LC Min

Minutes of Licence Committee of 16 June 2004 at 21 Bloomsbury Street at 09.00 a.m.

Present

Members [redacted]

Executive [redacted]

Centre:	**Newcastle Fertility Centre at LIFE,**
Centre No:	**0017**
Person Responsible:	**Professor Alison Murdoch**

Initial Application for a Research Licence: Derivation of human embryonic stem cell lines using Nuclear transfer and Parthenogenetically Activated Oocytes

1. Apologies were received from [redacted]

2. [redacted] was present throughout the meeting of the Licence Committee to provide clinical advice. [redacted] provided written clinical / scientific advice to the Licence Committee and was present for part of the meeting to provide further clinical / scientific advice.

3. [redacted] declared that the Centre at which he works also holds a research licence involving the derivation of human embryonic stem (hES) cells.

4. [redacted] presented the Centre's application for a research licence to create embryos by cell nuclear replacement and by parthenogenetically activating oocytes. These embryos will then be used to derive embryonic stem cell lines.

5. The Committee noted that cell nuclear replacement (CNR) is a process whereby the nucleus of an adult human cell is transferred into a donated egg that has had its nucleus removed. The egg is then artificially activated to create an embryo. Parthenogenesis (Greek for *virgin birth*), is a technique in which an egg cell is activated without

being fertilised by a sperm cell i.e. a human egg cell develops into an embryo without the genetic input from sperm.

6. CNR could, potentially, be used to produce cells / tissues for patients that would not be rejected by their immune system. A somatic (adult) cell would be taken from the patient and injected into an enucleated donor egg and after artificial activation the embryo would be cultured to the blastocyst stage. Embryonic stem cells would be isolated from the inner cell mass of the blastocyst and differentiated *in vitro* to produce cells or tissues for transplantation. Using these cells / tissues in therapy would have advantages over using embryonic stem cells isolated from embryos created by IVF, because the genetic material would be derived from the person to be treated and so would not be rejected by their immune system.

7. The Committee noted that the House of Lords Select Committee Report on Stem Cell Research, published in February 2002, stated: "*Although there is a clear distinction between an IVF embryo and an embryo produced by CNR (or other methods) in their method of production, the Committee does not see any ethical difference in their use for research purposes up to the 14 days limit. The Committee concludes that, even if CNR is not itself used directly for many stem cell-based therapies, there is still a powerful case for its use, subject to strict regulation by the HFEA, as a research tool to enable cell-based therapies to be developed. However, as with embryos created by IVF for research, CNR embryos should not be created for research purposes unless there is a demonstrable and exceptional need which cannot be met by the use of surplus embryos.*"

8. The Committee also noted that in its response to the House of Lords Select Committee Report, published in July 2002, the Government stated:
"*… …. All embryos, however created, deserve the same protection and that they are subject to the controls and safeguards of the 1990 Act and 2002 Research Purposes Regulations. … … CNR may prove to be a powerful tool in our understanding of how cells work and how they may be controlled to repair disease and injury. However … … The Government believes that the existing controls over embryo research in the 1990 Act and by ethics committees are sufficiently robust to allow the HFEA to oversee this aspect of embryology.*"

The Legal Framework

9. The HF&E Act 1990 states that licences shall not be granted for research on human embryos unless the Authority is satisfied that the project of research is "*necessary or desirable*" for one or more of the purposes set out in Schedule 2 to the HF&E Act (as amended by the Research Purposes Regulations 2001). The HF&E Act further requires that such licences can only be granted if the Authority is satisfied that

any proposed use of embryos is "*necessary for the purposes of the research*".

10. The HF&E Act 1990 prohibits the *"replacing of the nucleus of a cell of an embryo with the nucleus taken from a cell of any person, embryo or subsequent development of an embryo"*. Cell nuclear replacement is excluded from this prohibition since it involves nuclear substitution into an egg, not an embryo. However, as the technique involves the creation and use of embryos outside the body, it falls within the terms of the HF&E Act and thus comes under the jurisdiction of the HFEA.

11. In response to the passing of the Research Purposes Regulations (2001) the ProLife Alliance applied for a judicial review, contending that embryos created by cell nuclear replacement were outside the scope of the 1990 Act, and therefore unregulated in the UK. On 15 November 2001, the High Court agreed with the ProLife argument.

12. The Government immediately introduced legislation to cover cell nuclear replacement and similar techniques. The legislation outlawed any attempts at reproductive cloning,by making it unlawful to transfer to a woman an embryo created other than by means of fertilisation.The Human Reproductive Cloning Act was passed on 4 December 2001.

13. In an appeal against the earlier ruling of the High Court, the Government was successful with the effect that embryos created by cell nuclear replacement are within the scope of the 1990 Act. The Court of Appeal ruled, in January 2002, that an embryo is an embryo, whether created by fertilising an egg with sperm, or by cloning. Furthermore, in allowing the Government's appeal, Lord Phillips, the senior civil judge in England, said: *"I hold that an organism produced by CNR falls within the definition in the Act."*

14. ProLife Alliance petitioned the House of Lords and was granted leave to appeal. The case went to the House of Lords and judgement was given against the ProLife Alliance in April 2003.

Research Application

15. The Committee noted that the Centre is proposing to use eggs donated from women undergoing *in vitro* fertilisation and women having routine gynaecological procedures e.g. hysterectomies and / or oophorectomies. The adult nuclei to be used for transfer will be obtained from three sources:
    - Stem cell lines – nuclei from cells from the Centre's existing derived ES cell line.
    - Women undergoing a gynaecological procedure – a skin biopsy will be taken from a woman undergoing a routine gynaecological operation.
    - A patient with Type 1 diabetes – a skin biopsy will be taken from one patient who has Type 1 diabetes.

After nuclear transfer the egg will be activated using different chemical, mechanical, and/or electrical stimuli. To derive parthenotes, the Centre is proposing to artificially activate eggs using different chemical, mechanical, and/or electrical stimuli and then culture the resulting embryos until they reach the blastocyst stage.

16. The Committee noted that the women being asked to donate oocytes prior to undergoing a gynaecological procedure will not be asked to take stimulatory hormone treatment as the oocytes collected will be matured *in vitro* prior to be used in the research project.

17. The Committee noted that the use of embryos created by cell nuclear replacement and by parthenogenetically activating oocytes will be used under the Centre's existing research licence (R0145) to derive human embryonic stem cell lines and to carry out epigenetic studies on the resulting embryos. Therefore, the Committee noted that if a licence was granted for this research project then the Centre's existing research licence (R0145) would need to be varied to include the use of embryos created by cell nuclear replacement and the creation of embryos by parthenogenetically activating oocytes.

18. Creating embryos by cell nuclear replacement and the derivation of stem cell lines from these embryos will allow researchers to find ways of switching back adult cells to the same stage as early embryonic cells so that they can be grown into whatever tissue is required by the patient to treat their disorder. In addition creating embryos using nuclei taken from a diabetic patient will allow the Centre to derive a stem cell line from a patient with a specific disease which will allow researchers to understand the underlying mechanisms of the disease and develop new therapeutic methods.

Licensing History

19. The Committee noted that the Centre currently has two research licences from the HFEA. One is to study the epigenetics of preimplantation embryos and derived stem cells (R0145), this project was first licensed on 1 August 2003 and is licensed until 31 July 2006, and one to investigate the effect of blastomere removal for preimplantation genetic diagnosis on subsequent embryonic development (R0122) which was first licensed in 2000 and for which a further 3 year licence was granted in March 2003. However, the Committee noted that the Centre has had a HFEA licence to use human embryos to derive stem cell lines since 2000 (R0126).

20. The Committee noted that the Centre has submitted all necessary progress reports. The Centre has submitted 4 progress reports relating to the research project R0126 covering the period from 19/10/00 to 23/06/03. Originally the Centre has estimated that it would use 290 embryos per annum in this project of research.

- Progress report 1: 19/10/00 – 15/05/01
  73 embryos were donated to the research project during this period; 51 were suitable for use in research and were used to familiarise the researcher with the handling of human embryos.
- Progress report 2: 16/05/02 – 31/12/02
  207 embryos were donated to the research project during this period; 51 (25%) reached the blastocyst stage. 5 of the blastocysts were used to optimise microsurgical techniques. The inner cell mass of all the remaining blastocysts were removed. No stem cell lines were derived.
- Progress report 3: 01/01/02 – 03/05/02
  160 embryos were donated to the research project during this period; 91 (57%) reached the blastocyst stage. 20 of the blastocysts were explanted whole into culture. The inner cell mass of all the remaining 71 blastocysts were removed. No stem cell lines were derived.
- Progress report 4: 01/12/02 – 23/06/03
  458 embryos were donated to the research project during this period; 114 (25%) reached the blastocyst stage. The inner cell mass of all the blastocysts were removed. One human embryonic stem cell line was successfully derived. A sample of this line was deposited into the UK Stem Cell Bank on 19 May 2004.

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21. The Centre has submitted one progress report relating to the research project R0145 covering the period from 23/06/03 until 11/02/04. During this period 149 fresh embryos and 79 frozen embryos were donated to this research project. 33 (22%) of the fresh embryos and 17 (26%) of the frozen / thawed embryos reached the blastocyst stage. One serum-free human embryonic stem cell line was derived in August / September 2003 but did not survive in culture. The Committee noted that this progress report had been reviewed by a Member of the Authority and was deemed to be satisfactory.

22. The Committee also noted that there are no additional conditions on either of the Centre's two research licences nor are there any additional conditions on the Centre's treatment licence.

Peer Review

23. The Committee noted that the research application had been reviewed by two, non-British, external peer reviewers and that both reviewers recommended that the project be licensed.

24. The reviewers did raise a few issues mainly relating to the lack of detailed protocols in the Centre's original application. These issues were addressed by the Centre and sent to the peer reviewers for further comment. One of the reviewers stated that as he had recommended that the project be licensed in the first instance he did not wish to comment further on the revised protocols. The second

reviewer stated that he was satisfied with the revised information submitted by the Centre.

25. The Committee noted that the peer reviewers considered that the proposed work was necessary or desirable for specified purposes and had agreed that the staff team are suitably qualified, and that the scientific methodology is sound.

HFEA Inspection

26. The Committee noted the report of the inspection of the Centre held on 27 May 2004 which was found to be satisfactory.

27. The Committee noted the following issues raised during the Centre's inspection:
    - The role of the Person Responsible – it was noted that Professor Murdoch is being proposed as the Person Responsible (PR) for this new project of research and that she is also PR of the centre's treatment licence and of one of the Centre's other research licences (R0145). It was discussed whether these roles should be separated in order to avoid any conflict of interest that might arise if the 2 roles are held by one person. The Committee noted that the Centre has recently recruited a Research Nurse, who will be in post by August 2004. This person will be responsible for discussing research with patients and, if applicable, obtain their consent to the donation of gametes and / or embryos to the Centre's research projects.
    - The scientific inspector asked for more detailed protocols to be submitted. The Centre complied with this request and the Scientific Inspector has stated that she is happy with the revised protocols.
    - The number of embryos donated to research by individual couples. The Committee noted that the Centre has explained that cryopreservation is discussed with all patients and that the Centre's policy is only to freeze embryos if there are at least 4 embryos of good quality. The Committee also noted that the Centre had stated that some patients elect not to have any surplus embryos cryopreserved, even if of good quality. This is partly influenced by the fact that the NHS does not fund the cryopreservation of embryos. The Committee considered the Centre's policy of only freezing embryos if at least 4 good quality embryos were available may have an impact on the selection of embryos for research. The Committee asked for this to be further investigated.

28. The Committee noted that the Centre works closely with PEALS (Policy, Ethics and Life Sciences) Research Institute at the International Centre for Life. Professor Erica Haimes, who leads PEALS, and Professor Murdoch have a joint Wellcome Trust grant to study patients' views on donating embryos for research on preimplantation genetic diagnosis and stem cell therapies and that the HFEA has developed a patient questionnaire which will be used to

gather evidence about patients' experiences as part of the inspection and licensing process.

Public Opinion

29. The Committee noted the correspondence received by the HFEA from members of the public regarding this application. Correspondence had been received form the following individuals and / or organisations:

30. The Committee noted that a number of issues were raised including:

Key issue	No. of responses (%)
Knowledge gained through 'therapeutic cloning' could facilitate 'reproductive cloning'	9 (47%)
Creation of embryos for research is unacceptable	14 (74%)
Exploitation of women	6 (32%)
Shortage of human eggs (for use in treatment)	2 (11%)
Commercialisation of gametes and embryos	7 (37%)
Proposed work to be undertaken in a fertility centre – conflict of interest	4 (21%)
Excess number of embryos would be used	3 (16%)
Unethical to embark of research which has little chance of success	8 (42%)
HFEA should await an international ban on 'reproductive cloning'	8 (42%)
Cell lines derived from cloned embryos could be dangerous	3(16%)

Key issue	No. of responses (%)
Embryos would be 'killed'	1 (5%)
House of Lords Select Committee stated that embryos should only be created by CNR if 'exceptional need' – the HFEA should adopt this criteria	1 (5%)
Creation of embryos by parthenogenesis is unethical. These embryos are probably not viable therefore creation of non viable embryos goes against the 'special status of embryo' upon which the HF&E Act is based	1 (5%)

31. The Licence Committee noted that the HF&E Act 1990 permits the creation of embryos for research. It was also noted that the creation of embryos for research may only be carried out if the researchers have the effective consent of each person whose gametes are to be used to bring about the creation of the embryo and to the use of that embryos for research purposes.

32. The Committee discussed whether the knowledge gained through this research project could be used to facilitate 'reproductive cloning'. The Committee noted that the Human Reproductive Cloning Act 2001 prohibits "*the replacing in a woman a human embryo which has been created otherwise than by fertilisation*", therefore 'reproductive cloning' is illegal in the UK. The Committee agreed that the fact that technology might be misused outside of the UK should not represent an absolute prohibition on the Licence Committee's ability to grant a licence in accordance with the statutory criteria.

Activities to be authorised

33. The Licence Committee discussed the three activities of the proposed research project and whether these were necessary or desirable for one or more of the following purposes –

(2) (a) Promoting advances in the treatment of infertility;
(b) Increasing knowledge about the causes of congenital disease;
(c) Increasing knowledge about the causes of miscarriages
(d) Developing more effective techniques of conception; or
(e) Developing methods for detecting the presence of gene chromosome abnormalities in embryos before implantation
(f)(i) Increasing knowledge about the development of embryos,
(ii) Increasing knowledge about serious disease, or
(iii) Enabling any such knowledge to be applied in developing treatments for serious disease.

34. In reference to the first activity to derive human embryonic stem (hES) cell lines from human embryos created by the transfer of nuclei taken from the Centre's existing hES cell line into enucleated oocytes, the Committee was satisfied that this activity was necessary or desirable

for "*increasing knowledge about the development of embryos*". In making this decision the Committee noted the opinion of the peer reviewers.

35. In reference to the second activity to derive human embryonic stem (hES) cell lines from human embryos created by the transfer of nuclei taken from skin biopsies from women undergoing gynaecological procedures into enucleated oocytes, the Committee was satisfied that this activity was necessary or desirable for "*increasing knowledge about the development of embryos*" and for "*enabling any such knowledge to be applied in developing treatments for serious disease*". In making this decision the Committee noted the opinion of the peer reviewers.

36. The Committee then discussed whether the proposed use of embryos was necessary for the purposes of research. The Committee agreed that it was satisfied that the use of embryos was necessary for the purpose of "*increasing knowledge about the development of embryos*" and for "*enabling any such knowledge to be applied in developing treatments for serious disease*". In making its decision the Committee accepted the opinion of the peer reviewers that this work must be done in humans. The Committee was satisfied that the proposed use of embryos, created by CNR, is necessary for the purposes of the research as the creation of embryos by CNR is the only way to enable hES cell lines to be derived which will be antigenically matched to the recipient. In addition the Committee noted that this research will enable the researchers to gain knowledge about cell reprogramming and non-controlled differentiation of human stem cells which, again could not be achieved by using another model. Therefore, the Committee was satisfied that there was a demonstrable and exceptional need to create embryos through CNR as the aims of the research could not be achieved by any other means.

37. The Committee discussed the proposed number of oocytes to be used in the project of research and agreed that the number of oocytes to be used is proportionate for the proposed project of research but that this should be kept under review through the receipt and analysis of regular progress reports.

38. In reference to the third activity to derive human embryonic stem (hES) cell lines from human embryos created by the transfer of nuclei taken from skin biopsy from a patient who has Type 1 diabetes, the Committee discussed whether this activity was necessary or desirable for "*enabling any such knowledge to be applied in developing treatments for serious disease*" and whether the use, and creation of embryos by CNR, was necessary for this purpose of research. The Committee noted the correspondence received from [redacted] which had included a report entitled "*In search of a cure for diabetes: an evaluation of current research avenues*". This report stated that:

" *Significant progress has been made in the transplant of human pancreatic tissue. However, this procedure is only available to a small minority of diabetics. ..... Researchers are now looking at alternative sources .... Including* [material] *taken from animals and ... generated from embryonic and adult stem cells.* The report concluded that there are serious dangers associated with implanting material derived from hES cell lines as such implants have displayed uncharacterised growth and more promising results have been achieved using material derived from either adult stem cells or from animal sources.

39. The Committee was also advised by its clinical / scientific advisor that: "*Stem cell lines derived from embryos created from nuclei taken from skin cells of a patient with Type 1 diabetes will not provide a resource that is currently the best course for progressing research into our understanding of the cause of, or appropriate treatments for, this disease. These embryos and stem cells are likely to contain DNA with multiple genetic variants (polymorphisms) which taken together with environmental factors might have contributed to the development of the disease in this patient. However, embryos or stem cells derived from embryos of one single affected patient will, with current technology, not allow us to gain sufficient additional further knowledge to currently justify the use of embryos".*

40. The Committee agreed that it could not, at this time, be satisfied that this activity is necessary or desirable for the purposes set out in the HF&E Act 1990 (as amended). Therefore the Committee agreed that it would not grant a research licence for this activity but would adjourn and reconsider the application for this activity upon receipt of independent expert opinion on the genetics of diabetes and whether the use of hES cell lines derived from embryos created by CNR using the nuclei taken from a cell of a patient with Type 1 diabetes would be necessary or desirable for increasing the knowledge about this disease or enabling such knowledge to be applied in developing treatments for serious disease.

41. The Committee was advised that, if the statutory tests are satisfied, the Committee has discretion as to whether to grant a Licence and that the discretion must be exercised in accordance with normal Public Law principles.

42. The Committee discussed the Centre's Patient Information and Consent Forms and highlighted particular areas of concern. In particular the Committee asked that the following changes be made:

- The patient information on the future feedback of information obtained following tests on stem cell lines needs to be amended to state: "*It is important that you appreciate that any cell lines derived from your donated embryos carry your genes and future research on these cell lines may include genetic analyses. For instance researchers may determine the genetic make-up of the stem cell*

lines (a process called 'finger printing'). However the researchers will not have access to details to link this information to you personally.
It is possible that tests performed on your stem cell line may reveal information about your health status. You can choose to receive i) no feedback under any circumstances; ii) feedback on clinically confirmed results of analytical tests for conditions [a] for which there are treatment options either currently available or potentially available in the future [b] which have no known current treatment options. Both partners in the donating couple will be offered these choices.

- The sentence "*For some eggs will take out the nucleus containing your genetic material and replace it with the nucleus from someone else into the egg*" should be amended to read "*For some eggs will take out the nucleus containing your genetic material and replace it with the nucleus* ***taken from a cell*** *from someone else into the egg.*"
- The last line "*Thank you for agreeing to take part in this important research*" should be removed from the end of the consent form.
- The consent form should be amended in line with the MRC consent form for use for patients donating gametes / embryos for the derivation of hES cell lines.

43. The Committee discussed the role of the Person Responsible and noted that it is proposed that the Person Responsible position would be held by the same person as that of the treatment licence. The Committee noted that the Centre had appointed a Research Nurse who would have responsibility for discussing and obtaining patients' consent to research. However, the Committee noted that some of the women being asked to participate in this research project would be general gynaecology patients and would, therefore, not necessarily see the Research Nurse. In addition some of these patients will be under the care of Professor Murdoch in her role as a Consultant Gynaecologist. Furthermore, due to the Committee's concern regarding the Centre's freezing policy, it considered that the separation of the role of Person Responsible was even more important. The Committee was concerned to avoid any conflict of interest arising out of Professor Murdoch's several roles with regard to this project and the treatment service at Centre 0017. The Committee felt that it would be difficult for one person to carry out the duties of Person Responsible in relation to both treatment and research. The Committee considered that the duties should be carried out by separate individuals for the Research Licence and the Treatment Licence.

44. The Licence Committee was of the opinion that it did not have sufficient information to enable it to determine the application for the grant of a new research licence. The Committee agreed that it would adjourn and reconsider the application upon receipt of expert opinion on the genetics of diabetes and whether the use of hES cell lines derived from embryos created by CNR using the nuclei taken from a cell of a patient

with Type 1 diabetes would be necessary or desirable for increasing the knowledge about this disease or enabling such knowledge to be applied in developing treatments for serious disease.

45. The Committee agreed that the Centre should be invited to submit revised Patient Information and Consent Forms taking account of the matters referred to in paragraph 42 (above). The revised documentation will then be taken into account when the Committee meets again to make a determination on the application

46. The Committee also agreed that the Centre should be informed that the Committee did not think that it would be appropriate to grant a licence with the same Person Responsible as in relation to the Centre's Treatment licence. The Committee felt that the Centre should have the opportunity to submit a revised application nominating a different individual as Person Responsible. If the Centre is not minded to submit a revised application, the Centre should have the opportunity to make further written submissions addressing the Committees concerns about there being one Person Responsible for both licences. The revised application or written submissions will then be taken into consideration by the Committee when it next meets.

47. As regards the application for variation of the existing research licence (R0145), the Committee agreed that it would be inappropriate to consider the application for variation in isolation from the application of the grant of a new licence. The Committee also had the same reservations about the fact that the Person Responsible under the Centre's Treatment licence is the same as under Research Licence (R0145). The Committee was particularly concerned that the proposed variation would involve the use of embryos created by CNR and by parthenogenesis under the existing research licence. The Committee agreed that the Centre should be informed that the Committee did not think it would be appropriate for the existing research licence to be varied to include these activities whilst the Person Responsible under licence R0145 remains the same as under the Centre's Treatment licence. The Committee considered that the Centre should have the opportunity to submit a revised application for variation of Research Licence (R0145) nominating a different individual as Person Responsible. If the Centre is not minded to submit a revised application for variation, the Centre should have the opportunity to make further written submissions as outlined in paragraph 47 above,

Signed: [redacted] Date: 23.06.04

[redacted] (Chair)