



## University of California San Francisco Brain Tumor SPORE Update

Fall 2004

### ...A Message From the Director

Modern imaging techniques like computerized tomography (CT) and magnetic resonance imaging (MRI) have revolutionized diagnostics in all fields of medicine, enabling physicians to obtain detailed scans of tissues with minimal discomfort to their patients. These technologies are vital at all stages in the treatment of patients who have brain tumors: in the initial diagnosis, for surgical planning, for the identification of postoperative complications, and in monitoring for recurrence or progression. Cutting-edge imaging technologies, such as magnetic resonance spectroscopy imaging (MRSI) and perfusion MRI (pMRI), are under active investigation by both clinical and basic science researchers to determine what applications they may have in obtaining a better understanding of brain tumors.

In the Specialized Program of Research Excellence (SPORE) for the study of brain tumors at the University of California San Francisco (UCSF), we are especially interested in MRSI because it can provide information about specific metabolites in the brain (such as N-acetylaspartate, choline, and lactate) and changes they undergo that may be prognostic for patients with a brain tumor. One of the four major translational research projects in our SPORE grant, led by investigators **Sarah Nelson PhD** and **Susan Chang MD**, is Prognostic Value of MRSI Parameters for Patients with Glioma—work that aims to determine whether quantitative information derived from data obtained from MRSI scans of patients with glioma are predictive of their response to therapy. In this project, as in any neurosurgical research using radiologic techniques, Department of Neurological Surgery investigators work closely with our colleagues in the Department of Radiology at UCSF, including the Neuroradiology Section and the Section of Interventional Neuroradiology.

In November 2002, the Department of Radiology received permission from the UC Board of Regents to enter into a lease agreement for approximately 50,000 square feet of commercial space at China Basin Landing close to UCSF's new development at Mission Bay, which includes the Cancer Research facility. This site will house San Francisco's first T3 MRI unit, as well as other clinical and research MRI and CT scanners, new laboratories, and clinical space. The expanded prospects for research provided by this new facility are a foundation for hope, giving the gifted investigators of UCSF's brain tumor SPORE greater opportunities to work collaboratively and to exercise their commitment to making more rapid progress toward an eventual cure for brain tumors.

Mitchel S. Berger MD  
Director, UCSF Brain Tumor SPORE  
and UCSF Cancer Center Neurologic Oncology Program



### Funded Translational Projects and Investigators

#### San Francisco Bay Area Adult Glioma Survival Study

Principal Investigator: **Margaret Wrensch PhD**

Clinical Co-Principal Investigator: **Michael Prados MD**

#### Prognostic Value of MRSI Parameters for Patients with Glioma

Principal Investigator: **Sarah Nelson PhD**

Clinical Co-Principal Investigator: **Susan Chang MD**

#### Development of Novel Targeted Therapeutics for Brain Tumor Treatment

Principal Investigator: **John Park MD**

Clinical Co-Principal Investigator: **Mitchel Berger MD**

#### Exploiting the PI3-Kinase Pathway in Human Glioma Therapy

Principal Investigator: **David Stokoe PhD**

Clinical Co-Principal Investigator: **Daphne Haas-Kogan MD**

### Career Development Awardees

#### Nalin Gupta MD, PhD

Tumor-associated inflammation as a new target for glioma therapy

#### Fredrick Gorin PhD

The development of novel therapeutic agents directed towards preventing tumor recurrence in malignant gliomas

### Developmental Research Awardees

#### Joseph Costello PhD

New targets for therapy of glioblastoma multiforme unmasked by demethylation

#### Collin Collins PhD

Identification of chimeric transcripts in brain tumors using end sequence profiling

#### Russell Pieper PhD

Determining and predicting tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) sensitivity in primary glioblastoma multiforme

## SPORE Career Development Research in Progress



**Joseph Costello PhD**

**Principal Investigator**

*Assistant Professor of Neurological Surgery*

*Principal Investigator, BTRC*

**Project Title:** New targets for therapy of glioblastoma multiforme unmasked by demethylation

**Project Summary:** Methylation is required in normal brain cells for chromosome stability and the repression of gene expression. Glioblastoma multiforme (GBM) tumorigenesis is known to be accompanied by a genome-wide loss of methylation, but the exact genomic regions affected and the downstream consequences of demethylation are not known. We propose that the loss of methylation occurs in part on gene promoters, which leads to gene reactivation that in turn has two possible consequences, depending on the type of gene that is affected. First, if the promoter gene is a positive regulator of cell growth (i.e., an oncogene), then the hypomethylation-induced gene reactivation will contribute to increased cell proliferation. Second, if the promoter gene is normally silent in all types of normal brain-cell types, then the gene activation will result in expression of a protein that is not present in normal brain cells and is tumor-specific; such demethylation of genes silent in normal brain cells has been shown in studies of melanoma in which the MAGE (melanoma antigen) gene is activated by tumor-specific hypomethylation.

Discovery of hypomethylation-induced reactivation of a growth-promoting gene would immediately provide a new target for the therapy of GBMs. Unmasking activation of a gene that is not normally expressed in the brain could be useful for the development of tumor-specific therapies or of a potential vaccine against GBM. To test our hypothesis, we will: 1) use a methyl-acceptor assay to identify *de novo* and progressive GBMs that exhibit genome-wide hypomethylation; 2) use a new methylation-detection array to identify normally methylated promoters that are targets of tumor-specific hypomethylation; and 3) determine whether loss of methylation results in gene reactivation in GBMs. These studies should lead to new therapeutic approaches and new targets for existing therapies for patients with GBM.

## SPORE Developmental Research in Progress



**Nalin Gupta MD, PhD**

**Principal Investigator**

*Assistant Professor of Neurological Surgery*

*Principal Investigator, BTRC*

**Project Title:** Tumor-associated inflammation as a new target for glioma therapy

**Project Summary:** Our hypothesis is that both tumor-induced and treatment-induced inflammation contribute to glioma progression. Transformed astrocytes and conventional radiation therapy or chemotherapy independently activate components of the general inflammatory response through direct cytotoxic effects and a number of poorly defined interactions with the host microenvironment. Some of these interactions contribute to the injury of normal tissue by worsening brain edema and by activating mediators of inflammation.

No effective therapeutic agent has been developed specifically to treat the effects of inflammation in patients with brain tumors. Our preliminary data implicate a specific cytokine, monocyte chemoattractant protein (MCP-1), as a key participant in the inflammatory response. MCP-1 is produced by many cell types, functions as a 'homing factor' for cells involved in the inflammatory response (macrophages), and is consistently overexpressed in malignant glioma. Activated macrophages mediate other aspects of the inflammatory response, such as lymphocyte migration and permeability of blood vessels. It was intriguing to learn that the receptor for MCP-1, CC chemokine receptor 2 (CCR2), is also overexpressed in malignant glioma. These findings suggest that cytokines may also function as positive regulators of growth in tumor cells.

Successful modification of the inflammatory response would benefit virtually all patients with malignant brain tu-

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## Featured Translational Research Project



### Exploiting the PI3-Kinase Pathway in Human Glioma Therapy

*Principal Investigator: David Stokoe PhD*

*Clinical Co-Principal Investigator: Daphne Haas-Kogan MD*

Glioblastoma multiforme (GBM), the highest-grade glioma, is an aggressive brain tumor that is uniformly fatal. It is the most common malignant primary neoplasm of the brain, diagnosed in approximately 10,000 new patients each year in the United States. Intense efforts to improve surgical, radiation therapy, and chemotherapy approaches to the treatment of gliomas have failed to increase long-term disease control substantially. For decades, the median survival of patients with GBM has remained approximately 1 year. Although standard antineoplastic therapies have produced little clinical progress, genetic analyses of gliomas have increased our understanding of the molecular pathogenesis of these tumors. The promise of targeting genetic alterations in gliomas with novel therapies has generated great scientific and clinical enthusiasm. Nonetheless, the development of clinically effective new agents requires a deeper understanding of the mechanisms by which genetic alterations are responsible for the development of gliomas and their resistance to therapy.

Dysregulation of the phosphoinositide 3-kinase (PI3-kinase) signaling pathway plays a key role in the development of gliomas. Agents that inhibit elements within this pathway are currently being tested in clinical trials; however, which patients may benefit from such inhibitors remains unclear. An important mechanism of PI3-kinase activation is through the epidermal growth factor receptor (EGFR). The *EGFR* gene is amplified in many malignant gliomas, resulting in increased protein expression. Our work since the funding of the SPORE grant has focused on a recent phase I clinical trial in which patients with stable or progressive malignant glioma were treated with an EGFR inhibitor, erlotinib (Tarceva, OSI-774), with or without the chemotherapeutic agent temozolomide. Of 41 patients from whom we obtained tissue, 8 showed a response to the therapy. We found a statistically significant correlation between response to erlotinib and both EGFR protein expression and *EGFR* gene amplification. We also examined the activation status of the PI3-kinase pathway in these tumors by analyzing the phosphorylation of a PI3-kinase effector termed PKB/Akt. We found a strong, significant inverse correlation between phospho-PKB/Akt expression and both response to erlotinib and time to progression. Among 22 patients expressing phospho-PKB/Akt, none responded to EGFR inhibition and thus PKB/Akt activity was the strongest predictor of a response to erlotinib. Based on these results, we plan a clinical trial in which patients with glioma will be stratified for treatment according to the molecular features of their tumors as determined before therapy begins.

We have also been interested in the genetic and epigenetic alterations that occur in low-grade gliomas and influence PI3-kinase signaling. In earlier work, we showed that the levels of PTEN, a tumor-suppressor protein that antagonizes PI3-kinase signaling, are reduced in grade 2 oligoastrocytomas, even though there are no mutations present on the *PTEN* gene. We have recently shown that both grade 2 astrocytomas and grade 2 oligoastrocytomas often display methylation of the *PTEN* promoter, an aberration that is absent in normal brain specimens and is rarely observed in GBM. Methylation of promoter regions is thought to result in silencing of downstream genes. Support for the idea that methylation and mutation may represent alternative ways to inactivate PTEN function is provided by the fact that GBMs showing methylation of the *PTEN* promoter have been found to be mutually exclusive of the GBMs with mutations in PTEN coding sequences. Methylation of the *PTEN* promoter and PKB/Akt phosphorylation have often been found in the same tumors, suggesting that methylation of *PTEN* is functionally and biologically important. Therefore, methylation of the *PTEN* promoter may be an alternate mechanism by which PI3-kinase signaling is increased in low-grade gliomas; this suggests new therapeutic approaches for patients with these tumors. Both demethylating agents, to reverse methylation of the *PTEN* promoter, and rapamycin, which displays particular efficacy against tumors with high PKB/Akt phosphorylation, are drugs that potentially could be used to treat patients with low-grade gliomas.

<http://neurosurgery.medschool.ucsf.edu/>

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mors undergoing conventional treatment, but specific inhibitors of the MCP-1/CCR2 system are not currently available. Statins, a class of pharmacologic inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), reduce the inflammatory response associated with disorders such as multiple sclerosis. Some of the statins can also cross the blood-brain barrier. The effects of these agents in patients with brain tumors are not known. Our study aims to define the basic biologic role of MCP-1 and CCR2 in glioma progression and to assess the effectiveness of pharmacologic inhibition of these components of the inflammatory response. We have two specific aims for this study.

1. To establish an intracranial tumor model in transgenic knockout mice that lack a specific cytokine (MCP-1) or its cognate receptor (CCR2). This aspect of the study will directly address the role of this cytokine/receptor pair in the growth of glioma.

2. To test the statins, pharmacologic inhibitors of inflammation, as anti-tumor agents. We plan to examine the effect of the statins by directly measuring the response they elicit in glioma cells and tumors both *in vitro* and *in vivo*. Should our hypothesis be correct, future experiments would test the statins used in combination with radiation therapy or chemotherapy.