CAROLINAS HEALTHCARE SYSTEM
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Phase I/II Study of Donor Lymphocyte Infusion with Methotrexate GVHD Prophylaxis to Hasten Immune Reconstitution after $CD34^+$ Cell-Selected Transplant

Adult and Parent of Minor Recipient
When we say "you" in this consent form, we mean you or your child; "we" means the doctors and other staff.

INTRODUCTION

Dr. Andrew Gilman and his associates are asking you to participate in this research study at Levine Children's Hospital (LCH)/Carolinas Medical Center (CMC)/Carolinas HealthCare System (CHS).

Details about this study are discussed below. You are being told this information so that you can decide in a free and informed manner whether you want to participate. You will be given a copy of this consent form. You are urged to ask your study doctor, or staff members who may assist them, any questions you have about this study at any time. Please ask for an explanation of any words you do not understand. You may want to talk about the study with your family or friends before you decide to be in it.

You are being asked to take part in this research because you have received a T-cell (cells that fight infections)-depleted (reduce the number of) blood stem cell transplant. Specifically, you have to have been treated on the LCH BMT 09-01 (TCD) study to participate in this companion study.

A major risk of T-cell depleted transplants is delayed immune system (ability to fight infections) recovery which can increase the risk of life-threatening infections. Some small studies have shown that giving a donor lymphocyte infusion (DLI) which contains T cells helps speed up immune recovery after transplant. However, these T cells can cause graft-versus-host disease (GVHD). GVHD occurs when T cells from the donor attack certain tissues or organs (for example the skin, liver, intestines) of the transplant recipient. Methotrexate will be given with DLI to prevent GVHD. Methotrexate is a chemotherapy drug that is used to treat cancer and autoimmune diseases (the immune system attacks tissues in the body). Methotrexate has been used for many years immediately after bone marrow (soft tissue inside of bones) transplantation. It is given to prevent GVHD from the donor lymphocytes (T cells) passed with the bone marrow.

The purpose of this study is to find a dose of DLI given with methotrexate that will speed up immune recovery without giving severe GVHD.
Approximately 60 people will participate in this research at Levine Children's Hospital/Carolinas Medical Center.

HOW THE STUDY WORKS

Study Procedures

If you agree to participate in this study, you will be asked to sign this consent form. You will have the following tests and procedures to make sure that you are eligible:

- Physical exam and medical history,
- Vital signs (blood pressure, pulse, temperature, breathing rate),
- Blood tests to determine health status. Approximately 5-7 ml (1 teaspoon) of blood will be drawn,
- Lymphocyte markers (proteins that identify different types of white blood cells in the blood),
- Pregnancy test.

Treatment

The T cells will be frozen at the time that they are removed from the original donor during stem cell collection. They will be thawed and infused (injection into a vein) on day 30 after transplant. The infusion may be delayed up to 12 days if necessary. You will receive Rituximab 200 mg/m2 IV on the day of infusion. It can be given +/- 1 day if necessary. You will receive Methotrexate into a vein as follows:

Day 1 (approximately 24 hrs after DLI infusion): methotrexate 10 mg/m^2
Day 3 after DLI: methotrexate 10 mg/m^2
Day 10 after DLI: methotrexate 10 mg/m^2
Day 17 after DLI: methotrexate 10 mg/m^2
Day 24 after DLI: methotrexate 10 mg/m^2
Day 31 after DLI: methotrexate 7.5 mg/m^2
Day 38 after DLI: methotrexate 7.5 mg/m^2
Day 45 after DLI: methotrexate 5 mg/m^2
Day 52 after DLI: methotrexate 5 mg/m^2
Day 59 after DLI: methotrexate 5 mg/m^2
Day 66 after DLI: methotrexate 5 mg/m^2
Day 73 after DLI: methotrexate 5 mg/m^2
Day 80 after DLI: methotrexate 5 mg/m^2

The dose of T cells will be increased from one group to the next. The T cell dose that you receive will depend on the group in which you are placed. The six groups are:

Group 1: 30,000 T cells/kg of body weight
Group 2: 40,000 T cells/kg of body weight
Group 3: 50,000 T cells/kg of body weight
Group 4: 60,000 T cells/kg of body weight
Group 5: 80,000 T cells/kg of body weight
Group 6: 100,000 T cells/kg of body weight

The dose of the T cell infusions will be increased to find a dose that provides the best recovery of the immune system without causing severe GVHD. At least three patients tested will be treated in each group before the dose of T cells is increased. It is possible that additional patients will be treated at the same dose if moderate GVHD requiring prolonged treatment is seen.

Follow up
You will be required to have check-ups (includes physical exam and vital signs) and blood drawn (about 4 teaspoons) for this study These visits will overlap with routine visits after transplant at day 60, 100, and 120 then 6, 9, 12 and 24 months after the transplant.

Length of Study
You will receive the DLI over 5-15 minutes. You will be required to have check-ups and blood drawn for two years after the transplant for this study. The follow up visits should take approximately 1 to 2 hours.

RISKS
As a result of your participation in this study, you are at risk for some side effects. You should discuss these with the study doctor and your regular health care provider. You will always be able to stop your participation in this study at any time.

You may experience the side effects listed below. There may also be other side effects that are unknown at this time. The risks of the infusion are as follows:

Rituximab
Less Likely:
- Fever
- Chills

- Nausea
- Weakness
- Headache
- Low blood pressure
- Itching
- Rash
- Wheezing/difficulty breathing
- Abdominal pain
- Vomiting
- Anemia
- Achy joints and muscles
- Dizziness
- Congestion
- Low blood counts.
- Suppression of certain parts of your immune system resulting in a greater
- Risk of infections
- Slower recovery of B cells (a white blood cell that makes antibody to fight infection) resulting in a longer period of receiving IVIG (antibodies from donor blood)

Rare but Serious:

- Angioedema (a condition characterized by an itchy rash and swelling of areas of the skin and mucous membranes [the lining of some of the mouth and nose], as part of an allergic reaction)
- Severe reactivation of hepatitis B infection and liver failure
- Progressive multifocal encephalopathy (Most people have been infected as children with a virus called JC virus. In most cases this virus does not cause any problems, but in very rare cases of patients who receive rituximab, this virus can become active again, leading to severe damage to the brain tissue.

Methotrexate

Likely:

- Hair loss
- Lowering of blood counts

Less likely:

- Inflammation of the liver

- Mouth sores
- Nausea and vomiting
- Diarrhea
- Rash
- Infection due to weakened immune system

Rare but serious:

- Inflammation of the lung
- Liver damage
- Kidney damage

Donor lymphocyte infusion

Transfusion of blood cells can pass infectious diseases such as cytomegalovirus (CMV), hepatitis B and C and Human Immunodeficiency virus (HIV, the virus that causes AIDS) to the recipient. The donor lymphocytes are taken from the stem cell collection used for transplant. The donor is screened for viruses, but there still remains a very small possibility that these viruses could be passed to you. A transfusion reaction could also occur and may include a fever, rash, and difficulty with breathing, high or low blood pressure, or changes in your heart rate. There is a rare chance of a severe transfusion reaction which can be life-threatening and even fatal (death). You will be given medications prior to the infusion to help prevent these signs of a transfusion reaction and you will be monitored closely during the infusion.

Graft-versus-host disease

Graft-versus-host disease (GVHD) is a reaction in which the donor T cells attack the recipient's body. It ranges from a mild skin disorder to severe involvement of skin, liver, and/or gut and it may be fatal for some patients. Details of GVHD are as follows:

A. **Acute GVHD** generally occurs within 1 - 4 weeks of giving donor T cells, but it may occur after a longer period of time. Acute GVHD can lead to:
    - Skin damage – sunburn-like rash, peeling,
    - Burn
    - Intestinal damage – diarrhea, nausea, vomiting, stomach pain, bleeding
    - Liver damage – yellow skin, decreased liver function

    Severe acute GVHD can also uncommonly affect the lungs.
B. **Chronic GVHD** usually occurs more than 100 days after giving donor T cells, but may occur earlier. Chronic GVHD can be life-threatening. It can also result in patients not feeling well and being able to do normal activities, sometimes for a long time. Chronic

GVHD can affect many parts of the body. The most commonly affected areas are the skin, mouth, liver, and eyes. Chronic GVHD can cause:

- Skin rash, skin thickening, dark color of skin, loss of color of the skin, loss of hair, thin hair, and gray hair.
- Dry mouth and eyes, mouth sores
- Joint pain and stiffening, inability to move joints
- Nausea, vomiting, diarrhea, abdominal cramps, weight loss, decreased appetite, inability to absorb medications or food, difficulty swallowing
- Liver inflammation
- Lung damage, cough, shortness of breath, wheezing
- Breakdown of red blood cells and platelets
- Rarely, inflammation and weakness of muscles and heart damage
- Weak immune system and increased risk of infection

Blood Drawing

Risks associated with drawing blood from your arm include temporary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting is also possible, although unlikely.

Reproductive Risks

The risks to an unborn baby or breastfeeding child from the study therapy are not known at this time. Females who are pregnant or who are breastfeeding a child may not participate in this research study. If you are a female capable of becoming pregnant, a serum (blood) pregnancy test will be required before you begin the research. The study doctor will discuss appropriate contraception methods to use during your participation in the study.

EXCLUSION CRITERIA

You cannot participate in this study if you have active GVHD or have had more than mild GVHD; have active viral, bacterial or fungal infections; have significant lung, kidney or liver problems; and if you are pregnant.

BENEFITS

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with your condition in the future.

ALTERNATIVE PROCEDURE/TREATMENT

You have the option of not participating in this research. Choosing to not participate will not change the care that you receive in any way. If you decide not to participate in this study, you would receive standard medical therapy. Before you decide to be in this research, your doctor will discuss the other options that are available and will tell you about the potential benefits and risks of these options.

ADDITIONAL COST

You or your insurance carrier is responsible for payment of all procedures including clinic or hospital costs, laboratory tests, and doctor's fees. Your insurance company may not pay for research treatments. You may wish to discuss coverage with your insurance company before agreeing to participate in this research study.

COMPENSATION

Every effort to prevent injury as a result of your participation will be taken. It is possible that you could develop complications or injuries as a result of participating in this research study.

In the event of injury resulting from this research, we will provide or arrange for treatment as necessary. This treatment, as well as other medical expenses, will be billed to you or your insurance company in the usual manner.

You are not waiving any legal rights you may have by signing this form.

You will not receive any compensation for being in this research study. There are no plans to provide financial compensation to you should this occur.

WITHDRAWAL

Taking part in this research study is voluntary. You do not have to participate in this research. If you choose to take part, you have the right to stop your participation at any time. If you decide not to participate or if you decide to stop your participation in the research at a later date, there will be no penalty or loss of benefits to which you are entitled. This will not in any way harm your relations with your doctors or with Carolinas Healthcare System. In other words, your decision not to participate in this research or to stop taking part in the research will not affect your access to medical care.

Your research doctor may take you out of the study without your prior permission. Some possible reasons for this are: continuing the research would be harmful, your condition has become worse,

you become pregnant, study instructions are not followed or if you experiences serious side effects.

During the course of the research you will be informed of any new findings that may affect your willingness to continue participation in this research.

If you will be participating in another clinical trial at Carolinas Medical Center or elsewhere while in this research, you should discuss the procedures and/or treatments with your physician or the investigators. This precaution is intended to protect you from possible side effects from interactions of research drugs, treatments or testing.

CONFIDENTIALITY

The records of this study will be kept private. In any sort of report we might publish, we will not include any information that will make it possible to identify a patient. Your record for this study may, however, be reviewed and/or photocopied by Miltenyi Biotec, Inc., the manufacturer of the CliniMACS device, by Carolinas HealthCare System, or by representatives of the Food and Drug Administration or other government agencies. To that extent, confidentiality is not absolute.

Medical records are considered confidential and records are kept in a secured area accessible to those involved in your treatment. All data entered into a computer will be coded. No data that may be linked with you will be entered on any network computer allowing access to confidential information. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Although we will make every effort possible to maintain confidentiality, there is however, a slight risk of loss of confidentiality.

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

AUTHORIZATION

If you wish to take part in this clinical study, you will be asked to sign this consent form. It allows the study sponsor and the study investigator to collect, process and pass on to the sponsor organizations any relevant personal health information collected from you during the study. These are activities routinely carried out during all clinical studies.

You have been told that personal information about you (including sensitive personal health information, such as your medical history and your racial/ethnic origin if relevant to the study) will be reviewed, collected on a computer database, stored in electronic or manual files, audited, and/or otherwise processed by:

- the clinical study investigator, Dr. Gilman, and research staff,
- Miltenyl Biotech, Inc.,
- regulatory or other governmental authorities of the United States and other countries,
- Carolinas HealthCare System employees,
- other persons or agencies as required by law or allowed by federal regulations.

You have been told that your personal data are being collected and processed to:

- check your suitability to take part in the study,
- monitor your treatment with the study therapy,
- compare and pool treatment results with those of other subjects in clinical studies,
- support the development of the study treatment.

You have been told that your personal information may be processed within the U.S. or elsewhere in the world or transferred to or from the U.S. for review, processing and/or storage by an associated company or a carefully selected third-party organization. By signing this document, you explicitly consent to the transfer of your personal information, including sensitive personal information, collected during this clinical study, for review, processing and/or storage. Your personal health information may be further shared by the groups above. If shared by them, the information will no longer be covered by the Privacy Rule. However, the groups are committed to keeping your personal health confidential.

You may refuse this authorization to transfer your personal information. If you choose not to agree to this authorization, you might be ineligible to participate in the study. If you decide not to sign this authorization, that will not harm your relations with your doctors or with Carolinas HealthCare System.

You have the right to inspect your medical record at any time. Your research record may be unavailable until the conclusion of the study. At that point, it will be available. Please speak with the study doctor if you desire to access your record.

You have been told whenever your personal information is processed, it will be kept confidential and secure, to the best of our ability. It will be used only for the purpose for which it was collected.

This authorization does not have an expiration date. You have been told that according to the guidelines for good clinical practice, the study investigator and sponsor will keep your personal information for at least 6 years. If you do not withdraw this authorization in writing, it will remain in effect indefinitely. If you wish to revoke authorization to use your personal information, you will notify the study doctor in writing at:

Andrew Gilman, MD
Director, Pediatric Blood and Marrow Transplantation
Levine Children's Hospital
Carolinas Medical Center
PO Box 32861
Charlotte, NC 28232-2861
Ph: (704) 381-6800

Some of the data obtained from your record prior to your revocation may still be used if considered necessary for the study.

FINANCIAL INTEREST OF THE INVESTIGATOR

The doctors will receive no benefits in any form from the company that manufactures the investigational device being tested in this study.

QUESTIONS

The researchers doing the study at Carolinas HealthCare System are Dr. Gilman and his associates. You may ask them any questions you have now. If you have questions later, you may contact them at 704-381-6800.

The Institutional Review Board is a group of people who review the research to protect your rights. If you have questions about the conduct of this study or about your rights as a research subject, you may call the chairperson of the Institutional Review Board of Carolinas HealthCare System for information regarding patients' rights in a research study. You can obtain the name and number of this person by calling (704) 355-3158.

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CONSENT

I have read the above information. I have asked any questions I had, and those questions have been answered. I agree to be in this study and provide authorization for use of my personal health information. To the best of my knowledge, I am not currently pregnant and will avoid becoming pregnant for the duration of my participation in the study. Dr. Gilman, one of his associates, or their designee will give me a copy of this form.

Patient (Representative*) Print Name	**Date**	**Time**

Patient (Representative*) Signature	**Date**	**Time**

Signature of Person Obtaining Consent	**Date**	**Time**

Investigator Signature	**Date**	**Time**

*Identity of representative:
_____Next of Kin
_____Parent/Guardian
_____Healthcare Power of Attorney