ELSA-RESEARCH CONSORTIUM

„Human artificial gametes: framing the normative issues of using artificial human gametes in research, cell-based therapy and assisted reproductive technologies“

Principal Investigators: Thomas Heinemann / Hans-Georg Dederer / Tobias Cantz – Research Fellows: Barbara Advena-Regnery / Franziska Enghofer / Susan Sgodda

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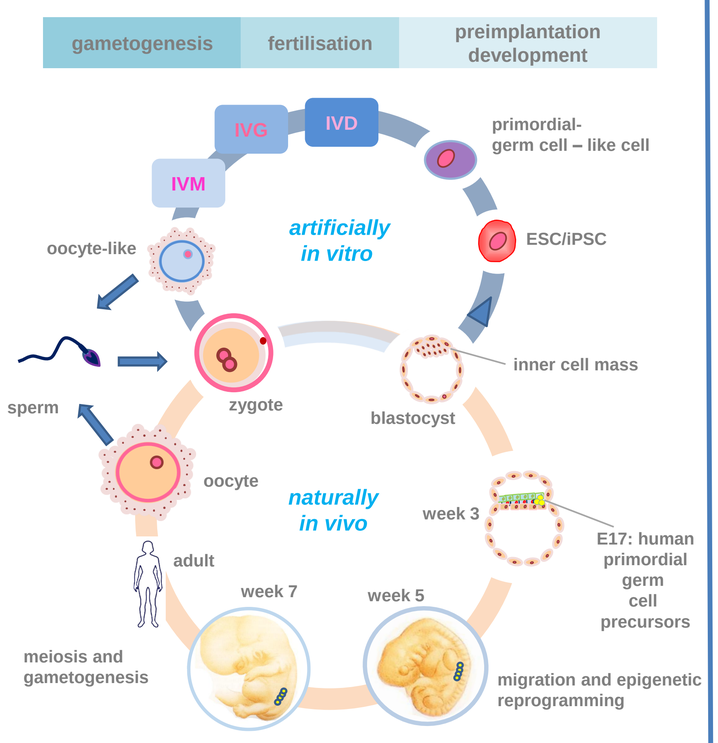
Worldwide around 16 % of all couples are confronted to the diagnosis sterility (van den Akker 2012) and in many cases no medical causation can be identified. In the last ten years basic research on the generation of artificial gametes has been progressed with the complete in vitro generation of artificial gametes from embryonic or induced pluripotent stem cells in the species mouse. To answer the question if the findings of mouse research can be applied to human beings and which ethical and legal consequences would arise, we will, within the framework of the research group “HumArGam”, evaluate the interdisciplinary aspects of human artificial gametes in the contexts of basic research, therapy and assisted reproductive technologies. Considering the field of basic research, it can be assumed that the use of artificial gametes will be evaluating the processes of gametogenesis, fertilisation and preimplantation development in biomedical aspects. Above all the processes of human in vitro gametogenesis, in particular in vitro differentiation (IVD), in vitro growth (IVG) and in vitro maturation (IVM), could be characterized more precisely. Subsequent experiments of fertilization and preimplantation development could demonstrate the functionality of in vitro derived artificial gametes. Based on the results of basic research, the quality management of artificial gametes in the field of clinical use could be improved. Well-established methods restoring fertility in the context of reproductive medicine are cryoconservation of sperm and ovarian tissue which could be harvested prior to cancer treatment or immunosuppressiva therapy and brought back into patient via application in ICSI or autologous transplantation. Conceivable application of experimental mouse system include direct in vitro gametogenesis, autologous transplantation of naturally obtained spermatogonial stem cells (SSCs) or SSCs generated from induced pluripotent stem cells (iPSs) into the physiological niche with the aim of colonization and differentiation to fully functional sperm. Ramathal et al. 2014 showed the direct transplantation of iPS-cells into the physiological niche (seminiferous tubuli) and the following differentiation into sperm. The proof of functionality is still in progress. Whenever transmitting translating techniques from research to application, one has to consider a risk-benefit assessment for incidence of meiotic errors, aberrations, de novo mutation rate and rate of tumorigenesis. Considering the use of artificial gametes in ART, new technologies could enable genetic parenthood to couples which are impaired in fertility by nature for example single parents, same sex couples or groups (multiplex parenting).

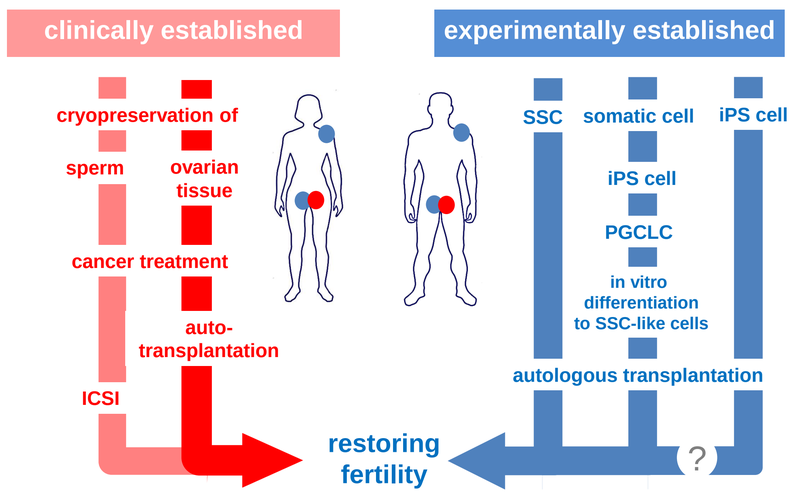
LABORATORY RESEARCH

Studies on human artificial gametes



THERAPY

Artifical germ cell progenitor cells as celluar transplant für treatment of infertility

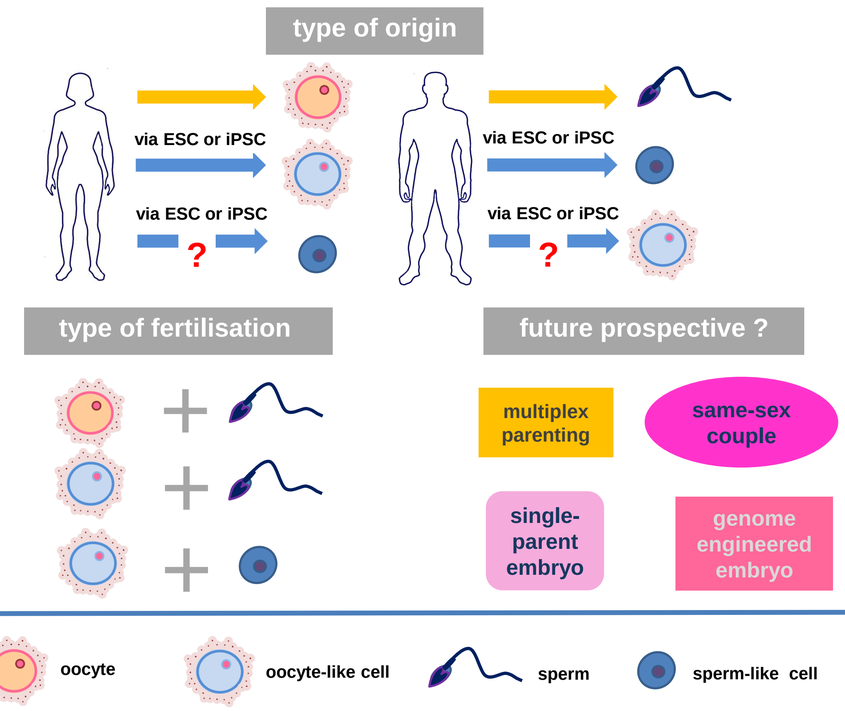


risk- and safety-assessment

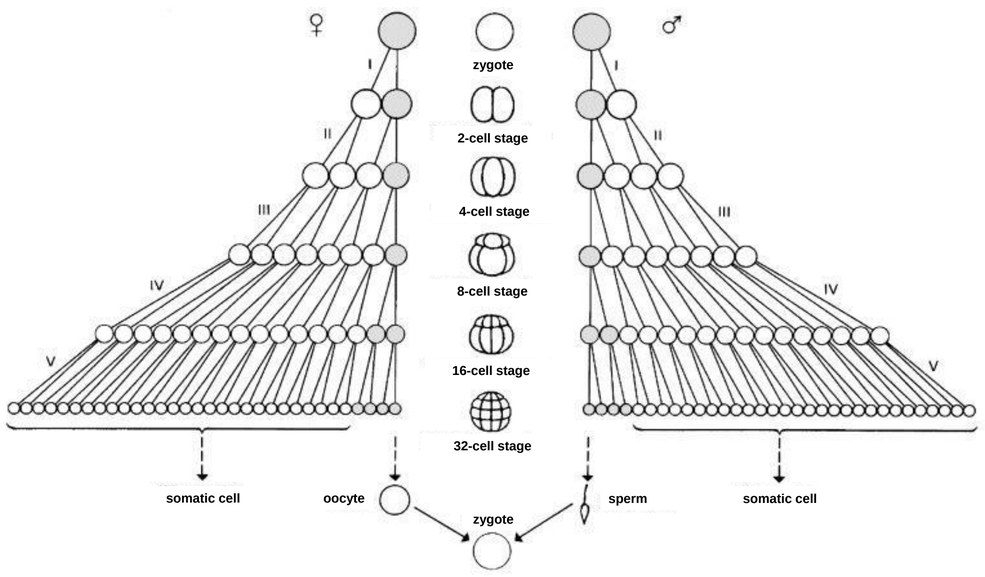
- meiotic errors
- accidental mutations
- stable function in the physiological niche (cancer-free)

ASSISTED REPRODUCTIVE TECHNOLOGY (ART)

Use of artifical gametes in assisted reproductive technologies



oocyte · oocyte-like cell · sperm · sperm-like cell



GENETIC LINK BUT INTERRUPTION OF THE GERM LINE: CONSEQUENCES FOR IDENTITY AND CONTINUITY OF HUMAN DEVELOPMENT

Right of self-determination
Personal rights
Freedom of reproduction
Freedom of scientific research
Informed consent

- **Understanding of the concepts of family, motherhood, fatherhood and genetic relationship**
- **Social and cultural understanding of origin**
- **Responsibility**
- **Child‘s well-being**

- **Concept of nature / good**
- **Ontological status**
- **Relevance of biological determination for the ethics**
- **Relation of biological dates and ethical, social and cultural understandings**
- **Naturalistic fallacy**

In human reproduction potentially immortal germ line cells transmit different properties from generation to generation in an uninterrupted process. Biological and genetic parents are those of whom the germ cells derive from. However, human artificial gametes are produced from somatic cells. The continuity of the germ line is interrupted. Nevertheless, the genetic relationship between parents and children continues. From an ethical perspective, it is not only the single individual with its rights to be considered, but its role within the succession of generations as well.

Legal classification of human artificial gametes

Hypothesis: *in vitro*-generation of *functional* human gametes is possible

TPA

TPA is applicable to tissue (Sec. 1(2), 1a(4) TPA)
↓
Artificial gametes = single human cell
↓
Applicability of the TPA-regulations

§ 1a(4) TPA:
“Tissue are all elements of the human body made up of cells […], *including single human cells”*

TPA-TissR

- Applicable to tissue according to Sec. 1a(4) TPG, *i.e.* also to artificial gametes
- Sec. 6 TPA-TissR (special provision for gametes) is applicable to artificial gametes as well

EPA

Germ cells according to Sec. 5(2) EPA?
↓
Legal interpretation of Sec. 5(2) EPA taking into account wording, context, purpose and the historical circumstances
↓
Artificial gametes = germ cells according to Sec. 5(2) EPA

Germ line cells according to Sec. 5(1), 8(3) EPA?

Sec. 8(3) EPA:
Germ line cells are all cells that “lead from the fertilised egg cell in one cell line to the egg and sperm cells of the resultant human being [..].”

- Do artificial germ cells lead from the fertilised egg cell *in one cell line* to the gametes of the resultant human being?
- In accordance with the „natural“ germ line or ideas of „naturalness“ of the germ line (-)
- However, also “artificial“ germ lines could be covered by the term “germ line“ used in the EPA?
- No, otherwise violation of the prohibition of analogy in criminal law (Art. 103(2) BL)

↓
Artificial gametes ≠ germ line cells according to Sec. 5(1), 8(3) EPA

MPA

- Artificial, not completely matured gametes = tissue engineered products **= ATMP** according to Sec. 4(9) MPA, Art. 2(1)(a) ATMP-Regulation
- Artificial, completely matured gametes **≠ ATMP** because Sec. 4(30)(2) MPA is also applicable to artificial gametes

Sec. 4(30)(2) MPA:
„Human sperm or egg cells (germ cells) […] are *neither medicinal products* nor tissue preparations.“

PA

Artificial gametes as patentable inventions according to Sec. 1a(2) PA, Art. 5(2) Dir 98/44/EC, Sec. 2(1), (2)(1)(2) PA, Art. 6(1), (2)(b) Dir 98/44/EC?
↓
- Are there “processes for modifying the germ line genetic identity of human beings” involved?
- Is the commercial exploitation contrary to “ordre public” or morality?
- Applicability of Sec. 1a(1) PA, Art. 5(1) Dir 98/44/EC

Current legality of the different scenarios

Research

concerning the gametes themselves — IVF-experiments

(+)

- Sec. 5(1) EPA (-), because artificial gametes ≠ germ line cells according to Sec. 5(1), 8(3) EPA
- Sec. 5(2) EPA (-), there is no fertilisation

(-)

- Sec. 5(1) EPA (-)
- Sec. 5(2) EPA? Is the genome of the artificial gametes “artificially altered”?
- Sec. 1(1)(2), 2(1) EPA (+), because artificial gametes = germ cells (egg and sperm) under the EPA = embryo according to Sec. 8(1) EPA after fertilisation

Therapy

provisions to be respected

Data protection law
Regulations of the TPA-TissR
Provisions of the TPA, esp. those covering cell-biopsy, Sec. 8 *et seqq.* TPA
Medicinal products-regulations, esp. for cell-biopsy, reprogramming/ differentiation and marketing authorisation

?

- Sec. 5(1) EPA (-), because artificial gametes ≠ germ line cells in accordance with Sec. 5(1), 8(3) EPA
- Sec. 5(2) EPA? Is the genome of the artificial gametes “artificially altered”? Is the genome of a natural gamete “artificially altered” if it is fertilised by/ fertilises an artificial germ cell?

ART

new ways of reproduction — general legality

Adequacy of the family law, esp. the law of descent?
Sec. 1591 *et seq.* CC?
Homosexuals‘ parenthood
Sec. 1(1)(7) EPA?
Solo-parenthood
Sec. 6 EPA?
Sec. 173 Criminal Code?
Motherhood of postmenopausal women
Parenthood of deceased persons
Sec. 4(1)(3) EPA?

?

Applicability of the therapy-requirements (except: medicinal products-regulations at the time of the complete maturation of the gametes)

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TP 1 (Ethik) – Prof. Dr. med. Dr. phil. Thomas Heinemann, PTHV
TP 2 (Recht) – Prof. Dr. jur. Hans-Georg Dederer, Universität Passau
TP 3 (Naturwissenschaft) – Prof. Dr. med. Tobias Cantz. Medizinische Hochschule Hannover

PHILOSOPHISCH-THEOLOGISCHE HOCHSCHULE VALLENDAR
Kirchlich und staatlich anerkannte Wissenschaftliche Hochschule in freier Trägerschaft

Medizinische Hochschule Hannover

UNIVERSITÄT PASSAU

GEFÖRDERT VOM
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