H-17946- ADMINISTRATION OF TGF-B RESISTANT LMP-SPECIFIC CYTOTOXIC T-LYMPHOCYTES TO PATIENTS WITH RELAPSED EBV-POSITIVE LYMPHOMA

Background

In this document "you" signifies either you or your child.

You have a type of lymph gland cancer called Hodgkin Disease, non-Hodgkin Lymphoma or lymphoepithelioma (throughout the rest of this consent these 3 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).

We are asking you to volunteer to be in a research study using special immune system cells called TGFb-resistant LMP-specific cytotoxic T lymphocytes (DNR-CTL), a new experimental therapy. You may have already thought a lot about being in this study. You may even have already made a decision about whether to be in the study. Even 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.

Some patients with Lymphoma show signs of infection with the virus that causes infectious mononucleosis Epstein Barr virus (EBV) before or at the time of their diagnosis of the Lymphoma. EBV is found in the cancer cells of up to half the patients with Lymphoma, suggesting that it may play a role in causing Lymphoma. The cancer cells infected by EBV are able to hide from the body's immune system and escape being killed by releasing a substance called Transforming Growth Factor-beta (TGFb). We want to see if special white blood cells (called T cells) that have been given a gene which we hope will let them survive against TGFb and have been trained to kill EBV infected cells, can also survive in your blood and kill the tumor.

We have used this sort of therapy with specially trained T cells to treat a different type of cancer that occurs after bone marrow and solid organ transplant called post transplant lymphoma. In this type of cancer we were able to successfully prevent and treat post transplant lymphoma. However when we used a similar approach in Hodgkin disease some patients had a partial (some) response to this therapy, but no patients had a complete (total) response.

In a follow-up study we tried to find out if we could improve this treatment by growing T cells that recognize two of the proteins expressed on Lymphoma cells called LMP-1 and LMP2a. These special T cells were called LMP-specific cytotoxic T-lymphocytes (CTLs). Although some patients had tumor responses, CTL therapy alone did not cure patients who had a lot of disease. We think that a reason for this is that the tumor cells are releasing TGFb, which is a substance that inhibits the growth and function of CTLs. For this reason we want to find out if we can make the CTL resistant to TGFb by putting in a new gene called TGFb resistance gene. We hope but do not know that this will improve this treatment for relapsed lymphoma. These TGFb-resistant LMP-specific cytotoxic T lymphocytes are an investigational product not approved by the Food and Drug Administration.

This research study is sponsored by National Institutes of Health.

Purpose

The purpose of this study is to find the largest safe dose of TGFb resistant LMP-specific cytotoxic T cells, to learn what the side effects are and to see whether this therapy might help patients with Hodgkin

disease, non-Hodgkin Lymphoma and lymphoepithelioma.

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 50 subjects will participate in this study. About 20 of those will be treated on this study.

We already tested a biopsy of your tumor to see if your tumor cells are EBV positive and to see if you were eligible for the study. We then took 60-70 ml (12 teaspoonfuls) of blood from you, which we then used to grow T cells. We first grew a special type of cell called dendritic cells, which stimulated the T cells and we added a specially produced human adenovirus that carries the LMP1 and LMP-2a genes into the dendritic cells. Addition of a gene to the cells is known as gene transfer. Adenoviruses are the types of viruses commonly found in the human respiratory system that can cause a respiratory infection. Respiratory illnesses caused by adenovirus infections range from the common cold to pneumonia. These dendritic cells were then treated with radiation so they could not grow and they were then used to stimulate T cells. The stimulation trained the T cells to kill cells with LMP on their surface. We then made more LMP-specific CTLs by stimulating them with EBV infected cells (which we made from your blood infecting them with EBV [called B95] in the laboratory). We also put the adenovirus that carries the LMP1 and LMP2 genes into these EBV infected cells so that we increase the amount of LMP1 and LMP2, which these cells have.

Again, these EBV infected cells were treated with radiation so they cannot grow. Once we made sufficient numbers of T cells we tested them to see if they kill cells with LMP on their surface. To make sure that these cells won't attack your tissues we tested the cells against your skin cells or against T cells that we grew in the laboratory.

To make these CTL resistant to the effects of the TGFb released by the tumor we put in a new gene called a mutant TGFb receptor. We used a mouse retrovirus that had been changed to stop it from causing infection to add the mutant TGFb receptor to the cells. Retroviruses differ from adenoviruses in that they enter the cell's DNA (genetic material) to make permanent changes to the cell. The risks of retroviruses will be discussed later in this consent form.

WHAT THE INFUSION WILL BE LIKE
After making these cells the cells were frozen. If you agree to participate in this study, at the time you are scheduled to be treated, the cells will then be thawed and injected into you over 10 minutes. You may be pretreated with Tylenol (acetaminophen) and Benadryl (diphenhydramine). Tylenol and Benadryl are given to prevent a possible allergic reaction to the T cell administration. Initially two doses of T cells will be given two weeks apart. If after your second infusion there is a reduction in the size of your lymphoma (or no increase) on CT or MRI scans as assessed by a radiologist, you can receive up to six additional doses if it would be to your benefit, if you would like to receive more doses, and if there is enough product remaining to give you additional doses. This is a dose escalation study, which means that we do not know the highest dose of T cells with the new gene that is safe. To find out we will give the cells to 2 participants at one dose level. If that is safe we will raise the dose given to the next group of

participants. The dose you will get will depend on how many participants get the agent before you and how they react. The investigator will tell you this information. This will help you think about possible harms and benefits. Since the treatment is experimental, what is likely to happen at any dose is not known

All of the Treatments will be given by the Center for Cell and Gene Therapy at Texas Children's Hospital or Houston Methodist Hospital.

FOLLOW-UP STUDIES
We will follow you after the injections. Initially, at each visit about 10ml (2 teaspoonfuls) of blood will be taken every other week for 6 weeks after the first injection and then every 3 months for 1 year to monitor your blood chemistry and hematology. To learn more about the way the T cells are working in your body, an extra 20-50 mls (4-10 teaspoons) of blood will be taken before each infusion and then 2-4 hours after each infusion, 3-4 days after each infusion (optional depending on patient preference) and then weekly for 4 weeks and at weeks 6 and 8 after the first infusion. Blood will then be taken 4 weeks later and then every 3 months for 1 year, then once every 6 months for the first four years and then yearly thereafter for the next 10 years. Total time participation for this study will be 15 years.

We will use this blood to test to look for the frequency and activity of the cells that we have given; that is, to learn more about the way the T cells are working and how long they last in the body. We will also use this blood to see if there are any long-term side effects of putting the new gene (mutant TGFB receptor) into the cells. In addition to the blood draws, because you have received cells that have had a new gene put in them you will need to have long term follow up for 15 years so we can see if there are any long term side effects of the gene transfer. Once a year you will be asked to have your blood drawn and answer questions about your general health and medical condition. The investigators may ask you to report any recent hospitalizations, new medications, or the development of conditions or illness that were not present when you enrolled in the study and may request that physical exams and/or laboratory tests be performed if necessary. We will also ask you to participate in the long-term follow-up phase if you leave the study early.

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.

In the event that a tumor biopsy is performed for clinical reasons we will request permission to obtain excess sample to learn more about the effects of the treatment on your disease.

In the event of death, we will request permission to perform an autopsy to learn more about the effects of the treatment on your disease and if there were any side effects from the cells with the new gene. 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
- Photographs, videotapes, and/or audiotapes of you

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 NATIONAL INSTITUTES OF HEALTH (NIH) 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, NATIONAL INSTITUTES OF HEALTH (NIH) 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 Tower, CAGT, 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

Similar types of T cells that are trained to recognize EBV (but without the new mutant TGFb receptor gene) have been given to over 60 patients to prevent lymphoma after transplant and to 24 patients with Hodgkin's disease or lymphoma. Most patients had no side effects. In some patients with a lot of disease the cells have caused inflammation leading to fever and flu-like symptoms as well as swelling at the tumor site. This swelling could be potentially dangerous and even life threatening depending on the site.

It is possible that the T cells will cause an allergic reaction, which could include itching, rash and shortness of breath (potentially life-threatening).

As mentioned previously, in this study we are using two sorts of gene transfer (putting a new gene in a cell). The first uses a virus called adenovirus to put a gene into dendritic cells and EBV infected cells

that will be used in the laboratory to stimulate the T cells. Adenovirus is a common virus found in human respiratory systems. In its normal state, it can reproduce and cause a respiratory infection. Respiratory illnesses caused by adenovirus infections range from the common cold to pneumonia. As the T cells will be grown for several weeks after contact with the dendritic cells we think it is very unlikely that any adenovirus or dendritic cells will be injected with the T cells. However, should you receive any adenovirus or dendritic cells, these may cause an inflammatory reaction. There is one report of a patient in a gene transfer study who received a large dose of adenovirus into a blood vessel leading to his liver who died. We will also test the T cells before we use them to reduce the likelihood that any of your cells that we have infected with EBV will be injected with the T cells.

Another possible side effect is that some of the B cells or the B95 EBV virus will be injected with the T cells into your body. We think this is unlikely because the B cells have been treated with radiation to stop them from growing, and an antiviral drug that prevents release of EBV has been added to the cultures.

The second type of gene transfer in this study uses a virus known as a retrovirus to deliver the gene into the T cells. This is known as a retroviral vector. 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 retroviral vector adds the gene it carries into the human DNA this is called integration. Integration can occur anywhere in human DNA, and most integration does not harm the cell or the patient. However, there is a chance that there may be some parts of human DNA where integration may affect other genes. For example, if integration turned on a gene that caused the cell to grow this could cause uncontrolled increase in the numbers of cells, which could result in cancer. 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.

If you have a needle stick for blood collection, there is a risk of bruising or bleeding at the site of the needle stick and a risk of discomfort or pain at the site. There is also a very small risk of infection at the site of the needle stick.

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.

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

Because of potential or unknown effects of the study on a fetus, if you are a woman of child-bearing potential, you must have a negative serum pregnancy test prior to entry into this study.

We will watch you very carefully for any side effects. If there are serious 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: It is possible that your immune system may begin to kill the cancer cells, making the Lymphoma go into remission or go away. Additionally, your participation may help the investigators better understand how the immune system can fight Lymphoma. This could benefit other patients with Hodgkin disease, non-Hodgkin Lymphoma or lymphoepitheliomia. 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: no further treatment, or other treatment with chemotherapy and radiation. 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 therapy.

Subject Costs and Payments

You will not be charged for the manufacture/production of the modified T cell product or for any evaluations that are being done solely as part of your participation in this research project. You may be charged for some research related costs including the infusion of the product. You will be charged for any tests or treatments that are being done as standard treatment for your Lymphoma.

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: Dr. Helen Heslop at 713-441-1450 during the day and 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.

People who give medical care and ensure quality from the institutions where the research is being done, the National Institutes of Health, National Cancer Institute, agents of the Food and Drug

Administration, and regulatory agencies such as the U.S. Department of Health and Human Services will be allowed to look at sections of your medical and research records related to this study.

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.

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 _____

H-17946- ADMINISTRATION OF TGF-B RESISTANT LMP-SPECIFIC CYTOTOXIC T-LYMPHOCYTES TO PATIENTS WITH RELAPSED EBV-POSITIVE LYMPHOMA

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

H-17946- ADMINISTRATION OF TGF-B RESISTANT LMP-SPECIFIC CYTOTOXIC T-LYMPHOCYTES TO PATIENTS WITH RELAPSED EBV-POSITIVE LYMPHOMA

Background

In this document "you" signifies either you or your child.

You have a type of lymph gland cancer called Hodgkin Disease, non-Hodgkin Lymphoma or lymphoepithelioma (throughout the rest of this consent these 3 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).

We are asking you to volunteer to be in a research study using special immune system cells called TGFb-resistant LMP-specific cytotoxic T lymphocytes(DNR-CTL), a new experimental therapy. You may have already thought a lot about being in this study. You may even have already made a decision about whether to be in the study. Even 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.

Some patients with Lymphoma show signs of infection with the virus that causes infectious mononucleosis Epstein Barr virus (EBV) before or at the time of their diagnosis of the Lymphoma. EBV is found in the cancer cells of up to half the patients with Lymphoma, suggesting that it may play a role in causing Lymphoma. The cancer cells infected by EBV are able to hide from the body's immune system and escape being killed by releasing a substance called Transforming Growth Factor-beta (TGFb). We want to see if special white blood cells (called T cells) that have been given a gene which we hope will let them survive against TGFb and have been trained to kill EBV infected cells, can also survive in your blood and kill the tumor.

We have used this sort of therapy with specially trained T cells to treat a different type of cancer that occurs after bone marrow and solid organ transplant called post transplant lymphoma. In this type of cancer we were able to successfully prevent and treat post transplant lymphoma. However when we used a similar approach in Hodgkin disease some patients had a partial (some) response to this therapy, but no patients had a complete (total) response.

In a follow-up study we tried to find out if we could improve this treatment by growing T cells that only recognized one of the proteins expressed on Lymphoma cells called LMP-2a. These special T cells were called LMP-2a specific cytotoxic T-lymphocytes (CTLs). Although some patients had tumor responses, CTL therapy alone did not cure patients who had a lot of disease. We think that a reason for this is that the tumor cells are releasing TGFb, which is a substance that inhibits the growth and function of CTLs. For this reason we want to find out if we can make the CTL resistant to TGFb by putting in a new gene called TGFb resistance gene. We hope but do not know that this will improve this treatment for relapsed lymphoma. These TGFb-resistant LMP-specific cytotoxic T lymphocytes are an investigational product not approved by the Food and Drug Administration.

This research study is sponsored by National Institutes of Health.

Purpose

The purpose of this study is to find the largest safe dose of TGFb resistant LMP-specific cytotoxic T cells(DNR-CTL), to learn what the side effects are and to see whether this therapy might help patients

with Hodgkin disease, non-Hodgkin Lymphoma and lymphoepithelioma.

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 50 subjects will participate in this study. About 20 of those will be treated on this study.

We already tested a biopsy of your tumor to see if your tumor cells are EBV positive and to see if you were eligible for the study. We then took 60-70 ml (12 teaspoonfuls) of blood from your donor, which we then used to grow T cells. We first grew a special type of cell called dendritic cells (or monocytes), which stimulated the T cells and we added a specially produced human adenovirus that carries the LMP 1 and LMP-2a genes into the dendritic cells(or monocytes). Addition of a gene to the cells is known as gene transfer. Adenoviruses are the types of viruses commonly found in the human respiratory system that can cause a respiratory infection. Respiratory illnesses caused by adenovirus infections range from the common cold to pneumonia. These dendritic cells (or monocytes) were then used to stimulate T cells. The stimulation trained the T cells to kill cells with LMP on their surface. We then made more LMP-specific CTLs by stimulating them with EBV infected cells (which we made from your blood or your donor's blood by infecting them with EBV [called B95] in the laboratory). We also put the adenovirus that carries the LMP1 and LMP2 genes into these EBV infected cells so that we increase the amount of LMP1 and LMP2, which these cells have.

These EBV infected cells were treated with radiation so they cannot grow. Once we made sufficient numbers of T cells we tested them to see if they kill cells with LMP on their surface. To make sure that these cells won't attack your tissues we tested the cells against your skin cells or against T cells that we grew in the laboratory.

To make these CTL resistant to the effects of the TGFb released by the tumor we put in a new gene called a mutant TGFb receptor. We used a mouse retrovirus that had been changed to stop it from causing infection to add the mutant TGFb receptor to the cells. Retroviruses differ from adenoviruses in that they enter the cell's DNA (genetic material) to make permanent changes to the cell. The risks of retroviruses will be discussed later in this consent form.

WHAT THE INFUSION WILL BE LIKE

After making these cells the cells were frozen. If you agree to participate in this study, at the time you are scheduled to be treated, the cells will then be thawed and injected into you over 10 minutes. You may be pretreated with Tylenol (acetaminophen) and Benadryl (diphenhydramine). Tylenol and Benadryl are given to prevent a possible allergic reaction to the T cell administration. Initially two doses of T cells will be given two weeks apart. If after your second infusion there is a reduction in the size of your lymphoma (or no increase) on CT or MRI scans as assessed by a radiologist, you can receive up to six additional doses if it would be to your benefit, if you would like to receive more doses, and if there is enough product remaining to give you additional doses. This is a dose escalation study as we do not know what the highest dose of T cells with the new gene is safe. To find out we will give the cells to 2 participants at one dose level. If that is safe we will raise the dose given to the next group of

participants. The dose you will get will depend on how many participants get the agent before you and how they react. The investigator will tell you this information. This will help you think about possible harms and benefits. Since the treatment is experimental, what is likely to happen at any dose is not known.

All of the Treatments will be given by the Center for Cell and Gene Therapy at Texas Children's Hospital or Houston Methodist Hospital.

FOLLOW-UP STUDIES
We will follow you after the injections. Initially, at each visit about 10ml (2 teaspoonfuls) of blood will be taken every other week for 6 weeks after the first injection and then every 3 months for 1 year to monitor your blood chemistry and hematology. To learn more about the way the T cells are working in your body, an extra 20-50 mls (4-10 teaspoons) of blood will be taken before each infusion and then 2-4 hours after each infusion, 3-4 days after each infusion (optional depending on patient preference) and then weekly for 4 weeks and at weeks 6 and 8 after the first infusion. Blood will then be taken 4 weeks later and then every 3 months for 1 year, then once every 6 months for the first four years and then yearly thereafter for the next 10 years. Total time participation for this study will be 15 years.

We will use this blood to look for the frequency and activity of the cells that we have given; that is, to learn more about the way the T cells are working and how long they last in the body. We will also use this blood to see if there are any long-term side effects of putting the new gene (mutant TGFB receptor) into the cells. In addition to the blood draws, because you have received cells that have had a new gene put in them (DNR-CTL) you will need to have long term follow up for 15 years so we can see if there are any long term side effects of the gene transfer. Once a year you will be asked to have your blood drawn and answer questions about your general health and medical condition. The investigators may ask you to report any recent hospitalizations, new medications, or the development of conditions or illness that were not present when you enrolled in the study and may request that physical exams and/or laboratory tests be performed if necessary. We will also ask you to participate in the long-term follow-up phase if you leave the study early.

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.

In the event that a tumor biopsy is performed for clinical reasons we will request permission to obtain excess sample to learn more about the effects of the treatment on your disease.

In the event of death, we will request permission to perform an autopsy to learn more about the effects of the treatment on your disease and if there were any side effects from the cells with the new gene. 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
- Photographs, videotapes, and/or audiotapes of you

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 NATIONAL INSTITUTES OF HEALTH (NIH) 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, NATIONAL INSTITUTES OF HEALTH (NIH) 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 Tower, CAGT, 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

Similar types of T cells that are trained to recognize EBV (but without the new mutant TGFb receptor gene) have been given to over 60 patients to prevent lymphoma after transplant and to 24 patients with Hodgkin's disease or lymphoma. Most patients had no side effects. In some patients with a lot of disease the cells have caused inflammation leading to fever and flu-like symptoms as well as swelling at the tumor site. This swelling could be potentially dangerous and even life threatening depending on the site.

It is possible that the T cells will cause an allergic reaction, which could include itching, rash and shortness of breath (potentially life-threatening).

As you are receiving donor LMP-CTL after a bone marrow transplant from a related or unrelated donor, there is the possibility that these donor T cells might try to attack other parts of your body and cause

graft versus host disease (GVHD). GVHD occurs when cells from your bone marrow donor (graft) recognize that your body's tissues (host) are different from those of the donor. When this happens, cells from the donor may attack your skin, liver and/or intestines. If you have GVHD after the transplant you may not be able to get the cells. If you have GVHD after the T cells have been given, we will treat you appropriately.

As mentioned previously, in this study we are using two sorts of gene transfer (putting a new gene in a cell). The first uses a virus called adenovirus to put a gene into dendritic cells and EBV infected cells that will be used in the laboratory to stimulate the T cells. Adenovirus is a common virus found in human respiratory systems. In its normal state, it can reproduce and cause a respiratory infection. Respiratory illnesses caused by adenovirus infections range from the common cold to pneumonia. As the T cells will be grown for several weeks after contact with the dendritic cells we think it is very unlikely that any adenovirus or dendritic cells will be injected with the T cells. However, should you receive any adenovirus or dendritic cells, these may cause an inflammatory reaction. There is one report of a patient in a gene transfer study who received a large dose of adenovirus into a blood vessel leading to his liver who died. We will also test the T cells before we use them to reduce the likelihood that any of your cells that we have infected with EBV will be injected with the T cells.

Another possible side effect is that some of the B cells or the B95 EBV virus will be injected with the T cells into your body. We think this is unlikely because the B cells have been treated with radiation to stop them from growing, and an antiviral drug that prevents release of EBV has been added to the cultures.

The second type of gene transfer in this study uses a virus known as a retrovirus to deliver the gene into the T cells. This is known as a retroviral vector. 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 retroviral vector adds the gene it carries into the human DNA this is called integration. Integration can occur anywhere in human DNA, and most integration does not harm the cell or the patient. However, there is a chance that there may be some parts of human DNA where integration may affect other genes. For example, if integration turned on a gene that caused the cell to grow this could cause uncontrolled increase in the numbers of cells, which could result in cancer. 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 retroviralvectors 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.

If you have a needle stick for blood collection, there is a risk of bruising or bleeding at the site of the needle stick and a risk of discomfort or pain at the site. There is also a very small risk of infection at the

site of the needle stick.

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.

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

Because of potential or unknown effects of the study on a fetus, if you are a woman of child-bearing potential, you must have a negative serum pregnancy test prior to entry into this study.

We will watch you very carefully for any side effects. If there are serious 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: It is possible that the DNR-CTL may begin to kill the cancer cells, making the Lymphoma go into remission or go away. Additionally, your participation may help the investigators better understand how the immune system can fight Lymphoma. This could benefit other patients with Hodgkin disease, non-Hodgkin Lymphoma or lymphoepitheliomia. 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: no further treatment, or other treatment with chemotherapy and radiation. 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 therapy.

Subject Costs and Payments

You will not be charged for the manufacture/production of the modified T cell product or for any evaluations that are being done solely as part of your participation in this research project. You may be charged for some research related costs including the infusion of the product. You will be charged for any tests or treatments that are being done as standard treatment for your Lymphoma.

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: Dr. Helen Heslop at

713-441-1450 during the day and 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.

People who give medical care and ensure quality from the institutions where the research is being done, the National Institutes of Health, National Cancer Institute, agents of the Food and Drug Administration, and regulatory agencies such as the U.S. Department of Health and Human Services will be allowed to look at sections of your medical and research records related to this study.

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.

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 _____

H-17946- ADMINISTRATION OF TGF-B RESISTANT LMP-SPECIFIC CYTOTOXIC T-LYMPHOCYTES TO PATIENTS WITH RELAPSED EBV-POSITIVE LYMPHOMA

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