Research Licence Inspection Report

Project Title Research Licence Number Person Responsible Nominal Licensee Inspection type Licence expiry date Date Renewal fee paid	**Development of a model to study implantation in the human** R0111 Karen Turner Ian Sargent **Interim** 31 August 2009
Project Title Research licence Number Person Responsible Nominal Licensee Inspection type Licence expiry date Date Renewal fee paid	**To derive human embryonic stem cells and trophoblast cell lines** R0143 Karen Turner Helen Mardon **Interim** 31 August 2009
Project Title Research licence Number Person Responsible Nominal Licensee Inspection type Licence expiry date Date Renewal fee paid	**To develop pre-implantation genetic diagnosis (PGD) for mitochondrial DNA disease** R0149 Karen Turner Stephen Kennedy **Interim** 31 August 2009
Centre Number	0035
Centre Name	Oxford Fertility Unit
Centre Address	Level 4, Women's Centre John Radcliffe Hospital, Headington, Oxford, OX3 9DU
Treatment centres donating to these research projects	0035 – Oxford Fertility Unit 0139 – Bath Assisted Conception Clinic 0064 – BMI The Chiltern Hospital Fertility Services Unit
Inspection date	9th May 2007
Licence Committee Date	25th July 2007
Inspector(s)	Wil Lenton, Tony Knox, Bryan Woodward

About the Inspection:

The purpose of the inspection is to ensure that research is carried out 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 makes the decision about the centre's licence renewal application. The report is also available to patients and the public following the Licence Committee meeting.

Brief Description of the Projects

Project **R0111**: "**Development of a Model to Study Implantation in the Human**"
Licensed since: 9th March 1998.

The lay summary of the project is as follows:

> Pre-implantation embryos produce a range of factors which are important in the implantation process. One such factor, called HLA-G, is believed to play a key role in preventing the implanting embryo from being rejected by the mother's immune system. Recent reports in the literature have suggested that measuring HLA-G in the culture medium from IVF embryos may allow embryologists to predict which embryos are most likely to implant and form pregnancies. If true, this could have a major impact on IVF success rates as it would provide a way of selecting the "best" embryos to transfer. However, not all researchers agree with these findings and there are some doubts about the accuracy of the test for HLA-G. We have therefore investigated the expression of HLA-G at different stages of embryo development and, contrary to the published work, have been unable to find it in the early stages (2-8 cell) when IVF embryos are normally replaced in the mother. We are now extending our studies in collaboration with eight other IVF Units as part of a European Network of Excellence set up to investigate the control of embryo implantation. We have also set up novel experimental models to explore further the molecular events that underpin implantation. These have revealed other factors, including soluble growth factors that are produced by both the embryo and the endometrium, and proteins that exist in a matrix surrounding the cells that make up the endometrium that appear to be important in implantation. We will now work out at what stage in the implantation process they are important and what their function is. In addition there are likely to be many other molecules that are produced in the endometrium as the embryo implants that are required for successful implantation. We are identifying such molecules by a technique called DNA microarray profiling, and will go on to validate their production and function in our experimental model systems.

References:

Sargent IL, Swales AK, Ledee N, Kozma N, Tabiasco J and LeBouteiller P (2007) sHLA-G production by human IVF embryos : can it be measured reliably ? J.Reprod Immunol (in press)

Yao YQ, Barlow DH and Sargent IL. (2005) Differential expression of alternatively spliced transcripts of HLA-G in human blastocysts and inner cell masses. J Immunol, 175 8379-8385

Chobotova K, Spyropoulou I, Carver J, Manek S, Heath JK, Gullick WJ, Barlow DH, Sargent IL and Mardo, HJ (2002) Heparin binding epidermal growth factor and its receptor ErbB4 mediate implantation of the human blastocyst. Mechanisims of Devlopemnt. 119, 137-144.

Carver J, Martin K, Spyropoulou I, Barlow D, Sargent IL and Mardon, HJ (2003) An in vitro model for stromal invasion during implantation of human blastocyst. Human Reproduction. 18, 2 283-290

Project **R0143**: "**To derive human embryonic stem cells and trophoblast cell lines**"
Licensed since: 2003.

The lay summary of the project is as follows:

There is considerable scientific and medical interest in the possibility that stem cells may make new treatment approaches possible for many chronic diseases, including diabetes, heart disease and nervous system diseases such as Parkinson's disease. These new therapies will be possible because stem cells, which are found in the very early embryo, have the potential to form every cell type in the body. It is now possible to isolate these cells from the embryo, maintain them in culture in their stem cell state in the laboratory, and, alternatively, tweak them to develop into different cell types, such as heart, bone and muscle cells.

This project seeks to understand how to maintain stem cells in culture, and how to promote them to develop into different cell types. Stem cells will be obtained from the very early embryo, at a stage known as the blastocyst at about six days after conception, when it is smaller than a pinhead and contains just one hundred cells. At this early stage, there are just two types of cells, the stem cells and another type of cell, known as the trophectoderm that will go on to develop into the placenta. Stem cells will be isolated and grown in culture. The factors controlling their maintenance as stem cells as well as the molecular instructions that direct their development into different cell types will be studied. The trophectoderm will also be isolated and cultured so that we can understand what factors are important in development of the placenta.

The overall aims of our research are to improve our understanding of how stem cells can be maintained and controlled to develop into specific cell types, to study diseases of pregnancy that involve abnormalities in the cells which will ultimately become the placenta. It is anticipated that our discoveries will contribute not only to the design of new stem cell based treatments in the future, but to our understanding of how such diseases develop in the first place.

Project **R0149**: "**To Develop Pre-implantation Genetic Diagnosis (PGD) for Mitochondrial DNA Disease derive human embryonic stem cells and trophoblast cell lines**"
Licensed since: 20 May 2004.

The lay summary of the project is as follows:

Mitochondrial diseases affect about 1 in 10,000 people in the UK. Examples include Maternally inherited Leigh Syndrome (MILS), Myoclonic epilepsy and ragged red fibres (MERRF) syndrome, Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS), and Pearson syndrome. The diseases may involve any parts of the body that have a high energy demand (such as brain, heart muscle and liver), because mitochondria are the "power houses" in cells.

Some women are carriers of defective mitochondrial genes. This means that they carry both normal and damaged mitochondrial genes, and can pass these devastating conditions on to any children they may have. It is particularly difficult to advise these women about the size of their individual risk, because the rules governing transmission of mitochondrial genes are not well understood.

The aim of this research is to establish the techniques for identifying defects in mitochondrial DNA in human embryos created by IVF to allow the selection of non-affected embryos for transfer to the mother. This technique is referred to as pre-implantation genetic diagnosis (PGD).

We have demonstrated that we can successfully sample embryos and have started to develop our analysis of their mitochondrial genes. So far we have identified one woman in whom we were able to assess the way that the mitochondrial genes are transmitted. Preliminary results from this woman's embryos were generally encouraging. Further work is required to provide basic scientific information and enable us to determine whether PGD will be useful in certain mtDNA diseases.

		R0111	R0143	R0149
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

There have been no changes in premises since the last inspection.
A number of staff changes have occurred. The PR has supplied the Executive with names and CV's of new staff members.

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

R	**PR to ensure robust double-witnessing procedures in place in relation to its activities**
A	**Complied Y/N** **Yes**

Summary for Licence Committee

- The inspectorate were satisfied that the centre is well organised and that work has progressed in two out of the three projects.
- With respect to research project R0149, where no significant developments have occurred since the previous inspection, it is recommended that the centre inform the Authority when the new Scientific lead, Dr Dagan Wells is in post.
- PR to inform the Authority when the new research nurse is in post.
- PR to ensure that updated information concerning research projects is regularly disseminated to nursing staff.

The inspectorate recommends the continuation of the research licence(s) without additional conditions.

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:

- Leadership and management
- Staffing

Staff R0111

Principal investigator	Ian Sargent
Scientists	4 research embryologists 2 clinical embryologists
Laboratory technicians	0
Support staff (receptionists, record managers, quality and risk managers etc)	1 Research Nurse

Staff R0143

Principal investigator	Helen Mardon
Research technicians	1
Scientists	2
Support staff (receptionists, record managers, quality and risk managers etc)	2

Staff R0149

Principal investigator	Joanna Poulton
Research technicians	0
Scientists	1
Support staff (receptionists, record managers, quality and risk managers etc)	2

Highlighted areas of firm compliance

Renewal applications for the three projects have been submitted to the HFEA as required.

The three research projects are led by the same PR. The PR has extensive knowledge of the regulatory requirements of the HFEA as an external advisor for the HFEA and has managed the projects since their inceptions.

The inspection team were informed by both the PR and individual research staff that informal meetings between the principal investigators and the researchers occur on a weekly basis.

A more formal research meeting between the PR and principal investigators is held as and when required, which is usually 1-2 per year. Progress of the projects and all matters relating to the projects are discussed and minuted as evidenced by the team during the inspection.

Funding has been identified for each project as detailed below;

	R0111	R0143	R0149
Funding source	European Network of Excellence on Embryo Implantation Control (EMBIC) Medical Research Council (MRC) The Wellcome Trust	MRC	IVF Unit Research Funds

The inspection team were informed by the PR that as requested by the Licence Committee double witnessing was now checked when embryos are transferred to research. This was observed when patient notes were reviewed.

There is an anticipated change to new premises within the next twelve months.

Areas for improvement

No research nurse was in post during the time of the visit.

Executive recommendations for Licence Committee

The centre should inform the Authority once a research nurse is in post

2. Premises and equipment

Desired Outcome: The premises and equipment are safe, secure and suitable for their purpose.

Summary of findings from inspection:

- Suitability of premises

Highlighted areas of firm compliance
The embryos utilised in the research programmes are securely stored within the laboratory cryostorage area. Low-nitrogen alarms were in place together with a low-oxygen sensor which was connected to an external audio/visual alarm. Both the research laboratory and image-analysis rooms were seen to be securely locked, with keypad access. Equipment within the research laboratory was seen to have up to date service logs.
Areas for improvement
None
Executive recommendations for Licence Committee
No improvement required

3. Donation of material

Desired outcome: Ensure donors are recruited in a proper way and their consent is respected.

Summary of findings from inspection:

- Recruitment of donors
- Ensuring prospective donors have access to further guidance
- Ensuring prospective donors have time to consider donation properly
- Donor and patient records

Highlighted areas of firm compliance
The pathway for donation of material to research begins when new patients attend a unit open evening. The process is mentioned as part of the general presentation. Information is then sent to all couples prior to their initial consultation, together with other general information and consent forms. This will then be followed up with further information upon request during the first consultation. Counselling is available at all times should couples require further information/clarification.
Areas for improvement
None
Executive recommendations for Licence Committee
No improvement required

4. Patient information and consents

Desired outcome: Ensure that patients are informed in order to give informed consent

Summary of findings from inspection:

- Patient information
- Consent forms

Highlighted areas of firm compliance
The patient information and consent form for project R0143 is currently designed by the UK Human Embryonic Stem Cell group. Patient information is updated as required as part of the audit process. Full discussions take place with trained nursing staff and/or counsellor prior to consents being signed by the patients. It is made known that these consents can be varied or withdrawn at any time by the patients. The process of transfer of embryos to research staff is double-witnessed, both in the notes and in the research laboratory. The embryos are anonymised in the research laboratory log-book (IVF cycle number converted to research code number). Research workers subsequently work with material which has research coding.
Summary of audit of patient records
Patients notes observed on the day of inspection found to be satisfactory.
Areas for improvement
In the absence of a specific research nurse coordinator, nursing staff should be kept up to date with current research information if they are to speak to patients about research projects.
Executive recommendations for Licence Committee
PR to ensure that updated information concerning research projects is regularly disseminated to nursing staff.

5. Scientific practice R0111

Desired outcome: Procedures are robust to ensure material is used appropriately

Summary of findings from inspection:

- Use of material
- Progress in achieving aims and objectives

Use of Material

Six hundred and thirty five (635) fresh embryos together with one hundred and eighty two (182) frozen embryos were used during the period covered by this report

Project objectives

To develop in vitro models to study how human embryo attaches, invades and interacts with the different cell populations of the endometrium during implantation and the molecules involved in these processes.

Lay summary of research undertaken

Pre-implantation embryos produce a range of factors which are important in the implantation process. One such factor, called HLA-G, is believed to play a key role in preventing the implanting embryo from being rejected by the mother's immune system. Recent reports in the literature have suggested that measuring HLA-G in the culture medium from IVF embryos may allow embryologists to predict which embryos are most likely to implant and form pregnancies. If true, this could have a major impact on IVF success rates as it would provide a way of selecting the "best" embryos to transfer. However, not all researchers agree with these findings and there are some doubts about the accuracy of the test for HLA-G. We have therefore investigated the expression of HLA-G at different stages of embryo development and, contrary to the published work, have been unable to find it in the early stages (2-8 cell) when IVF embryos are normally replaced in the mother. We are now extending our studies in collaboration with eight other IVF Units as part of a European Network of Excellence set up to investigate the control of embryo implantation. We have also set up novel experimental models to explore further the molecular events that underpin implantation. These have revealed other factors, including soluble growth factors that are produced by both the embryo and the endometrium, and proteins that exist in a matrix surrounding the cells that make up the endometrium that appear to be important in implantation. We will now work out at what stage in the implantation process they are important and what their function is. In addition there are likely to be many other molecules that are produced in the endometrium as the embryo implants that are required for successful implantation. We are identifying such molecules by a technique called DNA microarray profiling, and will go on to validate their production and function in our experimental model systems.

Progress of research

Good progress continues to be made with this project, despite some minor setbacks such as;

1. failure of a research microscope
2. immunohistochemistry problems
3. change in clinical IVF medium

Future work is planned to build on the last twelve months progress, with possible collaboration with research teams in other European countries.

A peer-reviewed paper has been submitted for publication and future funding from three sources has been identified.

Executive recommendations for Licence Committee

None

Areas not covered in by this inspection

None

	Purpose or purposes of the research project	**Currently licensed purposes**	**Proposed licence purposes**
4.3.1	promoting advances in the treatment of infertility *Human Fertilisation and Embryology Act 1990 Sch 2 3(2)(a)*	☒	☐
4.3.3	increasing knowledge about the causes of miscarriages *Human Fertilisation and Embryology Act 1990 Sch 2 3(2)(c)*	☒	☐
4.3.6	increasing knowledge about the development of embryos *Human Fertilisation and Embryology (Research Purposes) Regulations 2001 s2(a)*	☒	☐

6. Scientific practice R0143

Desired outcome: Procedures are robust to ensure material is used appropriately

Summary of findings from inspection:

- Use of material
- Progress in achieving aims and objectives

Use of material
Sixty-six fresh embryos were utilised in the period covered by the report.
Project Objectives
The objectives of the project are to; i) derive new human embryonic stem cell lines from blastocysts, and ii) determine the expression and function of specific extracellular matrix molecules in human embryonic stem cell renewal and differentiation. In order to chieve this blastocysts are grown in culture from day two or day three embryos that are surplus to clincial requirements and donated by couples attending the Oxford IVF Unit. They are then either processed for stem cell derivation or detection of extracellular matrix components.
Lay summary of research undertaken
Of the 66 two or three-day old embryos that were donated for this research, only 6 underwent further development in culture and progressed to blastocysts of sufficient quality to process for stem cell derivation. All 6 were subjected to immunosurgery but none remained viable subsequent to this treatment, and did not survive in culture on the mouse embryonic feeder cell layers.
Progress of research
It is widely accepted that successful human embryonic stem cell derivation depends upon starting with only the highest quality blastocysts. Lower numbers of blastocysts than expected were obtained, because the clinical laboratory has changed the embryo culture media, resulting in a higher number of high quality embryos, a higher proportion of which the patients have opted to have cryopreserved. This has meant a reduction in the number of good quality spare embryos for this research.
Executive recommendations for Licence Committee
None
Areas not covered in by this inspection
None

	Purpose or purposes of the research project	**Currently licensed purposes**	P**roposed licence purposes**
4.3.6	increasing knowledge about the development of embryos *Human Fertilisation and Embryology (Research Purposes) Regulations 2001 s2(a)*	X	☐
4.3.8	enabling any such knowledge to be applied in developing treatments for serious disease *Human Fertilisation and Embryology (Research Purposes) Regulations 2001 s2(c)*	X	☐

7. Scientific practice R0149

Desired outcome: Procedures are robust to ensure material is used appropriately

Summary of findings from inspection:

- Use of material
- Progress in achieving aims and objectives

Use of material
No significant developments have occurred since the previous inspection.
Project Objectives
Remain the same. 1) Feasibility study of PGD for selected mtDNA diseases. 2) Study mtDNA bottleneck using supernumerary fertilised oocytes following ICSI treatment and those arrested during development from control women. 3) Perform Y-specific PCR which is relevant to aneuploidy and potentially to mtDNA diseases with a higher penetrance in males.
Lay summary of research undertaken
The research has not proceeded as planned because of; a) continued difficulties in training existing staff to perform biopsy techniques and b) the lack of a suitable scientific lead. The situation will change, however, from September 2007 onwards with the recruitment to the Oxford Biomedical Research Centre of Dr Dagan Wells from Yale University. Dr Wells, who will be a member of the Nuffield Department of Obstetrics & Gynaecology, is also planning to set up a clinical PGD service within the Oxford Fertility Unit.
Progress of research
No further progress has been made with this project due to the issues mentioned above. This situation is due to be rectified from September 2007 with the arrival of an experienced research worker who will take the scientific lead in this project.
Executive recommendations for Licence Committee
Centre to inform the Authority when the proposed scientific lead for this project is in post.
Areas not covered in by this inspection
None

	Purpose or purposes of the research project	Currently licensed purposes	Proposed licence purposes
4.3.5	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)*	☒	☐

Report compiled by:

Name: Wil Lenton

Designation: Inspector

Date: 9th May 2007

Appendix A: Centre Staff interviewed

Karen Turner, Person Responsible for R0111, R0143 and R0149

Five other members of the team took part in meetings with the inspection team.

Appendix B: Licence history

R0111

Status	Licence	Type	Active From	Expires
Active	R0111/4/a	Research Project	01/09/2006	31/08/2009
Active	R0111/3/b	Research Project	01/11/2003	31/10/2006
Replaced by new version	R0111/3/a	Research Project	01/11/2003	31/10/2006
Expired	R0111/2/a	Research Project	10/04/2000	30/04/2003
Expired	R0111/1/b	Research Project	10/03/2000	09/04/2000
Expired	R0111/1/a	Research Project	09/03/1998	09/04/2000

R0111: No recommendations or conditions

R0143

Status	Licence	Type	Active From	Expires
Active	R0143/2/a	Research Project	01/09/2006	31/08/2009
Active	R0143/1/b	Research Project	14/08/2003	31/08/2006
Replaced by new version	R0143/1/a	Research Project	14/08/2003	31/08/2006

R0143 Recommendation

That the centre considers incorporating the generic information on all their licensed projects into the detailed format used in the UK Stem Cell Bank Consent Form. This would ensure that all the projects are presented equitably. Most points on the format apply to all the projects; however, the stem cell project form will include additional points.

R0149

Status	Licence	Type	Active From	Expires
Active	R0149/2/a	Research Project	01/09/2006	31/08/2009
Active	R0149/1/b	Research Project	03/06/2004	30/04/2006
Replaced by new version	R0149/1/a	Research Project	03/06/2004	30/04/2006

R0149: No recommendations or conditions

Appendix C:
RESPONSE OF PERSON RESPONSIBLE TO INSPECTION REPORT

Centre Number: 0035

Name of PR: Karen Turner

Date of Inspection: 9th May 2007

Date of Response…19th June 2007……

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

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

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).

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

25 July 2007
21 Bloomsbury Street London WC1B 3HF

MINUTES Item 7

Research Projects:
R0111 – Development of a model to study implantation in the human
R0143 – To derive human embryonic stem cells
R0149 – To develop pre-implantation genetic diagnosis (PGD) for mitochondrial DNA disease
All three projects are based at Oxford Fertility Centre (0035)
Interim Inspection

Members:

Richard Harries – Chair, Lay Member
Clare Brown, Lay Member
Maybeth Jamieson, Consultant Embryologist, Glasgow Royal Infirmary
William Ledger – Professor of Obstetrics and Gynaecology, University of Sheffield
Rebekah Dundas – Lay Member

In Attendance:

Marion Witton – Head of Inspection
Frances Clift, Legal Adviser
Joanne McAlpine, Acting Committee Secretary
Barbara Lewis, Observer

Conflicts of Interest: members of the committee declared no conflicts of interest in relation to this item.

The following papers were considered by the Committee:

- papers for Licence Committee (69 pages)
- no papers were tabled.

1. The papers for this item were presented by Mr Wil Lenton, HFEA Inspector. Mr Lenton informed the Committee that the interim inspection visit took place on 9 May 2007 and the centre was found to be well organised.

2. Mr Lenton informed the Committee that a higher number of embryos have been used on project R0111. There embryos are obtained fresh and some are sub-optimal. Mr Lenton also informed the Committee that the centre is trying to

utilise embryos which are at different stages in order to reduce the number of embryos used in research.

3. Mr Lenton confirmed that all embryos are anonymised and a research number is allocated to the donated embryos when they are transferred to the research laboratory.

4. Mr Lenton informed the Committee that that a new Scientific Lead and Research Nurse are due to be appointed and the Executive will be informed when this occurs.

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

Signed…….. … Date……..
Richard Harries (Chair)