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 the pace of discovery in cancer research, and UCSF Cancer Center Neurologic Oncology Program and UCSF Department of Neurological Surgery 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.

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**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 indentify 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 the novo GBM was associated with the lower-grade glioma hypermethylation profile.

**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.


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of the Society for Neuro-Oncology, Dallas, TX.

*Adapted in part from: Hashizume R, Ozawa T, Dinca E, Prados M, Banerjee A, James D, Gupta N. Bioluminescent imaging and a rationale for clinical testing in human patients. Investigators at UCSF also continue to develop intranasal delivery for blood-brain barrier and inhibit tumor growth. Further testing in this new model of pediatric brainstem tumors may provide patients and could provide an alternative to direct injection or convection-enhanced delivery of drugs. Intranasal delivery glioma. Because intranasal delivery is a non-invasive method of drug administration, it is especially appealing for pediatric tumor response to therapeutic agents can be non-invasively measured using BLI.

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