



Human Fertilisation and Embryology Authority
Scientific and Clinical Advances Group

Committee:	Scientific and Clinical Advances Group
Meeting Date:	16 th June 2005
Agenda Item:	8
Paper Number:	SCAG (06/05)02, Annex A and Annex B
Paper Title:	Mouse blastomeres and developmental potential: Implications for PGD
Author:	Katy Berry
For Information or Decision?	Information and Comment
Resource Implications:	<i>None</i>
Organisational Risk:	<i>(high/medium/low)</i>
Recommendation to the Committee:	<p>Members are asked to:</p> <ul style="list-style-type: none"> • Note the research presented in this paper; • Comment on the relevance of this in the context of PGD.

1. Background

1.1 Recently, there have been several publications that have discussed the potential of cells in the early mouse embryo. The Zoenicka-Goetz¹ paper suggests that as early as the 4-cell stage, blastomeres have different developmental potential. In the context of PGD, this might mean that removal of one cell could have more of an effect on development than others and perhaps this should be taken into account when performing an embryo biopsy. This paper is attached in Annex A, and summarized below.

1.2 A publication² from a different group has been included in Annex B, the data in this paper does not support that presented in the work from Zoenicka-Goetz and is included for comparison.

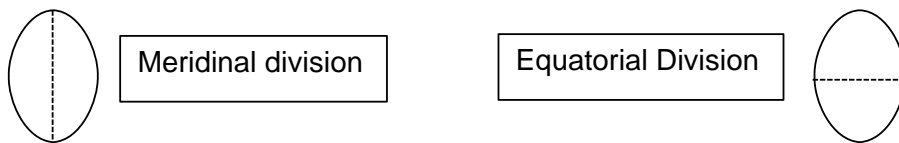
¹ Piotrowska-Nitsche *et al.*, *Development* **132** 479-490

² Motosugi *et al.*, *Genes and Development* **19** 1081-1092

- 1.3 It is important to note that the two papers are not necessarily directly comparable because they are looking at different times in development and using slightly different techniques. Both papers were included to present a balance of views within the field.
- 1.4 The HFEA horizon scanning panel (HHSEP) were asked their opinion on the publication and the possible implications for PGD, two responses that we have received summarized below.

2. Summary of Zoenicka-Goetz paper (Annex A)

- 2.1 This paper examines the developmental potential of individual mouse cells at the four-cell stage by making chimeras of all one type of a specific cell. The blastomeres are distinguished at the four-cell stage based on the order of division and the position of one of these cells relative to the polar body.
- 2.2 If the first cell division of the two cell embryo is meridinal (M) followed by equatorial (E), it is classed as an ME embryo. Conversely, if the first division is equatorial followed by a meridinal division, these are said to be EM embryos. The equatorial cells were further distinguished by their position with respect to the polar body. Those that were proximal to the polar body were classed e1; those that were distal were classed as e2.



- 2.3 IN ME embryos, the progeny of the meridinally-derived cells contribute predominantly to the embryo. The progeny of the equatorially derived cell are likely to contribute to the extra-embryonic tissue. In EM embryos, the progeny of the earlier dividing equatorial cell is equally likely to contribute to embryonic and extra-embryonic tissue therefore no pattern was noted.
- 2.4 In order to examine the developmental potential of the blastomeres at the four cell stage, chimeric embryos were produced with four cells of the same type. For example, four e2 from ME embryos, four e2 from EM embryo and controls using four meridinally derived cells. Chimeric embryos that were derived from four e2 cells from ME embryos had a lower chance of survival compared to the control groups. This was also shown to be dependent on the inheritance of components of the vegetal.
- 2.5 Although the work does not suggest that the fate is determined and that the

cells are not capable of forming other cell lineages, it does suggest that not all four of the cells of the four cell stage embryo have equal ability to develop when combined with like cells.

3. Summary of Hiiragi paper (Annex B)

- 3.1 This paper initially looked at the role of sperm entry point in mouse embryonic polarity. This showed that there was no difference in developmental potential of blastomeres at the two-cell stage with respect to sperm entry point.
- 3.2 This group also then went on to produce chimeric embryos at the two-cell stage to examine the developmental potential of the blastomeres. They did not label either of the cells but simply made a chimera out of two different embryos. This would mean that half of the embryos would be made totally of one cell type. The prediction was that if one of the cells was fated to be trophectoderm and one to be embryo proper, in half of the chimeras, the embryos would fail to develop.
- 3.3 This experiment showed all of the chimeras formed blastocysts and 60% of the embryos gave rise to live mouse pups (this was equivalent to the control situation). This suggests that embryos at the two-cell stage do not differ in developmental potential.
- 3.4 The group demonstrate that the first time that embryonic polarity is seen in the mouse embryo is at the blastocyst stage. They showed this by differentially labelling the blastomeres at the two cell stage and seeing where the blastocoel forms in relation to the two populations of cells. The blastocoel was shown to form at multiple points within the cell types.

4. Summary of the responses from HHSEP

- 4.1 We have not yet received all the responses back yet from the panel and not all have commented on the research. I have included two relevant comments from the panel below.
- 4.2 "At present, their finding is controversial. In such research, we may well produce different results and conclusions by separate research groups. Such situation is recently reported by Science magazine (Science 308, 782-, 6 May 2005). In any case, all the groups agree that it is not strong restriction or difference in developmental fate, but only relative frequency or tendency, which can be altered by chance or developmental events. Thus, we must watch the progress in the research."³

³ Norio Nakatsuji (Kyoto University- Japan)

4.3 "Obviously this issue needs to be kept under review - however other evidence points to the regulative nature of mammalian embryos while existing PGD techniques have not shown up any problems."⁴

5. Conclusions/ recommendations

- **Members are asked to note the research presented here;**
- **Members are asked to comment on the data in the context of safety of PGD.**

⁴ Peter Andrews (Sheffield University- UK)