



INFORMATION ON THE USE OF GAMETES AND/OR EMBRYOS WHICH CANNOT BE USED FOR YOURSELF FOR TRAINING AND SCIENTIFIC RESEARCH

Dear Madam, Partner,

This information is intended to clarify which scientific research may be carried out with gametes (sperm cells or egg cells) and embryos which **cannot** be used for yourself. This information should enable you to decide whether you consent to the use of these gametes and embryos for scientific research, carried out in collaboration with the Leuven University Fertility Centre (LUFC). In addition, real gametes and embryos are needed to train laboratory staff to perform difficult techniques to a high standard. This information should enable you to decide whether you consent to the use of these gametes and embryos for the training of laboratory staff.

Which gametes and embryos?

During the course of your treatment, gametes and/or embryos will be created or will form. These gametes and/or embryos will be used in the first place for your fertility treatment. However, there are numerous situations and/or reasons some gametes and/or embryos are no longer eligible for use in your treatment. Examples include:

- **Gametes:**

Sperm cells which are no longer needed for diagnostic or therapeutic purposes; egg cells which are not in a suitable stage of development and therefore not suitable for IVF and/or ICSI; egg cells which cannot be fertilised because there are no sperm cells

- **Embryos:**

Embryos of insufficient quality for embryo transfer or freezing; embryos which are found to be abnormal after preimplantation genetic testing and therefore cannot be implanted in the uterus; embryos which have not survived the freezing and thawing process; unfertilised or abnormally fertilised egg cells which cannot be implanted in the uterus.

Your decision regarding the donation of gametes and/or embryos for scientific research and/or training is on a **voluntary basis** and has no influence on your further treatment. It neither increases nor reduces your chances of success.

If you do not consent to the use of these gametes and embryos for scientific research and/or training, they will be destroyed immediately. Please note that the residual biological material produced as part of your fertility treatment (residual material does not include egg cells, sperm cells or embryos) may be stored in the UZ Leuven biobank for use in scientific research. If you object to this, you should notify LUFC by registered letter.

The following points are important:

- The confidentiality of your names and other personal data is strictly guaranteed.
- Your data will be processed in accordance with the European General Data Protection Regulation (GDPR). The confidentiality of the names and other personal data of you and your partner is strictly guaranteed. The research material will be encoded using 'pseudo-anonymisation', which means that your clinical data will also remain confidential.

The research described in the appendix has been commissioned by UZ Leuven and/or KU Leuven, and they are therefore responsible for the processing of data. If you have any questions about how we use your data or about exercising your right to inspect, correct or cancel any further processing, you can contact your doctor/researcher at any time at the following address: LUFC, UZ Leuven, Herestraat 49, 3000 Leuven, Belgium. If you subsequently have any further issues or wish to lodge a complaint, you can contact UZ Leuven at dpo@uzleuven.be (UZ Leuven studies) or KU Leuven at privacy@kuleuven.be (KU Leuven studies).

Finally, you also have the right to submit a complaint on the way your data has been treated to the Belgian regulator responsible for enforcing the data protection legislation: Data Protection



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Authority/Gegevensbeschermingsautoriteit (GBA), Drukpersstraat 35, 1000 Brussels, Belgium. Tel. +32 2 274 48 00. E-mail: contact@apd-gba.be; Website: www.gegevensbeschermingsautoriteit.be

- Every research protocol in which the gametes and embryos may be used has received prior approval from the Ethics Committee Research of UZ Leuven and KU Leuven and/or the Ethics Committee of the Faculty of Medicine (KU Leuven) and from the Federal Commission for Medical and Scientific Research on Embryos in vitro.
- The scientific research may be carried out in collaboration with commercial partners, but only on condition that the research has been approved as stipulated above.
- The scientific research will be carried out in accordance with the Law of 11 May 2003 on in vitro research on embryos
- The scientific research may concern the following topics, among others:
 - development of new procedures to improve the IVF/ICSI, CRYO and PGT (preimplantation genetic testing) programme;
 - stem cell research;
 - research on analysis techniques for unfertilised egg cells or embryos during the first 14 days of the preimplantation period;
 - research to understand the biology of gametes and embryonic development during the first 14 days of the preimplantation period.
- All data resulting from the analysis of study samples will be encoded and stored in a secure environment, with no public access, at UZ/KU Leuven and/or at collaborating partners, with strict procedures to protect your privacy. The code will remain in the sole possession of LUFC and UZ Leuven before and after publication of the study. On publication of the study results, the encoded data will be placed in a public database with controlled access, which means that a third party can only access the data with the approval of the KU Leuven/UZ Leuven Data Access Committee (DAC). The DAC will be expanded to include the principal investigators from the studies. The transfer of the data will be covered by a Data Access Agreement (DAA), which determines the conditions for use of the data.
- Scientific research sometimes involves genetic analysis of the studied gametes and/or embryos. The DNA sequences which may subsequently be obtained as part of the research will be published in a secure (non-public) database (such as the European Genome Archive, dbGaP, etc.), which can only be consulted by approved, qualified researchers after the consent of the original authors. The DNA sequences are encoded in order to preserve confidentiality. Nonetheless, whilst unlikely, it is theoretically possible that another researcher could trace your identity on the basis of the research results. For this reason, you may indicate in the agreement on training and scientific research that you do not consent to the genetic analysis of the embryos and the associated publication of the (encoded) research data.
- In most cases, the selected research will be performed in the institution to which you donate the gametes and/or embryos for scientific research, namely LUFC. However, scientific research is increasingly carried out in collaboration with other Belgian university institutes, private sector companies or foreign research institutes. In such cases, it is sometimes necessary to share certain personal data with external researchers; however, LUFC will never reveal your name or identity. Where scientific research is carried out in collaboration with other institutes or companies, it must still be approved by the ethics committee of the institute to which the embryos are donated and by the Federal Commission for Medical and Scientific Research on Embryos in vitro. In the agreement you will be able to decide whether the gametes and/or embryos you donate for scientific research may also be used in research that is carried out in collaboration with other Belgian research institutes, foreign research institutes and private-sector companies.
- If disease-related mutations or chromosomal deviations are found by chance, this information will not be passed either to you or your attending physician.
- Participation in this research carries no financial benefits or additional costs.
- You give your consent to any requests for patents for inventions which may ensue from the scientific research to which you have given your consent, and you consciously waive any claim to payment or compensation.



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- Under the Law of 11 May 2003 on research on embryos in vitro, it is prohibited:
 - ◆ to implant human embryos into animals or chimeras to create hybrid beings;
 - ◆ to implant embryos on which research has been carried out into humans, except where the research has been carried out with a therapeutic purpose for the embryo itself or as part of an observation method which does not harm the integrity of the embryo;
 - ◆ to use embryos, gametes and embryonic stem cells for commercial purposes;
 - ◆ to carry out research or treatments aimed at the selection or improvement of non-pathological genetic characteristics of the human species;
 - ◆ to carry out research or treatments aimed at gender selection, except for the prevention of gender-specific diseases;
 - ◆ to carry out reproductive human cloning;
 - ◆ to carry out research on embryos after the first fourteen days of development, not including the period of freezing.

In the appendix you will find a list of current projects being carried out at LUFC involving scientific research on gametes and/or embryos which cannot be used for yourself. If you would like additional information, please contact the laboratory at LUFC, Herestraat 49, 3000 Leuven, Belgium (tel. +32 16 34 08 12 or e-mail: fertiliteitscentrum@uzleuven.be).

You have the **right to refuse** to donate gametes and/or embryos for scientific research and/or training of laboratory staff. In that case, you should indicate in the agreement that you **do not consent** to this.


If you DO consent to the use of your gametes and/or embryos that cannot be used for yourself for the purpose of scientific research and/or training of laboratory staff, you should also indicate this in the agreement. You can specify your consent for scientific research and indicate the research projects for which your gametes and/or embryos may not be used. You can also choose whether to give consent for the performance of a genetic analysis and the sharing of genetic information with other researchers. Finally, you should decide whether you will permit collaboration with other Belgian university institutes, private-sector companies or foreign research institutes. If you consent to this, you must also consent to certain personal data being shared with other researchers.

It is possible to **withdraw your consent** until your gametes and/or embryos are used for training and/or scientific research. Withdrawal of your consent is valid at the request of one of you. If one or both of you wish to withdraw your consent, you should communicate this in writing to Leuven University Fertility Centre, Contract Administration/Contractenadministratie, UZ Leuven, Herestraat 49, 3000 Leuven, Belgium. On withdrawal of the consent, the gametes/embryos will be destroyed



AGREEMENT ON TRAINING AND SCIENTIFIC RESEARCH USING GAMETES AND/OR EMBRYOS WHICH CANNOT BE USED FOR YOURSELF

The Leuven University Fertility Centre,
UZ Leuven,
represented by
Professor Karen Peeraer

 and Ms
born on / /
and partner
born on / /
residing at
.....

Hereinafter referred to as LUFC, for the first part,
for the second part,

Hereinafter referred to as the prospective parents,

Hereby declare that they have agreed as follows:

- The prospective parents hereby declare that they have received, read and understood the 'Information on the use of gametes and/or embryos that cannot be used for yourself for training and/or scientific research' together with the appendices, and that this information is sufficient to enable them to make an informed choice to donate their gametes and/or embryos which cannot be used for themselves for the purpose of scientific research and/or training. The donation of these gametes and/or embryos is entirely voluntary. The consent can be withdrawn up to the moment of use. If one or both of you wish to withdraw consent, you should communicate this in writing to LUFC, Contract Administration/Contractenadministratie, UZ Leuven, Herestraat 49, 3000 Leuven, Belgium. **On withdrawal of the consent, the gametes/embryos will be destroyed.**
- If the prospective parents consent to use for scientific research, they are free to decide for which type of research the donated gametes and/or embryos may be used. If they may be used for several or all research projects, LUFC will be free to decide for which research the donated gametes and/or embryos will be used in order to make optimum use of this material.

Give your decision by checking a box .

Based on the information received:


- the prospective parents consent** to the use of gametes and/or embryos which cannot be used for themselves*
- for training of laboratory staff
 - for scientific research
 - for all projects described in the appendix
 - but NOT** for the projects with numbers (enter as applicable):
S.....; S.....; S.....; S.....
- the prospective parents do NOT consent** to the use of gametes and/or embryos which cannot be used for themselves

**If the gametes/embryos are not suitable for scientific research, or if the number of gametes/embryos available for research exceeds the required number, the gametes/embryos will be destroyed.*

The prospective parents have understood from the 'Information on the use of gametes and embryos which cannot be used for yourself for training and scientific research' that scientific research sometimes involves genetic analysis of the studied gametes and/or embryos. The data obtained in this way as part of the research will be published in genetic (non-public) databases (such as European Genome Archive, dbGaP, etc.), which can only be consulted by approved, qualified researchers after the consent of the original authors.




AGREEMENT ON TRAINING AND SCIENTIFIC RESEARCH USING GAMETES AND/OR EMBRYOS WHICH CANNOT BE USED FOR YOURSELF

 The prospective parents

- give consent for genetic analysis and the sharing of genetic information via databases
- do not give consent for genetic analysis and the sharing of genetic information via databases


In most cases, the selected research will be performed in the institution to which you donate the gametes and/or embryos for scientific research. However, scientific research is increasingly carried out in collaboration with other Belgian university institutes, private-sector companies or foreign research institutes. In such cases, it is sometimes necessary to share certain personal data with external researchers; however, LU FC will never reveal your name or identity. In these cases, the research must still be approved by the ethics committee of the institute to which the embryos are donated and by the Federal Commission for Medical and Scientific Research on Embryos in vitro.

 The prospective parents declare that the gametes and/or embryos they are donating for scientific research may also be used in research that is carried out in collaboration with (several options are possible)


- a research institute within Europe
- a research institute outside Europe
- a private-sector company


 The prospective parents

- give consent for their personal data to be shared with other researchers
- do not give consent for their personal data to be shared with other researchers

Done in duplicate in Leuven on /...../....., with one original for LUFC and the other for the prospective parents.

Professor Karen Peeraer
Manager of LUFC tissue bank

 read and approved
signature of prospective mother

 read and approved
signature of partner

Please complete and sign and date one copy of this agreement and return it to LUFC, Contract Administration/Contractenadministratie, UZ Leuven, Herestraat 49, 3000 Leuven, Belgium, or contractenLUFC@uzleuven.be



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APPENDIX: CURRENT RESEARCH PROJECTS AT LUFUC

S Project number	Project title
	Laboratory techniques: for training of laboratory staff
S57132	Methylome, genome and transcriptome characterisation of human egg cells
S58250	Genome, epigenome and transcriptome analysis of in vitro fertilised preimplantation embryos to gain an understanding of (epi)genomic dynamics and the impact on early development.
S59351	Analysis of the mechanisms underlying chromosomal instability during early embryogenesis.
S62765	Definition of ion channels as crucial components during embryo implantation.



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APPENDIX: CURRENT RESEARCH PROJECTS AT LUFC

Methylome, genome and transcriptome characterisation of human egg cells S57132

Expected completion date: August 2021.

Doctor/researcher: Professor Karen Peeraer (UZ Leuven).

Coordinating lead researcher: Professor Thierry Voet (KU Leuven).

Collaboration with the Babraham Institute (Babraham, Cambridge, United Kingdom) and the Wellcome Trust Sanger Institute (Hinxton, Cambridge, United Kingdom).

When an egg cell is fertilised by a sperm cell, the first cell in the development of an embryo and an individual is created. This first cell will multiply and ultimately produce all the cells that make up the human body. Because all cells in our body originate from that first cell, they will all contain a copy of the DNA of that first cell. The DNA present in a cell is also referred to as the **genome**, and carries the information that is needed for the development and functioning of the cell.

Our bodies contain many different types of cells (e.g. muscle cells, brain cells, etc.). Each cell type needs only part of the information present in the DNA in order to function correctly. The specific parts of the DNA used by each cell type are determined by the **epigenome**. This consists of markers which are attached to the DNA and which regulate the accessibility of the information contained in the DNA. In other words, these markers allow information from the DNA to be used by a cell or block its use by the cell. During the formation of the egg cell and the sperm cell, and also during the further development of the embryo and the foetus, these markers have to be modified and applied. The **methylome** referred to in the title of this project is a specific collection of markers in the epigenome.

In order to be able to use the information in the DNA, that information must also be copied in the RNA. The RNA present in the cell is also called the **transcriptome**.

The purpose of this project is to use new technology to study the genome, methylome and transcriptome of individual human egg cells in order to characterise possible differences between egg cells and to compare their properties with those of mammals. This is important to understand the specific biology of the human egg cell. Mistakes in the genome, methylome or transcriptome of an egg cell can potentially lead to development disorders in the embryo and, later, the child, as well as to miscarriage or congenital disorders. This research will increase the understanding of such mistakes, and will also prove its value in the future in studying the potential effects of new artificial reproductive techniques on the biology of the human egg cell.

The research methods require genome-wide analysis of genetic material (DNA/RNA) of the donated egg cells and stored DNA of the prospective mother.

This study was approved by the local Ethics Committee Research on 21 April 2016, and has also been approved by the Federal Commission (ADV_063_UZ-KU Leuven).



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Genome, epigenome and transcriptome analysis of in vitro fertilised preimplantation embryos to provide insight in (epi)genomic dynamics and the impact on early development. S58250

Expected completion date: August 2021.

Doctor/researcher: Professor Karen Peeraer (UZ Leuven).

Coordinating lead researcher: Professor Thierry Voet (KU Leuven).

Collaboration with the Wellcome Trust Sanger Institute (Hinxton, Cambridge, United Kingdom) and the Babraham Institute (Babraham, Cambridge, United Kingdom).

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The purpose of this project is to understand how the genome, epigenome and transcriptome in cells evolve and potentially acquire errors during the development of the embryo. This is necessary in order to understand the biology of normal embryonic development, but also to discover and understand the origin of developmental disorders, congenital disorders and miscarriages. These errors in development can be the result of mistakes in the genome, epigenome and transcriptome which occur during the development of the embryo.

The research methods require genome-wide analysis of genetic material (DNA/RNA) which is obtained from the donated gametes and/or embryos, blood and genetic material of the prospective parents and, if available, family members.

This study was approved by the local Medical Ethics Committee on 19 May 2016, and has also been approved by the Federal Commission (ADV_062_UZ-KU Leuven).



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APPENDIX: CURRENT RESEARCH PROJECTS AT LUFc

Analysis of the mechanisms of chromosomal instability during early embryogenesis. S59351

Expected completion date: September 2021.

Doctor/researcher: Professor Karen Peeraer (UZ Leuven).

Coordinating lead researcher: Professor Joris Vermeesch (UZ Leuven).

The genetic material (DNA) in our cells is structured in the form of chromosomes. Each human cell contains 23 pairs of chromosomes (46 chromosomes per cell). During fertilisation, the 23 maternal and 23 paternal chromosomes come together to form the zygote, which goes on to develop into an embryo through multiple cell divisions. During each cell division, the genetic material of the original cell is doubled and proportionally distributed between the two daughter cells.

Research at KU Leuven has shown that the first cell divisions during the development of a human embryo after in vitro fertilisation (IVF) are susceptible to chromosomal instability, a phenomenon which causes a deviating number of chromosomes (aneuploidy) and a deviating structure of the chromosomes in the embryonic cells. The presence of these abnormal cells in preimplantation embryos is linked to a low chance of success for IVF and pregnancy.

We have recently developed a new method, which detects chromosomal deviations accurately in the cells of a preimplantation embryo. This method has been validated and implemented in routine preimplantation genetic diagnosis (PGD). Using this technique in studies on cattle has enabled us to discover a new and previously unknown type of cell division. In contrast to normal cell division, in which genetic material from the mother and father comes together, these embryos contain abnormal cells with only maternal and/or only paternal material. This phenomenon could be the cause of phantom pregnancies and other genetic disorders in embryos and developing foetuses.

In this study we will collect both unfertilised and abnormally fertilised egg cells as well as normally fertilised embryos which are not suitable for embryo transfer or freezing, for research on the underlying mechanisms of this chromosomal instability.

A better understanding of the causes of chromosomal instability in human preimplantation embryos and of the developmental capacity of these embryos could lead to strategies for detecting and preventing these deviations in human embryos in both fertile couples and couples with fertility problems.

The research method can entail genome-wide analysis of the genetic material (DNA/RNA) which is obtained from the donated gametes and/or embryos, blood and genetic material of the prospective parents and, if available, family members.

This study was approved by the local Medical Ethics Committee on 26 August 2016, and has also been approved by the Federal Commission (ADV_068_UZ-KU Leuven).



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APPENDIX: CURRENT RESEARCH PROJECTS AT LUFc

Definition of ion channels as crucial components during embryo implantation. S62765

Expected completion date: June 2023.

Doctor/researcher: Professor Karen Peeraer (UZ Leuven).

Coordinating lead researcher: Professor Joris Vriens (KU Leuven).

Infertility is described as the inability to become pregnant after at least 12 months of unprotected sexual relations; it affects more than 10% of the general population. In many cases, these couples turn to modern reproductive techniques such as in vitro fertilisation (IVF) to overcome their problems, but here, too, the chances of success are low. One of the chief causes of the low success rate during IVF procedures is the failure of the implantation of the embryo in the uterus.

Successful embryo implantation depends on three key factors: a competent embryo of good quality; a receptive uterus wall; and optimum communication between the embryo and the uterus wall. This latter point means that signals given by the embryo during its development must be received by the cells located in the uterine wall. Those cells then activate certain mechanisms which prepare the uterus for the attachment and implantation of the embryo.

Sadly, little is known about which signals are crucial for successful implantation of the embryo and how these signals can be received by the cells in the uterine wall. These signals can moreover be either chemical (due to certain molecules being released by the embryo) or physical (caused by contact between the embryo and the uterus wall). An ion channel is a protein contained in the cell membrane which transports ions in and out of the cell. Together with receptors (proteins which are located in membranes and to which a molecule can attach itself in order to elicit a response), they are ideal candidates for establishing this communication.

The purpose of this study is to examine what role certain ion channels and/or receptors play during the attachment and implantation of the embryo. The experiments will provide us with a better insight into the various mechanisms that are needed to guarantee successful implantation. This study will also enable us to investigate whether certain influences exerted on ion channels/receptors (e.g. strengthening or weakening the function) have an effect on the attachment of the embryo. This could ultimately lead to an improvement in present IVF techniques.

These research methods require human day-five embryos which cannot be used by the patient themselves and which have been donated for scientific research.

This study was approved by the local Ethics Committee Research on 20 August 2019 and by the Federal Commission on 21 October 2019, ADV_081_UZ-KULeuven).