



## Research Licence Interim Inspection Report

Project Title	Platform technologies underpinning human embryonic stem cell derivation
Centre Name	Roslin Cells Ltd
Centre Number	0202
Research licence Number	R0136-3-a
Centre Address	Roslin Institute, Roslin Biocentre, Roslin EH25 9PS
Treatment centres donating to this research project	0067 St Mary's Manchester 0019 Aberdeen 0004 Ninewells 0044 University College, London 0201 Edinburgh Infirmary Edinburgh Infirmary (not licensed by the HFEA)
Inspection date	9 January 2008
Licence Committee Date	2 April 2008
Inspector(s)	Dr Vicki Lamb
	Miss Lydia Harley
Person Responsible	Dr Paul De Sousa
Nominal Licensee	Mr Malcolm Bateman
Licence expiry date	30 June 2010

### **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 25 January 2007 and 9 January 2008.

### **Brief Description of the Project**

#### **Lay Summary**

The aim of our research is to derive human embryonic stem cells in a manner which would permit those cells to be used in developing treatments for patients with degenerative diseases, such as Parkinson's and diabetes.

Current techniques for deriving stem cells use products which are themselves derived from human or animal cells. Furthermore these techniques are conducted in standard laboratory facilities. This means there is a risk that the cells derived in this way could acquire a disease-producing agent, such as a virus, which could be passed on to subsequent generations of those cells. Consequently, no cells derived in this way, or arising from cells derived in this way, can be transplanted into a patient.

Our research will investigate ways to eliminate the current reliance on human/animal cell based products and we will also develop techniques and protocols to carry out this work in "clean room" facilities. If we are successful, the stem cells we produce could be used as the starting point for producing cells to be used in therapies to address degenerative diseases.

Our research will also investigate the isolation of human embryonic stem cells from eggs and embryos which are clinically unsuitable for infertility treatment. To achieve this we will use methods to **grow**, mature and/or activate the egg or embryo. If successful, embryonic stem cells will be derived from eggs or embryos which could not have been used in the donor's infertility treatment. Our research will not involve fertilising eggs with sperm. Instead eggs which are either immature or which failed to fertilise will be activated artificially. If we can isolate embryonic stem cells as a result of this process, they will contain only maternal genetic material. Such cells would allow further research into the influence of maternal genes on the development of the embryo.

<b>Research activities</b>	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

The centre wish to amend the lay summary by the addition of one word as highlighted in the summary above.

A new laboratory at the centre is now in use for unlicensed purposes. The PR would like this room to be approved for use for licensed purposes. This does not require a variation of the licence as this laboratory is within the curtilage of the current licensed premises.

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

The licence was issued without any additional conditions.

### Issues for consideration from the 2007 renewal report

<b>Recommendation</b>	<b>Action taken</b>
Mandatory training undertaken should be recorded in staff training logs.	Staff training logs were seen on the day of the inspection. These showed records of all training undertaken.
The PR should ensure that a written adverse incident handling policy which meets the HFEA requirements is developed.	This was seen by the inspectorate during the inspection
Some slight amendments to the patient information were recommended by the inspectorate and the Licence Committee. <ul style="list-style-type: none"> <li>• Patient information makes it clear to IVF patients that they may wish to consider donating embryos which will not be used in any ongoing treatment. These embryos may be unsuitable for freezing, but care should be given to how the patient information refers to</li> </ul>	These amendments have been made.  Patient information now states: This project will use human embryos which would not be used in any ongoing treatment and would be otherwise discarded.

<p>them. In particular, embryos should not be identified as merely “unsuitable” nor as “not needed”, since some patients may still ‘need’ their embryos but be unable to afford further treatment.</p> <ul style="list-style-type: none"> <li>• Patient information should clearly state that patients can withdraw their consent to the use of material in research at any point “until the eggs have been transferred to the research project”. Attempts to define this point differently (particularly using clinical terms) may not be easy for donors to understand.</li> <li>• All patient information should not only remind patients about this possibility of withdrawing consent but should provide a contact name and contact details should they wish to do so.</li> </ul>	<p>Patient information now states: You can change your mind at any time until the embryos have been used in research.</p> <p>Patient information now contains a contact name, telephone number and e-mail that is specific for each donating centre.</p>
<p>The Committee agreed that the lay summary of work undertaken which had been received was insufficiently lay-friendly and asked that this be re-written and re-submitted for publication on the Authority’s website.</p>	<p>A revised version was submitted to the executive and considered to be sufficiently lay-friendly.</p>

### Summary for Licence Committee

<p>This is a report on the first interim inspection since the renewal inspection in January 2007.</p> <p>The research is currently licensed for the following purposes:</p> <ul style="list-style-type: none"> <li>• Human Fertilisation and Embryology Act 1990 Schedule 2 3(2)(a) Promoting advances in the treatment of infertility.</li> <li>• Human Fertilisation and Embryology Act 1990 Schedule 2 3(2)(b) Increasing knowledge about the causes of congenital disease</li> <li>• Human Fertilisation and Embryology Act 1990 Schedule 2 3(2)(c) Increasing knowledge about the causes of miscarriages</li> <li>• Human Fertilisation and Embryology (Research Purposes) Regulations 2001: 2(2)(b) Increasing knowledge about serious disease.</li> <li>• Human Fertilisation and Embryology (Research Purposes) Regulations 2001: 2(2)(c) Enabling any such knowledge to be applied in developing treatments for serious disease.</li> </ul> <p>The centre has suitably qualified and experienced staff and the premises are secure and</p>
---

appropriately equipped. All recommendations from the 2007 inspection have been addressed.

The inspectorate recommend that the Licence Committee approve the following changes:

- The centre wish to amend the lay summary by the addition of one word as highlighted in the summary above.
- The PR would like a new laboratory to be approved for use for licensed purposes. This does not require a variation of the licence as this laboratory is within the curtilage of the current licensed premises.

Additionally, the inspectorate recommend that the following changes are made to the centres documentation:

- Amend SOPs at the donating centres and the research centre to add what to do if a patient withdraws consent.
- Amend the acquisition checklist to include the signatures of the staff that witnessed the identity of the embryos when they were put into the transport container.

#### **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
- Organisation of the centre
- Resource management
- Staffing
- Funding

### Full time equivalent staff

Principal investigator	1
Scientists	6
Support staff (receptionists, record managers, quality and risk managers etc)	3

### Highlighted areas of firm compliance

The executive have been informed of staff leaving and new staff joining the centre. CVs for new staff have been submitted and their experience and qualifications appear to be suitable for their respective roles.

Current funding for the project, from Scottish Enterprise Edinburgh and Lothian (SEEL), runs through to 30 September 2008 by which time Roslin Cells Ltd hopes to be self-sustainable through sales revenues of hESCs and associated enabling technology and extramural grant support.

A quality manager has been appointed and all SOPs provided to the inspection team were seen to be version controlled and had been reviewed in the past year.

Training records were seen for a selection of staff and evidence of training since the last inspection was apparent.

The centre staff have audited one of the donating centres. This was Aberdeen and was visited in October 2007. They also conducted an initial visit to Dundee in November 2007 and this will be followed by a formal audit during 2008. Formal audits of the other donating centres are scheduled for 2008. During the audit the donating centre's quality systems and facilities were reviewed. The centre found the audited donating centre met their requirements.

The written adverse incident handling policy was shown to the inspection team during the visit as well as the incident log. This demonstrated appropriate reporting of incidents to the HFEA.

The organisation chart was seen and discussed during the inspection. The chart demonstrated clear reporting lines within the organisation.

The inspection team were informed that there are weekly operational meetings, monthly executive meetings and bimonthly special purpose meetings. The minutes for these meetings were made available to the inspection team.

The PR has completed parts 1, 2 and 3 of the PR entry programme.

**Issues for consideration**

None

**Executive recommendations for Licence Committee**

None

**Areas not covered in this inspection**

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

<b>Highlighted areas of firm compliance</b>
<p>The inspection team were taken on a tour of the premises but did not enter the therapeutic derivation laboratory. It was possible to see into two of the rooms of this lab through viewing panels. This facility consists of a series of three rooms with increasing levels of air quality. Researchers will change in the first room, which has a background air quality of grade D. The next room is to be used for preparation of material/media and storage of reagents. The final room, which staff can only enter with full body suits, will be used for the derivation of embryonic stem cells. This room has a grade B background air environment. Entrance to this laboratory is restricted to authorised personnel by use of a key pad lock. Logs of air pressure within the various areas were made available for inspection.</p> <p>The centre staff confirmed that the research records are kept securely within the PR's office.</p> <p>The cryostorage facilities were shown to the inspection team but no embryos are stored on the premises, and the storage facilities are for cells only. All donated frozen embryos are thawed prior to transport to Roslin Cells.</p>
<b>Issues for consideration</b>
<p>The PR would like to add another laboratory to the licensed premises. This lab is within the current curtilage and therefore does not require a variation of the licence. This laboratory was shown to the inspection team. Security is maintained by means of a keypad lock on the door, CCTV in the outside area and security guards with dogs patrolling the grounds at all times. The windows are frosted. The lab contains a laminar flow hood, hot block, incubator and a microscope. To minimise the risk of contamination, the policy is that outdoor clothes must be covered, hair must be covered, shoes must be changed and gloves worn. The method for doing this was demonstrated to the inspection team.</p>
<b>Executive recommendations for Licence Committee</b>
<p>The executive recommend that the new laboratory is approved for use for licensed activity.</p>
<b>Areas not covered in this inspection</b>
<p>Safety of equipment Servicing and maintenance of equipment</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:

- Ensuring prospective donors have access to further guidance
- Ensuring patient consent is not breached
- Donor and patient records

#### Highlighted areas of firm compliance

A checklist was shown to the inspection team that is completed at the donating centre. This ensures that the patients have consented to donate their embryos to research and that the correct embryos are transferred to the research centre. The original copy of the consent form is kept at the donating centre and a copy is sent to the research centre. An anonymised version of this checklist is provided to the research team and stored within the research files. This process was explained to the inspection team and examples of completed checklists were provided during the inspection.

All supplying centres have written protocols for the provision of information to people wishing to donate oocytes/embryos to research. These protocols were submitted with the renewal application but were not provided on this occasion as this was an interim inspection.

The centre staff do not have access to donor identifying information as all the samples are anonymised prior to being sent to the centre. All records audited during the inspection were seen to be anonymised.

The transport incubators were shown to the inspection team. These have their own batteries which are fully charged prior to the transfer. A temperature recorder is placed into the incubator when the embryos are loaded. This records the temperature during the transportation and can be read at the research centre to confirm whether the correct temperature was maintained at all times.

It was explained to the inspection team that the staff at the research centre telephone the donating centre when the oocytes/embryos are received.

#### Issues for consideration

The process for patients to withdraw consent for their embryos to be used in research was discussed. The inspection team received verbal confirmation that this process is made clear in patient information, which states that the patients should contact the research nurse at their treatment centre. Although this situation has never occurred, probably due to the short window of time between the oocytes/embryos being donated and being used, the procedure should be made explicit in the SOPs both at the donating and research centres.

#### Executive recommendations for Licence Committee

SOPs, both at the donating and research centres, should be updated to include the procedure for when patients withdraw their consent.

<b>Areas not covered in this inspection</b>
Recruitment of donors Ensuring prospective donors have time to consider donation properly Prevention of coercion of prospective donors

**4. Patient information and consents**

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

Summary of findings from inspection:

- Consent forms for projects deriving embryonic stem cells

<b>Outcome of audit of records</b>
Six sets of records were examined during the course of the inspection. These covered all five donating centres. No discrepancies were identified.
<b>Highlighted areas of firm compliance</b>
Patient information and consent forms were not provided to the inspection team as this was an interim inspection.  Verbal confirmation was provided to the inspection team that patient information has been updated to include the name and contact details of the person they should contact if they wish to withdraw consent for their eggs or embryos to be used in the research. This person is the research nurse at the donating centre, who would then contact the researchers to inform them that consent had been withdrawn.
<b>Issues for consideration</b>
None
<b>Executive recommendations for Licence Committee</b>
None
<b>Areas not covered in this inspection</b>
Patient information for projects deriving embryonic stem cells

## 5. Scientific practice

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

Summary of findings from inspection:

- Standard operating procedures
- Minimisation of material loss and wastage
- Ability to achieve set aims and objectives

### Use of material

In the last 12 months 36 immature eggs, 6 clinically unusable eggs and embryos, 6 surplus fresh embryos and 96 surplus frozen embryos have been donated to the project. This is less than that estimated in the renewal application due to the following reasons:

- Fewer immature eggs have been received for the project than were anticipated. This has been due to the provision of alternative non-surgical sterilisation treatments. This trend is expected to continue in 2008.
- No embryos have been received from centre 0201 due to delays in completing the National Research Ethics Services (NRES) process for approval of the cross-centre standardised patient information and consent forms.
- Only frozen embryos have been received from centre 0044 due to a change in the ACU freezing policy.
- MRC support for centre 0067 ended in June 2007.
- Only frozen embryos have been received from centre 0019 due to refurbishment of clinic facilities, and this trend is expected to continue as this centre has changed the emphasis of its research.
- Donation of embryos from centre 0004 began part way through 2007.

In the next year the PR expects to use 50 immature oocytes, 400 failed to fertilise oocytes, 50 fresh embryos and 200 frozen embryos.

### Project objectives

The project objectives are as follows:

- i) to derive new hESC lines in high specification facilities that will comply with UK and European Union regulations and directives for the provision of therapeutic grade cells.
- ii) to refine culture environments supporting hESC derivation and maintenance by evaluating alternative recombinant or synthetic substitutes for poorly defined soluble and insoluble components currently used.
- iii) to evaluate the properties of hESCs from different sources of embryos. These include: fertilised fresh or frozen blastocysts; clinically unusable and parthenogenetically activated immature or failed to fertilise eggs; and clinically unusable abnormally fertilised eggs (ie. more than 2 pronuclei); the latter categories providing opportunities to derive parthenogenetic and aneuploid hESC lines.
- iv) refine methods for egg maturation in vitro by evaluating a role for neurotrophin mediated cell signalling.

#### Lay summary of research undertaken

We have completed refurbishment of laboratory facilities and implementation of a quality management system which we have assessed to be in compliance with relevant UK and EU legislation and directives for the therapeutic use of human cells and tissues. Accordingly we will apply to the Human Tissue Authority for accreditation for this purpose.

At the time of writing we had produced 2 new human embryonic stem cell lines (hESCs) under a new protocol which does not require direct contact of hESCs with any other helper cells. This is valuable to preclude inadvertent transmission of pathogens across cells.

We have also developed an improved understanding of protein signalling factors that control the maturation and subsequent developmental competence of human eggs. Specifically we have learned that signalling via a specific molecule, brain derived neurotrophic factor (BDNF) mediates some of the important changes which hormone stimulation causes in cumulus cells that surround and support an egg during the process of maturation.

Our future work will continue the development of methods to derive new embryonic stem cells without the reliance on products derived from human or animal cells and the development of techniques for deriving therapeutic grade stem cells in "clean room" facilities. We will also seek to develop methods to produce developmentally competent eggs from small ovarian follicles requiring in vitro growth. This will be of value to develop fertility treatments for women who have cryopreserved ovarian tissue prior to chemotherapy. This will also benefit the development of alternative sources of eggs for embryo stem cells and regenerative medicine that will not conflict with donor reproductive interests.

#### Highlighted areas of firm compliance

The centre staff report that they have submitted two papers for publication from this work.

Three stem cell lines in advanced stages of growth and characterisation have been isolated in the past year.

The inspection team were informed that an application to the HTA for a licence will be submitted by the end of January 2008.

The PR is aware that it is necessary to keep the executive informed about any changes to the research project. A discussion about possible future avenues of research took place during the inspection.

#### Issues for consideration

The inspection team noted that the identity of the embryos is only checked by one person on receipt at the centre. The centre staff explained that this is due to the embryos frequently being received out of normal working hours. The inspection team suggested that the acquisition checklist should be amended to include the signatures of the staff that witnessed the identity of the embryos when they were put into the transport container. This will ensure that evidence is available in the research records that two people have witnessed the identity of the embryos used in research at his centre.

Executive recommendations for Licence Committee
The acquisition checklist should be amended.
Areas not covered in this inspection
Quality assurance systems

Report compiled by:

Name: Vicki Lamb

Designation: Inspector

Date: 29 January 2008

## Appendix A: Centre Staff interviewed

PR and seven members of the team

## Appendix B: Licence history for previous 3 years

Licence	Status	Type	Active From	Expiry Date
R0136/3/b	Active	Research project	01/12/2007	30/06/2010
R0136/3/a	Replaced by new version	Research project	01/07/2007	30/06/2010
R0136/2/b	Expired	Research project	10/01/2005	30/06/2007
R0136/2/a	Replaced by new version	Research project	01/07/2004	30/06/2007

There are no conditions on the current licence.

### Research Licence Committee 28 November 2007

The papers were presented by Sarah Hopper, HFEA Inspector. Ms Hopper informed the Committee that the Person Responsible for centre 0202 has applied to change the name of the centre to Roslin Cells Limited and for the standard licence condition 3)ei to be modified. The Committee decided that the licence should be varied to apply the change to the condition to change the centre name.

### Research Licence Committee 9 May 2007

The papers were presented by Sarah Hopper, HFEA Inspector. Ms Hopper informed the Committee that the licence for this project expires in June 2007 and that the current NL will be leaving and an application had been received for Mr Malcolm Bateman to take up this role. The Committee decided to grant a licence for the research for a period of three years and approved Mr Malcolm Bateman as the new Nominal Licensee for the project.

### Research Licence Committee 26 July 2006

The Committee noted that licensed work will be taking place within a temporary laboratory inside the existing premises whilst the main laboratory is refurbished.

### Research Licence Committee 12 January 2005

The papers were presented by Chris O'Toole, Head of Research Regulation. Dr O'Toole explained that a request had been made by the licence holder of R036 to vary that licence in order to allow the use of embryonic material from the research projects licensed under R0156 and R0158. The Committee agreed to vary the licence as requested.

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

Centre Number...0202.....

Name of PR...Dr Paul De Sousa.....

Date of Inspection.....9 January 2008.....

Date of Response.....11 February 2008.....

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

Our application to the HTA was submitted as projected.

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

Name...Paul De Sousa.....

Date...11 February 2008.....

**2. Correction of factual inaccuracies**

Please let us know of any factual corrections that you believe need to be made (NB we will make any alterations to the report where there are factual inaccuracies. Any other comments about the inspection report will be appended to the report).

We also welcome comments about the inspection on the inspection feedback form, a copy of which should have been handed out at the inspection. If you require a copy of the feedback form, please let us know.

Please return this section of the report to:  
Dr Chris O'Toole  
Head of Research Regulation, HFEA  
21 Bloomsbury Street  
London  
WC1B 3HF