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Stem Cell-Derived Human Gametes: The Public Engagement Imperative

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The implications of scientific breakthroughs are rarely faced up to in advance of their realization. Stem cell-derived human gametes, a disruptive technology in waiting, are likely to recapitulate this historic pattern absent active intervention. Herein we call for the conduct of thoughtful *ante hoc* deliberations on the prospect of stem cell-derived human gametes with an eye toward minimizing potential untoward *post hoc* regulatory or statutory impositions.

History is littered with scientific breakthroughs that forced wholesale revision of erstwhile axioms. Closely trailing perceived threats to stability have all too often fomented ill-informed, indeed shortsighted, regulatory or statutory constraints (Box 1). The specter of reproductive cloning, the derivation of human embryonic stem cells, and the prospect of germline modification have all marched down this path. There is little reason to believe that stem cell-derived human gametes, now within the realm of possibility, will fare any better [1]. Therein, however, lies an opportunity to replace historic *post hoc* vetting patterns with *ante hoc* consensus-seeking deliberations toward a rational, culture-compatible framework. Contemplating the safety and efficacy of stem cell-derived human gametes may well be premature at present. Exploring their ethical, societal, and legal implications, however, could not be timelier.

The *in vitro* genesis of human gametes may be accomplished via organ or cell cultures [2]. Organ cultures of human gonadal substrate are limited by inaccessible starting materials, the derivation of which requires an invasive surgical procedure [2]. Organ cultures are further constrained by the number of gametes so generated [2]. Cell cultures of human embryonic stem cells, clerically denounced for their embryonic origin, may be hampered from serving as gamete precursors. However, cell cultures of human induced pluripotent stem cells (iPSCs), unimpeded by doctrinal considerations, are widely accepted as gamete antecessors. The *in vitro* specification of human primordial germ cell-like cells and of oogonia has been accomplished [3]. However, the *in vitro* reconstitution of the entire cycle of the human germ line remains to be accomplished [3]. A challenge yet to be resolved is the derivation of human somatic gonadal cells in support of *in vitro* gametogenesis. Overcoming this hurdle may require transdifferentiation or stem cell-derived somatic gonadal cells. Whether stem cell-derived human germ cells can be educed across gender lines remains uncertain.

New Scientific and Therapeutic Opportunities

The availability of stem cell-derived human gametes and stage-specific germ cells stands to herald novel scientific and therapeutic opportunities [1]. Similar considerations apply to somatic cell nuclear transfer, the conduct of which would no longer be rate limited by the availability of surgically recovered human oocytes. New scientific fields may include functional genomics, germ–somatic cell interactions, epigenetic reprogramming, or meiotic recombination [1]. Clinical advances are similarly anticipated from autologous iPSC-derived human gametes. The enablement of genetic parenthood in new contexts is one such example [1]. The reversal of infertility due to germ cell failure associated with azoospermia, premature menopause, cancer therapy, or gonadal extirpation is certain to feature prominently [1]. The growing phenomenon of delayed childbearing could potentially be similarly addressed. Autologous mutation-free iPSC-derived oocytes could also enable a donor-independent approach to the prevention of mitochondrial DNA diseases in progeny at risk via mitochondrial replacement therapy (MRT) [4]. The quest for 'savior siblings' in search of a cure for an ailing sibling could be simplified as well. Finally, reparative gene editing could be applied to iPSC-derived gametes of probands compromised by heritable infertility [5]. Apart and distinct from the preceding considerations, it is highly likely that iPSC-derived human gametes will irretrievably disrupt the current clinical practice of *in vitro* fertilization (IVF). Absent the need for egg retrieval or donation, IVF is likely to be transformed into a laboratory-exclusive process.

Liberal Eugenics

The ethical concerns over stem cell-derived human gametes center largely on the commodification of human reproduction and the prospect of liberal eugenics [1,6]. The ethical conundrum raised by commodification is epitomized by the inexhaustible complement of stem cell-derived human gametes and, by extension, preimplantation embryos. For some, the creation of large numbers of preimplantation embryos (sometimes referred to as 'embryo farming') for the purpose of selecting or genetically engineering desirable traits (i.e., liberal eugenics) raises two complementary concerns: first, that the creation of large numbers of embryos, many of which will be discarded, devalues the moral worth of the human embryo; and second, that embryo selection represents an untoward desire for mastery and human perfectionism in which

Box 1. Society, Science, and Suspicion

The notion that scientific revolutions and their societal fallout follow a predictable pattern was first introduced in 1962 by Thomas S. Kuhn, PhD [(1962) *The Structure of Scientific Revolutions* (1st edn), Chicago University Press]. Inherent to this view is the observation that the post-discovery scramble is prone to regulatory or statutory moratoria. Seen as byproducts of fear by Cass R. Sunstein [(2005) *Laws of Fear: Beyond the Precautionary Principle* (1st edn), Cambridge University Press], these adverse societal reactions are not beyond attenuation. It is here that *ante hoc* participatory public engagement is of the essence. Applying such to the prospect of stem cell-derived human gametes might curtail potential heavy-handed societal reactivity. Doing so may assure the rational progression of this disruptive technology.

reproduction becomes manufacture. In the eyes of some, individually directed liberal eugenics comports with the right to maximize the wellbeing of would-be progeny through selection if not enhancement [6]. Others question the moral validity of liberal eugenics as inconsistent with liberal theory and as representing some of the evils of state-mandated eugenics [7]. Additional ethical concerns are represented by the prospect of 'iterative *in vitro* reproduction' (iIVR) through successive generations of stem cell-derived human gametes [8]. To date, the state of active scholarship on the ethics of stem cell-derived human gametes remains modest but growing. In this context, mention must be made of the brief 'forward look' on 'artificial gametes' issued by the Nuffield Council on Bioethics (http://nuffieldbioethics.org/wp-content/uploads/NCOB-Forward-Look-2016-Artificial-gametes.pdf). Building on this transatlantic foundation could not be timelier.

Social Implications

The societal overtones of stem cell-derived human gametes are proving equally challenging. Much of the debate revolves around the notion of genetic ancestry [9]. To some, the linkage of family making to genetic relatedness is outdated [10]. Viewed in this light, parenting options could be expanded to include single, same-sex, and multiplex parenthood [11]. Postmenopausal motherhood could also become a reality, replete with the uncertainty of rearing children subject to premature orphanhood [12]. Partial consideration of these matters has been the subject of scholarly as well as formal deliberative initiatives [9,12,13]. The debate over same-sex reproduction resembles that which is emerging for the application of MRT to lesbian partners. It is a debate between those who view MRT as a reproductive right that should be extended to same-sex couples and those who seek to limit MRT to the prevention of mitochondrial DNA diseases. The debate over multiplex parenting, in turn, revolves around the question of limiting the number of genetic parents to the traditional two (or possibly three with MRT) as distinct from embracing a more fractional form of parenthood made possible by somatic cell-derived human gametes. To use an aphorism, it would 'take a village' to conceive, not merely raise, a child.

Finally, consideration would have to be accorded to the position of organized religion on the prospect of somatic cell-derived human gametes. In this context, the objection of the Catholic Church to nonconjugal forms of reproduction is bound to be raised. Less clarity exists at this time on the stance of other denominations. The support extended by the Church of England to MRT, a striking example of mutual accommodation, might in time be extended to the prospect of somatic cell-derived human gametes.

Legal Implications

The legal challenges introduced by stem cell-derived human gametes occupy an uncharted area of jurisprudence for which the current law is unprepared [1]. Consideration could be given to the placement of limits on the number of embryos to be created in the first place. Circumscription of the number of selection-eligible embryos could be similarly explored. Queries about the practice of embryo cryopreservation and/or destruction will doubtless follow. Novel legal challenges are likely to bear as well on the possibility of unwitting nonconsensual parenthood due to misappropriated somatic cells turned gametes [1,14]. Whether the state can and will protect against the unauthorized imposition of parenthood remains to be established [14]. At the very least, legal and genetic parenthood may have to be selectively severed [12]. Applicable deliberative forums have yet to be convened and new legal constructs need to be explored. Neither the USA nor the UK has sponsored or enacted statutes of relevance to the matter of stem cell-derived human gametes. Japan, by contrast, intent on the preservation of human dignity, prohibits the use of stem cell-derived human gametes in the creation of human embryos solely for research purposes [15].

Participatory Public Engagement

It was 1971 when Nobel Laureate James D. Watson first argued for prospective public engagement in the assessment of emerging technologies. Testifying before a congressional committee, Dr Watson maintained that 'it is not a question for a group of scientists to decide . . . it is a decision which the people as a whole must make'. Famously dubbed the 'participatory turn' in science–society relations, citizen participation in the governing of science has been ascendant (Box 2) [16]. A seminal Institute of Medicine report titled *Society's Choices* lent further support for the indispensability of public input. In the context of reproductive medicine, public engagement subsumed a leading role in the adjudication of MRT in the UK. Patient focus groups as

Box 2. Participatory Public Engagement to Assess Societal Views

Anticipatory deliberation of the prospect of stem cell-derived human gametes will require participatory public engagement to assess societal views. All but indispensable for emerging technologies, public outreach is broadly practiced by several member nations of the EU. A comparable American experience has yet to evolve. A seminal Institute of Medicine report titled *Society's Choices* lent further support for the indispensability of public input. Although extensive public outreach is not part of the FDA mandate, that capacity could be expanded. Enlargement of the evolving 'FDA Patient Engagement Collaborative' would be a good place to start. Requesting input by way of the Federal Register or by way of open-hearing forums or workshops might also be entertained. Much could be learned from the UK in this context, wherein the decision to legalize MRT relied heavily on participatory public outreach and engagement. Similar more recent UK-based efforts have focused on novel genetic technologies.

well as public surveys were carried out. It was this effort that permitted the Human Fertilisation and Embryology Authority to conclude that 'there is general support for permitting mitochondria replacement'. A comparable public dialog and opinion survey of genetic technologies was recently concluded by the Royal Society. A similar effort would have to be dedicated to the prospect of stem cell-derived human gametes if counterproductive regulation is to be avoided.

Concluding Remarks

The advent of stem cell-derived human gametes is bound to engender controversy and attract regulatory and statutory attention. It is in this context that bioethical and legal discourse and well-balanced discussions are vital. To advance this important cause, we call on learned societies, professional associations, bioethics enterprises, advisory boards, think tanks, national academies, nationally sanctioned commissions, appointed councils, assembled task forces, and other qualified institutions to contemplate the matter of stem cell-derived human gametes in keeping with local mores. Legislative bodies and regulatory agencies would have to be similarly engaged. Failure to act would have to be viewed as a missed opportunity to reject outdated 'after the fact' reactivity. Dr Watson's admonition 'if we do not think about the matter now, the possibility of our having a free choice will one day suddenly be gone' could not be more applicable.

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References

1. Cohen, I.G. *et al.* (2017) Disruptive reproductive technologies: the prospect of *in vitro* gametogenesis. *Sci. Transl. Med.* 9, eaag2959
2. Nagamatsu, G. and Hayashi, K. (2017) Stem cells, *in vitro* gametogenesis and male fertility. *Reproduction* 154, F79–F91
3. Yamashiro, C. *et al.* (2018) Generation of human oogonia from induced pluripotent stem cells *in vitro*. *Science* 362, 356–360
4. Ma, H. *et al.* (2015) Metabolic rescue in pluripotent cells from patients with mtDNA disease. *Nature* 524, 234–238
5. Mulder, C.L. *et al.* (2016) Spermatogonial stem cell autotransplantation and germline genomic editing: a future cure for spermatogenic failure and prevention of transmission of genomic diseases. *Hum. Reprod. Update* 22, 561–573
6. Agar, N. (1998) Liberal eugenics. *Public Aff. Q.* 12, 137–153
7. Fox, D. (2007) The illiberality of 'liberal eugenics'. *Ratio* 20, 1–25
8. Sparrow, R. (2014) *In vitro* eugenics. *J. Med. Ethics* 40, 725–731
9. Edwards, H.N. (1987) Changing family structure and youthful well-being. *J. Fam. Issues* 8, 355–372
10. Horowitz, J.E. (2012) Non-traditional family building planning. *Adv. Exp. Med. Biol.* 732, 115–130
11. Palacios-González, C. *et al.* (2014) Multiplex parenting: IVG and the generations to come. *J. Med. Ethics* 40, 752–758
12. Cutas, D. and Smajdor, A. (2015) Postmenopausal motherhood reloaded: advanced age and in vitro derived gametes. *Hypatia* 30, 386–402
13. Smajdor, A. and Cutas, D. (2014) Artificial gametes and the ethics of unwitting parenthood. *J. Med. Ethics* 40, 748–751
14. Cohen, I.G. (2008) The Constitution and the rights not to procreate. *Stanf. Law Rev.* 60, 1135–1196
15. Ishii, Y. *et al.* (2013) Ethical and legal issues arising in research on inducing human germ cells from pluripotent stem cells. *Cell Stem Cell* 13, 145–148
16. Jasanoff, S. (2003) Technologies of humility: citizen participation in governing science. *Minerva* 41, 223–244

Forum

New Insights and Perspectives in Fanconi Anemia Research

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Fanconi anemia is a rare, cancer-prone disease with mutations in 22 genes. The primary defect results in altered DNA repair mechanisms that fuel a severe proinflammatory condition in the bone marrow, leading to cellular depletion of the hematopoietic system and eventually to bone marrow failure. During the past three decades, a plethora of dysfunctions have been highlighted in the Fanconi anemia phenotype, but recent research allows us to glimpse an even more complex scenario where defective lipid metabolism could have important consequences in hematopoietic stem cell differentiation.

Fanconi anemia (FA; Box 1) patients suffer from a progressive failure in bone marrow (BM), eventually resulting in severe hematological complications [1]. Fine-tuning of