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Subject-information document and the accompanying consent form for the generation and use of induced pluripotent stem cells (iPS cells) for healthy control individuals without any known genetic disease (related or unrelated to the patient with a genetic disease)

Dear Sir/Madam,

Subsequent to the conversation with the researcher you hereby receive written information concerning the scientific research for which your collaboration was requested. We do not ask you to immediately decide. Please take your time before deciding on your willingness to participate. Should you have questions that you would like to discuss with an expert physician not directly involved in this research, you can contact the independent physician listed at the end of this information document

In this letter it is assumed that the reader is the person asked for his or her collaboration. We realize that this may not always be the case. Perhaps you read this letter as a parent/representative of a minor child, or as a representative of an adult who himself/herself is unable to discuss the matter with the researcher. In those cases the healthy control individual whose cooperation is being asked is a different individual than the person reading this letter and discussing with the researcher. In order to prevent making this letter unnecessarily complicated, the letter is addressed to the healthy control individual - even though in practice the conditions may be different.

The ultimate goal for which we ask your collaboration is to:

- 1) reveal the disease mechanisms responsible for various genetic diseases;
- 2) discover new treatment modalities.

For this research it is important to acquire tissue material from healthy control individuals for comparison with material from patients with a certain genetic disease. Cells involved in disease X are for example cells Y and Z. These cells are normally very difficult to obtain, because they require radical actions, which are only feasible if an operation has been scheduled. In addition, cells Y and Z can only be maintained for a brief period in a laboratory, making it impossible to study the disease mechanisms or to test potential new drugs.

Since a few years it is possible to derive stem cells from fresh regular body cells (i.e. a small sections of skin, or cells present in urine or blood) in the laboratory. These, so-called, induced pluripotent stem cells (iPS cells) are immortal and can be kept in the laboratory for an infinite period. In laboratories these stem cells can be used to produce different cell types of our body (such as heart muscle cells, or neurons). Scientific research has illustrated that these new cells can have disease features that are identical to those of diseased cells that occur in the patient's body. For example, if heart muscle cells are generated from iPS cells derived from a patient with irregular heartbeats, then the heart muscle cells exhibit an irregular beating similar to the one observed in the patient. The heart muscle cells generated from cells of a healthy control individual show a normal heartbeat. For these reasons the comparison of heart muscle cells derived from control iPS cells with the ones derived from patient iPS cells is extremely useful for studying the disease and for testing new drugs.

We therefore request your permission to obtain from you some live cells, such as a small piece of skin, or some blood, urine, or hairs, which we will use for research.

More information on the iPS cell research and the implications of your participation is provided below.

1. What are iPSC?

It is customary to designate the newly formed stem cells with the term iPSC cells, which is an acronym for 'induced pluripotent stem' cells.

iPS cells can be generated from cells of a variety of sources, such as skin, blood, urine or hairs. The advantage of iPS cells is that they have a very long lifespan, and can be used to make other cell types such as muscle cells, neurons, and liver cells. They can be frozen and stored for a very long period.

Currently the iPS cells are used for research in the following areas:

- Research on the genetic code that is underlying the disease;
- Development of techniques to correct the genetic code;
- Testing of potential new drugs and treatments.

iPS cells made from your body material that you donated will be used as control material for research on new treatment options, for instance for testing new drugs. Also the iPS cells can be used in research on aiming at the formation of new cells or tissues for cell-transplantation therapies. In the future this may yield iPS cell-derived specialized cells that could be used for transplantation to replace dysfunctioning cells or tissues in patients. In the research phase these options may be evaluated in animal models.

2. What does participation to this study means and what are the risks?

2.1. You are asked to donate some blood, a piece of skin, some urine or a number of hairs for the generation of iPS cells. Donation of the material usually takes place in the out-patient clinic. If possible we will try to combine this with a planned consultation.

- Skin biopsy: A small part of the skin is cleaned with Lugol's iodine and ethanol. We will employ local anesthesia. Next we will remove a fragment of a few millimeters of your skin with a hollow needle. After the biopsy procedure the tiny wound will be dressed, and you will be instructed on further wound care.
Possible adverse reactions. Pain at the site of the wound is usually very limited. Bleedings and infections are very rare. Wounds normally heal leaving a small, usually nearly invisible scars. The biopsy is taken from a part of your body that is barely visible in daily life.
- Blood collection: Blood will be taken by a routine procedure. Two tubes are sufficient.
Possible adverse reactions: You may possibly suffer from some discomfort, and bruising at the site where the needle was inserted. There is a very small risk of fainting during the procedure.
- Hair biopsy: We will carefully collect a couple of hairs including the follicle.
Possible adverse reactions : none.
- Urine: We will ask you to collect urine. Urine naturally contains live cells.
Possible adverse reactions: none.

If another biopsy or surgery has been scheduled, we all ask permission to collect blood or tissue samples during the scheduled procedure. We will only use the blood or tissue for research if it is not required for other diagnosis- or treatment-related procedures.

2.2. Collecting medical information

We will also ask you questions on your ethnic and geographic background. Below in this document you will find information on how your personal information is protected.

3. What are the possible advantages for me when participating in this research?

You or your family will not directly benefit from your participation in this research. Your participation will help researchers further to better understand disease. This knowledge may be very valuable for developing better treatment. It will however require much research and time before iPS cells can contribute to improving treatment.

4. What are potential disadvantages for me when participating in this research?

Besides the risks involved with the collection of body materials as listed above, there are other aspects to take into account when deliberating your participation in our scientific research.

The results of the research with your body materials will usually be published in scientific journals. In the publications we will not disclose healthy control individual names, or any other information that would make you identifiable.

It can also not be excluded that the research on your body material reveals that you have an increased chance of developing a specific disease. If your employer or insurance company becomes aware of this information, it could potentially have consequences for you. We will do our utmost to prevent this from happening. This is a legal requirement and we believe that the risk of medical information falling in the wrong hands is extremely small.

Another aspect is that scientific research on body material can reveal that specific health risks are connected to a particular region or country or ethnic background. This could mean that knowledge becomes available on people with this geographic or ethnical roots. This can be an advantageous but it does not necessarily have to be this way.

5. Are there rules for conducting scientific research using human body materials?

Our scientific research with body materials must comply with all applicable legislation and rules. These rules are very strict and detailed. Research using human iPS cells could lead to experiments in which cells or tissues are transplanted into experimental animals. It could also lead to research on the inherited features of your body material and studies to determine the DNA-sequence of your genes. The body material you donated and the materials derived thereof cannot be acquired for your personal usage.

6. Can I install limitations to the use of my cells?

By participating to his scientific research you agree with the execution of this research as written in this letter. It will not be possible to impose limitations on the use of the materials you donated or materials derived thereof. No limitations are accepted on the use of iPS cells or impose limitations on the clinical use of materials. Similarly, you are not at liberty to impose limitations on the research that being performed on or with the materials that you donated. You can be assured that your healthy material will be used as control for research aiming at studying diseases and new treatment modalities.

You are free to decide on your participation in this research, but after your donation, you are not entitled to reclaim any materials donated or claim any products that have been developed with the aid of the material you donated.

Should you have any questions on the rules and regulations pertinent to scientific and medical research with human body materials, please do not hesitate to contact the LUMC researcher with your questions.

7. How is the confidentiality of my personal information safeguarded?

Your name, date of birth, and other personal and identifying information will be removed from the material dossier used for the scientific research. Your personal information will be retained in an anonymous coded format (i.e. not with your personal registration number of LUMC patient number) in a LUMC research database. This code can only be coupled with your identity by your treating physician. None of the other researchers will be able to trace your identity.

Scientific biomedical research thrives on collaborations between your hospital and other hospitals and research institutions in the Netherlands and abroad. Often the collaborations involve the exchange of body materials or cells. In case we share iPS cells, we will only reveal your gender and age at the time of donation. Your name or other personal information will not be disclosed, only the anonymous code. As stated before, only your treating physician will be able to link this code with your personal information.

The iPS cells and the associated information will therefore remain anonymous for the scientists involved in the research. In this manner your privacy will remain protected.

8. What if I refrain from participating in this research?

Your participation in this scientific research is completely voluntarily. There is no need to participate in the research if you have any hesitations. Your decision on your participating in this research will in no way affect the current or future clinical care offered by the LUMC.

9. What if I change my opinion and prefer to abstain from further participation?

If you decided to participate but change your opinion afterward and choose to opt out, please let us know. We have the following options for you.

- You can withdraw your permission to be contacted in the future with requests to participate in this type of scientific research.
- You may withdraw your permission to use the original material that you donated, such as the donor blood sample, the urine sample, the skin biopsy, or the isolated hairs up until the moment that your material is used to generate iPS cells
- Once iPS cells were generated you can request that all remaining donated materials be destroyed.
- If requested we can have all anonymous codes removed that link the iPS cells to your personal information. In addition, we can request the removal of these codes from all materials that were shared with other institutions. We will use the iPS cells with very limited information for further research but the materials can then no longer be linked to your personal information. Nobody will ever be able to link the material to your personal information. We will not destroy the iPS cells once these cells have been generated, nor can we retrieve cells that have been shared with researchers at other institutions.

10. Is there a financial compensation for my participation?

You will not receive a financial compensation for your participation for this scientific research. Your donated body materials will be used as control material for the research. This can contribute to research products which are developed on the basis of the donated material. These research products can be used for future research and in principle they can be commercialized. For example, iPS cells can be used for the generation of specialized cells such as blood vessel cells, heart muscle cells or neurons. Such research is being performed worldwide and aims at the generation of healthy and diseased cells. If successful this could represent an important possibility to test drugs in such cells first - before they are given to the patient. Thus your body material can be used to generate biological products which in turn can be used for follow up research aiming at the development of new drugs. In that case the original donor of the body material will not receive financial compensation.

11. Are you insured while participating in this research?

Because the risks associated with your participation in the research are deemed negligible, the LUMC's medical ethical research committee decided that additional insurance is not necessary.

12. Which medical ethical research committee approved this research?

This research has been approved by the medical ethical research committee of the Leiden University Medical Center.

13. Will I be contacted at a later time point?

We may wish to contact you in the future.

- We could contact you with a request to provide new body materials or with questions on your health status. We would like to inform you that in such case you are in no way required to provide such materials or information.
- At this moment we do not anticipate that the iPS cell research will provide new information on your health. Should we obtain relevant information on your health we will contact you to discuss whether you would like to obtain the new information.
- We may contact you if the iPS cells made from your body material can be used for research that is not covered in this information document. This could involve research with new techniques or on new applications that we cannot yet anticipate.
- We can inform you in general terms on the type of research that is performed with iPS cells from you or from other donors and on the scientific and medical progress that is being made. (Please inform us if your contact details change, so that we can keep you informed.)

If you decide to participate in this research, you can indicate below if you do NOT want to be contacted by the research team.

14. Is there anything more you want to know?

For questions or information regarding the research please feel free to contact your treating physician or the principal scientist. Alternatively, you could contact an independent physician who is an expert in this field, but not directly involved in this research project.

Contact details:

Primary researcher:

Independent physician:

Permission agreement

for using my body materials for generating iPS cells

I have been informed sufficiently on the aims of the research. I received and read the written documentation and have been given ample options to ask questions. All of my question have been answered. I have been given ample opportunities to consider my participation in this research. I will retain the right to withdraw my permission to participate in this research at any time, and can do so without cause or motivation.

I permit you to isolate (more than one option can be given):

- skin biopsy
- blood sample
- Urine sample
- Hair biopsy

Furthermore I permit :

- The use of these body materials for the generation of iPS cells
- To share samples of my body materials with researchers at other institutions.

Please tick this box if you do not want to be contacted by the research team (as per section 13 of this information document).

Patient information

Last name and initials :

Date of birth :

Signature :

In case of re-consent for previously donated tissue:

I hereby agree that this permission agreement replaces all previously signed informed consents forms and is valid for all tissues donated by me in the past.

Patient information

Last name and initials :

Date of birth :

Signature :

The undersigned declares that the person identified above was informed verbally as well as in writing on the research outlined above. In addition, he or she declared that withdrawal from participation will have no effect on the medical treatment that the person will be offered now or in the future.

Name: :

Function: :

Signature :

Date :