Update on alternative methods to derive embryonic and embryonic-like stem cells

Strategic delivery:	☒ Safe, ethical, effective treatment	☐ Consistent outcomes and support	☐ Improving standards through intelligence
Details:			
Meeting	Scientific and Clinical Advances Advisory Committee (SCAAC)		
Agenda item	9		
Paper number	HFEA (15/10/2018)01		
Meeting date	15 October 2018		
Author	Rasheda Begum, Scientific Policy Officer		
Output:			
For information or decision?	For information		
Recommendation	Members are asked to: • consider the progress of research (since June 2016) into alternative methods to derive embryonic or embryonic-like stem cells; • advise the Executive if they are aware of any other recent developments; • reflect on whether their views have changed in the light of recent research.		
Resource implications	None		
Implementation date	None		
Communication(s)	Information updates summarised in this paper and SCAAC's view will be used to update the paper 'Alternative methods to derive stem cells' used by the HFEA Licence Committee when considering research licence applications which involve the use of viable embryos for research purposes.		
Organisational risk	☒ Low	☐ Medium	☐ High
Annexes	None		

1. Introduction

1.1. Human embryonic stem cells (hES cells) have the potential to form every other type of cell in the body. They are important for research into cell biology, drug testing and disease modelling, and could potentially be used in therapies for patients.

1.2. hES cells are derived from cells of human embryos. Currently the only way to derive hES cells involves using viable embryos but researchers are investigating alternative methods of deriving hES cells, or hES-like cells, that do not involve the use of viable embryos.

1.3. Section 3A(1)(c) of Schedule 2 of the HFE Act 1990 (as amended) requires embryo research to be "necessary or desirable" for defined purposes. If alternative methods of deriving hES or hES-like cells are developed, it may not be necessary for research groups to use viable embryos. It is, therefore, important for the Authority to keep up to date with developments regarding these alternative methods so that the HFEA Licence Committee can bear them in mind when considering research licence applications in line with the Act.

1.4. Alternative methods to derive hES-like cells has been brought to SCAAC as a standing high priority item for a number of years. Following discussions at the Committee's June 2018 meeting, this topic will now be considered together with embryo-like entities (ELEs) as one standing high priority item. As ELEs were discussed at the June 2018 meeting, this paper only covers alternative methods to derive hES-like cells. The two topics will be combined in the next literature review in one to two years.

2. Induced pluripotent stem cells

2.1. One alternative way to derive hES-like cells is by producing induced pluripotent stem cells (iPS cells). iPS cells are adult somatic cells which have been reprogrammed to an embryonic stem cell-like state. This process is controlled by mediators including transcription factors which bind to DNA and alter gene expression, and also by epigenetic changes which involve changes to the information in the genome over and above that contained in the DNA sequence.

Recent developments in iPS cells

2.2. In a study by Zhang et al., 2018, DNA repair mechanisms were compared between iPS cells and ES cells. Ionizing radiation was applied to the cells and fidelity of DNA damage repair was measured. In iPS cells, there was lower DNA damage repair capacity, and this was also observed in mice derived from iPS cells. It was suggested that the high rate of tumorigenesis observed in iPS cells could be a result of genomic instability.

2.3. Gene expression and neuronal differentiation potential was compared between genetically unmatched human ES cells and iPS cells in a study by Marei et et al., 2017. Human iPS cells were derived by transfecting human epidermal fibroblasts with DNA expressing pluripotency genes. Gene expression profiles were very similar between iPS and ES cells. The cells were cultured in differentiation medium and the researchers were successfully able to derive neural progenitor cells and motor neurons.

2.4. A study by Horikawa et al., 2017 found that an endogenous variant of the gene p53 was key for reprogramming human fibroblasts to iPS cells. Overexpression of the variant in iPS cells led to fewer number of somatic mutations, compared to iPS cells where p53 was inhibited.

2.5. In a review by Assou et al., 2018, it was suggested that quality control measures could be introduced for using iPS cells in research and clinical use, as genetic abnormalities occurring in iPS cells may limit their usefulness and safety. They proposed minimum screening measures that should be done inhuman iPS cell genomes, for example for clinical use this included karyotyping, p53 mutation screening and exome sequencing.

2.6. In a study by Weltner et al., 2018, it was shown that human skin fibroblasts could be reprogrammed into iPS cells using CRISPR. CRISPR is a technique used in genome editing which can cut a certain gene out of the genome and replace it with a different gene. In this study, a modified version of the CRISPR system was used to activate pluripotency genes.

2.7. Levels of mtDNA in human ES cells and iPS cells were measured in a study by Zambelli et al., 2018. It was observed that mtDNA levels in ES and iPS cells were similar to levels in cells used to establish them i.e. oocytes and the inner cell mass for ES cells and source fibroblasts for iPS cells. They found there were increased mutated mtDNA variants in iPS cells, suggesting that screening of iPS cells can identify lines with pathogenic mutations.

2.8. Molecular and functional characteristics of human iPS cells were compared with somatic cell nuclear transfer (SCNT) derived ES cells in a study by Zhao et al., 2017. iPS cells and SCNT-ES cells were generated from the same dermal fibroblasts. Gene expression was found to be similar between the iPS cells and SCNT-ES cells. The authors suggested iPS cells are a viable solution for replacing SCNT-ES cells.

iPS cells in clinical applications

2.9. The first clinical trial using iPS cells has been carried out in Japan (Mandai et al., 2017). The trial investigated the safety and adverse-event profile of using iPS cells for treatment of neovascular age-related macular degeneration, a condition that leads to vision loss. The iPS cells were derived from skin fibroblasts obtained from two patients and the fibroblasts were differentiated into retinal pigment epithelial cells. One of the patients did not receive treatment as concerns were raised about genetic changes that occurred in the iPS cells. The remaining patient underwent surgery to transplant a sheet of retinal pigment epithelial cells under the retina. The procedure did not result in complications therefore was implied to be safe, though best corrected visual acuity (a measure of best distance vision with glasses or contacts lenses) was not improved.

2.10. Shafa et al. 2018 assessed the clinical potential of human iPS cells generated using a cGMP-compliant process. These cells were able to differentiate into cells from all three embryonic germ layers. Specialised cells were produced bearing characteristics of neural stem cells, definitive endoderm and cardiomyocytes. Additionally, cells from the three germ layers were produced from the same iPS cell lines, showing that the iPS cells were not biased towards a specific lineage.

3. Naïve state pluripotent stem cells

3.1. Two states of pluripotency are present in mammals: naïve and primed. iPS cells resemble primed pluripotent state found in post-implantation epiblast. Naïve pluripotency occurs in the pre-implantation stage when there is more differential capacity.

3.2. In a study by Kilens et al., 2017, human PS cells were reprogrammed to a naïve state by overexpression of pluripotency genes and specific culture conditions. The naïve iPS cells were benchmarked against epiblast cells and similar gene expression was observed.

3.3. In a study by Wang et al., 2018, transcription analysis of naïve iPS cells derived from human fibroblasts showed similarity of gene activation found during embryonic development from late embryogenesis to pre-implantation stages. In late stages of reprogramming, there was similar gene expression found in the 8-cell-stage embryo.

4. Conclusions

4.1. SCAAC last considered research in this area in June 2016, where it was agreed that scientists are still in the early stages of understanding human development and that it remains necessary to produce human embryonic stem cells for the purpose of research. These provide the gold standard of pluripotent cells to which other stem cell technologies can be compared, and to aid the understanding of normal development of cells.

4.2. Researchers and clinicians outside of the UK appear to be in the early stages of investigating iPS cells for use in patients. In Japan, the first clinical trial of iPS cells took place that investigated treatment using iPS cells for treatment of macular degeneration of the eye. A second clinical trial has been approved that will investigate using iPS cells in heart transplants, also in Japan.

4.3. There are issues of genomic instability of iPS cells, though this could be overcome by screening via sequencing for mutations, though there needs to be more research into the feasibility of such screening.

4.4. There is increasing understanding of naïve PS cells, which have more potential than primed PS cells as they have similarities to early stage embryonic cells.

4.5. SCNT seems to be used less frequently, researchers may be more in favour of using iPS cells as this doesn't require an egg donor. Using iPS cells may also carry fewer ethical concerns as SCNT still requires creation of an embryo to derive stem cells whereas iPS cells can be derived from adult cells.

5. Recommendations

5.1. Members are asked to:

- consider the progress of research (since June 2016) into alternative methods to derive embryonic or embryonic-like stem cells;
- advise the Executive if they are aware of any other recent developments;
- reflect on whether their views have changed in the light of recent research.

5.2. Information updates summarised in this paper and SCAAC's view will be used to update the paper 'Alternative methods to derive stem cells' used by the HFEA Licence Committee when considering research licence applications which involve the use of viable embryos for research purposes.

6. References

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