HUMAN-ANIMAL COMBINATIONS FOR BIOMEDICAL RESEARCH

A CONSULTATION PAPER

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SINGAPORE

8 January 2008

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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).

Contacting the Bioethics Advisory Committee

The BAC welcomes views, comments, suggestions and other feedback on the issues raised in this Consultation Paper and on any bioethical issues within the BAC's remit. All feedback should be addressed to:

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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*.

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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.

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

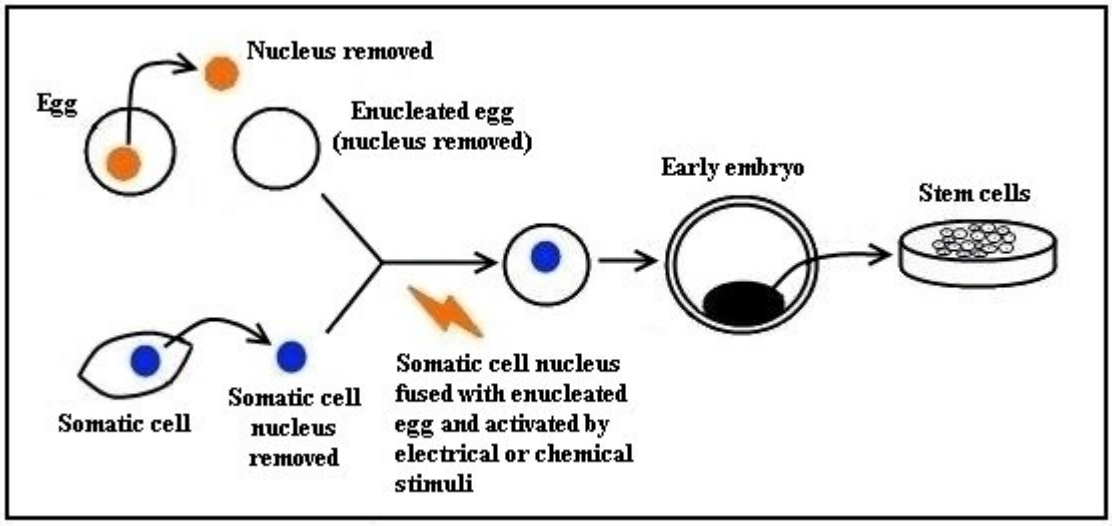

Figure 1. Derivation of stem cells using SCNT

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.

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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.

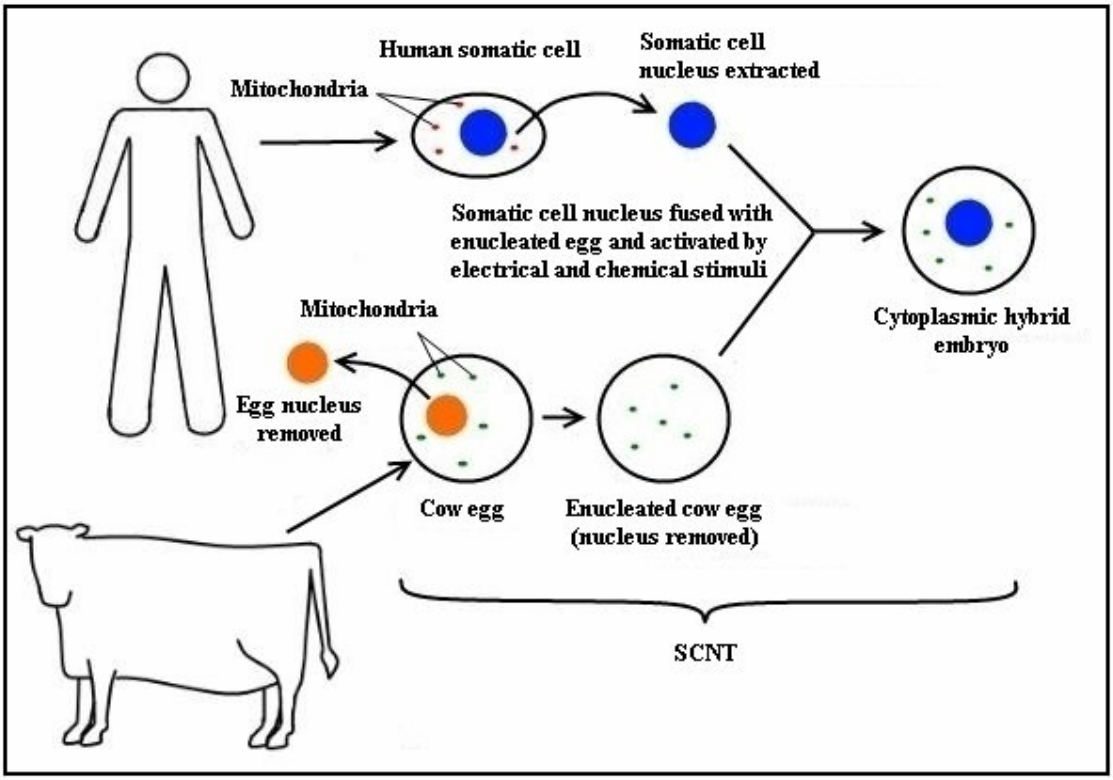

Figure 2. The creation of a cytoplasmic hybrid embryo by SCNT

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

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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.

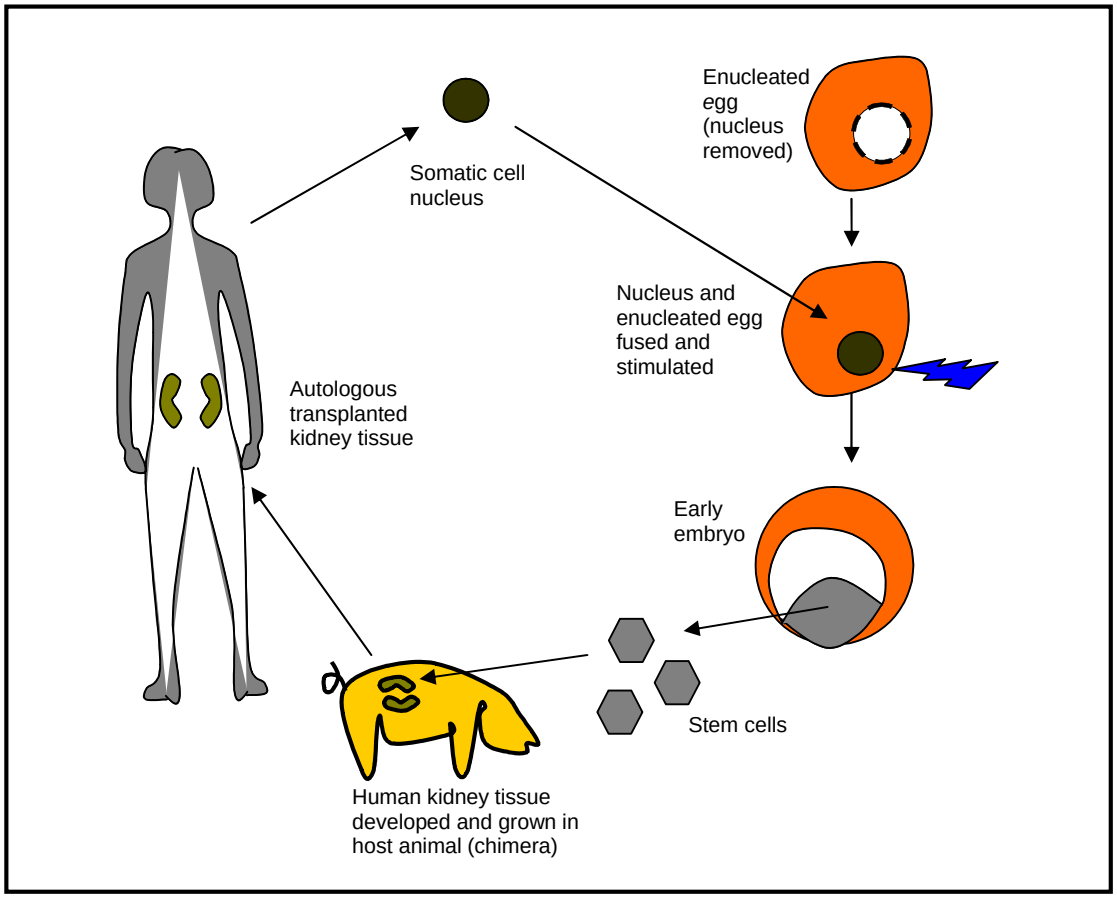

Figure 3. Schematic possible use of an animal host in the growth of organs (e.g. kidneys) derived from cloned human stem cells by SCNT.[19]

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]

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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?

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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.

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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.

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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	
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	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

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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.
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