

Research Licence Committee Meeting

18 June 2008

21 Bloomsbury Street London WC1B 3HF

MINUTES Item 1

Research Project R0183: The generation of human embryonic stem cells by transferring a human cell into recipient pig eggs

Based at the Clinical Sciences Research Institute, University of Warwick (0305)

Initial Application

Members:

Emily Jackson – Chair, Lay Member
Richard Harries, Lay Member
Maybeth Jamieson, Consultant Embryologist, Glasgow Royal Infirmary
Neva Haites, Professor of Medical Genetics, University of Aberdeen

In Attendance:

Trish Davies, Director of Regulation/
Deputy Chief Executive
Chris O'Toole, Head of Research Regulation
Claudia Lally, Committee Secretary

Providing Legal Advice:

Mary Timms, Field Fisher Waterhouse

Conflicts of Interest: members of the Committee declared that they had no conflicts of interest in relation to this item.

The following tabled papers were considered by the Committee:

- papers for the Committee (166 pages)
- one paper was tabled: legal advice for the Committee (5 pages).

1. The papers for this application for a research licence were presented by Chris O'Toole, Head of Research Regulation. Dr O'Toole informed the Committee that this proposed project of research would involve deriving stem cell lines which carry the genetic mutations responsible for producing a serious heart disease called cardiomyopathy. The cell lines would be derived by obtaining nuclei from skin cells taken from patients suffering from the disease. These nuclei would be inserted into pig oocytes which have had their nuclei removed. These will then be activated to produce embryos. These embryos will be cultured to the blastocyst stage, at which point the stem cell lines would be derived. The majority of the mitochondrial DNA of these stem cells will initially be of pig origin. Different experiments will then be performed to increase the proportion of human mitochondria in the stem cells; some cells will have only human mitochondrial DNA. Further experiments will then be carried out to compare cellular function in

these different variations; for example cells containing a mixture of pig and human mitochondrial DNA would be compared with cells where the mitochondrial DNA is fully human. The stem cells generated in the research will be also be compared to both embryonic stem cells derived from fertilised oocytes and induced pluripotent stem cells derived from somatic cells.

2. Dr O'Toole reported that the Person Responsible has stated on his application that the study falls under three research purposes under the Human Fertilisation and Embryology (Research Purposes) Regulations 2001 ("the Regulations"), paragraphs 2(2)(a),(b) and (c):

- to increase knowledge about the development of embryos
- to increase knowledge about serious disease; and
- to enable any such knowledge to be applied in developing treatments for serious disease.

Dr O'Toole further informed the Committee that the research application was sent to three peer reviewers all of whom recommended that the application be accepted. Of the three reviewers, one agreed that the research should be licensed under the three research purposes selected by the Person Responsible. Another peer reviewer added a fourth research purpose: "to increase knowledge about the causes of congenital disease" (Schedule 2 to the Human Fertilisation and Embryology Act 1990, paragraph 3(2)(b)). The third peer reviewer agreed with the Person Responsible that the research should be licensed for the research purposes stated in paragraphs 2(2)(a) and (b) of the Regulations, but disagreed that it would come under the research purpose stated in paragraph 2(2)(c) of the Regulations.

3. Dr O'Toole stated that the research project had been approved by the Medical School's Ethics Committee and the University of Warwick's Animal/Human Ethics Committee. Local Research Ethics Committee (LREC) approval had not yet been sought, because the LREC had indicated that it would require the project to have HFEA approval before it could be considered. Dr O'Toole also confirmed that the Person Responsible for the project had satisfactorily completed the Person Responsible Entry Programme (PREP) assessment and, by virtue of his previous research experience, was clearly suitable to be the Person Responsible for this project. She reported that the premises for the proposed research are situated in the University Hospital in Coventry and the inspection of the premises found them to be secure and suitable for the research. Dr O'Toole drew the Committee's attention to the findings of the inspection visit carried out on 18 March 2008 and highlighted the fact that no issues of concern were raised at the inspection. Dr O'Toole informed the Committee that the licence fee for this application has been paid and that the Nominal Licensee was, in the judgement of the Executive, a suitable person to hold a licence.

4. The Committee asked Dr O'Toole whether the HFEA has received views from the public in relation to this particular application and Dr O'Toole replied that it had not.

The members of the Executive withdrew while the Committee discussed the case and reached a decision

The Committee's Decision

5. The Committee agreed that the scientific case for this research project was well and fully presented in the application and that the comments by the peer reviewers were dealt with in depth by the Person Responsible in his reply. The Committee further noted the Person Responsible's full response to the issues raised by the inspection team at the recent inspection visit. This response was appended at pages 16 to 17 of the inspection report.

6. The Committee noted that the project has not yet received Local Research Ethics Committee approval. However, the Committee took into account that it would not be legal to commence this research without such approval. For this reason the Committee decided that this issue would not prevent them from granting a licence if all other points were satisfied; rather, the issue could be addressed by way of adding a licence condition.

7. The Committee considered whether this research project is one for which a licence may be granted under the Human Fertilisation and Embryology Act 1990. The Committee decided that that this precise project of research involves the creation and use in research of a "live human embryo" within the meaning of section 1 of the Human Fertilisation and Embryology Act 1990, and that, consequently, this research project is prohibited except in pursuance of a licence granted by the Authority.

8. In reaching this decision, the Committee followed the approach set out by the House of Lords in the case of *R(Quintavalle) v the Secretary of State for Health [2003] UKHL 13*. In particular, the Committee took into account the following points:

a) in enacting the 1990 Act, Parliament opted for a strict regime of control in this area, and did not intend any activity within this field to be unregulated: there was to be no free for all;

b) an embryo created by this method falls within the same genus of facts as other embryos covered by the 1990 Act, in particular, such an embryo has a full human nuclear genome and is live.

9. The Committee identified the activities under consideration as the storage of embryos, the creation and use of embryos for research and the derivation of

human embryonic stem cell lines. The Committee agreed that these activities are not prohibited under the Human Fertilisation and Embryology Act 1990.

10. The Committee considered whether the activities covered by the project of research appear either necessary or desirable for one or more of the purposes as set out in paragraph 3(2) of Schedule 2 to the 1990 Act or in paragraph 2(2) of the Human Fertilisation and Embryology (Research Purposes) Regulations 2001. The Committee considered the stated aims of the project and the evaluation of the project by the three peer reviewers and agreed that in the context of the project of research these activities appear to be necessary or desirable for the following purposes:

- Human Fertilisation and Embryology (Research Purposes) Regulations 2001:
2(2)(a) to increase knowledge about the development of embryos.
- Human Fertilisation and Embryology (Research Purposes) Regulations 2001:
2(2)(b) to increase knowledge about serious disease

In reaching this decision the Committee took into account the fact that these two purposes were the only ones selected by all three peer reviewers. The Committee noted that there may be some ambiguity in the word “applied” in the research purpose stated in paragraph 2(2)(c) of the Regulations: “to enable any such knowledge to be applied in developing treatments for serious disease”. The Committee noted that, while in the future, the knowledge gained may be applied in developing treatments, it was not envisaged that the knowledge developed in the course of this research project would be applied in treatments for disease during the duration of the research licence. This point notwithstanding, however, the Committee felt that it was important to note that the ultimate purpose of the knowledge to be acquired in the research was its eventual application in the treatment of serious disease.

11. The Committee based its decision that the research was necessary or desirable for the research purposes stated in paragraphs 2(2)(a) and (b) of the Regulations on the statements in all three peer reviews that the proposed research will address important issues in the advancement of knowledge about the development of embryos and about our understanding of serious disease. In particular, the Committee singled out two aspects of the research. Firstly, the Committee considered the proposed generation of stem cell lines bearing genetic mutations which cause serious cardiac diseases in later life to be likely to provide a resource for further studies. The Committee noted that generating such lines would allow studies to increase knowledge about the development of cardiomyopathy, for example by identifying the time of onset of abnormalities in cardiomyocyte physiology. The other aspect of the research which was cited by the Committee in support of its decision that the research was necessary or

desirable for the purposes stated in paragraphs 2(2)(a) and (b) of the Regulations, was the proposed study of the role of mitochondrial DNA in sustaining or inhibiting cellular function in early embryonic development, and the proposal to create a stem cell from a hybrid embryo, but with fully human mitochondrial DNA. The Committee agreed that the factors to be explored in these experiments were fundamental to the development of knowledge about the mechanisms of early embryo development.

12. In making its decision that the research was necessary or desirable for the research purposes stated in paragraphs 2(2)(a) and (b) of the Regulations, the Committee also took into account the proposed use of oocytes from pigs and agreed that this aspect of the research was necessitated by the fact that human eggs are donated to research only in small numbers. The use of non-human eggs is therefore the only way that this particular research project could take place.

13. The Committee agreed that they were satisfied that the proposed research could not be undertaken without the creation and use of human embryos. In making this decision the Committee took into account the comments by the three peer reviewers about the issues raised by the use of induced pluripotent (iPS) cells. The Committee noted the comments (at page 147 of the Committee papers) by one of the peer reviewers that although induced pluripotent cells may be a future alternative, it has not been possible to derive such cells from cardiac patients, and it is consequently not known whether cardiomyocytes derived from them will reflect the disease phenotype. Furthermore, the Committee noted that the use of viral agents in the creation of iPS cells may rule out such cells from use in developing treatments for the disease. The Committee also considered the comments by the peer reviewers on the possible use of adult stem cells for this research, and noted the comment (at page 148 of the Committee papers) by one of the peer reviewers that the only candidate adult stem cells would be cardiac progenitor cells. The reviewer suggested that the technology for the use of such cells is still new and not yet robust and that obtaining such cells would require a cardiac biopsy to be performed.

14. In coming to the conclusion that pluripotent cells derived from somatic cells would not be suitable substitutes in this proposed project of research the Committee also noted that the proposed project may contribute towards the development of the use of pluripotent cells in future projects of research, in that it aims to compare the stem cells created using pig oocytes with pluripotent stem cells derived from somatic cells.

15. The Committee considered the patient information and consent forms and agreed that the header to the patient information leaflet (at pages 109 and 110 of the Committee papers) requires to be changed to include reference to the fact that the research involves the creation of hybrid embryos using pig oocytes. At present, this information is not introduced until the fourth paragraph of the leaflet,

but the Committee felt that this aspect of the research should be made clear at the outset. Subject to this change, the Committee agreed that it was satisfied with the patient information and consent forms.

16. The Committee agreed that, based on the information in the inspection report and the comments made by Dr O'Toole today about the premises, the Person Responsible and the Nominal Licensee, the requirements for the grant of a licence under Section 16 of the Human Fertilisation and Embryology Act 1990 were satisfied, and decided to grant a licence for the research for a period of one year. A one year licence was granted (rather than the 3 years requested by the Centre) to reflect the fact that this is a licence for a new research project based at new premises and with a Person Responsible not previously licensed by the HFEA.

17. The Committee decided that the following condition is to apply to the licence:

- Research work is not to commence until such time as the Executive has received evidence that the research has been approved by a Local Research Ethics Committee

Signed..... Date.....
Emily Jackson (Chair)