



University of California San Francisco Brain Tumor SPORE Update Spring 2003

...A Message From The Director

Two years ago, the National Cancer Institute (NCI) of the National Institutes of Health (NIH) invited applications for a new Specialized Program of Research Excellence (SPORE) grant for brain tumor research. After an intensive 18-month selection process, UCSF submitted a proposal comprising four major translational research projects chosen from a pool of more than 15 proposals developed by Brain Tumor Research Center (BTRC) investigators and their collaborators in the UCSF brain tumor community. The grant application received the highest rating of all proposals submitted to the NCI. In the summer of 2002, UCSF received one of two Brain Tumor SPORE grants awarded in the United States.

Receipt of an NIH/NCI SPORE grant for brain tumor research brings the BTRC full circle from its beginnings in 1972, when the approval of an NIH Cancer Center research grant inaugurated the BTRC and made it the first such categorical Center approved by the NCI. While the overarching goal of research in the BTRC has always been to define the basic nature of human brain tumors and ultimately to cure them, the primary short-term objective has been to improve existing therapies and develop new therapies for human brain tumors through translational research.

The SPORE grant provides funding to focus on the kind of intensive bench-to-bedside translational research projects at which the BTRC has excelled since its inception. Basic research in the BTRC, funded by an NCI Project Program Grant for nearly 30 years, has provided innovative therapies to the Brain Tumor Center, the clinical arm of the Neurological Surgery Department at UCSF. A member of both the North American Brain Tumor Consortium and the Pediatric Brain Tumor Consortium, the Brain Tumor Center's Clinical Neuro-Oncology Program at UCSF has an international reputation for excellence in testing experimental brain tumor treatments and providing important feedback to colleagues in research. We are excited to inaugurate the clinical and basic science research partnerships of the SPORE grant under the umbrella of the UCSF Comprehensive Cancer Center's Neurologic Oncology Program, and we will keep the brain tumor research community up to date on our research through this new biannual newsletter.

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

Gabriele Bergers PhD
Hypoxia and Neovascularization: Cause or Consequence?

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 Developmental Research in Progress



Andrew T. Parsa MD, PhD

Principal Investigator

Assistant Professor of Neurological Surgery

Principal Investigator, BTRC

Project Title: Antigen-Specific Modeling of Glioma Immunotherapy

Funding Agency: National Cancer Institute/SPORE

Total Project Period: 1 year

Co-Investigators: Abul K. Abbas MD

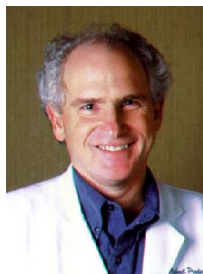
Collaborators: Lawrence Fong MD, Sang-Mo Kang MD, Lewis Lanier PhD

Project Summary: Active immunotherapy is dependent upon evoking an immune response with tumor-related antigens. Several clinical protocols have been designed to treat patients who have a glioma, including the use of dendritic cells, local delivery of immunostimulatory cytokines, and genetic modification of glioma cells. These clinical protocols have been uniformly unsuccessful, generating the hypothesis that the preclinical model systems used to test these treatments are inherently flawed. Our preliminary results have confirmed the suspected immunological limitations of the two most widely used animal models of glioma. The C6/Wistar system was shown to be allogeneic, resulting in a prolific host graft rejection often misinterpreted as a treatment response. We further demonstrated that retroviral transfection with virtually any construct can increase the immunogenicity of 9L cells, confounding interpretation of immune responses in a syngeneic system. Collectively, these results establish the need for a more appropriate model system that lends itself to studying mechanisms of efficacy in glioma immunotherapy.

This project is designed to study basic tenets of immunology while providing readily-translatable treatment plans. A murine model of glioma generated from transgenic strains engineered to overexpress oncogenic V¹²Ha-ras in astrocytes will be used. In the murine system, V¹²Ha-ras can cause expansion of major histocompatibility complex (MHC)-restricted, specific T-cells readily detected by tetramer analysis. For the first time, we have at our disposal a relevant glioma model for immunotherapy with molecular reagents to address the following:

- (1) T-cell trafficking in the central nervous system (CNS): The routes of T-cell traffic in the CNS after peripheral stimulation with a tumor specific peptide (e.g., V¹²Ha-ras) will be identified. We hypothesize that homing efficiency is independent of tumor burden.
- (2) Antigen-presenting cells in the CNS: The source of CNS antigen presentation during progressive phases of tumor development will be identified. We hypothesize that antigen-presentation efficiency decreases with increasing tumor burden.
- (3) Epitope spreading in antiglioma immunity: Syngeneic cells will be genetically modified to appear as allografts. We hypothesize that peripheral vaccination with artificial allografts will foster epitope spreading and result in increased tumor-specific immunity.
- (4) In vivo loading of dendritic cells (DC): The basic hypothesis that in vivo DC loading with Flt3 ligand is more effective than conventional protocols will be tested. In addition we will compare a variety of antigenic stimuli including tumor lysates and tumor-derived heat shock proteins to determine the optimal source of antigen.

This Month's Featured Translational Research Project



San Francisco Bay Area Adult Glioma Survival Study

Principal Investigator: Margaret Wensch PhD

Clinical Co-Principal Investigator: Michael Prados MD

Three important goals of clinical research pertinent to glioma are to choose the best treatment available for each patient, to enhance stratification of patients so that new treatments can be more quickly and accurately evaluated, and to provide better information to patients and their families on what they can expect as a result of their disease. Unambiguous diagnosis is a cornerstone for each of these goals. Currently, however, glioma diagnosis is based primarily on assessments of tumor morphology, which are inherently subjective. There is an urgent need to determine readily standardized tumor characteristics to refine subtype classification of glioma within and between histologic categories, and to determine patient characteristics related to prognosis above and beyond those used currently by the Radiation Therapy Oncology Group to stratify patients into prognostic groups.

This project will address these needs by examining survival in relationship to several tumor markers that define genetic subtypes of gliomas and are thought to be potentially important in prognosis. In addition to consideration of known prognostic indicators such as age, the study also will consider survival as a function of patients' characteristics, including a variety of polymorphisms in DNA-repair and carcinogen-metabolizing genes, personal and family medical histories, diet, smoking, and alcohol consumption before diagnosis, and other demographic factors such as education.

Investigators will determine vital status for 881 patients studied in two population-based case series collected in the San Francisco Bay Area between 1991-1994 (series 1) and between 1997-1999 (series 2) as part of a previous study by Dr. Wensch. Data on whether subjects received radiation and/or chemotherapy will be included along with data on standard characteristics, lifestyle and demographic factors, and potentially relevant tumor markers to determine survival as a function of established, potential, and as yet unstudied prognostic indicators. To validate results from this study, the investigators will gather data from adult patients with glioma who are enrolled prospectively in a clinical trial in the UCSF Neuro-Oncology Program. Up to two tumor markers and two constitutive polymorphisms identified during the study will be assessed in 100 patients who have glioblastoma multiforme.

The information about survival derived from this project is expected to be useful to clinicians in planning and refining treatments, while information about other factors will be useful in providing patients with a clearer picture of their probable outcomes based on their individual characteristics.

This study provides a unique opportunity to examine survival in a large, population-based group of patients with epidemiologic risk-factor data, constitutive DNA specimens, and tumor-marker data, and to use these data to generate ideas and preliminary evaluation of markers that can then be incorporated into prospective clinical trials for validation. Furthermore, once survival data are collected, this already unusual epidemiologic resource of glioma material will also become a valuable resource for clinical markers; it will be possible using this resource to rapidly evaluate whether or not new tumor markers have prognostic significance.

All UCSF Brain Tumor SPORE projects are in their first six months of research activity. We expect to have publications resulting by the end of this year. The following publications list presents a sample of the researchers' extensive experience in their fields and preliminary research preparation done for the current projects.

Bergers G, Javaherian K, Lo KM, Folkman J, Hanahan D. Effects of angiogenesis inhibitors on multistage carcinogenesis in mice. *Science* 1999;284:808-12.

Binder DK, **Berger MS**. Proteases and the biology of glioma invasion. *J Neurooncol* 2002;56:149-58.

Burton EC, Lamborn KR, Feuerstein BG, **Prados M**, Scott J, Forsyth P, Passe S, Jenkins RB, Aldape KD. Genetic aberrations defined by comparative genomic hybridization distinguish long-term from typical survivors of glioblastoma. *Cancer Res* 2002;62:6205-10.

Burton EC, Lamborn KR, Forsyth P, Scott J, O'Campo J, Uyehara-Lock J, **Prados M**, **Berger M**, Passe S, Uhm J, O'Neill BP, Jenkins RB, Aldape KD. Aberrant p53, mdm2, and proliferation differ in glioblastomas from long-term compared with typical survivors. *Clin Cancer Res* 2002;8:180-7.

Chen P, Aldape K, Wiencke JK, Kelsey KT, Miike R, Davis RL, Liu J, Kesler-Diaz A, Takahashi M, **Wrensch M**. Ethnicity delineates different genetic pathways in malignant glioma. *Cancer Res* 2001;61:3949-54.

Dowling C, Bollen AW, Noworolski SM, McDermott MW, Barbaro NM, Day MR, Henry RG, **Chang SM**, Dillon WP, **Nelson SJ**, Vigneron DB. Preoperative proton MR spectroscopic imaging of brain tumors: correlation with histopathologic analysis of resection specimens. *AJNR Am J Neuroradiol* 2001;22:604-12.

Ermoian RP, Furniss CS, Lamborn KR, Basila D, **Berger MS**, Gottschalk AR, Nicholas MK, **Stokoe D**, **Haas-Kogan DA**. Dysregulation of PTEN and protein kinase B is associated with glioma histology and patient survival. *Clin Cancer Res* 2002;8:1100-6.

Graves EE, **Nelson SJ**, Vigneron DB, Verhey L, McDermott M, Larson D, **Chang S**, **Prados MD**, Dillon WP. Serial proton MR spectroscopic imaging of recurrent malignant gliomas after gamma knife radiosurgery. *AJNR Am J Neuroradiol* 2001;22:613-24.

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Hanahan D, **Bergers G**, Bergsland E. Less is more, regularly: metronomic dosing of cytotoxic drugs can target tumor angiogenesis in mice. *J Clin Invest* 2000;105:1045-7.

Li X, Lu Y, Pirzkall A, **McKnight T**, **Nelson SJ**. Analysis of the spatial characteristics of metabolic abnormalities in newly diagnosed glioma patients. *J Magn Reson Imaging* 2002;16:229-37.

McKnight TR, Noworolski SM, Vigneron DB, **Nelson SJ**. An automated technique for the quantitative assessment of 3D-MRSI data from patients with glioma. *J Magn Reson Imaging* 2001;13:167-77.

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Park JW. Liposome-based drug delivery in breast cancer treatment. *Breast Cancer Res* 2002;4:95-9.

Parsa AT, Chi JH, Hurley PT, Jeyapalan SA, Bruce JN. Immunomodulation of glioma cells after gene therapy: induction of major histocompatibility complex class I but not class II antigen in vitro. *Neurosurgery* 2001;49:681-8; discussion 688-9.

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Ware ML, **Berger MS**, Binder DK. Molecular biology of glioma tumorigenesis. *Histol Histopathol* 2003;18:207-16.

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Wrensch M, Minn Y, Chew T, Bondy M, **Berger MS**. Epidemiology of primary brain tumors: current concepts and review of the literature. *Neuro-oncol* 2002;4:278-99.

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. The SPORE 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.