Research Licence Inspection Report

Project Title	**Mitochondrial DNA disorders: Is there a way to prevent transmission?**
Research licence no	R0153
Licence expiry date	31 August 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 **R0153** entitled "**Mitochondrial DNA Disorders: Is there a way to prevent transmission?**" has been licensed since 2005.

The lay summary of the project is as follows:

Mitochondria are organelles that convert the food we eat into energy. There are many mitochondria in every cell of our body. Each mitochondrion has its own DNA which is separate from 'nuclear' DNA. Nuclear DNA contains genetic information in the cell which influences the make up of the whole body however, mitochondrial DNA only provides instructions on how mitochondria behave. If these genes are damaged an affected person may develop severe disease leading to disability and death. Mitochondrial genes are inherited only through the mother who may pass the disease on to her children. At present no treatment for mitochondrial diseases exists.

Previous studies in mice have shown it is possible to prevent the transmission of mitochondrial disease by moving the pronuclei (pronuclei ultimately develop into an embryo's nucleus containing the embryo's 'nuclear' DNA) from an egg containing bad mitochondria to another egg which only contains good mitochondria.

In experiments conducted on mice, eggs developed normally and non affected mice were born after the procedure. These experiments are very encouraging but there are many differences between mouse and human eggs.

We are proposing to determine if moving the pronuclei could ever be used for our patients by taking abnormally fertilised human eggs (which cannot be used for treatment) and transferring the pronuclei from one egg to another. Following this transfer we would monitor the possible carry-over of mitochondria between eggs and will determine whether the egg then develops normally.

We hope that these studies will provide vital information as to whether we could ever prevent the transmission of mitochondrial diseases from mother to child.

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

- 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 considered 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)
- 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)

		R0153
Research activities	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, with peer-reviewed publications produced.

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 the peer reviewers for the project R0153. 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 executive supports the renewal of the licence for research project R0153 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.

The Person Responsible (PR) for this licence has changed. Professor Alison Murdoch has been proposed as the new PR. Professor Murdoch is the PR of the two other research licences at centre 0017 and she has satisfactorily completed the PR Entry programme.

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

Professor Murdoch has been proposed as the new Person responsible for this research licence.

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	R0153
Funding source	Muscular Dystrophy Campaign Glaxo Smith Kline British Lottery Fund

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 **R0153**

Entitled "**Mitochondrial DNA Disorders: Is there a way to prevent transmission?**"

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

Embryos	Fresh	Frozen
Total number received	322	0
Total number used	252	0

Expected useage over next 12 months

	Material	Expected usage
8.3.1	Fresh Eggs*	0
8.3.2	Frozen Eggs	0
8.3.3	Failed to Fertilise Eggs	
8.3.4	Fresh Embryos	250
8.3.5	Frozen Embryos	0

* If immature eggs will be used please indicate

Project objectives, work undertaken and results

Project **R0153**
Entitled "**Mitochondrial DNA Disorders: Is there a way to prevent transmission?**"

The objectives given in 2007 are unchanged. These are:

1. *To determine whether embryos derived from pronuclear transfer zygotes are capable of development to the blastocyst stage.*

2. *To evaluate the cytogenetic, epigenetic and gene expression profiles of embryos derived from pronuclear transfer zygotes.*

3. *To determine the extent of mitochondrial DNA carry-over from the donor zygote.*

Research undertaken to date.

Work to date has focussed on Objectives 1 and 2

Results

Our work to date has provided evidence that pronuclear transfer is compatible with onward development of human zygotes. We have also demonstrated that pronuclear transfer results in very low levels of mitochondrial carryover. These findings provide proof of principle that pronuclear transfer is a feasible option for prevention of transmission of mitochondrial disease in humans. However, further work is required to optimise the procedure.

Lay summary of research undertaken

We have used abnormally fertilised human zygotes to test the feasibility of pronuclear transfer as a means of preventing transmission of mitochondrial disease from a mother to her children. Our work indicates that pronuclear transfer is compatible with onward development of human zygotes. We have also demonstrated that pronuclear transfer results in very low levels of mitochondrial carryover. This means that a minimal amount of mutated mitochondrial DNA would be transferred from the zygote of an affected woman to the donor zygote. These findings provide proof of principle that pronuclear transfer is a feasible option for prevention of transmission of mitochondrial disease in humans. However, further work is required to optimise the procedure to increase its efficiency.

Renewed objectives
The central focus of this project will be to refine procedures to enable us to offer pronuclear transfer as successful clinical treatment. To do this we believe we need to address the following research questions:

1) Optimisation of karyoplast fusion techniques
2) Optimisation of PN extraction technique to minimise carryover of mitochondria
3) Determine whether the PN procedure predisposes embryos to chromosomal and

epigenetic aberrations.

Peer reviewers comments

The peer reviewer supported the renewal of the research licence. The reviewer stated that: "*the objectives of the study as originally licensed, remain worthwhile and it does appear that continuation of the work may yield results which are of significant clinical benefit to particular patient groups*."

The reviewer considered 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)
- 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)

The peer reviewer agreed that the use of human embryos is justified. The reviewer stated that: **"***The work described draws on previous studies using animal models and the applicants indicate that they will continue to undertake supporting studies using mouse zygotes. However, the work represents what is currently the best prospect of providing a successful clinical treatment for women whose fertility is compromised by mitochondrial disease and in order to achieve this it is necessary that protocols are developed using human embryos.*"

The peer reviewer agreed that the creation of human embryos is necessary. The reviewer provided that: "*Although the application does not strictly involve the creation of embryos by cell nuclear replacement it does involve pronuclear transfer techniques between zygotes but these techniques are integral to the studies being undertaken*."

Issues for consideration

The centre had not disclosed details of how donated embryos have been used within this research project. This was also noted independently by the peer reviewer for the renewal of licence R0153.

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.

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 8

Research Project R0153: Mitochondrial DNA disorders: is there a way to prevent transmission?
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
Dr Leonard, HFEA Inspector
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 (39 pages)
- no papers were tabled.

1. The papers for this item were presented by Chris O'Toole, Head of Research Regulation. She reminded the Committee that this project aims to determine whether it is possible to prevent the transmission of mitochondrial disease by removing the pronuclei of a fertilised egg and transferring it into another fertilised egg with the pronuclei removed. Dr O'Toole informed the Committee that in 2007 the research project used 252 fresh embryos but the centre have failed to provide a breakdown of embryos usage data. She further informed the Committee that this has been commented on by the peer reviewer who, despite recommending that the research licence be renewed, stated that it was difficult to assess the progress of the research on the basis of the very general report provided by the centre. Dr O'Toole confirmed that the Person Responsible has

agreed that more information will be provided in connection with future applications.

2. Dr O'Toole summarised the main findings of the inspection report. She confirmed that the premises where the research is based have recently been refurbished and updated. Other than the issue of disclosure of data, no significant areas for consideration were highlighted in the report. As part of the renewal application, the centre has applied for Professor Alison Murdoch to be Person Responsible. Dr O'Toole confirmed that Professor Murdoch 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 received from the centre.

3. The Committee discussed with Dr O'Toole and Dr Leonard the fact that the centre failed to provide a breakdown of embryo-usage to date prior to the inspection, and that this was noted by the peer review for the project. Dr O'Toole reported that during the inspection visit to the centre a compromise was reached whereby the centre would provide more details about embryo usage, though this need not include reference to specific research methodologies. Dr O'Toole further reported that this supplementary information has not been received from the centre to date.

4. In response to a question from the Committee regarding the amount of information available to the Committee, the Legal Adviser drew the Committee's attention to Section 16(4) of the Human Fertilisation and Embryology Act 1990 which states that where the Committee is of the opinion that the information provided by the Centre is insufficient to enable it to determine the application, it need not consider the application until the Centre has provided it with such further information as the Committee may require.

The Committee's Decision

4. 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.

5. The Committee identified the activities under consideration as the storage of embryos and the use of donated embryos in research. The Committee agreed that these activities are not prohibited under the Human Fertilisation and Embryology Act 1990.

6. 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)(b) to increase knowledge about serious disease

- 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 represents the best current prospect of providing a successful clinical treatment for women whose fertility is compromised by mitochondrial disease.

7. The Committee agreed that the use of embryos is necessary for the purpose of the research. In making this decision, the Committee considered the statement by the peer reviewer that because the research aims to develop treatments for women it is necessary that human embryos are used in the research.

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

9. 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 did however have concerns about the level of information provided by the Centre and therefore decided that this licence should not be issued until the centre has provided to the Executive the extra information about the usage of embryos in the research to date (as referred to in paragraph 3 above).

Signed..... Date 27.6.09
Emily Jackson (Chair)