Research Licence Renewal Inspection Report

Project Title	Analysis of Chromosomes in Human Preimplantation embryos using FISH and CGH
Centre Name	London Fertility Centre
Centre Number	0088
Research licence Number	R0169-3-a
Centre Address	Cozens House, 112a Harley Street London, W1G 7JH United Kingdom
Treatment centres donating to this research project	0088 London Fertility Centre 0068 Leicester
Inspection date	22/07/2008
Licence Committee Date	15 November 2008
Inspector(s)	Wil Lenton (Chair, HFEA Executive) Bryan Woodward (External inspector) Gillian Walsh (HFEA Executive)
Fee Paid - date	Yes – 14 August 2008
Person Responsible	Dr Diamantis Daphnis
Nominal Licensee	Mr Lawrence Ashford
Licence expiry date	31 December 2008

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, seventh edition 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 01/06/2007 and 01/06/2008.

Brief Description of the Project

Certain IVF patient groups have been identified as being at high risk of producing embryos with chromosomal abnormalities. These chromosomal abnormalities usually cause failure of implantation following repeated IVF embryo transfers, or miscarriages. In a minority of cases the embryos can develop to cause a pregnancy affected by a chromosomal abnormality such as trisomy 21 (Down's syndrome). Preimplantation genetic screening (PGS) is a technique, which allows embryos produced during an IVF treatment cycle to be tested for specific chromosomal abnormalities. Following the screening procedure only embryos that are identified as being normal for the chromosomes being analysed are considered for embryo transfer. Due to the increased selective power provided by this procedure, PGS may reduce miscarriage rates and improve both implantation rates and live birth rates in specific patient groups. The screening process involves looking at the chromosomes present in a single cell taken from a 3 day old embryo. PGS relies on the fact that chromosomally, this cell should be an identical copy of the remaining cells in the embryo. By inference if the cell is normal, it likely came from a normal embryo, and if it was abnormal from an abnormal embryo. Previous studies have shown that many human embryos are not made up of chromosomally identical cells. These embryos are called mosaic embryos. Mosaicism can affect the reliability and hence the benefits of PGS.

Our study aims to analyse single biopsied cells using comparative genome hybridization (CGH) or microarray techniques both of which can detect all the chromosomes in the cell. The results will be compared with the results obtained from the remaining embryo using FISH (a simpler technique able to reliably detect between 5 and 9 chromosomes in a single cell). This strategy will allow us to further investigate the incidence of mosaic embryos and the degree of mosaicism. In this way, we may be able to determine whether mosaicism is linked with a specific patient profile, such as age or IVF techniques such as embryo freezing and what degree of mosaicism an embryo can tolerate. This will ultimately improve the management of patients requesting PGS and help our understanding of early human development

Licensed research activities	Research on human embryos	**X**
	Storage of licensed material	**X**
	Creation of embryos for research	
	Derivation of human embryonic stem cells	
	Cell nuclear replacement	

Changes/ improvements since last inspection

One staff change has occurred since the last inspection, which the Authority has been informed about.

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

C	None

Summary for Licence Committee

Progress has been achieved in relation to the stated aims of the research project, and the principal investigator (and PR) has recently had a peer reviewed paper published in a scientific journal, concerning work undertaken as part of the project.

Issues from the last inspection have generally been resolved, but a number of recommendations from the present inspection are noted for the attention of the Committee;

- Formal minutes could be taken at research meetings in order to give structure and chronology to the decision-making process.
- A formal SOP to be written for the testing of the low oxygen alarm.
- A SOP to be written for the transfer of donated research material from storage at Cozens House, to the new research laboratory at 53 Portland Place.
- The relatively poor thaw rate (50%) experienced over the last twelve months, could probably be improved by better communication between 0068 and 0088, concerning the freezing/thawing solutions used on the donated material.

Both the peer reviewer and inspection team support the renewal of the research licence. (3 years)

Proposed licence variations

None

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	1
Scientists	0
Laboratory technicians	1
Support staff (receptionists, record managers, quality and risk managers etc)	0

Highlighted areas of firm compliance
The research PR has been in post since 2007 and was aware of the HFEA adverse incident reporting requirements. Monthly meetings occur with collaborators at local centres 0245 (UCL) and 0070 (Bridge) to discuss progress made with the research project, together with any other relevant issues. No formal minutes are made of the meetings, but notes are recorded in laboratory books. The research laboratory is secure and has restricted staff access to those personnel presently on the licence. The centre has a quality management system in place and all submitted documents; the patient information, patient consents and protocols, had evidence of version control. The research work is funded via Life-Force Research Limited (a registered charity) and has received ethical approval from an appropriately-constituted local research ethics committee (LREC).

Issues for consideration
Formal minutes could be taken at research meetings in order to give structure and chronology to the decision-making process.
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
Embryo biopsies are performed at centre 0088 and then the fixed, anonymised samples are transported to a local centre (0245) for subsequent genetic analysis. All equipment within the research lab is regularly serviced and maintained as evidenced by the relevant log books. All licensed material used within the research project is securely stored within locked cryodewars, which are fitted with low-nitrogen alarms. There is a low-oxygen monitor in place connected to an audio/visual alarm. The alarm system is tested weekly.
Issues for consideration
A formal SOP to be written for the testing of the low oxygen alarm.
Executive recommendations for Licence Committee
A SOP to be written for the transfer of donated research material from storage at Cozens House, to the new research laboratory at 53 Portland Place.
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
Donors are recruited from two centres; centre 0088 and centre 0068. The same recruitment and consenting procedure applies in both centres. Reference to the research project is first made to patients in their annual invoice for storage. This billing includes a deposition form which outlines their options; continued storage, allowing embryos to perish, donation to another couple or donation to research. Patients who indicate interest in donating embryos for research are sent further information and two copies of the consent form, one for the patient to keep. The patient information provides contact details should a patient require further information. Patient information also includes contact information for a counsellor should patients wish to discuss the implications of donating embryos to research. Embryos received from centre 0068 are accompanied by the patients' consent forms. These are checked upon arrival then filed and details added to the database. Following the last inspection a written procedure is now in place for when patients wish to withdraw consent to research, at any point up to when the embryos are used. This is also explained in the patient information. A system is now in place to ensure that all donated material is used within the time period indicated in patient consent forms.
Issues for consideration
None.
Executive recommendations for Licence Committee
None.
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
No discrepancies found during notes audit.
Highlighted areas of firm compliance
The patient information and consents for the research project were reviewed and considered to be compliant by the Executive. Patients are sent information about the project and are provided with contact details should they require further information. The consent forms are also included with this literature and patients can therefore keep one copy of their consent form for reference. As highlighted in the last inspection report, both the information sheet and consent form, given to patients donating material from centre 0068, have been amended to inform them that identifying information will be seen by research staff performing licensed activities at centre 0088.
Issues for consideration
None.
Executive recommendations for Licence Committee
None.
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
Frozen embryos for the research project are donated by patients at the London Fertility centre (0088) and the Leicester Fertility centre (0068). In the period 01/06/07-01/06/08, 38 frozen embryos were donated from centre 0088 and 22 frozen embryos from centre 0068. In total 60 embryos were donated to the project and all were utilised within the specified time period. It is anticipated that between 80-100 embryos will be utilised over the next 12 months.
Project objectives
The microarray analysis is the next part of the project to be carried out and hopefully provide results regarding the embryos' full chromosomal complement, as well as smaller gene defects from one single cell or from a handful of cells. Blastocyst biopsy will be perfected, which will allow more cells to be removed to achieve higher rates of results from array-CGH. Recent unpublished data from Wells *et al* (personal communication) have shown 75% pregnancy rate for women in advanced maternal age and/or recurrent IVF failure undergoing PGS whilst performing blastocyst biopsy and subsequently carrying out array-CGH.
Lay summary of research undertaken
This study was designed to look at the abnormalities occurring at the cleavage stage of development and if these abnormalities persist until later in development (blastocyst stage). The chromosomes that were selected are chromosomes that have been linked with early embryonic death, recurrent miscarriages as well as specific diseases. This research, so far, supports the previous evidence that specific chromosomes are more prone to exhibit abnormalities whilst carrying out IVF and should be investigated further. This research project showed that running a successful PGS program using these chromosomes, for specific group of patients, can aid in preventing the transfer of abnormal embryos and possibly reducing the risk of miscarriages. Furthermore, it showed that development of embryos to the blastocyst stage does not guarantee normal embryos, which is in agreement with previous studies (Sandalinas *et al,* 2001). During the study so far, the combination of CGH and FISH clearly demonstrated that chromosome breakage is rather frequent and can persist up until the blastocyst stage of preimplantation development.

Peer reviewers comments

The peer reviewer fully supported the renewal of the research licence, noted the recent publication of the PR, and stated that there was no doubt that the continuation of the project could be very helpful to the broad scientific and reproductive medicine community.

It was also noted that the poor embryo survival rate could also be improved by better scrutiny of freezing/thawing solutions.

Issues for consideration

The PR has recently had a peer reviewed paper published in a scientific journal, from work undertaken as part of the project.

> D.D. Daphnis, E. Fragouli, K. Economou, S. Jerkovic, I.L. Craft, J.D.A. Delhanty and J.C. Harper (2008). Analysis of the evolution of chromosome abnormalities in human embryos from Day 3 to 5 using CGH and FISH. *Mol Hum Reprod*, **14**(2), 117-125

Executive recommendations for Licence Committee

The relatively poor thaw rate (50%) experienced over the last twelve months, could probably be improved by better communication between 0068 and 0088, concerning the freezing/thawing solutions used on the donated material.

Both the peer reviewer and inspection team support the renewal of the research licence. (3 years)

Areas not covered in this inspection

None.

Report compiled by:

Name……Wil Lenton……..

Designation……Regulatory Inspector……..

Date……..22 July 2008……

Appendix A: Centre Staff interviewed

The PR and 1other staff member.

Appendix B: Licence history for previous 3 years

Licence	Status	Type	Start date	Expiry date
R0169/3/a	Active	Research Project	01/01/2008	31/12/2008
R0169/2/a	Active	Research Project	01/01/2007	31/12/2007
R0169/1/a	Active	Research Project	01/01/2006	31/12/2006
R0140/1/a	Expired	Research Project	01/10/2003	30/09/2004

- The R0140 was allowed to expire due to the research PRs departure from the centre.
- In 2006 the project R0140 was renewed as R0169 by the research PR Dr Alan Thornhill.

Appendix C:

RESPONSE OF PERSON RESPONSIBLE TO INSPECTION REPORT

Centre Number…….0088……..

Name of PR…… Danny Diamantis Daphnis, PhD ……

Date of Inspection…… 22/07/2008 ……

Date of Response…… 22/10/2008 …….

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

1. Formal minutes of meetings with collaborating research centres have already been performed following inspection. Minutes attached to the inspection report
2. An SOP for Low Oxygen Alarm has been drafted – awaiting QM controlled document
3. An SOP for the transfer of material from 112a Cozens House to 53 Portland Place has been drafted – awaiting QM controlled document
4. As stated during the inspection the PR for Research has already contacted centre number 0068 and appropriate thawing media will be purchased as required

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

Name……. Danny Diamantis Daphnis, PhD …….

Date……22/10/2008……..

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

19 November 2008
21 Bloomsbury Street London WC1B 3HF

MINUTES Item 1

Research Project RO169: Analysis of Chromosomes in Human Preimplantation embryos using FISH and CGH based at London Fertility Centre (0088)
Licence Renewal

Members of the Committee:	In Attendance:
Emily Jackson, Lay Member – Chair	Chris O'Toole, Head of Research Regulation
Richard Harries, Lay Member	Claudia Lally, Committee Secretary
Neva Haites, Professor of Medical Genetics, University of Aberdeen	
Maybeth Jamieson, Consultant Embryologist, Glasgow Royal Infirmary	Providing Legal Advice to the Committee: Sarah Ellson, FFW Solicitors

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

The following papers were considered by the Committee:

- papers for Licence Committee (54 pages)
- no papers were tabled.

1. The papers for this item were presented by Wil Lenton, HFEA Inspector. Mr Lenton informed the Committee that the renewal inspection of this project took place on 22 July. The inspection found that progress had been achieved in relation to the stated aims of the project and the Person Responsible had recently had a peer reviewed paper published in a scientific journal based on the findings of the research to date.

2. Mr Lenton drew the Committee's attention to the peer review of the project, which supported the renewal of the licence for a period of three years.

3. Mr Lenton briefly described the main findings of the inspection, summarised at page 4 of the report, and directed the Committee to the response to these findings by the Person Responsible, appended to the report at page 13. Mr Lenton informed the Committee that all the issues raised at the inspection have now been dealt with satisfactorily by the research team. Mr Lenton concluded by informing the Committee that the inspectorate recommends that the licence be renewed for a period of three years.

The Committee's Decision

4. The Committee applied the statutory tests in considering the application. To start, the Committee identified the activities under consideration as the storage of embryos and the use of donated embryos for research. The Committee agreed that these activities are not prohibited under the Human Fertilisation and Embryology Act 1990.

5. The Committee agreed that the activities appear to be necessary or desirable for the following specified purposes:

   - Increasing knowledge about the causes of miscarriages
     Human Fertilisation and Embryology Act 1990 Schedule 2 3(2)(c)

   - Developing methods for detecting the presence of gene or chromosome
     Abnormalities in embryos before implantation
     Human Fertilisation and Embryology Act 1990 Schedule 2 3(2)(e)

   - Increasing knowledge about the development of embryos
     Human Fertilisation and Embryology (Research Purposes) Regulations 2001 S 2(a)

   In making this decision, the Committee took account of the fact that chromosomal abnormalities affect the development of embryos and can lead to miscarriage. Therefore it is important that technologies are developed to identify these abnormalities.

6. The Committee agreed that they were satisfied that the proposed research could not be undertaken without the use of human embryos.

7. The Committee considered the patient information and consent forms being used for the project and agreed that these were appropriate.

8. The Committee decided that they were satisfied as to the suitability of the Person Responsible, the Nominal Licensee, and the premises. The Committee also noted that the renewal fee had been paid.

9. The Committee agreed that the statutory tests for the granting of a licence were satisfied and decided to renew this licence for a period of three years.

Signed..... Date 18.12.08
Emily Jackson (Chair)