

Consensus Statement: Science, Ethics and Policy Challenges of Pluripotent Stem Cell-Derived Gametes

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For centuries, scientists have investigated how eggs and sperm (gametes) develop in mammals. Most of this work has been in non-human animals, particularly the mouse. The capacity to grow human pluripotent stem cells (PSCs) *in vitro** will facilitate research on human egg and sperm development. As a result, the day is now foreseen when it will be possible to derive eggs and sperm from PSCs in the laboratory. This line of research raises social and ethical issues that may be viewed differently in different cultures. The goal of this document is to inform public discussion about the state of the science and its potential social implications and to make recommendations about policy and practice.

State of the Science

- 1) PSC-derived gamete research has considerable scientific value and potential both for understanding basic mechanisms of gamete biology and overcoming clinical problems.
 - a) Human PSCs have proven to give rise *in vitro* to cells with characteristics of the earliest stages of germ cells (progenitors of eggs and sperm).
 - b) These cells are being used to explore important scientific questions such as the role of specific genes in early germ cell development.
 - c) No method has yet been described that produces human gametes capable of fertilization *in vitro* from a PSC.
 - d) Some steps along the developmental pathway of PSC-derived gametes have been achieved in other species *in vitro*.
 - e) Some steps along the developmental pathway of human germ cells that originated *in vivo* have been achieved *in vitro*.
 - f) These steps are being used to explore important scientific questions including the interaction between germ cells and supporting somatic cells.
- 2) Based on published data and theoretical considerations, it is probable that human eggs and sperm will be derived partly or entirely *in vitro* from PSCs. The pace of scientific progress is difficult to predict. Unanticipated findings can either accelerate or slow the pace of progress. With this caveat, the derivation of human eggs and sperm *in vitro* from PSCs, in whole or at least in part, is anticipated within 5 to 15 years.

However, it should be noted that:

* *Human pluripotent stem cells* (PSCs) are cells that have the capacity to develop into all the different cells in the human body. These cells have been isolated from several different sources, including early human embryos and human adult cells that have been induced in the laboratory to revert to pluripotent stem cells. *In vitro* is a biological term meaning outside a living organism, and is used in contrast to *in vivo*, meaning within a living organism.



- a) It is likely to be very difficult to derive eggs that could be used for reproduction from XY (chromosomally male) cells.
 - b) There are biological and technical reasons that will make it even more difficult, or even impossible, to derive sperm that could be used for reproduction from XX (chromosomally female) cells.
- 3) Tests exist to measure some aspects of the viability and functionality of gametes. These tests can be applied to cells derived from PSCs. In order to determine whether a method for derivation is producing functional gametes, however, it is necessary to establish the capacity of these cells for fertilization and early embryogenesis**.
- 4) Similar research involving other mammalian species, including those important to agriculture, is also being conducted. The results from all lines of research will inform one another.

Potential Social Implications

- 1) PSC-derived gamete research could lead to the development of additional options for assisted human reproduction.
- 2) Advances in PSC-derived gamete research are likely to result in applications directed towards ends for which there will be substantial societal agreement. For example, PSC-derived gamete research will generate knowledge that should facilitate the development of new ways to prevent and treat infertility, genetic disease, and some cancers, including germ cell cancers.
- 3) Until the validity and reliability of techniques for deriving gametes from PSCs have been established, the capacity for fertilization will need to be tested, and resulting embryos grown to at least the blastocyst stage (made up of about 100 cells), which is the earliest at which reasonable estimates about functionality can be determined. This work will involve the deliberate generation of embryos in vitro solely for research purposes.
- 4) Currently, the availability of eggs and embryos for research and assisted reproduction requires eggs from women, with attendant burdens and risks for women from whom eggs are obtained. Once PSC-derived gamete research produces gametes capable of fertilization, the need to obtain eggs from women could be reduced. Additionally, greater numbers of embryos may be produced for research and potentially for human reproduction.
- 5) Advances in PSC-derived gamete research may facilitate applications directed towards ends that will be socially controversial, such as germ line genetic modification for the correction of disease mutations, introduction of disease resistance, other forms of biological enhancement, increased possibilities for embryo selection or the birth of genetic offspring of same-sex parents (but, see State of the Science, 2a and 2b).
- 6) Many of the scientific advances anticipated from PSC-derived gametes will be gained not by research on embryos, but by research solely on gametes developing in vitro; for example, the role of specific genes in germ cell development, the origins of chromosome abnormalities, and the development of fertility treatment for people with gonadal injury or disease.

** Throughout this document, all references to research on human embryos assume compliance with existing guidelines, for example, the prohibition on growing human embryos in vitro beyond 14 days.

Recommendations

- 1) PSC-derived gamete research must conform to ethical principles and norms of practice and comply with existing oversight mechanisms. As this research progresses, researchers, research institutions and funders must consider whether these mechanisms remain sufficiently robust to ensure the highest standards for ethical integrity. Specific attention should be paid to protecting the rights and interests of the human sources of cells from which gametes are obtained, including a requirement to obtain specific consent before any PSC-derived gametes are used for reproduction.
- 2) Journal editors should also support and promote high standards for ethical integrity in PSC-derived gamete research. For example, on request from editors, authors should provide assurance of adherence to local policy, including appropriate approval by ethics review committees.
- 3) Oversight structures must be in place prior to any attempts to use PSC-derived gametes in human reproduction. Oversight should include the development of appropriate standards for preclinical data. Initial attempts should be conducted only in the context of research. In addition, the health and well-being of women participants, their developing fetuses, and pregnancy outcomes should be monitored carefully. The health and well-being of children born should also be monitored in long-term follow-up studies.
- 4) In considering policies governing the regulation of applications, a distinction should be made between objections that are based on technical or safety concerns and objections that reflect other moral considerations. Technical and safety concerns have the potential to be resolved over time by additional scientific research and advances, while other moral considerations may continue to be the focus of public debate.
- 5) Public policies carry great power to facilitate or restrict scientific exploration in the area of PSC-derived gamete research. Policy makers should be circumspect when regulating science. When enacted, policies governing science nationally and internationally ought to be flexible, so as to accommodate the rapidity of scientific advance as well as changes of social values.
- 6) Societies have the authority to regulate science, and scientists have a responsibility to obey the law. However:
 - a) Policy makers should refrain from interfering with scientific inquiry unless there is substantial justification for doing so that reaches beyond disagreements based solely on divergent moral convictions. Any interference with scientific inquiry should be derived from reasonable concerns about demonstrable risks of harm to persons, societal institutions, or society as a whole.
 - b) In the case of PSC-derived gametes, as with all science, it is important to target policy specifically to those dimensions of the research or its applications that have proved to be unacceptable, and that these policies be proportionate to the magnitude of what is morally at stake.
- 7) We encourage informed public debate amongst scientists, policy makers and the public to ensure that scientific data and societal values are adequately and accurately represented in the development of policies for controversial applications of PSC-derived gametes. ***

*** This consensus statement is being issued in memory of Anne McLaren, who was, among many other things, a member of the Hinxtion Group. She is missed.

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