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
<table>
<thead>
<tr>
<th>Protocol</th>
<th>Novel Agent</th>
<th>Agent Type</th>
<th>Mol. Target</th>
<th>Immuno-therapy</th>
<th>Other</th>
<th>Correlative Studies</th>
<th>PK/PG</th>
<th>Biology/Genomics</th>
<th>Immune correlates</th>
<th>Neuro-Imaging</th>
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PBTC Role in COG Phase 3 Clinical Trials (2014-2019)

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

<table>
<thead>
<tr>
<th>COG Protocol</th>
<th>Title</th>
<th>PBTC Study</th>
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<tbody>
<tr>
<td>ACNS1422</td>
<td>A Phase 2 Study of Reduced Therapy for Newly Diagnosed Average-Risk WNT-Driven Medulloblastoma Patients</td>
<td>Not applicable</td>
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<tr>
<td>ACNS1721</td>
<td>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</td>
<td>PBTC-027 and PBTC-033</td>
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<td>ACNS1723</td>
<td>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)</td>
<td>Not Applicable</td>
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<tr>
<td>ACNS1831</td>
<td>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)</td>
<td>PBTC-029</td>
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</table>

- 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 (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

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

Teresa Purzner, James Purzner, Taylor Buckstaff, Giorgio Cozza, Sharareh Gholamin, Jessica M. Rusert, Tom A. Hartl, John Sanders, Nicholas Conley, Xuecai Ge, Marc Langan, Vijay Ramaswamy, Lauren Ellis, Ulrike Litzenburger, Sara Bolin, Johanna Theruvath, Ryan Nitta, Lin Qi, Xiao-Nan Li, Gordon Li, Michael D. Taylor, Robert J. Wechsler-Reya, Lorenzo A. Pinna, Yoon-Jae Cho, Margaret T. Fuller, Joshua E. Elias, Matthew P. Scott

SHH ➔ PTCH ➔ SMO ➔ SUFU ➔ GLI2 ➔ GLI2 target genes (Gli1, Ccnd1, Ptc1...)

Purzner, et al. Sci Signaling 2018
PBTC-053: Efficacy of CK2 inhibitors against SHH medulloblastoma

**Figure A**: Tumor flank injection (left) followed by treatment and sacrifice. Record growth and treatment. Stop therapy (day 33) and record morbidity (day 100).

**Figure B**: Tumor volume (mm³) over time (days). TBB (n = 8) compared to Control (n = 8). P = 0.015.

**Figure C**: Tumor volume (mm³) over time (days). GDC-0449 (n = 8) compared to TBB (n = 8) and Control (n = 8). P = 0.0012.

**Figure D**: Images of SHH MB (mouse) treated with GDC-0449 and TBB.

**Figure E**: Survival (%) over time (days). SHH MB (mouse) treated with CX-4945 (n = 7) and Control (n = 7). Treatment ended. P = 0.0003.

**Figure F**: Survival (%) over time (years). SHH MB (human) with High (n = 18) and Low (n = 161) groups. P < 0.05.
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.
Scientific Directions

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  - ADAM-10 Inhibitor INCB7839 targeting microenvironmental neuroligin-3
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  - TTFIELDS (supratentorial and infratentorial)
  - Others

- Novel immunotherapies
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