ROYAL SOCIETY OF NEW ZEALAND RESPONSE TO THE ACART DISCUSSION DOCUMENT ON THE USE OF HUMAN GAMETES AND EMBRYOS IN RESEARCH

The following is the official response submitted on 2nd March 2007 from the Royal Society of New Zealand to the discussion paper released by the Advisory Committee on Assisted Reproductive Technology on the Use of Human Gametes and Embryos in Human Reproductive Research: Determining Policy for New Zealand.

This response was prepared by Dr Kathleen Logan of the RSNZ Policy Unit with substantial input from Fellows, Members and the Council of the RSNZ, in addition to feedback from other relevant people in the science community. The contributing scientists were from Auckland and Otago medical schools, who, in turn consulted colleagues in their own institutes and Australia, as well as people located in other centres. Thus, the response reflects the views of the Royal Society's membership and the science community.

OVERVIEW

The Royal Society of New Zealand, New Zealand's Academy of Sciences, is instituted under an Act of Parliament to promote and advance science and technology in New Zealand. Our role according to our Act includes the provision of advice to government on scientific issues or on issues that may impact on the ability for science to proceed in New Zealand. In providing this advice, we analyse the issues, consult with scientists, technologists and other affected persons and written advice is first ratified by the Council of the Society, made up of elected members representing the Society membership.

In analysing the issues around the use of human embryos in research, we recognise that there is a diversity of spiritual, ethical and cultural feelings among the public regarding the status of embryos. While we respect people's views on these, we also recognise that the current legal status of embryos is that they may be cultured up to day 14 but no longer. This point is a stage in embryonic development that precedes the primitive streak, which is an identifiable specialisation of the inner cell mass of the blastocyst post-hatching and implantation. Before day 14 of development, in vivo, the embryo has the potential to become more than one viable organism (e.g. twin embryos) or could fail to implant, depending on various maternal or embryonic factors at that time of development.

The fact that cells can be removed from embryos at early stages of development (i.e. up to approximately morula stage) enables pre-implantation diagnosis for genetically inherited diseases. Also lines of stem cells can be derived from the inner cell mass of blastocysts and may be used for therapeutic research. In New Zealand, very little research on human embryos is undertaken, yet it is useful to have the ability, for example, to develop stem cell lines so that biomedical research in New Zealand can keep up with international developments, should it be of interest to New Zealand.

Pre-implantation genetic diagnosis (PGD) is permitted in New Zealand under guidelines that limit its use to testing for severe, genetically inherited disease where there is a familial history. To support this medical treatment, we believe there should be facility for therapeutic research to be undertaken to improve such testing. If we are to give rights to undertake a medical treatment in New Zealand, we should enable research that underpins such treatments, as responsible members of the international biomedical research community. Therefore, we recommend that pre-14-day human embryo research in New Zealand be permitted. (In the remainder of this paper, when the RSNZ refers to the 14-day limit, we mean the 'designated day' under the HART Act 2004, i.e. for a human or hybrid embryo, the 14th day after formation or the day on which the primordial streak appears, whichever is first.)

The source of embryos can be a contentious issue. We recommend that all sources of embryos, including 'spare' embryos produced during IVF treatment be allowed to be used for research, providing informed consent for research is given by the donating parties at the time of gamete collection (or a suitable stage thereafter). As with the usual human ethical considerations around informed consent, we recommend that affected donors should be assured that their medical treatment would not be impacted by their decision to donate (or not) their spare embryos or gametes to research.

Regarding frozen embryos, the current rules state that they must be destroyed after 10 years. However, it may be practical to use these embryos for research on freeze-thawing techniques, or other research related to IVF and also for fundamental embryological research, (such as basic biology of embryos, physiology, biochemistry etc), before they were destroyed (or in the process of destroying them). Consent for this research must be obtained prior to the use of these frozen embryos in research.

Considering the potential difference in basic physiology between a 'viable' embryo and one judged to be 'non-viable' at the time when embryos are processed through IVF, it may be advantageous to be able to use embryos that would otherwise be viable. That is, surplus viable embryos produced during IVF that could otherwise be frozen for use in a future embryo transfer procedure could instead be used for research, with consent from the donors. The processes of IVF, PGD and other treatments involving embryos would be enhanced by more research on basic biological processes of the healthy embryo. Allowing research only on 'non-viable' embryos would skew the ability of researchers to gain a good understanding of the biology of viable ones. In this respect, therefore, we recommend that embryos be allowed to be produced specifically for use in research, with informed consent, and providing that any fertility treatment of the donors is not compromised.

ACART's discussion paper has explained current science but has not considered the emergence of new sources of "embryos" which may add further complexity to the current debate. We recommend that any source of embryos should be allowed for research, with the usual ethical approvals and limitations, and that only clinical treatments be subject to debate about the source of embryos.

Following previous policy discussions in 2002 by the Council of the RSNZ, a position was taken to advise government to introduce legislation to ban in New Zealand the implantation of any embryo whose genetic material has been derived from a human somatic cell (i.e. a fully differentiated body cell). The Council also recommended that New Zealand's proposed legislation on artificial human reproduction should be worded to permit appropriate research on human embryonic stem cells by approved laboratories, subject to control by rigorous national ethical and practical guidelines. This policy position still stands.

Answers to specific questions in the discussion paper are below.

Q1. What are your views on whether research, or aspects of research, using gametes should be prohibited, subject to a moratorium, or permitted on a case-by-case basis subject to ethical approval following the development of guidelines?

We think research on gametes should proceed subject to approval by ethics committees. The guidelines to approve research should be based on minimal restrictions (on a case-by-case basis). This is the basis on which other human cell research is undertaken.

Minimal restrictions should be placed on gamete research because haploid cells are simple cells that have less developmental potential than most somatic cells. They are distinct from zygotes and embryos. Therefore, we see no reason for research on haploid cells to be restricted other than that they be obtained via informed consent.

Q2 What are your views on whether research, or aspects of research, using embryos should be prohibited or permitted etc?

We recommend that embryo research be permitted, subject to ethical approvals for the use of human tissue (with informed consent). We suggest guidelines are adhered to, such as the 14-day limit of embryonic development. Where cells are removed from the embryo, or where the embryo is in an abnormal anatomical form that would prevent development of the primitive streak, it may be possible to permit research on those cells for longer than 14 days, subject to ethical approval on a case-by-case basis.

We also recommend that implantation of any modified embryo (genetically, or by somatic cell nuclear transfer or other technique that alters the genetic composition of the embryo), or chimeric embryo, be banned or subject to a moratorium for 5 years. There may be a time in the future when severe, genetically-inherited diseases might be alleviated by some alteration of gene coding, overcoming mal-expression of single-gene mutations or impacting epigenetic factors. However, there is currently no evidence that this is safe for human implantation. Also there needs to be a wider discussion on artificially genetically modified humans before such treatments can be considered (see answer to question 6).

Q3 The discussion paper outlines four reasons for doing gamete and embryo research, including: basic research, fertility and infertility, prevention of hereditary diseases, or curing human diseases in general. What are your views on these?

We believe that research on gametes and embryos for all the purposes outlined above should be allowed. We recommend that all in vitro research should be allowed, subject to the 14-day development limit and other ethical guidelines. Limiting the *purposes* of research allowable (e.g. only fertility research) creates a context in which scientists could disguise the true, or possible alternative, intents of their research. For example knowledge gained in fertility research could usefully contribute to the basic knowledge that enables other treatments such as the cure of another disease. It is arguable that the purpose of the research should not be a factor in determining ethical approval, as knowledge is separable from the uses to which it is put. While there are limits to this argument, we urge caution

against proscribing uses or applications (of knowledge) under which research is permissible.

We recommend that the implantation of an embryo that has been subjected to research, particularly those genetically modified, be banned or subject to a moratorium for 5 years. There may be instances where research on embryos to treat hereditary diseases is undertaken, but we advise caution against the implantation of embryos on which such research has been undertaken, until suitable tests (i.e. on animals) have proven safety and efficacy.

However, we see no reason to ban the research (e.g. genetically altered embryo research up to 14 days' development) that may underpin such future uses. The approval to undertake research can be separated from the consideration of whether any discoveries from that research should be used in clinical treatment. In each case, the usual ethical approvals must be met.

Q4. What are your views on the sources of gametes and embryos for use in research, including: donated non-viable IVF embryos; donated viable IVF embryos; embryos created via IVF specifically for research purposes; embryos created via somatic cell nuclear transfer for research; hybrid embryos created for research; donated gametes.

We do not object to any source of embryos for the use in research in vitro up to the 14-day development limit. We think that informed consent is required from the donors, including donors of gametes that may be used subsequently for the production of embryos or hybrid embryos for research.

It is unlikely that an egg donor will donate specifically for research (as opposed to IVF treatment or some other fertility treatment) due to the invasive and potentially risky medical procedures required of women donating eggs. Such donations would normally only occur when the woman is donating an egg for the purposes of creating an embryo for implantation. In such a case there seems no difference between creating extra embryos specifically for research from her eggs, and using 'spare' embryos created, but not needed, for IVF treatment. In rare cases, an altruistic donor may wish to donate gametes or embryos for research even though they are not undergoing IVF (for example, to contribute to research on a rare genetic disorder from which the donor suffers). In this case, the informed consent should clearly include an accurate indication of the risks to the donor of the medical procedure.

There may be alternative sources of gametes and embryos in the future, and we recommend the use in research be allowed, but not in clinical treatment. Some examples include gametes sourced from foetal material (which, itself, would be subject to ethical approvals for human tissue). This would require and/or contribute to further understanding of oocyte and sperm development. In addition, embryos could theoretically be produced from totipotent cells sourced via novel methods (see 'potential technologies' in section 11 below).

We recommend against the implantation of embryos previously used in research due to the unknown factors impacting embryonic development during novel in vitro treatments. However, if the research exposes the embryo to conditions that are substantially the same as normally permitted IVF conditions and procedures (i.e. not really 'novel' in vitro treatment) then implantation may be justified but special permission would need to be granted on a case-by-case basis, (based on safety).

Q5. What are your views on whether genetic modification of gametes should be prohibited or permitted etc?

Genetic modification of cells, including gametes, may contribute to fundamental scientific knowledge about biochemical, molecular and physiological processes and we do not oppose such modification for use in research.

However, genetically modified gametes should not be used for the production of embryos for implantation, or for other clinical treatments until safety and efficacy are proven.

Q6. What are your views on whether genetic modification of embryos should be prohibited or permitted etc?

We do not object to genetic modification of embryos used solely in research, as this technique may contribute to new embryonic stem cell lines, or other tools for research and it may enable research that contributes to our knowledge of embryonic or human development or diseases. Genetic modification and experimentation, including RNA inhibition, DNA-methylase alteration and other molecular processes, provide particularly useful tools for understanding basic biological functions and pathways of normal- and disease-state cells and embryos. To ban this particular technique for research, when allowing other techniques would appear to be an unequal application of regulation and would unjustly restrict some valuable areas of research.

However, we advise that implantation or other clinical treatments using such embryos be banned, or subject to a moratorium until such time as a cogent and compelling argument is proposed on the benefits and safety of this practice. In addition there are ethical considerations surrounding the permanence of altering hereditable characteristics of humans and impacts on the population (gene pool) and on society (cultural aspects, particularly Whakapapa). For example, altering the heritable genetic identity of an individual has implications for humankind. The consequences are not limited to the individual, but can be transmitted to different societies in subsequent generations. We recommend that if a time came where the safety and efficacy of such therapeutic genetic modification were proven, and New Zealand were to consider allowing them, then it would place them under a moratorium until other nations had reached a similar conclusion. Coordinating an international response to such developments could, in fact, become part of the role of the international oversight panel mentioned in the answer to question 7 below.

We also recommend, as with other embryo research, that the 14-day limit be mandatory, unless it is shown that the genetic modification halts cell division or embryonic development at a stage before the usual 14-day stage (pre-primordial streak stage), in which case approvals may be granted on a case-by-case basis for extended research.

Q7. What are your views on whether the import and export of gametes should be prohibited or permitted etc?

Gametes, as with other human tissues, should only be allowed to be imported and exported to enable research where there are shortages or benefits of exchanging tissue samples. New Zealand, in particular, may suffer from a small number of gamete donors due to the small size of the country's population. It is particularly important to restrict import and export of gametes to countries and institutions that have an 'approved status'.

It would be expected that the export and import be undertaken solely in the spirit of research without commercialisation of the human tissue. Permits should be obtained that limit imports and exports to: instances where a local supply is not available or appropriate; specimens that are subject to biosecurity regulations (e.g. healthy specimens or kept in laboratory containment); and gametes from countries with a regulatory framework that enforces informed consent and guidelines similar to, or more stringent than, those in New Zealand, and acceptable to New Zealand. In cases where anonymous donation has occurred then the gamete should not be used for clinical treatment (i.e. implantation of embryo following IVF, or artificial insemination) since in New Zealand we have laws enabling offspring to gain access to information about their biological parents.

Donors of gametes must provide consent to such export, and be provided with information that their personal data may be de-linked from the sample with the result that their gametes could be used for various kinds of research that they will not be told about (including hybrid embryos for research, for example) but that the gametes will be subject to similar restrictions as in New Zealand. Countries agreeing to imports and exports would need to support, and be subject to, an international oversight panel, to ensure that the ethical guidelines of each jurisdiction are aligned with each other (and acceptable to each other) and enforced in those countries. It may be useful to maintain a list of banned countries or institutions that fail to meet the criteria of ethical oversight. The international union of science academies (ICSU) may be prepared to undertake the role of providing an international oversight panel.

Q8. What are your views on whether the import and export of embryos should be prohibited or permitted etc?

As with question 7, we think it should be allowed on a case-by-case basis subject to need, ethical guidelines in the country of origin and export, and that the embryos not be used for implantation. The latter is because access to information about biological parents, as enforced for children of IVF in New Zealand, may be severely limited if embryos are sourced for implantation from overseas, particularly if data from donating parents is not obtained in the same way as it is in New Zealand. However, research using imported and exported embryos, subject to the recommendations described above (Q7) should be allowed.

Q9. Principle (f) of the HART Act states that the needs, values and beliefs of Māori should be considered and treated with respect. We are interested in your views on how this principle could be incorporated into New Zealand's policy position on gamete and embryo research. What are your views on the tikanga (described) etc.

We know that throughout society a widespread variety of beliefs are held, and within the science community, scientists also hold widespread beliefs which may affect an individual's choice whether or not to undertake research on embryos (or animals or children etc). Māori similarly hold widespread views, as widespread as their roles in society.

The principles outlined in the discussion document, in particular Whakapapa, (genealogical descent of all living things) and Whanaungatanga (support among relatives and obligation to consult with relatives on decisions of a personal nature, such as IVF, and donating embryos for research) may be supported within ethical guidelines associated with the use of embryos in research.

We recommend that, when obtaining informed consent from people who identify with Māori ethnicity, beliefs or culture, the individual be advised that they may consult with their whānau when making their decision on whether to donate embryos, (or undertake IVF). A clinician or scientist should be prepared to provide information to whānau members on the nature of the research or treatment to which the donor is consenting (with permission from the donor, of course, when disclosing information of a personal nature).

With respect to principles such as Wairua and Mauri, attitudes to these may vary as widely as spiritual attitudes of all peoples in society. Allocation of individual identity (or a 'soul', spirit, Wairua or Mauri) to a person may be applied at conception, implantation, quickening (during 2nd trimester of pregnancy), at birth, or any other time, depending on the feelings of the people involved. We can suggest that the needs of Māori in this regard are respected by implementing the principles of informed consent, so that each individual (or individual and their whānau, if relevant) can make a decision based on their own cultural and spiritual feelings.

While Māori views and principles should be considered, they should not be allowed to override the views of beliefs of other cultures or ethnicities, and we feel the above principles of individual (or collective) informed consent, based on the beliefs of the individual involved, will cater for the needs of all peoples.

Q10. Principle (g) of the HART Act states that the different ethical, spiritual and cultural perspectives in society should be considered and treated with respect. How can this be incorporated into NZ's policy position?

Similar to our answer in Q9, the principles of informed consent are respectful of different ethical, spiritual and cultural perspectives of individuals.

As for society, general feelings of many people ('the majority') tend to dictate policy while options for those with alternative views are enabled through freedom of choice.

That is, people can choose to undertake IVF or PGD or not, or to donate embryos or not, based on their spiritual or ethical beliefs about embryos etc. The principle here respects individuals' diversity of opinions, but can not enable all opinions in society to be appeased. Further discussion on ethical, spiritual and cultural perspectives of society is given in section 11 below.

In general, society allows research to proceed because there is inherent good in increasing knowledge (bearing in mind, however, that the *use* of knowledge may have disparate outcomes). In the case of embryo research, benefits may be, for example, fundamental knowledge relating to embryonic development, human disease, or fertility treatments. Benefits may also relate to improvement of (commercially applied) IVF or other fertility treatments, such as PGD. We can not expect to undertake clinical treatments in New Zealand if we fail to contribute to the knowledge required for improvements to such treatments. We are part of the international collaboration of health research and must be responsible for our fair contribution to the sharing of knowledge about human health.

Q11. Do you have any further comments to make that have not been covered in the questions set out above?

Minimal and well-justified regulation of research.

If approval is given to conduct research on embryonic tissue where ethical criteria are met, a fine balance must be struck between the assessment and approval process and research practice, so that progress is not overly hindered. It would be a great shame to approve this promising field of biomedical research, only to stall it in a morass of bureaucracy so the net effect is no progress at all.

Limitations such as moratoria should be well-justified, with built-in, timely reassessment, such as every 5 years, to review new discoveries, technologies and evidence of safety.

Ethical, spiritual and cultural perspectives of society.

Scientists make a distinction between cells, anatomically recognisable body parts and individuals when conducting research, with consequent increasing levels of ethical committee oversight. This can be seen in the light of some assumptions about general views held by members of society.

Virtually all people mourn the death of a person, or grieve over the loss of a body part. However, few consider the day to day loss, death or turnover of bodily cells as warranting concern. The latter is a requirement of healthy living. Religious philosophies and traditional ethnic world views have developed without the knowledge of the existence of cells and the regularity of their death.

Currently, research on cells is undertaken with few ethical concerns, while research on human tissues and people requires increasing levels of human ethics approval. Research on gametes poses very little concern, and research on embryos prior to the formation of anatomically recognisable body parts should similarly pose little concern. However, research after this stage does pose concerns, (due to the existence of anatomically recognisable tissues, namely the primordial streak), and for this reason there is a general consensus among scientists to retain a ban on such research (i.e. post-14 days).

This perspective is dependent on society accepting that the embryo is a mass of cells without the potential to become a human *unless implanted into the uterus of a woman*. The 'potential' for a new human to develop obviously exists at all stages of zygotic and embryonic development but ceases to be a possibility if the embryo is not implanted. Therefore, there is a general consensus among scientists that embryos used in research should not be implanted.

It could be argued that gametes and, indeed, early embryos are shed or turned over in the body like many other cells, and do not necessarily warrant grief or special consideration. Some people believe that a person's soul or life force is in all their cells, a view that precludes blood transfusions and organ donation for those individuals. Society does not hold consensus over this view but respects it by enabling individuals to choose not to have a blood transfusion. This analogy points to the opportunity for individual choice while not restricting the choices of others. Therefore, there is a strong consensus that informed consent should be the basis on which cells or tissues are obtained for use in research, so individuals may express their cultural, ethical and spiritual preferences.

Potential technologies

It has been recommended that the RSNZ alerts ACART to the possibility that all somatic cells may be converted to totipotent cells, without nuclear transfer.

The viability of embryos created by somatic cell nuclear transfer implies that the cytoplasm of the oocyte contains substances that are able to reverse the loss of cellular potency that occurs during development. These substances are likely to be proteins (e.g. demethylases) or possibly RNAs with catalytic properties. The identification of totipotency-producing substances is possible and may occur in the future as technologies already exist to fully catalogue the proteins and mRNAs in a given cell.

If substances that reverse the loss of potency are known, then it may be possible that most somatic cells could be made totipotent by injecting these substances into their cytoplasm. Such totipotent cells would differ from SCNT embryos and all natural embryos, as both their nuclear and mitochondrial DNA would have exactly the same sequence as a living individual. That living individual may therefore benefit from the cell being used to generate cells (or an organ) for therapeutic uses.

This alternative route for stem cell line production may, in future, alter the debate over the use of human embryonic stem cells (which are currently preferred over adult stem cells due to their totipotency), and may even result in a new source of embryos for research.

CONCLUSION

The Royal Society of New Zealand considers the quest for scientific knowledge through research to be a valid and worthwhile endeavour, and supports the use in research of human gametes and embryos from any source, within an ethical framework.

We have provided advice based on a general consensus among researchers involved in embryo or gamete research, reproductive technologies, research ethics, and research regulation. The advice recommends adhering to some fundamental ethical limits, including: the necessity for informed consent from donors of cells or tissues for research; a morphologically-based 14-day limit of in vitro culture of embryos; and the prevention of implantation of embryos that have been used in research. In particular the RSNZ supports a ban or moratorium on implantation of embryos formed by somatic cell nuclear transfer, or those genetically modified. We believe that international exchange of gametes and embryos should be subject to comparable ethical regulatory systems enforced in each corresponding country, and have suggested that an international oversight panel be set up to monitor institutes and legislation. This panel could potentially be provided by the international union of academies of sciences (ICSU).

Finally we hope that the limits on research will be minimal and well-justified, and that the ethical approval system will not overly hinder research, but will enable it to proceed.