



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
Centre Address	Cozens House, 112a Harley Street, London W1G 7JH
Treatment centres donating to this research project	Leicester Fertility Centre 0068
Inspection date	7 th June 2007
Licence Committee Date	25 th July 2007
Inspector(s)	Miss Sarah Hopper (Lead)
	Dr Vicki Lamb
Fee Paid - date	Pending
Person Responsible	Dr Diamantis Daphnis
Nominal Licensee	Mr Lawrence Ashford
Licence expiry date	31/12/2007

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 August 2006 and June 2007.

Brief Description of the Research Project and PR

The Research project is entitled: Analysis of chromosomes in human preimplantation embryos using FISH and CGH.

The project was originally licensed under purposes laid down in Schedule 2 of the Human Fertilisation and Embryology Act 1990; 3(2)(e) to develop methods for detecting the presence of gene or chromosome abnormalities in embryos before implantation.

Lay Summary:

“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 both on day 3 and day 5. 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 as well as the incidence of mosaicism in day

3 and day 5 embryos. 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 embryos in different stages of development”.

Work under this licence involves the biopsy of day three embryos to remove two cells on day three and plan to do 5-7cells on day five. These cells are then tested, one with Comparative Genomic Hybridisation (CGH) and one with microarray analysis, to determine chromosome constitution. This analysis is carried out at the Human Genetics and Embryology Laboratories, University College, London (centre 0245) and plan to utilise the services of the Bridge Fertility Centre (Centre 70). Post biopsy the embryos will be cultured to assess developmental competence.

The PR has been in post since January 2007.

Activities of the Centre	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

- There have been no changes in staff or equipment since the last inspection.

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

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Summary for Licence Committee

Progress has been achieved in relation to the stated aims of the research project.

Two areas of non-compliance were noted during the inspection;

- Six breaches were noted during the inspection. Embryos donated to research had been stored beyond the statutory storage period. The PR must develop an effective bring-forward system to ensure that embryos are used before the statutory storage period expires.
- One set of embryos which were awaiting use in research had been generated using donor sperm but the donor's consent to research had not been confirmed. The PR should ensure that the valid consent to research is in place for both gamete providers before embryos are used in research.

The following recommendations were also made:

- It is recommended that the PR should document the steps that should be taken if a patient withdraws consent for use of the embryos in research
- The laboratory protocol for research (Lab Pro 15) mentions that embryos can be used in research projects including ES cell lines research. However, the centre is not licensed for this project and therefore the protocol does not correspond to the aims and objectives of the licence. Furthermore, the protocol could possibly mislead/confuse any new members of staff. When questioned regarding this, the PR explained that the protocol needed updating and that it would be reviewed appropriately.

The peer reviewer supported the renewal of the research licence. The Executive recommend renewal of the licence for 1 year.

Proposed licence variations

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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
Laboratory technicians	1
Administrators	n/a
Collaborators	2
Support staff (receptionists, record managers, quality and risk managers etc)	n/a

Summary

The PR oversees and coordinates the research project activities. Embryo biopsies are carried out at the London Fertility Centre by three of the embryologists and the genetic analysis occurs at UCL by the principal investigator.

Meetings are held on a monthly basis with the co-supervisor and principal investigator at UCL. The PR also meets with the Bridge genetics department twice a month. No minutes are kept of these meetings but the PR stated that communications are logged electronically.

Information about the research project is shared with other members of staff at centre 0088 during the monthly unit meetings. The PR also has the opportunity to disseminate research information to the staff at the satellite centres at quarterly meetings.

The PR stated that he contacts Leicester Fertility Centre (Centre 0068) to discuss research project issues via telephone but he has not actually met the team yet.

All submitted documents; the patient information, patient consents and protocols, had evidence of version control.

The project is funded by Life-Force Research Limited. It has received ethical approval from an ethics committee which is properly constituted; the committee has a lay representation of more than five members and members which are independent of the research project.

Issues for consideration

The PR wishes to send slides for analysis to the genetic diagnosis service at the London Bridge Gynaecology and Genetics Centre (0070) in addition to using the laboratory service at University College Hospital (centre 0245). The genetic diagnosis service at centre 0070 is already used for clinical diagnostic work for PGS cases conducted at the centre and the treatment licence at centre 0088 was varied to reflect this on the 11th October 2006. Patient information should be updated to reflect that work will be performed in collaboration with centre 0070.

Executive recommendations for Licence Committee

The Licence Committee are asked to note that the genetic analysis element of research work will be conducted at centre 0245 and centre 0070 in the future.

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

Summary
<p>The first stage of research is conducted in the clinical laboratory at centre 0088. Within this laboratory the embryos are biopsied, cultured and fixed. Following fixation the slides are taken to Human Genetics & Embryology Laboratories, centre 0245 for analysis either by FISH, CGH or microarray techniques. The slides are labelled with the patient number which is non-identifying to the collaborator.</p> <p>During the inspection it was noted the laboratory is manned during working hours and secured out of office hours.</p> <p>The research team have the necessary equipment required to undertake the stated objectives.</p> <p>Embryos donated to research are stored in locked dewars. Those donated by patients at centre 0088 are not moved from their original locations and donated embryos transferred from centre 0068 are allocated a space within the general dewars on arrival. All of the dewars were seen to be fitted with temperature probes connected to alarms. A low oxygen alarm is present in the cryostore and all alarms are connected to an autodialler system.</p> <p>The equipment within the laboratory had up to date service contracts which were examined during the inspection.</p>
Issues for consideration
<p>It is suggested that the general research protocol is revised to ensure that all laboratory staff are aware that any fixed material leaving the London Fertility Centre should be non-patient identifying.</p>
Executive recommendations for Licence Committee
<p>None</p>
Areas not covered by this inspection
<p>Laboratory premises at 0245 were not assessed as part of this inspection.</p>

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

Summary

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.

Patients are able to withdraw consent to research at anytime up to when they are used, this is explained in the patient information although the exact process to be followed is not documented.

Issues for consideration

Although the PR was able to articulate the response which would be taken by laboratory staff if a patient was to withdraw their consent to research, this procedure has not been formalised as a SOP. It is recommended that the PR should document the response that should be taken if a patient withdraws consent for use of the embryos in research

During the audit of the research file it was noted that patient consent forms had been breached on six occasions; embryos were still in storage despite the fact that the statutory storage period had expired (see Section 4).

One set of embryos donated to research had originally been created using donor sperm; however, the sperm donors consent to research had not been checked. The PR must ensure that a robust system is in place to ensure that all gamete providers' consents are complied with.

Executive recommendations for Licence Committee
Note the breach of statutory storage period on six occasions.
Note that embryos which were due to be used in research were donated without evidence of the consent of one of the gamete providers. Had the embryos been incorporated in the research project this could have lead to a breach of the gamete provider's consent.
Areas not covered on this inspection
Donor and patient records at centre 0068

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

Summary
<p>The patient information and consents for the research project are considered satisfactory by the Executive.</p> <p>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.</p> <p>According to the PR each patient's consent to research is witnessed before embryos are used in research; two members of staff have to match the signatures on the completed research form with the original HFEA consent forms (previously 006/007 forms and now WT and MT forms). This procedure was also explained in the disposal of cryopreserved embryos protocol which was submitted with the application.</p>
Summary of records audit
<p>5 sets of research notes were examined for appropriate consents. In one set of records it was noted that the consent for research from a sperm donor had not been checked. The PR did not have a policy of checking these consents prior to embryo use in research and was advised that the consent forms from both gamete providers must always be reviewed to ensure valid consent.</p> <p>A check of the entire research file found that six sets of embryos were in storage even though the statutory storage period had expired.</p>
Issues for consideration
<p>At the last inspection it was recommended that the patient information and consent forms should be amended to explain to patients from centre 0068 that identifying information, which is present on consent forms and the labelling of embryo storage vessels, will be disclosed to members of the laboratory team at centre 0088. The patient information has not been changed to reflect this.</p>
Executive recommendations for Licence Committee
<p>Note that a recommendation made at a previous inspection has not been complied with.</p>
Areas not covered on this inspection
<p>The original patient files at centre 0068 were not inspected.</p>

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
<p>The centre expected to use approximately 100 frozen embryos per year. 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 01/06/06-01/05/07 53 embryos were received from centre 0088 and 48 embryos from centre 0068. In total 101 embryos were received and of these 82 have been used within the project. The remaining embryos are still in storage awaiting incorporation into the project.</p> <p>In the next year the PR plans to use 100 frozen embryos in the project.</p>
Summary of audit of stored material
<p>Material for research is stored in general dewars. Laboratory staff audit the contents of the dewars on a rolling basis, and in the last year tanks were audited between June 2006-March 2007. The most recent audit report submitted to the HFEA stated that some discrepancies had been noted and responded to.</p> <p>Inspectorate audit of stored material: Two embryos donated to research were tracked from the research file to the dewar. No discrepancies were noted.</p>
Renewed project objectives
<p>The PR stated that:</p> <p>“To complete the first stage of this study, we wish to analyse at least 40 human embryos. Ideally, 2 cells need to be analysed from each embryo with a CGH single cell result from 90% of the cells. We have recently modified our culture policy for treatment to allow more blastocyst culture (in the hopes of increasing implantation and reducing multiple gestation rates). As a result more spare embryos donated for research may develop into blastocysts, thus providing sufficient working material to draw valid, scientific conclusions from our results with a view to publication”.</p>
Summary of research undertaken
<p>The PR reported that:</p> <p>“A total of 77 embryos have been thawed and at least one cell from each embryo was biopsied for CGH. Approximately 70% (55) were spread and sent to the genetics lab for FISH. 36/55 (65%) of the embryos had at least one cell to carry out FISH on day 5. FISH was able to give a result for 29/36 (81%) of the embryos. 27% of the embryos were found to be normal for the chromosomes tested. 45% of the embryos showed a chaotic complement and 25% revealed low level mosaicism. Only one embryo (3%) was found to be completely abnormal</p>

(in this case haploid).”
CGH results are still awaited; the PR has given UCH a deadline for these results and expects them to be submitted before the licence expires.
Peer review comments (if applicable)
The Peer Reviewer stated that: “This is an ongoing and interesting study which will produce results of value to developmental geneticists and which may offer genuine clinical benefits to some patient groups. The rate of progress is inevitably constrained by the availability of material, however, the applicants have an excellent track record within the field, and within these constraints should be well placed to produce a positive outcome”.
The Peer Reviewer recommended that the application be accepted in its current form.
Issues for consideration
The laboratory protocol for research (Lab Pro 15) mentions that embryos can be used in research projects including FISH, PCR projects, ES cell lines. However, the centre is not licensed for research on ES cell line projects and therefore the protocol does not correspond to the aims and objectives of the licence. Furthermore, the protocol could possibly mislead/confuse any new members of staff. When questioned regarding this, the PR explained that the protocol needed updating and that it would be reviewed appropriately.
Executive recommendations for Licence Committee
None
Areas not covered on this inspection
None

Report compiled by:

Name: Sarah Hopper

Designation: Inspector

Date: 8th June 2007

Appendix A: Centre Staff interviewed

The PR.

Appendix B: Licence history for previous 3 years

Licence	Status	Type	Start date	Expiry date
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 088

Name of PR: Dr Danny Daphnis
Date of Inspection: 07/07/2007

Date of Response: 12/07/2007

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

LabPro14 has been amended to include:

1. To ensure all relevant consents are in place when allocating embryos for research.
2. The procedure of withdrawal of consent
3. ES lines project has been removed from protocol
4. That all fixed material is non patient-identifying and is referenced by patient number

Separate patient information sheets and consent forms have been generated (attached) for the centre 0068 which provides research embryos

PR has asked for a more rapid response from UCL regarding the CGH results of the study and they are expected by the end of summer 2007.

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

Signed.....

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).

Page 1:

States the Inspection Date as 8th June, but we were inspected on 7th June. This is definitely a factual inaccuracy.

Page 2-3: Lay Summary change of the last two paragraphs

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 both on day 3 and day 5. 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 as well as the incidence of mosaicism in day 3 and day 5 embryos. 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 embryos in different stages of development”.

Work under this licence involves the biopsy of day three embryos to remove two cells on day three and plan to do 5-7 cells on day five. These cells are then tested, one with Comparative Genomic Hybridisation (CGH) and one with microarray analysis, to determine chromosome constitution. This analysis is carried out at the Human Genetics and Embryology Laboratories, University College, London (centre 0245) and plan to utilise the services of the Bridge Fertility Centre (Centre 70). Post biopsy the embryos will be cultured to assess developmental competence.

Page 4: Summary for Licence Committee

There were only 4 x Breeches of embryos which were stored after their storage period had expired and not 6 as stated.

The PR does check the presence of valid donor consents before usage of embryos. However, PR does not check consents are in place when allocating embryos to research. Therefore, the protocol will be amended to ensure all relevant consents are in place when allocating embryos for research. The Centre does not believe that this section has been worded correctly as the consents are checked prior to the usage of the embryos for research.

Page 4: Recommendations

LabPro14 (attached) states the procedure of withdrawal of consent.

The ES lines project has been removed from protocol, however, PCR is licensed since PCR is an integral part of the CGH protocol

Page 5: Summary

Minutes of the unit meeting minutes (attached) whereby evidence is provided regarding the update of research project to staff of LFC

Page 6: Issues for consideration

UCL is referred to as centre 0245 in the whole document apart from page 6 where it is referred to as centre 0044

Page 7: Issues for consideration

LabPro14 (attached) states that all fixed material is non patient-identifying and is referenced by patient number.

Page 10:

Separate patient information sheets and consent forms have been generated (attached) for the centre 0068 which provides research embryos.

Page 12:

States Date as 8th May but we were not inspected until 7th June so this is definitely a factual

inaccuracy

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