Pediatric Brain Tumor Foundation Renews Support for Institute at UCSF

This year, the Pediatric Brain Tumor Center at UCSF was awarded an additional three years of funding from the Pediatric Brain Tumor Foundation (PBTF) as one of three PBTF Institutes in North America.

The PBTF was founded by Mike and Dianne Traynor in 1991, and their tireless efforts transformed the foundation into the world’s largest philanthropic organization dedicated to supporting the search for the causes of and cures for childhood brain cancer. Sadly, Mike passed away in 2009, and Dianne in 2012. At UCSF we will miss their friendship and dedication to our fight against childhood brain tumors, and we will continue our work and partnership with the PBTF in honor of their legacy.

The PBTF Institute at UCSF is built around three research projects. It also includes a tissue bank and animal core to provide support for translational research.

**Spatial, Temporal and Cellular Origins of Pediatric Glioma**

*Principal Investigators: David Rowitch MD, PhD and Arturo Alvarez-Buylla PhD*

Drs. Rowitch and Alvarez-Buylla are investigating oligodendrocyte progenitors as possible cells of origin for pediatric glioma and also studying how underlying genetic alterations found in high-grade pediatric glioma may interact with these progenitors in certain regions and stages of development to lead to tumor formation.

Although genetic alterations in the developing nervous system are not well characterized, the BRAFV600E mutation has become interesting to pediatric brain tumor researchers because it is activated in approximately 20% of pediatric brain tumors, but only 3% of adult tumors. There is also increasing evidence that oncogenic mutations may cooperate in specific ways with spatially distinct progenitor cells to drive glioma. Recently, our team has shown that oligodendrocyte transcription factor 2 (Olig2) is expressed in 100% of pediatric gliomas, raising the question of whether oligodendrocyte progenitors could initiate pediatric gliomagenesis.

Our Team

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Using mouse models of BRAF<sup>V600E</sup> Ink4a-Arf−/−, pediatric gliomas, the investigators will test which regions (dorsal vs. rostral) and which stages of postnatal development tumors with this mutation are most likely to form in. They will also examine whether the BRAF<sup>V600E</sup> mutation acts on particular subsets of oligodendrocyte precursors to cause them to become tumorigenic. This glioma modeling effort parallels a pre-clinical study done at UCSF, which showed that targeted inhibitors of BRAF and CDK4/6 were highly effective in preventing mortality in a mouse model of pediatric glioma (see Upcoming Personalized Medicine Trial for Malignant Pediatric Astrocytoma, below).

**MYCN and Medulloblastoma Tumorigenesis**

Principal Investigator: William A. Weiss MD, PhD

In the previous funding cycle, Dr. Weiss and his colleagues showed that aberrant expression of the protein MYCN contributes to the pathogenesis of medulloblastoma. Based on that finding, the Weiss laboratory will develop humanized mouse models for medulloblastoma through the mis-expression of MYCN and MYCNT58A in human cerebellar stem cells and in human cerebellar-derived glial progenitor cells. Transplanting the transduced progenitor cells into the brains of immunocompromised mice may lead to new mouse models for medulloblastoma that could clarify the biology of this common childhood cancer, as well as provide a clinically relevant platform for testing targeted therapies.

**Genetics and Biology of Diffuse Intrinsic Pontine Gliomas**

Principal Investigators: Nalin Gupta MD, PhD, Joanna J. Phillips PhD, and C. David James PhD

Diffuse intrinsic pontine gliomas (DIPG) are primary CNS tumors that arise in children. Despite aggressive therapy, children with DIPG have remarkably poor outcomes. In the previous funding cycle, this research group developed new model systems to study DIPG, and investigated a number of emerging therapeutic strategies as candidates for Phase I clinical trials. This project will continue to focus on the biology of DIPGs and on identifying targets for future therapeutic development.

The specific goals of the project are:

- Establish a bank of primary cell cultures and develop DIPG xenografts that will be molecularly profiled and used for pre-clinical therapeutic testing
- Determine how alterations in the tumor microenvironment influence DIPG tumor biology, with a focus on the microglia/macrophage response. Preliminary studies demonstrate a robust tumor-associated microglia/macrophage response in pediatric gliomas and this response may create a favorable environment for tumor progression.

**Upcoming Personalized Medicine Trial for Malignant Pediatric Astrocytomas**

UCSF is developing clinical trials for pediatric astrocytomas that exhibit both a BRAF<sup>V600E</sup> mutation and homozygous deletion of cyclin-dependent kinase inhibitor 2A (CDK2A).

Researchers at the Pediatric Brain Tumor Center found that while the BRAF<sup>V600E</sup> mutation is common in pediatric tumors, it did not form tumors from neural progenitor cells unless it was paired with CDK2A deletion. The study, published this year in *Proceedings of the National Academy of Sciences*, also demonstrated that combination therapy of BRAF and CDK inhibitors significantly extended survival in a mouse model of pediatric astrocytoma. Patients with BRAF<sup>V600E</sup> mutant brain tumors will soon be eligible for a trial testing single-agent vemurafenib (a BRAF inhibitor similar to PLX4720, which was used in the preclinical studies at UCSF). Future trials will focus on combination therapies, the most promising being a combination of vemurafenib and the CDK 4/6-specific inhibitor PD0332991.

The clinical trial of vemurafenib has been added to the next phase of UCSF’s Specialized Program of Research Excellence (SPORE) for Brain Tumors and was made possible by the preclinical research funded by the Pediatric Brain Tumor Foundation.

**Further reading:**

Pediatric Brain Tumor Clinical Trials

Questions about patients’ participation in the following clinical trials can be directed to the nurse practitioner by calling 415.476.3831.

**Newly Diagnosed Tumor**

**Diffuse Intrinsic Pontine Glioma (DIPG)**
A Phase I/II study of suberoylanilide hydroxamic acid (SAHA, vorinostat) and local irradiation, followed by maintenance SAHA in children with newly diagnosed diffuse intrinsic pontine gliomas (Children’s Oncology Group Study ACNS0927)

**High-Grade Glioma**
A randomized Phase II/III study of vorinostat (IND# 71976) and local irradiation OR temozolomide and local irradiation OR bevacizumab and local irradiation followed by maintenance bevacizumab (IND # 7921) and temozolomide in newly diagnosed high-grade glioma (Children’s Oncology Group Study ACNS0822)

**Ependymoma**
Phase III randomized trial of post-radiation chemotherapy in patients with newly diagnosed ependymoma ages 1 to 21 years (Children’s Oncology Group Study ACNS0831)

**Medulloblastoma and Primitive Neural Ectodermal Tumor (PNET)**
A study evaluating limited target volume boost irradiation and reduced dose craniospinal radiotherapy (18.00 Gy) and chemotherapy in children with newly diagnosed standard-risk medulloblastoma: a Phase III double randomized trial (Children’s Oncology Group Study ACNS0331)

**Efficacy of carboplatin administered concomitantly with radiation and isotretinoin as a pro-apoptotic agent in other-than-average-risk medulloblastoma/PNET patients (Children’s Oncology Group Study ACNS0332)**

**A Phase III randomized trial for the treatment of newly diagnosed supratentorial PNET and high-risk medulloblastoma in children < 36 months old with intensive induction chemotherapy with methotrexate followed by consolidation with stem cell rescue vs. the same therapy without methotrexate (Children’s Oncology Group Study ACNS0334)**

**Atypical Teratoid/ Rhabdoid Tumor**
Treatment of atypical teratoid/rhabdoid tumors of the central nervous system with surgery, intensive chemotherapy, and 3-D conformal radiation (Children’s Oncology Group Study ACNS0333)

**CNS Germ Cell Tumors**
Phase II Trial of response-based radiation therapy for patients with localized central nervous system germ cell tumors (Children’s Oncology Group Study ACNS1123)

**Recurrent Disease**
A Phase I and pharmacokinetic study of AZD6244 for recurrent or refractory pediatric low-grade glioma (PBTC 029)
A Phase I study to evaluate the safety and pharmacokinetics of panitumumab in children with solid tumors (Amgen Study 20050252)

**Temozolomide with irinotecan versus temozolomide, irinotecan plus bevacizumab for recurrent/refractory medulloblastoma/CNS PNET of childhood: a COG randomized Phase II screening trial (Children’s Oncology Group Trial ACNS0821)**

**A Phase II study of sunitinib (NSC# 736511, IND# 74019) in recurrent, refractory or progressive high-grade glioma and ependymoma brain tumors in pediatric and young adult patients (Children’s Oncology Group Trial ACNS1021)**

**A Phase II randomized trial of lenalidomide (NSC # 703813, IND # 70116) in pediatric patients with recurrent, refractory or progressive juvenile pilocytic astrocytoma and optic pathway gliomas (Children’s Oncology Group Trial ACNS1022)**

**A Phase 1 study of imetelstat, a telomerase inhibitor, in children with refractory or recurrent solid tumors and lymphoma (Children’s Oncology Group Trial ADVL1112)**

**A Phase 1 study of XL184 (cabozantinib) in children and adolescents with recurrent or refractory solid tumors, including CNS tumors (Children’s Oncology Group Trial ADVL1211)**

**Trials Studying Late Effects of Treatment**
Neurocognitive brain tumor study: a prospective, UCSF study to test the feasibility of a computerized neurocognitive training program in children with brain tumors

Neuropsychological, social, emotional and behavioral outcomes in children with cancer (Children’s Oncology Group Trial ALTE07C1)

A Phase II placebo-controlled trial of modafinil to improve neurocognitive deficits in children treated for a primary brain tumor (Children’s Oncology Group trial ACCL0922)
To schedule an appointment or refer a patient, call (415) 353-7500

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