# Research Licence Inspection Report

| | |
|---|---|
| Project Title<br><br><br>Research Licence Number<br>Person Responsible<br>Nominal Licensee<br>Inspection type<br>Licence expiry date<br>Date Renewal fee paid | **Improving Methods for Pre-Implantation Genetic Diagnosis of Inherited Genetic Disease and Predicting Embryo Quality**<br>R0075<br>Peter Braude<br>Virginia Bolton<br>**Renewal**<br>31 August 2006 |
| Project Title<br><br><br>Research licence Number<br>Person Responsible<br>Nominal Licensee<br>Inspection type<br>Licence expiry date | **Correlation of Embryo Morphology with Ability to Generate Embryonic Stem Cell Lines and Subsequent Growth and Differentiative Characteristics**<br>R0133<br>Stephen Minger<br>Peter Braude<br>**Progress**<br>30 April 2008 |
| Centre Number | 0102 |
| Centre Name | Assisted Conception Unit, Guy's & St Thomas' Hospital NHS Trust |
| Centre Address | 4th Floor, Thomas Guy House<br>St Thomas Street<br>London<br>SE1 9RT |
| Treatment centres donating to these research projects | 0102 - Assisted Conception Unit, Guy's & St Thomas' Hospital NHS Trust<br>0144 - The Woking Nuffield Hospital<br>0006 - The Lister Fertility Clinic |
| Inspection date | 2 May 2006 |
| Licence Committee Date | 26 July 2006 |
| Inspector(s) | Debra Bloor, Tony Knox |

## About the Inspection:

The purpose of the inspection is to ensure that research is carried out in compliance with the HF&E Act 1990, Code of Practice, licence conditions and directions and that progress is made towards achieving the stated aims of the project.

The report is used to summarise the findings of the inspection highlighting areas of firm compliance and good practice, as well as areas where improvement may be required to meet regulatory standards. It is primarily written for the 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.

This report covers the period between 20 December 2005 and 2 May 2006.

## Brief Description of the Projects

Project **R0075** entitled "**Improving Methods For The Biopsy and Diagnosis of Inherited Genetic Disease of Human Pre-Implantation Embryos**" has been licensed since 1994.

The lay summary of the project is as follows:

Preimplantation genetic diagnosis (PGD) is an early alternative to prenatal diagnosis (PND) and is suitable for a small group of patients who are at substantial risk of conceiving a pregnancy affected by a known genetic defect. PGD has been applied in a number of centres around the world for a variety of indications, including the analysis of numerical and structural chromosomal abnormalities, identification of sex for X-linked disease and detection of specific genetic defects in monogenic disorders such as cystic fibrosis.

During PGD, a one or two cell biopsy is removed from an embryo created in vitro and a diagnostic test is carried out on the biopsied cell(s). The genetic status of the embryo is inferred on the basis of the result of the diagnostic test on the biopsy and unaffected or carrier embryos are replaced into the uterus. Therefore, for PGD to be feasible, techniques must be available which allow for the diagnosis of a particular gene defect on just one or two cells.

The thrust of this research project is to move forward existing technology to allow PGD to be applied in new disease areas and to develop new technology to improve the process of biopsy and embryo selection with the ultimate aim of enhancing the clinical success of the treatment.

Embryos which are surplus to treatment and have been donated to research with patients' consent will be used in one of two ways. Embryos will be tested for reliability and accuracy. For improvements in embryo selection procedures after PGD, embryos will be scored depending on their perceived quality and then subjected to procedures which allow an analysis of either their complete chromosome complement or the location and status of key regulatory molecules which may play in important role in early development. It is hoped that this data will improve methods of selecting embryos with high implantation potential.

Project **R0133** entitled "**Correlation of Embryo Morphology with Ability to Generate Embryonic Stem Cell Lines and Subsequent Growth and Differentiative Characteristics**" has been licensed since April 2002.

The lay summary of the project is as follows:

Stem cells are unique cell populations which are able to undergo both self renewal and differentiation. Although stem cells have been found in a wide variety of adult tissues, embryonic stem (ES) cells, which have been isolated from the inner cell mass (ICM) of blastocyst stage embryos, are thought to maintain a higher potential for differentiation into a multiple array of cell types. Mouse ES cells can be expanded indefinitely in culture in an undifferentiated state, whilst retaining the capacity of early embryonic cells to differentiate into derivatives of all three primary germ layers (Robertson, 1987). Extrapolation of these properties to human cells would provide a renewable source of tissue for a range of transplantation therapies (Trounson, 2002). Derivation of mouse ES cells is a relatively straightforward, although specialised, process but so far derivation and long term culture of human ES cells has proved extremely technically demanding. Only nine human ES cell lines are currently available commercially despite over 71 having been derived (Vastag, 2003). The remaining 62 have not been successfully cultured or characterised (Vastag, 2003). Many outstanding issues remain to be resolved regarding ES cell derivation and subsequent usefulness, not least regarding whether the behaviour of the isolated ICM can be used to gain information about the viability and implantation potential of the originating embryo. We propose to isolate ICM from human blastocysts surplus to therapeutic requirements after preimplantation genetic diagnosis and, following careful morphological and cytogenetic analysis of the parent embryo throughout its development, correlate embryo characteristics with the proliferative, karyoptypic and differentiative behaviour of both the resulting ICM and any ES cell lines derived from them. Should ES lines of suitable morphology be derived as a result of this work, we propose to undertake further studies on the isolation and differentiation of neural and pancreatic islet progenitor cells from human ES cell cultures.

References:

Robertson, E. J. (1987). "Teratocarcinomas and embryonic stem cells." IRL press, Oxford.
Trounson, A. (2002). Human embryonic stem cells: mother of all cell and tissue types. Reprod Biomed Online. 4, 58-63.
Vastag, B. (2003). Medical news & perspectives: effort launched to study stem cell lines, train researchers how to nurture them. JAMA. 289, 1092.

| | | R0075 | R0133 |
|---|---|---|---|
| **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 or procedures since the last inspection although refurbishment of some laboratory areas is planned in the next year.

There have been some staff changes in the research teams of both projects.

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

Licences R0075 and R0133 were issued without additional conditions.

## Summary for Licence Committee

Progress has been achieved in relation to the stated aims of both research projects. All aspects of practice that were reviewed in the course of the inspection were found to be largely compliant with the requirements of the HF&E Act 1990, Code of Practice, licence conditions and directions.

A small number of issues were identified in the course of the inspection which warrant consideration and these are summarised below:

- A number of scientists/support staff who are working on the research licences do not appear on the HFEA centre's database;
- A number of errors were observed when carrying out an inspection of consents to research in a sample of patient records;
- Under the auspices of project licence R0133 embryos have been grown in culture until they have formed outgrowths at which time they have then been transferred to other licensed laboratories.

The persons responsible for both projects should consider the recommendations of the

inspection team in relation to these issues and implement any changes that are considered necessary.

The application for renewal of licence R0075 was considered by an external peer reviewer: the reviewer supports the renewal of the licence.

The inspection team also support the renewal of licence R0075 and the continuance of research licence R0133.

## Proposed licence variations

None

## Report of Inspection findings

### 1. Organisation

Desired Outcome: The research 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
- Funding

**Staff R0075***

| | |
|---|---|
| Principal investigator | Peter Braude |
| Scientists | 1 senior research fellow, 1 PhD student, 1 molecular biologist |
| Laboratory technicians | 2 |
| Support staff (receptionists, record managers, quality and risk managers etc) | Staff at centre 0102 |

**Staff R0133***

| | |
|---|---|
| Principal investigator | Stephen Minger |
| Research technicians | 2 |
| Scientists | 2 including 1 PhD student, |
| Support staff (receptionists, record managers, quality and risk managers etc) | Staff from centre 0102 |

*There is overlap between staff working on projects R0075 and R0133.

| Highlighted areas of firm compliance |
|---|
| The PR of R0075 has extensive knowledge of the regulatory requirements of the HFEA as he was previously a member of the Human Fertility and Embryology Authority and is an accredited consultant at centre 0102. The PR has managed the project since its inception in 1994 and has over 30 years experience in human embryology and IVF. He is the holder of MRC programme and project grants in human embryo research. The CV of the senior research fellow working on R0075 documents extensive appropriate experience and publishing history.<br><br>The CV of the PR of project R0133 documents extensive appropriate experience and publishing history. The PhD student who recently joined the research team for project R0133 has relevant and valuable embryology experience.<br><br>One member of the research team reported receiving fire training and basic life support training in the time covered by this report although training records were not made available to the inspection team. A recently appointed member of the team reported appropriate |

induction opportunities.

It is reported that both projects have ongoing funding.

## Issues for consideration

The inspection team were concerned that because the role of the nominal licensee is held by the consultant embryologist at centre 0102 this could compromise the separation of clinical and research roles. It was reported that patient's treatments are always prioritised over research and that this is evidenced by recent discussions about extended culture of embryos for clinical use. In the course of extended culture, embryos which may have been considered too poor for transfer or freezing at early cleavage stages may produce embryos suitable for subsequent clinical use, thus reducing the availability of embryos for research.

A number of scientists/support staff working on the research projects do not appear on the HFEA centre's database. These staff members may not have access to identifying information however, the persons responsible for both projects should ensure that there is a robust procedure in place to inform the HFEA when new staff are recruited to work on the project(s).

All staff should receive opportunities for continued professional development and mandatory health and safety training and training should be documented. Staff training records should be made available during future inspections.

## Executive recommendations for Licence Committee

None

## Areas not covered in by this inspection

Organisation of the centre
Resource management
Research governance

## 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
- Storage facilities
- Safety of equipment

| Highlighted areas of firm compliance |
| --- |
| Manipulation of viable embryos is carried out on licensed premises.<br><br>Embryos are stored in a designated security area with controlled access under the auspices of the licence of centre 0102. No discrepancies were found in the course of a spot check audit tracing an embryo from file to dewar and from dewar to file.<br><br>Researchers are advised of the date of expiry of consent to storage of frozen material and evidence was seen that embryos are not stored after the gamete donors consent to storage expires.<br><br>The cryostore is fitted with a low oxygen level alarm and the centre has a written protocol outlining the appropriate response to the alarm. |
| Issues for consideration |
| None |
| Executive recommendations for Licence Committee |
| None |
| Areas not covered in by this inspection |
| Servicing and maintenance of equipment |

## 3. Donation of material

Desired outcome: Donors are recruited appropriately and any research carried out on their embryos is in accordance with their consent.

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
- Ensuring patient consent is not breached
- Donor and patient records

| Highlighted areas of firm compliance |
|---|
| Donation to both projects is coordinated by a designated individual who is not directly involved in the patient's treatment.<br><br>Donation is broached by members of the embryology team at centre 0102 or in communications from staff at centres 0144 or 006 to patients whose embryos are approaching the end of the consented storage period. Patients who express an interest in donating to research are then contacted by the stem cell research coordinator who provides relevant patient information and consents. It is reported that this process ensures that patients receive suitable opportunity to consider the implications of donation. Patient information provides contact details for the donation coordinator and principle investigators ensuring that prospective donors can access further guidance if required.<br><br>Centrally held records reviewed in the course of the inspection contained necessary information to allow tracking of individual embryos and cross reference to patient records. A file was also reviewed which documented the system for identifying the imminent expiry of storage consents. The file demonstrated that the system for ensuring that patient storage consents are not breached is robust. |
| Issues for consideration |
| None |
| Executive recommendations for Licence Committee |
| None |
| Areas not covered in by this inspection |
| Prevention of coercion of prospective donors |

## 4. Patient information and consents

Desired outcome: Patients are provided with appropriate information which allows them to give informed consent.

Summary of findings from inspection:

- Patient information
- Consent forms
- Patient information for projects deriving embryonic stem cells
- Consent forms for projects deriving embryonic stem cells

### Highlighted areas of firm compliance

Patient information and consents comply with all of the requirements outlined in standard licence conditions and the 6th Code of Practice (COP).

### Summary of audit of patient records

Witnessing of the transfer of embryos to research was documented appropriately in all of the records reviewed. At the time of transfer of embryos to research is witnessed, the operator and witness sign confirm that the patients donating embryos have completed appropriate consents to research.

Five sets of records from patients who donated embryos to R0075 were reviewed.

Consent forms in three of these five sets of records were present and consistent with the use of the material in research. Errors were identified in two sets of records are these are summarised below:

1. In one set of records the embryos donated had been created with donor sperm and the donor had not consented to research. Staff considered that the members of the team who witnessed the transfer and checked consents were not familiar with the requirement to check for donor consent to research;
2. In one set of records both gamete providers had indicated that they did not consent to the use of their embryos in research in 006 and 007 forms and there were no additional consents to research in the records. On reviewing the notes members of the team were not able to identify why embryos had been used without consent as witnessing had been carried out by experienced and knowledgeable members of staff.

Minutes from a meeting held in March 2006 showed that the centre has agreed to use stickers to mark the records of patients who have not consented to research. While it was acknowledged that the use of stickers might not prevent all errors, they might provide an additional check and may have prevented the error identified in 2 above.

Three sets of records from patients who donated embryos to R0133 were reviewed.

Consent forms in two of these three sets of records were present and consistent with the use of the material in research. An error was identified in one set of records are this is summarised below:

3. Embryos were filed as having been used in project R0133 but the gamete donors had

not specifically consented to donation of embryos for stem cell research. Members of the team reviewed the file and commented that the embryo(s) had been cultured to assess their ability to outgrow but that there had been no intention to derive stem cells in the absence of appropriate consent. The inspector advised that where this occurs, this should be clearly documented in the record.

## Issues for consideration

The centre should consider providing additional training for staff on what consents are required before embryos can be used in research. The centre should carry out their own spot check audit of consents and if further errors are identified, then a complete audit of consents and investigation into the likely causes of errors should be carried out.

The use of embryos without consent (at 2 above) should be reported to the HFEA as an incident.

## Executive recommendations for Licence Committee

None

## Areas not covered in by this inspection

None

## 5. Scientific practice R0075

Desired outcome: Research is carried out in accordance with licence conditions and makes progress towards achieving stated aims

Summary of:

- Use of material
- Progress in achieving aims and objectives
- Peer review

| Use of material |
| --- |
| Three hundred and forty fresh and frozen embryos were donated to the project in the time covered by this report: 234 were used in the research project. Twelve eggs that had failed to fertilise were also donated to and were used in the project. |
| **Project objectives** |
| 1. To improve accuracy of PGD and to estimate the reliability of those diagnoses by examining embryos deemed not suitable for transfer.<br>2. To apply genetic techniques to an increasing range of genetic diseases<br>3. To improve methods of assessing embryo quality in order to improve embryo selection procedures at embryo transfer.<br><br>The team reported that progress was faster and more exciting than anticipated in most areas. |
| **Lay summary of research undertaken** |
| We have been very successful in developing the technology of preimplantation testing for a range of serious genetic disorders including Huntington's disease, sickle disease, spinal muscular atrophy, epidermolysis bullosa, and cystic fibrosis. In addition to performing nearly 400 cycles of diagnosis for patients, which makes this unit the most active and successful in the UK, we have developed a substantial new method, preimplantation genetic haplotyping - PGH. This allows application of preimplantation testing to a wider range of diseases,including sex linked disorders where we can now detect unaffected males in addition to females. PGH also provides a higher level of accuracy in diagnosis, as well reducing the number of embryos in which diagnosis cannot be obtained. We have successfully applied this technique to Duchenne muscular dystrophy, cystic fibrosis for rarer haplotypes, recurrent hydatidiform mole, and intend further development for myotonic dystrophy,variants of epidermolysis bullosa, and Alport's syndrome,amongst other sex-linked disorders.Further research will look at effect of mosaicism on diagnosis, ability to detect frequent trisomies, and impact of mitochondrial function during early development. |
| **Peer reviewers comments** |
| The application to renew the research licence for this project was subject to external peer review. The reviewer recommended that the application be accepted without any changes |

| |
|---|
| and commented that as a preliminary study, a significant amount of work and outcome results have been achieved in relation to the objectives. The reviewer also commented that more data are required to make the information gained more meaningful. |
| Issues for consideration |
| None |
| Executive recommendations for Licence Committee |
| None |
| Areas not covered in by this inspection |
| None |

## 6. Scientific practice R0133

Desired outcome: Research is carried out in accordance with licence conditions and makes progress towards achieving stated aims

Summary of:

- Use of material
- Progress in achieving aims and objectives

| Use of material |
| --- |
| The centre received 67 fresh and frozen embryos in the time covered by this report: 42 were used in the research project. |
| **Project objectives** |
| 1. To derive human embryonic stem cell (hESC) lines with discrete genetic mutations relevant to human disease.<br>2. To derive hESC lines without the use of animal products.<br>3. To derive hESC lines without the use of animal products under good manufacturing practice (GMP) laboratory conditions.<br><br>Three hESC lines were derived during the first year of the project. These have been passaged onto human feeder cells and human cells that support hESC pluripotency in serum containing medium have been identified. Funding has been secured for the establishment of a GMP-level hESC derivation facility. Building plans have been finalised and it is anticipated that construction of the facility will be complete in September 2007.<br><br>The PR reported that progress was hampered by a lack of embryology expertise but that this has been resolved by the recruitment of an experienced embryologist. The main source of material for the project is embryos not suitable for transfer following pre implantation diagnosis (PGD) for single gene disorders. Fewer than expected embryos were available because the treatments undertaken in the last year have been largely for the diagnosis of chromosomal translocations and these embryos are not suitable for this work. However, this lack of material has not hampered progress and the team report having focussed on down stream differentiation of the existing stem cell lines. |
| **Lay summary of research undertaken** |
| There has been significant interest in the therapeutic and scientific potential of human embryonic stem (ES) cells since they were first isolated in 1998. If human ES cells could be differentiated into suitable cell types, stem cells might be used in cell replacement therapies for degenerative disease such as Type 1 diabetes and Parkinson's disease, or to repopulate the heart following myocardial damage. However there is a significant shortage of high quality human ES cell lines and few research groups have experience in the propagation and manipulation of these cells. It is thus essential for the development of human stem cell technology and for the larger goal of cellular replacement therapy for human disease that additional human cell lines are generated. |

We are addressing this important issue using the combined expertise of the Stem Cell Biology Laboratory and the Assisted Conception Unit ant the King's College London. With local ethical approval and under licence from the UK Human Fertilisation and Embryology Authority, we have been establishing high quality human ES cell lines from a novel source of human embryos. To date, we have derived three human ES cell lines, including one that encodes the most common genetic mutation resulting in cystic fibrosis. In addition, much of our work is focussed on the generation of human ES cell-derived therapeutically important cell populations including neural, retinal, pancreatic, cardiac, and endothelial stem cells. The tightly regulated yet permissive environment in the UK for human stem cell research, coupled with the government's commitment to the establishment of a centralised stem cell bank offers the UK the opportunity to be a leading player in the field of human regenerative medicine.

## Issues for consideration

In the time covered by this report, embryos have been grown in culture until they have formed outgrowths at which time they have then been transferred to non licensed laboratories. Section 3) (a) of the Human Fertilisation and Embryology Act 1990 states that a licence cannot authorise keeping or using an embryo after the appearance of the primitive streak, where the primitive streak is to be taken to have appeared in an embryo not later than the end of the period of 14 days beginning with the day when the gametes are mixed, not counting any time during which the embryo is stored. Where whole embryos are cultured to form outgrowths the centre should consider how it can be demonstrated that they have complied with the Act to terminate culture after 14 days.

## Executive recommendations for Licence Committee

None

## Areas not covered in by this inspection

Peer review

Report compiled by:

Name……Debra Bloor…….

Designation……HFEA inspector……..

Date…25 May 2006……

## Appendix A: Centre Staff interviewed

Peter Braude, Person Responsible R0075
Stephen Minger, Person responsible R0133

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

## Appendix B: Licence history for previous 3 years

**R0075**

| Status | Licence | Type | Active From | Expires |
|---|---|---|---|---|
| Active | R0075/8/b | Research Project | 13/06/2005 | 31/08/2006 |
| Replaced by New Version | R0075/8/a | Research Project | 01/09/2003 | 31/08/2006 |
| Expired | R0075/7/a | Research Project | 01/06/2003 | 31/08/2003 |

R0075/8/b, R0075/8/a
No conditions

Recommendation:

- The Committee recommended that your centre amend the patient information to make clear that consent to use of patients' material can be withdrawn up to the point it is used in research

R0075/7/a
No conditions, no recommendations

**R0133**

| Status | Licence | Type | Active From | Expires |
|---|---|---|---|---|
| Active | R0133/2/b | Research Project | 29/06/2005 | 30/04/2008 |
| Offer licence sent but not acknowledged | R0133/2/a | Research Project | 01/05/2005 | 30/04/2008 |
| Replaced by New Version | R0133/1/a | Research Project | 15/04/2002 | 30/04/2005 |

No conditions or recommendations have been applied to any of the licences listed above.

**Appendix C:**
RESPONSE OF PERSON RESPONSIBLE TO INSPECTION REPORT – **R0075**

Centre Number……0102……

Name of PR…Peter Braude…….

Date of Inspection……2 May 2006……..
Date of Response …23rd June 2006

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

**Staff on licence:** The members of staff on the licence have been reviewed and corrected. Notification will be made by the HFEA centre 0102 administrator on employing new licensable staff members and when staff leave. In answer to specific query; [redacted] is employed by the genetics centre as a molecular biologist and performs analyses on embryo biopsy samples. [redacted] is the quality control officer for 0102; hence is involved in overseeing implementation of ISO and maintaining laboratory standards and records. She is not hands on in the 0075 project. [redacted] is involved in culturing stem cells for the R0133 project; trophoblast removed for this from PGD embryos may be required for confirmation of diagnosis for R0075.

**Consents:** A training morning was held three weeks ahead of the inspection visit to revisit conditions for obtaining embryos for research and the flow diagram for handling revisited. This will be held about 6 monthly for the ACU as part of the regular Thursday morning training / research meeting, as is available in the research protocol manual

**Incident report:** The use of embryos without consent has been reported to the HFEA as requested despite the embryo not being used in research. Stickers indicating that embryos are not to be used for research are in use (example appended). This does not obviate the need to check consents prior to any use but serves as an additional reminder.

**NO**

**Professional development;** We strongly encourage continued development and provide funds for staff to attend meetings on a regular basis. [redacted] all attended ESHRE this year and other meetings. Training records are part of ISO accreditation and will be maintained as such.

**Nominal Licensee:** We understand the possible perceived conflict, but in reality decisions about 'spare material' are made by the clinical embryology team independently of any research needs. However we are suggesting changes to the Licensees for the projects (below).

In the light of (1) the overlap between the projects, (2) the majority of concerns related to a common consenting process and staff, (3) the initial stem cell derivation taking place within the facilities of 0102 rather than in the Wolfson Centre, (4) the intended stem cell facility in the

ACU new build during the licence period, (5) concerns over the 0075 nominal licensee being involved in embryo selection; we propose a change in the PR and nominal licensees to enable conformity of monitoring and reporting.

The PR for both licences 0075 and 0133 should be Professor Braude, and the Nominal Licensee for both to be Mr Yacoub Khalaf, PR for centre 0102. This has the agreement of Mr Khalaf, Dr Bolton, Dr Minger and Professor Braude (letters enclosed).

Signed……

Name……Prof Peter Braude……..

Date……28th June 2006……..……

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).

RESPONSE OF PERSON RESPONSIBLE TO INSPECTION REPORT – **R0133**

Centre Number…0102……

Name of PR……Stephen Minger…….

Date of Inspection……2 May 2006……..

Date of Response 23rd June , 2006

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

**Staff on licence:** The members of staff working on R0133 was reviewed and updated when the last progress report was sent to the HFEA on April 5, 2006. Since the R0133 licence was renewed in May 2005, we have recruited two new MRC-funded Research Associates, [redacted] as well as [redacted], a human embryologist who is pursuing a joint PhD in the Stem Cell Biology Lab and the Guy's ACU. All three are involved in the routine propagation of human embryonic stem cells, whilst [redacted] is primarily responsible for the derivation of new embryonic stem cell lines with Dr Minger. CVs for all three members of staff were forwarded to the HFEA with the Progress Report in April 2006. In addition, [redacted] who is already listed on the HFEA data base is also involved in the culturing of human embryonic stem cells.

**Licensing of the Stem Cell Biology Laboratory**. To the best of our knowledge, the Stem Cell Biology Labs at King's College London has been licensed by the HFEA since the R0133 human embryonic stem cell licence was granted in May 2002. Our original labs in the Hodgkin Building were inspected and approved in Feb 2002, and yearly since then. We moved into our current laboratories in the Wolfson Centre for Age-Related Diseases in March 2004, and these were inspected most recently on Dec 20, 2005. This is the first time that an issue has been raised about the licensing of our labs and we believe that this may be a misunderstanding.

**Use of Intact Blastocysts for Stem Cell Derivation**. There have been limited occasions where intact but zona pellucida-depleted blastocysts have been cultured on mouse embryonic fibroblasts as a means of attempting to derive embryonic stem cells in our lab. This occurred initially when we were first attempting to derive human embryonic stem (hES) cells in 2002. Although the blastocysts usually attached to the feeder layers and there was some limited cellular outgrowth, the inner cell mass seemed to be lost in the midst of expanding trophectoderm and thus no cell lines were derived. In all of these cases, none of the blastocysts survived on mouse feeders for more than 7-10 days, and this method of attempting to derived hES cell lines was abandoned. From 2002- June 2005, we exclusively used immunosurgery to selectively destroy the trophectoderm and to isolate the inner cell mass. Using this method, we successfully derived three hES cell lines between 2002-2004. With the departure of [redacted] in June 2005, we continued our attempts to derive hES cells lines but without the collaboration of a dedicated human embryologist. However, by this time there were several reports in the scientific literature demonstrating the successful derivation of human embryonic stem cell lines by plating intact 6-day old blastocysts onto mouse feeder layers which in some cases seem to support the expansion of the inner cell

mass at the expense of the trophectoderm. Lacking the skills required to perform immunosurgery, we thus attempted to replicate these other reports by plating intact blastocysts onto mouse feeder layers. Similar to our previous experience, we achieved no significant outgrowths from the blastocyst and no cell lines were established using this method. Since the addition of [redacted] to our research team in Jan 2006, we have once again been using immunosurgery or other physical means of disaggregating the blastocyst and isolating the inner cell mass to attempt to derive hES cell lines.

Although placing an intact 6-day blastocyst onto feeder layers and culturing it for an additional 8 days might appear to be violating the 14-day limit for embryo culturing, it is our contention that this is not the case. It is clear that the feeder layers do not support the normal developmental progression of human embryos, and in cases where the blastocyst does survive plating and generate expandable populations of inner cell mass cells that give rise to a population of embryonic stem cells, these would invariably be microdissected from the remaining blastocyst-derived cells within 7-10 days of plating, thus disaggregating whatever remains from the original blastocyst and rendering it incapable of any normal embryonic development.

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

**26 July 2006**
**21 Bloomsbury Street London WC1B 3HF**

**MINUTES Item 7**

**Research Project: R0075 Improving Methods for preimplantation genetic diagnosis of inherited genetic disease and predicting embryo quality, based at Assisted Conception Unit, Guy's and St Thomas' hospital NHS Trust (0102)**
**Licence Renewal**
**Also, progress reports were presented on research project R 0133**

Members:
Emily Jackson, Lay Member – Chair
Ivor Brecker, Lay Member
Richard Harries, Lay Member
Clare Brown, Lay Member
Maybeth Jamieson, Consultant Embryologist, Glasgow Royal Infirmary

In Attendance:
Chris O'Toole, Head of Research Regulation
Claudia Lally, Secretary to the Committee

Providing Legal Advice:
Graham Miles, Morgan Cole Solicitors

Providing Scientific Advice:
Neva Haites, Professor of Medical Genetics, University of Aberdeen

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 (134 pages)
- no papers were tabled.

1. The papers for this item were presented by Chris O'Toole, Head of Research Regulation. Dr O'Toole informed the Committee that the peer review of the project had been favourable. However, a potential breach of the Human Fertilisation and Embryology Act 1990 had been reported by the inspection team, namely the use in the research project of an embryo from patients who had indicated that they did not consent to the use of their embryos in research. The Committee noted that the patients might have provided consent in an additional consent form but that no such form was included in the patient notes.

2. The Committee noted this serious breach of the Act and requested that the Executive record this breach in the centre's licensing history. The Committee agreed that the centre must take steps to ensure that this never happens again. The Committee asked that the centre indicates to the Executive the additional training and safeguards it intends to put in place to ensure that it cannot happen again, and also indicate a timescale by which these will be completed. The Committee further requested the Executive makes this issue a focus for the next inspection.

3. The Committee noted what the inspection team identified as a slight blurring of roles between the research personnel and staff involved in the treatment of patients. The Committee agreed to remind the centre that where patients are to be approached about the possibility that they might enter an egg sharing arrangement in which a proportion of their eggs would be donated for use in research those patients must not receive information, consenting and / or counselling concerning the research from clinical personnel involved in the project of research.

4. The Committee noted that the list of research purposes for the licence had not been captured on the faxed peer review form, and asked the Executive for clarification on these points with the peer reviewer.

5. The Committee noted the progress report for research project R0133.

6. The Committee noted that the centre had applied to change the Person Responsible for the project of research. On the basis of the information contained in the committee papers, the Committee agreed that Professor Peter Braude and Mr Yacoub Khalaf are suitable people to be the Person Responsible and Nominal Licensee respectively and agreed that this change would be recorded in the licenses for project R0075 and R0133.

7. The Committee agreed to apply the statutory tests in considering the renewal application for project R0075. The Committee identified the activity to be authorised by the licence as the removal of blastomeres from embryos and the fixing of embryos.

8. Members agreed that this activity is not prohibited under the Human Fertilisation and Embryology Act 1990 (the Act).

9. Members agreed that the activity is necessary or desirable for the following purposes:

- developing methods for detecting the presence of gene or chromosome abnormalities in embryos before implantation

*Human Fertilisation and Embryology Act 1990 Schedule 2 s3(2)(e)*

- increasing knowledge about serious disease
  *Human Fertilisation and Embryology (Research Purposes) Regulations 2001 s2(b)*

10. The Committee agreed that they were satisfied that the use of embryos is necessary for the purpose of the research.

11. The Committee agreed that they were satisfied with the consent forms and patient information provided by the centre.

12. The Committee were satisfied that the requirements for the grant of a licence under Section 16 of the Human Fertilisation and Embryology Act 1990 are satisfied, and decided to grant a licence for the research for a period of three years.

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