H-33954- ADMINISTRATION OF TGF- BETA RESISTANT T CELLS TO PATIENTS WITH EBV-POSITIVE NASOPHARYNGEAL CARCINOMA (RESIST-NPC)

Background

In this document "you" signifies either you or your child. You are invited to take part in a research study. Taking part in a research study is completely voluntary. Please read this information and feel free to ask any questions before you agree to take part in the study.

You have a type of cancer called nasopharyngeal carcinoma (NPC), which has either come back or not gone away after the best treatment we know for this disease. 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.

Most patients with NPC show evidence of infection with the virus that causes infectious mononucleosis Epstein Barr virus (EBV) before or at the time of their diagnosis. EBV is found in the cancer cells of almost all patients with advanced stage NPC, suggesting that it may play a role in causing the disease. The cancer cells infected by EBV are able to hide from the body's immune system and escape destruction. We want to see if special white blood cells, called T cells, that have been trained to recognize and kill special parts of EBV infected cells can survive in your blood and affect the tumor.

We already have given EBV-specific T cells to 30 patients with active NPC and have seen anti-tumor activity in 14 of 30 patients. We are now trying to find out if we can improve this treatment.

First, we want to give T cells where more of the cells recognize at least two of the four EBV proteins expressed on NPC cells. We call these cells NPC-specific T cells.

Second, we found that T cells work better if we add a receptor to the T cells called DNR (Dominant Negative Receptor). DNR makes T cells resistant to TGFbeta, a factor secreted by cancer cells that helps them escape being killed by the immune system. In this study we will therefore place the DNR gene into NPC-specific T cells. We call these cells DNR.NPC-specific T cells. DNR.NPC-specific T cells are the cells that you will be treated with on this study if you choose to participate.

DNR.NPC-specific T cells are an investigational product not approved by the Food and Drug Administration.

In other clinical studies using T cells, some investigators found that giving chemotherapy before the T cell infusion can improve the amount of time the T cells stay in the body and therefore the effect the T cells can have. Giving chemotherapy before a T cell infusion is called lymphodepletion since the chemotherapy is specifically chosen to decrease the number of lymphocytes in the body. Decreasing the number of your lymphocytes first should allow the T cells we infuse to expand and stay longer in your body, and potentially kill cancer cells more effectively.

The chemotherapy we will use for lymphodepletion is a combination of cyclophosphamide and fludarabine. Cyclophosphamide and fludarabine are the chemotherapy agents most commonly used for lymphodepletion in immunotherapy clinical trials.

This research study is sponsored by Baylor College of Medicine.This research study is funded by the National Institutes of Health.

Purpose
The purpose of this study is to find the largest safe dose of DNR.NPC-specific T cells, to learn what the side effects are and to see if this therapy might help patients with EBV-positive nasopharyngeal carcinoma after lymphodepleting chemotherapy.

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.

About 14 people will be treated on this study.

Earlier you gave blood for us to make DNR.NPC-specific T cells in the lab. To grow NPC-specific T cells we used special cells called antigen-presenting cells, which train your T cells to be NPC specific. Antigen presenting cells, so called monocytes or dendritic cells, were grown/isolated from your blood. In addition, we used a cell line called K562 as antigen-presenting cells that had genes put inside it, which encourage your T cells to grow. K562 cells are cancer cells. As such, if injected they could cause cancer. The cells have been treated with radiation so they cannot grow.

These antigen-presenting cells are coated with a specially produced mixture of LMP, EBNA1 and BARF protein fragments called peptides. These coated antigen-presenting cells were then used to generate your NPC-specific T cells in the presence of growth factors. To get the DNR to attach to the surface of these NPC-specific T cells, we also inserted the DNR gene into the NPC-specific T cells to create the DNR.NPC-specific T cells. This is done with a virus called a retrovirus that has been made for this study. This virus will carry the DNR gene into the cells.

Once we made sufficient numbers of DNR.NPC-specific T cells, we froze the cells and tested them to make sure they recognized EBV proteins present in NPC.

If you agree to this treatment you will receive cyclophosphamide and fludarabine for 3 days before receiving the DNR.NPC-specific T cells. The cyclophosphamide and fludarabine will be given intravenously (through a needle inserted into a vein or your port-a-cath). If you are a female of child-bearing potential, we will give you a pregnancy test within one week prior to the first dose of cyclophosphamide or fludarabine. If you are pregnant, you will not be able to participate in the study. The study doctor will be notified.

This is a dose escalation study. This means that at the beginning, patients will be started on the lowest dose (1 of 2 different levels for the part of the study with lymphodepleting chemotherapy) of T cells. Once that dose schedule proves safe, the next group of patients will be started at a higher dose. This process will continue until all dose levels are studied. If the side effects are too severe, the dose will be lowered or the T-cell infusions will be stopped.

The T cells will be thawed and infused through a central line, if you have one, or through a vein in your arm over 1 to 10 minutes. You may receive a dose of Tylenol and Benadryl before the infusion to help reduce the chance that you have a reaction to the infusion. We will then monitor you in clinic for 1 to 4 hours after the infusion.

All of the treatments will be given by the Center for Cell and Gene Therapy at Texas Children's Hospital or Houston Methodist Hospital. We will follow you in the clinic or through communication with your primary doctor after the T-cell infusion.

Medical tests before treatment:
Before being treated, you will receive a series of standard medical tests:
Physical exam
Imaging Study
Blood tests to measure blood cells, kidney and liver function
Measurements of your tumor by routine imaging studies. We will use the imaging study that was used before to follow your tumor: Computer Tomogram (CT), Magnetic Resonance Imaging (MRI), or Positron Emission Tomography (PET/CT)

Medical tests during and after treatment:
You will receive standard medical tests during and after treatment:
Physical exams
Blood tests to measure blood cells, kidney and liver function
Imaging study 6 weeks after the T-cell infusion

To learn more about the way the DNR.NPC-specific T cells are working and how long they last in the body, an extra 60ml or 3ml/kg of body weight of blood (whichever is less) will be taken pre-chemotherapy, on the day of the T-cell infusion (before and at the end of the T-cell infusion), 1, 2, 3, 4, and 6 weeks after the T-cell infusion and every 3 months for 1 year, every 6 months for 4 years, then yearly for a total of 15 years. One additional blood sample might be drawn 3 to 4 days post the T-cell infusion; this is optional. This volume is considered safe, but may be decreased if you are anemic. In addition to the blood tests, you will receive 2 imaging studies as stated above.

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

During the entire duration of the study (15 years), the maximum total amount of blood that may be collected is 384 teaspoons.

If you have a tumor biopsy performed while you are on study, a sample of this will be used for research purposes (if a sample can be obtained).

These specimens and information about your circumstances may be used in other research being

conducted in immune therapy. Left over samples might also be used in future genetic studies. Any information obtained in these future studies will not be given back to you. Although there will be a record identifying under what circumstances these specimens were obtained, under all circumstances your identity will be kept confidential.

This study will continue until this study has completed enrolling subjects.

You will receive supportive care for acute or chronic toxicity, including blood components or antibiotics, and other intervention as appropriate

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 NIH: NATIONAL INSTITUTES OF HEALTH 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, NIH: NATIONAL INSTITUTES OF HEALTH 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
1102 Bates Avenue
Feigin Tower, 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 treatments including side effects that we cannot predict. Many side effects will go away shortly after treatment is stopped, but in some cases, the side effects may be long lasting or permanent. Some side effects may be life threatening. We will try to provide you with the best treatments for your side effects.

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

Side Effects of T-cell Therapies targeting EBV proteins:

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. As the T cells will be grown for several days after contact with the antigen-presenting cells (K562 cells or your cells with the EBV proteins) it is possible that these cells could be injected with your T cells. This is unlikely because we will test the T cells before we use them and we will also wash the cells several times so there should not be any protein remaining. However, we cannot completely exclude this possibility.

A small percentage of patients that receive this type of therapy develop a life threatening complication known as a cytokine release syndrome (CRS). 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. In addition, a small percentage of patients, who have received a particular type of T cell that attacks leukemia, a type of blood cancer, have developed drowsiness, sleepiness, or have become unresponsive. This complication can also be life threatening. As for CRS, there are treatments available for this complication.

Side Effects of the DNR:

The DNR renders T cells resistant to TGFbeta. We have tested DNR T cells extensively in the laboratory and could not detect a difference in the side effects of DNR T cells and unmodified T cells.

Side Effects of the Gene Transfer:

To get the DNR and the antibody to attach to the surface of the T-cell, we must deliver the gene for the DNR and 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 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, there is 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.

Side effects of lymphodepletion chemotherapy with cyclophosphamide and fludarabine:

Potential risks and side effects related to cyclophosphamide include:

Likely:
Loss of appetite, Nausea; Vomiting; Fewer white blood cells in the blood (A low number of white blood cells may make it easier to get infections); Hair loss; Decreased ability of the body to fight infection; Absence or decrease in the number of sperm which may be temporary or permanent which may decrease the ability to have children.

Less likely:
Abnormal hormone function which may lower the level of salt in the blood; Abdominal pain; Diarrhea; Fewer red blood cells and platelets in the blood; A low number of red blood cells may make you feel tired and weak; A low number of platelets may cause you to bruise and bleed more easily; Bleeding and inflammation of the urinary bladder; Absence or decrease of monthly periods which may be temporary or permanent and which may decrease the ability to have children; Temporary blurred vision; Nasal stuffiness with IV infusions; Skin rash; Darkening of areas of the skin and finger nails; Slow healing of wounds; Infections.

Rare but serious:
Heart muscle damage which may occur with very high doses and which may be fatal; Abnormal heart rhythms; Damage and scarring of lung tissue which may make you short of breath; A new cancer or leukemia resulting from this treatment; Damage or scarring of urinary bladder tissue; Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, chills and fever; Infertility which is the inability to have children.

Potential risks and side effects related to fludarabine include:

Likely:
Loss of appetite; Nausea or the urge to vomit; Decreased number of red blood cells, white blood cells (neutrophil/granulocyte), and/or platelets (a blood cell that helps clot blood); Muscle weakness of the whole body; Cough; Shortness of breath; Fatigue or tiredness; Fever; Infection; Pain.

Less likely:
Skin rash with the presence of macules (flat discolored area) and papules (raised bumps); Diarrhea; Irritation or sores in the lining of the mouth, voice box, throat, and windpipe; Vomiting; Commonly known as "pins and needles," where part of the body (typically a foot or hand) begins to tingle and becomes numb, or "falls asleep"; Blurred vision, double vision and/or loss of vision (blindness); Fear of light; Inflammation of the lungs that may cause difficulty breathing and can be life-threatening; Chills; An increase in the number of a type of white blood cell (called eosinophils) in the blood; Agitation or restlessness; Confusion; Weakness or paralysis (loss of muscle function) caused by damage to peripheral nerves (those nerves outside of brain and spinal cord); Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning ; Pain of the urinary tract ; Inflammation (swelling and redness) of the paranasal sinuses which may or may not be a result of infection.

Rare but serious:
Severe rash with redness, pain and/or blisters. When pressure is applied to an area, the skin will detach from the lower layers; A rare autoimmune disorder called Evan's syndrome in which the body makes antibodies that destroy the red blood cells, platelets and white blood cells; Sudden damage to the red blood cells (hemolytic anemia) which could cause a rapid decrease in the number of red blood cells such that you may be tired, weak, feel short of breath, and may require a blood transfusion; Coma and/or abnormal brain function; Convulsion or seizure; Blindness; A rare disorder that damages the material that covers and protects nerves in the white matter of the brain. The disorder may cause headaches, loss of coordination, clumsiness, loss of language ability, memory loss, vision problems, and weakness of the legs and arms that gets worse; Inflammation (swelling and redness) of the bladder not due to urinary tract infection; Severe potentially life-threatening damage to the lungs which can lead to fluid in the lungs; Bleeding from the lungs.

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.

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

DMSO:

One of the ingredients added to the cells is Dimethyl sulfoxide (DMSO). It is used as a preservative. When the cells are given to you the DMSO may cause you to have a funny taste in your mouth. Some people say this tastes like garlic. It may also make your breath and skin smell like garlic.

Risk of Blood draws: Pain/discomfort at the site of the needle stick. Bruising and/or bleeding at the site of the needle stick. There is also a very small risk of infection at the site of the needle stick.

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.

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 after the study has concluded:

* 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.

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 therapy. 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 manufacture or preparation of the DNR.NPC-specific T cells (the investigational product), 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 charged for some research related costs including the chemotherapy (fludarabine and cyclophosphamide) and the infusion of the DNR.NPC-specific T cells. You or your insurance company are both responsible for medical services that are 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.

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: CHRISTOPHER DERENZO at 832-824-6856 during the day and 832-826-0860 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.

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-33954- ADMINISTRATION OF TGF- BETA RESISTANT T CELLS TO PATIENTS WITH EBV-POSITIVE NASOPHARYNGEAL CARCINOMA (RESIST-NPC)

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-33954- ADMINISTRATION OF TGF- BETA RESISTANT T CELLS TO PATIENTS WITH EBV-POSITIVE NASOPHARYNGEAL CARCINOMA (RESIST-NPC)

Background

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

You have a type of cancer called nasopharyngeal carcinoma (NPC), which has either come back or not gone away after the best treatment we know for this disease. 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.

Most patients with NPC show evidence of infection with the virus that causes infectious mononucleosis Epstein Barr virus (EBV) before or at the time of their diagnosis. EBV is found in the cancer cells of almost all patients with advanced stage NPC, suggesting that it may play a role in causing the disease. The cancer cells infected by EBV are able to hide from the body's immune system and escape destruction. We want to see if special white blood cells, called T cells, that have been trained to recognize and kill special parts of EBV infected cells can survive in your blood and affect the tumor.

We already have given EBV-specific T cells to 30 patients with active NPC and have seen anti-tumor activity in 14 of 30 patients. We are now trying to find out if we can improve this treatment.

First, we want to give T cells where more of the cells recognize at least two of the four EBV proteins expressed on NPC cells. We call these cells NPC-specific T cells.

Second, we found that T cells work better if we add a receptor to the T cells called DNR (Dominant Negative Receptor). DNR makes T cells resistant to TGFbeta, a factor secreted by cancer cells that helps them escape being killed by the immune system. In this study we will therefore place the DNR gene into NPC-specific T cells. We call these cells DNR.NPC-specific T cells. DNR.NPC-specific T cells are the cells that you will be treated with on this study if you choose to participate.

Earlier you gave blood for us to make DNR.NPC-specific T cells in the lab. To grow NPC-specific T cells we used special cells called antigen-presenting cells, which train your T cells to be NPC specific. Antigen presenting cells, so called monocytes or dendritic cells, were grown/isolated from your blood. In addition, we used a cell line called K562 as antigen-presenting cells that had genes put inside it, which encourage your T cells to grow. K562 cells are cancer cells. As such, if injected they could cause cancer. The cells have been treated with radiation so they cannot grow.

These antigen-presenting cells are coated with a specially produced mixture of LMP, EBNA1 and BARF protein fragments called peptides. These coated antigen-presenting cells were then used to generate your NPC-specific T cells in the presence of growth factors. To get the DNR to attach to the surface of these NPC-specific T cells, we also inserted the DNR gene into the NPC-specific T cells to create the DNR.NPC-specific T cells. This is done with a virus called a retrovirus that has been made

for this study. This virus will carry the DNR gene into the cells.

Once we made sufficient numbers of DNR.NPC-specific T cells, we froze the cells and tested them to make sure they recognized EBV proteins present in NPC.

DNR.NPC-specific T cells are an investigational product not approved by the Food and Drug Administration.

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Purpose
The purpose of this study is to find the largest safe dose of DNR.NPC-specific T cells, to learn what the side effects are and to see if this therapy might help patients with EBV-positive nasopharyngeal carcinoma.

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.

About 14 people will be treated on this study.

If you agree to this treatment you will receive two infusions of DNR.NPC-specific T cells. The second infusion will be given 2 weeks after the first infusion. If you are a female of child-bearing potential, we will give you a pregnancy test within one week prior to the first infusion. If you are pregnant, you will not be able to participate in the study. The study doctor will be notified.

This is a dose escalation study. This means that at the beginning, patients will be started on the lowest dose (1 of 3 different levels) of T cells. Once that dose schedule proves safe, the next group of patients will be started at a higher dose. This process will continue until all 3 dose levels are studied. If the side effects are too severe, the dose will be lowered or the T-cell infusions will be stopped.

The T cells will be thawed and infused through a central line, if you have one, or through a vein in your arm over 1 to 10 minutes. You may receive a dose of Tylenol and Benadryl before the infusion to help reduce the chance that you have a reaction to the infusion. We will then monitor you in clinic for 1 to 4 hours after the infusion.

All of the treatments will be given by the Center for Cell and Gene Therapy at Texas Children's Hospital or Houston Methodist Hospital. We will follow you in the clinic or through communication with your primary doctor after the T-cell infusion.

Medical tests before treatment:
Before being treated, you will receive a series of standard medical tests:
Physical exam

Imaging Study
Blood tests to measure blood cells, kidney and liver function
Measurements of your tumor by routine imaging studies. We will use the imaging study that was used before to follow your tumor: Computer Tomogram (CT), Magnetic Resonance Imaging (MRI), or Positron Emission Tomography (PET/CT)

Medical tests during and after 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
Imaging study 8 weeks after the 1st T-cell infusion

To learn more about the way the DNR.NPC-specific T cells are working and how long they last in the body, an extra 60ml or 3ml/kg of body weight of blood (whichever is less) will be taken on the day of the T-cell infusion (before and at the end of the T-cell infusion), 1, 2, 3, 4. 6, and 8 weeks after the T-cell infusion and every 3 months for 1 year, every 6 months for 4 years, then yearly for a total of 15 years. One additional blood sample might be drawn 3 to 4 days post the 1st T-cell infusion; this is optional. This volume is considered safe, but may be decreased if you are anemic. In addition to the blood tests, you will receive 2 imaging studies as stated above.

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

During the entire duration of the study (15 years), the maximum total amount of blood that may be collected is 372 teaspoons.

If you have a tumor biopsy performed while you are on study, a sample of this will be used for research purposes (if a sample can be obtained).

These specimens and information about your circumstances may be used in other research being conducted in immune therapy. Left over samples might also be used in future genetic studies. Any information obtained in these future studies will not be given back to you. Although there will be a record identifying under what circumstances these specimens were obtained, under all circumstances your identity will be kept confidential.

This study will continue until this study has completed enrolling subjects.

You will receive supportive care for acute or chronic toxicity, including blood components or antibiotics, and other intervention as appropriate

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 NIH: NATIONAL INSTITUTES OF HEALTH 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, NIH: NATIONAL INSTITUTES OF HEALTH 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
1102 Bates Avenue
Feigin Tower, 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 treatments including side effects that we cannot predict. Many side effects will go away shortly after treatment is stopped, but in some cases, the side effects may be long lasting or permanent. Some side effects may be life threatening. We will try to provide you with the best treatments for your side effects.

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

Side Effects of T-cell Therapies targeting EBV proteins:

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. As the T cells will be grown for several days after contact with the antigen-presenting cells (K562 cells or your cells with the EBV proteins) it is possible that these cells could be injected with your T cells. This is unlikely because we will test the T cells before we use them and we will also wash the cells several times so there should not be any protein remaining. However, we cannot completely exclude this possibility.

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 DNR:

The DNR renders T cells resistant to TGFbeta. We have tested DNR T cells extensively in the laboratory and could not detect a difference in the side effects of DNR T cells and unmodified T cells.

Side Effects of the Gene Transfer:

To get the DNR and the antibody to attach to the surface of the T-cell, we must deliver the gene for the DNR and 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 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, there is 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.

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

DMSO:
One of the ingredients added to the cells is Dimethyl sulfoxide (DMSO). It is used as a preservative. When the cells are given to you the DMSO may cause you to have a funny taste in your mouth. Some people say this tastes like garlic. It may also make your breath and skin smell like garlic.

Risk of Blood draws: Pain/discomfort at the site of the needle stick. Bruising and/or bleeding at the site of the needle stick. There is also a very small risk of infection at the site of the needle stick.

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.

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 after the study has concluded:

* 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.

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 therapy. 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 manufacture or preparation of the DNR.NPC-specific T cells (the investigational product), 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 may be charged for some research related costs including the infusion of the DNR.NPC-specific T cells. You or your insurance company are both responsible for medical services, that are 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.

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 Heslop, MD 832-824-4594

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.

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-33954- ADMINISTRATION OF TGF- BETA RESISTANT T CELLS TO PATIENTS WITH EBV-POSITIVE NASOPHARYNGEAL CARCINOMA (RESIST-NPC)

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