Human Fertilisation and Embryology Authority

Minutes of the Licence Committee

Meeting held at Finsbury Tower, 103-105 Bunhill Row, London, EC1Y 8HF on
16 July 2015

Minutes – item 3

Centre 0017 (Newcastle Fertility Centre at Life) – Change of research objectives and lay summary, R0152

Members of the Committee:	Andy Greenfield (Chair, lay) Kate Brian (lay) Margret Gilmore (lay) Anita Bharucha (lay)
Legal Adviser:	Ros Foster, Browne Jacobson
Members of the Executive:	Sam Hartley – Head of Governance and Licensing Trent Fisher – Secretary

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:

- executive report
- previous committee minutes for the last three years
    - 22/05/2015 variation, adjourned
    - 31/10/2014 change of PR
    - 08/05/2014 licence renewal
    - 21/06/2013 interim inspection
    - 23/05/2013 interim inspection, adjourned

The committee also had before it:

- HFEA protocol for the conduct of Licence Committee meetings and hearings
- 8th edition of the HFEA Code of Practice
- Human Fertilisation and Embryology Act 1990 (as amended)
- decision trees for granting and renewing licences and considering requests to vary a licence (including the PGD decision tree)
- guidance for members of the Authority and committees on the handling of conflicts of interest approved by the Authority on 21 January 2009
- guidance on periods for which new or renewed licences should be granted

- standing orders and instrument of delegation
- indicative sanctions guidance
- HFEA directions 0000 – 0012
- guide to licensing
- compliance and enforcement policy
- policy on the publication of Authority and committee papers.

Background

1. Research project R0152 ‘Towards improving assisted reproductive technologies for the treatment of infertility and prevention of disease’ has been licensed since August 2004.

2. Centre 0017 has applied to update the research project’s objectives and the lay summary.

Discussion

3. The committee considered the papers that included an executive report and licensing minutes for the past three years.

4. The committed noted that application was first considered by the Executive Licensing Panel, which referred the matter to the Licence Committee.

5. The committee noted the inspectorate’s recommendations to:
    - approve the updates to the research objectives; and
    - approve the updates to the lay summary.

Decision

6. The committee agreed to approve the updates to the centre’s lay summary and the updates to the research objectives. The committee was content that the revised objectives and lay summary were consistent with the activities and purposes for which the project was licensed.

7. The committee noted that the Executive Licensing Panel had referred the application to the Licence Committee as it did not have sufficient expertise to take a view on this application. The Committee reminded the executive to ensure that appropriate expertise was available to advise the panel or committee in future, as required. The committee further noted that it was entirely appropriate for a licensing committee to consider the changes to this project in light of the recent changes to the legislation regarding Mitochondrial Donation.

Signed: Date: 27 July 2015

Andy Greenfield (Chair)

Executive Up-date Report

Purpose of this inspection report

The HFEA licenses and monitors establishments undertaking human embryo research. Licences for individual research projects can be granted for up to three years. This is a report of a desk-based assessment following an application to vary an existing licence. The Authority's Executive Licensing Panel uses the application and this report to decide whether to vary the licence and, if so, whether any additional conditions should be applied to the licence.

Date of assessment: 02/07/2015

Inspector: Dr Douglas Gray

Purpose of inspection: Up-dated lay summary and research objectives associated with the licence.

Inspection details:
The report covers the findings from the assessment and communications received from the centre.

Date of Executive Licensing Panel: 16 July 2015

Centre Details:

Project title	Towards improving assisted reproductive technologies for the treatment of infertility and prevention of disease.
Centre name	Newcastle Fertility Centre at LIFE
Centre number	0017
Research licence number	R0152
Centre address	Bioscience Centre, International Centre for Life, Times Square, Newcastle upon Tyne, NE1 4EP
Person Responsible (PR)	Dr Meena Choudhary
Licence Holder	Dr Mary Herbert
Treatment centres donating to this research project	Newcastle Fertility Centre at Life (0017), The Gateshead Fertility Unit (0170)
Date licence issued	01/08/2014
Licence expiry date	31/07/2017
Additional conditions applied to this licence	None

Section 1: Summary report

Brief description of the centre and its licensing history:

The Newcastle Fertility Centre is based within the International Centre for Life. The research laboratory is located within the same unit as the treatment and storage centre. Research project R0152 has been licensed since August 2004.

The licence was last renewed in August 2014 following a desk-based assessment. In November 2014 Dr Alison Murdoch stood down as the PR and Dr Meena Choudhary was appointed. We last visited the centre in February 2015 for a routine interim inspection.

On 11 March 2015 the PR requested a variation to add storage of gametes to their licence. On 29 march 2015 the PR also requested to amend the lay summary and objective 1 of the project.

On 8 May 2015 the PR requested a further amendment to objective 3 of the project.

Both applications were presented to Executive Licensing Panel (ELP) on 22 May 2015. ELP agreed the variation to include storage of gametes but adjourned a decision on the up-dated lay summary and objectives and referred this decision to the Licence Committee.

This report sets out the proposed updated lay summary and objectives. Annex 1 shows the changes as they relate to the original lay summary and objectives.

Summary for licensing decision:

The PR has requested the updates to broaden their mitochondrial donation research to include the technique of polar body transfer. The inspection team are satisfied that these amendments do not constitute a new research project but represent a change in the approach proposed to meet the objectives of the currently licensed research. We consider the information provided to potential donors remains consistent with the research project, its aims and purposes and that consent given prior to this change remains effective. The PR has confirmed that no amendment is required to the ethics committee approval granted for the research.

Recommendation:

The committee is asked to note the centre's updated lay summary and a research objective described below.

Section 2: Summary of the research project

Lay summary of the research project:

The proposed lay summary of the research project is as follows:

'The focus of our research is to extend the scope of assisted reproductive technologies (ART) to prevent transmission of mitochondrial DNA (mtDNA) disease and to improve outcomes of ART for the treatment of infertility. During the next three years, we propose to pursue the following aims.

(1) Develop new clinical treatments to minimise transmission of mtDNA mutations from a mother to her child. This part of the research programme will build on previous work in which we demonstrated that it is technically feasible to transfer nuclear genetic material, contained in pronuclei, between fertilised human eggs. We propose to further optimise and test the safety of pronuclear transfer and related techniques.
(2) Improve the outcome of infertility treatments through gaining a better understanding of the cellular and molecular events occurring during pre-implantation development in vitro, and to determine how these are affected by the routine laboratory procedures.
(3) Investigate the pathways leading to chromosomal abnormalities in eggs and embryos. We hope that these investigations will help us to better understand the mechanisms underlying chromosomal abnormalities in eggs of older women.'

Objectives of the research:

The proposed objective 1of the research project is as follows:

Mutations in mtDNA can cause a range of fatal and debilitating diseases. Reports from our lab (Craven et al, 2010, Nature: 465) and others (Tachibana et al, 2013, Nature:493) indicate that inheritance of mtDNA can be uncoupled from inheritance of nuclear DNA by transplanting the nuclear genome between eggs. This can be done either before fertilisation by transplanting the meiosis II spindle (MST) and its associated chromosomes, or after fertilisation by transplanting the pronuclei (PNT) between fertilised eggs. More recently, there has been a report of successful polar body transfer in mouse oocytes (Wang et al, 2014 Cell:157). This is an attractive option, which in mice results in minimal carryover of mtDNA, and raises the possibility of obtaining more than one maternal genome from each patient oocyte. While PNT has been the major focus of our research to date and our ongoing efforts are aimed at optimising it, we also propose to test the efficacy of MST and PBT in human oocytes.

Our primary objective is to maximise the production of good quality blastocysts and to perform a range of studies, including chromosomal analysis and gene expression studies, to compare PNT blastocysts with unmanipulated controls. We will also test the effect of PNT/MST on cell cycle and reprogramming events during the earliest stages of development. In accordance with the recommendations of the HFEA Expert Panel, we will generate ESC lines to compare those derived PNT/MST blastocysts with controls. These lines will also be used to investigate the fate of karyoplast-associated mtDNA.

While our proof of concept work on PNT was conducted using abnormally fertilised eggs, these have a limited potential for onward development, and are therefore of limited value in our endeavours to further optimise and test the safety of PNT. Thus, progress in towards clinical treatments requires a supply of oocytes donated and fertilised specifically for this research project. Where possible, we will use mouse zygotes to develop and perform initial tests of

experimental techniques. However, there are species differences and any meaningful tests of safety and efficacy require the use of human oocytes and zygotes.

Recent advances in our understanding of how key developmental events are regulated during the pre-implantation period make it possible to perform more in depth analysis of embryo quality than was previously possible. We believe that the application of these advances to assess the effect of laboratory interventions will contribute to improved treatment outcomes.

The proposed objective 3 of the research project is as follows:

Investigation of molecular and genetic events leading to formation of normal oocytes and embryos. This part of our research is focussed on understanding the mechanisms underlying meiotic chromosome segregation errors. Using mouse oocytes we have shown that female ageing is accompanied by depletion of the chromosome-associated protein complex known as cohesin and its protector Sgo2 (Lister et al, Current Biology, 2010). Cohesin is a conserved protein complex, which clamps sister chromatids together from the time of DNA replication until they segregate to daughter cells during cell division. Cohesin is required to maintain the unique chromosome structure required for accurate segregation during the meiotic divisions. Genetic analysis of human oocytes indicates that premature dissolution of centromeric cohesion is the leading cause of aneuploidy in oocytes form older women (reviewed in Herbert et al, 2015, CSH Perspectives in Biology: 7). This implies that, as in mice, the mechanisms governing protection of cohesion between sister centromeres become defective during female ageing. We therefore propose to test the clinical significance of our work in mice by investigating cohesin and other proteins know to be important for accurate segregation during meiosis. A greater understanding of the mechanistic basis for the association between female age and oocyte aneuploidy will provide insights into the possibility of developing intervention strategies to improve reproductive outcomes in older women.

Our experiments in human oocytes will be informed by our work in the mouse and will require a source of immature oocytes (GV stage and MI oocytes) from consenting women. While we have previously obtained these oocytes from women undergoing ICSI treatment, the supply of immature oocytes is limited, especially from older women. We therefore propose to recruit altruistic donors from young and older age women using different stimulation regimes to optimise and standardise recruitment of immature oocytes. We also propose to use ovarian tissue (and oocytes when available), from women undergoing gynaecological surgery.

Experiments will involve live cell imaging, cytological, genetic, and biochemical studies. Some experiments will involve oocyte vitrification to facilitate the design of controlled experiments. While our investigations are mainly focussed on MI oocytes, we will also perform a series of experiments to investigate the regulation and outcome of the second meiotic division. In this case, oocytes will be activated to trigger exit from MII arrest.

In addition, we propose to use some of the nuclear transplantation techniques developed in Aim 1, to gain a better understanding of the relative contributions of nuclear and cytoplasmic factors to female age-related meiotic errors. This part of the work is highly complimentary to the experiments described in Aim 1 and will help to inform our decisions on the wider therapeutic application of techniques for preventing mtDNA disease. For example, we envisage that we will gain insight into whether transplantation of the MII spindle might exacerbate chromosomal defects in oocytes of older women.

This part of our work is funded by the MRC and has also been awarded funding from the EU Horizon 2020 programme. The latter will be performed under the auspices of the recently funded GermAge project.

Annex 1: changes to lay summary and objectives 1 and 2

Lay summary

The focus of our research is to extend the scope of assisted reproductive technologies (ART) to prevent transmission of mitochondrial DNA (mtDNA) disease and to improve outcomes of ART for the treatment of infertility. During the next three years, we propose to pursue the following aims.

Develop new clinical treatments to minimise transmission of mtDNA mutations from a mother to her child. This part of the research programme will build on previous work in which we demonstrated that it is technically feasible to transfer nuclear genetic material, contained in pronuclei, between fertilised human eggs. We propose to further optimise and test the safety of pronuclear transfer ~~between fertilised eggs. We will also test the efficacy of an alternative procedure known as meiosis II spindle transfer in which the nuclear genome is transferred between unfertilised eggs.~~and related techniques.

Improve the outcome of infertility treatments through gaining a better understanding of the cellular and molecular events occurring during pre-implantation development in vitro, and to determine how these are affected by the routine laboratory procedures.

Investigate the pathways leading to chromosomal abnormalities in eggs and embryos. We hope that these investigations will help us to better understand the mechanisms underlying chromosomal abnormalities in eggs of older women.

Objective 1

~~To develop new clinical treatments to minimise transmission of mtDNA mutations.~~ Mutations in mtDNA can cause a range of fatal and debilitating diseases. Reports from our lab (Craven et al, 2010, Nature: 465) and others (Tachibana et al, 2013, Nature:493) indicate that inheritance of mtDNA can be uncoupled from inheritance of nuclear DNA by transplanting the nuclear genome between eggs. This can be done either before fertilisation by transplanting the meiosis II spindle (MST) and its associated chromosomes, or after fertilisation by transplanting the pronuclei (PNT) between fertilised eggs. ~~The latter approach~~More recently, there has been a report of successful polar body transfer in mouse oocytes (Wang et al, 2014 Cell:157). This is an attractive option, which in mice results in minimal carryover of mtDNA, and raises the possibility of obtaining more than one maternal genome from each patient oocyte. While PNT has been the major focus of our research to date~~. Our~~ and our ongoing ~~work aims to optimise PNT procedure and~~ efforts are aimed at optimising it, we also propose to test the efficacy of MST and PBT in human oocytes.

Our primary objective is to maximise the production of good quality blastocysts and to perform a range of studies, including chromosomal analysis and gene expression studies, to compare PNT blastocysts with unmanipulated controls. We will also test the effect of PNT/MST on cell cycle and reprogramming events during the earliest stages of development. In accordance with the recommendations of the HFEA Expert Panel, we will generate ESC lines to compare those derived PNT/MST blastocysts with controls. These lines will also be used to investigate the fate of karyoplast-associated mtDNA.

While our proof of concept work on PNT was conducted using abnormally fertilised eggs, these have a limited potential for onward development, and are therefore of limited value in our

endeavours to further optimise and test the safety of PNT. Thus, progress in towards clinical treatments requires a supply of oocytes donated and fertilised specifically for this research project. Where possible, we will use mouse zygotes to develop and perform initial tests of experimental techniques. However, there are species differences and any meaningful tests of safety and efficacy require the use of human oocytes and zygotes

Recent advances in our understanding of how key developmental events are regulated during the pre-implantation period make it possible to perform more in depth analysis of embryo quality than was previously possible. We believe that the application of these advances to assess the effect of laboratory interventions will contribute to improved treatment outcomes.

Objective 3

Investigation of molecular and genetic events leading to formation of normal oocytes and embryos. This part of our research is focussed on understanding the mechanisms underlying meiotic chromosome segregation errors. Using mouse oocytes we have shown that female ageing is accompanied by depletion of the chromosome-associated protein complex known as cohesin and its protector Sgo2 (Lister et al, Current Biology, 2010). Cohesin is a conserved protein complex, which clamps sister chromatids together from the time of DNA replication until they segregate to daughter cells during cell division. Cohesin is required to maintain the unique chromosome structure required for ~~normal~~accurate segregation during the meiotic divisions. ~~In this project, we will~~Genetic analysis of human oocytes indicates that premature dissolution of centromeric cohesion is the leading cause of aneuploidy in oocytes form older women (reviewed in Herbert et al, 2015, CSH Perspectives in Biology: 7). This implies that, as in mice, the mechanisms governing protection of cohesion between sister centromeres become defective during female ageing. We therefore propose to test the clinical significance of ~~these findings~~our work in mice by ~~comparing~~investigating cohesin ~~levels between oocytes from young and older women.~~other proteins know to be important for accurate segregation during meiosis. A greater understanding of the mechanistic basis ~~underlying~~for the association between female age and oocyte aneuploidy will provide insights into the possibility of developing intervention strategies to improve reproductive outcomes in older women. ~~For these experiments we require immature oocytes (GV stage and MI oocytes) from consenting women undergoing ICSI treatment. These will be vitrified and stockpiled to facilitate the design of controlled experiments in which to perform direct comparison of levels of chromosome-associated cohesin in oocytes obtained from young and older women.~~

Our experiments in human oocytes will be informed by our work in the mouse and will require a source of immature oocytes (GV stage and MI oocytes) from consenting women. While we have previously obtained these oocytes from women undergoing ICSI treatment, the supply of immature oocytes is limited, especially from older women. We therefore propose to recruit altruistic donors from young and older age women using different stimulation regimes to optimise and standardise recruitment of immature oocytes. We also propose to use ovarian tissue (and oocytes when available), from women undergoing gynaecological surgery.

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