Publications


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

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**A Message From the Director**

The Department of Neurological Surgery at the University of California, San Francisco (UCSF) is pleased to announce that the Brain Tumor Specialized Program of Research Excellence (SPORE) grant awarded to us in 2002 has been renewed for another 5-year cycle. Since 2002, SPORE funding has helped to maximize the potential of UCSF investigators to do translational brain tumor research and greatly reinforced the value of translational brain tumor research on the UCSF campus. In 2008, a new unified space in the Hellen Diller Family Cancer Research Building at the UCSF Mission Bay campus will house all investigators in the Brain Tumor Research Center, the Division of Neuro-Oncology, and the UCSF Brain Tumor SPORE Program.

The next phase of the SPORE Program has expanded to include the new project “Heat Shock Protein Vaccine Development: Glioma Immunoresistance and PI3K/Akt/mTOR Pathway Activation” (page 3). This exciting project arose from the convergence of the work of two investigators supported by the UCSF Brain Tumor SPORE Career Development and Developmental Research Programs, and exemplifies the type of translational work the SPORE mechanism is intended to support. The structure that facilitates communication between UCSF SPORE investigators allowed Andrew Parsa MD, PhD and Russell Pieper PhD, whose projects examined different aspects of the regulation of apoptosis in glioma cells, to identify a common thread in their work and arrive at a new hypothesis. This new hypothesis asserted that B7-H1, a cell-surface protein that Parsa showed to suppress T-cell function and help gliomas escape from immunosurveillance, might be among the subset of anti-apoptotic proteins Pieper demonstrated to be translationally upregulated by Akt (page 2). When this was proved correct, a new translational research project to study the role of the PI3K/Akt/mTOR pathway in the sensitivity of glioma cells to immune vaccines was formed. Ultimately, the results of this project may help to stratify patients and enhance clinical trials, providing a clear example of the way in which the SPORE program can bring basic and applied investigators together to move laboratory findings into the clinical setting.

**Funded Translational Projects and Investigators**

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Clinical Co-Principal Investigator: Michael Prados MD

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Principal Investigator: Sarah Nelson PhD  
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Principal Investigator: Russell Pieper PhD  
Clinical Co-Principal Investigator: Andrew Parsa MD, PhD

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Graeme Hodgson PhD  
Characterization of microRNAs in astrocytomas

Soonne Cha PhD  
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James Rubenstein PhD  
CSF biomarkers of brain tumors

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**Glioma Immunoresistance and PI(3)K/Akt/mTOR Pathway Activation**

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Parsa MD, PhD, Pieper found that the expression of a second protein, B7 homolog 1 (B7-H1), a cell-surface protein, was controlled by the cell-signaling pathway that connects Akt to the mammalian target of rapamycin (mTOR). Akt may escape TRAIL-induced apoptosis. Inhibition of the Akt/mTOR pathway sensitized short-term cultures of GBM cell lines and xenografts to TRAIL-induced apoptosis. This is controlled by the cell-signaling pathway that connects Akt to the mammalian target of rapamycin (mTOR), suggesting a means by which GBM that are deficient in phosphatase tensin homolog (PTEN) and overexpress B7 homolog 1 (B7H1), induces apoptosis in CD8+ T cells, impairs cytokine production, and diminishes the cytotoxicity of activated T cells. In work leading up to this SPORE project, Andrew Parsa MD, PhD and Russell Pieper MD, PhD found much higher levels of B7H1 in gliomas lacking functional phosphatase and tensin homolog (PTEN) — a tumor suppressor gene commonly deleted or mutated in high-grade gliomas. Loss of PTEN activates the cell-signaling pathway that links phosphatidylinositol-3-OH kinase (PI(3K)) to Akt and the mammalian target of rapamycin (mTOR). Parsa and Pieper discovered that activation of Akt increases translation of the gene transcript for B7H1 (CD274). Although the CD274 transcript is found in many tissues, the B7H1 protein is not commonly expressed (Nature Medicine, 2007). Linking B7-H1 to PTEN loss has provided Parsa and Pieper with a rationale for targeting the PI(3)/Akt/mTOR pathway to optimize adaptive immune responses.

Additional evidence shows that the PI(3)/Akt/mTOR pathway is also linked to inhibition of innate immune responses. c-FLICE inhibitory protein (FLIP) inhibits the function of NK cells and is increased in cells with the PI(3)/Akt/mTOR pathway activation. NK cells attack tumor cells through a variety of mechanisms, one of which is mediated by tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL). By binding to caspase 8, FLIP prevents activated TRAIL receptors that are bound to the membrane of NK cells from connecting to the apoptotic machinery (page 2). Collectively, by killing or disabling the function of CD8+ T cells and NK cells, B7H1 and FLIP could limit the efficacy of glioma immunotherapy even if an immune response is provoked by treatment. This SPORE project will further investigate these findings through in vitro studies that directly examine whether or not activation of the PI(3)/Akt/mTOR pathway in glioma suppresses innate and adaptive immune response. The findings are also being applied to an ongoing clinical trial of a brain tumor vaccine.

UCSF is currently beginning the second phase of a clinical trial testing a heat shock protein vaccine for glioma. Heat shock proteins bind to tumor antigens and present them to immune cells. The vaccine is generated by isolating heat shock protein-antigen complexes from a patient’s own tumor tissue, creating a highly individualized therapy. When the complexes are injected back into the body in the form of the vaccine, they encounter the immune system and may trigger a stronger immune response against the tumor-specific antigen. In the first phase of the trial, the vaccine generated an immune response in all patients. Parsa and Pieper retrospectively examined the status of the PI(3)/Akt/mTOR pathway of these patients and found that those with high levels of Akt had a lower overall survival rate than those with normal levels. It is estimated that approximately 50% to 60% of gliomas lack functional PTEN and overexpress Akt. In the second phase of the vaccine trial, the investigators will continue to evaluate the connection between activation of the PI(3)/Akt/mTOR pathway and survival. Further evidence may lead to a phase III trial of the vaccine in an enriched population of patients, based on the PI(3)/Akt/mTOR pathway status of their tumor tissue. In future trials it may be possible treat patients whose tumors express high levels of B7H1 and FLIP, with Akt inhibitors to impede the production of these immunosuppressive proteins. Ultimately, successful immunotherapy will be tailored to the specific biological characteristics of each patient. By examining the role of a critical pathway in immunoresistance, this SPORE project may increase the therapeutic benefit of immunotherapy for brain tumors.

The UCSF Brain Tumor SPORE includes a new project that aims to optimize immunotherapy for patients with gliomas by examining biological processes that may counteract the protective effect of a vaccine. The vaccine studied in this project elicits both an adaptive immune response (led by CD8+ T cells) and an innate response (led by natural killer (NK) cells). A number of proteins produced in the glioma microenvironment play a role in suppressing anti-tumor immunity. One of these proteins, FLIP, expressed in glioblastoma cells, and this project was designed to investigate the biology and therapeutic potential of microRNAs found in adult neural stem cells and tumor-derived stem cells. MicroRNAs are small, non-coding RNAs that regulate diverse cellular processes, such as differentiation, proliferation, and apoptosis. The Hodgson laboratory has identified several microRNAs, including miR-124a and miR-137, which are highly expressed in non-neoplastic brain tissue but not expressed in glioblastoma. When transfected into neural stem cells, miR-124a and miR-137 were found to induce neuron-like differentiation. Similarly, neuron-like differentiation was observed following miR-124a or miR-137 transfection to neurosphere cultures derived from mouse oligodendrogliomas and human glioblastomas. Most recently, these microRNAs have been shown to inhibit proliferation of glioblastoma cells. These results suggest that microRNAs may be useful therapeutic agents for the treatment of glioblastoma.
protein that induces death in T cells, was also controlled by PTEN, and that the loss of PTEN function increased levels of B7H1 and contributed to the escape of GBM cells from elimination by the immune system. These studies suggested that brain tumors lacking functional PTEN are immune to apoptosis induced by TRAIL (itself secreted by cells of the immune system) or T cells, and that one pathway controls both types of tumor survival. Further investigation demonstrated that TRAIL-resistant cells can be made sensitive to TRAIL by inhibiting mTOR. What remains to be determined is if TRAIL or a combination of TRAIL and rapamycin can be delivered by cells of the immune system) or T cells, and that one pathway controls both types of tumor survival.

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An unexpected observation that arose during these studies was that the PTEN/Akt pathway controlled Akt may escape TRAIL-induced apoptosis. Inhibition of the Akt/mTOR pathway sensitized short-term cultures suggesting a means by which GBM that are deficient in phosphatase tensin homolog (PTEN) and overexpress B7 homolog 1 (B7-H1) to TRAIL.

Recent studies have indicated that neural stem cells may be the origin of human glioblastoma. Most recently, these microRNAs have been shown to inhibit proliferation of glioblastoma cells. These results suggest that microRNAs may be useful therapeutic agents for the treatment of glioblastoma.

The long-term objective of this proposal was to improve the therapy of glioblastoma multiforme (GBM) by better understanding the determinants of resistance and sensitivity to the therapeutic death ligand TRAIL (TNF-related apoptosis-inducing ligand). TRAIL is an attractive therapeutic molecule because it binds to TRAIL receptors in GBM and induces apoptosis in tumor cells, but not in normal cells. While many types of tumors are sensitive to TRAIL, GBM is largely resistant. Results from the first year of work on this project showed that one regulator of apoptosis is the molecule c-FLICE inhibitory protein (FLIP) — a protein that binds to caspase 8 and blocks apoptosis following activation of TRAIL receptors. FLIP expression is controlled by the cell-signaling pathway that connects Akt to the mammalian target of rapamycin (mTOR). By binding to caspase 8, FLIP prevents activated TRAIL receptors that are bound to the membrane of NK cells from connecting to the apoptotic machinery (page 2). Collectively, by killing or disabling the function of CD8+ T cells and NK cells, B7H1 and FLIP could limit the efficacy of glioma immunotherapy even if an immune response is provoked by treatment. This SPORE project will further investigate these findings through in vitro studies that directly examine whether or not activation of the PI(3)K/Akt/mTOR pathway in glioma suppresses innate and adaptive immune response.

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 Cancer 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.

The UCSF Brain Tumor SPORE includes a new project that aims to optimize immunotherapy for patients with gliomas by examining biological processes that may counteract the protective effect of a vaccine. The vaccine studied in this project elicits both an adaptive immune response (led by CD8+ T cells) and an innate response (led by natural killer (NK) cells). A number of proteins produced in the glioma microenvironment play a role in suppressing anti-tumor immunity. One of these proteins, B7 homolog 1 (B7-H1), induces apoptosis in CD8+ T cells, impairs cytokine production, and diminishes the cytotoxicity of activated T cells. In work leading up to this SPORE project, Andrew Parsa MD, PhD and Russell Pieper PhD found much higher levels of B7H1 in gliomas lacking functional phosphatase and tensin homolog (PTEN) — a tumor suppressor gene commonly deleted or mutated in high-grade gliomas. Loss of PTEN activates the cell-signaling pathway that links phosphatidylinositol-3-OH kinase (PI(3)K) to Akt and the mammalian target of rapamycin (mTOR). Parsa and Pieper discovered that activation of Akt increases translation of the gene transcript for B7H1 (CD274). Although the CD274 transcript is found in many tissues, the B7H1 protein is not commonly expressed (Nature Medicine, 2007). Linking B7-H1 to PTEN loss has provided Parsa and Pieper with a rationale for targeting the PI(3)K/Akt/mTOR pathway to optimize adaptive immune responses. Additional evidence shows that the PI(3)K/Akt/mTOR pathway is also linked to inhibition of innate immune response. c-FLICE inhibitory protein (FLIP) inhibits the function of NK cells and is increased in cells with PI(3)K/Akt/mTOR pathway activation. NK cells attack tumor cells through a variety of mechanisms, one of which is mediated by tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). By binding to caspase 8, FLIP prevents activated TRAIL receptors that are bound to the membrane of NK cells from connecting to the apoptotic machinery (page 2). Collectively, by killing or disabling the function of CD8+ T cells and NK cells, B7H1 and FLIP could limit the efficacy of glioma immunotherapy even if an immune response is provoked by treatment. This SPORE project will further investigate these findings through in vitro studies that directly examine whether or not activation of the PI(3)K/Akt/mTOR pathway in glioma suppresses innate and adaptive immune response. The findings are also being applied to an ongoing clinical trial of a brain tumor vaccine.