

**Minutes of the twenty-second meeting of the Scientific and Clinical  
Advances Group held on Thursday 21<sup>st</sup> February 2008, Bloomsbury Street**

**PRESENT:**

**Members**

Neva Haites (Chair)  
Clare Brown  
Daniel Brison  
Richard Gardner  
Melanie Davies  
Richard Harries  
Chris Barratt  
Peter Braude  
Maybeth Jamieson  
Robin Lovell-Badge

**Executive**

Tim Whitaker  
Charles Lister  
Hannah Darby  
Helen Richens

**Observers**

Andy Earnshaw (DH)

**1. Apologies**

1.1. Apologies were received from Roger Neuberg, David Barlow and Lorraine Young.

**2. Minutes of the meeting of 29<sup>th</sup> November 2007**

2.1. The minutes were approved subject to the following comment on epiblast stem cells (EpiSCs) (13.10):

- The two papers on mouse EpiSCs both found that these contributed very poorly, if at all, to chimeras made by injecting them into mouse blastocysts. Mouse EpiSCs have many properties in common with human ES cells, and they are both distinct from mouse ES cells. Therefore human ES cells may also be bad at making chimeras after injection into human or animal blastocysts. The one paper where this was attempted with mouse blastocysts suggested that the contribution was very poor. However, it is conceivable that both EpiSCs and human ES cells would contribute well to post-implantation epiblast.

**3. Matters arising**

3.1. The Chair passed on comments from Roger Neuberg about endometrial scratching. He thought that the technique may have future relevance for patients though it is unlikely to have a significant impact on success rates. Further studies are being carried out in Israel.

**4. Chair's business**

4.1. The group discussed whether the HFEA should record the method used to cryopreserve embryos. Most of the group supported this in order to provide outcome data for patients and to assess the safety of techniques such as vitrification.

4.2. The group agreed there were issues of how the HFEA analyses and presents the data it collects. One member thought there should be a systematic review of

data for research purposes. However another member thought this was outside the HFEA's remit.

- 4.3. One member raised the point that data has been collected on PGD for the last 10 years but nothing had been published. However another member pointed out that data quality has only been achieved in the last year.
- 4.4. The group discussed how the HFEA was planning to publish more data and whether it is the role of the HFEA or the professional bodies to collect and publish long term data on the safety of techniques.
- 4.5. The Chair agreed to talk to the Chair of the Information and Communication Committee (ICC) about the issues raised.

**Action: Neva Haites**

- 4.6. The Chair informed SCAG that Authority members thought there should be a lay summary of SCAG's minutes.

**Action: Helen Richens**

## **5. Review of PGS**

- 5.1. Hannah Darby presented a literature review of studies that analysed the outcomes of PGS for different categories of patients. Members were asked to consider and approve: the conclusions from the literature review; the recommendations to amend the Code of Practice and provide patient guidance; and the recommendations on blastomere biopsy and tissue typing. BFS and ASRM recommendations on PGS were also presented.
- 5.2. One member clarified that references to *biopsy* in the paper meant *single cell biopsy*.
- 5.3. The group briefly discussed if the age at the onset of puberty would be a better indicator than maternal age, but decided that it would not.
- 5.4. The group discussed the risk of blastomere biopsy. One member raised concerns about the small sample size of follow up studies. Members asked to be updated on follow up studies by Joyce Harper from the PGD consortium.

**Action: Daniel Brison**

- 5.5. The group agreed that patient information should state that there are ongoing studies into the safety of embryo biopsy.
- 5.6. Members thought that centres that carried out embryo biopsy should contribute to the European database. Members discussed whether this could be made a requirement.
- 5.7. One member thought that the HFEA should publish data on centres that carried out PGS and PGD. This would put into perspective how few centres do PGS or PGD and how few cycles are carried out in the UK. This would be useful for patients

to know. It was pointed out that PGD and PGS are done infrequently compared to IVF and ICSI.

- 5.8. The same member also raised the issue that PGD and PGS has been carried out in the UK for 10 years without any figures about cycles being published in any annual report. The member thought that this was a breach of duty under terms of the HFE Act.
- 5.9. Maybeth Jamieson declared a conflict of interest as she has a research licence for embryo biopsy.
- 5.10. The group thought that the safety issues of 1 versus 2-cell biopsies were not being addressed. A study in Brussels will have data on this soon.
- 5.11. One member informed the others that there are three main groups, outside the UK, that carry out the majority of PGS work and these groups have the most to lose if PGS was shown not to work. These groups were the ones that criticised studies that showed PGS did not have a beneficial effect.
- 5.12. Another member told the group that there are a number of randomised trials coming out in the next 4 months on PGS. The group also thought someone from the Executive should attend a meeting on PGS in mid-March in Groningen at which some of these studies would be presented and discussed.

**Action: Hannah Darby**

- 5.13. The group discussed the best way to collect data and one member commented that the Committee should have a statistician.
- 5.14. One member mentioned that Mr Taranissi published a paper on PGS in 2006 and stopped doing PGS on the basis that it did not work.
- 5.15. Another member thought that PGS should only be performed if it was part of a trial.
- 5.16. The group approved of the recommendations made by the Executive in the literature review but wanted more data and information. They thought that figures from the HFEA and data from the upcoming studies should be analysed. Recommendations could then be presented to the Authority and the Authority could make a decision on how licence committee should proceed.

**Action: Hannah Darby**

- 5.17. The group thought that patient information should not be updated until after the issue had been to Authority. They thought the risks would need to be expanded and it should be in line with the BFS guidelines. One member pointed out that this would need careful handling so that it did not have a negative impact on patients who were mid-cycle.

## **6. Treatment for mitochondrial disease**

- 6.1. Helen Richens introduced this paper. The group was updated on advances in germinal vesicle transfer, pronuclei transfer and microcytoplasm cryopreservation. This included an update on three papers identified by Justin St John on mitochondrial DNA transmission. Members were asked to: note the developments; consider whether germinal vesicle transfer or pronuclei transfer would be safe for treatment; and consider whether centres would be likely to want to use microcytoplasm cryopreservation for research or treatment.
- 6.2. The group were informed that the HFEA had not yet received the progress report from the research group at Newcastle Fertility Centre at Life.
- 6.3. One member clarified that references to *heteroplasmy* in the paper meant *tri-parental heteroplasmy*.
- 6.4. The group thought that microcytoplasm cryopreservation was not a viable technique. They thought the mouse model was not relevant to human oocytes and there was a risk of destroying the oocyte. One member pointed out that vitrification of oocytes can offer survival rates of 96%, so there would not be a demand for this technique.
- 6.5. The group discussed the implications of the Human Fertilisation and Embryology Bill on treatment for mitochondrial disease. One member thought there might be some debate in the House of Commons over the apparent lack of equity between altering the mitochondrial DNA and altering nuclear DNA.
- 6.6. The DH observer clarified that the Bill will allow research on altering both mitochondrial and nuclear DNA. Regulations may allow this for treatment of mitochondrial disease in the future if it was shown to be safe for treatment.
- 6.7. DH felt that the amendment that would allow this without needing further regulations would be too large a leap forward and that having regulation-making powers was the best option. Although research into mitochondrial disease is progressing well, there is little evidence on its safety. The group felt that SCAG's advice on the safety issues would be significant. There are also issues of legal parenthood of the child and public perception of the issues that DH need more time to address.
- 6.8. The group discussed that an informed regulator (HFEA and MHRA) should decide whether the techniques could be permitted for treatment, not Parliament. The regulation-making powers would only come into force if the regulator recommended it. The group thought that advice from SCAG could feed through the HFEA to inform Parliament, along with advice from other bodies.
- 6.9. One member noted that the FDA had banned previous research on cytoplasm transfer in the US because of safety concerns.
- 6.10. One member remarked that just because embryos reach blastocyst stage does not mean that they could continue normal development. It was noted that Jo Poulton had carried out research into recombination between mitochondrial DNA.

- 6.11. The group briefly discussed how mouse oocytes could be centrifuged to separate the organelles, so that pronuclei could be removed without removing mitochondria. Justin St John was thought to carry out a similar technique.
- 6.12. The group discussed the cross-talk and interaction between the nucleus and mitochondria. They thought that the difference in mitochondrial DNA transmission and mitochondrial replication in different tissues and cells was due to differing energy requirements.
- 6.13. The group concluded that the safety issues of these techniques have not yet been addressed. They discussed how safety could be assessed through more animal models and through research in other countries. Members thought there was a gap between animal and human models. There were also concerns that if these techniques were carried out in other countries this would lead to patient pressure in the UK. The group thought that there needed to be published literature on the safety issues of pronuclei and germinal vesicle transfer, and wondered if Justin St John could do this.

## **7. Gene transfer into male germ lines and embryos**

- 7.1. This paper was presented by Hannah Darby. The group was updated on techniques for gene transfer into male germ lines and embryos, and what the implications for this research will be under the Bill. Members were asked to consider: the likely timescale of introduction; any safety and ethical issues; and what research applications the HFEA may expect to receive.
- 7.2. Robin Lovell-Badge gave the group an update on gene transfer techniques. There are various techniques including microinjection into the pronuclei, viral vectors, targeted gene therapy and the use of restrictive enzymes. These vary in efficiency and the techniques which integrate DNA at random can cause mutations.
- 7.3. Currently the most efficient method is the 'sleeping beauty' vector. This is integrated largely at random so there is a risk of inactivating genes, leading to mutations. This technique has been used in chickens and rats.
- 7.4. The group discussed that the risk of mutation was a reason for gene transfer not to be used in therapy, but was not an issue in research. They thought that the timeline for gene transfer research was very short and that the HFEA would receive applications to use this technique in research as soon as the Bill is implemented.
- 7.5. Members thought that there were huge safety issues for gene transfer into male germ lines. The DH observer clarified that spermatogonial stem cells and early sperm cells are in the Bill's remit. However techniques on Sertoli cells are not. Therefore if early sperm cells were genetically altered, they would not be permitted for treatment under the Bill. Whereas gene transfer that specifically targeted only Sertoli cells would not be covered by the Bill.
- 7.6. Members thought that there were many potential reasons for likely research applications for gene transfer into embryos. These include research into early human embryo development and the role of particular genes and growth factors

involved, research into genetic backgrounds and research into the fate of different cells.

- 7.7. The Bill has taken away all inhibitions on genetically altering human embryos for research. The group thought that there were large ethical and public interest issues and that these should be referred to ELAG for debate.

**Action: Hannah Darby**

## **8. Alternatives to embryonic stem cells**

- 8.1. This paper was introduced by Helen Richens. The group was updated on various techniques that could potentially produce embryonic stem (ES) cells or ES-like cells without destroying viable embryos. These included induced pluripotent stem (iPS) cells, parthenogenetic embryonic stem (pES) cells, ES cells from poor/non-viable embryos, ES cells from single blastomeres, nuclear transfer into zygotes and ES-like cells from other tissues.
- 8.2. The two areas identified as advancing most rapidly were induced iPS cells and ES cells from single blastomeres. Members were also informed of a further paper on iPS cells just published by Yamanaka's group.
- 8.3. Members were asked to consider the advances in the different techniques and decide if any information should be passed on to Research Licence Committees.
- 8.4. The group discussed iPS cells. Members thought that these were very useful for research, for example to study patient-specific diseases, but not therapy.
- 8.5. One member clarified the issue of using viral vectors to get iPS cells. c-MYC, used in some iPS studies, is an oncogene. Further studies have shown that it is not necessary but the technique is less efficient without it. However any viral vectors have the potential to be mutagenic. US groups are investigating alternative ways to reprogramme cells into iPS cells, for example using proteins, however this is a long way off.
- 8.6. The group discussed how many cell lines would need to be created to get a match for patients. The population is very variable and cells would only be appropriate for some people. Some lines would need to be an exact match, for example bone marrow cells need to be patient-specific.
- 8.7. The group thought that ES-like cells from other tissues had very peculiar properties and could potentially be dangerous. One member noted that just because cells express markers of pluripotency does not mean that they are pluripotent.
- 8.8. The group thought that pES cells contribute well to some tissues but not others.
- 8.9. The group discussed Robert Lanza's recent work on deriving ES cells from single blastomeres. They were concerned that some centres may want to offer patients the chance to derive a ES cell line from a blastomere of an embryo as an insurance policy for that future child. The group thought this should not be allowed as it raised serious ethical issues and there would be no guarantee that

they would be able to get an ES cell line from that blastomere. The group thought that this work was a political move in the US.

- 8.10. The group thought that it was hard to determine when an embryo is non-viable. They queried whether every cell of an embryo has the same potential and could make ES cell lines. One member noted that a previous experiment managed to produce 4 individual cattle from a 4-cell embryo.
- 8.11. The group concluded that information on alternatives to ES cells should be passed on to Licence Committee as they are legally obliged to be aware of the issues.
- 8.12. The group discussed whether this and information on the outcomes of human embryo research should also be made available in a paper to the wider public.
- 8.13. Members thought that the paper should emphasise that currently the only feasible way to derive ES cells suitable for therapy was from viable embryos. It should also emphasise that this may change in the future and all areas are being explored, and it is useful to compare the different techniques. One member commented that there had been a previous workshop on the outcomes of research which may be useful. The paper could build on previous literature reviews carried out on alternatives to ES cell research. The paper should also distinguish adult and ES cell work.
- 8.14. Members thought the paper should be made available quickly in time for the Bill and wanted to know if it would have to receive Authority approval.

**Action: Tim Whitaker**

- 8.15. The group thought the Executive should consider the most appropriate way to communicate this information to the Licence Committee and the wider public.

**Action: Executive**

## **9. Any other business**

- 9.1. The Chair informed the group that she had received a letter from the North East England Stem Cell Institute (NESCI) about artificial gametes. The NESCI were concerned that the Bill may not permit the use of artificial gametes in treatment. They were offering to give information on Professor Nayernia's research at the University of Newcastle to assist the HFEA in providing information after the issue was raised during the debate at third reading in the House of Lords.
- 9.2. The DH observer clarified that DH were still considering the safety and timescale of artificial gametes.
- 9.3. It was suggested that a meeting should be arranged as soon as possible to discuss artificial gametes. NESCI should be invited to present their information, and MHRA should possibly also be included.

**Action: Hannah Darby**

**10. Date of next meeting**

10.1. The next meeting will be held at 2pm on Wednesday 21<sup>st</sup> May 08.