H-26617- PHASE I STUDY OF THE ADMINISTRATION OF EBV CTLS EXPRESSING CD30 CHIMERIC RECEPTORS FOR RELAPSED CD30+ HODGKIN'S LYMPHOMA AND CD30+ NON-HODGKIN'S LYMPHOMA (CAR CD30)

Background

In this consent form, "you" signifies you or your child.

Please read this information and feel free to ask any questions before you agree to take part in the study.

You are invited to take part in a research study. You have a type of lymph gland cancer called non-Hodgkin Lymphoma (NHL) or Hodgkin's Lymphoma (HL) (throughout the rest of this consent these 2 diseases will be referred to as "Lymphoma"). Your lymphoma has come back or has not gone away after treatment (including the best treatment we know for these cancers) or you are newly diagnosed but cannot receive standard treatment. Because there is no standard treatment for your cancer at this time or because the currently used treatments do not work fully in all cases, you are being asked to volunteer to take part in a gene transfer research study using special immune cells. You may have already thought about being in this study. You may even have made a decision about whether to be in the study. If this is true for you, it is important that we give you this information and talk about it before we start you in the study.

The body has different ways of fighting infection and disease. No single way seems perfect for fighting cancer. This research study combines two different ways of fighting disease: antibodies and T cells. Antibodies are proteins the protect the body from diseases caused by germs or toxic substances. They work by binding those germs or substances, which stops them from growing and causing bad effects. T cells, also called T lymphocytes, are special infection-fighting blood cells that can kill other cells, including tumor cells or cells that are infected with germs. Both antibodies and T cells have been used to treat patients with cancers: they both have been shown promise, but have not been strong enough to cure most patients. We hope that both will work better together.

We have found from previous research that we can put a new gene into T cells that will make them recognize cancer cells and kill them. We now want to see if we can attach a new gene to T cells that will help them do a better job at recognizing and killing lymphoma cells.

The new gene we will put in T cells makes and antibody called anti-CD30. This antibody sticks to lymphoma cells because of a substance on the outside of the cells called CD30. Anti-CD30 antibodies have been used to treat people with lymphoma, but have not been strong enough to cure most patients.

For this study, the anti-CD30 antibody has been changed so that instead of floating free in the blood it is now joined to the T cells. When an antibody is joined to a T cell in this way it is called a chimeric (combination) receptor. These chimeric receptor-T cells seem to kill some of the tumor, but they don't last very long and so their chances of fighting the cancer are unknown.

We have found that T cells that are also trained to recognize the virus that causes infectious mononucleosis (called Epstein Barr Virus or EBV) can stay in the blood stream for many years. These are called EBV specific Cytotoxic T Lymphocytes (EBV CTLS). By joining the anti-CD30 antibody to the

EBV CTLs, we believe that we will also be able to make a cell that can last a long time in the body and recognize and kill lymphoma cells. We call the final cells CD30 chimeric receptor EBV CTLs. There is also some evidence that patients whose tumors are EBV negative also benefit from this study treatment if their tumor expresses CD30. If we are successful, we hope that these new cells may be able to work longer and target and kill lymphoma cells. However, we do not know that yet. These CD30 chimeric EBV CTLs are an investigational product not approved by the Food and Drug Administration.

This research study is funded by the Leukemia and Lymphoma Society.

Purpose
The purpose of this study is to find the biggest dose of CD30 chimeric EBV CTLs that is safe to administer, to see how long they last, to assess what the side effects are, and to evaluate whether this therapy might help people with lymphoma.

Procedures
The research will be conducted at the following location(s):
Baylor College of Medicine, TCH: Texas Children's Hospital, and TMH: The Methodist Hospital.

Approximately 18 people may be treated on this study.

Earlier, you gave us blood to make CD30 chimeric-EBV CTLs in the laboratory. These cells were grown and frozen for you. To get the CD30 antibody to attach to the surface of the T cell, we inserted the antibody gene into the T cell. This is done with a virus called a retrovirus that has been made for this study and will carry the antibody gene into the T cell. Because you will have received cells with a new gene in them you will be followed for a total of 15 years to see if there are any long term side effects of gene transfer. In the event of death, we will request permission to perform an autopsy to learn more about the effects of this intervention on your disease.

When you enroll on this study, you will be assigned a dose of CD30 chimeric receptor-EBV CTLs. The dose level of cells that you will receive will not be based on a medical determination of what is best for you, instead the dose is based on the order in which you enroll on the study relative to other participants. Subjects enrolled earlier in the study will receive a lower dose of cells than those enrolled later in the study. The risks of harm and discomfort from the study treatment may bear some relationship to the dose level. The potential for direct benefit, if any, may also vary with the dose level. To enroll on this study you will need to have recovered from toxic effects of previous chemotherapy for at least one week and not be receiving any other investigational agents. You cannot have received any tumor vaccines within the previous six weeks.

You will be given an injection of cells into the vein through an IV line at the assigned dose. Before you receive the injection, you may be given a dose of Benadryl and Tylenol to minimize any possible allergic reaction. The injection will take 1-10 minutes. We will follow you in the clinic after the injection for up to 4 hours. The study treatment will be given by the Center for Cell and Gene Therapy at Texas Children's Hospital or Houston Methodist Hospital.

Medical tests before study treatment—
Before being treated, you will receive a series of standard medical tests:
Physical exam
Blood tests to measure blood cells, kidney and liver function
Pregnancy test for women of child bearing potential
Measurements of your tumor by scans and/or bone marrow studies

Medical tests during and after study treatment—
You will receive standard medical tests when you are getting the infusions and after:
Physical exams
Blood tests to measure blood cells, kidney and liver function
Measurements of your tumor by scans (CT/MRI/or PET) and/or bone marrow studies at time of infusion and at 8 weeks after the infusion

To learn more about the way the CD30 chimeric receptor-EBV specific T cells are working and how long they last in the body, extra blood will be drawn. The total amount on any day is about 10 teaspoons (or less than half a teaspoon per pound of weight for children). This volume is considered safe, but may be decreased if you are anemic.

This blood may be drawn from a central line if you have one. On the day you receive the cells, blood will be taken before the cells are given and several hours afterwards. Other blood will be drawn one week after the infusion, 2 weeks, 3 weeks (optional), 4 weeks, 6 weeks and 8 weeks after the infusion, every 3 months for 1 year, every 6 months for 4 years, then yearly for a total of 15 years. The total blood drawn during your participation in this study will not exceed 300 teaspoons.

During the time points listed above, if the T cells are found in your blood at a certain amount an extra 5ml of blood may need to be collected for additional testing.

If you have a biopsy of your tumor or bone marrow studies while on this study, we may ask to have a piece of tumor or bone marrow to look for CD30 chimeric receptor-EBV specific T cells. We will also look at any scans you have as standard of care.

These specimens and information about your circumstances may be used in other research being conducted in immune therapy. Although there will be a record identifying under what circumstances these specimens were obtained, under all circumstances your identity will be kept confidential. There is a small risk for the loss of confidentiality. However, study personnel will make every effort to minimize this risk.

Please initial here to confirm if you agree or not to allow any leftover samples to be kept for the purpose of future medical research being conducted in immune therapy.

_____ Yes _____No

If you decide to withdraw at any time during the study both samples and data collected during your participation will be maintained.

Research related health information

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

If you sign this document, you give permission to people who give medical care and ensure quality from Baylor College of Medicine, TCH: Texas Children's Hospital, and TMH: The Methodist Hospital to use or disclose (release) your health information that identifies you for the research study described in this document.

The health information that we may use or disclose (release) for this research includes:

- Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.
- Specific information concerning HIV
- Demographic information (name, D.O.B., age, gender, race, etc.)
- Billing or financial records

The health information listed above may be used by and or disclosed (released) to researchers, their staff and their collaborators on this research project, the Institutional Review Board, Baylor College of Medicine, TCH: Texas Children's Hospital, TMH: The Methodist Hospital, and LEUKEMIA & LYMPHOMA SOCIETY and their representatives.

Agents of the U.S. Food and Drug Administration may inspect the research records including your health information. Agents of regulatory agencies such as the U.S. Department of Health and Human Services will be permitted to inspect the research records including your health information.

A Data and Safety Monitoring Board will have access to the research records including your health information.

Use or Disclosure Required by Law

Your health information will be used or disclosed when required by law.

Your health information may be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability and conducting public health surveillance, investigations or interventions.

Baylor College of Medicine, TCH: Texas Children's Hospital, and TMH: The Methodist Hospital are required by law to protect your health information. By signing this document, you authorize Baylor College of Medicine, TCH: Texas Children's Hospital, and TMH: The Methodist Hospital to use and/or disclose (release) your health information for this research. Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

Please note that the research involves treatment. You do not have to sign this Authorization, but if you do not, you may not receive research-related treatment. To maintain the integrity of this research study, you generally will not have access to your personal health information related to this research until the study is complete. However, your health information that is necessary to your care will be provided to you or your physician. At the conclusion of the research and at your request, you generally will have access to your health information that Baylor College of Medicine, TCH: Texas Children's Hospital, and TMH: The Methodist Hospital maintain in a designated record set, which means a set of data that includes medical information or billing records used in whole or in part by your doctors or other health care providers at Baylor College of Medicine, TCH: Texas Children's Hospital, and TMH: The Methodist Hospital to make decisions about individuals. Access to your health information in a designated record set is described in the Notice of Privacy Practices provided to you by representatives of the specific institution where you are being enrolled into this research study which are: Baylor College of Medicine, TCH: Texas Children's Hospital, and TMH: The Methodist Hospital.

Please note that you may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, researchers, their staff and their collaborators on this research project, the Institutional Review Board, LEUKEMIA & LYMPHOMA SOCIETY and their representatives, regulatory agencies such as the U.S. Department of Health and Human Services, FDA, Baylor College of Medicine, Data and Safety Monitoring Board, TCH: Texas Children's Hospital, and TMH: The Methodist Hospital may still use or disclose health information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. If you revoke this Authorization, you may no longer be allowed to participate in the research described in this Authorization.

To revoke this Authorization, you must write to: Helen Heslop, MD, Feigin Center, 1102 Bates Street, Suite 1630, Houston, TX 77030.

This authorization does not have an expiration date. If all information that does or can identify you is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes.

No publication or public presentation about the research described above will reveal your identity without another authorization from you.

Potential Risks and Discomforts

While on this research study you are at risk for side effects from the study treatments. There may also be other side effects that we cannot predict. Other drugs will be given to make side effects less serious

and less uncomfortable. Many side effects will go away shortly after treatment is stopped, but in some cases, side effects may be long lasting or permanent. Some side effects may be life threatening.

Patients are watched carefully and treatment is stopped if serious side effects develop.

Side Effects of the CD30 Antibody:
There are several antibodies that are similar to CD30 and have been given to patients with cancer. Those antibodies have been given with few side effects although some patients had decreases in their blood counts. These side effects are unlikely in this study where the antibody is stuck to the T cells.

One other side effect is that the antibody may react with normal cells, such as normal immune system cells that have CD30 on their surface, as well as lymphoma cells. In that case you would not have cells which help you fight infection and you would have a higher risk of some types of infection. If this happened, we would treat you with steriods to try and kill the CD30 chimeric receptor-EBV CTLs we have given you.

In one study at another site using T cells with a different antibody specific for colon cancer stuck to them, a patient who received these cells developed breathing problems after the infusion and died several days later. The investigators think this may have been due to the antibody cross reacting with lung cells. This patient also received a much bigger dose of T cells than in this study and had other treatment before getting the cells so we think it is unlikely that this problem would occur in this study but do not know for sure.

Also, mild and reversible nausea, diarrhea, fatigue, fever, headache, pruritus (itching), and cough have occurred and some patients developed problems with their thyroid.

Side Effects of the T cells:
Similar types of T cells have been given to patients with cancers and infections. Usually the patients have no problems with the infusions. With the increased doses of T-cells, there is a possibility that the harmful effects could increase, though in previous studies we have seen very minimal problems. In some patients with large tumors, the cells have caused inflammation leading to fever and flu-like symptoms, as well as swelling within the tumor. This swelling could be potentially dangerous and even life threatening depending on the site of the tumor.

Another possible side effect from the EBV CTLs is that some of the EBV-infected B cells will be injected with the T cells into your body. We think this is unlikely because the B cells are treated with radiation to stop them from growing and an antiviral drug that prevents release of EBV is added when we make the cells.

A small percentage of patients that receive this type of therapy develop a life threatening complication known as a cytokine storm. This complication causes high body temperature, increased heart rate, and low blood pressure. This complication can be life threatening. There are treatments for this

complication.

Side Effects of the Gene Transfer:
To get the antibody to attach to the surface of the T cell, we must deliver the gene for the antibody into the T cells. This is done with a virus called a retrovirus that has been made for this study. The retrovirus (a special virus that can carry a new gene into cells) has been altered so it should not be able to come out of the T cells and infect other cells. When retroviral vectors enter a normal cell in the body, the gene it carries goes into the DNA (genetic material) of the cell. Human DNA contains thousands of genes. When the retrovirus adds the gene it carries into the human DNA this is called integration. Integration can occur anywhere in DNA and most integration does not harm the cell or the study subjects. However, thereis a chance that there may be some parts of human DNA where integration may turn on or off other genes. For example, if it turned on a gene that made a substance that caused the cell to grow it might cause uncontrolled increase in the numbers of cells, which could result in cancer. Conversely, if it turned off a gene that made a substance that limits cell growth, it might have the same effect. There was one study in mice where cancer occurred, but most other animal studies have shown this risk to be very low with the type of retrovirus we are using.

Some patients who have received marrow stem cells modified with retroviral vectors to correct immunodeficiency disorders have developed leukemias that are due to the vectors. To date this has only been seen in patients being treated who have received stem cells treated with retroviral vectors for immunodeficiency conditions. No leukemias or other cancers have been seen in hundreds of patients who have received T cells modified with retroviral vectors. However, the risk of developing cancer is a risk of receiving products that contain a retroviral vector.

Acetaminophen (Tylenol): Rarely large doses or long term usage can cause liver damage, rash, itching, fever, lowered blood sugar. These side effects are unlikely at the doses being used for this study.

Acetaminophen (Tylenol) with codeine: Side effects for acetaminophen are the same as those listed above. Side effects for codeine include lightheadedness, dizziness, drowsiness, nausea, vomiting, loss of appetite and sweating. Rarely, codeine can cause allergic reactions.

Benadryl: Drowsiness, dizziness, headache, irritability, stomach upset, vision changes (e.g., blurred vision), decreased coordination, or dry mouth/nose/throat may occur

Blood Draws: pain, bruising, lightheadedness, potential for infection

Because of potential or unknown effects of the study on a fetus, if you are a woman of childbearing potential, you must have a negative serum pregnancy test prior to entry into this study. There also may be an increased risk of miscarriage for any women of childbearing potential who may wish to become pregnant in the future and should be reported to study staff if this is experienced during the time you are followed on this study.

Since this is a research study, there may be risks that are currently unknown. We will watch you very carefully for any side effects. If there are bad side effects, we will stop the treatment.

There may be unknown risks or discomforts involved. Study staff will update you in a timely way on any new information that may affect your decision to stay in the study. There is a small risk for the loss of confidentiality. However, the study personnel will make every effort to minimize these risks.

Potential Benefits

The benefits of participating in this study may be: that your immune system may begin to kill the cancer cells. This could make the cancer grow more slowly, or get smaller, or go away for a while. This benefit is at best only possible, and may not happen to you. Your participation may help the investigators better understand how the immune system can fight this disease. However, you may receive no benefit from participating.

Alternatives

The following alternative procedures or treatments are available if you choose not to participate in this study: other treatments with chemotherapy, radiation, or surgery. Your doctor will discuss these other options with you. Additionally, the same alternatives are available if, after participation in this research project, you are not responding to the study treatment. You may also choose to receive no further treatment for your tumor. If this is your decision, your doctor will help manage your symptoms and will discuss this with you.

Subject Costs and Payments

You will not be charged for the preparation or manufacture of the CD30 chimeric receptor-EBV CTLs, nor will you be charged for the laboratory studies done to monitor how well these T cells are working and to measure how long they stay in your body. You or your insurance company may be responsible for some research related costs including the infusion of the product. You or your insurance company are both responsible for medical services that are part of the standard of care for your cancer.

You will not be paid for taking part in this study.

This institution does not plan to pay royalties to you if a commercial product is developed from blood or tissue obtained from you during this study.

Research Related Injury

If you are injured as part of your participation in this study, there are no plans to pay you.

Research personnel will try to reduce, control, and treat any complications from this research. If you are injured because of this study, you will receive medical care that you or your insurance will have to pay for just like any other medical care.

Women of Childbearing Potential

It is possible that the medicines used in this study could injure a fetus if you or your partner becomes pregnant while taking them. Because of the potential risks involved, you or your partner should not become pregnant while you are participating in this study.

If you are sexually active or become sexually active and can get pregnant or can get your partner pregnant, you must agree to use one of the following forms of birth control every time you have sex and for (6) months afterwards:

* oral contraceptives ("the pill"),
* intrauterine devices (IUDs),
* contraceptive implants under the skin, or contraceptive injections,
* condoms with foam.

Should you become pregnant while on this study, you must immediately notify the study personnel.

The investigator will assist you in finding appropriate medical care. The investigator also may ask to be allowed to continue getting information about your pregnancy. You can choose not to provide this information.

Subject's Rights

Your signature on this consent form means that you have received the information about this study and that you agree to volunteer for this research study.

You will be given a copy of this signed form to keep. You are not giving up any of your rights by signing this form. Even after you have signed this form, you may change your mind at any time. Please contact the study staff if you decide to stop taking part in this study.

If you choose not to take part in the research or if you decide to stop taking part later, your benefits and services will stay the same as before this study was discussed with you. You will not lose these benefits, services, or rights.

The investigator, HELEN E HESLOP, and/or someone he/she appoints in his/her place will try to answer all of your questions. If you have questions or concerns at any time, or if you need to report an injury related to the research, you may speak with a member of the study staff: HELEN E HESLOP at 832-824-4662 during the day and 713-441-1450 after hours.

Members of the Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals (IRB) can also answer your questions and concerns about your rights as a research subject. The IRB office number is (713) 798-6970. Call the IRB office if you would like to speak to a person independent of the investigator and research staff for complaints about the research, if you cannot reach the research staff, or if you wish to talk to someone other than the research staff.

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.

The National Institutes of Health and the National Cancer Institute may have access to your records for research purposes. Coded information may be provided to the NIH/NCI such as Patient ID, Patient Zip code, Patient country code and Patient Birth date (month/year). However, in the event of an audit NIH/NCI might have access to more information that is part of your research record.

If your child is the one invited to take part in this study you are signing to give your permission. Each child may agree to take part in a study at his or her own level of understanding. When you sign this you also note that your child understands and agrees to take part in this study according to his or her understanding.

Please print your child's name here _____

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Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

Subject	Date
Legally Authorized Representative Parent or Guardian	Date
Investigator or Designee Obtaining Consent	Date
Witness (if applicable)	Date
Translator (if applicable)	Date