

Human Fertilisation and Embryology Authority Prioritisation of Horizon Scanning Issues 2006

Committee:	Scientific and Clinical Advances Group
Meeting Date:	30 th November 2006
Agenda Item:	6
Paper Number:	SCAG(11/06)02
Paper Title:	Prioritisation of Horizon Scanning Issues 2006
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For Information or Decision?	Decision
Resource Implications:	To be informed by the decision and will be fed into the business planning process for 2007/2008.
Organisational Risk:	Medium
Recommendation to the Committee:	Members are asked to <ul style="list-style-type: none"> • Consider and discuss the issues presented in this paper • Comment on the work recommendations from the executive • Prioritise issues to inform the business planning process for 2007/2008.
Evaluation:	The horizon scanning process is continually evaluated but a longer term evaluation will be carried out after several years of the horizon scanning process.

1. Prioritisation of issues

- 1.1 The issues identified and presented in the previous paper (SCAG(11/06)01) were prioritised using the following criteria:
- time scale for likely introduction
 - patient demand/impact if it were to be introduced
 - feasibility – would it be possible to carry out in the lab
 - ethical issues raised or public interest
 - risks evaluation of further consideration or not.
- 1.2 High and medium priority issues are presented in Annex A to this paper with recommendations for the high priority issues on what further work the Executive feel is required.
- 1.3 Annex B to this paper contains briefings on each of the high priority horizon scanning issues including some information about the technique and a recommendation on what further work is required. The

aim is to discuss the issues, the priority status that they have been given and to make a decision on which issues are highest priority to inform work planning for SCAG and the policy team for 2007/2008. The issues that were considered to be medium risk are also included for information so members can consider these alongside those issues identified as high priority. Members may be of the view that some of the medium priority issues should be considered to be high priority.

2. Recommendations

2.1 Members are asked to

- Consider and discuss the high priority issues presented in this paper
- Comment on the list of high priority issues and make any changes to this list
- Comment on the work recommendations from the Executive
- Prioritise longer term issues to inform the business planning process for 2007/2008.

List of priority conditions

High priority issues

Issues that fall into this category will meet at least three of the following criteria:

- likely to have a high patient demand / clinic use
- introduction within 2-3 years
- technically feasible
- ethical or public interest aspects

Issue	Description	Work recommendation
Dry storage of sperm	The desiccation of sperm as an alternative to cryopreservation for storage purposes.	Committee paper for consideration by SCAG in 2007.
<i>In vitro</i> growth of oocytes	<i>In vitro</i> growth (IVG) of oocytes refers to the development, in the lab, of oocytes from immature (preantral) follicles (earlier than the stage from which <i>in vitro</i> maturation is carried out).	Invited speaker to inform SCAG on technique. Committee paper for consideration by SCAG in 2007.
Metabolomics	A non-invasive assay of embryo viability whereby the embryo with the best chance of implanting is selected by analysis of by-products of metabolism in the culture medium.	Committee paper for consideration by SCAG in 2007. Invited speak to inform SCAG.
Use of 'dead' embryos in embryo research	Embryos that have stopped dividing can be used for the derivation of human embryonic stem cells. These embryos could arguably be described as 'dead' and thus fall outside regulation.	Committee paper for consideration by SCAG and ELC in 2007.
Human embryonic stem cell lines derived from single blastomeres	A single blastomere is taken from a developing human embryo and cultured overnight for the derivation of a human embryonic stem cell line that doesn't result in destruction of an embryo.	This matter was brought up at a previous SCAG meeting and is presented separately in Paper 03.

Medium priority issues

Members may wish to consider whether any of the medium priority issues should also be considered by SCAG in 2007.

Issues that fall into this category will meet at least two of the following criteria:

- likely to have a high patient demand
- introduction within 2-3 years
- technically feasible
- ethical or public interest aspects

Issue	Description
Testicular stem cell transplantation (TSCT)	The transplantation of male germ cells into sterilised recipients where they develop into mature sperm capable of fertilisation. Could be used to restore fertility in per-pubertal cancer patients.
Xenografting of immature testicular tissue	Testicular tissue grafted into another species (mouse) continues to produce spermatogonia. This technique could be used as a way of preserving the fertility of pre-pubertal cancer patients. If carried out, this would present significant ethical concerns.
IVF within microfluidic channels	The miniaturisation of the the IVF procedure to take place within microfluidic channels requires lower total numbers and concentrations of sperm, providing an alternative to ICSI for low sperm count in males.
Cloning and RNAi	Maternal and embryonic transcripts of genes of interest can be temporarily knocked down. Could use to knockdown genes with negative effect on viability or implantation for CNR, for example, knockdown of CDX2 for stem cell derivation from CNR embryos. The most likely use for this would be to circumvent legislation where the potential of an entity determines whether or not it is regulated.
Embryo culture from blastomere biopsy (embryo splitting)	Blastomeres removed from a developing embryo can be used to develop new embryos. This could be utilised in research or for increasing the number of embryos available for transfer in IVF. This is currently banned, however may have implications for PGD.
<i>In vitro</i> spermatogenesis	A process by which male germ stem cell like cells or primary spermatocytes are isolated from testicular tissue and differentiated into haploid male germ cells <i>in vitro</i> . This technique could be used for the treatment of azoospermia patients (males who cannot produce sperm). Sperm derived in this way could then be used in ICSI.

Ongoing horizon scanning issues

The following issues have been identified previously in the horizon scanning process and are ongoing. These issues may also need to be considered during the 2007/2008 business year. Members may wish to consider these issues when prioritising the new horizon scanning issues.

Issue	Previous consideration	Date for reconsideration
Germinal vesicle transfer (GVT)	Members were of the opinion that studies/evidence of the technique need to be accumulated as they are produced. It was decided that this technique would be reviewed in a year's time.	September 2007
<i>In vitro</i> derived gametes	Members were of the opinion that the development of eggs from stem cells should be considered by SCAG again in a year and that the HFEA would not receive a licence application for this within the next couple of years.	September 2007
Deriving stem cells from individual blastomeres	Members considered this previously. This is being reconsidered at this meeting.	Depending on the view of SCAG after the discussion at this meeting, members may wish for this to be reconsidered during 2007.
Microarrays and PGD	Members were of the opinion that the science necessary for the use of this technology is not advanced enough yet and members were of the opinion that this technology may be available for therapeutic use in three to five years.	Recommendation – Monitor and reconsider at some point in 2007

Horizon scanning briefing Dry storage of sperm

1. Dry storage of sperm

- 1.1 Sperm is routinely stored in a cryopreserved state. The main drawbacks of cryopreservation are the requirement of low-temperature freezers for transportation and storage, and the cellular damage caused by low temperatures. Cryoprotectants are used to minimise the freezing damage to sperm, making cryopreservation a generally successful storage technique.
- 1.2 Dry storage of sperm has been suggested as an alternative to cryopreservation that offers the possibility of the transportation and storage of sperm to be done at ambient temperature, which would significantly reduce the cost/logistics of low-temperature preservation and shipping of spermatozoa. It could also reduce the complications associated with removal of cryoprotectants.
- 1.3 Dried sperm are defined as 'dead' because they are non-motile and physically damaged. However, despite drastic physical alterations in sperm structures (damage to plasma membranes of head and tail, head-tail separation, acrosome detached from head), the nucleus remains intact and although they are unable to fertilise *in vivo* or *in vitro* they are able to produce live offspring with ICSI.
- 1.4 The desiccation of sperm cells for dry storage has been achieved using freeze-drying techniques where the sample is first frozen to subzero temperatures and then the water is sublimated. Using this technique, mature spermatozoa have been completely desiccated, stored and following ICSI have resulted in live offspring in mice, rabbits, rats and fish. More recently, convective drying has been introduced as an alternative desiccation technique. Convective drying using nitrogen gas offers a simpler and less expensive alternative to freeze drying, with the potential to perform the entire protocol at room temperature.

2. Who the technique could be used by, what is the likely impact?

- 2.1 The dry storage of sperm could be an alternative to routine cryopreservation and used in any circumstance where the storage of sperm is required.

3. What is the likely timescale of introduction of this technique?

- 3.1 For a long time, mouse was the only species in which freeze-dried sperm had been shown to support development to term. However, unlike human sperm, mouse spermatozoa do not contribute centrosomes to the zygote, leaving the possibility that freeze-drying might not be applicable to humans. Now it has been reported that the use of freeze-dried rabbit sperm, which contribute centrosomes to the zygote similarly to humans, has resulted in the birth of a full term rabbit kit. This indicates the freeze-drying technique could potentially be transferred to humans.
 - 3.2 The convective drying technique for sperm storage requires more refinement. Live born pups were obtained using sperm desiccated by this method and stored for one month in a refrigerator, although this technique has only been applied to mouse sperm. With further research there is potential for convective drying to be applied to human sperm.
- 4. Ethical/public interest consideration**
- 4.1 Increasing the storage possibilities of sperm might make it easier for transportation from abroad, which may benefit donor supplies.
 - 4.2 If dry storage of sperm proves to be an effective and safe technique there should be no additional ethical issues than with cryopreservation although, it would result in the use of ICSI where it may not have been necessary had the sperm been cryopreserved. This could be seen as an additional risk associated with drying sperm.
- 5. Risks**
- 5.1 As far as we are aware, there are currently no groups trying this technique with human sperm so it is likely that the introduction of this technique is not immediate so not carrying out further research on this may not present significant risk.
 - 5.2 However, if it were to be introduced, it is likely to be something that the HFEA would have to consider in terms of safety. Therefore by not monitoring this area, the technique could be developed and a licensed centre may wish to use it prior to the HFEA having an opportunity to consider the issue.
- 6. Level of work recommendation**
- 6.1 We recommend that this issue is monitored. If members agree that this should be considered further, we would recommend this issue be re-considered in SCAG later in the year in 2007.

Horizon scanning briefing

***In vitro* growth of oocytes**

1. *In vitro* growth of oocytes

1.1 As part of the issues identified from horizon scanning 2005 we considered *in vitro* maturation (IVM) of oocytes (this is the maturation of oocytes from the germinal vesicle stage – the final stage of maturation of an oocyte). *In vitro* growth (IVG) of oocytes refers to the development, in the lab, of oocytes from immature (preantral) follicles (earlier than the stage from which *in vitro* maturation is carried out).

1.2 IVG of oocytes has been done in various animal species and live pups have been produced from mouse eggs that were grown *in vitro*. There are groups working on development of this technique in humans.

2. Who the technique could be used by, what is the likely impact?

2.1 *Treatment*

Initially, this technique is most likely to be used by women who have had ovarian tissue cryopreserved. There has been some limited success with autologous ovarian tissue transplantation (when the cryopreserved tissue is replaced back in the patient from whom it was removed) to mature the oocytes *in vivo* or re-establish ovarian function however there are concerns that this technique could re-introduce cancerous cells back into the patient. In the longer term, if this technique were demonstrated to be safe and effective, this could be used as an alternative for all women undergoing IVF removing the need for them to have a stimulated cycle to produce eggs. If it were to be used in all treatment, this technique would have a significant impact.

2.2 *Research*

In research, this technique is likely to be developed alongside *in vitro* derived gametes as it is likely that any immature oocyte-like structures that are produced, for example from stem cells, would need to be ‘grown’ and matured. In order to test any oocytes grown *in vitro* it would be necessary to fertilise them to ensure that they are able to produce an embryo. This would require a research licence from the HFEA. If oocytes grown *in vitro* were shown to be effective, it would remove some of the ethical concerns about the provision of eggs for research from stimulated cycles.

3. What is the likely timescale?

3.1 To date this technique has been carried out in animals and live births have been seen in mice. There are groups working on human *in vitro* growth

currently so it is likely that this technique could be introduced within 2-3 years.

4. Ethical/public interest consideration

- 4.1 If IVG were to be introduced in treatment, it would be a new technique and, as is often the case when new techniques are introduced, there would be some safety concerns until the technique becomes more established. On the other hand, if this technique were shown to be safe and effective for treatment, there may be ethical concerns associated with *not* using IVG but continuing to stimulate women, risking OHSS.
- 4.2 For research there could be ethical concerns about creating embryos purely for the purpose of testing the effectiveness of the process.

5. Relevant legislation

- 5.1 It is a standard licence condition on all licenses issues by the HFEA that:
“any oocytes obtained from ovarian tissue, shall not be used in any treatment services until such a time as the Authority is satisfied that sufficient evidence on safety and efficacy is available to justify the introduction in to clinical practice of the replacement of embryos resulting from cryopreserved ovarian tissue.”¹
- 5.2 The last part of the condition is particularly relevant for this issue because if cryopreserved tissue were used this would of course involve the *‘replacement of embryos resulting from cryopreserved ovarian tissue’*. For this technique to be introduced in treatment, this licence condition would have to be reconsidered.

6. Risks

- 6.1 It is unlikely that any consideration carried out on this technique by the HFEA would slow up any application for human use of IVG as its introduction is not likely to be very immediate.
- 6.2 If there were not any work carried out on this, there is a risk that an application could be received and the HFEA would not have considered this issue. Although there is currently a licence condition preventing the replacement of any embryos in treatment that resulted from cryopreserved tissue – it is also possible for IVG to result in mature oocytes without coming from cryopreserved tissue, this would not be relevant to all possible treatment applications. It is also likely that a research application

¹ HFEA Code of Practice (6th Edition) Appendix H – Licence Conditions

will be received to test any oocytes grown *in vitro* prior to any clinical applications.

7. Level of work recommendation

- 7.1 We recommend that further details about IVG are obtained specifically on the progress of human IVG research. Further details on this technique can be written up and considered at a future SCAG meeting, perhaps with an invited speaker, at which members can come to a view about the future use of this technique. At this stage we do not think it is necessary to carry out any specific policy review on this issue. Committee consideration of the technique will be sufficient.
- 7.2 If members feel that further work on this issues is appropriate, this can either be done as a specific horizon scanning issue or it could be combined as part of the further considerations and updates on *in vitro* derived gametes.

Horizon scanning briefing Metabolomics

1. Metabolomics

- 1.1 Currently, embryos are chosen for transfer based on morphology. Embryos are scored according to a graded system that has been suggested to be a good measure of embryo viability and likelihood of implantation. However, this system is somewhat subjective and sometimes unsuccessful. There remains a need to identify more accurately those embryos with the highest developmental potential, which will in turn allow a reduction in the number of embryos transferred and decrease multiple births.
- 1.2 Metabolomics has been suggested as an alternative, objective method of identifying those embryos with the best chance of implanting. Metabolomics represents a non-invasive technique for analysing the metabolism (the biochemical processes) of an individual embryo. The assay involves measuring the levels of nutrient up-take or by-products of cell metabolism in the culture medium in order to identify metabolomic differences in viable versus non-viable embryos.
- 1.3 A researcher in the US, in collaboration with a commercial company, has carried out two clinical studies investigating the use of metabolomic profiling to assess embryo viability. They have used markers of oxidative stress to analyse embryo viability. Studies revealed differences in metabolomic profiles from culture media obtained from embryos that caused pregnancy compared with those that did not.
- 1.4 Similarly, research groups in the UK are looking at respiration rates, glucose consumption and amino acid turnover as markers of embryos most likely to implant and result in live birth.

2. Who the technique could be used by, what is the likely impact?

- 2.1 Anyone undergoing IVF could benefit from development of this technique. By measuring the viability of embryos, it could be possible to pick one with best chance of implanting and increase success rates for IVF significantly.
- 2.2 An accurate and reliable method of embryo selection would facilitate the use of single embryo transfer which would likely result in a reduction in the high number of multiple births and associated premature deliveries that are commonly observed in IVF.

3. What is the likely timescale of introduction of technique?

- 3.1 As soon as the metabolites that indicate which embryos are most likely to implant are identified, this technique could be introduced quickly. One researcher is ready to start clinical trials.

4. Ethical/public interest consideration

- 4.1 If this technique were to be introduced by a commercial company, it is likely that this could result in an increased cost of treatment which is likely to be transferred to patients. However, successful use of this technique could significantly improve success rates and reduce the number of multiple births.

5. Risks

- 5.1 There is not likely to be a significant risk of not carrying out further work on this issue because how embryos are selected in a clinic is not something that the HFEA directly regulates. However, as it is something that could have a significant impact on the field, particularly with respect to single embryo transfer, it is something that the organisation should be aware of.

6. Level of work recommendation

- 6.1 A review of the literature and ongoing studies in this area will be presented to SCAG for further consideration during 2007. Any views of SCAG could then be fed into the ongoing project on multiple births.

Horizon scanning briefing

Deriving human embryonic stem cell (hESC) lines from dead embryos

- 1. Deriving hESC lines from dead embryos**
 - 1.1 From our horizon scanning work deriving human embryonic stem cells from dead embryos was identified, and prioritised, as an issue that will have an impact on assisted reproduction in the near future. This technique involves deriving hES cells from embryos which have arrested before they reach blastocyst stage (likely to be mainly embryos created in the process of IVF treatment).

- 2. Who the technique could be used by, what is the likely impact?**
 - 2.1 This is a method to obtain hESC lines without destroying viable developing embryos. A large proportion of embryos created for IVF treatment arrest and do not develop into blastocysts. Arrested embryos do not continue their cleavage after 24 hours of observation. However, not all blastomeres within the arrested embryo are abnormal nor are responsible for developmental arrest.
 - 2.2 Arrested/dead embryos could be an additional resource to donated developing/live embryos which could be used to derive hESC lines or study early human development.

- 3. What is the timescale of introduction of deriving hES cells from dead embryos?**
 - 3.1 A European group Zhang et al (2006) demonstrated that hESC lines can be derived from arrested embryos from IVF treatment.
 - 3.2 Thirteen embryos, created by IVF, which had stopped developing at the blastocyst stage (6 to 7 days after fertilisation) were used. The team waited 24-48 hours to check that the embryos were no longer dividing to determine that the embryos were no longer viable. The zona pellucida was removed from the embryos and they were plated on mouse or human feeder cells. hES cell outgrowths were separated into clumps.
 - 3.3 From one embryo the group derived a fully characterised hESC line which was pluripotent and could differentiate into all three germ layers both in the dish and in live mice.
 - 3.3 The same group attempted to culture 119 embryos which were arrested at an earlier stage (4-10 cells). This attempt was not successful.

4. Ethical/public interest consideration

- 4.1 The issues raised by this technology will be around ensuring people undergoing IVF treatment give informed consent to this.
- 4.2 There may be concerns raised, particularly from religious groups, regarding using dead embryos and disrespect for the dead.
- 4.3 Pro-life groups may consider the use of dead embryos more respectful to human life than using live embryos for research.
- 4.4 There may be concerns regarding potential conflicts of interest in clinics which carry out IVF treatment and embryo research. Patients may fear that embryologists may be more likely to class embryos as non-viable and therefore the success of their treatment may be compromised.
- 4.5 The ability of these cells to give rise to embryonic stem cells may prompt concerns that embryos that have not divided in 24 hours are still viable and could still potentially be considered for use in treatment.

5. Risks

- 5.1 The use of dead embryos is not within the remit of the HTA or the HFEA. There is currently a gap in the regulation which needs to be addressed. Consideration will need to be given to whether arrested embryos can actually be classed as dead. There is a risk that arrested embryos, if transferred to the womb, could continue to grow and implant.
- 5.2 If non-dividing embryos were no longer considered to be 'live', centres carrying out HFEA licensed embryo research using arrested/dead embryos may no longer need to be licensed by the HFEA. There is a risk that some embryo research which is currently regulated by the HFEA will no longer be within our remit.
- 5.3 Stem cells derived in this way would not be required to be deposited in the UK Stem Cell Bank. There is a risk that this will hinder the progress of stem cell research and future use of stem cells in the UK. The Steering Committee have been alerted to this fact.
- 5.4 There is a risk that there may be a conflict of interest at centres which carry out IVF and embryo research.
- 5.5 There is a risk that dead embryos may be genetically abnormal.

6. Level of work recommendation

- 6.1 The Executive recommend that SCAG consider a committee paper on this issue in 2007 in order to:
- form a view on the use of this technology and whether it could be a viable alternative to using live embryos for research involving study of early human development or creation of hESC lines
 - form a view on whether arrested embryos should be classed as dead or alive
- 6.2 Further consideration may need to be given to a definition for embryo death and whether arrested embryos (the cells of which can be induced to grow separately) are dead or alive, and therefore whether research projects involving use of arrested embryos should be licensed by the HFEA.
- 6.3 The ethical and legal issues surrounding the use of this technique will be considered by the Ethics and Law Committee. Consideration will also need to be given to how this gap in the regulation can be addressed.