Research Licence Inspection Report

Project Title	**Derivation of human embryonic stem cell lines using nuclear transfer and parthenogenetically activated oocytes**
Research licence no	R0152
Licence expiry date	31 July 2008 (Renewal)
Centre Name	**Newcastle Fertility Centre at Life**
Centre Number	0017
Centre Address	Bioscience Centre, International Centre for Life, Times Square, Newcastle upon Tyne, NE1 4EP
Person Responsible	Professor Alison Murdoch
Nominal Licensee	Dr Mary Herbert
Donating treatment centres	0017
Inspection date	15 May 2008
Licence Committee Date	18 June 2008
Inspector(s)	Wil Lenton Andrew Leonard Janet Kirkland
Fee Paid - date	Yes

About the Inspection:
The purpose of the inspection is to ensure that centres are providing a quality service for patients in compliance with the HF&E Act 1990, Code of Practice, licence conditions and directions.

The report is used to summarise the findings of the inspection highlighting areas of firm compliance and good practice, as well as areas where further improvement is required to improve patient services and meet regulatory standards. It is primarily written for the Licence Committee who make the decision about the centre's licence renewal application. The report is also available to patients and the public following the Licence Committee meeting.

This report covers the period between 01/01/2007 and 31/12/2007.

Brief Description of the Projects

Project **R0152** entitled "**Derivation of human embryonic stem cell lines using nuclear transfer and parthenogenetically activated oocytes**" has been licensed since 2004.

The lay summary of the project is as follows:

It is recognised that human embryonic stem cells offer a great potential for therapies for many diseases such as diabetes. These stem cells are derived from embryos which are created for IVF treatment but which are not suitable for treatment. If stem cell treatments are to reach their full potential we need to derive stem cell lines which are genetically similar to the recipient so they will not be rejected. This may require the application of techniques such as nuclear transfer and parthenogenic activation. Nuclear transfer involves the transfer of genetic material from adult skin cells to eggs which have had the cell's nucleus removed. Parthenogenic activation involves an egg being artificially stimulated by chemical or electronic means in order to make the egg start embryo development. The present application is to undertake some of the initial studies that are needed to understand methods that will develop this technology.

The Person Responsible considers that project is necessary or desirable for the following purposes:

- Increasing knowledge about the development of embryos
  Human Fertilisation and Embryology (Research Purposes) Regulations S2(2)(a)
- Increasing knowledge about serious disease
  Human Fertilisation and Embryology (Research Purposes) Regulations S2(2)(b)
- Enabling any such knowledge to be applied in developing treatments for serious disease
  Human Fertilisation and Embryology (Research Purposes) Regulations S2(2)(c)

However, the peer reviewer stated that that the research was necessary or desirable for the following purposes:

- Increasing knowledge about the development of embryos
  Human Fertilisation and Embryology (Research Purposes) Regulations S2(2)(a)
- Enabling any such knowledge to be applied in developing treatments for serious disease
  Human Fertilisation and Embryology (Research Purposes) Regulations S2(2)(c)

Research activities		**R0152**
	Use of donated embryos for research	✓
	Storage of licensed material	✓
	Creation of embryos in vitro	✓
	Derivation of human embryonic stem cells	✓
	Cell nuclear replacement	✓

Summary for Licence Committee

Laboratory refurbishments at centre 0017 were completed in July 2007 and state-of-the-art facilities are now in place for both clinical and research work.

Although there had been preliminary procedural difficulties associated with this project (R0152) progress has been made.

Funding is in place for continuation of this project.

The centre failed to provide a breakdown of embryo-useage data prior to the inspection, which was noted by both peer reviewers for this project. Following a constructive discussion about the issue, the centre agreed to provide such data in the future, (which need not include reference to specific research methodologies).

The Person Responsible is an experience clinician and has satisfactorily completed the PR Entry programme.

The executive supports the renewal of the licence for research project R0152 for three years.

Changes/ improvements since last inspection

State-of-the-art laboratories are now back in full-time use at centre 0017 after being closed for refurbishment between January 2006 and July 2007.

Some staff changes have occurred and the centre has informed the Authority of these changes.

Additional licence conditions and recommendations and actions taken by centre since last inspection

The PR was granted a three year licence with no additional conditions.

Proposed licence variations

None.

Breaches of the Act, Standard Licence Conditions or Code of Practice: The table below sets out matters which the Inspection Team considers may constitute breaches of the Act, Standard Licence Conditions and/or the Code of Practice, and their recommended improvement actions and timescales. The weight to be attached to any breach of the Act, Standard Licence Conditions or Code of Practice is a matter for the Licence Committee;-

No potential breaches were observed on the day of the inspection visit.

Report of Inspection findings

1. **Organisation**

Desired Outcome: The centre is well-organised and managed and complies with the requirements of the HFE Act.

Summary of findings from inspection

Evidence of: *(Delete areas not reporting on)*

- Leadership and management
- Organisation of the centre
- Resource management
- Staffing
- Research governance
- Funding

Full time equivalent staff

Principal investigator(s)	Alison Murdoch, Mary Herbert
Scientists	1Research registrar, 1 PhD student, 1 research associate, 1 junior research associate, 1 research assistant, 2 research nurses.
Laboratory technicians	1
Research coordinator	1
Support staff (receptionists, record managers, quality and risk managers etc)	Staff at centre 0017

Highlighted areas of firm compliance
Both principal investigators associated with all three research projects have extensive knowledge of the regulatory requirements of the HFEA. An induction process is in place for new research staff which includes similar inputs as for new staff at centre 0017 (ie NHS Trust plus unit specific elements) together with input from the University. Documented evidence of research staff having access to CPD was observed during the inspection. There have been some staff changes in the time since the last inspection and the HFEA has been provided with updated staff lists. Regular monthly research meetings take place and the minutes kept electronically.

Funding has been identified for this project as detailed below;

Project	R0152
Funding source	Medical Research Council (MRC)

Issues for consideration

None

Executive recommendations for Licence Committee

None

Areas not covered in this inspection

None

2. Premises and equipment

Desired Outcome: The premises and equipment are safe, secure and suitable for their purpose.

Summary of findings from inspection: *(Delete areas not being reported on)*

- Suitability of premises
- Storage facilities
- Safety of equipment
- Servicing and maintenance of equipment

Highlighted areas of firm compliance
The laboratory facilities at donating centre 0017 have been extensively refurbished between January 2006 and July 2007. A separate research laboratory is in use which utilises the same state-of-the-art equipment, which was observed during the inspection. Access to the facilities are restricted and kept secure when not in use. Service and maintenance contracts are in place with both the University and external contractors, although most of the recently upgraded equipment is still under manufacturer's warranty. The cryovessels used to store material donated to research are the same as used at centre 0017 and as such have an appropriate O_2 monitor in place, with external audio/visual alarm. Liquid nitrogen levels are monitored on a regular basis. Annual health and safety inspections are coordinated by the University.
Issues for consideration
None
Executive recommendations for Licence Committee
None
Areas not covered in this inspection
None

3. Donation of material

Desired outcome: Ensure donors are recruited in a proper way and their consent is respected.

Summary of findings from inspection: *(Delete areas not being reported on)*

- Recruitment of donors
- Ensuring prospective donors have access to further guidance
- Ensuring prospective donors have time to consider donation properly
- Prevention of coercion of prospective donors
- Ensuring patient consent is not breached
- Donor and patient records

Highlighted areas of firm compliance
The centre has a robust system in place for the recruitment and screening of donors. Donation is coordinated by a designated individual who is not directly involved in the patient's treatment. There have been no changes to recruitment procedures which were found to be appropriate Hard logs were observed illustrating the witnessing and transfer of embryos to research. There is a hard log system in place for tracking the fate of embryos used in the research programmes. Donated embryos were tracked from patients notes to the point of end use. No discrepancies were observed. No altruistic egg donors are presently being used by the centre.
Issues for consideration
Although there is a process for the periodic review of stored donated material no formal written SOP is in place.
Executive recommendations for Licence Committee
A written SOP for the periodic review of stored donated material to be formalised.
Areas not covered in this inspection
None

4. Patient information and consents

Desired outcome: Ensure that patients are informed in order to give informed consent

Summary of findings from inspection: *(Delete areas not being reported on)*

- Patient information
- Consent forms
- Patient information for projects deriving embryonic stem cells
- Consent forms for projects deriving embryonic stem cells

Outcome of audit of records
Six sets of patient's notes were reviewed during the inspection. No discrepancies were found.
Highlighted areas of firm compliance
During staff interviews it was established that appropriate information was disseminated to patients at different stages of their treatment cycles. Information about research projects was also available in the waiting room. Patients could contact either the research coordinator or research nurse if they had any further queries and had access to an independent counsellor if required. Consent forms were observed to be appropriately completed within patient notes.
Issues for consideration
There was no record of patients having been sent and/or discussed relevant background information concerning research. During discussions it was concluded that a tick-box be established within the notes to denote that such information had been sent/discussed.
Executive recommendations for Licence Committee
A record to be established within the notes indicating that information about research projects had been sent and/or discussed with patients.
Areas not covered in this inspection
None

5. Scientific practice

Desired outcome: Procedures are robust to ensure material is used appropriately

Summary of findings from inspection: *(Delete areas not being reported on)*

- Standard operating procedures
- Quality assurance systems
- Minimisation of material loss and wastage
- Ability to achieve set aims and objectives

Use of material

Project **R0152**
Entitled "**Derivation of human embryonic stem cell lines using nuclear transfer and parthenogenetically activated oocytes**

Useage 01/01/2007 to 31/12/2007

Eggs	Fresh	Failed to fertilise	Frozen
Total number received	19	1170	0
Total number used	19	56	0

Expected useage over next 12 months

	Material	Expected usage
8.3.1	Fresh Eggs*	400
8.3.2	Frozen Eggs	0
8.3.3	Failed to Fertilise Eggs	200
8.3.4	Fresh Embryos	0
8.3.5	Frozen Embryos	0

* If immature eggs will be used please indicate

Project objectives, work undertaken and results

Project **R0152**
Entitled "**Derivation of human embryonic stem cell lines using nuclear transfer and parthenogenetically activated oocytes**"

There have been no changes in the objectives of the original application and all work proposed remains consistent with these objectives. There have been technical modifications in the procedures used as a result of recent publications and experience elsewhere.

Research undertaken to date.

Substantial work has been undertaken in the development of a custom designed isolator/incubator system for nuclear transfer. This provides a uniquely controlled environment in which the procedures can be undertaken.
We have also established a collaboration with Dr Shoukhrat Mitalipov (Oregon USA) who has successfully derived an ES cell line in the non-human primate (Nature 2007). Several exchange visits have been made to develop the appropriate techniques prior to the availability of fresh human eggs.
Following approval and funding for egg sharing, the first experiments using fresh eggs were carried out in Dec 2007.

Results

The main results so far have been in addressing the ethical and regulatory difficulties in obtaining fresh eggs for research. We have successfully obtained permission from the HFEA and funding from the MRC. The programme has been established. Over 100 women have contacted us about the scheme and 19 been programmed for treatment.
In the meantime we have continued to make progress with the animal model and development of activation procedures.

Lay summary of research undertaken

We have shown in our research under this licence that it is necessary to use eggs for nuclear transfer immediately after they have been taken from the donor. Previously we had used eggs that has failed to fertilise and were thus donated 48 hours after retrieval.
For the duration of this licence, we have developed the programme of egg sharing, obtained the necessary approval and funding. This scheme started in Dec 2007.
In the meantime we have also worked on the techniques that are needed for successful nuclear transfer and ES cell derivation using failed to fertilise eggs and animal models.

Related publications

1. Choudhary M, Nesbitt M, Leary C, Murdoch AP. (2006) Donation of fresh oocytes for Nuclear Transfer research – A new approach. RBM online (12,2 301-302)
2. Vanessa Hall Duane Compton, Petra Stojkovic, Maria Nesbitt, Mary Herbert, Alison Murdoch and Miodrag Stojkovic. 2007 Developmental competence of human in vitro aged oocytes as host cells for nuclear transfer Human Reproduction 22:52-62
3. K Jayaprakasan, M Herbert, E Moody, J A Stewart, A P Murdoch 2007 Estimating the risks of Ovarian Hyperstimulation Syndrome (OHSS) during egg donation for research. Human Fertility (10(3)183-187
4. Gurdon J, Murdoch A 2008 Nuclear Transfer and iPS May Work Best Together. Cell Stem Cell (in press).

Peer reviewers comments

The peer reviewer supported the renewal of this research project and stated that the research was necessary or desirable for the following purposes:

- Increasing knowledge about the development of embryos
  Human Fertilisation and Embryology (Research Purposes) Regulations S2(2)(a)
- Enabling any such knowledge to be applied in developing treatments for serious disease
  Human Fertilisation and Embryology (Research Purposes) Regulations S2(2)(c)

The reviewer raised a number of issues relating to the number of embryos used in this project of research. The Person Responsible confirmed that patients had consented to the donation of 1170 failed to fertilised embryos to the research project but only 56 were required and therefore used in the research project.

The peer reviewer agreed that the use of human embryos is necessary. The reviewer stated that: *"SCNT to eggs creates embryos for research which are subsequently destroyed to isolate cells from the inner cell mass and derive embryonic stem cell lines. Induced pluripotency (iPS) cells also derived by reprogramming skin fibroblasts but by other means, are a potential alternative but the evidence that they are entirely equivalent to human embryonic stem cells is not yet available and viral vectors are required to derive them. Thus until that time SCNT will be required to produce patient derived lines for potential clinical application and the methodology requires development. In the light of scarcity of fresh normal human eggs as SCNT recipients, egg sharing, parthenogenesis and the use of failed to fertilize eggs are proposed as alternatives. Some of the plans are likely to achieve decisive results towards future aims of the application (patient derived lines for therapy)."*

The peer reviewer also agreed that the creation of embryos by SCNT is necessary to obtain inner cell masses from which human embryonic stem cell lines can be derived. The reviewer also considered the use of human embryonic stem cells necessary for the proposed future work as, "*for development of many future treatments for multiple diseases, human embryonic stem cells or similar are the only option at present (although adult stem cells may be suitable for a limited number of purposes). For reasons stated above, recently produced near human embryonic stem cell equivalents (iPS cells) can only be derived by (viral) insertion and ectopic expression of several pluripotency genes. This is presently not considered compatible with*

clinical application in cell based therapy."

Issues for consideration

The centre had not disclosed details of how donated embryos have been used within theis project of research. This was also noted independently by the peer reviewer.

A discussion about the need for such data was undertaken during the inspection. The inspectorate was informed by the PR and NL that they were reluctant to divulge specific useage details, as the Authority could not give assurances about non-disclosure to interested third parties under the Freedom of Information Act. It was then agreed that details of embryo useage could be made available, without disclosure of specific research methodologies. The centre agreed to supply such data on embryo useage.

Progress has been made in all research projects as indicated in the supplied progress report and licence renewal applications.

Executive recommendations for Licence Committee

Henceforth the centre should supply embryo useage data with future progress reports/licence renewal applications, which identifies donated embryo useage within individual research projects, without disclosing specific research methodologies.

Areas not covered in this inspection

None

Report compiled by:

Name……. Wil Lenton……

Designation…….Regulatory Inspector……

Date……. 15 May 2008……

Appendix A: Centre Staff interviewed

PR, NL and three other members of staff

Appendix B: Licence history for previous 3 years

R0145

Status	Licence	Type	Active From	Expires
Active	R0145/3/a	Research Project	01/01/2007	31/12/2009
Expired	R0145/2/b	Research Project	01/10/2006	31/12/2006
Expired	R0145/2/a	Research Project	01/08/2006	30/09/2006
Expired	R0145/1/a	Research Project	05/08/2003	01/08/2006

No conditions or recommendations have been applied to the licence.

R0152

Status	Licence	Type	Active From	Expires
Active	R0152/2/a	Research Project	01/08/2005	31/07/2008
Expired	R0152/01/a	Research Project	11/08/2004	31/07/2005

No conditions or recommendations have been applied to any of the licences listed above.

R0153

Status	Licence	Type	Active From	Expires
Active	R0153/1/a	Research Project	08/09/2005	31/08/2008

The licence committee that granted the licence imposed an additional condition requiring the submission of six monthly progress reports.

Appendix C:
RESPONSE OF PERSON RESPONSIBLE TO INSPECTION REPORT

Centre Number……

Name of PR……

Date of Inspection……..

Date of Response……

Please state any actions you have taken or are planning to take following the inspection with time scales

I have read the inspection report and agree to meet the requirements of the report.

Name……

Date……

2. Correction of factual inaccuracies

Please let us know of any factual corrections that you believe need to be made (NB we will make any alterations to the report where there are factual inaccuracies. Any other comments about the inspection report will be appended to the report).

We also welcome comments about the inspection on the inspection feedback form, a copy of which should have been handed out at the inspection. If you require a copy of the feedback form, please let us know.

Please return this section of the report to:
Dr Chris O'Toole
Head of Research Regulation, HFEA
21 Bloomsbury Street
London
WC1B 3HF

Research Licence Committee Meeting

18 June 2008
21 Bloomsbury Street London WC1B 3HF

MINUTES Item 9

Research Project R0152: Derivation of human embryonic stem cell lines using nuclear transfer and parthenogenetically activated oocytes
Based at Newcastle Fertility centre at Life (0017)
Licence Renewal

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 (52 pages)
- no papers were tabled.

1. The papers for this item were presented by Chris O'Toole, Head of Research Regulation. Dr O'Toole informed the Committee that this project aims to derive human embryonic stem cells using nuclear transfer and parthenogenic activation. Dr O'Toole further informed the Committee that progress with this project has been hampered by a refurbishment of the laboratories and by the availability of good quality of eggs. During 2007 the research project used 19 fresh eggs and 56 failed to fertilise eggs. The centre has recently received a grant from the MRC to approach women about egg sharing for research and it is hoped that the research will now progress at a faster pace. Dr O'Toole informed the Committee that the Person Responsible for the research has satisfactorily completed the Person Responsible Entry Programme (PREP) assessment, that the Nominal Licensee, Mary Herbert, is a suitable person to hold a licence, and that the licence renewal fee has been paid.

The Committee's Decision

2. The Committee noted and endorsed the recommendation in the inspection report that the centre needs to implement a formal, written standard operating practice for the periodic review of stored donated material and in addition should keep a record of patients who have been sent background information or who have discussed the research with the research coordinator or research nurse.

3. The Committee identified the activities under consideration as the storage of embryos, the use of donated embryos in research, the creation of embryos in vitro and the derivation of human embryo stem cell lines. The Committee agreed that these activities are not prohibited under the Human Fertilisation and Embryology Act 1990.

4. The Committee considered whether the proposed activities 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 peer reviewer 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)(c) to enable any such knowledge to be applied in developing treatments for serious disease

In reaching this decision the Committee took into account the comment by the peer reviewer that the work aims to create patient specific stem cells for potential future treatments for disease.

5. The Committee agreed that this use and creation of embryos is necessary for the purpose of the research. In making this decision, the Committee took into account the comment by the peer reviewer that induced pluripotent (iPS) cells could not be used in place of stem cells since iPS cells are derived by viral insertion and the use of such cells is presently not considered compatible with clinical application.

6. The Committee agreed that they were satisfied about the consent forms and patient information, based on the remarks of the Executive.

7. The Committee noted Dr O'Toole's comments today and in her report about the suitability of the Person Responsible, the Nominal Licensee and the premises, and agreed that the requirements for the grant of a licence under Section 16 of the Human Fertilisation and Embryology Act 1990 were satisfied. The Committee decided to renew the licence for a period of three years. The Committee considered that 3 years was an appropriate period given that this is a well-established Centre.

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