Research Licence Interim 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
Centre Address	53 Portland Place London, W1B 1QZ
Treatment centres donating to this research project	0088 – London Fertility Centre 0068 Leicester Fertility Centre
Inspection date	28 April 2009
Licence Committee Date	15 July 2009
Inspector(s)	Mr Wil Lenton – Lead Inspector (HFEA) Mrs Gill Walsh – Clinical Inspector (HFEA) Mr Stephen Lynch – Scientific Advisor (External)
Fee Paid - date	N/A
Person Responsible	Dr Danny Daphnis
Nominal Licensee	Mr Lawrence Ashford
Licence expiry date	31 December 2011

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, sixth 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 02/06/2008 and 01/03/2009.

Brief Description of the Project

Project No: R0169c

Title: Analysis of Chromosomes in Human Preimplantation embryos using FISH and CGH

The project commenced in 1 January 2006 and the current licence is due to expire in 31 December 2011.

The project is licensed for the following activities:

- storage of embryos
- use of donated embryos for research

The project is licensed for the following purposes:

- increasing knowledge about the causes of miscarriages
  Human Fertilisation and Embryology Act 1990 Sch 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 Sch 2 3(2)(e)
- increasing knowledge about the development of embryos
  Human Fertilisation and Embryology (Research Purposes) Regulations 2001 s2(a)

Lay Summary of project R0169.

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 (named biopsy). 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

Furthermore, we would like to analyse the metabolic activity during embryo development. This can be achieved by utilising innovative technologies which are non-invasive to the embryo and are performed in the media the embryos are cultured in. It has been very recently suggested that there is correlation between embryonic metabolic activity and embryo implantation. This means that by assessing an embryo's metabolic activity we can predict its implantation rate. This can help IVF clinics accurately select the best embryo for transfer which would give a desired pregnancy. Such result can reduce multiple births and provide patients with higher pregnancy rates.

During this multi-step study we propose to investigate the possible correlation between morphology, genetic status and metabolic activity of an embryo. We aim to combine our experience in analysing genetic abnormalities at the embryonic level with the metabolic results. If such correlation exists it might be possible to predict the embryos' genetic status by assessing morphology and metabolic activity. This will eliminate the invasive examination of embryos by biopsy and reduce the cost of selecting the embryo with the greatest potential of implanting and giving a healthy pregnancy.

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

Changes/ improvements since last inspection

Formal minutes of meetings with collaborating research centres are now being taken/documented.

An SOP for the Low Oxygen Alarm is now in place

An SOP for the transfer of material from 112a Cozens House to 53 Portland Place is now in place

Ongoing communication with centre 0068 is underway in order to maximise the survival of donated embryos upon thawing.

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	**N/A**
A	**Complied Y/N**

Summary for Licence Committee

There has been no further progress made in the research project since the last inspection (22/07/08) due to the opening of new centre 0088 premises and the need to validate/standardise new premises, equipment and processes

No licensed material donated to research has been thawed and utilised within the new research laboratory to date.

As the new premises at 0088 have been operational since September 2008 and with clinical laboratory practices and outcomes reported as satisfactory, research work is scheduled to recommence in the very near future.

Once project work recommences the expected usage of licensed material is proposed to be in the region of 100 fresh embryos together with 50-70 frozen embryos.

The PR proposes a new objective, to combine genetic analysis (using FISH and CGH) together with embryo metabolic activity measurements to investigate the correlations (if any) between embryo morphology, metabolic activity and genetic status. The proposed studies aims to facilitate more accurate embryo selection within the clinical setting and facilitate more successful elective single embryo transfer (eSET). New patient information and consent forms have been formulated for the above-mentioned proposed new research objective.

As a consequence of the new research objective, The centre wishes to include, 'promoting advances in the treatment of infertility' (*Human Fertilisation and Embryology Act 1990 Sch 2 3(2)(a)*) as an additional purpose for their research project.

The executive recommend the continuation of the centre's licence.

Proposed licence variations

1. The centre wishes to include, 'promoting advances in the treatment of infertility' (*Human Fertilisation and Embryology Act 1990 Sch 2 3(2)(a)*) as an additional purpose for their ongoing research project.

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	1
Laboratory technicians	0
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. Meetings with collaborators at local centres 0245 (UCL) and 0070 (Bridge) to discuss progress made with the research project, together with any other relevant issues generally occur every 2 months. Formal minutes are now made of the meetings, which were evidenced by the inspectorate. 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
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 research laboratory has been relocated to new 0088 premises at 53 Portland Place, but due to validation/standardisation of equipment and processes within the new clinical laboratory, no further research work has been undertaken since the last inspection. The new premises were last inspected on 5th September 2008 and licensed for use at Licence Committee on 11 September 2008. Storage of licensed material for use in research is mainly at the former premises (Cozens House, 112A Harley Street) which is now centre 0308. Appropriate equipment such as low nitrogen alarms and low oxygen monitors were seen to be in place at centre 0308. All such critical equipment is regularly monitored and service contracts are in place providing adequate maintenance. A SOP was seen to be in place for the transfer of licensed material between the two centres, which are only a 5-10 minute walk away.
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
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. 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

Outcome of audit of records
No audit of records took place as no research work had been undertaken since the previous inspection (22/07/08)
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. New patient information and consent forms were supplied for future work to be undertaken which proposes to assess both genetic analysis and embryo metabolic studies.
Issues for consideration
None.
Executive recommendations for Licence Committee
None.
Areas not covered in this inspection
Notes audit - as no work has been undertaken since the last inspection.

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
- Ability to achieve set aims and objectives

Summary
There has been no further progress made in the research project since the last inspection (22/07/08) due to the opening of new centre premises (0088) and the need to validate/standardise both new premises, equipment and processes. No licensed material donated to research has been thawed and utilised within the new research laboratory to date. As the new premises at 0088 have been operational since September 2008 and with laboratory practices and outcomes reported as satisfactory, research work is scheduled to recommence in the very near future. Once project work recommences the expected usage of licensed material is proposed to be in the region of 100 fresh embryos together with 50-70 frozen embryos.
Renewed project objectives
From the submitted progress report the PR states, ' The microarray analysis is the next part of the project which will kick off and 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 The new area of metabolomics is proposed to be investigated. Using metabolic activity measurements we will be able to provide a rapid, non-invasive procedure during in vitro fertilization (IVF) cases. Current metabolomics instruments are designed to aid in the assessment of viable embryos with the greatest reproductive potential. Through the use of a highly sensitive method of biomarker identification, metabolic analysis can be performed in just minutes, requiring only a small amount of spent culture media. Metabolic activity measurement provides objective assessment of viability without compromising the embryo, helping guide treatment options for patients undergoing IVF.

Advantages of the metabolic activity measurements include:

- Non-invasive assessment of embryo viability
- Complete analysis in less than one minute
- Requires small sample size (10µL) of spent culture media
- Small, user friendly instrumentation (*proposed instrument to be used ViaMetric™ from Molecular Biometrics, US*)
- Assimilates easily into current laboratory practice

There have been some studies indicating the use, practicality and positive results by combining embryo morphology assessment with metabolic activity measurements (Botros *et al,* 2008; Seli *et al,* 2008; Scott *et al,* 2008; Vergouw *et al,* 2008)

We propose to take the above mentioned studies a step further and attempt to combine our experience with genetic analysis using FISH and CGH along with the metabolic activity measurements using the *ViaMetric™* instrument and investigate the correlations (if any) between embryo morphology, metabolic activity of embryos and genetic status of embryos. This will enable us to achieve better and more accurate selection of embryos that will give rise to pregnancy. Hopefully, the addition of metabolic activity measurements in clinical patients (following our study) can promote elective single embryo transfer (eSET) since the embryo selected would be most viable one.'

Summary of research undertaken

No research work has been undertaken over the last 6 months, due to relocation to new premises.

Project work is due to recommence in the very near future.

New objectives have been proposed to study the combined effects of genetic analysis with measurement of embryo metabolic activity in order to ascertain whether this dual approach can give rise to more accurate selection of viable embryos within the clinical setting.

Peer reviewers comments

N/A

Issues for consideration

The centre propose to include Reprogenetics and Dr Dagan Wells as scientific collaborators in forthcoming research work.

Executive recommendations for Licence Committee

As indicated in the progress report and due to renewed objectives the centre wish to include the additional research purpose, 'promoting advances in the treatment of infertility' (*Human Fertilisation and Embryology Act 1990 Sch 2 3(2)(a)*) on their licence.

Areas not covered in this inspection
None.

Report compiled by:

Name…….....Wil Lenton……

Designation…….....Inspector…….....

Date…….....28 April 2009……

Appendix A: Centre Staff interviewed

The research PR.

Appendix B: Licence history for previous 3 years

Licence	Status	Type	Start date	Expiry date
R0169/4/a	Active	Research Project	01/01/2009	31/12/2011
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……. Dr Danny Daphnis …….

Date of Inspection…….28th April 2009……..

Date of Response……12th June 2009……

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

UCL collaboration will recommence with embryos thawed and utilised for the combination analysis of chromosomes (i.e CGH and FISH) and metabolomics.

Upon receiving the authorised minutes of the LC the PR is ready thaw and utilise embryos with Reprogenetics to kick-start the CGH-Array part of the project.

One of London Fertility Centre's Quality Objectives is to continue to participate in research projects to aid our understanding of treatment techniques and processes. London Fertility Centre (LFC) has a long history of research and pioneering techniques and is committed to continuing research activity. LFC is pleased with the contents of this HFEA interim inspection report

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

Name……. Dr Danny Daphnis ……..

Date……12/6/2009……

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).

None

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

HFEA Research Licence Committee Meeting

15 July 2009

21 Bloomsbury Street London WC1B 3HF

Minutes – Item 8

London Fertility Clinic (0088; R0169) – Interim Report

Members of the Committee:

Emily Jackson (lay) – Chair
Richard Harries (lay)
David Archard (lay)
Lesley Regan (clinician)
Hossam Abdalla (clinician)

Committee Secretary:
Kristen Veblen

Legal Adviser:
Sarah Ellson, Field Fisher Waterhouse

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 (43 pages)
- no tabled papers.

The Committee also had before it:

- HFEA Protocol for the Conduct of Licence Committee Meetings and Hearings
- 7th edition of the HFEA Code of Practice
- Human Fertilisation and Embryology Act 1990 (as amended)
- HFEA (Licence Committees and Appeals) Regulations 1991 (SI 1991/1889)
- Decision Trees for Granting and Renewing Licences and Considering Requests to Vary a Licence; and
- Guidance for members of Authority and Committees on the handling of conflicts of interest approved by the Authority on 21 January 2009.

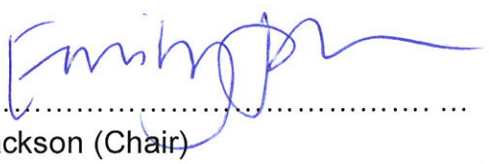
1. The Committee considered the report of the interim inspection conducted on 28 April 2009 and the response of the PR received 12 June 2009. The

Committee also considered the supplied progress report and the patient information sheet and consent form.

2. The Committee considered that this study is designed to investigate the incidence of mosaic embryos and the degree of mosaicism to determine if it was linked with a specific patient profile and the extent to which an embryo can tolerate mosaicism. Additionally, the study will analyse metabolic activity during embryo development. Ultimately, the outcome of this study will improve understanding of early human development and will assist in the selection of an embryo which will yield the best chance of implantation and a healthy pregnancy.
3. The Committee noted the goals of the study:
    - Increasing knowledge about the causes of miscarriages *HFE Act 1990 (as amended) Schedule 2 3(2)(c)*
    - developing methods for detecting the presence of gene or chromosome abnormalities in embryos before implantation *HFE Act 1990 (as amended) Schedule 2 3(2)(e)*
    - increasing knowledge about the development of embryos *HFE (Research Purposes) Regulations 2001 s2(b)*
4. Further these goals, the Committee noted and agreed with the addition of a further purpose of "promoting advances in the treatment of infertility" (*HFE Act 1990 (as amended) 2 3(2)(a)).*

<u>The Committee's Decision</u>

5. The Committee decided that the licence should continue with no additional conditions.



30.7.09.

Signed..... ... Date.....

Emily Jackson (Chair)