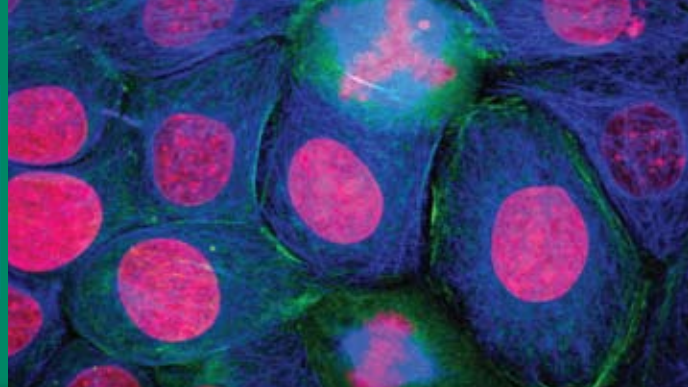




CEDARS-SINAI

**Samuel Oschin Comprehensive
Cancer Institute**



ADVANCES IN CANCER

SEPTEMBER 2008

Gene Therapy Strategy Elicits GBM Tumor Regression

Maria Castro, PhD and Pedro Lowenstein, MD, PhD

A new gene therapy approach that attracts and “trains” immune system cells to destroy deadly brain cancer cells also provides long-term immunity, produces no significant adverse effects and – in the process of destroying the tumor – promotes the return of normal brain function and behavioral skills.

This study (IACUC # 2201) was conducted in a recently developed laboratory rat model of glioblastoma multiforme (GBM) that closely simulates outcomes in humans and supports the translation of this procedure to human clinical trials early next

year. Results of the study were published in *Molecular Therapy*.

Glioblastoma multiforme, the most common and deadly type of primary brain cancer, usually claims the lives of 90 percent of patients within 24 months of diagnosis. It is extremely difficult to treat for a variety of reasons. GBM tumors grow rapidly, often becoming large before a diagnosis is made. Also, cells readily infiltrate neighboring brain tissue, hampering

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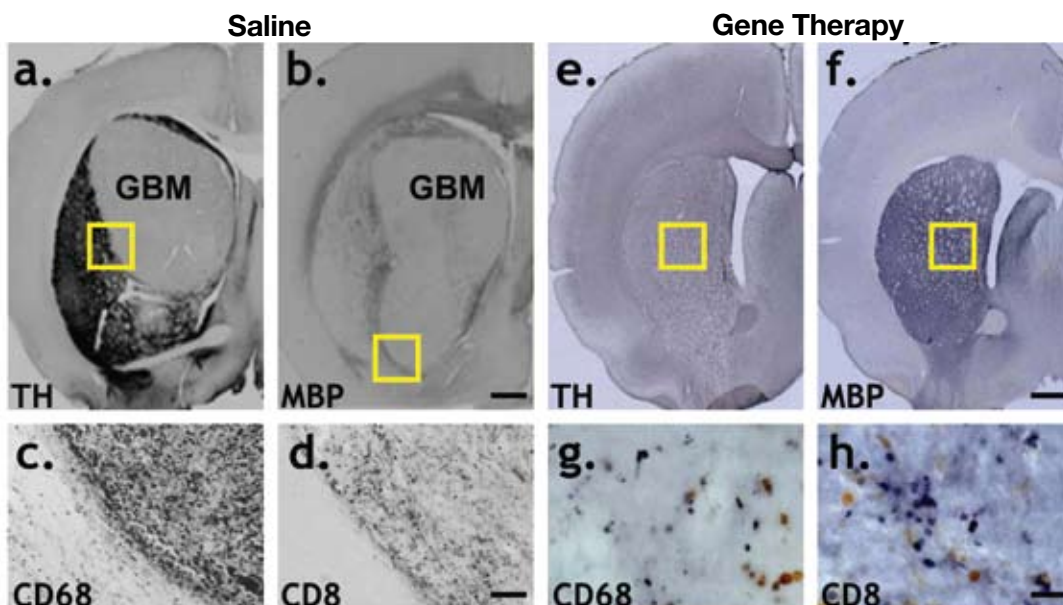
Cancer Clinical Trials at Cedars-Sinai

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Intratumoral treatment with Flt3L and HSV1-TK gene therapy eradicates large intracranial syngeneic glioma (GBM) in rats. Lewis rats bearing large syngeneic intracranial brain tumors were treated with an intratumoral injection of either (a-d) saline or (e-h) adenoviral vectors expressing Flt3L and HSV1-TK. All saline treated animals died ~5 days after treatment while ~70% of gene therapy-treated animals survived long term (a,b). Immunoreactivity with markers for tyrosine hydroxylase (TH) and myelin-basic protein (MBP) reveals displaced nerve terminals (TH+) and axon bundles (MBP+) within the striatum of saline-treated animals (e,f). However, normal brain architecture is completely restored in long-term survivors (c,d). Immunoreactivity for macrophages/activated microglia (CD68) and CD8+ lymphocytes (CD8) was widespread throughout the tumor in saline-treated animals (g,h), but minimal in gene therapy-treated, long-term survivors.

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complete surgical removal. Chemotherapy and radiation therapy are useful adjuvants, but sadly remain unable to eliminate all residual GBM cells, which frequently become resistant to the treatments.

The blood-brain barrier also prevents chemotherapy from effectively reaching tumor cells, and key cells needed to launch and sustain a systemic anti-tumor immune response – dendritic cells or antigen-presenting cells – do not naturally occur within the brain.

The research team used a gene therapy approach to sidestep these challenges, using a virus stripped of its disease-causing genes as a vehicle to deliver two therapeutic proteins directly into the tumor cells. One protein, FMS-like tyrosine kinase 3 ligand (Flt3L), drew dendritic cells into the brain. Another protein, herpes simplex virus type 1 thymidine kinase (HSV1-TK), combined with the antiviral ganciclovir (GCV), killed tumor cells. Dendritic cells clean up debris from dying cells and in

the process alert immune system cells of the existence of foreign glioma antigens. Newly “educated” immune system cells then swarm to the tumor cells to destroy them.

Humans with GBM often suffer behavioral abnormalities that affect concentration, memory and balance. In the animal studies, tumors induced abnormal behavior. The research team found that as the tumors grew, they displaced and compressed nerve terminals and impulse-conducting axons. But long-term survivors who had received the gene therapy did not have long-term injury or behavioral impairment resulting from the tumor or the treatment. Gene therapy eliminated the tumor mass and reversed the deficits that were caused by the tumor.

In an earlier study, the research team used HSV1-TK and GCV alone to treat GBM and found that about 20 percent of the animals survived. By adding the dendritic-cell inducing Flt3L, the survival rate jumped to about 70 percent. Systemic immune activity was

sustained, even fending off a “re-challenge” with additional tumor cells. In this study, the researchers reported that this therapy could also revert behavioral abnormalities caused by the growing tumor in the brain.

These findings constitute a significant milestone in creating an effective treatment for GBM. This therapy significantly improved survival rate, induced long-lasting systemic anti-tumor immunity, and resolved the neuropathological abnormalities caused by the tumors, which has been a stumbling block to many promising treatments.



Dr. Castro is Co-Director and Dr. Lowenstein is Director of the Cedars-Sinai Board of Governors Gene Therapeutics Research Institute. Both are principal investigators of the study.
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Recruitment Underway for Cancer Clinical Trials

The following is a partial list of cancer-related clinical trials currently underway at the Samuel Oschin Comprehensive Cancer Institute. For more information about eligibility criteria or to refer a candidate for participation, please contact the Principal Investigator for the study of interest.

Brain Tumors

A Phase I trial of tumor associated antigen-pulsed dendritic cell immunotherapy for patients with newly diagnosed and recurrent glioblastoma and brain stem glioma (IRB# 6657). S. Phuphanich.

A Phase I trial of surgical resection with gliadel wafer placement followed by vaccination with dendritic cells pulsed with tumor lysate for patients with malignant glioma (IRB# 9789). J. Yu.

A Phase III Randomized Study of Neuradiab in combination with external beam radiation and temozolomide versus external beam radiation and temozolomide in patients with newly diagnosed glioblastoma multiforme (IRB# 14462). R. Chu.

A Phase III, randomized, parallel group, multi-center in recurrent glioblastoma subjects to compare the efficacy of AZD2171 [Recentin™] monotherapy and the combination of AZD2171 with lomustine to the efficacy of lomustine alone (IRB# 13750). S. Phuphanich.

A Phase I/II clinical trial to evaluate dose limiting toxicity and efficacy of intralesional administration of Reolysin for the treatment of patients with histologically confirmed recurrent malignant gliomas (IRB# 13574). J. Yu.

Breast Cancer

Blood, tissue, saliva and clinical data collection for breast cancer research (IRB# 3870-03). B. Karlan.

Prospective cohort of carriers of mutations in BRCA1 and BRCA2 (IRB# 4049). B. Karlan.

Phase II open-label trial of an oral PARP inhibitor, AZD 2281, in women with advanced breast cancer who carry a BRCA 1 or 2 mutation (IRB# 11828). W. Audeh.

The Gilda Radner Hereditary Cancer Detection Program (IRB# 1080). B. Karlan.

Lung Cancer

Phase II, randomized, double blinded, placebo controlled dose and schedule finding trial to evaluate the safety and efficacy of AMG 531 for treatment of chemotherapy-induced thrombocytopenia in subjects with advanced non-small cell lung cancer already receiving gemcitabine and platinum (IRB# 10128). R. Natale.

A multi-center, randomized, double-blind, placebo-controlled, Phase III study of single-agent Tarceva (erlotinib) following complete tumor resection with or without adjuvant chemotherapy in patients with Stage 1B-IIIa non-small cell lung carcinoma who have EGFR-positive tumors (IRB# 10207). R. Natale.

A study to evaluate whether selenium yeast tablet can prevent new lung cancers in people with surgically removed non-small cell lung cancer as compared to patients taking a placebo yeast (IRB# 3596). R. McKenna.

A study comparing the removal of an entire lobe of the lung (lobectomy) versus the removal of a smaller portion of the lobe of the lung (sublobar resection) for small (< 2 cm) peripheral non-small cell lung cancer tumors (IRB# Pro00013599). R. McKenna.

A study that compares overall survival in high risk patients with stage I non-small cell lung cancer receiving either lung surgery followed by brachytherapy or lung surgery alone (IRB# Pro00008305). R. McKenna.

Collection of tissues and/or lymph nodes for molecular profiling of non-small cell lung cancer (IRB# Pro00011549). R. McKenna.

A study that compares overall survival in high risk patients with stage I non-small cell lung cancer receiving either lung surgery followed by brachytherapy or lung surgery alone (IRB# Pro00008305). R. McKenna.

A tissue/blood/specimen/anatomical part and/or cell collection study (IRB# 3017). R. McKenna.

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After Aggressive Treatment, Experimental Gene Therapy Could Be Next Step for GBM Patients

Adam Mamelak, MD and Pedro Lowenstein, MD, PhD

Glioblastoma multiforme (GBM) is the most common type of brain tumor in adults, accounting for more than 25 percent of all brain tumors diagnosed. The median survival, which is less than 12 months post-diagnosis, has remained essentially unchanged for the past several decades despite major advances in surgery, chemotherapy and radiation therapy.

Surgical success is often limited by a poorly defined tumor border due to the highly infiltrative nature of GBM and its close proximity to vital brain structures. Residual glioma cells often become resistant to radiation and chemotherapeutic agents, giving rise to recurrent GBM tumors, a hallmark of this progressive disease. While aggressive surgical resection can be combined with chemotherapy and radiation therapy to reduce tumor burden, GBM usually recurs within six to 12 months. The following fictionalized case study is a composite of facts from two individual cases for the purpose of illustrating potential disease progression and the possible therapeutic options available to GBM patients.

GBM case study (fictionalized)

A 25-year-old female presents to a local medical center with severe headaches associated with confusion and loss of left-sided peripheral vision. An MRI is ordered and a large mass is found in the right parietal occipital area. Surgical resection is not recommended due to the large tumor size and location. A biopsy reveals that the tumor is GBM and the patient is recommended for radiation therapy and chemotherapy with Temazolamide.

The patient comes to Cedars-Sinai for a second opinion. Based on her young age and the size of her tumor, she is recommended for surgery to remove as much tumor as possible, followed by radiation therapy and chemotherapy.

A craniotomy and resection of the tumor is performed, and a postoperative scan reveals that nearly all of the enhancing tumor is successfully removed. The patient exhibits some confusion and memory problems immediately after surgery, but these rapidly improve. She then receives a combination of radiation therapy and chemotherapy and has a remarkable clinical response with complete resolution of all swelling and symptoms other than a partial visual field deficit. She resumes normal activities.

Tumor recurrence

The patient's condition remains stable for five years. When tumor recurrence is noted on a surveillance MRI scan, the patient receives a dose of Gamma Knife® radiation to the small area of recurrence. She then begins an experimental chemotherapy trial which works well and keeps her tumor progression in check for another 1.5 years. Most recently, further tumor progression is noted. Because the patient is in good clinical condition with a recurring tumor mass that can still be resected, she is a potential candidate for a gene therapy clinical trial planned at Cedars-Sinai for early 2009.

Using viruses for gene therapy

The brain's blood-brain barrier and lack of a lymphatic drainage system means that the organ has immune privilege and therefore cannot mount a typical immune defense against cancer or infection. Once activated, immune system cells can cross the blood-brain barrier and attack pathogens or tumors; however, it is not possible to mount an effective immune response from the brain itself because it lacks antigen-presenting cells.

Cedars-Sinai scientists have been engaged in animal-based studies in an effort to engineer the brain's microenvironment to induce the migration of antigen-presenting cells to the brain and mount an immune response against deadly tumors. Researchers used a viral vector to encode the Flt3 Ligand gene and deliver it into the brains of test animals. They discovered that this molecule overcame the brain's immune privilege and elicited an anti-glioma immune response. The upcoming gene therapy clinical trials will test

the safety and effectiveness of using genetically engineered viruses to transport genes and/or proteins into cells in human subjects.

Clinical trials planned

The proposed experimental treatment will consist of delivering two different viral vectors directly into the tumors: Adv/HSV-1-TK with the goal of killing dividing tumor cells while preserving normal non-dividing cells surrounding the tumor, and Flt3 Ligand with the goal of attracting immune cells directly to the brain. Such immune cells will then be exposed to the dead tumor cells, allowing researchers to monitor whether the immune cells launch an effective anti-tumor immune response. If the treatment is proven effective, it may be possible to further eliminate tumor cells which have escaped neurological resection.

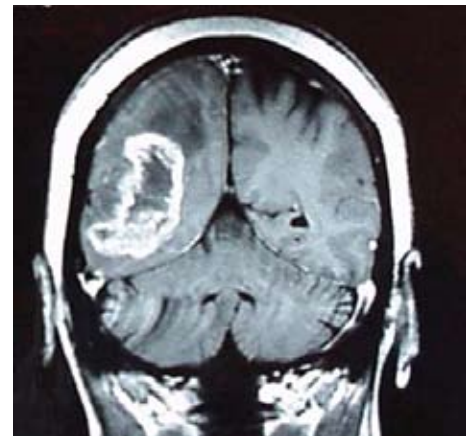
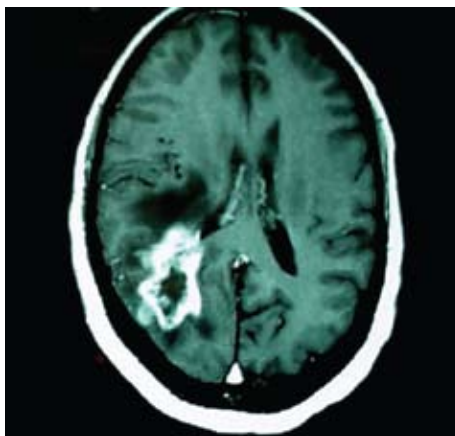
The discovery of a mechanisms to overcome the immune privilege in the brain has the potential to open up very exciting therapeutic possibilities for treating primary and metastatic brain cancers and brain infections. Such therapies may soon offer a new source of hope to the young woman in the prior case study, as well as other brain tumor patients who find they have limited treatment options.



Dr. Mamelak is Co-Director of the Cedars-Sinai Pituitary Center and Director of Minimally Invasive Intracranial Neurosurgery at Cedars-Sinai.



Dr. Lowenstein is Director of the Board of Governors Gene Therapeutics Research Institute at Cedars-Sinai.



MRIs of glioblastoma multiforme. Median survival is less than 12 months post-diagnosis.

Cancer Clinical Trials at Cedars-Sinai

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Ovarian Cancer

A randomized Phase III trial of maintenance chemotherapy comparing 12, monthly cycles of single agent paclitaxel or xyotax (ct-2103) (ind# 70188) versus no treatment until documented relapse in women with advanced ovarian or primary peritoneal cancer who achieve a complete clinical response to primary platinum/taxane chemotherapy (IRB# 8439). I. Cass.

A randomized, double-blind, placebo controlled, Phase II trial of paclitaxel in combination with amg 386 in subjects with advanced recurrent epithelial ovarian or primary peritoneal cancer (IRB# 12334). B. Karlan.

A Phase II, multicenter, randomized, blinded, placebo-controlled trial of carboplatin and gemcitabine plus bevacizumab in patients with platinum-sensitive recurrent ovary, primary peritoneal or fallopian tube carcinoma (IRB# 11412). B. Karlan.

A study to compare the safety and efficacy of AZD2281 and liposomal doxorubicin in patients with advanced BRCA1 or BRCA2-associated ovarian cancer who have failed previous platinum-based therapy (IRB# 14796). B. Karlan.

The Gilda Radner Hereditary Cancer Detection Program (IRB# 1080). B. Karlan.

Phase II/III abagovomab maintenance therapy for ovarian cancer in complete remission after first line chemotherapy (IRB# 11081). A. Li.

Phase III study comparing phenoxodiol with carboplatin to carboplatin alone for advanced, recurrent ovarian, fallopian tube or primary peritoneal cancer (IRB# 11644). B. Karlan.

A randomized treatment trial with carboplatin, paclitaxel plus bevacizumab or placebo in women with previously untreated stage III or IV ovarian or peritoneal primary cancer (IRB# 8484). I. Cass.

Prostate Cancer

Prostate patient profiles project (P4) (IRB# 3979). D. Agus.

Phase Ib/II evaluation of RAD001 with docetaxel and bevacizumab in patients with metastatic androgen-independent prostate cancer (IRB# 10405). M. Gross.

Characterization of circulating tumor cells of metastatic prostate cancer patients using gene markers (IRB# 11799). M. Gross.

A Phase II study of Ixabepilone prior to surgery for high-risk localized prostate cancer (IRB# 13963). M. Gross.

A Phase I/II, open-label, multiple-dose study of the safety, tolerability and pharmacokinetics of TAK-700 in advanced prostate cancer (IRB# 14175). D. Agus.

Stem Cell Transplantation

A Phase I study of myeloablative chemotherapy and autologous peripheral stem cell transplantation without the use of blood products (IRB# 2827). M. Lill.

A Phase I study of non-myeloablative chemotherapy with allogeneic peripheral blood stem cell transplantation for the treatment of malignancy without the transfusion of blood products (IRB# 3329). M. Lill.

A Multi-center Phase III study of autologous transplantation for patients with multiple myeloma comparing melphalan 280mg/m² + amifostine with melphalan 200mg/m² + amifostine (IRB# 10017). M. Lill.

Principal Investigators

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