Pediatric Brain Tumor Consortium (PBTC)

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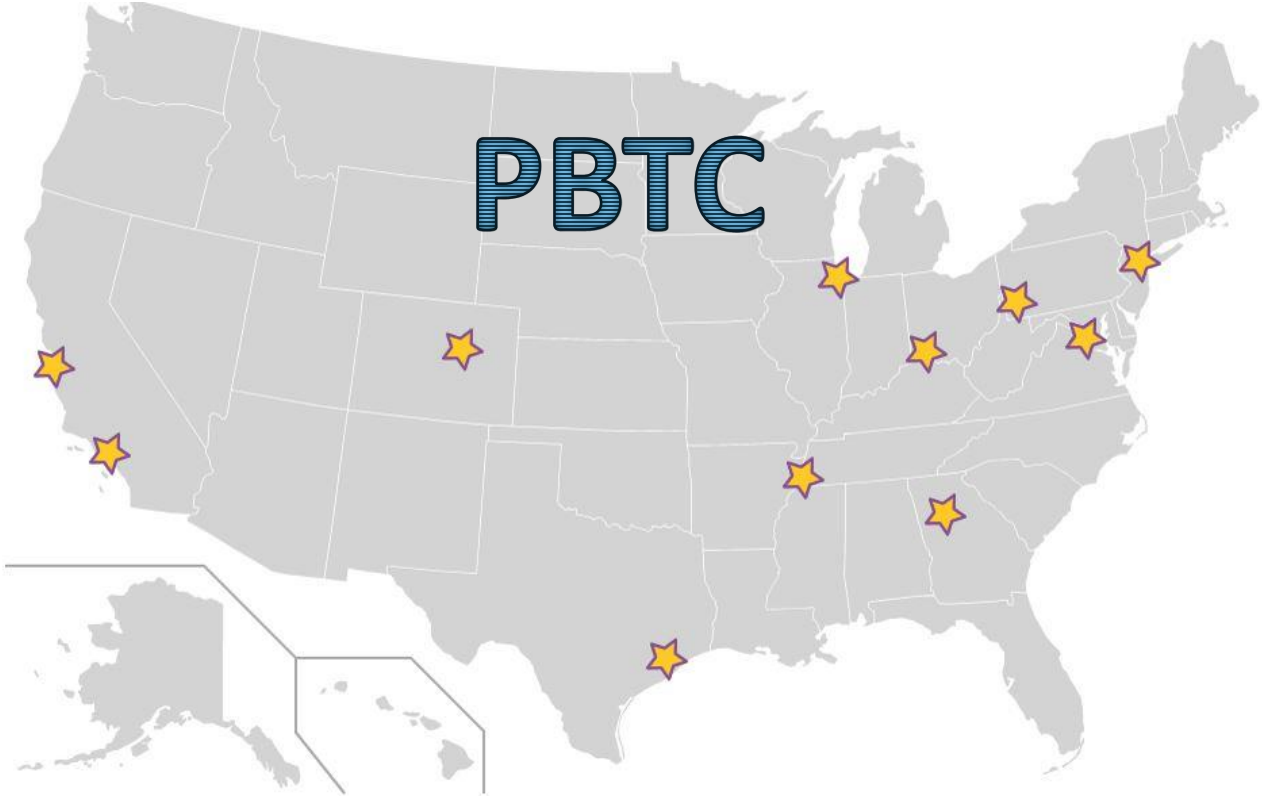
NIH NATIONAL CANCER INSTITUTE

BSA Meeting - June 2019

Background

- Supported through successive FOAs since 1999
- SJCRH leads PBTC OBDMC (PI Arzu Onar-Thomas)
- PBTC Chair: Ira Dunkel (MSKCC)
- Primary source of NCI-sponsored clinical trials for children with relapsed / refractory brain tumors



Participating sites: CA Children's Hospital Los Angeles, CA Lucile Packard Children's Hospital Stanford, CO Children's Hospital Colorado, DC Children's National Medical Center (Washington, DC), GA Children's Healthcare of Atlanta, IL Ann & Robert H. Lurie Children's Hospital of Chicago, MD NIH-Pediatric Oncology Branch, NY Memorial Sloan Kettering Cancer Center, OH Cincinnati Children's Hospital Medical Center, PA Children's Hospital of Pittsburgh, TN St. Jude Children's Research Hospital, TX Texas Children's Cancer Center.

Clinical Trials by Agent Type and Correlative Studies										
		Agent Type			Correlative Studies					
Protocol	Novel Agent	Mol. Target	Immuno-therapy	Other	PK	PG	Biology/ Genomics	Immune correlates	Neuro-Imaging	QOL
026	Vorinostat	x					x			
029B/C	Selumetinib	x			x		x		x	
033	Veliparib	x			x	x	x		x	
037	HSV1716		x					x	x	
039	PEGIntron		x				x		x	
041	p28	x			x	x	x			
042	Palbociclib	x			x	x	x			
043	Pomalidomide		x		x			x		
045	Pembrolizumab		x				x	x	x	
047	Panobinostat	x			x	x	x			
048	Optune			x					x	x
049	Salvolitinib	x			x		x			
050	Everolimus + Ribociclib	x			x		x			
051	APX005M		x		x		x	x		x
053	CX-4945	x			x		x			

PBTC Role in COG Phase 3 Clinical Trials (2014-2019)

- Two of 4 COG phase 3 clinical trials are based on PBTC results.

COG Protocol	Title	PBTC Study
ACNS1422	A Phase 2 Study of Reduced Therapy for Newly Diagnosed Average-Risk WNT-Driven Medulloblastoma Patients	Not applicable
ACNS1721	A Phase 2 Study of Veliparib (ABT-888, IND # 139199) and Local Irradiation, Followed by Maintenance Veliparib and Temozolomide, in Patients with Newly Diagnosed High-Grade Glioma (HGG) Without H3 K27M or BRAFV600E Mutations	PBTC-027 and PBTC-033
ACNS1723	A Phase 2 Study of Dabrafenib (NSC# 763760, IND# TBD) with Trametinib (NSC# 763093) After Local Irradiation in Newly-Diagnosed BRAF V600-Mutant High-Grade Glioma (HGG)	Not Applicable
ACNS1831	A Phase 3 Randomized Study of Selumetinib (IND # 77782) Versus Carboplatin/Vincristine in Newly Diagnosed or Previously Untreated Neurofibromatosis Type 1 (NF1) Associated Low-Grade Glioma (LGG)	PBTC-029

- Two other COG CNS Tumor Committee protocols that are under review by CTEP are based on the results of PBTC-029.

Other PBTC and COG CNS Committee Interactions

- The CNS Committee Chair Dr. Maryam Fouladi served as the PBTC Chair during 2013-2016 and is currently a member of the PBTC Steering and Executive Committees.
- The PBTC OBDMC Director and Lead Statistician Dr. Onar-Thomas serves as the Lead Statistician for the COG CNS Committee and is a member of COG Scientific Council.
- Drs. Dunkel and Fangusaro are on the COG CNS Steering Committee.
- The results from PBTC and COG phase 2 trials that treated recurrent malignant brain tumors were combined in a meta-analysis to generate information that can be used in future study designs.
- The PBTC has shared its disease assessment criteria with COG and in turn has modified some of the language in its templates based on COG trial guidance.
- The PBTC has taken active steps to encourage its member institutions to enroll on the Pediatric MATCH study that is being run by NCI and COG.

PBTC Operations Accomplishments 2014-2019

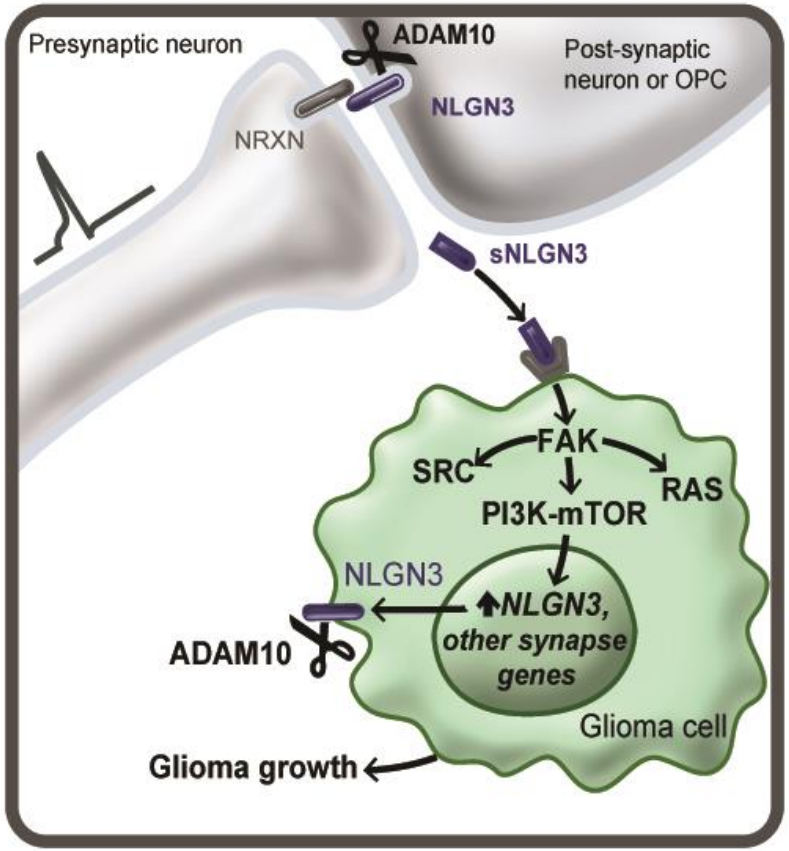
- Integrated with CTEP clinical trials infrastructure
  - Medidata Rave
  - CTSU procedures (OPEN, RSS, etc.)
  - Pediatric CIRB
- Adopted central monitoring with 100% source data verification
- Rigorous review of site performance with competition to allow new institutions to join PBTC
- PBTC worked with SJCRH Clinical Trials Administration as well as the SHCRH Regulatory Affairs Team to put processes and policies in place to allow SJCRH to serve as IND sponsor for PBTC trials.

PBTC Scientific Directions

Scientific Directions

- Novel agents based on the distinctive biology of pediatric brain tumors
  - ADAM-10 Inhibitor INCB7839 targeting microenvironmental neuroligin-3
  - CK2 inhibitor targeting hedgehog pathway signaling in SHH medulloblastoma
  - Relevant kinase inhibitors (BRAF, MEK, MET, MTOR)
- Novel local therapies
  - Convection Enhanced Delivery (CED) of ^{131}I-8H9 (Souweidane, MSKCC)
  - Intrathecal ^{131}I-8H9 for children with high risk brain tumors (Kramer, MSKCC)
  - TTFields (infratentorial)
  - Others
- Novel immunotherapies

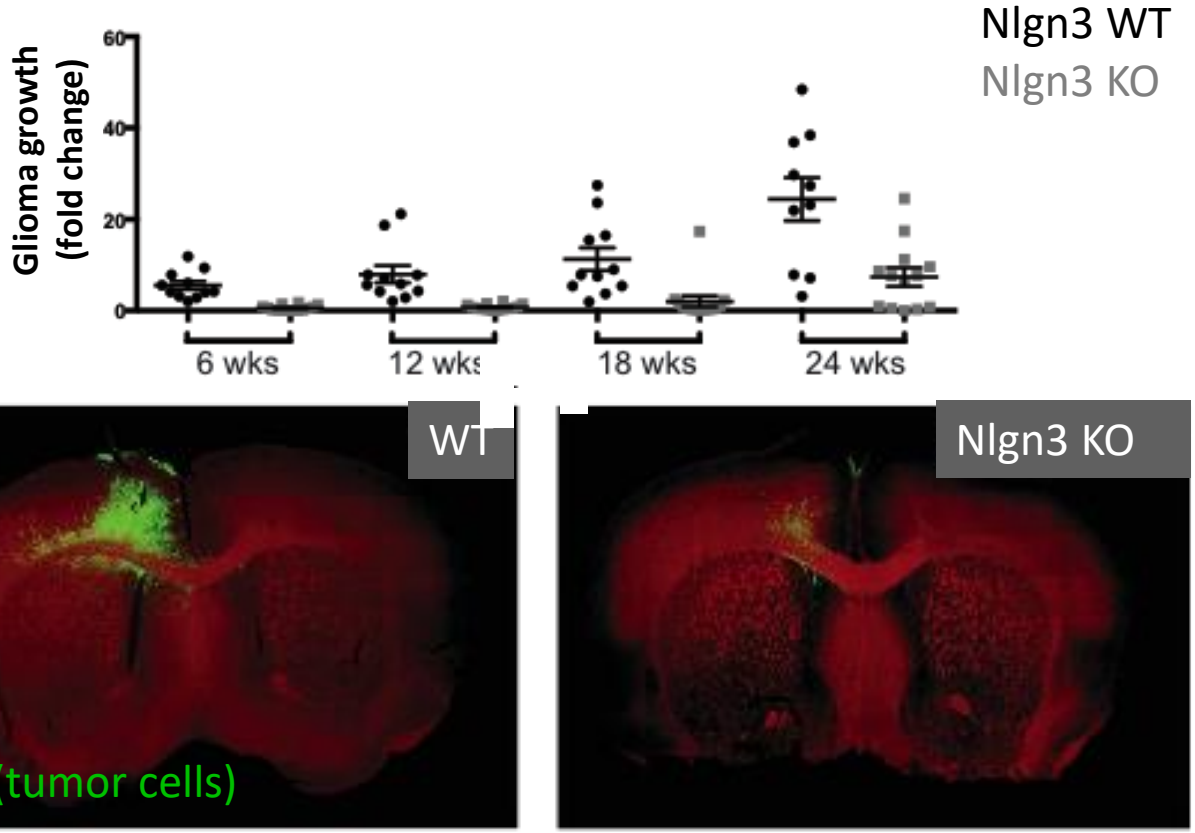
PBTC-056: Mechanisms of NLGN3-mediated glioma growth



- Interaction with neuron and glioma cell
- Neuronal stimulation results in the cleavage and secretion of NLGN3, a postsynaptic adhesion molecule
- ADAM10 is the enzyme that cleaves NLGN3
- NLGN3 binds to glioma cell and stimulates mitosis through focal adhesion kinase
  - RAS, SRC, and m-TOR

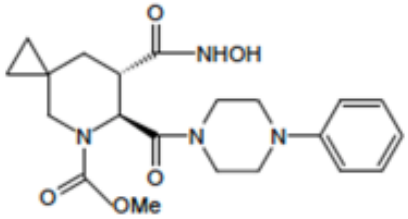
Venkatesh and Monje (2015) *Cell*
Venkatesh and Monje (2017) *Nature*

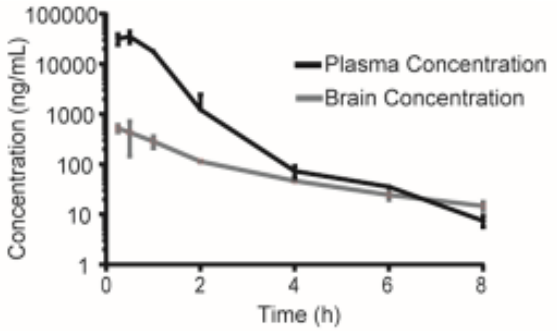
PBTC-056: Neuroligin-3 is necessary for glioma growth



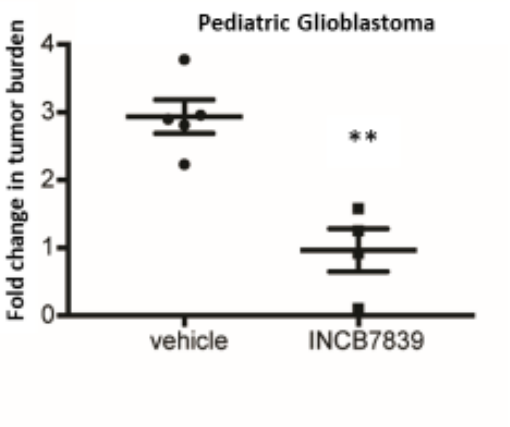
Venkatesh and Monje (2017) *Nature*

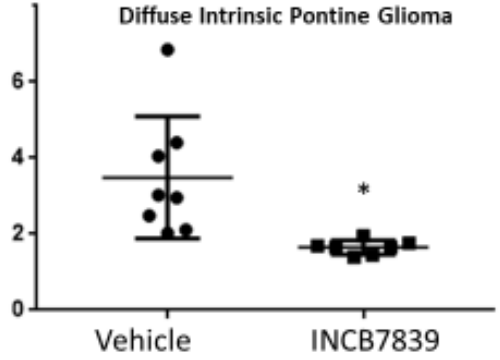
Incyte INCB7839: Inhibits ADAM10 and blocks glioma growth

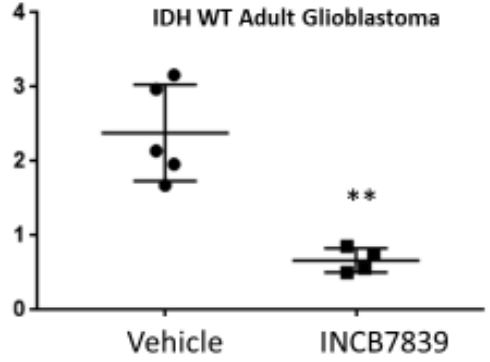




- CSF Penetration
- Up to 4 hours
- Irreversible inhibitor







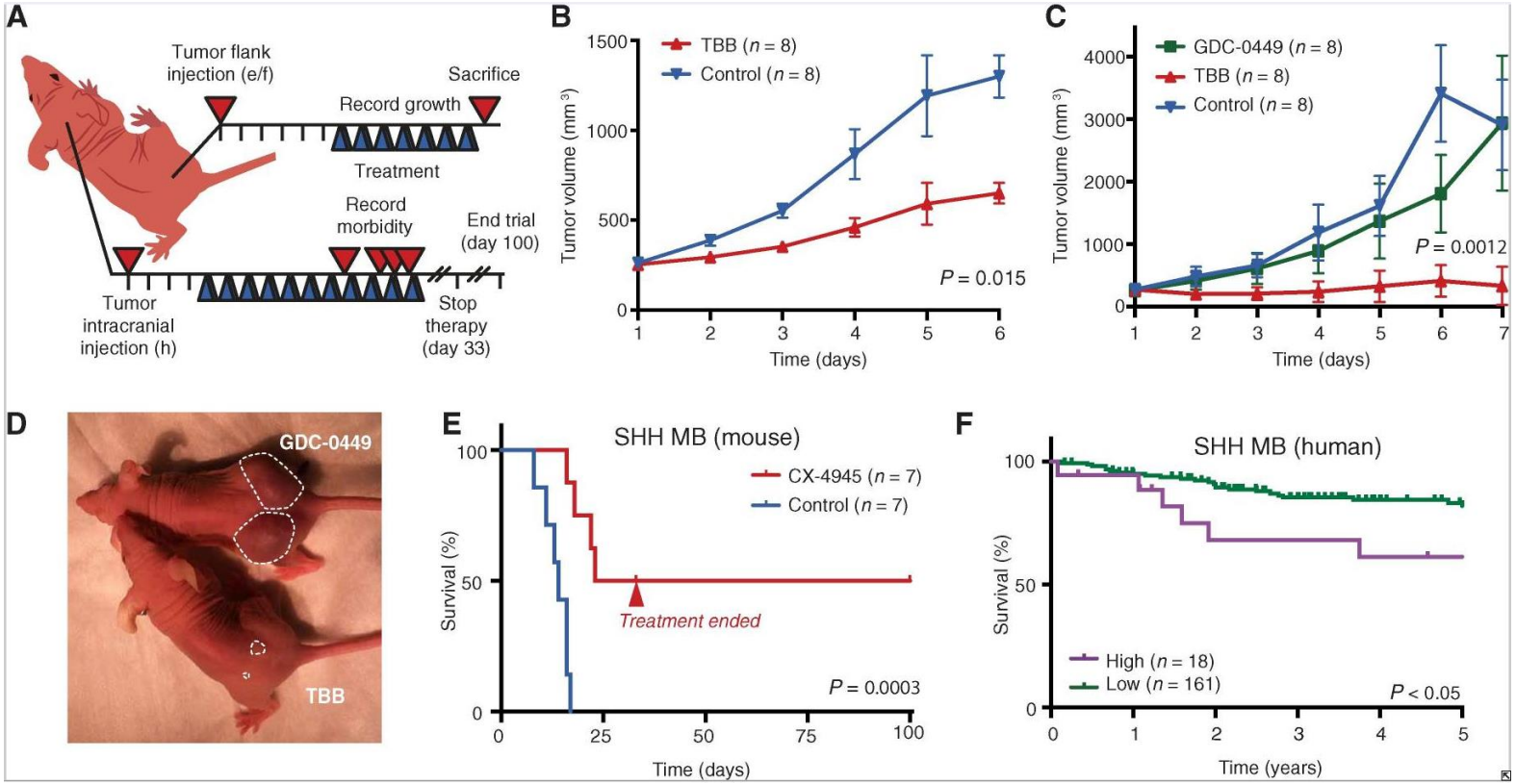
Venkatesh and Monje (2017) *Nature* and unpublished data

CANCER THERAPY

Developmental phosphoproteomics identifies the kinase CK2 as a driver of Hedgehog signaling and a therapeutic target in medulloblastoma

Teresa Purzner[1,2]*, James Purzner[1,2], Taylor Buckstaff[3], Giorgio Cozza[4], Sharareh Gholamin[5], Jessica M. Rusert[6], Tom A. Hartl[1], John Sanders[7], Nicholas Conley[8], Xuecai Ge[1,9], Marc Langan†, Vijay Ramaswamy[10,11], Lauren Ellis[1], Ulrike Litzenburger[12], Sara Bolin[13], Johanna Theruvath[14], Ryan Nitta[13], Lin Qi[15], Xiao-Nan Li[15], Gordon Li[13], Michael D. Taylor[11,16], Robert J. Wechsler-Reya[6,17], Lorenzo A. Pinna[18,19], Yoon-Jae Cho[20,21,22]‡, Margaret T. Fuller[1]‡, Joshua E. Elias[7], Matthew P. Scott[1]*

PBTC-053: Efficacy of CK2 inhibitors against SHH medulloblastoma



Purzner, et al. Sci Signaling 2018

PBTC-053: Role of the PBTC in translating discoveries to the clinic

Finally, our collaboration with Senhwa was solidified by the PBTC, the nonprofit consortium created by the National Cancer Institute to improve treatment of primary brain tumors in children. Without federally funded, multi-institutional collaborations, like the PBTC, the cost and expertise required for designing and implementing trials for children with brain cancer would have been well out of our reach.

Teresa Purzner (PBTC-053 Co-Investigator), The Conversation (https://theconversation.com/drug-development-is-no-longer-just-for-big-pharma-researchers-at-bio-x-explain-103421)

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  - TTFields (supratentorial and infratentorial)
  - Others
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PBTC RFA Plans

Enhancements Proposed

- Increase capacity for clinical trials
- Increase number of member institutions
  - Scientific input
  - Accrual support for phase 1-2 and pilot studies
- Enhance ability to continue collaborative interactions with COG CNS Committee

Budget

- PBTC under-resourced at present ($2,218,314 direct and $2,711,850 total cost)
  - Additional member institutions (6 sites at $80,000 per site)
  - Increase support for OBDMC ($400,000)
  - Leadership funds to support participation of COG CNS Committee members ($125,000)

- Request $3.3 million direct costs with total costs of $4.0 million

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