

**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.

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 al⁴ 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

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

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 HIV⁹, 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
Chairman
Human Embryo and Chimera Research Working Group
Bioethics Advisory Committee
11 Biopolis Way
#10-12 Helios
Singapore 138667

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
RIMA

: Dr Abdul Razak Chanbasha
Chairman, RIMA

With inputs from : Jameelah Sheikh Mohamed
and Muhd Ibnur Rashad



Institute of
Bioengineering and
Nanotechnology

Institute of Bioengineering and Nanotechnology
31 Biopolis Way
The Nanos, #04-01
Singapore 138669
Tel : +65 6824 7000 Fax : +65 6478 9080
www.ibn.a-star.edu.sg

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.



Institute of
Bioengineering and
Nanotechnology

Institute of Bioengineering and Nanotechnology
31 Biopolis Way
The Nanos, #04-01
Singapore 138669
Tel : +65 6824 7000 Fax : +65 6478 9080
www.ibn.a-star.edu.sg

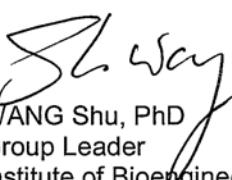
58. Even human embryonic stem cells are introduced into closely related, developing organisms, such as higher primates (monkeys or apes), the genetic materials of human stem cells will not be stably present in animal cells and pass down to the next generation of the tested primates. Hence, the risk of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

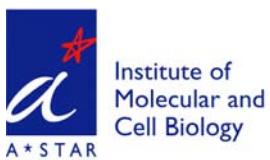
General comment:

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



Institute of
Molecular and
Cell Biology

IMCB
Institute of Molecular and Cell Biology

61 Biopolis Drive
Proteos
Singapore 138673
Tel: (65) 6586 9755 Fax: (65) 6779 1117

www.imcb.a-star.edu.sg

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



IMB
Institute of Medical Biology
8A Biomedical Grove
#06-06 Immunos
Singapore 138648
Tel: (65) 6407 0150 Fax: (65) 6464 2049
www.imb.a-star.edu.sg

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. Tumorigenicity 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?

A handwritten signature in black ink that reads "Alan Colman".

Alan Colman MA PhD
Executive Director
Singapore Stem Cell Consortium



**KK Women's and
Children's Hospital**
SingHealth

Tel: (65) 6293 4044
Fax: (65) 6293 7933
100 Bukit Timah Road
Singapore 229899
www.kkh.com.sg
Reg No 52839081C

11 February 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 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

Hospital of Choice for Women and Children

Members of the SingHealth Group

Changi General Hospital • KK Women's and Children's Hospital • Singapore General Hospital
National Cancer Centre Singapore • National Dental Centre • National Heart Centre • National Neuroscience Institute • Singapore National Eye Centre
SingHealth Polyclinics



KK Women's and
Children's Hospital
SingHealth

Tel: (65) 6293 4044
Fax: (65) 6293 7933
100 Bukit Timah Road
Singapore 229899
www.kkh.com.sg
Reg No 52839081C

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 handwritten signature in black ink, appearing to read 'Tay Eng Hseon'.

A/Prof Tay Eng Hseon
Chairman Medical Board

Hospital of Choice for Women and Children

Members of the SingHealth Group

Changi General Hospital • KK Women's and Children's Hospital • Singapore General Hospital
National Cancer Centre Singapore • National Dental Centre • National Heart Centre • National Neuroscience Institute • Singapore National Eye Centre
SingHealth Polyclinics

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

Sender's Fax: 6533 5700
Sender's DID: 6530 0229
Sender's Email: represent@lawsoc.org.sg

Our Ref: LS/87/2008
Your Ref:

10 March 2008

BY FAX AND POST

Fax No. 6478 9956
No. of Pages: 6
(including this page)

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

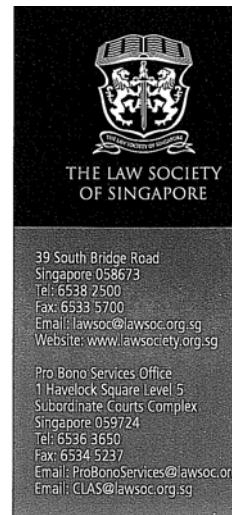
We are pleased to enclose our ad hoc committee's feedback on the matter for your consideration.

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.



Council Members 2008

Michael Hwang, SC (President)
Malathi Das (Vice President)
Yap Teong Liang (Vice President)
Andrew Ong (Treasurer)

Philip Jeyaretnam, SC (Immediate Past President)
Gan Hsiang Chye
Jimmy Yim, SC
Gary Pryke
Lok Vi Ming, SC
Young Chee Foong
Wong Siew Hong
Francis Xavier
Leo Cheng Suan
Joseph Tan
Rajan Chettiar
Lisa Sam
Michael S Chia
Anand Nalachandran
Lee Terk Yang
Laura Liew
Smitha Menon
Wilma Muhundan

Secretariat
Chief Executive Officer
Chua Lik Teng

Representation & Law Reform
Alvin Chen

Conduct
Yashodhara Dhoraisingham

Compliance
Yashodhara Dhoraisingham
Sharmaine Lau

Pro Bono Services
Lim Tangyu

Communications/ Membership Interests
Shawn Toh

Publications
Sharmaine Lau

Finance
Clifford Hang

Information Technology
Michael Lee

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**



LScCommentsBAC(100308)Final

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 NACLR (National Advisory Committee on Laboratory Animal Research) Guidelines. Our NACLR 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



Islamic Religious Council of Singapore • Singapore Islamic Hub • 273 Braddell Road • Singapore 579702 • www.muis.gov.sg • Tel: 6359 1199 • Fax: 6253 7572

MUI OMB 02/01

DID: 63591440
FAX: 62591735

21 May 2008

Dr John Elliott
Research Fellow
Secretariat,
Bioethics Advisory Committee
11 Biopolis Way,
#10-12 Helios
Singapore 138667

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
-

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
சிங்கபூர் திருச்சபைகளின் சென்ற மன்றம்

3 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

'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

A handwritten signature in black ink, appearing to read 'Robert Solomon'.

Bishop Dr Robert Solomon
President
National Council of Churches of Singapore

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

B1-27 The Adelphi,
1 Coleman Street,
Singapore 179803
Tel: 6336 8177 Fax: 6336 8178
Email: admin@nccs.org.sg
Website: www.nccs.org.sg

**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.

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 its 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 identity⁸ 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

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), Appendix 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:

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

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 prerogatives²⁵ 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 other 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.

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:

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 CONCERN 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 Regulation 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 Report of 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

³⁸ Lachm-Kaplan, O. Daniels, R. & Trouson A. *Reprod. Biomed. Online* 3, 205-211(2001).
http://www.ncbi.nlm.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 oocytes*. *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 oocyte 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'.⁴² 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.

⁴² Coghlan, 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 France⁴⁴ 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_xenotriplanti_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.



Tel: (65) 6324 8910
Fax: (65) 6324 8810
National Dental Centre
5 Second Hospital Avenue
Singapore 168938
www.ndc.com.sg

Reg No 199505641 M

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.

Members of the SingHealth Group

Changi General Hospital • KK Women's and Children's Hospital • Singapore General Hospital
National Cancer Centre Singapore • National Dental Centre • National Heart Centre • National Neuroscience Institute • Singapore National Eye Centre
SingHealth Polyclinics

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, cytoplasmic 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:

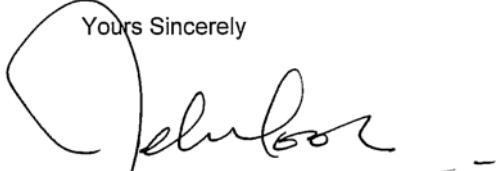
I have no objections to this aspect of medical research, which I think will be the way forward.

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

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.

Best regards,

Thank you.

Yours sincerely,

A handwritten signature in black ink.

DR LEE SUAN YEW
CHAIRMAN
NATIONAL MEDICAL ETHICS COMMITTEE



Ministry of Health, Singapore
College of Medicine Building
16 College Road
Singapore 169854
TEL (65) 6325 9220
FAX (65) 6224 1677
WEB www.moh.gov.sg



**National
University
Hospital**

5 Lower Kent Ridge Road
Singapore 119074
Tel: (65) 6779 5555 Fax: (65) 6779 5678
Website: <http://www.nuh.com.sg>
Company Registration No. 198500843R

13 February 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 *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.

Page 2
13 February 2008

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



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

A handwritten signature in black ink, appearing to read 'Ong Choon Nam'.

Professor Ong Choon Nam
Director
Office of Life Sciences

Centre for Life Sciences
28 Medical Drive, #05-02, Singapore 117456 Tel: (65) 6516 4040 Fax: (65) 6776 4382
Website: www.ols.nus.edu.sg
Company Registration No: 200604346E

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 researchers 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 it 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 play a 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

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 embryos. 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 mitochondria, 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 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.

Raffles Hospital

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

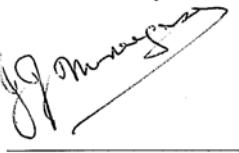
Dear Prof Lee

CONSULTATION PAPER ON HUMAN-ANIMAL COMBINATIONS FOR RESEARCH

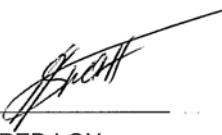
Thank you for your invitation to comment on the Bioethics Advisory Committee's consultation paper entitled "Human-Animal Combinations for Biomedical Research".

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.

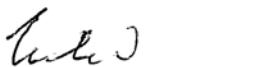
Yours sincerely



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

Comments from Singapore Medical Council

Received via email on 10 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



**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 novo* 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

1 of 3

Research & Collaborate

Society of Bioscience & Technology
www.socbioscience.org

58 Tras Street, #02-01, Singapore 079877, ROS Registration No: 2007/2004

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 novo* hybrids that are universally illegal (For instance, to develop an indestructible or invincible being

2 of 3

Research & Collaborate

Society of Bioscience & Technology
www.socbioscience.org

58 Tras Street, #02-01, Singapore 079877, ROS Registration No: 2007/2004

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 -

新加坡道教協會

会址：新民路一百五十九号，永德大厦三楼二号A
(LOBBY 1), 新加坡邮编 575625
通讯处：新加坡武吉班让邮政信箱288号，邮编916810
电话：(65) 6295 6112 主线/6295 6113 传真：(65) 6295 6119
电邮址：info@taoism.org.sg 网址：<http://www.taoism.org.sg>



TAOIST MISSION (SINGAPORE)

Registered Address: 159 Sin Ming Road, #03-02A
Amtech Building (Lobby 1), Singapore 575625
Postal Address: Bukit Panjang P.O. Box 288, Singapore 916810
Tel: (65) 6295 6112-main / 6295 6113 Fax: (65) 6295 6119
e-mail: info@taoism.org.sg URL: <http://www.taoism.org.sg>

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 Advisory 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/mlzw/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 mitochondria itself is a separate organelle with its own nucleus containing its own 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 occurrence. 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 al¹ 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 blastocyst 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 blastocyst 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 research⁴ 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, HIV⁹ and hepatitis B¹⁰ 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)

References

1. Chen Y et al. Embryonic stem cells generated by nuclear transfer of human somatic nuclei into rabbit oocytes. *Cell Research.* 2003;13:251-263
2. Andy Coghlan. Human-animal cybrids may not be possible. *New Scientist* 14 September 2007; 2621: 15
3. <http://news.bbc.co.uk/2/hi/health/7227861.stm>
4. Nussbaum J et al. Transplantation of undifferentiated murine embryonic stem cells in the heart : teratoma formation and immune response. *FASEB J.* 2007;21(7):1345-1357
5. Maitra A et al. Genomic alterations in cultured human embryonic stem cells. *Nat Genet* 2005; 37(10): 1099-1103
6. Baker M. Monkey stem cells cloned. *Nature.* 2007; 447(7147): 891
7. Prudhomme S et al. Endogenous retroviruses and animal reproduction. *Cytogenet Genome Res.* 2005;110(1-4):353-364
8. Prentice D, Tarne G. Adult versus embryonic stem cells : treatments. *Science* 2007 Jun 8;316(5830): author reply 1422-3
9. Keele BF et al. Chimpanzee reservoirs of pandemic and nonpandemic HIV-1. *Science.* 2006 ;313(5786):523-526
10. MacDonald DM et al. Detection of hepatitis B virus infection in wild-born chimpanzees (*Pan proglodytes* versus). Phylogenetic relationships between human and other primate genotypes. *J Virol* 2000; 74(9): 4253-4257
11. <http://www.telegraph.co.uk/earth/main.jhtml?xml=/earth/2007/11/16/scidolly116.xml&page=3>

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 cytoplasmatic 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 be 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 as 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

Cognose Lim Swee Keng 林瑞庆

CtS Cognoscere tenus Solve 康索

Cognize before Happening 察觉于发生之前

Solve beyond Causes 解决于根基之处

www.cts-ideas.com

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, Tetraethyl 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 MICheM
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 possibly 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.
- (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, Taoism, 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”.

(v) Were there pitfalls?

When one is at the forefront of research the way 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 are 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.
