Clinical Research Consent Summary
Sperm Donation

**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 & embryos. In vitro experiments (experiments performed outside of the body) will be conducted to test these techniques. Inherited genetic diseases are caused by mutations in genes found in egg & sperm 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. Stem cell lines may allow scientists to develop personalized medical therapies.

2. This project is 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 blood, sperm cells, and possibly a skin sample from you. The study will produce preimplantation embryos and stem cell lines that will be used for research purposes only.

5. The length of active participation is approximately two visits to the Center for Health and Healing for 1-3hrs to complete your donations. All samples can be obtained in one visit if this is preferable to the scientists and the participant.

6. The risks involved in study participation are minimal.

7. Samples collected during the study will be used for genetic research. All samples and stem cell lines will be saved for future research purposes only.
Clinical Research Consent and Authorization Form
Sperm Donation

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

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

CO-INVESTIGATORS:
- Paula Amato, M.D. (503) 418-3700
- David Battaglia, Ph.D. (503) 418-3700
- Thomas O'Leary, Ph.D. (503) 418-3700
- Sacha Krieg, M.D. (503) 418-3700
- Diana Wu, M.D. (503) 418-3700
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- Sanjiv Kaul M.D. (503) 494-3889

FUNDED BY: Oregon Health & Science University (OHSU)

PURPOSE:
You have been invited to participate in this research project because you:

- Are a healthy man between 21-60 years of age OR
- Are a man who between 21-60 years of age who is a carrier of an inherited gene mutation listed below
  - mutations in MYH7 gene (c.2605 C>T) causing Familial Hypertrophic Cardiomyopathy
  - mutations in MYBPC3 gene causing Familial Hypertrophic Cardiomyopathy
  - LDLR AND LDLRAP1 gene mutations causing Familial Hypercholesterolemia (FH)
- Are either in good general health OR
- Have been diagnosed with inherited genetic disease
- Are interested in donating semen, blood and a possible skin cell sample for research.
The purpose of this study is to test new techniques for correcting a gene mutation in eggs & sperms 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 are 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 oocyte (female reproductive cell) and sperm (male reproductive cell) combine to form the embryo (a collection of cells developed from a fertilized egg).

Germine gene editing is 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 sperm, a possible skin biopsy, 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 mutations. 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/tissue samples, 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 blood and skin 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:
If you are eligible to enroll in the study, and agree to donate semen, skin and blood, your active participation will last for approximately two hours. Your donation will be for research purposes only, no portion of your donation will be used for fertility treatment or the creation of children.

Screening:
The screening process will include a review of your medical history, demographics (date of birth, race and ethnicity), and any current medications you may be taking. You may be asked to give us health information about your relatives. This interview can be done in person at the OHSU IVF clinic or over the telephone. The process may take up to 30 minutes.

Enrollment & Donation:
If the results of your screening process allow you to continue in the study, you will be asked to come to the OHSU IVF clinic to provide your semen sample or you will be provided with an at home collection kit.

Blood Draw (1 visit, or combined with screening visits):
We will draw blood from a vein in your arm. We will collect about 2 tablespoons of blood. Your sample may be frozen and later thawed and used for future experiments. Genetic tests will be conducted.

Skin Biopsy (1 visit, or combined with screening visits):
If you are a patient diagnosed with an inheritable DNA mutation disorder and agree to participate in this study, you will also undergo a skin biopsy procedure. If you do not have a diagnosed DNA mutation, we may ask you to donate a skin sample depending on our research needs. During this procedure, an area of skin will be cleaned with an alcohol swab. A solution of diluted lidocaine (a drug that will numb the surrounding skin) will be injected. The provider will use a small tool called a core punch biopsy to remove a piece of skin about 1-3 mm in size (about the size of a small pencil eraser). A band-aid will be applied to the wound to prevent infection. This visit should take approximately 1 hour.

After your skin cells have been collected, they will be transferred to the OHSU Center for Embryonic Cell and Gene Therapy, located on the 13th floor of the Center for Health and Healing and used for this research study. Your samples may be frozen and stored in liquid nitrogen and later thawed and used for future experiments. Genetic tests will be conducted.

In the future, samples of your tissue and genetic information may be given to other researchers as part of a search for genetic disorders, or for other research purposes. The samples will be labeled as described in the CONFIDENTIALITY section.

SUBJECT ACCESS TO GENETIC INFORMATION:
The results of these studies will not be made available to you because the research is still in an early phase and the reliability of the results is unknown.

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. You will be required 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:**

**Semen Donation:**
Producing a semen sample does not cause any discomfort. However, you may feel embarrassed about the method used to collect it. If masturbation is against your religious beliefs, you may discuss alternate methods of collection with an OHSU health provider.

**Blood draws:**
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.

**Skin Biopsy:**
Prior to biopsy, the skin will be cleaned with an alcohol swab, and then a few milliliters of 1% lidocaine with epinephrine diluted 1:100,000 will be injected to achieve local anesthesia. Some people (fewer than 1 in 10,000) have an allergic reaction to lidocaine, the numbing medicine used in the shot. A 1-3 mm core punch biopsy instrument will be used to remove a piece of skin and the specimen will be placed on saline. You may experience some pain or discomfort from the biopsy procedure. Heavy bleeding from a skin biopsy is rare. There is a small chance, about 10%, that you may get an infection from the biopsy. Sterile conditions will be used to minimize any risk. A small scar will form at the biopsy site. The scar is usually much smaller than the original biopsy.

The side effects associated with the lidocaine and epinephrine used are listed below:

**Lidocaine and Epinephrine:**

**Common:**
- Bruising, redness, itching or swelling at injection site
- Dizziness
- Nausea

**Rare but serious:**
- Severe allergic reactions (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips or tongue)
- Blurred vision
- Chest pain
- Fainting
- Signs of infection in the affected area (e.g. oozing, pus discharge)
- Depression
- Drowsiness
- Vomiting
- Seizures
- Fast heart rate
- Slow heart rate

**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 to 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 special 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:
There will be no cost to you or your insurance company to participate in this study. If the results are deemed important for your health care, you may have the tests repeated in a clinical laboratory at your own expense. The costs of the 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. Note that this will probably make the results available to the third party carrier and to your clinical record.

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.

Upon completion of this study you will be paid $100 for semen and $50 for skin donation (if applicable) as compensation for your time and costs related to this study. We will ask you for your social security number for this purpose.

You may receive payment via a debit card. There may be fees (for example, if the card is inactive for more than six months), which will be deducted from the balance on your card. Details on how to use the card and any fees are included in the separate card member agreement and FAQ sheet.

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 human or animal.

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.

You may be removed from the study if the investigator stops the study, if you develop serious side effects or if you do not follow study instructions. 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.

We will give you a copy of this signed form.

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Social Security number (for tax purposes, we must have this in order to pay you)

Address (we must have this in order to pay you and send your check)

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.