June 2016

Dear Prof. Kelso,

Guidelines on clinical studies of xenotransplantation

Humane Research Australia Inc. is a not for profit organization that challenges the use of animal experiments and promotes the use of more humane and scientifically valid non animal methods of research

In 2004 the author[1] served on the Animal Issues Sub Committee which provided recommendations to the Xenotransplantation Working Party (XWP) as part of the National Health and Medical Research Council's review on this subject. In December 2004, the NHMRC recommended that clinical trials involving xenotransplantation should not be undertaken in Australia for a period of five years. The moratorium was sanctioned for good reason.

1. Continuing risks to the community
2. Public opinion
3. Animal welfare and suffering

Risk to the community

The uncertainty of risks of disease transmission, particularly across the species barrier, has been acknowledged by researchers. Clearly, this is not just a theoretical possibility but a very possible outcome. AIDS is already believed to have been contracted from chimpanzees. BSE and Ebola viruses originated from cross-species contamination. Some of the major flu epidemics from the start of last century were believed to have originated from pigs. Porcine Endogenous Retrovirus (PERV) has already been discovered in the animals intended to be used as source animals. With continued emergence of new zoonoses from unexpected sources, the inability to diagnose potential xenozoonotic viruses with current tests and their unknown pathogenic behaviour, the chances of cross-species infection seems to be exceedingly and unacceptably high. Even more alarming is that, even if detected, the viruses are largely untreatable.

The global panic over Swine flu could perhaps serve as a (very modest) precursor of how the world might react should a new zoonotic disease emerge from xenotransplantation. While the outbreak of the H1N1 virus was declared by the World Health Organisation to be a "public health emergency of international concern", a more

1 Formally Helen Rosser, representing Animals Auatralia.

virulent strain might easily have a much higher level of transmissibility and far more serious health consequences.

HRA has been advised by experts (including Prof. Peter Collignon, Director Infectious Diseases Unit and Microbiology Department, The Canberra Hospital) that the **concerns which resulted in the 2004 moratorium being announced remain unchanged.**

Not only would clinical trials be exposing the organ (or cell/tissue) recipient to major health risks, but these risks would also be extended to the recipient's carers and families and the wider community. Considering that viruses may initially show no obvious signs of disease and may spread beyond the recipient into the general population before they become evident, at what stage will researchers deem their patients as no longer carrying any risk? And during that period before the disease is identified or acknowledged, how many people are likely to have been exposed to that disease? We do not consider that the general public would be prepared to accept the risk of introducing another potentially untreatable human epidemic such as HIV/AIDS or bovine spongiform encephalopathy (BSE). Certainly an individual has the right to expose themselves to any risks involved in scientific research but to further expose that risk to the wider community, who have NOT given consent, is highly unethical. Indeed the number of individuals that could suffer and die from a new epidemic could greatly exceed those potential lives which xenotransplantation was supposed to have saved in the first place.

Chapter 3.6 of the draft guidelines acknowledges this risk and states:
"Xenotransplantation differs from most other medical research where it is research participants who are predominantly exposed to risks. In xenotransplantation, not only the research participant but also their identifiable contacts and members of the wider community may be exposed to risk. Xenotransplantation research involves some known and, potentially, some currently unknown infection risks to those other than the research participant. The possible risk of xenotransplantation causing novel or latent infectious and potentially untreatable diseases raises an ethical issue that cannot be addressed by the consent of the research participant alone, since others may also be exposed to risk by the research. Further, because of the possible public health risk, research participants will need to participate in long-term monitoring programs."

Public opinion / previous consultations
Having served on the XWP 'Animals Issues Sub-committee', being privy to the full set of submissions received and having gained a greater understanding of the issues at stake through the public consultation meetings, HRA has only strengthened its convictions in its opposition to such inhumane and risky research.

Clearly there is a great deal of opposition to xenotransplantation due to a number of serious issues. This has been expressed through the submissions received in the first round of consultation, as well as the overwhelming opposition at the public consultation meetings around Australia. We consider that the analysis of submissions tabled in the response paper[2] has misrepresented the overall view, as those 'inferred from text' have only agreed to clinical studies of xenotransplantation proceeding IF major hurdles can be overcome – which they likely cannot.
For example…

2 Animal-to-human transplantation research: How should Australia proceed? Response to the 2002 public consultation on Draft Guidelines and Discussion Paper on Xenotransplantation Table 2.1 Respondents. views about whether animal-to-human transplantation trials should proceed

The Salvation Army (Submission X035) recognizes the potential benefits to patients, but also suggest that the risk of the inadvertent transmission of infectious agents to recipients and the wider community is of concern. Despite the XWP being unable to allay that concern they have counted this submission as a 'yes' vote.

RSPCA (UK) (Submission X091) have also been designated as a 'yes' vote 'provided that animal welfare issues are adequately addressed'. It is clear from the nature of xenotransplantation that sufficient animal welfare standards could never be attained.

Even without this misinterpretation however, the number of submissions opposing clinical studies of xenotransplantation tripled those in favour (25:66).

Also worth considering is that of those submitters who were in favour of clinical studies proceeding, how many would have a vested interest? It is highly questionable that these views should be seen as being objective. (X016? X056? X080?). On the other hand, there are many submissions from medical experts that raise serious concerns and are strongly opposed to xeno research. These include:
Dr Anthony Raizis (X034), Dept. of Molecular Biology, Christchurch School of Medicine & Health Services NZ.
Dr Peter Collignon (X063), Infectious Diseases Physician & Microbiologist, Canberra Hospital.
Claude Reiss (X072), Molecular biologist, Sciences Enjeux Sante
Dr Judy Carman (X078), Epidemiologist, Flinders University
Surely such serious concerns by recognized experts should carry great weight in the decision process.

Suffering of animals

Housing

Special husbandry and housing conditions required for transgenic source animals is a major welfare concern. Adherence to strict levels of hygiene and disease control will reduce access to the outside environment and minimise human contact. Will the pathogen-free housing mean that pigs will not have access to nesting and rooting materials - important requirements for their environmental enrichment?

Pigs will be born by caesarean section with their mothers being killed and the piglets will therefore never have the opportunity to suckle and bond with their parent.

Surgical Procedures

In the creation of transgenic source animals, animals suffer from the processes of surgical embryo retrieval and embryo transfer. During the microinjection process for example, the host mother must be injected with hormones to ensure she is at the right stage of ovulation. The significant manipulation of the animals ovulation and oestrus cycle that takes place to ensure the availability of adequate embryos can lead to over-stimulation of the ovaries causing painful ovarian cysts or enlarged ovaries.

Animals can also become considerably stressed from the exposure to additional hormones, collection of eggs and implanting of the fertilised eggs.

Due to a lack of efficiency in the microinjection process, genes can often fail to reach the right target cells within the embryo and can cause painful abnormalities or even death.

Behavioural Problems

The presence of a transgene may also affect the animal's ability to perform normal behaviour. Beltsville pigs for example (genetically modified to express additional growth hormones), experienced such extreme welfare problems that normal behaviour was impossible for them. They suffered from lethargy, lameness, lack of coordination, thickened skin, gastric ulcers, severe synovitis, degenerative joint disease, pericarditis and endocarditis, cardiomegaly, paraketosis, nephritis and pneumonia.[3] It is suggested in the NHMRC's original discussion paper[4] that the genetic modification will involve "major changes to the source animal".

Even Dr Christian Barnard, a pioneer in organ transplantation was later opposed to the use of animals. "...I had bought two male chimps from a primate colony in Holland. They lived next to each other in separate cages for several months before I used one as a donor. When we put him to sleep in his cage in preparation for the operation, he chattered and cried incessantly. We attached no significance to this, but it must have made a great impression on his companion, for when we removed the body to the operating room, the other chimp wept bitterly and was inconsolable for days.
The incident made a deep impression on me. I vowed never again to experiment with such sensitive creatures."[5]

Conan, Scar, Belvedere and Frazer

According to recent correspondence*, "NHMRC is not aware of any animal-to-human xenotransplantation trials currently being undertaken in Australia, and is not currently considering any funding proposals to undertake animal-to-human xenotransplantation trials in Australia."*

Unfortunately however, animal to animal (usually pig to baboon) xenotransplantation continues.

- Frazer and Belvedere – both baboons rendered diabetic and will be recipients if sufficient islet cells are available.
- Scar – baboon transplanted with neonatal islet cells and on large doses of immunosuppressant drugs
- Conan – baboon, received a renal transplant (kidney from a transgenic pig) and then killed on Thursday 20th (February or March) 2014 due to the development of disseminated intravascular coagulation as diagnosed on haematological findings.

Summary

To conclude, based on the high risk of transmission of retroviruses and particularly the exposure to the wider community; the ethical and welfare issues concerning the use of animals; the limited level of acceptability by the public; the high cost in funding and resources; the probability of public funding being re-directed away from other urgent medical procedures; and considering the alternative and safer options that are already

3 Pursel, V.G., Pinkert, C.A., Miller, K.F., Bolt, D.J., Campbell, R.G., Palmiter, R.D., Brinster, R.L., & Hammer, R.E. (1989). Genetic Engineering of Livestock. Science 244, 1281-1288.

4 Draft guidelines and discussion paper on xenotransplantation page 42

5 Dr Christian Barnard, Good Life Good Death

available, Humane Research Australia cannot agree to the guidelines for clinical studies of xenotransplantation proceeding.

Despite our organisation's view however, we acknowledge that the decision as to whether or not clinical trials go ahead should be made by the community – providing they have the full information to enable them to make such an informed decision. For this reason we call for:

- Full public debate, making it a community decision rather than leaving it to the research community as it will be the general public that will pay the ultimate penalty of any fallout. This may follow a similar format to a referendum;
- Productivity Commission to report on the full economic impact of xenotransplantation should it be allowed to proceed – including the likelihood of an epidemic;
- A moratorium on all current pre-clinical xenotransplantation studies.

We certainly urge that the (expired) moratorium be extended until such time as these critical measures have been actioned.

Yours sincerely,
Helen Marston
Chief Executive Officer
Humane Research Australia