# Research Licence Interim Inspection Report

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| Project Title | Biochemistry of Early Human Embryos |
| Centre Name | University of York |
| Centre Number | 0062 |
| Research Licence Number(s) | R0067 |
| Centre Address | Department of Biology, University of York, PO Box 373, York, YO10 5YW |
| Donating treatment Centre numbers | 0052 – Clarendon Wing Leeds<br>0063 – St James' University Hospital, Leeds |
| Inspection date | 09/10/2008 |
| Licence Committee Date | TBC |
| Inspector(s) | Dr Andrew Leonard – Lead<br>Dr Vicki Lamb – Scientific Inspector |
| Fee Paid – date (if applicable) | N/A |
| Person(s) Responsible | Professor Henry Leese |
| Nominal Licensee | Dr Roger Sturmey |
| Licence expiry date | 31/01/2010 |

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**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, 7th edition of the HFEA 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 October 2007 and October 2008.

**Brief Description of the Research Project**

**The Research project is entitled:** BIOCHEMISTRY OF EARLY HUMAN EMBRYOS
Research for this project originally started in 1995. The current licence for R0067 is due to expire on the 31st January 2010.

**Licensed for the following purposes:**
The project was originally licensed under purposes laid down in Schedule 2 of the Human Fertilisation and Embryology Act 1990

- Promoting advances in the treatment of infertility
  *Human Fertilisation and Embryology Act 1990 Sch 2 3(2)(a*
- Increasing knowledge about the development of embryos
  *Human Fertilisation and Embryology (Research Purposes) Regulations 2001 s2(a)*
- Increasing knowledge about serious disease
  *Human Fertilisation and Embryology (Research Purposes) Regulations 2001 s2(b)*

**Licensed activities:**
- Storage of embryos
- Use of donated embryos for research

**Lay Summary for R0067:**
Up to 1 in 6 couples find difficulty in conceiving. For many, one solution to their infertility is In Vitro Fertilisation and Embryo Transfer (IVF-ET) the so-called "test tube baby" treatment, which was pioneered in the UK in the late 1970s. This treatment has helped many thousands of couples to have children, but success rates remain disappointingly low with a live birth rate per treatment cycle in the UK of only around 23%. Moreover, since 2, exceptionally 3 embryos may be transferred in a treatment cycle, there is a high risk of multiple births. While the birth of a baby is a cause for joy, multiple births can also bring problems; the babies are often underweight and peri-natal mortality is above average; the parents may also have problems coping with the arrival of a large family.

There is now good agreement amongst doctors and embryologists that a solution to these problems would be to transfer single embryos with a high chance of forming a pregnancy. However, we know very little about how human embryos are formed and what makes some embryos healthier than others. The aim of our work is therefore to carry out a detailed

examination of the development of the early human embryo. The focus is on nutrition and metabolism: how the embryo obtains and uses the nutrients it requires; for example, sugars and amino acids. In this way we will learn how to improve culture conditions and devise diagnostic methods that allow the transfer of single, healthy embryos with a high chance of giving rise to a pregnancy and minimise the risk of multiple births. Eventually, this will help ensure the health of babies born following natural conception as well as IVF. While we use cattle and pig embryos (made from abattoir-derived eggs) in our work, it is essential to carry out research on spare human embryos to ensure that the data reflect as closely as possible the situation in human IVF.

**Lay Summary of Research Undertaken:**
Over the past year, our research has focussed on the way in which amino acids (the building blocks of protein) are taken up by early embryos. We already knew that this 'Amino Acid Profiling' (AAP) was related to the health of the embryos since cattle, pig and human embryos which developed well in culture had a lower amino acid profile than embryos which fail to develop. In the case of human embryos, we also showed that embryos which were 'quieter' metabolically were more likely to give rise to a pregnancy following embryo transfer.

We have now shown that embryos with a higher amino acid profile have more molecular/cellular damage or are less well equipped to cope with normal levels of damage; these more 'active' embryos have to devote more of their nutrients, such as amino acids into repairing damage to the DNA, proteins and other cellular constituents. By contrast, a 'quiet' embryo operates at a higher level of efficiency than its less viable counterparts and therefore needs to consume only the minimum quantities of nutrients. Over the coming year, our intention is to develop a novel assay which will enable the detailed study of DNA damage in individual embryo cells.

We are then hoping to translate these biological findings into a diagnostic test with which to select 'quiet' embryos for transfer in order to maximise success rates while minimising the risk of multiple births, the main side-effect of IVF.

**Future work**
Work will continue to pursue:
Objective (i): To establish the value of non-invasive Amino Acid Profiling (AAP) in diagnosing the health of human IVF embryos prior to transfer

Objective (ii): To investigate the molecular basis of the relationship between Amino acid profiling and DNA damage in early human embryos.

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|---|---|---|
| **Activities of the Centre** | Research on human embryos | ✓ |
| | Storage of licensed material | ✓ |
| | Creation of embryos for research | |
| | Derivation of human embryonic stem cells | |
| | Cell nuclear replacement | |

**Changes/ improvements since last inspection**

The Centre have satisfied the requirements of the last inspection report in that:

- The Centre operate an effective bring-forward system to stop any embryos being stored over their consented storage periods.
- Embryo disposal is now witnessed.
- Document control mechanisms have been revised to ensure annual review of procedures and important documentation
- A risk assessment has been performed to cover the possibility of liquid nitrogen spillage or dewar failure in the embryo storage laboratory, given the lack of a low oxygen monitor. This found the level of risk to staff to be negligible and an oxygen monitor has not been fitted.
- The university employed driver who collects embryos from Centres 0052 and 0063 has been placed on the Licence
- The generic research information leaflet (form Clin 009) and project information have been modified to include the contact point and mechanism for withdrawing consent and contacts at the recruiting Centres and at Centre 0062 from whom further information about the research projects can be obtained.

Staff in the research laboratory has decreased in the last year and most licensed research work is now performed by a single post-doctoral research fellow. This researcher has taken over the role of Nominal Licensee

**Additional licence conditions and recommendations and actions taken by Centre since last inspection**

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|---|---|
| **C** | **None** |
| **A** | |

**Summary for Licence Committee**

The inspectorate were satisfied that the Centre is well organised and running compliantly with the HFE Act (1990). The inspectorate was impressed by the Centre's responses to issues raised by the licence interim inspection on 12th September 2007. Indeed the organisation of research, premises and equipment, donation processes and scientific/research activity were all considered satisfactory by the inspectorate. The only issue noted was that patient information requires minor amendments:

1) Patient information does not accurately describe the current funding source for the research, as required by HFEA Code of Practice, 7th edition, S.8.2.1. The information states the project is funded by the Medical Research Council and by the Wellcome Trust. These funding sources have lapsed and the project is currently funded by internal laboratory funds and by the Department of Biology, University of York, albeit external funds are being sought. Patient information should be updated to attain compliance with S.8.3.2 (a).

2) Patient information does not discuss the investigation of the correlation between embryo metabolism and DNA damage (i.e. Objective ii for the coming year). This is potentially a breach of the HFEA Code of Practice, 7th edition, S.8.3.2 (a) '….are given oral information, supported by relevant written material, which confirms: the specific research project, including *any tests that may be performed on embryos or cells from those embryos*….'. Patient information should be updated to attain compliance with S.8.3.2 (a).

The inspectorate recommend continuation of Research Licence R0067

**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
- Research governance
- Funding

**Full time equivalent staff**

| | |
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| Principal investigator | 1 |
| Laboratory scientists | 1 |
| Administrators | 0 |
| Collaborators | 4 |
| Support staff | 0 |

Summary

The Centre functions within the Department of Biology, University of York, which provides an appropriate level of health and safety, facilities and human resources support to the Centre. On inspection, the Centre seemed well organised in terms of premises, staffing, operations and interactions within the Department of Biology. The PR supplied an organisational chart

Several researchers have left the laboratory in the last year. The PR oversees the research project activities while they are performed by an experienced post doctoral research fellow; a second researcher will soon start work. Support and advice are also available from the ex-Nominal Licensee who works in the same building on a different project. Staff experience and numbers were considered appropriate for the project objectives defined for the next year and facilities/funding available. The team's small size allows easy coordination of activity by one to one discussion and email, with action points being documented in emails between the PR and NL. Interviews with the NL and PR and general research progress indicate appropriate leadership and management of the project.

The PR stated communication with the donating Centres, Centres 0052 and 0063, occurs regularly via email and telephone to determine when donated embryos can be collected. Fresh embryos are usually collected weekly by a regular university-employed driver who is on the licence, sometimes with the PR or NL. Frozen embryos are collected in batches in an appropriate transport container, again by the regular university employed driver. Work on frozen embryos has however stopped at the Centre for the immediate future. Visits by the PR and NL to Centre 0052 and 0063 allow discussion of the research project with the collaborators. The PR and NL provide seminars at Centre 0052 and 0063 annually to inform on research progress. The NL and PR liaise closely with the research nurses at Centre 0052 and 0063 to ensure research information and consenting procedures are compliant.

The Centre's research activities are currently funded by internal laboratory and departmental funds. Grant applications are in preparation for submission. They have received ethical approval from an appropriate ethics committee at York University. The planned multi-centre clinical trial to test the applicability in IVF clinical practice of the PR's 'quiet embryo' hypothesis has been suspended due to difficulties in securing funding for the project. The PR hopes that funding will be secured in the next year. Whether this occurs is out of his control and is in the hands of a private company who is coordinating the trial.

Embryo entry into storage and usage in experiments is recorded and witnessed on a spreadsheet log, evidenced as being appropriate during the inspection. Experimental notes and data are documented in laboratory notebooks and held on computer. The Centre has incorporated a GMP (Good Manufacturing Practice) approach in its research activities due to the clinical trial, and has developed a quality manual covering a wide variety of Centre activities. Mechanisms of research governance were considered appropriate

Issues for consideration

The Centre has an adverse incident reporting procedure, however when discussing non-conformities in centre activities, Centre staff were unsure what should be reported as adverse events to HFEA. It is recommended therefore that the PR and NL review the adverse incident reporting procedure to ensure it is compliant with the Code of Practice requirements and to report adverse incidents in future according to that procedure.

Executive recommendations for Licence Committee

None

Areas not covered on this inspection

None

## 2. Premises and equipment

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

Summary of findings from inspection:

- Suitability of premises
- Storage facilities
- Safety of equipment
- Servicing and maintenance of equipment

| Summary |
| --- |
| The research is carried out on a key pad secured corridor. The storage and culturing of embryos occurs in a locked laboratory, access to which is limited to staff on the HFEA research licence. This laboratory contains a biohazard cabinet, laminar flow hood, fridge/freezer, incubators and a lockable dewar for embryo storage containing no embryo on the day of inspection. Analysis of embryo extracts and media is undertaken in a second laboratory which is well equipped and maintained to GMP standards. The Centre also contains three offices and an open lobby area. Patient consents are stored in the PR's outer office, which is locked at night, in a locked filing cabinet. The premises were considered fit for purpose by the inspectorate.<br><br>Frozen embryos donated to research are stored in a locked dewar. The dewar is checked weekly when embryos are in storage and topped up with liquid nitrogen if required, evidenced by the filling log sheet. The Centre has a small spare dewar in case of emergency. The laboratory does not have a low oxygen alarm or direct air extraction system. This situation has been risk assessed as a requirement of the last inspection. The PR reported that work on frozen embryos has stopped at the Centre for the immediate future.<br><br>The sealed research consent forms which arrive with the transferred embryos are initially kept in a locked drawer in the licensed laboratory. After being checked by somebody on the licence but not associated with the research, they are stored in a locked filing cabinet in the PR's office. Document security was considered appropriate.<br><br>Carbon dioxide cylinders and the temperatures of incubators and fridge/freezers are checked each working day, evidenced by log sheets. The equipment within the laboratory had up to date service contracts and electrical safety testing labelling, which were evidenced during the inspection. Written procedures were in place for operating all equipment and a cleaning log for the incubators was observed. Equipment safety, servicing and maintenance were considered appropriate. |
| Issues for consideration |
| None |
| Executive recommendations for Licence Committee |
| None |
| Areas not covered by this inspection |
| None |

## 3. Donation of material

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

Summary of findings from inspection:

- Recruitment of donors
- Ensuring prospective donors have access to further guidance
- Ensuring prospective donors have time to consider donation properly
- Prevention of coercion of prospective donors
- Ensuring patient consent is not breached
- Donor and patient records

| Summary |
| --- |
| Donors are recruited from two Centres; Leeds General Infirmary (0052) and St. James' University Hospital, Leeds (0063). Patients at Centre 0052 and 0063 donate frozen embryos to research while fresh embryos are donated from 0052. Frozen embryos have been used in the past year but all work in the foreseeable future will use fresh embryos from Centre 0052.<br><br>Provision of information and the consenting process is managed by the recruiting Centres and is undertaken by research nurses. The research nurse has recently left Centre 0052 and this role is being covered by the Centre's nursing coordinator. The NL recently visited Centre 0052 to review patient research consenting procedures and the recruitment process and ensure that it is compliant. Evidence was provided of this meeting.<br><br>Research donation is first presented to patients at an introductory patient information evening, attended by new patients and Centre staff when the treatment processes are discussed. Research donation is next discussed by couples with their clinician at first consultation, normally more than 2 months before egg collection, when they can ask questions. They are provided with a research information pack and the research consent form at this time if interested in research donation, which they take away to read. Research consents are completed by the couple at home or at the Centre if advice from clinical staff or the Research Nurse is needed. If further guidance is needed, it is available from the research nurses and from the PR of Centre 0062. Consents are normally in place prior to or at the start of the treatment cycle. The inspectorate considered that the time for consideration of consent and availability of guidance were compliant with the Code of Practice, 7th edition. Centre 0062 has mechanisms in place to allow the appropriate disposal of research material if research consent is withdrawn before the material has been used. Patients are provided with a copy of the IVF research consent form if completed.<br><br>Embryos transferred from the recruiting Centres are accompanied by the patient's consent form and a copy of the Centre's embryo laboratory sheet in a sealed envelope. These are checked upon arrival by a person not involved in the research, but who is on the licence. If a discrepancy is found, the recruiting Centre is contacted and corrections are made as required. The embryos are given a unique research identification number and this is detailed on the embryo stock/experimentation spreadsheet log, along with the research number, estimated grade and statutory storage expiry date (if frozen). Fresh material is effectively reversibly anonymised but frozen embryos arrive with the patient's name on the storage straw. This is |

only seen by licensed personnel and cannot be avoided but the situation is described in the patient information used by Centres 0052 and 0063. Fresh embryos donated to research are transferred to a Petri-dish in the air flow cabinet then placed in the incubator. Embryos are re-graded and their culture location and subsequent gradings and media changes, with dates, are logged on the activity spreadsheet. Used media samples are stored for later amino acid profiling. Frozen embryos are logged and stored in the dewar; when used they are processed after thawing as for the fresh embryos. Procedures at the Centre ensure that the statutory storage period is not breached.

The inspectorate considered that patient/donor records are securely stored at the Centre.

The inspectorate consider that patient confidentiality and consenting are compliant with the Code of Practice, 7th edition

| Issues for consideration |
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| None |
| Executive recommendations for Licence Committee |
| None |
| Areas not covered on this inspection |
| Donor and patient records at Centre 0052 and 0063 |

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

| Summary |
| --- |
| The PR and NL have liaised with the donating Centres in the preparation of patient information and consent forms to ensure they are compliant. Patient information and consent forms were reviewed by the inspectorate. The availability of counselling is discussed in patient information, which also makes it clear that donation to research will not affect present or future treatment. The research licence no longer donates embryos used in metabolic analysis onward to Centre 0246 for stem cell derivation, therefore all mention of this work has been removed. Patient information and consents are version controlled and have review dates. The patient information and consent forms were considered fit for purpose with minor exceptions:<br><br>1) Patient information does not accurately describe the current funding source for the research, as required by HFEA Code of Practice, 7th edition, S.8.2.1. The information states the project is funded by the Medical Research Council and by the Wellcome Trust. These funding sources have lapsed and the project is currently funded by internal laboratory funds and by the Department of Biology, University of York, albeit external funds are being sought.<br><br>2) Patient information does not discuss the investigation of the correlation between embryo metabolism and DNA damage (i.e. Objective ii for the coming year). This is potentially a breach of the HFEA Code of Practice, 7th edition, S.8.3.2 (a) '….are given oral information, supported by relevant written material, which confirms: the specific research project, including *any tests that may be performed on embryos or cells from those embryos*….'. Patient information should be updated to attain compliance with S.8.3.2 (a). |
| Summary of records audit |
| Records were not audited as the patient notes are at Centres 0052 and 0063. |
| Issues for consideration |
| The IVF Research Consent Form does not provide the ability to limit consent to specific individual projects or vary consent, as required by Code of Practice, 7th Edition, G.5.13.1 (f,g). This issue was raised after the last inspection and the PR responded that it was not in the best interests of the research and the effective use of embryos, for the consent form to provide the facility for consent to be given to individual arms of R0067. Furthermore, he advised that the Centre have never been requested by somebody donating embryos to research, to allow specific donation down one arm of the project and not another. The inspectorate recommended this justification of non-compliance with Code of Practice Guidance was accepted when the report was considered at Licence Committee and noted that though there are several research objectives, they are encapsulated within one research |

project. The Licence Committee took no action. It is noted that in the coming year the research is encapsulated by two objectives only.

The proposed research may involve sequencing of embryonic DNA and other genetic investigations and samples are capable of being identified at the centre. The PR should ensure that information and consent forms provided to patients are compliant with HFEA Code of Practice, 7th edition, G.5.13.2 (a-f) and G.5.13.3 when the proposed research commences

| Executive recommendations for Licence Committee |
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| Note the need for amendments to the patient information as discussed in the summary above |
| Areas not covered on this inspection |
| The original patient files at Centre 0052 and 0063 were not inspected. |

## 5. Scientific practice

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

Summary of findings from inspection: *(Delete areas not being reported on)*

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

| Summary |
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| EMBRYO USAGE<br>Centre 0062 received more that the expected number of fresh (709 from Centre 0052) and frozen (81 from Centre 0052; 104 from Centre 0063) embryos between 31/05/2007 to 31/5/2008. By 31/5/2008, all but 22 frozen embryos had been used, and these were used by the time of this inspection.<br><br>In the previous year (01/09/06 to 31/08/07), the Centre used 528 fresh and 26 frozen embryos from Centre 0052, and none from Centre 0063, while between 01/10/04 and 20/09/05, the Centre used 645 fresh and 682 frozen embryos.<br><br>As in previous years, usage next year is estimated at 400 fresh and 100 frozen embryos. The inclusion of 100 frozen embryos is as a contingency in case work with frozen embryos re-starts, though this is at present not planned.<br><br>OTHER ITEMS<br>A large set of standard operating procedures has been developed by the Centre to regulate its activities, as discussed in Section 1 above. These procedures will be reviewed annually if possible, though due to staff limitations some delays are expected.<br><br>The PR considers the most important key performance indicator of research progress and effective use of donated embryos, is the production rate of research data and peer reviewed publications.<br><br>The storage and removal of embryos from the research dewar is witnessed, evidenced by examining the embryo storage and experimental log. A procedure is in place for witnessing. Embryo disposal is now appropriately witnessed.<br><br>The Centre maximise the data output from the embryos they receive by performing metabolic studies first and then using the embryos for other research purposes, such as histochemistry/molecular biology in-house to determine DNA damage. |
| Summary of audit of stored and biopsied material |
| Frozen licensed material is stored in a locked dewar. An audit of stored material is performed annually though embryos are normally used within a few weeks of being placed in storage. At present no embryos are in storage and the Centre have suspended work using frozen embryos for the foreseeable future. Thus no audit has recently been performed, neither was a HFEA inspectorate spot check. The Centre storage logs were reviewed over the last year |

and it was noted that all embryos had been used before the expiry of their consented storage periods.

Renewed project objectives

**Objectives defined at last inspection**

(i) to establish the value of non-invasive Amino Acid Profiling (AAP) in diagnosing the health of human IVF embryos prior to transfer.
(ii) to provide surplus human embryos, following non-invasive amino acid profiling (AAP) to the Institute for Stem Cell Research, University of Cambridge.
(iii) to investigate the relationship between Amino acid profiling and DNA damage in early human embryos.

**Redefined objectives at this interim inspection**

Funding for objective ii) above has stopped. Objectives i) and iii) are redefined as i) and ii)

*Objective (i): To establish the value of non-invasive Amino Acid Profiling (AAP) in diagnosing the health of human IVF embryos prior to transfer*
*Objective (ii): To investigate the molecular basis of the relationship between Amino acid profiling and DNA damage in early human embryos.*

Summary of research undertaken

*Objective (i):* To establish the value of non-invasive Amino Acid Profiling (AAP) in diagnosing the health of human IVF embryos prior to transfer

The proposed 400 patient clinical trial to establish the value of non-invasive Amino Acid Profiling (AAP) in diagnosing the health of human IVF embryos prior to transfer has not yet commenced, since the company sponsoring the work, and it parent company, have failed to secure sufficient funds. These companies are continuing to try and attract such funds from a variety of investment and commercial companies.

*Objective (ii):* To provide surplus human embryos, following non-invasive amino acid profiling (AAP) to the Institute for Stem Cell Research, University of Cambridge.

Funding for this project has now ceased and all the embryos earmarked for the study have been transferred to the Cambridge laboratory where attempts are being made to generate Embryonic Stem (ES) cells. The outcome is awaited.

*Objective* (iii): To investigate the relationship between Amino acid profiling and DNA damage in early human embryos.

This study has been carried out using *in vitro* produced pig, cow and human embryos. The extent of DNA damage was measured in all cells at the blastocyst stage. The proportion of cells in the blastocyst with DNA damage was compared with the amino acid profile determined at the blastocyst stage (cow and pig) or during early cleavage (human). In each case, there was a strong positive correlation between the extent of DNA damage and the amino acid profile (Figs 1, 2 and 3). These data are consistent with the ‘quiet embryo hypothesis’ which proposes that embryos with the highest metabolism have elevated requirements for nutrients (such as amino acids) due to the need to repair increased

molecular and cellular damage.

Figure 1

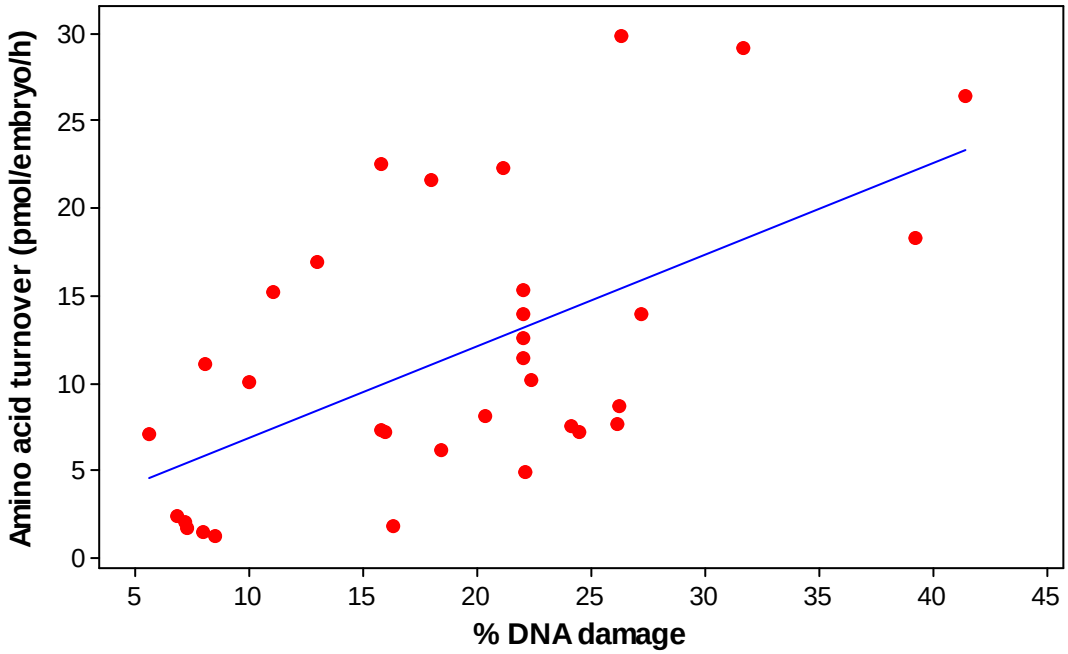
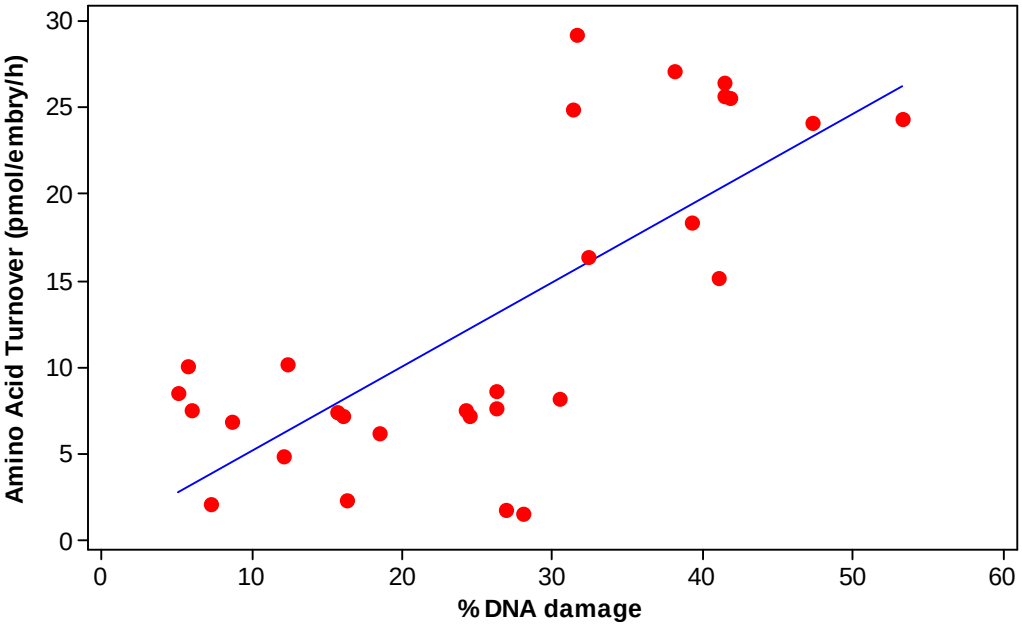



Figure 2




Figures 1 & 2 – Correlation between DNA damage and amino acid turnover of porcine (Figure 1, p=0.0001) and bovine (Figure 1, p=0.0001) blastocysts and DNA damage. Correlation tested by Pearson's Correlation.

Figure 3

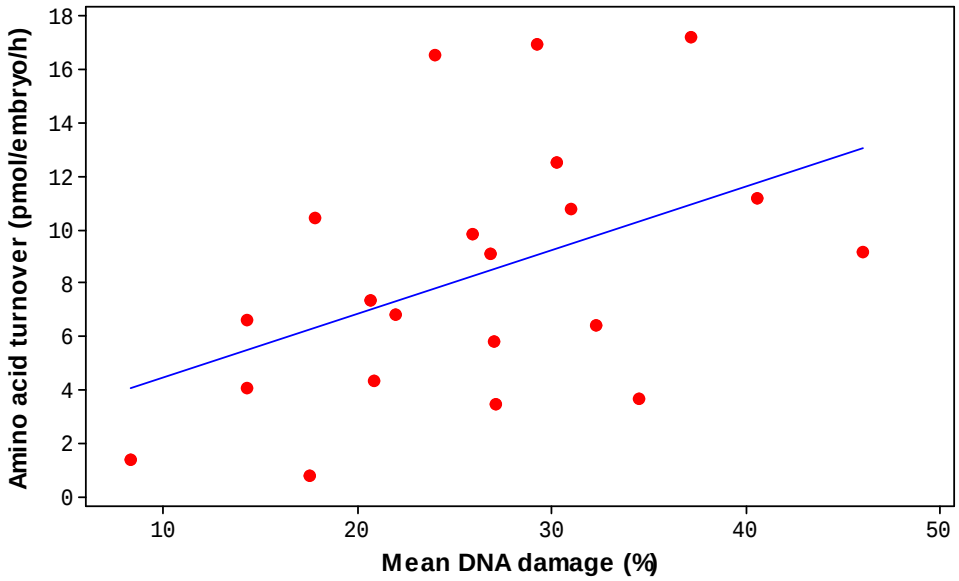



Figure 3 – Correlation between amino acid turnover on day 2 of development and mean DNA damage in human blastocysts. Pearson value = 0.479, p=0.028, n=21.

Figure 4 shows that there was no relationship between Embryo Grade (on which basis embryos are currently chosen for transfer) and DNA damage, highlighting the imprecision of human embryo selection on morphological grounds

Figure 4

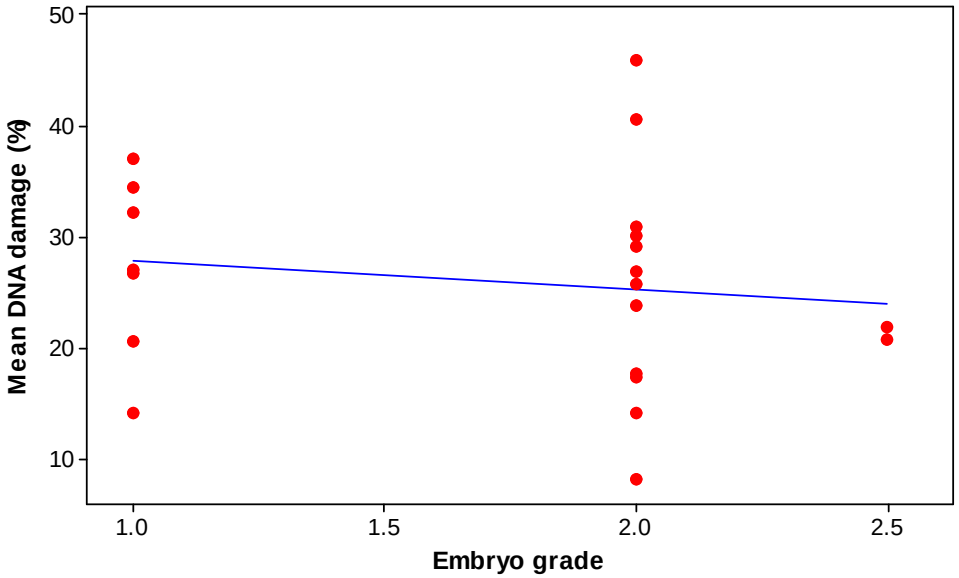



Figure 4 – Individual value plot of DNA damage versus embryo grade in human embryos. Grade 1 is “highest quality”.

**Future Work**

The intention is to develop a novel assay which will enable the detailed study of DNA damage in individual blastomeres. This will combine existing embryo culture methods and DNA damage assays with biophysical techniques, aimed at physically combing isolated DNA. Initially we will introduce a series of DNA repair proteins (starting with Oxidative Glycosylase (OGG)) to establish the types of DNA damage present in the blastomeres. This will be complimented by the combing assay, where we hope to stretch individual strands of DNA on a glass slide, using a receding meniscus. We will then use antibodies against specific DNA-associated proteins to look for their physical location on the genome. There is then the potential to sequence sections of the genome to discover if there is preferential repair occurring in the early embryo. All data will be related retrospectively to metabolic data collected non-invasively. These methods will initially be trialled on *in vitro*-produced cattle and pig embryos before being applied to human embryos donated for research.

We feel that the research will provide valuable information which relates to the question 'what makes a good embryo'? Our hypothesis is that a good embryo needs to expend less energy rectifying damage to the genome, transcriptome and proteome. If this is the case, it will provide a number of markers of embryo health; at the molecular and cellular levels – against which improvements in IVF technologies may be tested.

**Publications**

Eckert, JJ, Houghton FD, Hawkhead, JA, Balen AH, Leese HJ, Picton HM, Cameron IT and Fleming TP (2007). Human embryos developing in vitro are susceptible to impaired epithelial junction biogenesis correlating with abnormal metabolic activity. *Hum Rep*. **22**:2214-2224.

Kimber SJS, Sneddon SF, Bloor DJ, El-Bareg AM, Hawkhead JA, Metcalfe AD, Houghton FD, Leese HJ, Rutherford A, Lieberman BA and Brison DR (2008). Expression of genes involved in early cell fate decisions in human embryos and their regulation by growth factors. *Reproduction*.**135**:635-47.

The work for these two papers was mainly carried out in the period 2003-2006

Recent papers which have arisen from the MRC Co-operative on the *Development of the Early Human Embryo*.

Leese HJ, Sturmey RG, Baumann CJ and McEvoy TG (2007). Embryo viability and metabolism: obeying the quiet rules. *Human Reproduction* **22**: 3047-3050

Sturmey RG, Brison DR and Leese HJ (2008) Assessing embryo viability by measurement of amino acid turnover. Reproductive BioMedicine Online 2008 http://www.rbmonline.com/Article/3432 [e-pub ahead of print on 18 August 2008]

Sturmey, RG, Hawkhead JA, Barker EA & Leese HJ (2008) DNA damage and metabolic activity in the preimplantation embryo. Human Reproduction *in press*

Peer review comments (if applicable)

None required at this interim inspection

| Issues for consideration |
| --- |
| None |
| Executive recommendations for Licence Committee |
| None |
| Areas not covered on this inspection |
| None |

Report compiled by:

Name: Andy Leonard

Designation: Inspector

Date: 10th October 2008

## Appendix A: Centre Staff interviewed

The PR and NL

**Appendix B: Licence history for previous 3 years**

| Licence | Status | Type | Start date | Expiry date |
|---|---|---|---|---|
| R0067/7/a | Current | Research Project | 01/02/2007 | 31/01/2010 |
| R0067/6/b | Expired | Research Project | 01/02/2004 | 31/01/2007 |
| R0067/5/b | Expired | Research Project | 16/01/2001 | 31/01/2004 |
| R0067/4/a | Expired | Research Project | 15/01/1998 | 15/01/2001 |

No conditions or recommendations on Licences.

**Appendix C: Response of Person Responsible to Inspection Report**

Centre Number: 0062

Name of PR: Professor Henry Leese

Date of Inspection: 09/10/08

Date of Response: 17/10/08

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

(i) The patient information will be updated to describe the funding source accurately
(ii) The patient information will be updated to include the measurement of embryo metabolism and DNA damage

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

Signed……

Name Henry J Leese ……

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

**19 November 2008**
**21 Bloomsbury Street London WC1B 3HF**

**MINUTES Item 5**

**Research Project R0067: Biochemistry of early human embryos based at the University of York (0062)**
**Interim inspection**

| Members of the Committee: | In Attendance: |
|---|---|
| Emily Jackson, Lay Member – Chair | Chris O'Toole, Head of Research Regulation |
| Richard Harries, Lay Member | Claudia Lally, Committee Secretary |
| Clare Lewis-Jones, Lay Member | |
| Neva Haites, Professor of Medical Genetics, University of Aberdeen | Providing Legal Advice to the Committee: |
| Maybeth Jamieson, Consultant Embryologist, Glasgow Royal Infirmary | Sarah Ellson, FFW Solicitors |

Declarations of Interest: members of the Committee declared that they had no conflicts of interest in relation to this item.

The following papers were considered by the Committee:

- papers for Licence Committee (73 pages)
- no papers were tabled.

1. The papers for this item were presented by Andrew Leonard, HFEA Inspector. Dr Leonard explained that over the past year this project has focussed on how amino acids are taken up by early embryos. The research has shown that embryos with a lower take up of amino acids are more efficient and appear to have lower levels of molecular /cellular damage or to be better equipped to cope with this damage. Dr Leonard explained that the research group is currently generating funds for a trial to establish the value of non-invasive amino acid profiling in diagnosing the health of human IVF embryos prior to transfer.

2. Dr Leonard informed the Committee that the inspection visit to this centre took place on 9 October 2008. The inspection found that the requirements of the previous inspection report have all been satisfactorily addressed. In addition, the research was found to be well organised and compliant with the Code of Practice and Human Fertilisation and Embryology Act 1990. The minor recommendations made as part of the inspection have all been implemented by the Person Responsible, including the two minor

amendments required to be made to the information for patients considering donating embryos to the project.

The Committee's Decision

3. The Committee noted the findings of the inspection and endorsed the recommendations made by the inspection team. The Committee noted the response to the inspection by the Person Responsible and agreed that the research licence should continue with no additional conditions.

Signed..... Date..18.12.09
Emily Jackson (Chair)