Research Licence Inspection Report

Project Title Research licence no Licence expiry date	**Epigenetic studies of preimplantation embryos and derived stem cells** R0145 31 December 2009 (Progress Report)
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	Not applicable

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 **R0145** entitled "**Epigenetic Studies of Preimplantation Embryos and Derived Stem Cells**" has been licensed since 2003.

The lay summary of the project is as follows:

It is now clearly established that embryonic stem cells offer great potential for the understanding of disease and possibly for future treatments. At present the technology for successfully deriving and growing embryonic stem cells (ES cells) needs to be more reliable and efficient. Furthermore, considerable changes are necessary if the cell lines are to be suitable to use in treatment rather than just for research. The aims of this project are to improve the processes of culture of embryos and derivation of ES cells to meet the European Union Tissues and Cells Directive standards.
Stem cell lines so derived will be made available to the National Stem Cell Bank for further approved studies. The embryos used for this study are those of poor quality which are not suitable for treatment. If not used for research they would otherwise be discarded according to patient's consent.

The project is currently licensed under 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)

Research activities		**R0145**
	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.

Progress has been made in this project of research, with both human embryonic stem cell lines generated and peer-reviewed publications produced.

Funding is in place for continuation of the projects.

The centre failed to provide a breakdown of embryo-useage data prior to the inspection. 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 continuation of the licence for research project R0145.

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 licence was granted 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 the research projects carried out at centre 0017 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 as detailed below;

Project	R0145
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 **R0145**
Entitled "**Epigenetic Studies of Preimplantation Embryos and Derived Stem Cells**"

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

Embryos	Fresh	Frozen
Total number received	968	24
Total number used	927	12

Expected useage over next 12 months

	Material	Expected usage
7.3.1	Fresh Eggs	
7.3.2	Frozen Eggs	
7.3.3	Failed to Fertilise Eggs	
7.3.4	Fresh Embryos	800
7.3.5	Frozen Embryos	200

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Project **R0145**
Entitled "**Epigenetic Studies of Preimplantation Embryos and Derived Stem Cells**"

Since there is no guarantee of confidentiality of any information given in the application, it is not possible for us to give precise details of unpublished results or of the scientific methods in use.

The scientific objectives of project R0145 are;

A. *To optimise GMP-compatible methods for derivation, expansion and cryopreservation of ES cells. This requires the provision of facilities compatible with the new EU regulations and the development of a feeder free and animal product free system for culturing ES cells.*

B*. To optimise blastocyst culture, determine the optimum time for the isolation of the ICM and refine the mechanical methods of ICM isolation.*

C. *To define the pluripotent population within the ICM. It will also yield insights into the nature of the stem cell niche in the context of the human blastocyst.*

D. *To optimise methods for blastocyst cryopreservation and thawing and to determine the effect of freeze/thaw on the potential to produce stable ES cell lines. A secondary benefit will be to enable us to evaluate the efficacy of blastocyst cryopreservation as a possible alternative to cleavage stage freezing in the clinical IVF programme.*

E. *To better understand the nature and origin of chromosomal instability in ES cells and to assess the effect of environmental conditions on the maintenance of genomic integrity. This is important because the acquisition of chromosomal abnormalities by ES cells will be a major limitation to their therapeutic application.*

F. *To characterise the epigenetic status of blastocysts and ES cells. This will advance our understanding of the epigenetic control of pluripotency and differentiation and will also yield insights into the effect of environment on epigenetic stability.*

G. *To evaluate new developments in the derivation of ES cell lines e.g. to determine whether ES cell lines can be derived from the individual blastomeres removed from 4-12 cell embryos.*

H. *To continue to monitor and improve the process of giving information to and taking consent from patients for this research.*

All this work is ongoing.

Results

Objective A

1. *We have derived 5 new hESC lines and have made progress towards the elimination of animal products from the culture system.*
2. *We have developed a GMP-compatible method for freezing and thawing hESCs*
3. *We have completed the commissioning of two new GMP facilities and have prepared a set of GMP SOPs for derivation of clinical grade hESCs*

Objective B

4. *We have found that an increased proportion of embryos develop to the blastocyst stage when critical environmental parameters are controlled during open manipulations.*

Objective C

5. *(i) The inner cell mass of human blastocysts consists of a mosaic of Nanog negative and Nanog positive cells (ii) The proportion of Nanog positive cells declines between Day6 and Day 8. (Manuscript in preparation)*

Objectives D, E, G and F

6. *Work on these objectives has either not commenced or is at an at early stage of progress*

Objective G

7. *The data are currently being analysed*

Objective H

8. *This important area of our work is ongoing*

Lay summary of research undertaken

During the past year, we have completed the installation and commissioning of novel isolator technology to provide a controlled environment within which embryos can be grown and ES cells derived. We are continuing to develop the necessary processes for the production of clinical grade ES cell lines.
We have derived a further 5 ES cell lines.

Peer reviewers comments
Not applicable – interim inspection
Issues for consideration
The centre should supply embryo useage data with future progress reports / licence 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 7

Research Project R0145: Epigenetic studies of preimplantation embryos and derived stem cells
Based at Newcastle Fertility centre at Life (0017)
Progress Report

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:
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 (34 pages)
- no papers were tabled.

1. The papers for this item were presented by Chris O'Toole, Head of Research Regulation. Dr O'Toole reported that this project has progressed more slowly than usual due to the refurbishment of the laboratories which finished in July 2007. Notwithstanding this fact, the project has successfully generated human embryonic stem cell lines and produced peer-reviewed publications. Dr O'Toole informed the Committee that the project is ongoing and the objectives remain the same as when the research was first licensed. She further informed the Committee that the centre has ensured continuing funding for the research.

2. Dr O'Toole summarised the findings of the inspection report, highlighting that during 2007 a total of 927 fresh embryos and 12 frozen embryos were used and a further 5 stem cell lines had been created. Dr O'Toole reported that the Person Responsible has satisfactorily completed the Person Responsible Entry

Programme (PREP) assessment and the Executive supports the continuation of the licence.

The Committee's Decision

3. 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.

4. The Committee agreed that the licence should continue with no additional conditions.

Signed..... Date 27.6.08
Emily Jackson (Chair)