UPMC LIFE CHANGING MEDICINE

INFORMED CONSENT AND HIPAA AUTHORIZATION FORM

FOR SUBJECT PARTICIPATION IN A RESEARCH STUDY / Donor Informed Consent

TITLE OF CLINICAL TRIAL: Safety and Preliminary Efficacy of Donor-derived Regulatory Dendritic Cell (DCreg) Infusion and Immunosuppression Withdrawal in Living Donor Liver Transplant (LDLT) Recipients

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QUESTIONS ABOUT THE STUDY:
You can contact the study investigator if you have any questions about the study, concerns or complaints. Contact one of the investigators listed above at 412-647-5800 (24 hours)

If you have any questions about your rights as a research subject or wish to talk to someone other than the research team, please call the University of Pittsburgh Human Subjects Protection Advocate toll-free at 866-212-2668.

SOURCE OF SUPPORT: University of Pittsburgh Medical Center

INTRODUCTION:
You are invited to take part in this research study for adults between the ages of 18 and 55 who are scheduled for liver donation surgery, and whose care will be managed at the University of Pittsburgh Medical Center (UPMC). Before you can decide whether or not to take part in this study, we would like to explain why the study is being done, what will be expected of you, and the possible risks, benefits, and alternatives to participating in this study.

It is important that you understand the following:

- You can choose to be a part of this research study or choose not to participate. If you decide not to participate in this research study, your decision will not affect your routine

care.

- This study will be explained to you by the study team. You will have a chance to ask questions.
- You will have time to discuss your participation in this study with your family.
- If you sign this consent document, it means that you are agreeing to take part in this research study. You will be given a copy of your signed consent document for your records.

Why is this research being done?

The purpose of this research study is:
People who have liver transplants must take anti-rejection medication (immunosuppression) for the rest of their lives. If they stop their anti-rejection medications, their immune system may reject the transplanted liver. All anti-rejection medications have side effects. Because of the side effects of anti-rejection medications, an important goal of transplant research is to allow patient's body to accept and not reject their transplanted organ without long-term use of anti-rejection medications. This is called tolerance.

In this study, our goal is to develop a new and safe treatment approach that involves injecting immune cells called regulatory dendritic cells (DCreg) from you, the transplant donor, into the transplant recipient, prior to transplantation. We expect that this will make the recipient's body more accepting of, or tolerant to, the transplanted organ and facilitate the withdrawal of immunosuppressive medications without jeopardizing the function of the transplanted organ.

The purpose of this research is to study if donor DCregs are safe to be injected into recipients and to see how many of these recipients will develop tolerance after with drawl of immunosuppressive medications.

This study is the first time that donor DCregs will be infused into human liver transplant recipients. Extensive animal studies have shown no adverse effects on the recipient animals; however, we know from studies of other cell types that when recipients are exposed to donor cells, sensitization (a reaction against the transplanted organ) may occur. Throughout the study we will monitor the recipient of your liver for this. Sensitization does not make potential liver recipients ineligible for transplantation.

RESEARCH ACTIVITIES
This study is sponsored by the UPMC. The study will be conducted at UPMC Presbyterian and Montefiore locations. The study will enroll up to 15 living donor liver transplant recipients and their living donors.

Total duration of your participation in the study is no more than 3 months.

If you agree to participate the study will consist of the following:

SCREENING:
You have undergone rigorous screening as part of the standard of care prior to being deemed

eligible for liver donation surgery. Therefore, a separate screening visit specifically for the purposes of this study will not typically be needed. All donors are tested for HIV, Hepatitis B virus, Hepatitis C virus, syphilis and Cytomegalovirus (a common infection that can affect anyone) as part of our standard of care. For donors enrolled in this study, we will collect about 4 tbsp. of additional blood samples for HIV, and for research in transplantation within 7 days (before or after) of a procedure called leukapheresis (described below). In the unlikely event that two leukapheresis procedures are required, we may ask you to repeat some of these tests. These research tests help us learn more about your health. The results of the research tests will not be shared with you.

Similar to plasma donation, leukapheresis is a procedure that removes some parts of your blood (white blood cells called monocytes) and returns other part of your blood, back to your body. We will try to collect the above mentioned additional samples for research at the same time blood is drawn for standard of care testing so that we can review the test results prior to leukapheresis. Positive test results do not make you ineligible for the leukapheresis procedure itself. However, positive test results, with the exception of CMV, would deem the cells unusable. If the test results are obtained prior to the leukapheresis procedure, the procedure will be cancelled. If you have already undergone the leukapheresis procedure, the lab will be notified to destroy your donated cells

Donor leukapheresis:
You will undergo a 3 – 5 hour outpatient leukapheresis visit by the Institute for Transfusion Medicine at the 7 West Outpatient Transplant Unit about 28 to 15 days prior to your scheduled liver donation surgery. You will be asked to withhold caffeine for about 24 hour prior to the leukapheresis. If you take any diuretics (water pills) or any blood pressure medications you may be asked to hold those on the day of the leukapheresis procedure. The DCregs are prepared from certain blood cells called the monocytes. The lab can estimate the number of DCreg cells from the number of monocytes collected during the leukapheresis procedure. In the unlikely chance that the number of such cells (monocytes) collected is too low, we may ask you to return for a second leukapheresis procedure. This second leukapheresis procedure can be as soon as the following day. We will not know the exact number of DCreg cells manufactured until the day of infusion. In the unlikely event that the exact dose of the DCreg cells is too low, the cells will be discarded and will not be infused into the recipient.

About 6 tablespoons of blood will be collected for research at the time of leukapheresis.

Leukapheresis will be performed according to the Institute for Transfusion Medicine's standard operating procedures. **You will sign a separate consent form when you have leukapheresis**. This consent form will explain details of the leukapheresis, any medications you will receive before and during the leukapheresis, and any risks associated with the leukapheresis.

Leukapheresis will be performed via two separate peripheral venous access sites (a tube inserted into a vein in your arm), unless you have poor venous access and require insertion of a central venous line (a tube placed into a large blood vessel) catheter inserted into for blood collection.

You will be unable to undergo the leukapheresis procedure if you have an active infection unless

approved by the study doctor and collection facility medical director.

Prior to Liver Donation Surgery:
About 4 tbsp. of blood will be collected again for research purposes.

FOLLOW-UP PROCEDURES:
You will receive a follow-up phone call within 24 hours following blood donation and approximately 7 days after blood donation.

The total amount of blood drawn during your participation in the study will be about 12 tbsp.

STUDY RISKS:
Treatment and procedures in this research study may involve risks that are not possible to predict. You will be informed of any new risks that may be identified during the study. Please ask your study doctor or the research staff to explain any procedures or risks that you do not understand. You might have more problems as a result of participating in this research study than you would have if you continued routine treatment. These unknown risks may affect you during your participation in the research study and/or at some point in the future.

Risk of leukapheresis:
The risks include, but are not limited to the following:

Weakness, nausea or feeling faint as a result of decrease blood volume. Such episodes can be controlled readily by the immediate return of red blood cell and an increase in fluid replacement if necessary.

Tenderness/bruising at the needle site. Needles may be placed in one or two veins during the entire leukapheresis procedure. The presence of the needle and saline infusion may cause some local discomfort. If veins are not adequate to perform the procedure, a vascular access catheter will be inserted by a physician. The most common insertion sites are the subclavian and the jugular veins in the neck area and the femoral vein in the groin.

Localized infection at needle puncture site. This risk is extremely small because of aseptic technique is used throughout the procedure.

In very rare instances, people undergoing leukapheresis may experience complications that require a blood transfusion. The risks of receiving a blood transfusion include:

- Fatal transfusion reaction caused by administration of incompatible blood
- Although each blood component is screened, there is a possibility of transmitting infectious diseases or agents such as hepatitis, AIDS, cytomegalovirus, bacteria, malaria and other rare diseases.
- Alloimmunization: The production of antibodies against donor red cells, white blood cells or platelet antigens.
- Allergic reactions, fever or fever- like reactions and circulatory overload may also occur

Possible anticoagulant discomfort: Sodium citrate, an anticoagulant, is added to the blood to prevent clotting. Sodium citrate is metabolized by the body. Although it is not toxic it can sometimes cause temporary symptoms such as tingling/ numbness of the lips and/or fingers, muscle cramping, chilliness, feelings of anxiety and rarely convulsions during treatment.

Premature termination of procedure: Since the removal of blood and return of blood is accomplished through the use of needles and tubing, it is possible that clotting could occur in the needles or tubing and this may lead to the termination of the individual procedure. Loss of red blood cells due to leakage or breakage of the plastic tubing or containers may occur and thus prevent the return of the red blood cells to your body.

Hetastarch (a red cell sedimentation agent) may be used. Hetastarch has been reported to produce general reactions such as wheezing and certain allergic skin conditions. Side effects that have been reported include but not limited to: headache, vomiting, temporary weight gain, insomnia, fever and mild flu- like symptoms, edema, dizziness, chest pain, chills, anxiety and increased heart rate. It is uncertain whether these side effects are attributable to the hetastarch, the procedure, or additional medications that you may be receiving or some combination of these factors. Hypersensitivity reactions can occur even after Hetastarch has been discontinued.

Risk of Blood Draw:
The risks of having blood taken are discomfort, bleeding, fainting, small blood clot or swelling to the vein and area surrounding where the blood is drawn, bruising where the needle enters the skin and infection. There is also a very small chance of infection at the needle puncture site.

Risk of Breach of Confidentiality:
Although every effort is made to protect your confidentiality, there is a risk that someone else may inadvertently see your private health information.

Risk of Genetic Testing:
The risks associated with genetic studies include the potential for a breach of confidentiality which could affect future insurability, employability, or reproduction plans, or have a negative impact on family relationships and/or result in paternity suits or stigmatization.

HIV POLICY
As part of the screening process for this study your blood will be tested for infectious diseases including Hepatitis (the virus that causes liver disease) and HIV (the virus that causes AIDS). All information will be handled in compliance with the Pennsylvania law on HIV-related confidential information. You do not have to take part in this testing, however if you refuse you will not be able to participate in this study. Counseling is available to you before you make the decision to participate in this testing. Once you have the test performed it is a requirement that you be informed of the results if they are positive. If you test positive for HIV you will be referred by the study team for appropriate medical care and you will be excluded from this study.

A positive HIV test means that your blood sample tested positive for HIV and that repeat testing will be performed to confirm (prove) this finding. If your sample is proved to be positive for HIV, it means that you are a carrier of HIV. It also means that you can pass the virus to others by

intimate sexual contact, by sharing needles, and through donating blood and organs. A negative HIV test means that at this time, no antibody to HIV was found in your blood sample based on the result of the initial screening test, repeat screening tests, or a confirmatory test**.**
There can be individuals who have HIV test results that are called "false positive," that is, for some reason, the test indicates that HIV antibodies are present in the blood when they are not. There can also be false negative results which can have two possible meanings; the person has been infected with HIV, but that person's body has not yet made antibodies to the virus, or HIV antibody is present in the person's blood, but for some reason the test failed to detect it.

You may ask the study physician for more information on HIV testing prior to having this test performed.

STORING INFORMATION FOR FUTURE STUDIES:
We will store information from this study, including blood and tissue samples in a central Data Repository/Archive. The purpose of this is to make data (including information resulting from testing DNA) available for use in health research. Any information released to a central data repository will not contain your personal information.

Any leftover cells from the leukapheresis procedure will be stored indefinitely, as well. These samples will also be transferred to the central Data Repository/Archive.

A central data repository is a research resource. It collects, stores, and distributes information from many different people. The purpose of this collection is to make scientific information available for future studies, which may help future patients. Your data may be stored indefinitely and will not reveal your identity.

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information that we get from this research when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

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, nor does it protect you against genetic discrimination by all employers.

STUDY BENEFITS:
There will be no direct benefit to you from allowing your specimens to be used for research. The information learned during this study may help doctors know more about using donor DCregs to enable reducing and/or stopping immunosuppressive drugs for future liver transplant patients.

ALTERNATIVE TREATMENTS:
You are not required to participate in this study. If you decide not to participate in this study, then your liver recipient will not qualify to participate in this study but may still undergo the living donor liver transplantation.

NEW INFORMATION:
You will be promptly notified if any new information we learn during this research study may cause you to change your mind about continuing to participate in the study.

PRIVACY (Person) and CONFIDENTIALITY (Data):
Your personal details and information from the study are processed in accordance with United States data protection law, the Health Insurance Portability and Accountability Act (HIPAA), which is designed to protect your privacy. Efforts will be made to keep your personal information private. However, we cannot guarantee complete confidentiality due to the nature of the data being collected, which includes genetics and private health information.

Why is this information needed?
This information is needed to determine whether you meet the conditions for participation in this study, to compare your earlier test results to the findings from this study, and if possible, to use your previous exam results in place of, or in addition to, some of the exams needed for this study.

You will be identified by a code, and personal information from your records will not be released without your written permission. You will not be identified in any publication or in the sharing of your data about this study. After the study is completed, the data may be placed in a central storage location. These data will not include your name or other information that can identify you. The purpose is to make study data available to other researchers.

Your research data/samples and genetic data generated from samples may be shared with investigators and with federal repositories conducting other research; this information will be shared without identifiable information. These research data/samples may contribute to a new discovery or treatment. In some instances, these discoveries or treatments maybe be of commercial value and may be sold, patented, or licensed by investigators and the University of Pittsburgh for use in other research or the development of new products. You will not retain any property rights, nor will you share in any money that the investigators, the University of Pittsburgh, or their agents may realize.

What will be disclosed?
We will obtain the following information: your diagnosis, age, past medical history, diagnostic procedures, and results of any tissue biopsies or blood tests, including results of genetic tests that were already done as part of your standard evaluation at the Starzl Transplant Institute.

Who is requesting the Protected Health Information (PHI) for research?
In addition to the investigators listed on the first page of this authorization (consent) form and their research staff, the following individuals will or may have access to identifiable information (which may include your identifiable medical information) related to your participation in this

research study: Authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office may review your identifiable research information (which may include your identifiable medical information) for the purpose of monitoring the appropriate conduct of this study.

Authorized representatives of UPMC hospitals or other affiliated health care providers may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of (1) fulfilling orders made by the investigators for hospital and health care services (e.g. laboratory tests, diagnostic procedures) associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for internal hospital operations (i.e. quality assurance).

Authorized representatives from the Food and Drug Administration may review and or obtain your identifiable (which may include your identifiable medical information) related to your participation in this research study for the purposes of monitoring the accuracy and completeness of the research data. While the U.S. Food and Drug Administration understands the importance of maintaining the confidentiality of your identifiable research and medical information, the UPMC and University of Pittsburgh cannot guarantee the confidentiality of this information after it has been obtained by the U. S. Food and Drug Administration.

UPMC its designee(s), its collaborator, auditors, monitors, ethics committee, independent review boards and various government health agencies (such as the FDA) in this or other countries will have access to your records and data collected and may inspect and/or copy your medical records of this study. You also provide consent for the release of copies of your laboratory test results and medical reports for review as part of this research study. Information about your disease status may be requested and reviewed on a regular basis after you have completed all visits in this study. This is necessary to ensure that the study is performed according to the approved protocol, for participants' safety, and that the data collected is correctly recorded.

There are national and state laws that make the study doctor protect the privacy of your records. However, you do not have a guarantee of absolute privacy because of the need to share your information. After the study doctor shares your records with UPMC and others, the laws may no longer protect the privacy of your records. UPMC or others may share your records with other people who do not have to protect the privacy of your records.

How long will this information be made available to the researchers?
The investigators may continue to use and disclose, for the purposes described above, identifiable information (which may include your identifiable medical information) related to your participation in this research study for a minimum of 7 years and for as long (indefinite) as it may take to complete this research study.

In unusual cases, the investigators may be required to release identifiable information (which may include your identifiable medical information) related to your participation in this research study in response to an order from a court of law. If the investigators learn that you or someone

with who you are involved is in serious danger or potential harm, they will need to inform, as required by Pennsylvania law, the appropriate agencies.

We will protect your privacy and confidentiality of your records, as described in this document, but cannot guarantee the confidentiality of your research records, including information obtained from your medical records, once your personal information is disclosed to others outside UPMC or the University.

Do I have a right to revoke this authorization?
You always have a right to withdraw your authorization to allow the research team to review your medical records by contacting the investigator listed on the first page and making the request in writing.

You do not have to sign this authorization, but if you do not, you cannot participate in this research study or receive study-related treatment. If you withdraw this authorization in the future, you will no longer be able to participate in this study. Your decision to withdraw your authorization or not to participate will not involve any penalty or loss of access to treatment or other benefits to which you are entitled.

How long will this authorization be valid?
This authorization is valid for an indefinite period of time.

FDA CLINICAL TRIAL REGISTRY:
ClinicalTrials.gov is a website that provides information about federally and privately supported clinical trials. A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by US Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

WITHDRAWAL FROM STUDY PARTICIPATION:
You can, at any time withdraw from this research study; you can also withdraw your authorization for us to use your identifiable medical information for the purposes described above. This means that you will also be withdrawn from further participation in this research study. Any identifiable research or medical information obtained as part of this study prior to the date that you withdrew your consent will continue to be used and disclosed by the investigators for the purposes described above.

Your decision to withdraw your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.
If you decide to withdraw from study participation after, you should participate in additional monitoring follow-up procedures that are being conducted to measure the safety of the study.

If you withdraw your consent:
- You will not be able to continue in the study

- The study doctor will not be able to use or share any future health information unless it is necessary to protect the integrity of the study. The data collected before your withdrawal remains part of the study database and may not be removed.

Even if you leave the study early, the study doctor and study staff will still be able to use and share your record as described above unless you withdraw your consent to use and share your records.

It is possible that you may be removed from the research study by the researchers if, for example,

- If you do not follow your study doctor's instructions
- If your study doctor feels it is necessary for your health and safety
- Pregnancy
- If we find out you should not be in the study
- If the study is stopped or cancelled
- Unanticipated circumstances

If your study doctor decides that you should withdraw from the study due to any of the above reasons, you should participate in additional monitoring follow-up procedures that are being conducted to measure the safety of the study.

COSTS:

While you are in this study, you still need to receive regular medical care. You or your insurance carrier will still have to pay for the costs of your regular medical care that are not part of this study. These include cost of clinic/doctor visits, lab and radiology procedures that are not part of the study. You are encouraged to speak with your insurance company about what will be covered before agreeing to take part in this study.

UPMC will cover the costs of the tests that are done specifically for this study (for example, the leukapheresis and blood tests) and provide the study agent to you at no charge. Your health plan/insurance may pay for all tests and procedures that would normally be done as standard of care; that is, those procedures or tests that you would normally have as part of your regular medical care.

PAYMENTS:

We will reimburse you for certain study-related expenses such as travel or parking costs to attend in-person study visits.

We will compensate you for time spent at study visits that do not coincide with standard of care. Since the leukapheresis visit will be several hours long, we will pay you $80 for that visit. If you require 2 leukapheresis visits you will receive $80.00 for each visit. For shorter research-only visits, such as research blood draws, we will pay you $20.00. You will receive all payments at the end of each research visit for your participation in this study.

COMPENSATION FOR INJURY:

If you believe that the research procedures have resulted in an injury to you, immediately contact the Principal Investigator who is listed on the first page of this form. Emergency medical

treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. Your insurance provider may be billed for the costs of this emergency treatment, but none of those costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care. At this time, there is no plan for any additional financial compensation. You do not, however, waive any legal rights by signing this form.

VOLUNTARY PARTICIPATION:
Your participation in this research study is entirely voluntary. You may want to discuss this study with your family and friends and your personal physician before agreeing to participate. If there are any words you do not understand, feel free to ask us. The investigators will be available to answer your current and future questions.

Whether or not you provide your consent for participation in this research study will have no effect on your current or future relationship with the University of Pittsburgh. Whether or not you provide your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

As both your doctor and a research investigator, s/he is interested both in your medical care and the conduct of this research study. Before agreeing to participate in this research study, or at any time during your study participation, you may discuss your care with another doctor who is not associated with this research study. You are not under any obligation to participate in any research study offered by your doctor.

To formally withdraw your consent for participation in this research study you should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form.

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CONSENT TO PARTICIPATE:

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions, voice concerns or complaints about any aspect of this research study during the course of this study, and that such future questions, concerns or complaints will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator. I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations that occurred during my participation. By signing this form, I agree to participate in this research study. A copy of this consent form will be given to me.

_____	_____	_____
Participant's Printed Name	Participant's Signature	Date and Time

INVESTIGATOR CERTIFICATION:

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions, concerns or complaints as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____	_____
Printed Name of Person Obtaining Consent	Role in Research Study

_____	_____
Signature of Person Obtaining Consent	Date and Time