Brain tumors are among the most frightening and debilitating diseases. Even with the advent of sophisticated, new medical procedures – robotic surgery, focused radiation / proton beam therapy, and new wonder drugs – the treatments typically leave an indelible stamp on the patient’s remaining quality of life.

**Brain Tumors Facts**
Primary malignant brain tumors are largely therapy resistant tumors. Before early symptoms appear or are recognized, microscopic tumors spread into normal brain tissue.

**Surgery** cannot be used on diffuse tumors. Too small to be seen, or too deeply embedded in normal brain tissue, they are left behind when the major tumor bulk is removed.

**Radiation** cannot destroy these small tumor nests without injuring normal brain tissue.

**Chemotherapy** is ineffective. The “blood-brain barrier” prevents most drugs from reaching brain tissue in a high enough concentration to kill the tumor. Drugs not restrained by this barrier damage normal tissue.

**Immune Therapy - Unique Benefits**
Immune therapies hold very unique benefits for the treatment of brain tumors. The basis for this therapy is based on these facts.

1. **Specificity**: Immune cells exist to protect the body from foreign (“non-self”) agents. Immune cells called T-lymphocytes can be “trained” in the laboratory to kill with great specificity tissues bearing “non-self” proteins called antigens. This is why organ donations and blood transfusions involve matching antigen “tissue types.” Each individual has an antigen type (“HLA Type”), and all the cells in this individual’s body carry his/her particular “HLA type” marker.
Kills Multiple Tumor Cells

Brain tumor cells (green) are killed by an immune cell (blue) “trained” to recognize foreign HLA antigens on the tumor cell.

One immune cell kills three tumor cells within 8 minutes.

2. **Brain Cells**: Brain cells are unlike any other organ in the body in several ways. In particular, normal, healthy brain cells do not carry that individuals HLA antigen marker. In contrast, brain tumor cells DO carry the individual’s HLA marker.

3. **Immune Privileged Site**: The brain has unique barrier – the “blood-brain barrier” that protects it from blood-born substances. This barrier prevents the body’s immune cells from entering the brain. It also prevents chemotherapeutic agents from entering the brain, which is why chemotherapy is not used for these tumors.

4. **Surveillance Penetration**: Immune T-lymphocytes regularly crawl through solid body tissues, conducting immune surveillance within the organs.

Immune Therapy-Strategy

The immune therapy involves five steps.

**Step 1**: Obtain T-lymphocytes from the patient and an unrelated donor (with a different HLA antigen marker type).

This can be done as simply as drawing blood from which the T-lymphocytes are isolated.

**Step 2**: “Train” the donor’s T-lymphocytes to recognize and kill cells with the patient’s HLA Antigen markers (in the laboratory).

The donor and patient lymphocytes are mixed together after the patient’s cells have been treated to prevent them from dividing. Lymphocytes display the HLA antigen type of each individual. The patient’s lymphocytes serve as a target for the donor lymphocytes, which go on to divide to create an army of killer T-lymphocytes that recognize and destroy any cells they encounter that display the patient’s HLA antigen marker.

**Step 3**: During surgery to remove the tumor, insert the donor’s trained T-lymphocytes (Killer cells) into the brain cavity.
Cellular Immunotherapy with Alloreactive CTL
An Open Study at UCLA Medical Center
for Recurrent WHO Grade III Gliomas
Candidates Must Be Eligible for Surgical Resection of Tumor

ClinicalTrials.Gov Identifier: NCT01144247

Figure 3: Initial Treatment
Killer cells are placed into the brain cavity when the bulk of the tumor is removed.

The blood-brain barrier prevents the patient’s immune cells from entering the brain to attack the donor cells.

A very small reservoir is placed under the scalp at the time of surgery. Subsequent infusions of killer cells enter the brain through this reservoir.

Step 4: The killer immune cells seek out and destroy tumor cells. They crawl through the brain for about 2 weeks, recognizing and killing tumor cells that have infiltrated into normal brain tissue. Normal brain cells are unaffected. This is because brain tumor cells carry the HLA marker, but normal brain cells do not.

Step 5: A cycle of treatment is given every other month over the next 10 months (totaling 5 cycles of treatment). Each cycle consists of two treatments, one week apart.

Figure 4: Follow-on Treatments
Subsequent treatments are given by injecting the killer immune cells into the reservoir sitting just below the scalp.

- This hurts less than a pinprick.
- The reservoir does not show.
- Side-effects are mild flu-like symptoms that typically disappear within 24 hours.
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About this Clinical Trial

1. Previous Clinical Experience
   Eight (8) patients were treated previously with this immune therapy at the University of Colorado Medical Center
   - Six (6) patients with recurrent gliomas participated in a pilot study. Their long-term survival rate was 50%.
     - One patient lived 40 months after the initial immune therapy.
     - Two patients are alive today (16+ years later). Their remission is verified by annual check-ups with their neurosurgeons. They received no additional treatment for their cancer beyond the immune therapy.
     - Results of this study are described in:
   - Two (2) additional patients were treated by “compassionate waiver” outside of the pilot study.

2. Investigators
   - Linda Liau, M.D., Ph.D., is Professor of Neurosurgery at UCLA, Director of the Brain Tumor Program and Clinical Director of this study.
   - Timothy Cloughesy, M.D., is Director of Neuro-oncology at UCLA and Co-Clinical Director of this study.
   - Carol Kruse, Ph.D., is a Professor in the Department of Neurosurgery at UCLA. She is a tumor immunologist and serves as the Scientific Director of this study.

3. ClinicalTrials.Gov Reference Information is at
   http://www.clinicaltrials.gov/ct2/show/NCT01144247?term=NCT01144247&rank=1

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