Clinical Research Consent Summary
Discard and/or Excess Materials from IVF

TITLE: Evaluation of in vitro gene correction techniques in germ cells

PRINCIPAL INVESTIGATOR: Shoukhrat Mitalipov, Ph.D. (503) 418-0196

You are being asked to join a research study. You do not have to join the study. Even if you decide to join now, you can change your mind later.

1. The purpose of this study is to learn how well gene correction techniques work and what problems it might cause in human eggs & sperm. In vitro experiments (experiments performed outside of the cells normal environment) will be conducted to test these techniques. Inherited genetic diseases are caused by mutations in genes found in germ cells which may be passed from parent to child. We will try to correct these mutations by conducting in vitro experiments in fertilized eggs and make embryonic stem cell lines to study the outcomes. A stem cell line is a cell line with the potential to grow into many different types of cells that may allow scientists to develop personalized medical therapies.

2. This project is a collaboration between the Knight Cardiovascular Institute and the Center for Embryonic Cell and Gene Therapy. This study is being funded by Oregon Health & Science University.

3. We do not know if the techniques we are testing will work. This science will not result in any pregnancies or births. The embryos and stem cell lines will only be used for research.

4. If you choose to participate, we will collect leftover materials from your scheduled IVF procedures; which may include immature eggs, unfertilized eggs, discard/excess embryos. These are materials would be otherwise thrown away and not needed for your IVF treatment. We may also ask you to have one extra blood draw specific to this research.

5. There are risks involved in participating in the study.

6. Samples collected during the study will be used for genetic research.

7. All samples and embryonic stem cell lines will be saved for future research purposes only.
Clinical Research Consent and Authorization Form
Discard and/or Excess Materials from IVF

TITLE: Evaluation of in vitro gene correction techniques in germ cells

PRINCIPAL INVESTIGATOR: Shoukhrat Mitalipov, Ph.D. (503) 418-0196

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FUNDED BY: Oregon Health & Science University (OHSU)

PURPOSE:
You have been invited to participate in this research project because you:
- Are a woman of at least 21 years of age
- Have already chosen to undergo treatment for infertility
- Are interested in donating excess or discarded oocytes (egg cells), excess or discarded embryos, unfertilized eggs, and/or cumulus cells (cells that surround your eggs) for research and a blood sample for research

The purpose of this study is to test new techniques for correcting a gene mutation in egg & sperm cells in a laboratory experiment. We need to see if this technique works to correct the gene mutation and test what other problems this technique might cause. Genetic disease is the result of changes or mutations in your DNA. When these changes occur in the letters that make up a gene (DNA sequence), a severe illness can occur. These changes may be passed from parent to child during human reproduction. Genes are the units of DNA—the chemical structure carrying your genetic information—that determine many human characteristics that make us who we are. A copy of each parent’s DNA is passed on to the child when the egg

For Review ONLY
(female reproductive cell) and sperm (male reproductive cell) combine to form the embryo (a collection of cells developed from a fertilized egg).

Germline gene editing is a controversial topic currently being discussed by a range of stakeholders; including scientists, national leaders, ethicists, academics, and many more individuals. A consensus report was published upon the conclusion of the International Summit on Human Gene Editing which supports basic science experiments to be conducted in order to provide sufficient evidence regarding the safety and efficacy of gene editing tools. The knowledge gained from basic research studies, like this one, will add scientific data to the continued discussion of whether gene editing tools should be used in a clinical setting.

During this study, your donated eggs/embryos, cumulus cells (the cells that surround your eggs) and blood cells will undergo genetic testing. These tests will help researchers better understand human reproduction and development as it relates to embryonic stem cell research. Researchers will try to correct the faulty gene mutations in reproductive cells, including eggs, sperm, or early embryos provided by people carrying genetic diseases. This involves putting genes, gene products, (a biochemical material, either proteins or RNA, which is made when a gene is turned on) or chemicals into human reproductive cells. The researchers will then create human embryonic stem cells from the proposed corrected reproductive cells. An embryonic stem cell line is a cell line that has been developed from a human embryo.

The embryonic stem cell lines that researchers create have the potential to grow into many different types of cells. This research may lead to new knowledge about developing gene therapies.

At no time during this study will the reproductive cells you donate for research be used to establish a pregnancy. The donated cells will be used to develop basic knowledge about the genetic cause of disease and ways of fixing disease-causing gene mutations.

Your blood and reproductive cells, as well as stem cells created from your donations, will be stored indefinitely and may be used in future research. All reproductive cells donated will be used at the Center for Embryonic Cell and Gene Therapy only; DNA, stem cell lines, and/or established cell lines from your donations may be used in future IRB approved collaborations outside of OHSU. This research may involve genetic and/or stem cell research. Your donations will be used specifically for research purposes; none of your donations will result in an embryo being transferred with the intent of producing a viable fetus, nor will the stem cells created from your donation be used for therapeutic purposes.

Donated samples will not be used to create a pregnancy and will not be available to you for future fertility treatments.

PROCEDURES:
You have already decided to undergo treatment for infertility. You will receive this care even if you do not participate in this study. The details of that treatment have already been explained to you by your provider.

Once your eggs have been collected for your fertility treatment, the embryologist will evaluate the number, quality and maturity of those eggs. You may donate any IVF material that would be routinely discarded (thrown away) as part of the IVF process.

Examples of materials that would otherwise have been routinely discarded during your clinical procedures are listed below.
Eggs that would be eligible for this study include:
- Immature eggs that are not suitable for fertilization;
- Eggs that failed to fertilize; and
- Eggs that are abnormally fertilized.

Embryos that would be eligible for this study which require consent from both egg and sperm contributors include:
- Embryos that fail to develop and therefore are not suitable for embryo transfer or for cryopreservation;
- Frozen-thawed embryos that did not survive cryopreservation procedures and therefore are not suitable for embryo transfer.

You may be contacted at a later time to discuss donating stored frozen embryos or you have contacted the Center for Embryonic Cell and Gene Therapy (ECGT) specifically to donate your frozen embryos. We will not access this material without your explicit confirmation/consent to both the Center for Embryonic Cell and Gene Therapy and the clinic where your embryos are stored. Consent is required from both sperm and egg contributors.

Embryos that may be eligible for this study include:
- Embryos that were cryopreserved and are no longer needed for fertility purposes.

Consented: YES: ______ No: ______ Date: ___________________________

Clinic location of frozen Embryos: ___________________________________

Date stored at ECGT: _______________________________________________

- Embryos that were biopsied for Pre-implantation Genetic Diagnosis (PGD), were confirmed to carry a genetic abnormality, and are no longer needed for fertility purposes.

Consented: YES: ______ No: ______ Date: ___________________________

Clinic location of frozen Embryos: ___________________________________

Date stored at ECGT: _______________________________________________

Cumulus cells that would be eligible for this study include:
- Cells that surround eggs and are normally discarded before fertilization.

We may also collect a blood sample (about 2 tablespoons). If there is enough leftover blood collected from your hormonal assays during your routine IVF treatment, you would not need to give another sample. However, an additional blood draw, from a vein in your arm, may be needed if the initial blood sample does not yield enough for research purposes.

Materials collected for this study will be transferred to the Center for Embryonic Cell and Gene Therapy and used in experiments to create embryonic stem cell lines. Immature eggs that mature in a petri dish may be fertilized (using sperm donated for this research) to create embryos, from which researchers will derive stem cell lines. Creation of stem cell lines leads to destruction of embryos. This means that embryos will be destroyed for purposes of this study. You will have no opportunity to use this embryo for any reproductive or other purposes.
Materials may also be frozen and stored in liquid nitrogen and later thawed and used for future experiments. The stem cells are permanent cell lines that will continue to be studied indefinitely using various techniques.

SUBJECT ACCESS TO GENETIC INFORMATION:

If we discover new information that is important for your health care, either in this study or the future, you will be asked whether you wish to receive the results. It is recommended to have the test repeated in a clinical laboratory; results from your donation are performed in a research laboratory and therefore are not considered a clinical diagnostic tool. If you choose to receive these results they will be presented to you by one of the physicians approved in this research protocol; because genetic information is complex and sensitive, the results should further be discussed with a genetic counselor or your primary care provider who can answer your questions or discuss your concerns.

If you consent to this study, we may contact you again in the future to update your information or inquire about your specific healthcare history.

_______ Yes, I would like to receive the non-clinical research only findings if it is deemed important for my health care. I understand this is not a clinical diagnosis and must be repeated in a clinical laboratory. I understand all costs incurred for healthcare services are my responsibility.

_______ No, I would not like to receive non-clinical research only findings.

RISKS AND DISCOMFORTS:

Blood draw:
We will draw blood from a vein in your arm. You may feel some pain when your blood is drawn. There is a small chance the needle will cause bleeding, a bruise, an infection, or fainting.

Genetic testing:
Although we have made every effort to protect your identity, there is a small risk of loss of confidentiality. If the results of these studies of your genetic makeup were to be accidentally released, it might be possible that the information we will gather about you as part of this study could become available to an insurer or an employer, or a relative, or someone else outside the study. Even though there are discrimination protections in both Oregon law and federal law, there is still a small chance that you could be harmed if a release occurred.

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for most insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. Be aware that this new Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination if you have already been diagnosed with the genetic disease being tested.

BENEFITS:
You will not personally benefit from participating in this study. However, by serving as a subject, you may contribute new information which may benefit patients in the future.
ALTERNATIVES:
You may choose not to participate in this study.

CONFIDENTIALITY AND PRIVACY OF YOUR PROTECTED HEALTH INFORMATION:
We will take steps to keep your personal information confidential, but we cannot guarantee total privacy. Neither your name nor your identity will be used for publication or publicity purposes. As part of this study we may share a small amount of information about your genetic code and mutation in papers we publish about this study. This could mean that others could identify that you were in this study, but they could only do so if they also had your DNA so that they could “match” your genetic code to what was published. Other people would not be able to tell anything about you (such as your hair or eye color) from the small amount of your genetic code that we may publish.

We will create and collect health information about you as described in the Purpose and Procedures sections of this form. Health information is private and is protected under federal law and Oregon law. By agreeing to be in this study, you are giving permission (also called authorization) for us to use and disclose your health information as described in this form.

The investigators, study staff, and others at OHSU may use the information we collect and create about you in order to conduct and oversee this research study and store in a repository for future research.

We may release this information to others outside of OHSU who are involved in conducting or overseeing research, including:

- The Food and Drug Administration
- The Office for Human Research Protections, a federal agency that oversees research involving humans

Those listed above may also be permitted to review and copy your records, including your medical records.

We may also share your information with other researchers, who may use it for future research studies. A code number will be assigned to you, your cells and genetic information, as well as information collected about you. Only the investigators named on this consent and authorization form and their research staff will be authorized to link the code number to you. Other investigators who may receive samples of your tissue and genetic information for research will be given only the code number which will not identify you.

We will not release information about you to others not listed above, unless required or permitted by law. We will not use your name or your identity for publication or publicity purposes, unless we have your permission.

When we send specimens or information outside of OHSU, they may no longer be protected under federal or Oregon law. In this case, your specimens or information could be used and re-released without your permission.

We may continue to use and disclose protected health information that we collect from you in this study indefinitely.
Some of the information collected and created in this study may be placed in your OHSU medical record. While the research is in progress, you may or may not have access to this information. After the study is complete, you will be able to access any study information that was added to your OHSU medical record. If you have questions about what study information you will be able to access, and when, ask the investigator.

If you have any questions, concerns, or complaints regarding this study now or in the future, contact the principal investigator, Shoukhrat Mitalipov (503) 418-0196, or the research coordinator for this project at (503) 494-4831.

**COMMERCIAL DEVELOPMENT:**
Samples and information about you or obtained from you in this research may be used for commercial purposes, such as making a discovery that could, in the future, be patented or licensed to a company, which could result in a possible financial benefit to that company, OHSU, and its researchers. There are no plans to pay you if this happens. You will not have any property rights or ownership or financial interest in or arising from products or data that may result from your participation in this study. Further, you will have no responsibility or liability for any use that may be made of your samples or information.

**COSTS:**
You will be responsible for all costs for procedures related to your infertility treatment. These would be performed even if you were not in this study. These costs will be billed to your insurance. If you are uninsured, you will be billed for them. You will be responsible for any costs your insurance does not cover. In the event an additional blood draw is required solely for research purposes, the cost of this additional procedure will be covered by the researchers.

There will be no cost to you for participating in this research. If the results are important for your health care, you will be asked to have the tests repeated in a clinical laboratory. The costs for the repeat testing and the counseling necessary to be certain that you understand what the results mean may be billed to you or to your third party carrier.

**LIABILITY:**
If you believe you have been injured or harmed while participating in this research and require immediate treatment, contact Dr. Paula Amato (503) 418-3700 or (503) 494-8311 and ask to have the “on call” Reproductive Endocrinologist paged. If you have other questions or concerns that do not need immediate medical treatment, please contact Amy Koski (503) 494-4831 or (503) 360-6705.

You have not waived your legal rights by signing this form. If you are harmed by the study procedures, you will be treated. Oregon Health & Science University does not offer to pay for the cost of the treatment. Any claim you make against Oregon Health & Science University may be limited by the Oregon Tort Claims Act (ORS 30.260 through 30.300). If you have questions on this subject, please call the OHSU Research Integrity Office at (503) 494-7887. Oregon Health and Science University is also subject to the Oregon Genetic Privacy law (ORS 192.531 through ORS 192.549) and its requirements concerning confidentiality and the legal remedies provided by that law for breach of its requirements. You have not waived your legal rights by signing this form. For clarification on this subject, or if you have further questions, please call the OHSU Research Integrity Office at (503) 494-7887.
PARTICIPATION:
This research is being overseen by an Institutional Review Board ("IRB"). You may talk to the IRB at (503) 494-7887 or irb@ohsu.edu if:
  • Your questions, concerns, or complaints are not being answered by the research team.
  • You want to talk to someone besides the research team.
  • You have questions about your rights as a research subject.
  • You want to get more information or provide input about this research.

You may also submit a report to the OHSU Integrity Hotline online at https://secure.ethicspoint.com/domain/media/en/gui/18915/index.html or by calling toll-free (877) 733-8313 (anonymous and available 24 hours a day, 7 days a week).

You do not have to join this or any research study. You do not have to allow the use and disclosure of your health information in the study, but if you do not, you cannot be in the study. The participation of OHSU students or employees in OHSU research is completely voluntary and you are free to choose not to serve as a research subject in this protocol for any reason. If you do elect to participate in this study, you may withdraw from the study at any time without affecting your relationship with OHSU, the investigator, the investigator’s department, or your grade in any course. If you would like to report a concern with regard to participation of OHSU students or employees in OHSU research, please call the OHSU Integrity Hotline at 1-877-733-8313 (toll free and anonymous).

If you do join the study and later change your mind, you have the right to quit at any time. This includes the right to withdraw your authorization to use and disclose your health information. If you choose not to join any or all parts of this study, or if you withdraw early from any or all parts of the study, there will be no penalty or loss of benefits to which you are otherwise entitled, including being able to receive health care services or insurance coverage for services. Talk to the investigator if you want to withdraw from the study.

You may withdraw your consent to donate at any time up until the samples have been used for the purpose of research. If you withdraw your consent prior to the usage of your donated material by the researchers, your unused samples will be destroyed. Your identity and the data obtained from this study will be kept strictly confidential. Only the investigators listed above and their research staff will have access to identifying information and the data will be maintained indefinitely.

If you no longer want your health information to be used and disclosed as described in this form, you must send a written request or email stating that you are revoking your authorization to:

The Center for Embryonic Cell and Gene Therapy
3303 SW Bond Ave
Portland, OR 97239
koskia@ohsu.edu

Your request will be effective as of the date we receive it. However, health information collected before your request is received may continue to be used and disclosed to the extent that we have already acted based on your authorization.
Paula Amato, MD (503) 418-3700 and Shoukhrat Mitalipov, Ph.D., (503) 418-0196 have offered to answer any other questions you may have about this study.

Your health care provider may be one of the investigators of this research protocol, and as an investigator is interested in both your clinical welfare and in the conduct of this study. Before entering this study or at any time, you may ask for a second opinion about your care from another doctor. You do not have to be in any research study offered by your physician.

Your donated material may be developed into cell lines that researchers manipulate using the cell lines from animals. This means that the cells lines created from your sample may be combined with the cells of animals as part of this research. These cell lines will not be used for fertility purposes in either humans or animals.

In the future, the cells derived from your donation may be used to develop treatments for other individuals. By signing this consent and authorization form, you agree to donate without and restriction or indication for who may receive these treatments.

The lab responsible for the collection and storage of your sample has been certified by the Food and Drug Administration (FDA) and follows the Good Laboratory Practices required by that certification. The laboratory in which the research of your samples will take place has agreed to follow the National Institute of Health (NIH) guidelines for human stem cell research.

We will give you any new information during the course of this research study that might change the way you feel about being in the study.
SIGNATURES:

Your signature below indicates that you have read this entire form and that you agree to be in this study. Additionally, if you are donating unfertilized eggs, excess embryos, and/or discarded embryos a signature is required from the contributor of the male reproductive sperm cells. Note: Unfertilized eggs may not be consented if you are using an anonymous sperm donor as part of your fertility treatment.

We will give you a copy of this signed form.

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<th>Subject Printed Name (if donating embryos and/or unfertilized eggs)</th>
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<th>Person Obtaining Consent Printed Name</th>
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Complete if the participant is not fluent in English and an interpreter was used to obtain consent. Participants who do not read or understand English must not sign this full consent form, but instead sign the short form translated into their native language. This form should be signed by the investigator and interpreter only.

Print name of interpreter: ____________________________________________

Signature of interpreter: ____________________________________________ Date: __________

An oral translation of this document was administered to the subject in ______________ (state language) by an individual proficient in English and ______________ (state language).

See the attached short form for documentation.