# Research Interim Inspection Report

**Date of Inspection:** 28 February 2013
**Purpose of inspection:** Interim Inspection of Research Licence
**Length of inspection:** 3h
**Inspectors:** Wil Lenton

**Inspection details:**
The report covers the pre-inspection analysis, the visit and information received between 10 February 2011 and 10 May 2013.

**Date of Executive Licensing Panel:** 23 May 2013

## Centre details

| | |
|---|---|
| **Project Title** | Pluripotency reprogramming and mitochondrial biology during early human development |
| **Centre Name** | Newcastle Fertility Centre at Life |
| **Centre Number** | 0017 |
| **Research licence Number** | R0152-4-B |
| **Centre Address** | Bioscience Centre, International Centre for Life, Times Square, Newcastle upon Tyne, NE1 4EP |
| **Person Responsible** | Professor Alison Murdoch |
| **Licence Holder** | Professor Mary Herbert |
| **Treatment centres donating to this research project** | 0017 |
| **Date Licence Issued** | 1 August 2011 |
| **Licence expiry date** | 31 July 2014 |
| **Additional conditions applied to this licence** | None |

# Contents

## Purpose of the Inspection report

The purpose of the inspection is to assess whether research using human embryos is carried out in compliance with the Human Fertilisation and Embryology (HF&E) Act 1990 (as amended) and the Code of Practice and that progress is made towards achieving the stated aims of the project. The report summarises the findings of the inspection highlighting areas of firm compliance and good practice, as well as areas where improvement may be required to meet regulatory standards. It is primarily written for the Authority's Executive Licensing Panel (ELP) which makes the decision about the centre's licence.

# Report to Executive Licensing Panel

**Brief description of the centre and its licensing history:**
The centre is centrally-located within a science park, a five minute walk from Newcastle main train station. Research licence R0152 has been licensed since August 2004. The centre is also licensed to carry out treatment services and has been licensed since 1992.

In October 2009, the research Person Responsible (PR) applied for a variation to licence R0152, in order that the activities and objectives of two other research licences (R0145 and R0153) were incorporated into it. The variation was agreed in November 2009.

The PR has been in post since the inception of the licence in August 2004, has the appropriate qualifications and experience for the role and has successfully completed the PR Entry Programme (PREP).

A Research Licence Committee (RLC) meeting on 18/05/2011 renewed the centre's research licence for a period of three years, as well as varying it to include two new rooms, B2.20 and B2.28.

**Title of research project:** Pluripotency, reprogramming and mitochondrial biology during early human development

**Summary for licensing decision**
In considering overall compliance, the inspection team considers that it has sufficient information drawn from documentation submitted by the centre prior to inspection and from observations and interviews conducted during the inspection visit to draw a conclusion on the continuation of the centre's licence.

The ELP is asked to note that there are no areas of practice that require improvement.

**Recommendation to the ELP:**
The inspection team considers that overall there is sufficient information available to recommend the continuation of this centre's licence without additional conditions.

# Summary of project

## Updated lay summary of the research project:

Our work involving human embryos and gametes is conducted in the context of a research programme, which encompasses clinical, translational and basic science research.

A major focus of our research is to develop techniques to prevent transmission of mitochondrial DNA disease from mother to child. The mitochondria are tiny structures in our cells, which produce the energy required for cells to function properly. Mitochondria contain DNA, which encodes a small number of proteins required for the efficient production of energy. Mutations in mitochondrial DNA cause a broad spectrum of debilitating and fatal diseases.

The mitochondria in embryos are derived entirely from the egg. Women who carry mitochondrial DNA mutations produce eggs with widely varying levels of the mutation. It is therefore impossible to predict whether their children will be affected by mitochondrial DNA disease. There are no curative treatments for mitochondrial DNA disease and affected families face very difficult reproductive choices. We have therefore been working towards optimising new techniques to replace the egg's mitochondria with those from a donor egg. The ultimate aim of this part of our research is to be able to offer clinical treatments that will enable women who carry mitochondrial DNA mutations to have a genetically related child while greatly reducing the risk of transmitting disease.

A further aim of our research is to gain a better understanding of the causes of infertility and to study how the molecular events underlying the formation of normal sperm, eggs and embryos are affected by laboratory procedures used in IVF treatment. This part of the research is also important in helping us to study the effect of procedures involved in developing new techniques such as those described above.

Our research also includes the production of embryonic stem (ES) cells. Because embryos contain relatively few cells, ES cells, which divide indefinitely in the laboratory, provide a useful tool for performing more detailed studies on the safety of a variety of laboratory procedures including those aimed at preventing transmission of mitochondrial DNA disease.

In addition, ES cells hold great promise for developing treatments for degenerative diseases, including those caused by mutations in the mitochondrial DNA. A major goal of this area of research is to create patient-specific ES cells by using the egg to re-programme a differentiated cell, such as a skin cell, to an embryonic state. This research involves fusing a differentiated cell with an egg in a process known as nuclear transfer.

By pursuing the lines of investigation outlined above, we hope to improve the outcome of infertility treatments, and to make progress towards the wider application of IVF-based techniques to help prevent and treat degenerative disease. Our research is funded by the Wellcome Trust and by the MRC.

## Lay summary of the research undertaken

Since the last report, we have carried out the following work;

1. We have been successful in recruiting egg donors to enable us to make progress in developing techniques for preventing transmission of mitochondrial DNA disease.

2. We have worked on refining several aspects of the laboratory procedures associated with techniques to prevent transmission of mitochondrial DNA disease.

3. We have made progress in optimising a relatively new technique for cryopreservation of eggs, called vitrification. This is important for our work on mitochondrial disease. It will also enable us to offer egg storage as a clinical treatment for women whose fertility is at risk due to cancer treatment or other factors.

4. We have carried out studies to determine how the embryo assigns cells to their eventual fate of becoming either fetal or extra-embryonic tissues such as the placenta and yolk sac. By characterising such events we hope to develop new criteria to help us to test the likely safety and efficiency of a variety of laboratory procedures including those associated with preventing mitochondrial DNA disease.

5. We are actively involved in discussions with the regulators to ensure that we are fully compliant with the likely regulatory requirements should it be considered appropriate to introduce the techniques for preventing mitochondrial DNA disease into clinical practice.

6. We have used the findings of the studies described in point 4, to determine whether vitrification of embryos leads to improved development compared with conventional methods of cryopreservation.

7. We have performed studies to determine the therapeutic potential of nuclear transfer to treat degenerative diseases caused by mitochondrial DNA disease.

During the next year we will continue the objectives below and will specifically be working on the following:

- We will to continue the studies to improve the efficiency of techniques to prevent transmission of mitochondrial DNA disease.

- We will extend our work in optimising vitrification at different stages of development.

- We will continue to investigate the molecular and genetic events leading to formation of normal eggs, sperm and embryos. We hope that this part of our research will help us to better understand the factors that determine whether an embryo is capable of establishing a pregnancy.

## Updated objectives of the research:

The broad objectives of the research remain the same as were described and approved at the previous licence renewal in May 2011. In light of the research undertaken in the intervening two year period, the PR has supplied updated objectives in line with the present research.

Objective 1.
To optimise SCNT techniques using freshly harvested and vitrified mature human oocytes

Objective 2.
To compare the efficacy of different methods of artificial egg activation in promoting blastocyst development and nuclear reprogramming.

Objective 3.
To test the feasibility of performing SCNT with immature oocytes

Objective 4.
To optimise techniques of spindle (ST) and pronuclear transfer (PNT) to minimize carryover of mitochondria using Metaphase II oocytes and abnormally fertilized zygotes;

Objective 5.
To investigate mitochondria carryover following ST, PNT and SCNT

Objective 6.
To determine whether the egg reconstruction procedures predispose embryos to chromosomal and epigenetic aberrations.

Objective 7.
To derive human embryonic stem cells (hESCs) from embryos produced by SCNT, PNT and ST

Objective 8.
To determine whether the cell proliferation and partitioning of blastocyst cells to different lineages is influenced by (i) embryo culture conditions (ii) cryopreservation (iii) blastomere biopsy

Objective 9.
To derive hESCs from embryos donated by IVF patients including those with genetic disorders, such as those carrying mutations in mitochondrial and nuclear DNA.

## Donation and use of embryos:

| Number of embryos/project from 1 January to 31 December 2011 | | |
|---|---|---|
| | | |
| **a) Created for the project** | | |
| Total embryos created for research | 0 | |
| Total used in research | 0 | |
| Total stored for future use | 0 | |
| Total disposed of | 0 | |
| | | |
| **b) Donated to the project** | | |
| | **Fresh** | **Frozen** |
| Total donated | **1785** | **145** |
| Total received or thawed | **1785** | **145** |
| Total used in research | **1554** | **95** |
| Total disposed of | **231** | **50** |

| **Number of Eggs received / used** | **Source of Eggs** | | |
|---|---|---|---|
| | **Fresh** | **Failed to fertilise*** | **Frozen** |
| Total number donated: | **99** | **873** | **0** |
| Total number received or thawed for research: | **99** | **873** | **0** |
| Total number used for research: | **99** | **187** | **0** |
| Total number disposed of: | **0** | **686** | **0** |

**Projects involving the derivation of human embryonic stem cell lines**
Please state the number of stem cell lines derived: **0**

More ‘failed to fertilise’ cells were used than anticipated (873 vs150) due to an increase in patient donation to research. Unfortunately there was a high ‘drop-off’ rate within this group (873 to 187) due to the poor quality of the cells donated. All other egg/embryo usage was within the range indicated by the PR at the previous licence renewal.

## Publications:

Craven L, Elson J, Irving L, Tuppen HA, Lister LM, Greggains GD, Byerley S, Murdoch AP, Herbert M, Turnbull D. Mitochondrial DNA disease: new options for prevention. Human Molecular Genetics 2011 Aug; 20 (R2): R168-74. PMID: 21852248

Haimes E, Taylor K. Researching the Relationships between Tissue Providers, Clinicians, and Stem Cell Scientists. Cell Stem Cell 2011, 8(6), 613-615.

Haimes E, Taylor K. The contributions of empirical evidence to socio-ethical debates on fresh embryo donation for human embryonic stem cell research. Bioethics 2011, 25(6), 334-341.

Mitzkat A, Haimes E, Rehmann-Sutter C. How reproductive and regenerative medicine meet in a Chinese fertility clinic. Interviews with women about the donation of embryos to stem cell research. Journal of Medical Ethics 2010, 36(12), 754-757.

| Number of embryos/project from 1 January to 31 December 2012 | | |
|---|---|---|
| | | |
| **a) Created for the project** | | |
| Total embryos created for research | **112** | |
| Total used in research | **112** | |
| Total stored for future use | | |
| Total disposed of | | |
| | | |
| **b) Donated to the project** | | |
| | **Fresh** | **Frozen** |
| Total donated | **1147** | **89** |
| Total received or thawed | **1147** | **89** |
| Total used in research | **823** | **2** |
| Total disposed of | **324** | **0** |

| **Number of Eggs received / used** | **Source of Eggs** | | |
|---|---|---|---|
| | **Fresh** | **Failed to fertilise*** | **Frozen** |
| Total number donated: | **260** | **630** | |
| Total number received or thawed for research: | **260** | **630** | |
| Total number used for research: | **260** | **259** | |
| Total number disposed of: | **0** | **371** | |

*failed to fertilise' embryos are eggs that have been mixed with sperm (IVF or ICSI) but have not fertilised.

**Projects involving the derivation of human embryonic stem cell lines**
Please state the number of stem cell lines derived: **0**

More 'failed to fertilise' cells were used than anticipated (630 vs150) due to an increase in patient donation to research. Unfortunately there was a high 'drop-off' rate within this group (630 to 259) due to the poor quality of the cells donated.

More fresh eggs were donated to research than previously estimated as part of the licence renewal application process (260 vs 150). The PR stated that this was probably due to increased patient numbers undertaking licensed procedures, who subsequently agreed to consent to their cells being used in research.

Only two of the 89 donated frozen embryos were used in research. 87 remain in storage.

## Publications:

Touati SA, Cladière D, Lister LM, Leontiou I, Chambon JP, Rattani A, Böttger F, Stemmann O, Nasmyth K, Herbert M, Wassmann K. Cyclin A2 Is Required for Sister Chromatid Segregation, But Not Separase Control, in Mouse Oocyte Meiosis. Cell Reports: 2012: Cell Reports [Epub ahead of print] PMID: 23122964

Prathalingam N. Ferguson L, Young, L, Lietz G, Oldershaw R, Healey L, Craig A, Binaykia R, Seth R, Lister H, Murdoch A, Herbert M. Production and validation of a GMP grade human fibroblast line for supporting human embryonic stem cell derivation and culture. Stem Cells Research and Therapy 2012: 3(2): 12. PMID: 22472092

Hyslop L, Prathalingam N, Nowak L, Fenwick J, Harbottle S, Byerley S, Rhodes J, Watson B,' Henderson R,' Murdoch A, Herbert M. A novel isolator-based system to control physicochemical environment during laboratory processing promotes viability of human embryos PLoS ONE 2012: 7(2): e31010. PMID: 22393356

Choudhary M, Nesbitt M, Burgess L, Hyslop L, Herbert M, Murdoch AP. Egg sharing for research: A successful outcome for patients and researchers. Cell Stem Cell March 2012: 10(3): 239-240. PMID: 22385652

Leach Scully J, Haimes E, Mitzkat A, Porz R, Rehmann-Sutter C. Donating embryos to stem cell research: the "problem" of gratitude. *Journal of Bioethical Inquiry* 2012, 9(1), 19-28.

Alison Murdoch, Peter Braude, Aidan Courtney, Daniel Brison, Charles Hunt, James Lawford-Davies, Harry Moore, Glyn Stacey, Sebastian Sethe 2012 The Procurement of Cells for the Derivation of Human Embryonic Stem Cell Lines for Therapeutic Use: Recommendations for Good Practice Stem Cell reviews and Reports 8 :1, 91-99.

Haimes E, Taylor K, Turkmendag I. Eggs, ethics and exploitation? Investigating women's experiences of an egg sharing scheme. Sociology of Health and Illness 2012, 34(8), 1199-1214.

# Details of inspection findings

## Inspection findings

**Ensure that all licensed research by the centre meets ethical standards, and is done only where there is both a clear scientific justification and no viable alternative to the use of embryos**
(Guidance note 29, 30, 31)

What the centre does well.

The renewal of research licence R0152 was granted by a Research Licence Committee on 18 May 2011.

The peer reviewer for the renewal application agreed that the use of human embryos is necessary and justified for the proposed research and that the same results could not be obtained with adult stem cells or induced pluripotent stem cells.

Evidence of approval by an ethics committee was provided at the last licence renewal and was confirmed to be currently in place by the PR during the present inspection.

The activities licensed under project R0152 are the creation, use, keeping and storage of embryos. The renewal of the licence was approved to allow research for the following designated purposes:

- Increasing knowledge about serious disease
  *HFE Act 1990 (as amended) Schedule 2 3A(2)(a)*
- Developing treatments for serious disease or other serious medical conditions
  *HFE Act 1990 (as amended) Schedule 2 3A(2)(b)*
- Developing methods for detecting the presence of gene, chromosome or mitochondrion abnormalities in embryos before implantation
  *HFE Act 1990 (as amended) Schedule 2 3A(2)(g)*
- Increasing knowledge about the development of embryos
  *HFE Act 1990 (as amended) Schedule 2 3A(2)(h)*

What they could do better.

Nothing noted during present inspection

**Have respect for the special status of the embryo when conducting licensed activities**
(Guidance note 15, 18, 22, 25, 26)

What the centre does well.

During the review of centre documentation and the audit of ten sets of records it was established that;

- The centre has a documented procedure for ensuring that embryos do not develop beyond 14 days or the primitive streak has appeared (if earlier) (RLC R28).
- Comprehensive records of the embryos used in the research project, from donation to the project through to disposal at the end of the research process are maintained (RLC R13).
- Embryos are used for the purposes authorised by this licence (RLC R5 and R23).
- Embryos are used within the consented storage period (RLC R39).

The PR has ensured that appropriate records of embryo usage are maintained and that annual usage is reported to the HFEA (General Direction 0002 and RLC R13, R14 and R15).

What they could do better.

Nothing noted during present inspection

## Changes / improvements since the last inspection on 10 February 2011:

| Area for improvement | Action required | Action taken as evidenced during this inspection |
|---|---|---|
| N/A | | |

# Areas of practice that require the attention of the Person Responsible

The section sets out matters which the Inspection Team considers may constitute areas of non compliance. These have been classified into critical, major and others. Each area of non compliance is referenced to the relevant sections of the Act, Regulations, Standard Licence Conditions, Directions or the Code of Practice, and the recommended improvement actions required are given, as well as the timescales in which these improvements should be carried out.

## Critical area of non compliance

A critical area of non compliance is an area of practice which poses a significant direct risk of causing harm to a patient, donor or to an embryo. A critical area of non compliance requires immediate action to be taken by the Person Responsible

| Area of practice and reference | Action required and timescale for action | PR Response | Executive Review |
|---|---|---|---|
| Nothing noted during present inspection | | | |

## Major area of non compliance

A major area of non compliance is a non critical area of non compliance:

- which poses an indirect risk to the safety of a patient, donor or to an embryo through the procurement, use, storage or distribution of gametes and embryos, which do not comply with the centre's licence;
- which indicates a major shortcoming from the statutory requirements;
- which indicates a failure of the Person Responsible to carry out his/her legal duties
- a combination of several "other" area of non compliance, none of which on their own may be major but which together may represent a major area of non compliance.

| Area of practice and reference | Action required and timescale for action | PR Response | Executive Review |
|---|---|---|---|
| Nothing noted during present inspection | | | |

## Other areas of practice that requires improvement

Areas of practice that requires improvement is any area of practice, which cannot be classified as either a critical or major area of non compliance, but which indicates a departure from good practice.

| Area of practice and reference | Action required and timescale for action | PR Response | Executive Review |
|---|---|---|---|
| Nothing noted during present inspection | | | |

| Additional information from the Person Responsible |
|---|
| |

# HFEA Executive Licensing Panel Meeting

**23 May 2013**

Finsbury Tower, 103-105 Bunhill Row, London, EC1Y 8HF

## Minutes – Item 3

**Centre 0017 – (Newcastle Fertility Centre at Life) – Research Project R0152 Interim Inspection Report**

| Members of the Panel: | Committee Secretary: |
|---|---|
| Juliet Tizzard – Head of Policy and Communications (Chair)<br>Joanne Anton – Policy Manager<br>Hannah Darby – Senior Policy Manager | Rebecca Loveys |

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

**The Panel also had before it:**

- HFEA Protocol for the Conduct of Meetings of Executive Licensing Panel
- 8th edition of the HFEA Code of Practice
- Human Fertilisation and Embryology Act 1990 (as amended)
- Decision trees for granting and renewing licences and considering requests to vary a licence (including the PGD decision tree)
- Guidance for members of Authority and Committees on the handling of conflicts of interest approved by the Authority on 21 January 2009.
- Guidance on periods for which new or renewed licences should be granted
- Standing Orders and Instrument of Delegation
- Indicative Sanctions Guidance
- HFEA Direction 0008 (where relevant), and any other relevant Directions issued by the Authority
- Guide to Licensing
- Compliance and Enforcement Policy
- Policy on Publication of Authority and Committee Papers

**Consideration of Application**

1. The Panel noted that this is Research licence relating to research project R0152, 'Pluripotency, reprogramming and mitochondrial biology during early human development'.

2. The Panel noted that this Research licence was first issued in August 2004.

3. The Panel noted that the centre is also licensed to carry out treatment services and has been licensed since 1992.

4. The Panel noted that in October 2009 the research Person Responsible (PR) applied for a variation to licence R0152 in order that the activities and objectives of two other research licences (R0145 and R0153) were incorporated into it, and that this variation was agreed in November 2009.

5. The Panel noted that, in light of the research undertaken in the time since the licence was renewed in May 2011, the objectives of the research have been updated.

6. The Panel noted that an interim inspection took place on 28 February 2013 and that the Inspectorate identified no areas of non-compliance.

**Decision**

7. The Panel would like further clarification in relation to the objectives and purposes of the research. In particular, the Panel would like to be reassured that the Inspectorate is satisfied that the revised objectives of the research project are still consistent with the research purposes (as defined in the HFE Act) identified at the 2011 licence renewal.

8. The Panel agreed to adjourn its decision until further information had been provided by the Inspectorate regarding this issue.

Signed: Date: 4 June 2013

Juliet Tizzard (Chair)