

**Human Fertilisation and Embryology Authority
Scientific and Clinical Advances Group**

Committee:	Scientific and Clinical Advances Group
Meeting Date:	19 th April 2007
Agenda Item:	6
Paper Number:	SCAG (04/07)02
Paper Title:	Derivation of embryonic stem cell lines from a single blastomere
Author:	Hannah Darby
For Information or Decision?	Decision
Resource Implications:	No immediate resource implications.
Communication	If the view of SCAG varies greatly from the view SCAG came to on this technique in April and November 2006 then this will be communicated to ELC.
Recommendation to the Committee:	<p>Members are asked to:</p> <ul style="list-style-type: none"> • Discuss the findings of papers at Annex A and B and the PGD data presented at Annex C • Consider the implications for assisted conception. • Consider whether, in the light of the new findings of the paper at Annex B and the PGD data (Annex C), members wish to review their previous opinion.

1. Introduction

1.1 This issue was identified through the horizon scanning process. The derivation of stem cells from blastomeres has been suggested as an alternative source of embryonic stem cells which avoids destroying an embryo in the process of deriving the stem cell line¹.

1.2 In order to derive a stem cell line from an individual blastomere, a cell would be removed at the 8-cell stage (as it would be if PGD were being performed) and this cell would then be cultured *in vitro*. If cultured in the correct conditions, a

¹ The President's council on Bioethics report.

human embryonic stem cell (hESC) line could develop from the individual blastomere. The embryo from which the cell was removed would continue to develop and then be transferred back to the woman in the hope of establishing a pregnancy.

2. Previous SCAG consideration

2.1 This issue was identified through the horizon scanning process and first considered by SCAG in April 2006. At this meeting SCAG considered a paper (Chung et al, 2005 – Annex A) in which a single mouse blastomere was cultured to form an embryonic stem cell line. In this paper the individual mouse blastomere was cultured in the presence of other mouse embryonic stem cells to promote stem cell line growth.

2.2 At the April 2006 meeting members came to the view that the use of this technique in humans is not realistic. It is unlikely that parents would want to compromise the development of their embryos, and possibly their child, by removing a blastomere when there is such a low chance that the stem cells would be used. Also, if it is possible to produce therapeutic lines embryos will be specifically created for this purpose.

2.3 However, since the April 2006 meeting a paper has been published reporting that a group in the USA (Klimanskaya et al, 2006 – Annex B) have derived human embryonic stem cells lines from individual human blastomeres. At the November 2006 SCAG meeting members considered this study to be misleading because blastomeres were derived from disaggregated embryos and not from biopsy. This view was also expressed in Nature.

2.4 In the Klimanskaya et al study sixteen embryos were thawed and cultured to the 8-10 cell stage. The zona pellucida was disrupted and individual blastomeres mechanically separated. The separated blastomeres were cultured together in the same medium but arranged so as to avoid contact with each other. Nineteen embryonic stem-cell like outgrowths and two stable hESC lines were obtained.

2.5 When the hES cell cultures were allowed to overgrow or form embryoid bodies, they readily differentiated into cells of all three germ layers (pluripotency demonstrated by the formation of teratomas in NOD-SCID mice). The hES cells could also be differentiated *in vitro* into cells of specific therapeutic interest. Two stable hES cell lines were obtained.

2.6 At the November 2006 meeting SCAG considered that it would be valuable to review the situation, and possibly SCAG's view on the issue, in light of the new data. Members considered this to be a priority issue for consideration in 2007 and that there is a possibility that groups in the UK would want to use this technique.

3. Previous ELC consideration

3.1 This issue was considered by Ethics and Law Committee in July 2006. ELC members were of the opinion that parallels can be drawn between this technique and cord blood banking. In both situations there is the possibility of patients feeling pressure to bank the cells or cell lines for the future health of their child. They considered it important that, if the technique was introduced, patients should be made aware that currently there are very few conditions that may be treated using stem cells. Before this technique could be used it would be important to ensure that patients understand exactly what the technique involves and they give informed consent.

3.2 The Ethics and Law Committee will be seeking further legal advice about how the use of this technique could be licensed. They will consider this further later in 2007.

4. Potential uses/benefits of this technique

4.1 The procedure used by Klimanskaya et al to extract the blastomeres from embryos is similar to that used for PGD. Therefore blastomeres extracted in the process of PGD could be used for stem cell generation as well as genetic testing and blastocysts could be transferred, without affecting clinical outcome, at 5 days. However, this has not been tested as Klimanskaya et al did not carry out PGD and did not transfer any embryos following blastomere extraction.

4.2 Alternatively, depending on consideration of risks and benefits, blastomeres could be extracted from embryos which are not undergoing PGD and would not otherwise be undergoing embryo biopsy.

4.3 This technique is not necessary for the purpose of deriving stem cell lines in the UK because the use of embryos to derive these lines is legal. However, as embryos are not destroyed using this technique it would go some way to address ethical concerns. There are also other purposes for which people may wish to use this technique:

- Patient matched hESC lines in case the child/adult from which the cell line was derived develops an illness in the future (potential future personal use)
- hESC to be banked for use of any HLA-matched patient (potential future altruistic use)
- Stem cell line for the treatment of a HLA-matched sick older sibling

4.4 The above uses are dependent on the development of techniques that would allow the embryonic stem cell lines to be differentiated into cells that can

be used in the treatment of specific illnesses. It will need to be determined whether blastomere derived hESC lines differ from conventional hESC lines in their ability to form functional differentiated cell types.

5. Risks

5.1 If this technique is carried out on an embryo which is undergoing PGD this would delay the genetic testing. Consideration needs to be given to whether delaying genetic testing would have a negative effect on the embryo and whether two blastomeres could be removed (one for genetic testing, one for a stem cell line).

5.2 It is possible that removing a blastomere may have a negative effect on the development of embryos.

6. Safety of blastomere biopsy

6.1 The potential for this technique to be used clinically is largely dependent on whether removing a blastomere has a negative effect on the development of embryos. In order to assess this risk it is necessary to analyse data from the effect of blastomere biopsy when conducting PGD.

6.2 The ESHRE PGD Consortium collect data for PGD cycles and report on the current practice for PGD on a regular basis. The latest data published by the consortium is from 2003 (Annex C). After analysing the data the Consortium are of the view that it is becoming apparent that PGD babies are very comparable to ICSI babies in every respect, e.g. complications of pregnancy, characteristics at birth and major and minor malformations. All parameters e.g. weight, length and head circumference were comparable to those of ICSI babies and previous PGD Consortium reports. 4% of babies were born with malformations, which is comparable to that for ICSI. The main complication (as will all IVF babies) remains multiple pregnancies leading to morbidity and mortality in PGD offspring.

6.3 In a summary of the use of embryo biopsy Gianaroli (2000) is of the view that the number of cells observed 24 hours after blastomere biopsy is lower than expected, implying that either the reduction in cellular mass or the trauma associated with the procedure itself may have an effect on the rate of embryo growth. Nevertheless, compaction, blastocyst formation and hatching take place normally, giving rise to viable, normally growing babies.

6.4 Grace et al (2006) reported on the outcome of 330 PGD cycles performed at Guy's Hospital. They found the live birth rate to be 18% per cycle started, 21% per egg retrieval and 28% per embryo transfer. The live birth rate of PGD cycles for serious genetic disorders is affected by the number of embryos genetically suitable for transfer so it is not useful to compare it to live birth rate figures for

cycles which do not involve blastomere biopsy. Therefore live birth rates are not a useful parameter to consider whether or not blastomere biopsy negatively affects embryo development.

6.5 Few studies have been conducted on the clinical outcomes of PGD, particularly in relation to whether embryo biopsy has a negative effect on neonatal outcome.

7. Conclusions

7.1 Members are asked to:

- Discuss the findings of papers at Annex A and B and the data presented at Annex C.
- Consider the implications for assisted conception.
- Consider whether, in the light of the new findings of the paper at Annex B and the PGD data (Annex C), members wish to review their previous opinion.

8. References

1. Gianaroli. Human Reproduction, 15(suppl4), p69-75, 2000. Preimplantation genetic diagnosis: polar body and embryo biopsy.
2. Grace et al. BJOG. 113(12), 1393-401, 2006. Three hundred and thirty cycles of preimplantation genetic diagnosis for serious genetic disease: clinical considerations affecting outcome.