NUFFIELD COUNCIL ON BIOETHICS

Forward Look 2016

25 February

Artificial gametes

Introduction

1 The Forward Look session on artificial gametes began with presentations from invited speakers,[1] followed by discussion with assembled guests. This note summarises themes, and also policy and ethical questions, which emerged during the meeting.[2] It should not be assumed that everyone present agreed with all points made.

Emerging themes from presentations and discussions

The prospects for creating artificial gametes

2 Creating 'artificial gametes' refers to the idea of making germ cells from embryonic stem cells or induced pluripotent stem cells (IPSCs).

3 In the field of germ cell biology and development there is increasing interest in understanding the particular properties of the human germ cell lineage and the human germline cycle and in whether sperm and eggs can be created in vitro which could also potentially be advanced by new genome editing and improved genome sequencing technologies.

4 Recent proof-of-concept research[3] showed that mouse gametes can be derived *in vitro* from embryonic stem cells. Professor Surani's laboratory has looked at developmental specification of germ cells during the last 15 years and identified three key genes for this process providing the background research for the creation of artificial gametes. It recently became possible to create primordial (early) germ

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1 Dr Amel Alghrani, Senior Lecturer in Law, University of Liverpool, Professor Azim Surani, Director of Germline and Epigenomics Research, Member of the Physiology, Development and Neuroscience Department, The Gurdon Institute, and Professor Stephen Wilkinson, Professor of Bioethics, Lancaster University.

2 A background paper for this meeting was produced by Dr Anna Smajdor, Lecturer in Ethics, Norwich Medical School, University of East Anglia and Dr Daniela Cutas, Associate Professor of Practical Philosophy, Department of Historical, Philosophical and Religious Studies, Umeå University, Sweden. See: Nuffield Council on Bioethics (2015) Background paper: artificial gametes, available at: http://nuffieldbioethics.org/wp-content/uploads/Background-paper-2016-Artificial-gametes.pdf.

3 Zhou Q, Wang M, Yuan Y, et al. (2016) Complete meiosis from embryonic stem cell-derived germ cells in vitro *Cell Stem Cell* **18(3)**: 330-40.

cells[4] and the field is moving fast with studies in mice being most advanced,[5] although many details remain to be understood. Advances in somatic reprogramming more generally imply the breaking of the Weismann barrier.[6]

5 Current limitations relate in particular to the differences between mouse and human embryonic development[7] and the genetic vs. epigenetic (i.e. heritable but reversible DNA modifications regulating gene expression) contributions by sperm and egg in early human development (achieving the right balance will be critical for the creation of *in vitro* gametes).[8] In general, research on early embryos is limited by the current UK legal limit of 14-days before they have to be discarded.

6 Future aims of research in humans are:

- To obtain a better understanding of the role of key genes in germline development;
- To understand putative epigenetic mechanisms of inheritance;
- To develop methods for gametes from stem cells in culture;
- To investigate IPSCs for mutations affecting development; and
- To explore the potential of germline gene editing

Regulatory gaps and inconsistencies

7 New technologies in assisted reproduction have revolutionised how we think about reproduction, obstetrics, neonatology, and parenthood. It was suggested that while advances are happening fast, regulation is typically lagging behind or being reactive rather than proactive as was the case, for example, with cloning; it is therefore timely for the Council to approach the issue now as research is developing.

8 The HFEA's 2008 report on "Scientific horizon scanning" (2008/09) states that "Members of the Scientific and Clinical Advances Advisory Committee (SCAAC) thought, in May 2008, that the timescale for deriving gametes for treatment was between 5-10 years."[9] According to the HFEA, developments in the area are being monitored but there have been no further updates.[10] It was noted that, taking a different approach from the HFEA, the Council could examine the ethical issues involved in a broader manner and with greater parity of perspectives.

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4 Magnúsdóttir E and Surani MA (2014) How to make a primordial germ cell *Development* **141**: 245-52.

5 Hayashi K, Ogushi S, Kurimoto K, et al. (2012) Offspring from oocytes derived from in vitro primordial germ cell–like cells in mice Science 338(6109): 971-5.

6 Surani MA (2016) Breaking the germ line–soma barrier Nature Reviews Molecular Cell Biology 17(3): 136, doi:10.1038/nrm.2016.12.

7 Irie N, Weinberger L, Tang WWC, et al. (2015) SOX17 is a critical specifier of human primordial germ cell fate Cell 160(1/2): 253-68.

8 University of Cambridge news website(4 June 2015) Reprogramming of DNA observed in human germ cells for first time, available at: http://www.cam.ac.uk/research/news/reprogramming-of-dna-observed-in-human-germ-cells-for-first-time.

9 HFEA (2009) *Scientific horizon scanning at the HFEA, Annual report 2008/09*, available at: http://www.hfea.gov.uk/docs/Horizon_Scanning_Report.pdf.

10 HFEA (2009) *In vitro derived gametes*, available at: http://www.hfea.gov.uk/in-vitro-derived-gametes.html.

9 In such a project, the Council could also investigate a number of ethical issues that would need to be addressed in a more consistent regulatory framework that could accommodate artificial gametes.[11]

The de-geneticisation of human reproduction

10 The genetic link between parents and offspring appears very important to many people but it might be questioned to what extent this is justified, in particular against the background of risks and costs involved in developing technologies to preserve this link as well as available alternatives (donation of eggs and sperm; adoption).

11 Given that 'de-geneticisation' is arguably already ongoing in areas such as donor conception or surrogacy, it was questioned whether there would be anything of special ethical relevance in the use of artificial gametes for reproduction and/ or whether a new combination of ethical issues might be at stake. Issues of potential relevance discussed included:

- Who is the 'causal originator of a person'? What are the relevant factors in inheritance and the causal creation of a person, are these essentially about information, or material channels? What would this imply for the notion of "genetic determinism"?
- How is parental responsibility established?
- The widening of reproductive choices
- Donor anonymity and payment
- Does cell reprogramming as a technology and advances in epigenetics raise any particular issues?

Regulatory and policy questions

12 The wider implications for society and future generations from the use of artificial gametes were discussed, in particular whether the HFEA has the moral authority to license use of artificial gametes for treatment, given that when the HFEA was created this technology was not envisioned and due to the limited representativeness of the HFEA. Another issue highlighted was how parenthood is defined and ascribed.

Ethical questions

- **Identity and status**: What would the implications be for the identity of prospective children were artificial gametes used in treatment, and due to the 'democratisation of reproduction' more generally? For example, if a child can be created from one person, without a mother and/or father, what would the impact on the person be? What would be the significance of such a development in biological, social and legal contexts?
- **Language**: 'Artificial gametes' appears to be a term with problematic and/or misleading connotations. Issues around 'artificial' vs. 'natural' gametes might have the potential to be misleading in public debate and cause offence. Other proposed terms were '*in vitro*-derived gametes' or '*in vitro*-generated gametes'.

[11] For example, Margaret Brazier has criticised that there is "little conceptual depth" is underpinning the law in the area of reproduction (Brazier M (1999) Regulating the reproduction business? *Medical Law Review* **7(2)**: 166-93)).

- **Treatment vs. enhancement**: Is the distinction between treating infertility vs. enhancement meaningful? Some uses of the technology would appear to be treatments of pathologies; others would extend fertility to individuals who would not ordinarily have it. This raises the question whether infertility is a disease or more of a syndrome or symptom. There are cases of pathological and non-pathological infertility; however, what is or should be the norm or normal (biological) functioning? This also has potential implications for funding and access to artificial gametes and ART – some might argue that public health funding should prioritise what can clearly be considered as being about 'health' rather than about enhancing reproductive options. It could also have implications for risk assessment and whether developing treatments justifies higher levels of risk than developing enhancements.
- **Access to artificial gametes; funding and commercial potential**: Artificial gametes would offer the possibility of genetic reproduction to individuals who are not typically regarded as being infertile. Should everyone be given access to the technology as part of 'reproductive autonomy' and whether or not biological parenthood is important to them? Should treatment be publicly funded? The current HFEA Act, as influenced by the Warnock report, emphasises the importance of genetic relatedness.
- **Safety and welfare**: What are the safety issues that treatment with artificial gametes will raise as a novel, experimental treatment to be considered by the HFEA before licensing? Which level of risk will be deemed justifiable? What are legitimate welfare concerns that could be raised with the HFEA, including physical, mental and social welfare? It was suggested that currently a normative framework to evaluate the welfare of a child in the context of assisted reproduction is lacking, and that the welfare of the child is not given the paramountcy in this context which is it given in other legal contexts. How could the child's welfare be put back at the centre of attention should artificial gametes become available as part of treatment? What monitoring or follow-up should be in place for concerned families, given that there is likely to be a level of risk involved?
- **Consent:** What is the status of donors of gamete material for artificial gamete research and what would be the adequate approach to consent?

13 Additional issues raised:

- Is there a case for relaxing the 14-day rule for embryo research due to the emerging research opportunities in this field? It was suggested that the rule blocks an immense opportunity with new techniques in genome editing to study early human development; this issue has become even more pertinent since it was shown that mouse and human development differ in some important aspects
- Does this technology raise any particular misuse or dual use issues? It was suggested that there are potentially issues around enhancement and the availability of other technologies such as CRISPR, to regulate gene expression without genetic change in the future

14 In summary, it was suggested that the topic may not be suitable for a Nuffield Council Working Party since previous Council reports already offer substantial considerations on similar and overlapping issues; these might be pooled for a

position on artificial gametes and/or a direct public consultation. An issue of specific interest was, however, the ‘data dimension of reproduction’, i.e. the idea of germline and cells as data containers to be potentially repurposed.

15 It was also suggested that a workshop or similar event might be organised by the Council around the scientific advances outlined that have foregrounded questions about the 14-day rule regarding embryo research.