

# Physician's Bulletin



## Brain Tumors: Strategic Innovations

Brain tumors pose complex treatment challenges, and depending on tumor type, prognosis is often poor. For patients with glioblastoma, the most common type of primary brain tumor in adults, median survival is only 14 months.

Factors limiting treatment success include restricted transport of chemotherapy drugs across the blood-brain barrier, side effects of radiation, and practical complications of surgery and post-operative recovery. Researchers in the City of Hope Brain Tumor Program are actively developing innovative clinical strategies to improve brain tumor treatments and outcome.

### Neural Stem Cell Platform: First-In-Human Trials

A landmark pilot study using neural stem cells (NSCs) to treat gliomas recently received permission from the Food and Drug Administration to start testing this treatment strategy in brain tumor patients. This first-in-human, first-in-oncology trial utilizes NSCs that have the natural ability to hone in on malignancies, migrating to and distributing themselves within primary tumors as well as tracking down other tumor sites within the brain. In addition, NSCs can be genetically modified — for example,

to express an enzyme that converts a prodrug into a chemotherapy agent. The NSC strategy provides oncologists with a powerful new therapeutic platform: stem cells that can be grown, modified and applied to specific tumor types.

Beginning in early Summer 2010, the new study will enroll approximately 15 patients over the age of 18 with recurrent high-grade glioma. During resection, patients will receive local injections of genetically-modified NSCs. These stem cells express the activating enzyme cytosine deaminase (CD), which converts the prodrug 5-fluorocytosine (5-FC) into the chemotherapy agent 5-fluorouracil (5-FU). Patients will take 5-FC orally for seven days.

As the 5-FC crosses into the brain, the CD-expressing NSCs (which have migrated to residual cancer sites) are expected to convert the 5-FC into 5-FU. The 5-FU and its toxic metabolites should diffuse out of the NSC to selectively kill dividing tumor cells. This strategy is likely to have a large "bystander effect," meaning that one NSC can kill off many surrounding tumor cells while minimizing toxicity to healthy tissues.

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## DIRECTOR'S NOTE

*Alexandra M. Levine, M.D., M.A.C.P.*  
Chief Medical Officer,  
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Glioblastoma is diagnosed in more than 15,000 patients each year. In the context of all cancers, that number isn't overwhelming; however, the exceedingly poor prognosis for these patients makes the need for improved treatment particularly urgent.

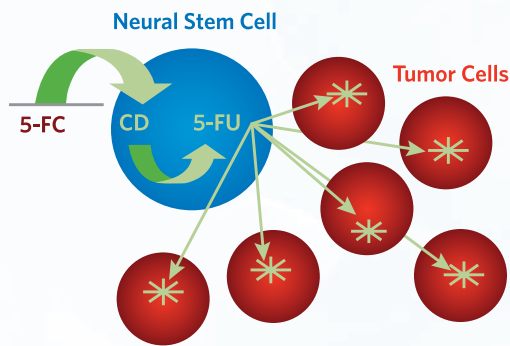


City of Hope's Brain Tumor Program devotes considerable resources to developing advanced, creative methods that aim to give the upper hand to patients battling glioblastoma as well as other brain malignancies. These highly advanced and complex approaches include immunotherapeutic procedures and gene transfer methods that seek to circumvent barriers that hinder effective treatment. We are particularly excited by a new, first-in-human clinical trial that will assess neural stem cells' ability to efficiently and safely target tumor cells.

In addition, our researchers are developing methods of measuring drug levels, and biological responses to those drugs, within the tumor environment, with an eye toward aiding drug development.

With these and other approaches, our ultimate goal is not simply to improve survival rates but to eradicate the lethal threat of glioblastoma altogether.

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*Localized production of chemotherapy (5-FU) by neural stem cells at sites of tumor cells.*

Results will be used to develop future trials of NSC-mediated therapy for primary brain tumors, using other therapeutic transgenes. Based on other preclinical data, tremendous potential exists for applying the new NSC-mediated treatment strategy to manage solid tumor metastases to the brain, such as breast cancer and melanoma.

## Second Generation Genetically Modified T Cells

A newly opened Phase I clinical trial of “second generation” cytolytic T cells utilizes genetically engineered lymphocytes to treat glioma patients who have relapsed following conventional therapies. The engineered T cells are attracted to the interleukin-13 receptor expressed by glioma cells, allowing them to locate and attack the malignancy.

Anti-inflammatory drugs are often necessary in managing brain tumor patients, however glucocorticoids such as dexamethasone are immunosuppressive, which could lower efficacy of the new therapy. This problem has been mitigated by eliminating the glucocorticoid receptors in the new T cells. In addition, a thymidine kinase (TK) “suicide” gene is engineered in to increase patient safety. During an adverse reaction, the patient could be given ganciclovir to eliminate the T cells. The TK gene can also be imaged to track progress of the therapy.

During biopsy to confirm glioma recurrence, a catheter is inserted into the tumor site, and a reservoir placed under the scalp. After a recovery period, the T cells are infused over a two-week period. A dose of IL-2 is also included to keep the T cells active and alive during the treatment. Magnetic resonance imaging and positron emission tomography imaging are used to evaluate whether the T cells are targeting the tumor.

The current trial will assess the new treatment’s overall safety and toxicity. A small previous trial using autologous genetically engineered T cells had promising results: the treatment was well tolerated and data were encouraging. Future versions of 2nd generation T cells could be modified to bind to other receptors such as Her-2/neu in breast and lung cancer.

## Immunogene Trial

Glioma patients who have not been treated previously may be candidates for a phase II clinical trial of a novel immunogene adjuvant therapy being conducted with Advantagene. Called GliAtak™ (AdV-TK plus

prodrug), the treatment uses an adenovirus vector to deliver the herpes simplex virus TK gene to residual glioma cells in the area of resection. After injection of the vector, the patient receives the prodrug valacyclovir, which is activated by TK to kill the cancer cells. Standard focal brain radiation therapy begins within a week of surgery.

Researchers believe that the dead cancer cells will also stimulate an immune response that will target residual tumor as well as malignant cells elsewhere in the brain. Once patients complete the two-week course of valacyclovir, they can begin standard treatment with temozolomide.

## CpG Oligonucleotides

Protected within the tumor microenvironment, glioma cells can suppress and evade immune attack. This ability can be overcome using immunostimulatory agents such as CpG oligonucleotides (CpG-ODN): In fact, high doses injected into the tumor site have been shown to eradicate gliomas in mouse models, although the treatment also stimulates a significant inflammatory response. A recent City of Hope study found that multiple injections of low-dose CpG-ODN were nontoxic, effectively eradicated tumors and triggered long-term immunity against glioma. This strategy will now be considered for human clinical trials.

Because the effects of CpG by itself tend to be short-lived, other research is evaluating whether nanotubes can be used to deliver CpG to macrophages, in combination with small interfering RNA (siRNA).

## Measuring Circulating Drug Levels

As an NCI-sponsored comprehensive cancer center, City of Hope continually performs clinical trials of new drugs and drug combinations. To help move promising new drugs into clinical trials more quickly, researchers in the Brain Tumor Program are investigating the use of intracerebral microdialysis in early drug development. During tumor resection, a microdialysis catheter is placed in the brain: The catheter’s semipermeable membrane allows researchers to continuously monitor drug levels as well as changes in levels of cytokines, chemokines and growth factors in response to treatment with a targeted agent.

## Referrals

To refer a patient for enrollment in a City of Hope Brain Tumor Clinical Trial, contact Behnam Badie, M.D., or Jana Portnow, M.D., at 626-471-9393 or via e-mail at [neurosurgery@coh.org](mailto:neurosurgery@coh.org).

# staff news and notes



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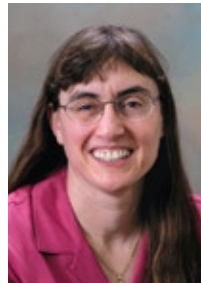
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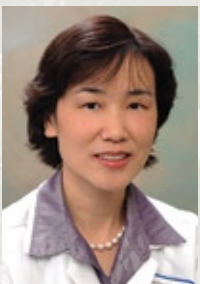
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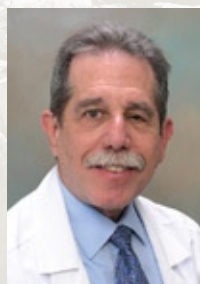
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Radiation Oncology

# clinical trials

## Newly Diagnosed

- 07107** **BrTK02, a Phase IIa Study of AdV-tk + Valacyclovir Gene Therapy in Combination with Standard Radiation Therapy for Malignant Gliomas.**  
Principal Investigator: Jana Portnow, M.D.
- 09066** **RTOG Phase III Double-blind Placebo-controlled Trial of Conventional Concurrent Chemoradiation and Adjuvant Temozolomide Plus Bevacizumab versus Conventional Concurrent Chemoradiation and Adjuvant Temozolomide in Patients with Newly Diagnosed Glioblastoma.**  
Principal Investigator: Nayana Vora, M.D.

## Recurrent Disease

- 07082** **Phase I Study of Cellular Immunotherapy for Recurrent/Refractory Malignant Glioma Using Intratumoral Infusions of GRm13Z40-2, An Allogeneic CD8+ Cytolytic T-cell Line Genetically Modified to Express the IL 13-Zetakine and HyTK and to be Resistant to Glucocorticoids, in Combination with Interleukin-2.**  
Principal Investigator: Behnam Badie, M.D.
- 08002** **A Pilot Feasibility Study of Oral 5-Fluorocytosine and Genetically-modified Neural Stem Cells Expressing E.Coli Cytosine Deaminase for Treatment of Recurrent High Grade Gliomas.**  
Principal Investigator: Jana Portnow, M.D. **(upcoming)**
- 07094** **RTOG Phase II Trial of Dasatinib in Patients with Recurrent Glioblastoma Multiforme.**  
Principal Investigator: Jana Portnow, M.D.

## Other Studies

- 08096** **RTOG A Randomized, Phase III, Double-blind, Placebo-controlled Trial of Memantine for Prevention of Cognitive Dysfunction in Patients Receiving Whole-brain Radiotherapy.**  
Principal Investigator: Nayana Vora, M.D.
- 07064** **A Pilot Feasibility, Dose-escalation Study Using Intracerebral Microdialysis to Assess the Neuropharmacodynamics of Temsirolimus in Patients with Primary or Metastatic Brain Tumors.**  
Principal Investigator: Jana Portnow, M.D.

*If you are interested in learning more about these clinical trials or are interested in referring a patient for enrollment, contact Behnam Badie, M.D., or Jana Portnow, M.D., at 626-471-9393 or via e-mail at [neurosurgery@coh.org](mailto:neurosurgery@coh.org). You may also visit <http://clinicaltrials.coh.org> and enter the IRB number for more details.*

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# DOCTOR'S CORNER



BEHNAM BADIE, M.D., F.A.C.S.

*Chief, Division of Neurosurgery*

*Professor, Department of Surgery*

*Director, Brain Tumor Program*

Behnam Badie, M.D., is an expert in the field of surgical neuro-oncology. He currently serves as chief of the Division of Neurosurgery and is also the director of the Brain Tumor Program at City of Hope.

Prior to joining City of Hope, Dr. Badie was an associate professor of neurosurgery and vice chair of academic affairs at the University of Wisconsin Medical School, where he was honored as the best teacher in 2002. He earned his Bachelor of Science degree in biochemistry magna cum laude and his medical degree from the University of California, Los Angeles (UCLA). He completed a seven-year residency in neurosurgery at UCLA. Dr. Badie has published more than 130 book chapters, abstracts and articles in peer-reviewed journals including the *Cancer Research*, *Clinical Cancer Research*, *Nanomedicine*, *Glia*, *Journal of Neurosurgery*, *Journal of Neuroimmunology* and *Journal of Neuroradiology*. He is a fellow of the American College of Surgeons and an active member of the American Association of Neurological Surgeons, Congress of Neurological Surgeons and the Society of Neuro-oncology.

Dr. Badie has clinical interests in the treatment of skull base tumors, acoustic neuromas, pituitary tumors, meningiomas and other nervous system tumors. His research focuses on brain tumor immunology. More specifically, his research team is attempting to develop novel immunotherapy approaches for malignant brain tumors through the activation of microglia and macrophages using nanoparticles. This research is currently funded by National Institutes of Health and various public and private foundations.

**New Patient Services**  
**800-826-Hope (4673)**

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**800-444-Phys (7497)**

**To reach any department at City of Hope, please call 626-256-HOPE (4673) and enter the extension indicated below.**

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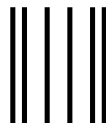
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**Radiation Oncology 68247**

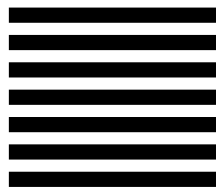
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## C M E C O R N E R

### Fifth Annual Conference on Breast & Gynecologic Cancer: Advances in the Prevention, Diagnosis and Treatment

Date: July 24, 2010

Location: City of Hope, Duarte, Calif.

Course directors: Robert Morgan Jr., M.D., F.A.C.P., Lucille Leong, M.D., Mark Wakabayashi, M.D., Joanne Mortimer, M.D., and I. Benjamin Paz, M.D.

8.25 AMA PRA Category 1 Credits™ will be offered.

### Third Annual Conference on How the Experts Treat Hematologic Malignancies

Date: August 12 to 14, 2010

Location: Hotel Casa Del Mar, Santa Monica, Calif.

Course Directors: Alexandra Levine, M.D., M.A.C.P. and Stephen Forman, M.D.

20 AMA PRA Category 1 Credits™ will be offered.

### Sixth Annual Oncology Congress

Date: October 15 to 17, 2010

Location: The Palace Hotel, San Francisco

This activity has been planned and implemented through the joint sponsorship of the New York Medical College and Reed Medical Education.

12.5 AMA PRA Category 1 Credits™ will be offered.

To register, visit [www.oncologycongress.com](http://www.oncologycongress.com) and use priority code COH.

### 10th Annual Conference on Womens Cancers

Date: November 11 to 13, 2010

Location: Wynn Las Vegas

Course Directors: Robert Morgan Jr., M.D., F.A.C.P. and Lucille Leong, M.D.

16 AMA PRA Category 1 Credits™ will be offered.

For additional information or to register for any of these educational events, contact the CME Department at 626-256-HOPE (4673), ext. 65622, or e-mail [cme\\_registration@coh.org](mailto:cme_registration@coh.org).