



University of California San Francisco Brain Tumor SPORE Update

Fall 2008

...A Message From the Director

Since 1992, the Specialized Program of Research Excellence (SPORE) at the National Cancer Institute (NCI) has been accelerating the pace of discovery in cancer research, and with recent developments it will now play an even more critical role in the advancement of research at the NCI. In a debriefing of the 2008 annual meeting of the American Association for Cancer Research, NCI Director John Niederhuber MD described how the SPORE program is now an integral part of the NCI's Division of Cancer Treatment and Diagnosis (DCTD), which has just formed a new Translational Research Program. As this new program begins to take shape, the NCI will rely on the experience of SPORE investigators to enhance all of its translational research efforts. This year, the annual SPORE meeting will instead be a translational research meeting that will bring SPORE investigators together with other clinicians and laboratory scientists engaged in translational research at the NCI to broaden the scope of the SPORE program's mission to move important laboratory discoveries from the bench to bedside.

In the current climate created by a shrinking NIH budget, biomedical researchers are facing unprecedented competition for research funding in the United States. The doubling of the NIH budget between 1998 and 2003 allowed for tremendous growth in infrastructure and new researchers recruited into the expanding field of biomedical research are now submitting proposals at a time when funding has all but grinded to a halt. Even within these challenging times, the SPORE program remains a top priority at the NIH and will continue to expand. Our own brain tumor SPORE at the University of California, San Francisco (UCSF) is also growing. In 2007, we added a new central translational research project ("Heat Shock Protein Vaccine Development: Glioma Immuno-resistance and PI(3)K/Akt/mTOR Pathway Activation") for a total of five core research projects. The UCSF brain tumor SPORE also continues to support junior faculty through the SPORE mechanisms of Career Development and Developmental Research Awards. We are excited to contribute to this new phase of the SPORE program as it becomes a part of the DCTD. Ensuring the vitality of the SPOREs is a necessary part of finding new ways to combat devastating diseases, including brain tumors, in a meaningful way.



Mitchel S. Berger MD

Kathleen M. Plant Distinguished Professor and Chairman,
UCSF Department of 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 MD**

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**

Heat Shock Protein Vaccine Development: Glioma Immuno-resistance and PI(3)K/Akt/mTOR Pathway Activation

Principal Investigator: **Russell Pieper PhD**

Clinical Co-Principal Investigator: **Andrew Parsa MD, PhD**

Career Development Awardees

Anuradha Banerjee MD

Intranasal Therapy for Pediatric Diffuse Pontine Gliomas

Graeme Hodgson PhD

Characterization of MicroRNAs in Astrocytomas

Soonme Cha PhD

Physiologic MRI Parameters as Surrogate Markers for the Molecular Profile of Gliomas

Developmental Research Awardees

Joseph Wiemels PhD

The Role of Autoantibodies to Glioma Neoantigens in Glioma Survival

James Rubenstein PhD

CSF Biomarkers of Brain Tumors

Bin Liu PhD

Developing Internalizing Human Antibody Targeting Brain Cancer Stem Cells

SPORE Career Development Research in Progress



Anuradha Banerjee MD

Principal Investigator

Associate Professor of Pediatrics & Neurological Surgery

Project Title: Intranasal Therapy for Pediatric Diffuse Pontine Gliomas

Project Summary*: Most infiltrative brainstem tumors in children are malignant gliomas and patients usually die within 2 years after initial diagnosis. These tumors cannot be surgically removed because of their location within the pons, and systemically administered chemotherapeutic agents have limited distribution to the brainstem. The goal of this SPORE project was to develop and characterize a robust rodent model of human diffuse pontine glioma that could be used to evaluate the efficacy of therapeutic agents delivered directly to the brainstem using techniques such as intranasal delivery. The model was created by implanting human glioblastoma cells into the pontine tegmentum of athymic rats. The cells were modified to express luciferase – an enzyme that can be measured non-invasively using bioluminescent imaging (BLI).

Banerjee and her colleagues have shown that in their rodent model, BLI can measure progressive tumor growth that correlates with histopathologic analysis and with tumor volume calculated by three-dimensional measurements from serial histologic sections. They have also used the model to evaluate the efficacy of the chemotherapeutic drug temozolomide. In their experiments, rats treated with temozolomide survived more than 50 days after implantation with tumor cells (controls were euthanized at 26 days and 31 days, when symptoms indicative of severe tumor burden appeared). BLI revealed a sustained decrease in luminescence over time in rats given temozolomide. The decrease in luminescence is consistent with the anti-tumor activity of the drug, which is responsible for the longer survival times of the treated rats. The orthotopic brainstem tumor model system developed through this SPORE project allows a reproducible assessment of survival and will greatly facilitate testing of pre-clinical therapeutic agents. Results have also indicated that tumor response to therapeutic agents can be non-invasively measured using BLI.

Future efforts will be focused on testing intranasal delivery of therapeutic agents in this model of pediatric brainstem glioma. Because intranasal delivery is a non-invasive method of drug administration, it is especially appealing for pediatric patients and could provide an alternative to direct injection or convection-enhanced delivery of drugs. Intranasal delivery of therapeutic agents in rats with supratentorial, intracerebral human tumor xenografts has been shown to bypass the blood-brain barrier and inhibit tumor growth. Further testing in this new model of pediatric brainstem tumors may provide a rationale for clinical testing in human patients. Investigators at UCSF also continue to develop intranasal delivery for treating brain tumors as part of the Pediatric Brain Tumor Foundation of the United States research program in conjunction with this SPORE project.

*Adapted in part from: Hashizume R, Ozawa T, Dinca E, Prados M, Banerjee A, James D, Gupta N. Bioluminescent imaging and therapeutic response in an experimental rodent brainstem tumor model. Presented on November 15-18, 2007 at the 12th Annual Meeting of the Society for Neuro-Oncology, Dallas, TX.

Featured Translational Research Project



San Francisco Bay Area Adult Glioma Survival Study

Principal Investigator: Margaret Wrensch PhD

Clinical Co-Principal Investigator: Michael Prados MD

Developing more sophisticated prognostic indicators for glioma and refining tumor classification within and between histological subtypes is essential for developing targeted therapies, and for providing effective therapy to individual patients while sparing them potentially unnecessary treatment. This project is making progress toward these goals by analyzing survival in relationship to both established and

novel prognostic factors. The primary aim of this project is to evaluate population-based case series of adult patients with glioma in order to better understand their survival as a function of characteristics such as personal and family medical histories, diet, smoking, and alcohol consumption prior to diagnosis, as well as other demographic factors such as education. Investigators are also evaluating the relationship between several immune markers and survival; determining if polymorphisms of the genes O6-methylguanine methyltransferase (MGMT) or p53 influence survival; and validating findings from the studies in adult glioma patients enrolled prospectively at the UCSF Neuro-Oncology Service.

Immune markers may be valuable predictors of individual tumor biology and there is a significant interest in studying the role of immune factors such as IgE, CD8 infiltrates, and CD14 in glioma. Project 1 investigators are aiming to better understand the mechanism of improved survival for glioma patients with increased IgE levels and are in the process of analyzing serum IgE markers from approximately 1000 glioma patients. They have also developed highly sensitive quantitative assays to measure the immune markers CD14 and CD23, and are looking to develop techniques for measuring a third immune marker: autoantibodies produced by glioma patients and controls against neoantigens produced in the tumor.

Another objective of this project was to collaborate with the researchers of SPORE Project 4 to perform methylation profiling of certain genes to reveal links between methylation and survival, as well as to possibly identify subtypes of glioma based on the methylation status of the tumor. Aberrant DNA methylation in human glioma affects clinically important genes such as MGMT and may be useful in classifying these heterogeneous tumors according to epigenetic pathways that are important in the pathogenesis of different forms of the disease. Preliminary analyses indicate patterns of methylated genes that differentiate most de novo GBMs (Grade IV tumors) from oligodendroglioma or anaplastic astrocytoma (Grade II and III tumors), as well as from secondary GBMs. Oligodendroglioma and anaplastic astrocytoma appear to have many more hypermethylated genes than de novo GBMs. Quantitative methylation-specific PCR of a 12-gene panel confirmed these results and also revealed that early age onset in de novo GBM was associated with the lower-grade glioma hypermethylation profile.

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2007 - 2008 Developmental Research Awardees

Kit S. Lam MD, PhD

In Vivo Optical Imaging of Orthotopic Glioblastoma Xenograft with OA03-Cy5.5

Paul Mischel MD

Identification of the Src Tyrosine Kinase Fyn as a Novel Dasatinib-sensitive Molecular Target in Glioblastoma Patients

Zena Werb PhD

Imaging the Tumor Microenvironment Around Developing Glioblastomas

2007 - 2008 Career Development Awardees

Elva D. Diaz PhD

Novel Role of the Mad Family Member Mad3 in Tumorigenesis

Anita Lal PhD

Predicting the Prognosis of Atypical Meningioma Patients Using Molecular Signatures

Claudia Petritsch PhD

Identification of Novel Diagnostic Markers and Therapeutic Approaches to Premalignant and Malignant Lesions of High-grade Oligodendroglioma

<http://spores.nci.nih.gov/>