CONSENT FOR CANCER RESEARCH

Project Title: Tacrolimus, mini-dose Methotrexate and Mycophenolate Mofetil versus Tacrolimus and Methotrexate for the Prevention of Acute Graft-versus-Host-Disease (NCT01951885)

Principal Investigator: Betty Hamilton, M.D. (CC) 216-445-7580

Cancer research studies are coordinated by physicians and scientists from Cleveland Clinic, University Hospitals and Case Western Reserve University (CWRU) through the NIH National Cancer Institute (NCI) designated Case Comprehensive Cancer Center (Case CCC). The goal of this collaboration is to enhance cancer treatment and research in Northeast Ohio. This study is being offered at Cleveland Clinic.

INTRODUCTION

We are asking you to participate in a clinical research study. The purpose of this document is to summarize your discussion with the research team and provide you with written information to help you decide whether you want to participate in research. Your decision is completely voluntary.

Your treating doctor may also be an investigator on this research study. If so, your doctor will have an interest in both your welfare and in the research study. You are not required to take part in this research study offered by your doctor. You may ask for a second opinion from another doctor who is not linked to this study. If you choose not to be in this study, the quality of your regular medical care will not be affected.

Please ask any questions you may have about the study or this consent form before signing it. Please take your time to make your decision. You will be given a copy of this form to keep.

PURPOSE

You are being asked to participate in this research study because you have a medical disease called a hematological or lymphoproliferative malignancy (cancer of the blood) and have agreed to undergo an allogeneic hematopoietic cell transplant. This means the stem cells you receive for your transplant will come from a donor. The details of the transplant procedure are explained in a separate consent form. When you have an allogeneic transplant, you may get another disease called graft-versus-host disease (GVHD). GVHD is a reaction that occurs when donor bone marrow or peripheral blood stem cells are infused into your body and sees your body as foreign. As a result, this damages many tissues and affects your immune system. Many organs of the body (skin, (including hair), eyes, mouth, liver, joints, muscles and bowel) can be damaged by this immune disorder. GVHD can cause skin rashes, feeling sick to your stomach, throwing up, abdominal pain, diarrhea and/or yellowing of the skin or eyes. In severe cases, it can cause death. You will be given drugs that have been shown to help prevent you from getting GVHD or to lessen the severity of it. You will start GVHD prevention around the time you get your donor cells and it can last many months after the transplant.

The purpose of this study is to compare the effectiveness two different combinations of GVHD medications to prevent or lessen the severity of GVHD. One is using a standard of treatment regimen consisting of Methotrexate and Tacrolimus. The other treatment plan uses a lower dose of Methotrexate with Tacrolimus and Mycophenolate.

All of the drugs being used in this study are approved by the U.S. Food and Drug Administration (FDA) for helping to prevent (or lessen the severity of) graft versus host disease. This study consists of two study groups. Group A will receive the standard dose of Methotrexate with Tacrolimus. Group B will receive a "mini-dose" of Methotrexate with Tacrolimus and Mycophenolate. If you decide to join the study, you will be randomly assigned to Group A or B. If you choose not to join the study, you will receive standard treatment for GVHD.

About 100 people will take part in this research study at Cleveland Clinic

Conflict of Interest Disclosure
One or more of the Investigators conducting this study serve as paid speakers, consultants or advisory committee members for a company that makes products used in this study. These financial interests are within permissible limits established by the Cleveland Clinic Conflict of Interest Policy. If you have any questions, please ask your study doctor or call the Institutional Review Board at 216-444-2924.

STUDY PROCEDURES
Your participation in this study will last for one year after your hematopoietic cell transplant. You will take the GVHD drugs in Group A or B for at least 100 days and then your doctor will begin to taper the medications if you do not show any signs of GVHD. The taper is usually done by approximately 180 days, but may be longer if there are signs or symptoms of GVHD.

Your doctor may decide to stop or adjust the dose of the GVHD drugs you are receiving before 100 days for many reasons including if:

- It is considered to be in your best interest
- Pregnancy occurs during the course of therapy
- The study is temporarily or prematurely suspended
- You experience excessive toxicity to one of the drugs

If you are removed from the research study, your doctor will explain to you why you were removed. Your doctor will decide with you, what further treatment is needed or available for GVHD treatment.

In addition, you can choose to stop participating in the research study at any time. However, if you decide to end your participation in this study, we encourage you to talk to your doctor first.

It is standard of care to be followed closely after your hematopoietic cell transplant. These details are discussed in the treatment consent for your transplant. All of the assessments, tests, hospital stays and follow up appointments for this study are part of the standard of care for your hematopoietic cell transplant.

Screening
The evaluations to determine if you are eligible for this study will take place during your staging appointments for your hematopoietic cell transplant. All of these test and assessments are done as part of your transplant evaluation. These include the following:

- Age, gender, race
- Medical history
- Complete physical exam
- Disease assessment of tumor or site involved
- Weight
- Performance status (ECOG or Lansky scores). These scores represent how a person's disease affects the daily living activities and abilities of the person.
- Laboratory test results including complete blood count and differential, liver enzyme tests, coagulation tests, and tests to see if you have been exposed to viruses such as cytomegalovirus (CMV) and the AIDS virus.
- Pregnancy test for female of childbearing age
- Pulmonary function testing

Randomization/Study Intervention
If these evaluations show that you are eligible to participate in this research study and you choose to participate in this study, you will be assigned to Group A or Group B by chance using a process similar to the flip of a coin. This process is called randomization. Neither you nor the study staff will select the group to which you will be assigned.

You will receive Tacrolimus starting the day before (day -1) you receive your donor cells (day 0) regardless of which group you are assigned to. Tacrolimus is given once a day and will continue for 100 days after your transplant. Tacrolimus will be given intravenously but will be changed to oral medication when you can tolerate it.

If you are in Group B, you will also receive Mycophenolate starting the day after (day +1) your transplant and continuing for 45. Mycophenolate is given two times a day. Mycophenolate will be given intravenously but will be changed to oral medication when you can tolerate it.

Both Tacrolimus and Mycophenolate can be tapered after day 100 and day 45 respectively if there is not any evidence of GVHD. This will be decided by your doctor.

If you are in Group A, you will receive one Methotrexate dose of 15 mg/m^2 on the day after your transplant (day +1) and one Methotrexate dose of 10 mg/m^2 on day +3, day +6, and day + 11. Methotrexate is given intravenously. This is considered the standard dose of Methotrexate.

If you are in Group B, you will receive a "mini-dose" of Methotrexate on day +1, day +3 and day +6. This "mini-dose" will be 5 mg/m^2 of Methotrexate.

Study Assessments
After your hematopoietic cell transplant, data will be collected. All of the test and assessments are standard of care for patients undergoing a hematopoietic cell transplant. The following is a list of parameters that will be followed in this study after your transplant:

- Performance status (ECOG or Lansky). These scores represent how a person's disease affects the daily living activities and abilities of the person.
- Disease/tumor assessments
- Weight
- Laboratory test including complete blood count and differential, liver enzymes and coagulation studies
- Laboratory tests to monitor for infection with the Cytomegaolvirus (CMV), a common virus which can cause infection when you are immunosuppressed.
- Degree of inflammation and sores (mucositis) in your oral cavity from chemotherapy and medications.
- GVHD monitoring
- Laboratory tests to determine the percent of donor white cells compared to your own white cells in your blood (chimerism studies) to monitor how well your donor cells are growing in your bone marrow.
- Tacrolimus serum levels
- Organ (liver, kidney and pulmonary) toxicity assessments
- Infection
- Need for parenteral nutrition, which is nutrition given intravenously through a catheter if you are unable to eat.
- Use of intravenous medicine to control your pain.

The above parameters will be followed for one year after your transplant.

RISKS
GVHD is caused by an immune attack on your tissues from the transplanted donor cells and there for all treatments for GVHD include drugs to suppress (turn off) this immune attack. All of the drugs in this study can increase your chance of infection including the standard treatment for GVHD. There for you will take several protective antibiotics and be watched carefully for an infections while you are being treated for GVHD. Tell your doctors immediately if you get a fever, chills, a cough or any other symptoms that might be part of an infection.

All of the drugs in this study can have risk and side effects, including the standard treatment for GVHD. Your doctors will watch you carefully for any side effects and will modify your treatment if they develop. The drugs used in this study may cause all, some or none of the side effects listed below. In addition, there is always the risk that you might experience side effects or other adverse reactions which other patients before you have not experienced

Side effects that we know about are described in the tables below. Side effects are categorized into either:

- Likely – This type of side effect is expected to occur in more than 20% of patients. This means that 21 or more patients out of 100 might get this side effect

- Unlikely – This type of side effect is expected to occur in 20% of patients or fewer. This means that 20 patients or fewer out of 100 might get this side effect
- Rare, but Serious – This type of side effect does not occur very often, in fewer than 2% of patients, but is serious when it occurs. This means that 1 or 2 patients (or fewer) out of 100 might get this side effect.

Risk and Side Effects of Tacrolimus

Likely	Less Likely	Rare but Serious
• Reversible, but sometimes irreversible damage to the kidneys • Loss of magnesium, calcium and potassium • High blood pressure • Tremors (shaking of the hands) • Increases in blood lipids/fats (cholesterol and triglycerides)	• Nausea • Vomiting • Liver problems • Changes to the brain that may cause confusion • Insomnia • Unwanted hair growth	• Seizures • Changes in vision • Dizziness • Red blood cell destruction • Progressive multifocal leukoencephalopathy, a rare disease caused by a virus which causes progressive damage to the white matter of the brain. • Posterior reversible encephalopathy syndrome (PRES), a rare neurologic syndrome typically including symptoms of elevated blood pressure, headache, confusion and possibly seizure

It is very important that you do not eat grapefruit or drink grapefruit juice while taking Tacrolimus. It is very important that you do not drink soft drinks containing bergamottin. Common soft drinks that have bergamottin are *Fresca, Squirt* and *Sunny Delight.*

Risk and Side Effects of Mycophenolate Mofetil

Likely	Less Likely	Rare but Serious
• Miscarriage • Birth defects • Diarrhea • Damage to unborn baby • Limited effectiveness of birth control • Stomach pain • Upset stomach • Vomiting • Headache • Tremors (shaking of the hands) • Low white blood cell	• Low red blood cell count (anemia) • Rash • Difficulty falling asleep or staying asleep • Dizziness • Uncontrollable hand shakes	• Difficulty breathing • Unusual bruising • Fast heartbeat • Excessive tiredness • Weakness • Blood in stool • Bloody vomit • Change in vision • Progressive multifocal leukoencephalopathy, a rare disease caused by a virus which causes progressive damage to the

count with increased risk of infection • Increased blood lipids/fats (cholesterols) • Swelling of the hands, feet, ankles, or lower legs		white matter of the brain.

Additional Information about Mycophenolate Mofetil (MMF)

- MMF could be damaging to an unborn baby if you are pregnant or become pregnant while receiving the drug.
- MMF can make birth control pills less effective and increase your chances of becoming pregnant while taking it.
- If you could become pregnant, you must use 2 effective forms of birth control for 4 weeks before starting MMF, during treatment, and for 6 weeks after stopping MMF.

Risk and Side Effects of Methotrexate

Likely	Less Likely	Rare but Serious

• High levels of liver enzymes in the blood which may mean liver irritation or damage	• Nausea
	• Vomiting
	• Loss of appetite
	• Diarrhea
	• Chills and/or fever
	• Inflammation and/or sores in the mouth, gums, throat and/or esophagus
	• Inflammation of the intestines which may cause bleeding
	• Sensitivity to sunlight and increased risk of sunburn
	• Fewer white blood cells, red blood cells and platelets in the blood.
	  • A low number of red blood cells can make you feel tired and weak.
	  • A low number of white blood cells can make it easier to get infections.
	  • A low number of platelets causes you to
		• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate
		• The rapid death of large numbers of tumor cells which can cause the potassium and phosphate salts and the uric acid in the blood to rise quickly and this could lead to a life-threatening irregular heart beat or damage to the kidneys.
		• Severe rashes which can cause loss of skin or damage to mucous membranes or which can cause peeling, redness and pain on the palms of the hands and soles of the feet
		• Damage, inflammation and/or scarring of lung

	bruise and bleed • Learning disability • Dizziness • Sense of not feeling well or tiredness • Drowsiness • Blurred vision • Rashes with itching and hives • Hair loss, inflammation of the hair follicles • Acne • Tearing and inflammation of the eyes • Darkening of the fingernails	tissue which may make you short of breath and cough • Seizures • Temporary damage to the brain such that you may experience headaches, drowsiness, difficulty speaking or forming words, blurred vision or temporary blindness, and decreased reflexes • Temporary loss of function or feeling in the lower part of the body (partial paralysis) • Severe damage to brain tissue which over time could lead to difficulty carrying out normal daily tasks or could lead to a coma. • Inflammation and scarring of the liver • Damage to the bone which could lead to arthritis pain and weakness of the bone • Inflammation of the heart • Fluid buildup around the heart • Damage to the kidney

Reproductive Health/Sexual Activity

Because the risk to an unborn child (human embryo, fetus) or pregnant/lactating woman is unknown, you can NOT participate in this study if you are a female of childbearing potential unless you have a current negative pregnancy test. In addition, whether you are male or female, you must agree to either complete abstinence from heterosexual intercourse or use (two) medically approved forms of birth control for the duration of the study. You will agree to inform your doctor immediately if:

1) you have any reason to think you may be pregnant

2) you find that there is now a risk of you becoming pregnant

3) you have stopped using a medically approved form of birth control Acceptable methods of birth control include: birth control pills, birth control implants (depo-provera), diaphragm, intrauterine device (IUD), cervical cap and condoms with spermicide.

BENEFITS
Although this study cannot be guaranteed to be of benefit to you, it is hoped that your taking part may help in the treatment of your GVHD. A possible advantage of this study is that one of the treatment regimens may lessen the severity of GVHD and also lessen the toxicity of side effects of the drugs used in the treatment of GVHD. However, you may not benefit from this treatment. It is also hoped that the information learned from this study will help your doctors better treat GVHD in patients having hematopoietic cell transplants in the future.

ALTERNATIVE PROCEDURES OF TREATMENT
If you do not wish to participate in this study, you will be treated with standard GVHD therapy according to the type of preparative regimen and type of donor being used for your allogeneic hematopoietic cell transplant.

COSTS AND COMPENSATION
Cleveland Clinic will pay for the costs of procedures, tests, visits, hospitalization or drugs in connection with this treatment. You or your insurance company will be responsible for all cost because GVHD treatment is standard of care for allogeneic hematopoietic cell transplants

For more information on clinical trial and insurance coverage, you can visit the National Cancer Institute's (NCI) website at
http://cancer.gov/clinicaltrials/understanding/insurance-coverage
You can print a copy of the 'Clinical Trials and Insurance Coverage' information from this website. Another way to get information is to call 1-800-4-CANCER (1-800-422-6237) and ask NCI for a free copy.

RESEARCH-RELATED INJURY
If injury occurs as a result of your involvement in this research, medical treatment is available from Cleveland Clinic or another medical facility but you/your medical insurance will be responsible for the cost of this treatment. A research injury is an injury that happens as a result of taking part in this research study. If you are injured by a medical treatment or procedure that you would have received even if you weren't in the study, that is not considered a "research injury". There are no plans for payment of medical expenses or other payments, including lost wages, for any research-related injury. To help avoid injury, it is very important to follow all study directions.

Further information about research-related injuries is available by contacting the Cleveland Clinic Institutional Review Board at (216) 444-2924

PRIVACY AND CONFIDENTIALITY
Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you volunteer to participate in this research, your protected health information (PHI) that identifies you will be used or disclosed to Dr. Betty Hamilton and the research staff at

Cleveland Clinic for the purposes of this research and to Case Western Reserve University for administration.

The PHI that we may use or disclose (release) for this research may include your name, address, phone number, date of birth, Social Security number, information from your medical record, lab tests, or certain information relating to your health or condition.

Some of the tests and procedures done solely for this research study may also be placed in your medical record so other doctors know you are in this study. Upon completion of the study, you may have access to the research information that is contained in your medical record.

In addition to the investigators and research staff listed above, your PHI may be looked at by other groups involved with the study such as the Cleveland Clinic Institutional Review Board, and the Case Comprehensive Cancer Center Protocol Review and Monitoring Committee. Your PHI may also be used by and/or disclosed (released) to:

- The Food and Drug Administration;
- The Department of Health and Human Services;
- The National Cancer Institute (NCI);
- Other Institutional Review Boards;
- Data Safety and Monitoring Boards;

Once your personal health information is released it may be re-disclosed and no longer protected by privacy laws.

Your research information may be used and disclosed indefinitely, but you may stop these uses and disclosures at any time by writing to Dr. Betty Hamilton, Cleveland Clinic R35, 9500 Euclid Avenue, Cleveland, OH 44195 or calling 216/445-7580. . Your participation in the research will stop, but any information previously recorded about you cannot be removed from the records and will continue to be used as part of this research. Also, information already disclosed outside the Cleveland Clinic cannot be retrieved. This will not affect your rights to treatment or benefits outside the research study.

The Cleveland Clinic will not use your information collected in this study for another research purpose without your written permission; unless the Cleveland Clinic Institutional Review Board (IRB) assures your privacy and confidentiality is protected. The IRB is a committee whose job it is to protect the safety and welfare of research subjects.

By signing this informed consent form, you are authorizing such access to your research and medical record information. If you choose not to sign this consent form, you will not be able to participate in this research study. This Authorization does not have an expiration date.

Voluntary Participation

Your participation in this research study is voluntary. Choosing not to participate will not alter your usual health care or involve any penalty or loss of benefits to which you are otherwise entitled. If you decide to join the study, you may withdraw at any time and for any reason

without penalty or loss of benefits. If information generated from this study is published or presented, your identity will not be revealed.

In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you will be notified so that you can decide whether or not to continue participating.

Termination of Participation
Your participation in this study may be discontinued by your doctor or the investigator in charge of the study without your consent for any reason, including but not limited to:

- His/her judgment that any condition or circumstance may jeopardize your welfare or the integrity of the study
- Your failure to follow instructions of your doctor or the investigator
- If the study is stopped by the investigator and/or your doctor before completion of the study.

Questions About the Research
If you have any questions, you can ask the Principal Investigator and/or research staff. Dr. Betty Hamilton can be reached at 216/445-7580.

Emergency and After-hours Contact Information
As a Cleveland Clinic patient, you should contact the page operator at (216) 444-2200 or toll free at (800) 223-2273, and ask for the oncologist (cancer doctor) that is on call.

If you have questions about your rights as a research subject, you may contact the Institutional Review Board (IRB) at Cleveland Clinic IRB 216-444-2924

Where Can I Get More Information?
You may call the National Cancer Institute's Cancer Information Services at:
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI website at http://cancer.gov

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo

You will get a copy of this form. If you want more information about this study, ask your study doctor.

US National Institutes of Health (NIH) Clinical Trial Database
A description of this clinical trial will be available on http://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.

OPTIONAL SAMPLE RESEARCH

Collection, Testing, and Storage of Human Subject Material

The purpose of this portion of the consent document is to provide you with information to help you decide whether you wish to donate extra tissue samples for research during a planned clinical evaluation in which samples would be obtained for clinical purposes also. Your decision is completely voluntary and will not affect your medical care or your eligibility to participate in a clinical study if you choose not to donate your tissue. You are being asked to donate tissue samples to the Research Sample Repository because you have consented to a graft versus host disease (GVHD) study. A repository is a place where tissue samples are frozen and stored to be used for research in the future. Research in GVHD depends on the availability of blood, tissue (skin, GI tract and liver biopsies) and bone marrow of transplant recipients and donors for laboratory studies. The exact studies are not known at this time but they will be studies to improve our understanding of GVHD. Samples will be stored indefinitely.

In addition to laboratory studies, correlation of clinical data such as age, sex, disease, treatment, progression may be used.

Your tissue will be used for research only. It will not be sold. You do not have to donate your tissue for research. You are free to say yes or no. Your regular medical care will not change.

Risks of Stored Material and Genetic Testing

There may be unknown risks associated with the storage of samples. The samples contain genetic information (i.e. DNA) therefore can potentially be used to determine paternity or for the release of private health information. However, there are no plans to test for specific genetic diseases with your samples. We will make every attempt to insure that your personal information will be confidential, but complete confidentiality cannot be guaranteed.

A new federal law, called the Genetic Information Nondiscrimination Act (GINA), effective May 21, 2010, generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on genetic information. This law generally will protect you in the following ways: (1) Health insurance companies and group health plans may not request your genetic information that we get from this research and may not use your genetic information when making decisions regarding your eligibility or premiums; and (2) Employers with 15 or more employees may not use your genetic information from this research when making a decision to hire, promote, or fire you or when setting terms of your employment. This new federal law does not apply to companies that sell life insurance, disability insurance, or long-term care insurance and does not protect you against discrimination based on an already diagnosed genetic condition or disease.

Benefits of Stored Materials and Genetic Testing

There are no direct benefits to you from the collection and storage of these samples. You will not receive any financial gain from studies done using your stored samples.

No matter what you decide, it will not affect the care you receive as part of the study.

SIGNATURE FOR SAMPLE RESEARCH

1. Check one box: Please indicate whether you agree to permit the study investigators to request and do research on your biopsy tissue and the blood that is collected for clinical care. Testing may be conducted at any time in the future if investigators obtain Institutional Review Board approval from your transplant center.

☐ Yes ☐ No _____Initials of Research Subject or Legal Guardian

SIGNATURE

Statement of Participant
I have read and have had verbally explained to me the above information and have had all my questions answered to my satisfaction. I understand that my participation is voluntary and that I may stop my participation in the treatment at any time. Signing this form does not waive any of my legal rights. I understand that a copy of this consent will be provided to me. By signing below, I agree to take part in this treatment.

_____
Printed name of Participant

_____ _____
Participant Signature (if 18 years or older) Date

Statement of Person Conducting Informed Consent Discussion
I have discussed the information contained in this document with the participant and it is my opinion that the participant understands the risks, benefits, alternatives and procedures involved with this treatment.

_____
Printed name of person obtaining consent

_____ _____
Signature of person obtaining consent Date

Permission of Parent/Legal Guardian
You and your child have had the above treatment explained to you and your child, in language that you and your child can understand, and you give permission for your child's participation.

_____ _____
Parent/Guardian Signature (if child is less than 18 years) Date

Child Assent Statement
I have had the above treatment explained to me in language I understand and I agree to participate.

_____ _____
Child Signature (Children above age 7) Date