1*$^{-/-}$)[23]. The transplanted rat stem cells were capable of developing into an entire pancreas within the resultant mice, generating rat-mouse chimeras which were mostly mouse but had entirely rat-derived pancreata[23]. Such a striking example of chimerism unequivocally demonstrated the competence of rat pluripotent stem cells to generate an entire pancreas—repetition of this experiment utilising hESCs (but pausing it at an earlier developmental stage) could test whether or not hESCs are capable of generating other tissues of therapeutic interest. Such a demonstration would be an *avant garde* advance in the utilisation of hESCs for cell replacement therapies.

Human-Animal Chimera Experiments

Many studies involving the transplant of human cells (besides hESCs) have demonstrated the utility of inter-species chimeras to illuminate the developmental potential and curative value of various human cell populations:

1. Human hematopoietic stem cells (stem cells that are precursors to the different kinds of blood cells, HSCs) transplanted into mice have been used to detect pluripotent stem cells.[i]

2. Human skin grafts in xenografted mice are useful for studying skin disease.[ii]

3. Human mesenchymal stem cells injected into rat embryos have been shown to give rise to organ tissue.[iii] Mesenchymal stem cells are usually bone marrow stem cells.

4. hESCs injected into chick embryos showed that they can proliferate and contribute to neural cells.[iv]

5. hESCs injected into foetal mouse brains showed that they can generate functional human neurons within the adult mouse brain.[v]

6. Transplants of human retinal stem cells into the eye and brain of foetal animals can address questions such as:

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[i] Guenechea G. et al. Distinct classes of human stem cells that differ in proliferative and self-renewal potential. *Nature Immunology* **2**(1), 75-82 (2001).

[ii] Raychaudhuri S.P. et al. Severe combined immunodeficiency mouse-human skin chimeras: a unique animal model for the study of psoriasis and cutaneous inflammation. *British Journal of Dermatology* **144**, 931-9 (2001).

[iii] Yokoo T. and Kawamura T. Ex vivo regeneration of the murine kidney from human mesenchymal stem cells. *Kidney International* **68**, 1967 (2005).

[iv] Goldstein R.A. et al. Integration and differentiation of human embryonic stem cells transplanted to the chick embryo. Developmental Dynamics **225**, 80-6 (2002).

Goldstein R.A. et al. Integration and differentiation of human embryonic stem cells transplanted to the chick embryo. Developmental Dynamics **225**, 80-6 (2002).

i) Can human stem cells integrate into a developing eye?

ii) What is the potential of adult stem cells to form tumours in an immune suppressed environment?

iii) Can human retinal stem cells form non-retinal tissues in a mammalian host?

7. Transplantation of hESC-derived β-cells into diabetic mouse models has demonstrated that such β-cells are capable of ameliorating hypoglycemia within diabetic organisms, and thus, they are likely to ameliorate diabetes within human patients[2].

Proof-of-Principle For hESC Transplantation Into Mouse Blastocysts

Most recently, experiments have been performed using hESCs transplanted into mouse blastocysts[24].

What were the important findings?

1. hESCs injected into mouse blastocysts multiply, intermingle and differentiate along with host cells.

2. hESCs tended to gravitate to the inner cell mass of the blastocysts (the physiological residence of pluripotent stem cells such as hESCs and their murine counterparts).

3. hESCs persisted in a few embryos that were transiently implanted into mice.

This study demonstrated the feasibility of human-animal chimera experiments with hESCs. This approach can be extended to using large collections of variant mice as hosts. Genetically modified or diseased hESCs can also be used in these experiments. This will then allow us to better understand the developmental capacity and pluripotentiality of hESCs and assess the capacity of hESCs to differentiate into clinically-relevant cell types suitable for cell replacement therapies for human patients.

Degree of Chimerism

A major concern about chimeric studies relates to the generation of chimeric animals that might have a high proportion of human cells that could confer them with human behaviours or characteristics.

This is largely restricted to the direct or indirect introduction of human neurons into animals, which might "humanise" them and potentially attribute them with self-awareness or other human cognitive properties. However, the transplantation of even large numbers of human neurons into non-human brains is unlikely to impart any degree of human consciousness[25]. It should also be noted that given the radically different gestational times of mice and humans (a mouse foetus' uterine development

time is one-fifteenth of a human foetus')[25], so it is extraordinarily unlikely that any kind of advanced human tissue could form from the transplanted hESCs.
This is substantiated by findings over decades of chimera research that chimeras between distantly related species have been found to be often nonviable and developmentally compromised. Although chimeras between related mouse strains (*Mus musculus* and *Mus caroli*) are viable[26], as are sheep-goat chimeras[27,28] and rat-mouse chimeras[23,29], it has been shown that mouse-vole chimeras and other chimeras of distant species are nonviable and rarely progress to an advanced stage *in utero*. Such studies strongly suggest that chimeras resultant from hESC transplantation into mouse blastocysts would be nonviable, thus abrogating most ethical concerns about developing an advanced being with contributions from both human and mouse cells. This assertion was affirmed by a recent study with hESC-mouse chimeras[12], where the majority of embryonic chimeras that implanted successfully and retained hESC-derived cells were developmentally abnormal and delayed—indeed, it appears that hESCs rarely persisted in embryos of normal form. Thus, it indeed appears therefore that rare mouse-human chimeras can be generated in which hESCs have limited contributions; nevertheless, such mouse-human chimeras are likely to be developmentally compromised and unable to fully develop.

Guidelines For Human-Animal Chimeric Studies

Two questions that would be important to address as part of the consideration to set guidelines for human-animal chimeric studies are:

1. The extent to which human cells can contribute to viable mouse–human chimera

2. The extent to which progression to later developmental stage can be followed

The intent of our studies is not to confer human attributes upon an animal. Rather, it is to assess the developmental potential of hESCs and potentially other human stem cell populations, thus testing whether or not these stem cells can make limited contributions to foetal development. Installation of appropriate safeguards is necessary to ensure limited total contribution of human cells to the chimera, to ensure limited specific contribution of human cells to the nervous system, and to ensure that human-animal chimeras do not become too advanced and progress beyond a developmental stage.

To this end, we suggest adoption of the following guidelines:

1. Distinguishing between human cells and animal cells within the nascent chimera. The transplanted hESCs can be labelled (with a fluorescent marker) such that they and all their progeny within the chimera are easily identifiable at all times[24]. Such a system will allow for determination of the extent of human cell contribution to the chimera and for determination of the chimeric tissues in which there are human cells.

2. Limiting the number of human cells transferred. Fewer human cells transplanted into the animal blastocysts would reduce the degree of human cell contribution since host cells will outnumber and overwhelm the human cells, thus minimising the risk of "humanising" non-human embryos. Previously, it has been demonstrated that the approximate number of donor cells transplanted into the host blastocyst determines the amount of contribution that the donor cells will have to the resultant chimera[27,28].

3. Choice of host animal for experiments involving early animal embryos. Experiments with hESCs on early animal embryos should only use evolutionarily distant animals such as mice that will likely yield nonviable embryos that will not develop to an advanced stage.

Conclusion

Human embryonic stem cells have significant therapeutic potential, and have already been used to ameliorate diseases, such as diabetes and spinal cord injury, within animal models[2,5]. Nevertheless, the extent of their therapeutic utility is dependent on the resolution of the extent of their pluripotency. Formal proof of the capacity of hESCs to differentiate into any cell type that a patient might require is still lacking, and indeed, there have been multiple allegations that hESCs indeed may not be pluripotent or may represent a "corrupted" cell type with minimal clinical or research relevance[14]. The complete exploitation of hESCs for therapeutic or research purposes will require determination of whether or not hESCs are authentically pluripotent—such a demonstration can only be made by testing whether or not hESCs can contribute differentiated progeny to foetal development[21]. To this end, here we propose the creation of limited animal-hESC chimeras wherein small numbers of hESCs are transplanted into non-human blastocysts to assess whether or not hESCs can respond to developmental signals and differentiate into therapeutically-relevant cell types. Preliminary tests performed elsewhere have shown that hESCs and their progeny often persist minimally within the mouse conceptus[24], suggesting that few human cells will ultimately remain within the chimera, thus reducing the chance of "humanisation" of the chimera.

We conclude that development of the proposed animal-hESC chimeras will extend the reach of regenerative medicine and stem cell research by validating or invalidating the pluripotency of hESCs, and such assays are unlikely to generate animal chimeras with human characteristics.

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STEM CELL RESEARCH AND INTERSPECIES FUSION: SOME PHILOSOPHICAL ISSUES

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In 1988, Harvard scientists patented the "OncoMouse" after successfully transferring a human cancer gene into a mouse. Since then, human neural stem cells have been transferred into the fetal brains of monkeys, chick embryos, fetal sheep, mouse brains and so on.[1] These are examples of biological research that creates, or is capable of creating, interspecies transgenics, chimeras, hybrids and xenografts. The aim of this paper is to discuss the main ethical issues arising from this kind of research.

1. What and Why

As the examples above show, it is now possible to transplant genetic or cellular material of one organism into another. If the host is prenatal, what results is a chimera. Chimeras can be intraspecies (when the organisms are of the same species) or interspecies (when the organisms are of different species). An interspecies chimera can be a combination of DNA sequences from different species, or a mixture of cells from different species (through somatic cell nuclear transfers), or a combination of cells from zygotes of different species. The term "transgenics" is sometimes used to refer to the results of gene transfer to distinguish them from chimeras. Chimeras are usually distinguished from hybrids (such as mules, "ligers," "geep," and hybridized plants) and xenografts (the products of grafting tissues from one species onto postnatal hosts of another species). Hybridization and xenografting occur naturally but also have been going on experimentally for some time. However, chimera research has only just begun, spurred on by advances in stem cell research. Most recent chimera research efforts involve transplanting human stem cells into prenatal nonhuman animals. The chimeras that result from these efforts allow scientists to study the development of certain human cells, such as bone-marrow stem cells, without involving human embryos or human patients. Stem cells, like drugs, need to be tested on nonhuman subjects first. In the case of many stem cells, tests can be done *in vitro*, but the results will be more accurate if their development can be observed in living animals. In the case of some stem cells, their development can take place and be observed only *in vivo*. This does not mean that chimeras must be used, as certain tests can be conducted on postnatal animals by xenografting. However, certain stem cells can only be successfully assayed in prenatal hosts. So far at least, scientists have been able to study human retinal stem cells only by transplanting them into preanatomic hosts such as embryonic mouse blastocysts, or postanatomic hosts such as the eyes and brains of

fetal monkeys. Other attempts at transplanting stem cells into postnatal hosts have only produced tumours.

2. The Issues

2.1 Health and Safety Risks

There are risks involved in the creation of chimeras. The crossing of species boundaries may allow diseases to transfer between humans and nonhumans. Zoonosis may be a big problem given threats such as avian influenza. Dangerous new strains of viruses and bacteria may pose new health and safety risks. (In 2001, Imperial College, London, was found guilty of breaching health and safety rules in a study that involved the creation of a chimera of the hepatitis C and dengue fever viruses.) In the longer terms, there is the risk of creating uncontrollable chimeric monsters.

2.2 Against Nature-Playing God

A cluster of issues comes under this heading. One is that a chimera is a life form artificially created and any such creation may be wrong, as it may be thought that the creation of life should be left to God or nature. Another is that, left alone, human and nonhuman tissues have their own, natural, ways of developing, which will be frustrated when they are merged together in chimeras. Also, it is often said that each species has it own natural integrity (and some say, dignity as well), and it is wrong to destroy it through chimera research.

2.3 The Repugnance Argument or the "Yuk" Factor

Some people find the idea of crossing species repugnant (although probably the majority have in mind hybrids and xenografts rather than chimeras). In the context of bioethics, the term "repugnance" was first used by Leon Kass against cloning.[2] He claims that there is "wisdom in repugnance" and if people find cloning repugnant then it is likely to be wrong. Many critics of stem cell research contend that Kass' claim applies especially to chimeras (as well as hybrids and xenografts).

2.4 The Imago Dei Argument

Related to the repugnance argument is the argument that since humans are created in (the Christian) God's image, any tempering with the human form is a tampering and an offence to God's image. One reason for the offence is that since animals are lower in the chain of being, to mix animal tissues with human tissues is to degrade the human form. John Paul II uses the term "original solitude" to describe the uniqueness and superiority of humans vis-à-vis the rest of nature.[3] Chimera research disturbs our "original solitude."

2.5 Moral and Social Confusion

Current social institutions and practices are based on long established and fairly entrenched views about humans and animals, and demarcation lines between the two groups. Chimeras can blur the demarcation lines and thus cause confusion. There will be new rights and obligations but it will be difficult to recognize them. Questions that may be asked include: What will happen to our meat-eating practice in a world in which many animals have human tissues in them? How are we to treat, say, monkeys that have human blood running through their veins?

2.6 Identity Problem and the Moral Status of Chimeras

The issues in 2.5 above are grounded in more deep-seated issues about the identity and the moral status of chimeras. On the assumption that the moral status of something can only be determined if we know what kind of a thing it is, i.e. its identity, we need to settle questions such as: What kind of a thing is a human-animal chimera? Is it human or nonhuman? When is a chimera human enough for certain moral standards to apply (such as being respected, not being used solely as a means to an end, etc.)? In particular, some people find the prospect of transferring cognitive capacities to nonhumans alarming.

The above are the main ethical issues arising from chimera research. There are other issues, such as the use of animals in research generally, the use and destruction of human embryos and so on, which are ignored in this paper either because they are no longer controversial, or because the ethical safeguards are well enough established, or because they relate to a larger research context and should be discussed in such context.

3. Discussion

Issue 2.1

The issue of health and safety risks can be addressed from the utilitarian point of view, which focuses on consequences. From this point of view, whether something ought to be permitted depends on the balance of benefits over harms. Whether the health and safety risks of doing something constitute an ethical barrier depends on what we stand to lose without doing it. Looking at the harms, or risks of harms, alone is not sufficient. The taking of any kind of drug has risks and the sensible thing to do is to weigh the risks against the benefits. It would be irresponsible, and perhaps morally wrong, not to immunize one’s children against deadly childhood diseases on the grounds that the vaccines are not risk-free. If chimera research promises to do no better than curing skin acnes then perhaps it is not worth the risks (not to mention the financial costs). What benefits can we expect from chimera research is largely a scientific question. The evidence so far indicates that the benefits are likely to be substantial, more than enough to justify the known risks. Naturally, there is an ethical responsibility on the part of scientists to discover as much as possible about health and safety risks and to minimize

them (just as there is an ethical – as well as legal – responsibility to produce safer vaccines and other drugs). The greater the threat of harm, the greater care scientists will have to exercise in conducting research. The threat can be estimated by estimating the actual harm and the probability of it occurring, and taking the product of the two. The harm of chimeric monsters being unleashed may be great, but the probability of this occurring is low enough for the threat to be regarded as minimal. One worrying kind of "monster" is a nonhuman animal with human cognitive functions. However, there is little likelihood of one being created if only dissociated human neural cells are used, and none if nonneural cells, such as human retinal stem cells, are used. Indeed, as long as the number of cells transferred is small enough, the host will retain its own characteristics. Even if the number is large, the anatomical constraints of the host are such that the development of human characteristics is unlikely. Still, in general, it is wise for the society to work with the scientific community to keep the probability of great harms occurring as low as possible through stringent rules regulating the number and kind of human cells transferred and the selection of host animals.

Issue 2.2

The "Playing-God" objection applies to a whole range of biomedical issues, ranging from IVF to gene therapy. In nonreligious terms, the claim is that anything "unnatural" is wrong. A number of things can be said about this claim. One is that nothing can be unnatural in the sense of going against the laws of nature. Scientific experiments, like everything else, must conform to the laws of nature. If "unnatural" is taken in this sense then there is no objection. If on the other hand by "unnatural" is meant "not how things turn out in nature" then the objection can be reduced to an absurdity, namely we should not take any medication for any illness (as this is not how a body heals itself in nature). Another point to make is that it is at least problematic to translate from what is the case to what ought to be the case. Whether something is right or wrong ethically must be based on ethical considerations (which, to be sure, have to be factually informed), rather than purely factual considerations.

In the case of chimera research, the objection is that scientists should not be playing God in harming species integrity and dignity and in creating new life forms. Species integrity and dignity will be discussed below, in relation to Issue 2.6. As for creating new life forms and other ways of "playing God," a number of things can be said:

- To some extent, this objection amounts to a misunderstanding of what scientists do. They do not create life as such; they just "rearrange" the ways life manifests itself. If this is also considered wrong then the reductio ad absurdum point above applies: many standard medical procedures are just "rearranging" how life manifests itself, typically from a diseased state to a healthy state and it is absurd to suggest that such medical intervention is wrong.

- How do we know what God's plans are when it comes to scientific knowledge and practice? Is it not possible that stem cell research is part of those plans?

- The "playing God" argument cuts both ways. In the euthanasia debate, many opponents of euthanasia claim that doctors should not be playing God in deciding who should die and when. If this claim is sound and if chimera research can save life then to stop it is to play God with respect to those whose lives can be saved.
- At least one scientist has claimed that Judaism permits us to "play God" as long as we play according to His rules.4 Indeed, we are encouraged to "play God" if "playing God" means to heal and to provide effective medical relief. What is forbidden in Judaism is stem cell research, or any kind of research, conducted for eugenic purposes: this would be playing against His rules.

Making the points above does not mean that the religious aspect of the "playing God" argument can simply be ignored. The underlying religious convictions may still be sincerely and strongly held, and a society, particularly a multi-religious one, has the responsibility to engage all of its members in a dialogue to ensure that good science can be done without violating anyone's fundamental rights, or offending anyone's dignity or religious sensibility.

Issue 2.3

Concerning the repugnance argument or the "yuk" factor, the obvious point to make is that repugnance is an emotional response. What role it plays in moral judgments is not clear. It may be argued that it should play no role at all. Leon Kass admits that the "repugnance argument" is not really an argument in the logical sense, but insists that repugnance cannot be ignored because there is "wisdom" in it. It is not clear what this claim amounts to. One possibility is that we are made by nature to feel repugnant against something so as to avoid it for our own good. For instance, we find that incest is repugnant and it turns out that there are good reasons to say that it is a bad thing and should be avoided. However, the case of incest shows that we should not object to something just because it is a taboo but because there are good reasons to say that it is a bad thing. On this interpretation, all that the "repugnance argument" shows is that we should find out whether there really are good reasons for objecting to chimera research other than the feeling of repugnance. Kass does not offer any. Repugnance is at best a symptom of what is wrong and there is no substitute for a proper diagnosis of what is wrong. Incidentally, while anthropologists have found that incest is near enough to being universally repugnant, a taboo in nearly all cultures, the idea of a biological chimera is not so. Repugnance against chimeras, if any, is not even a reliable symptom of something wrong. Kass is right in insisting that we should not become "souls that have forgotten how to shudder," but having shuddered, we should take a close look at what we are shuddering at before taking a swipe at it: it could well be a harmless crawling insect on the back or worse still a prized specimen!

Another way of cashing out Kass' "repugnance argument" is to put it in terms of Midgley's argument about emotions.[5] She claims that feelings and reasons are complementary: judgments of right and wrong are accompanied by feelings of approval and disapproval (and in the case of a serious wrong, a strong feeling such as

disgust, or repugnance). She concludes that strong emotional reaction should be taken seriously, for there may be good reasons for it, and even if there are no obvious good reasons, it should still be respected rather than summarily dismissed as "emotional." However, once again, all that the argument establishes is that we need to find out whether there are good reasons for reacting negatively to something and that, even if no good reasons are found, we should still respect the negative reaction. The practical question now is how to show respect for the negative reaction when there are no good reasons for it. Clearly, it is unreasonable to suggest that an activity should be stopped just because some people strongly object to it (without being able to offer good reasons for the objection). After all, many people did, and some still do, strongly object to interracial relations, kissing or holding hands in public and so on. Still, it may be said that just because a large number of people feel that something is repugnant, it is at least morally problematic. The problem is how to deal ethically with members of the community who react negatively to certain things for no apparent good reasons. There may be social and ethical costs to bear in allowing something like chimera research. The costs can be minimized through public dialogues, consultations and discussions. Whatever costs that remain, bearing in mind that not all people can be pleased all the times, will have to be weighed against the expected benefits. On available evidence, the benefits of chimera research seem substantial enough to absorb the ethical costs of going against the preferences of those who object on non-rational grounds, particularly if it can be ensured that such research does not violate anyone's fundamental rights.

Issue 2.4

In nonreligious terms, the "Imago Dei" argument inveighs against crossing species boundaries, typically on the grounds of preserving the dignity and integrity of the human species. This aspect of the argument will be discussed later in relation to Issue 2.6. In religious terms, the objection is directed at the crossing into the human form, which is regarded as holy insofar as it is the image of God. The point to notice straightaway is that this objection is rooted in the Judeo-Christian tradition (which does not mean that all followers of this tradition raise it). Other religious traditions do not seem to give rise to the same objection. Indeed, in some religions, the worshipped images often combine human and animal features, such as a human body with an elephant head. The "Monkey God," it seems, is human, monkey and God rolled into one.

Another point to make is that the argument does not make a distinction between the human form and tokens, or manifestations of that form. Chimera research does not alter and is not aimed at altering the human form as such even though it may alter the form of some token humans. Indeed, it may be said that chimera research aims at preserving the human form against diseases that threaten that form. Failing to make this distinction could well be an offense to all those humans unfortunate enough not to con*form* to the human form for whatever reason (does an amputee offend Imago Dei?). There is a danger of altering the human form if the human germline is systematically affected by chimera research but the risk of this is low. Naturally, there is a responsibility to keep it low. Also, a society has the responsibility to engage those

members of the society who take the Imago Dei argument seriously, through public dialogues, consultations and discussions.

Issue 2.5

In general, just because something causes confusion, it does not follow that it is a bad thing or that it should not be permitted. The emancipation of black slaves caused a great deal of economic and social confusion for the United States, but that is not a reason to say that it should not have happened. Many people complain that the women's liberation movement has caused a great deal of social confusion, but this not a reason not to emancipate women. When fundamental rights are concerned, the costs in terms of moral and social confusion may have to be born. It may be argued that those whose lives would be better off as a result of chimera research has a right to its benefits that may outweigh the costs in terms of moral and social confusion. However, the issue is more likely to be settled on the basis of the likelihood and the extent of social and moral confusion. It will be at least a concern if the confusion is so great as to outweigh any benefits to be had, but there is no evidence to show that this is the case with chimera research. We are already familiar with images of human-animal mixtures, in various religions, in folklores, in story books, in films and art works and so on. Many of us growing up with Sesame Street stories of Miss Piggy do not seem to have any trouble with eating pork. To be sure, we may think differently if some pigs do act like Miss Piggy, but the evidence so far indicates that they will fly before they do so. It is of course possible that those who raise this objection have in mind a confusion at a deeper level, having to do with the integrity and dignity of species, which would be threatened if species boundaries are breached. The thought is that there would be a moral confusion as the established moral order based on existing species boundaries would no longer apply. This aspect of the objection will be discussed below.

Issue 2.6

Many different ethical concerns arise from the fear that stem cell research, in creating interspecies organisms, will undermine the boundaries that now separate the species. As pointed out above, in one aspect, the "playing God" argument says that crossing species boundaries will harm the integrity and dignity of species. Another concern is that blurring the species boundaries will cause moral confusion insofar as there is an established moral order based on the hierarchy of species. Many writers have dismissed both concerns, arguing that they are based on a mistake, namely that there are rigidly fixed species boundaries.[6] They point out that biologists themselves do not believe in them: "The biological categorization of species is empirical and pragmatic," which means that "species categories are never real, ontological entities or natural kinds."[7] Indeed, there are many different concepts of species.[8] However, dismissing the idea of fixed species boundaries goes some way toward addressing the first concern, but does not settle the moral issue underlying the second, which can simply be shifted to the talk about kinds of things that we are perfectly familiar with. In our ordinary conceptual scheme, there is such a thing as the human kind, members of which we can easily identify and pick out, and distinguish from members of other

kinds. Mapped onto this conceptual scheme is a moral hierarchy of kinds on which the human kind occupies the top rung and the other kinds occupy the lower rungs according to how close they are to us in terms of anatomical and psychological development. For instance, we typically regard killing an insect not as serious as killing a cat, which in turn is not as serious as killing a monkey, a chimpanzee and a human being, in that order. The complaint against stem cell research is really based on this ordinary conceptual and moral framework.

There are two types of complaint. One is that chimeras, hybrids and so on invalidate our conceptual scheme concerning kinds and as a result causes moral confusion. Differently put, they will provide a metaphysical test that our conceptual scheme could well fail. We may no longer be sure about what we have taken to be the criteria for being a member of a certain kind. This type of complaint can be fairly easily dismissed. The introduction of interspecies entities, such as the "OncoMouse," does not lead to the elimination of kinds of beings as we know them anymore than the creation of "ligers" and "geep" leads to the elimination of lions and tigers and goat and sheep. Our ordinary conceptual scheme still applies to ordinary human beings and ordinary lions, tigers, goat and sheep. To be sure, the new entities could overwhelm the existing ones in a battle for survival. However, the likelihood of this occurring is so remote as to constitute no threat at all. Even if it ever came to pass, there would be no moral issue, as there would no longer be the human kind as we know it, for which it is a moral issue. What is not so remote is that there would be more and more entities that do not fit in any existing kind. However, conceptually, if we could cope with mules as a kind, there is no reason why we cannot cope with ligers and geep, or for that matter, onco-mice or humice, as new kinds of entities. That leads to the second type of worry, namely how we are to treat the individual new entities, or what moral status they possess.

To facilitate the discussion, it is useful to distinguish three possible varieties of chimeras and hybrids: (1) Those that can be said to belong to different kinds, that is, wholly of kind X *and* wholly of kind Y (and Z …), (2) Those that are wholly of one kind only but possess features of another kind and (3) Those that do not belong to any existing kind, neither fish nor fowl. It may be thought that (1) is logically impossible. However, DiSilvestro has argued that it is logically possible for one entity to be wholly of one kind and wholly of another kind.[9] He cites a theological view of the doctrine of Incarnation on which the entity Jesus is wholly human and wholly God. DiSilvestro then suggests what he calls the "Maximum Respect Principle" to determine the moral status of any such entity: it has the status of the kind that deserves the most respect. Thus, since God has a greater status than humans, the human Jesus who is also God deserves the moral status of God, which includes our worshipping Him. If this suggestion is right then any entity that is both wholly human and wholly animal has the higher moral status of a human, insofar as humans are ranked higher than animals on the moral scale. The only alternative to the Maximum Respect Principle is one that calls for recognizing the minimum status (the Minimum Respect Principle), or somehow adding the two (the Additive Principle), or subtracting the lower from the higher (the Substractive Principle), or averaging the two (the Averaging Principle).

None of the latter would work in the case of Jesus who cannot be respected just as a human being (as required by the Minimum Principle), or as more or less than God (as required by any of the other three principles). It looks like we have a reasonable principle to settle the question of the moral status of interspecies entities.

As it turns out, the ethical issue is much simpler than DiSilvestro has envisaged. This is so because even if he is right in his claim that (1) is logically possible, there is no evidence to suggest that it is biologically possible. Biological properties characteristic of a biological kind tend to preclude the development of biological properties characteristic of another kind. For instance, it has been pointed out that it is "highly unlikely that even a monkey chimera whose entire thalamocortical system was human-derived could possess human consciousness, as its neurons would lie in anatomically different networks."[10] This means that even if we take the capacity for human consciousness as sufficient for being a member of the human kind, it is still "highly unlikely" that there can be an entity that is wholly human and wholly simian or wholly something else. Stem cell research is likely to lead to entities of type (2) or (3). A type (2) entity is wholly of one kind but possesses characteristics of another kind. A monkey with human blood flowing through its vein remains wholly monkey, and only monkey, even though it is not an ordinary monkey. Likewise, a human being with a baboon heart remains wholly human, and only human, even though he or she is not an ordinary human. As such, the question of moral status does not arise: the monkey with human blood has the moral status of a monkey, no more and no less, and Baby Fae, had she survived and grown up with the baboon heart beating in her chest, would have retained the moral status of a human being, no more and no less. Entities of type (3) are somewhat more troublesome but still, as a minimum, we can say that if something is neither human nor simian then it does not have the status of a human being nor that of a monkey. What it has depends on our decision concerning where we would fit that kind of entities in our existing moral order. There is little problem if the new animal comes from different kinds of animals of the same moral status. (Thus, insofar as the goat and the sheep have the same moral status, the hybrid geep takes on that same moral status.) As for other entities, decisions need to be made. We might decide to place the "humouse" kind higher than the mouse kind, in which case we would give a "humouse" a greater moral status than we would a mouse. However, it will be a very long time, if ever, before there are enough entities of this type for us to have to start thinking of new kinds and their moral status, particularly if they remain laboratory specimens rather than proliferating as naturally living entities.

4. Conclusion

The ethical concerns about stem cell research are extensive and not unreasonable. It has major implications for our fundamental values, beliefs and practices. However, there does not seem to be any ethical barrier against it. Nevertheless, there is a continuing need for public dialogues and debates in order to gain as much consensus and support for the new science as possible. Ethical and other safeguards should also be in place to ensure public trust. There is little doubt that the health benefits will be substantial. But perhaps the greatest benefit is not something related to human health

and welfare. It has to do with the way we think of ourselves. Human-animal chimeras will confirm once and for all our continuity with the rest of nature, or as Barash puts it, our "glorious connection with the rest of life."[11]

NOTES

1. See *Science*, Vol.293 (2001), pp.1820-1824, *Developmental Dynamics*, Vol.225 (2002), pp.80-86, *British Journal of Haematology*, Vol.130 (2005), pp.276-283, and *Proceedings of the National Academy of Sciences*, Vol.102 (2005), pp.18644-18648.

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3. John Paul II, *Theology of the Body: Human Love in the Divine Plan* (Boston: Pauline Books and Media, 1979).

4. Yoel Jakobovits, "Judaism and Stem Cell Research," *Jewish Action*, Vol.62 (No.4, Summer 2002).

5. Mary Midgley, "Biotechnology and Monstrosity: Why Should We Pay Attention to the 'Yuk Factor'," *Hastings Center Report*, Vol.30 (2000), pp. 7-15.

6. Françoise Baylis and Jason Scott Robert, "Primer on Ethics and Crossing Species Boundaries," *http://www.actionbioscience.org/biotech/baylis_robert.html*, May 2006.

7. Phillip Karpowicz, Cynthia B. Cohen and Derek van der Kooy, "It Is Ethical to Transplant Hman Stem Cells into Nonhuman Embryos," *Nature Medicine*, Vol.10 (No.4, 2004), pp.331-335, at p.333.

8. R. Mayden, "A Hierarchy of Species Concepts: The Denouement in the Saga of the Species Problem," in M. Claridge, H. Dawah and M. Wilson (eds.), *Species: The Units of Biodiversity* (London: Chapman and Hall, 1997), pp.381-424.

9. Russell DiSilvestro, "A Neglected Solution to the Problem of the Metaphysical and Moral Status of the Human-Animal Chimera," *Ethics and Medicine*, Vol.20 (No.2, 2004).

10. Karpowicz et.al, *op.cit.*, p.334.

11. David P. Barash, "Humans Don't Stand Outside Nature," *Commentary, Seattle Post Intelligencer*, Wednesday, May 25, 2005.