



...A Message From The Director

One of the most energizing aspects of the NIH Specialized Program of Research Excellence (SPORE) grant for brain tumor research awarded to our center is the intensive collaboration it promotes, both within our institution and with other top research centers working towards the same goal: a cure for brain tumors. Each of our four SPORE translational research projects is the shared effort of a basic scientist paired with a clinical investigator. The structure of these SPORE partnerships is intended to move the results from the laboratory to clinical trial applications more rapidly than ever before.

In addition to our internal collaborations, we have had several rewarding opportunities to work with other leading brain tumor research investigators and programs during the past year. Last July, our team attended the 11th Annual SPORE Investigator's Workshop. This convocation was attended by members from all SPORE centers and comprised investigators studying 14 specialized types of cancer. We discussed future collaborations with our sister brain tumor SPORE center, the University of Alabama at Birmingham (UAB), as well as with the NIH-funded Mouse Models of Human Cancer Consortium. Dr. Sarah Nelson was invited to give a platform presentation on her project, Preliminary Analysis of the Prognostic Significance of MR Spectroscopy for Gliomas, featured on page 3 of this newsletter.

The Brain Tumor SPORE centers were able to meet again in January at the first annual Brain Tumor SPORE meeting. These meetings will be important catalysts for collaboration between centers as the Brain Tumor SPORE program continues to expand. This meeting was attended by UCSF, UAB, and representatives from the 2003 Brain Tumor SPORE grant awardees. The centers plan to gather again in January of next year.

This May marked the beginning of the second year of our SPORE grant. We look forward to more fruitful years of cooperation, collaboration, and the promotion of translational research.

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 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

Gabriele Bergers PhD

Hypoxia and Neovascularization: Cause or Consequence of Glioblastoma Multiforme Progression? Studies in Genetically Engineered Murine Tumor Models

Tracy Richmond McKnight PhD

Correlation of MRS Features of Glioma with Tumor Markers

Developmental Research Awardees

Andrew T. Parsa MD, PhD

Antigen-Specific Modeling of Glioma Immunotherapy

William A. Weiss MD, PhD

Stem Cells as Delivery Agents in the Treatment of Glioma

SPORE Career Development Research in Progress



Gabriele Bergers PhD

Principal Investigator

Assistant Professor of Neurological Surgery

Principal Investigator, BTRC

Project Title: Hypoxia and Neovascularization: Cause or Consequence of Glioblastoma Multiforme Progression? Studies in Genetically Engineered Murine Tumor Models.

Funding Agency: National Cancer Institute/SPORE/Sidney Kimmel Foundation

Collaborators: Randall Johnson PhD, William Weiss MD, PhD, Tarik Tihan MD, PhD

Project Summary: Hypoxia and Neovascularization in Glioblastoma Multiforme: Low-grade astrocytomas are able to grow by co-opting existing blood vessels in the brain. When they progress to fast-growing glioblastoma multiforme (GBM), the tumor tissue becomes hypoxic and necrotic, which in turn induces neovascularization to feed these poorly oxygenized areas. Mechanistically, hypoxia induces hypoxia-inducible transcription factor HIF-1 α , which—when bound to its constitutively present partner HIF-1 β —triggers gene expression for factors involved in glycolysis, survival, and neovascularization, including vascular endothelial growth factor (VEGF) and its receptors.

To reveal the significance of hypoxia and angiogenesis in astrocytoma progression, we created genetically engineered transformed astrocytes from murine primary astrocytes and deleted HIF-1 α or its target gene VEGF. Results from our studies so far have shown that tumor progression was greatly dependent on the microenvironment of the tumor, and HIF-1 α acted as either a negative or positive factor in progression depending on the microenvironment in which the tumor developed. Growth of HIF-1 α and VEGF-deficient astrocytomas in the subcutaneous space, a commonly used but questionable *in vivo* location of tumor growth, resulted in reduced growth, reduced vessel density, and severe necrosis. However, when the same

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Tracy Richmond McKnight PhD

Principal Investigator

Assistant Professor of Radiology

Principal Investigator, BTRC

Project Title: Correlation of MRS Features of Glioma with Tumor Markers

Funding Agency: National Cancer Institute/SPORE

Project Summary: Magnetic resonance (MR) spectroscopy (MRS) is currently used to aid in the clinical management of patients with glial tumors. Magnets with field strength greater than 1.5 Tesla are beginning to be used for both clinical and research purposes. The higher field strength translates into finer spatial resolution for multivoxel MRS and increased signal-to-noise (SNR) and chemical dispersion within each voxel. The gain in SNR and dispersive properties of the spectral data mean that instead of monitoring only five resonance peaks *in vivo*—corresponding to choline-containing compounds (Cho), creatine (Cre), N-acetylaspartate (NAA), lactate, and lipid—we will be able to monitor as many as 15-20 peaks reflecting levels of compounds such as glutamate (Glu), glutamine (Gln), GABA, pyruvate (Pyr), phosphocholine (PC), and glycerophosphocholine (GPC).

Accurate interpretation of these data, however, requires basic experiments that correlate specific MRS signatures to individual disease processes. The ability to correlate individual MRS signatures with molecular markers of tumor progression would further validate using *in vivo* MRS as a surrogate marker of tumor activity. In this project, we will perform basic experiments at the cellular level by using the non-destructive technique of high-resolution magic angle spinning (HRMAS) MRS. These experiments are designed to investigate the two following hypotheses: (1) the *in vivo* MRS peak corresponding

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Featured Translational Research Project



Prognostic Value of MRSI Parameters for Patients with Glioma

Principal Investigator: Sarah Nelson PhD

Clinical Co-Principal Investigator: Susan Chang MD

The objective of this project is to determine whether quantitative parameters derived from magnetic resonance (MR) spectroscopy imaging (MRSI) data are predictive of response to therapy for patients with gliomas. This is an important clinical question because gliomas are heterogeneous, infiltrative tumors with poorly defined margins. Although histological grade has been shown to be predictive of outcome in large-scale clinical trials, there is considerable variability between tumors of the same grade in terms of response to therapy and time to progression. The identification of new factors that predict treatment response is critical for tailoring therapy to individual patients' characteristics and is expected to have a significant impact on the criteria used to select patients for future clinical trials.

Recent studies using MRSI have provided compelling evidence that in vivo levels of metabolites such as choline, creatine, N-acetylaspartate, lactate, and lipid provide reliable measures of the spatial extent of the tumor. In our laboratory, we have used MRSI to derive a number of different quantitative parameters that are valuable for defining the metabolic activity and spatial extent of tumor. These include a choline to N-acetylaspartate index (CNI), a choline to creatine index (CCrI), a creatine to N-acetylaspartate index (CrNI), and a lactate plus lipid index (LLI). This project will determine if these indices provide information that is clinically relevant for the management of gliomas and will determine, by studying patients on clinical trial protocols at UCSF, if there is a basis for integrating the technology into the design of future clinical trials. Specific project aims are as follows:

Determine whether metabolic tumor burden correlates with clinical outcome for patients with newly diagnosed glioma.

Patients with Grade III and Grade IV glioma will be evaluated (i) before surgical resection and (ii) immediately before treatment with radiation therapy and chemotherapy in order to test the hypothesis that patients with a larger tumor burden have a worse outcome. For each of the metabolite indices CNI, CcrI, CrNI, and LLI, we will determine the highest value within the lesion, the sum of values within the anatomic lesion, and the volume of the region with value greater than 2.0. Patients will be followed to assess survival time and time to progression for Grade III and Grade IV gliomas. The metabolic parameters from the pre-treatment scan will be compared with the corresponding clinical endpoint to determine whether they are correlated with outcome. We will investigate whether the inclusion of metabolic parameters from the pre-surgical scan adds information that is relevant to clinical outcome.

Determine whether early changes in MRSI parameters correlate with treatment effects.

Patients with Grade II, III, and IV glioma will be evaluated (i) before therapy, (ii) at the first MR examination, and (iii) at a second follow-up MR examination in order to test the hypothesis that early changes in the metabolic parameters are predictive of clinical outcome. For each of the metabolite indices CNI, CCrI, CrNI, and LLI, we will determine the changes between the pre-treatment and follow-up scans in the highest value within the lesion, the sum of values within the anatomic lesion, and the volume of the region with value greater than 2.0. Patients with Grade II lesions will be treated with the chemotherapeutic agent Temodar, evaluated with MRSI after 2 and 4 cycles of treatment, and followed with conventional clinical imaging to determine time to progression. Patients with Grade III lesions will be treated with external-beam radiation therapy and adjuvant chemotherapy, evaluated with MRSI at the first and second post-irradiation scans, and followed clinically to determine survival time and time to progression. Patients with Grade IV lesions will be treated with external beam radiation therapy and adjuvant chemotherapy, evaluated with MRSI at the first and second post-irradiation follow-up scans, and followed clinically to determine survival time and time to progression.

Bergers, cont. from p. 2

cells were placed in the vascular-rich brain parenchyma, loss of HIF-1 α , but not loss of VEGF, caused astrocytomas to grow faster and penetrate the brain more rapidly and extensively. These results emphasize that HIF-1 α can play different roles in tumor progression, roles that are greatly dependent on the tumor microenvironment. (Blouw B, Song H, Tihan T, Bosze J, Ferrara N, Gerber H-P, Johnson RS, Bergers G. The hypoxic response of tumors is dependent on their microenvironment. *Cancer Cell* 2003;4:133-146.)

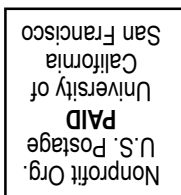
Transgenic mouse models of gliomagenesis: Recently developed transgenic mouse models of gliomagenesis hold great promise for advancing knowledge, but still have limitations. Either the tumors develop and kill the mouse too early to be of value for research, or the penetrance and grade of the tumor are too low to efficiently study glioblastoma formation. We intend to develop endogenous mouse tumor models in which single oncogenes or combinations of oncogenes are induced at specific time points in the brain of the adult mouse by utilizing tetracycline-inducible systems as well as virus-delivered oncogene systems to induce oncogene expression. We are currently focusing on four different oncogenes (H-ras, K-ras, c-myc, SV40Tag) that have already been shown to cause astrocytoma formation in conventional transgenic mouse models when expressed under an astrocyte-specific promoter. The goal is to establish mouse models that develop astrocytomas from normal astrocytes in their natural microenvironment in a timely and multi-step manner similar to the situation in human cancer.

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to choline-containing compounds is primarily a non-specific indicator of cell density, irrespective of the cell type; and (2) by determining the high-resolution MRS signature of the individual cell types found in infiltrative glial tumors, it is possible to distinguish resonance-peak alterations that are specific for malignant transformation from those alterations that arise from the overall increased cell density.

To determine the specific MRS signature that correlates with astrocytic malignancy, three different cell populations will be studied: normal human astrocytes immortalized with hTERT, and two strains of genetically engineered human astrocytes developed in Dr. Russell Pieper's laboratory that form phenotypically Grade III and Grade IV astrocytoma in animal models. The specificity of the HRMAS MRS resonance peaks identified in these cell populations will be validated in intact tissue specimens taken from tumors grown in animals implanted with the two transformed cell strains and correlated with in vivo MR measures of tumor aggressiveness, such as time to onset of contrast enhancement, relative cerebral blood volume, and increased MRS choline and lactate peaks. The tissue specimens will also be analyzed to determine the histologic grade of the tumor, proliferative/apoptotic ratio, and cell density to identify which features of malignancy are best characterized by the spectroscopic signature.

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



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