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New Career Development Awardees

New Developmental Research Awardees



**Validation of neuroimaging biomarkers of gliomas using molecular and genetic analysis of image-guided tissue biopsy**  
Soonme Cha PhD  
Department of Radiation Oncology,  
University of California San Francisco



**Characterization of microRNAs in astrocytoma**  
Graeme Hodgson PhD  
Department of Neurological Surgery,  
University of California San Francisco



**Characterization of tumor heterogeneity in patients with newly diagnosed glioblastoma multiforme using MR-based metabolic and physiologic imaging: implications for optimizing radiation therapy and targeted therapy in general**  
Andrea Pirzkall PhD  
Department of Radiation Oncology,  
University of California San Francisco



**Reversing hypomethylation and aberrant gene activation in glioblastoma multiformes via folate**  
Joe Costello PhD  
Department of Neurological Surgery,  
University of California San Francisco



**CSF biomarkers of brain tumors**  
James Rubenstein MD, PhD  
Division of Hematology/Oncology,  
University of California San Francisco



**Determining and predicting tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) sensitivity in primary glioblastoma multiforme**  
Russ Pieper PhD  
Department of Neurological Surgery,  
University of California San Francisco



...A Message From The Director



While our understanding of adult brain tumor biology is rapidly expanding and translating into new treatment options for patients, similar progress in pediatric brain tumor research is lacking. Because the disease is relatively rare in children, and surgical biopsies are not usually performed, obtaining specimens for research has been a formidable obstacle. As we design more studies aimed specifically at pediatric brain tumors, we are working to apply our growing knowledge of adult brain tumors and to assess the relevancy of those breakthroughs to pediatric research.

Specialized Program of Research Excellence (SPORE) Career Development Awardee **Nalin Gupta MD** is examining the role of tumor-associated inflammation in astrocytoma growth. Neoplastic astrocytes or treatments such as chemotherapy can induce an inflammatory response that damages healthy brain tissue. Results of that project indicate that the cytokines MCP-1 and TNF- $\alpha$ , and the MCP-1 receptor CCR2, all play key roles in the pathogenesis of inflammation in the central nervous system. The ubiquitous presence of MCP-1 and the CCR2 isoform CCR2A in glioblastoma multiforme suggests that the inhibition of this pathway could benefit patients with all types of brain tumors, including pediatric patients. In collaboration with other departmental investigators, Dr. Gupta has shown that radiation-induced central nervous system inflammation is reduced when the inflammatory response is attenuated. He and his colleagues are beginning to study a new class of small molecule inhibitors that block CCR2 activation. Because the developing nervous system in children is particularly sensitive to injury, pharmacological intervention offers the possibility of reducing the long-term effects of brain tumor therapy in this vulnerable population.

While we continue to apply our broader knowledge of adult brain tumors, we are committed to expanding studies specifically on pediatric brain tumors. The University of California San Francisco (UCSF) has led the formation of the California Children's Brain Tumor Consortium, a new clinical trials group of five member institutions. Tissue samples from pediatric patients treated at any one of these institutions will be put into a shared database, allowing further studies of pediatric brain tumors to take place. This will provide an additional resource for the investigators of UCSF's brain tumor SPORE in their efforts to improve therapies for children with brain tumors.

Mitchel S. Berger MD  
Kathleen M. Plant Distinguished Professor  
in Neurological Surgery  
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 Wrench 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

**Fredric 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

*New Career Development and Developmental Research Awardees Chosen for 2005-2006, see p. 4*

## SPORE Career Development Research in Progress



**Fredric Gorin MD, PhD**

**Principal Investigator**

*Professor of Neurology  
Department of Neurology and Center for Neuroscience  
University of California, Davis*

**Project Title:** The development of novel therapeutic agents directed towards preventing tumor recurrence in malignant gliomas

**Funding Agency:** National Institutes of Health/SPORE

**Co-Investigator and Collaborator:** Michael Nantz PhD, Professor of Chemistry, University of California, Davis

### **Project Summary:**

This SPORE project has demonstrated that glioma cells residing in poorly vascularized, perinecrotic tumor regions survive and proliferate. These cells have properties that make them resistant to conventional therapies, and therefore represent a source of tumor recurrence. Using BrdU analysis, investigators found densely-packed regions of glioma cells bordering areas of spontaneous necrosis in rats. These densely packed cells do not incorporate BrdU, but exhibit increased expression of a glucose transport protein (GLUT-1) when grown under acidotic (pH 6.5-6.8) or hypoxic conditions. Additional metabolic studies indicate that these perinecrotic glioma cells rely primarily on non-oxidative glycolysis to persist in their nutrient-deplete environment. Bordering the perinecrotic regions of GLUT-1-positive cells, were BrdU-positive glioma cells scattered throughout poorly vascularized, central regions of the tumors. These cells, which do not express high levels of GLUT-1, are thought to convert glucose-6-phosphate into nucleotide precursors for DNA replication. They arrest in different stages of cell cycle, but can proliferate if the environment becomes more favorable.

Although vascularized regions are thought to be the most prolific areas of cell replication within a tumor, the results of this SPORE project have shown that glioma cells residing in unfavorable microenvironments within a tumor are more resourceful than previously imagined. In order to target these cells, the neuroscience laboratory of Fredric Gorin MD, PhD, in conjunction with Michael Nantz PhD in the Department of Chemistry at the University of California Davis, has developed a new class of compounds designed to prevent the recurrence of tumor growth within poorly vascularized regions of glioblastomas. The new compounds are designed to block cell surface ionic transporters used by glioma cells to survive in hypoxic-ischemic environments. Unlike the parent compound amiloride, these new compounds do not appear to produce toxicity when infused into the brain of experimental animals. These compounds currently are being engineered as inactive prodrugs that can be taken chronically and become activated when they encounter cancer cells. More recently, Gorin, Nantz, and their colleagues have designed a new class of bio-activated compounds designed to prevent the avascular invasion of glioma and other aggressive cancers, including lung, breast, and colon. This research was possible through the generous support of the University of California San Francisco SPORE and the NS040489 award from the NIH.

### Recent Publications

Gorin F, Harley W, Schnier J, Lyeth B, Jue T. Perinecrotic glioma proliferation and metabolic profile within an intracerebral tumor xenograft. *Acta Neuropathol (Berl)* 2004;107(3):235-44.

Palandoken H, By K, Hegde M, Harley WR, Gorin FA, Nantz MH. Amiloride peptide conjugates: prodrugs for sodium proton exchange inhibition. *J Pharmacol Exp Ther* 2005;312(3):961-7.

Dr. Gorin can be reached at [fagorin@ucdavis.edu](mailto:fagorin@ucdavis.edu)

SPOREs were instituted by the National Cancer Institute in 1992 through a special appropriation from Congress to promote translational research focused on an organ-specific cancer or a highly related group of cancer types. SPOREs are intended to foster interaction between basic and applied scientists, promoting interdisciplinary research and providing them with the flexibility to rapidly test new approaches to the prevention and treatment of cancer.

## Featured Translational Research Project



### Prognostic Parameters for Patients with Glioma

*Principal Investigator: Sarah Nelson PhD*

*Clinical Co-Principal Investigator: Susan Chang MD*

This SPORE project is examining the clinical use of imaging methods that look not only at the structural components of a tumor, but at its biological components as well. Research has focused primarily on magnetic resonance spectroscopy imaging (MRSI), which identifies the chemical signatures of compounds found in the brain. Unlike conventional MRI, MRSI has been shown in previous studies to distinguish between normal brain tissue and regions of tumor and necrosis – an attribute that may prove more relevant for assessing the extent of tumor involvement and may potentially identify sub-regions of aggressive phenotype. Investigators develop indices that indicate the presence and/or ratio of metabolites such as choline, creatine, N-acetylaspartate, lactate, and lipids. These indices are then used to measure early changes in the biology of the tumor.

Initial results of this SPORE project confirm that metabolic and physiological parameters reflect spatial heterogeneity distinct from that seen in anatomic MR images and may be of prognostic value. Parameters found to be indicative of poor outcome include high levels of choline-containing compounds and lactate, low levels of creatine, and a low diffusion coefficient.

In a recent analysis of patients with gliomas who received MRSI after surgery, but prior to radiation therapy, even patients with presumed “gross total resection” based on conventional imaging criteria had significant residual metabolic lesions shown by elevated amounts of choline-containing compounds and reduced amounts of N-acetylaspartate. Using the metabolic lesions to guide radiation therapy could make it possible to administer an increased dose to areas of the tumor with aggressive phenotype and allow for a simultaneous reduction in the spatial extent of the presumed tumor margins in order to spare large volumes of normal brain tissue.

In addition to guiding treatment decisions, MRSI may be useful in determining whether or not a patient has responded to therapy. Currently, response to treatment is assessed by variations in the volume of the enhancing lesion seen on T1-weighted MR images, following the injection of gadolinium-DTPA or a similar agent. However, it is often difficult to differentiate between variations corresponding to tumor progression and those corresponding to the formation of treatment-induced necrosis or temporary alterations in the permeability of vessels damaged by radiation therapy. Initial results from this project suggest that conventional measures of treatment effects may both under- and over-estimate the extent of the tumor. This may result from changes in the vessel permeability of non-enhancing tumors that are falsely interpreted as an increase in tumor size, and to the formation of contrast-enhancing necrosis that is indicative of a positive response, but falsely interpreted as recurrence. Monitoring of intrinsic metabolic and physiological parameters of glioma before and after therapy as outlined in this SPORE project is being continued. The use of these new MR parameters would fundamentally change the definition of response to therapy and could therefore have a profound impact on patient care.

The SPORE grant awarded to UCSF funds four major translational research projects, each driven by a pair of applied and basic researchers, and each intended to create novel tools and therapies potentially useful in the treatment of human brain tumors. In addition, a Career Development Research Program included in the SPORE supports new investigators in the field, and a Developmental Research Program provides initial funding of promising projects that may develop into future SPORE projects.