The Children's Brain Tumor Tissue Consortium Annual Report 2014

CBTTC Operations Center

The Children's Brain Tumor Tissue Consortium Annual Report

Acknowledgments

The Consortium enrolled its 1000th subject in 2014 and now has over 900 unique tissue specimens. This milestone would not have been possible without the collaboration of the CBTTC Institutional Members at The Children's Hospital of Philadelphia (CHOP), The Children's Hospital of Pittsburgh, Seattle Children's Hospital, The Ann and Robert Lurie Children's Hospital of Chicago, Meyer Children's Hospital in Florence, Italy and the dedication and support of the Children's Brain Tumor Foundation, the Licensing Industry Merchandisers' Association, the Kortney Rose Foundation, countless volunteers and dedicated donors. In the years to come, these critical partnerships and ongoing commitments will safeguard our shared vision to improve prognostic testing, treatments and outcomes for children diagnosed with these devastating diseases.

Growth of the Repository

Enrollment

The past year has seen significant growth in clinical data annotation, specimen numbers and histological diversity within the repository. All member institutions successfully transitioned their retrospectively collected brain tumor specimens to the CBTTC Operations Center (OC) at the Children's Hospital of Philadelphia (CHOP) and began enrolling new prospective subjects in the fall of 2013.

Accelerating Pediatric Brain Tumor Research

•••

'The CBTTC is a collaborative research program dedicated to improving prognostic testing, treatments and outcomes for children diagnosed with these devastating diseases'

•••

Shown in Tables 1 and 2 below, to date, CHOP has enrolled over 500 subjects, The Children's Hospital of Pittsburgh enrolled 84 subjects, Seattle Children's Hospital enrolled 237 subjects and Lurie Children's Hospital enrolled 267 for grand total 1138 subjects.

Table1. Enrollment by Site

CBTTC Site	Subject Totals
CHOP	519
Seattle	237
PITT	84
Lurie	267
Meyer	30
E TN	1
Total	**1138**

Table 2. Breakdown of Enrollment Type

Prospective Subjects	Retrospective Subjects	
Submitted	Submitted	Pending
331	150	0
36	155	0
19	61	0
12	255	0
22	8	0
0	1	0
420	**630**	**0**

Specimens

The CHOP CBTTC OC received over 500 specimens from CBTTC member institutions' subjects during this reporting period including frozen tissue, cerebral spinal fluid, digital images of diagnostic tissue slides, tissue slides and blood from the patients and their parent as detailed in Table 3 below. All sites will continue prospective enrollment and per the CBTTC Constitution will submit annually 75% of all brain tumor cases to the CBTTC OC. In 2014-2015 we will focus on inclusion of these very important specimen types.

Table 3. Specimen Inventory Submitted by Site and Specimen Type

CBTTC Site	Blood Child	Blood Maternal	Blood Paternal	CSF Child	Tissue Flash Frozen	Tissue Freezing Media
CHOP	361	6	4	0	382	167
Seattle	35	0	0	7	139	0
PITT	6	0	0	0	73	0
Lurie	9	0	0	0	160	8
Meyer	40	0	0	0	63	22
E TN	0	0	0	0	1	0
Total	451	6	4	7	818	197

Histological Subtypes

Currently, there are over 25 histological subtypes within the CBTTC repository including: craniopharyngiomas, choroid plexus tumors, mixed histology glial tumors, pinealoblastoma, neurocytoma, meningioma, schwannomas, sarcomas, and dysembryoplastic neuroepithelial tumors, and others as detailed in Table 4. The graph below depicts current repository inventory of tumor types with at least 10 flash frozen specimens from unique subjects. Our goal is to continually increase histology subtypes represented in the repository and specimen totals.

Specimens Inventory: Flash Frozen Tissue, Count ≥ 10
(Multiple aliquots for one subject at one event equal 1)
*TISSFFRZ: Tissue Flash Frozen

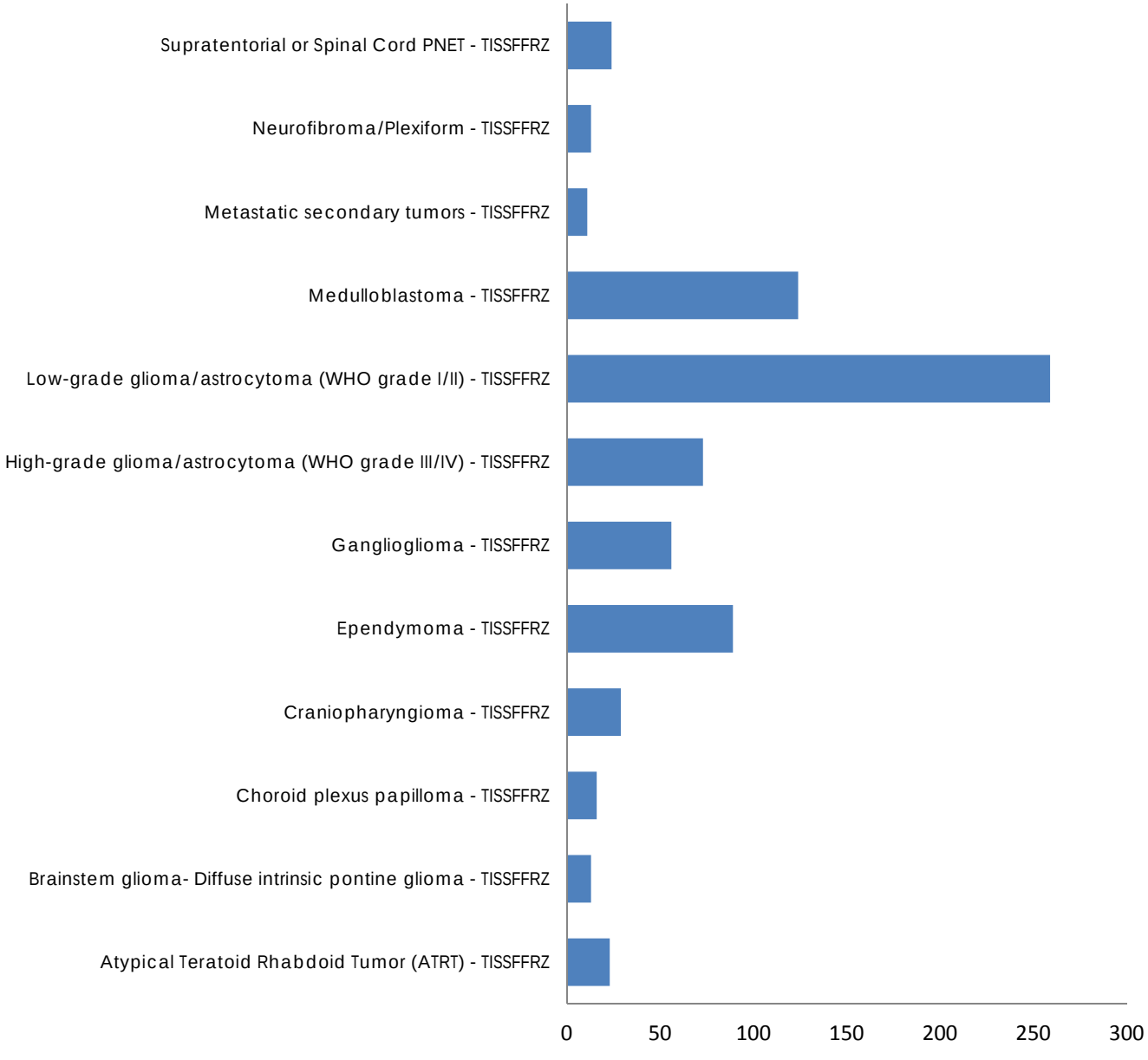

Table 4. Detailed Inventory of Specimen Types in the Repository by Diagnosis

Diagnosis & Specimen Type *TISSFFRZ: Tissue Flash Frozen *TISSFRZM: Tissue Freezing Media	Specimen Count *Multiple aliquots for one subject at one event equal 1
Atypical Teratoid Rhabdoid Tumor (ATRT) - BLD	14
Atypical Teratoid Rhabdoid Tumor (ATRT) - CSF	3
Atypical Teratoid Rhabdoid Tumor (ATRT) - PLASEDTA	4
Atypical Teratoid Rhabdoid Tumor (ATRT) - TISSCELC	3
Atypical Teratoid Rhabdoid Tumor (ATRT) - TISSFFRZ	27
Atypical Teratoid Rhabdoid Tumor (ATRT) - TISSFRZM	5
Brainstem glioma- Diffuse intrinsic pontine glioma - BLD	3
Brainstem glioma- Diffuse intrinsic pontine glioma - TISSCELC	1
Brainstem glioma- Diffuse intrinsic pontine glioma - TISSFFRZ	15
Brainstem glioma- Diffuse intrinsic pontine glioma - TISSFRZM	1
Choroid plexus carcinoma - BLD	3
Choroid plexus carcinoma - PLASEDTA	1
Choroid plexus carcinoma - TISSFFRZ	7
Choroid plexus carcinoma - TISSFRZM	1
Choroid plexus papilloma - BLD	7
Choroid plexus papilloma - PLASEDTA	1
Choroid plexus papilloma - TISSCELC	1
Choroid plexus papilloma - TISSFFRZ	17
Choroid plexus papilloma - TISSFRZM	4
Craniopharyngioma - BLD	16
Craniopharyngioma - DNA	6
Craniopharyngioma - PLASEDTA	2
Craniopharyngioma - TISSCELC	2
Craniopharyngioma - TISSFFRZ	31
Craniopharyngioma - TISSFRZM	5
Dysembryoplastic neuroepithelial tumor (DNET) - BLD	12
Dysembryoplastic neuroepithelial tumor (DNET) - CSF	1
Dysembryoplastic neuroepithelial tumor (DNET) - DNA	2
Dysembryoplastic neuroepithelial tumor (DNET) - PLASEDTA	3
Dysembryoplastic neuroepithelial tumor (DNET) - TISSCELC	2
Dysembryoplastic neuroepithelial tumor (DNET) - TISSFFRZ	22
Dysembryoplastic neuroepithelial tumor (DNET) - TISSFRZM	8
Dysplasia/Gliosis - BLD	11

Dysplasia/Gliosis - DNA	2
Dysplasia/Gliosis - PLASEDTA	1
Dysplasia/Gliosis - TISSCELC	2
Dysplasia/Gliosis - TISSFFRZ	9
Dysplasia/Gliosis - TISSFRZM	6
Ependymoma - BLD	34
Ependymoma - CSF	1
Ependymoma - PLASEDTA	14
Ependymoma - TISSCELC	6
Ependymoma - TISSFFRZ	92
Ependymoma - TISSFRZM	15
Ganglioglioma - BLD	24
Ganglioglioma - DNA	9
Ganglioglioma - PLASEDTA	7
Ganglioglioma - TISSCELC	6
Ganglioglioma - TISSFFRZ	59
Ganglioglioma - TISSFRZM	14
Germinoma - BLD	6
Germinoma - PLASEDTA	2
Germinoma - TISSFFRZ	3
Gliomatosis Cerebri - BLD	1
Gliomatosis Cerebri - TISSCELC	1
Gliomatosis Cerebri - TISSFFRZ	1
Gliomatosis Cerebri - TISSFRZM	1
High-grade glioma/astrocytoma (WHO grade III/IV) - BLD	44
High-grade glioma/astrocytoma (WHO grade III/IV) - BLDMAT	1
High-grade glioma/astrocytoma (WHO grade III/IV) - CSF	3
High-grade glioma/astrocytoma (WHO grade III/IV) - PLASEDTA	11
High-grade glioma/astrocytoma (WHO grade III/IV) - TISSCELC	5
High-grade glioma/astrocytoma (WHO grade III/IV) - TISSFFRZ	77
High-grade glioma/astrocytoma (WHO grade III/IV) - TISSFRZM	18
Low-grade glioma/astrocytoma (WHO grade I/II) - BLD	137
Low-grade glioma/astrocytoma (WHO grade I/II) - BLDMAT	3
Low-grade glioma/astrocytoma (WHO grade I/II) - BLDPAT	2
Low-grade glioma/astrocytoma (WHO grade I/II) - CSF	8
Low-grade glioma/astrocytoma (WHO grade I/II) - DNA	9
Low-grade glioma/astrocytoma (WHO grade I/II) - PLASEDTA	47
Low-grade glioma/astrocytoma (WHO grade I/II) - TISS	1

Low-grade glioma/astrocytoma (WHO grade I/II) - TISSCELC	27
Low-grade glioma/astrocytoma (WHO grade I/II) - TISSFFRZ	278
Low-grade glioma/astrocytoma (WHO grade I/II) - TISSFRZM	56
Malignant peripheral nerve sheath tumor (MPNST) - BLD	2
Malignant peripheral nerve sheath tumor (MPNST) - TISSCELC	2
Malignant peripheral nerve sheath tumor (MPNST) - TISSFFRZ	5
Malignant peripheral nerve sheath tumor (MPNST) - TISSFRZM	2
Medulloblastoma - BLD	50
Medulloblastoma - BLDMAT	1
Medulloblastoma - BLDPAT	1
Medulloblastoma - CSF	7
Medulloblastoma - PLASEDTA	8
Medulloblastoma - TISSCELC	8
Medulloblastoma - TISSFFRZ	130
Medulloblastoma - TISSFRZM	19
Meningioma - BLD	9
Meningioma - PLASEDTA	3
Meningioma - TISSCELC	1
Meningioma - TISSFFRZ	25
Meningioma - TISSFRZM	4
Metastatic secondary tumors - BLD	10
Metastatic secondary tumors - TISSCELC	6
Metastatic secondary tumors - TISSFFRZ	11
Metastatic secondary tumors - TISSFRZM	6
Neurocytoma - BLD	2
Neurocytoma - BLDPAT	1
Neurocytoma - PLASEDTA	1
Neurocytoma - TISSFFRZ	2
Neurofibroma/Plexiform - BLD	10
Neurofibroma/Plexiform - PLASEDTA	4
Neurofibroma/Plexiform - TISSCELC	5
Neurofibroma/Plexiform - TISSFFRZ	14
Neurofibroma/Plexiform - TISSFRZM	8
Non-germinomatous germ cell tumor - BLD	1
Non-germinomatous germ cell tumor - TISSCELC	1
Non-germinomatous germ cell tumor - TISSFFRZ	2
Non-germinomatous germ cell tumor - TISSFRZM	1
Oligodendroglioma - BLD	3

Oligodendroglioma - TISSCELC	1
Oligodendroglioma - TISSFFRZ	9
Oligodendroglioma - TISSFRZM	1
Other - BLD	52
Other - BLDMAT	2
Other - BLDPAT	1
Other - PLASEDTA	20
Other - TISSCELC	10
Other - TISSFFRZ	94
Other - TISSFRZM	17
Pineoblastoma - BLD	2
Pineoblastoma - TISSFFRZ	1
Supratentorial or Spinal Cord PNET - BLD	12
Supratentorial or Spinal Cord PNET - PLASEDTA	3
Supratentorial or Spinal Cord PNET - TISSCELC	2
Supratentorial or Spinal Cord PNET - TISSFFRZ	25
Supratentorial or Spinal Cord PNET - TISSFRZM	5
Teratoma - BLD	4
Teratoma - PLASEDTA	2
Teratoma - TISSCELC	1
Teratoma - TISSFFRZ	6
Teratoma - TISSFRZM	2

Clinical Data

Each pediatric brain tumor sample submitted to the CBTTC OC listed above is annotated with clinical data from a patient's medical record to present a full comprehensive picture of the nature of the patient's cancer. This necessitates extensive data abstraction, management, data quality control and coordination. The clinical data collected by the CBTTC includes, treatment data and follow up data for prospective subjects at specific time points including; 3 months, 6 months and 12 months then every six months thereafter. All CBTTC member sites are now submitting data in real time and the CBTTC OC provides monthly site exception reports and queries to ensure data standardization, quality and completeness.

Demographics

- Gender
- Subject Age at Initial Diagnosis
- Ethnicity
- Race

Diagnosis and Progression

- Initial Pathology Diagnosis
- Tumor Primary Location CNS
- Metastases at Submission
- Pathology Review
- Recurrent status
- Molecular Testing

History

- Cancer Predisposition
- Family History
- Other Medical Condition

Follow up post TX

- Tumor Molecular Test
- Tumor Site of Progression
- Recurrence Diagnosis
- Subject Clinical Status
- Tumor Primary Location
- Relapse Number
- Metastatic Site

Specimen

- Pathology Slide Images/Scans
- Pathology Report
- Sample Type

•••

By collecting and tagging clinical data to the specimens the CBTTC can provide investigators with critical details for understanding the molecular underpinnings of the tumors

•••

Scientific Projects

Next Generation Sequencer @ BGI

Currently, the CBTTC is supporting several projects focused on the genetic and molecular characterization of specific tumor subtypes. Data is shared in real time with consortium members. Genomic sequencing is performed on site at CHOP by the sequencing core, BGI@CHOP. To date 40 whole genomes have been sequenced.

Project 1. Genomic Investigation of Diffuse Fibrillary Astrocytoma. Funded by the PLGA foundation, this project supports the characterization of the genomic landscape of diffuse fibrillary astrocytomas. A major aim of the project is the elucidation of detailed genomic profiles of tumors via whole genome sequence analysis of 12 matched tissue/blood samples at 60x/60x coverage. This project also includes 3 samples provided by the Dana Farber Cancer Institute as part of a joint collaboration.

Project 2. Genomic Investigation of Gangliogliomas. Funded by the Voices Against Brain Cancers foundation, this project supports the characterization of the genomic landscape of gangliogliomas via whole genome sequence analysis of 8 matched tissue/blood samples at 60x/60x coverage.

Project 3. Genomic Investigation of Craniopharyngiomas. This project supports the characterization of the genomic landscape of craniopharyngiomas and is a joint effort between CHOP, Penn, and the Dana Farber Cancer Institute. The project includes whole genome sequencing of 5 matched pairs of tumor/blood, whole exome sequencing of 7 matching pairs of tumor/blood, and targeted sequencing of 30 additional FFPE samples.

Project 4. A Quantitative Unbiased Proteomics Approach to Decipher the Histone Modification Profiles of Pediatric and Adult Gliomas. Using tumor-derived glioma stem–like cells, the project aims to profile the histone modifications associated that contribute to the pathogenesis of adult and pediatric gliomas. This is a collaborative Penn/CHOP effort that will compile data from both adult and pediatric tumor- derived cells. This project is supported by a grant from the Institute for Translational Medicine and Therapeutics (ITMAT) at the University of Pennsylvania.

Project 5. Genomic Evaluation of Malignant Pediatric Cortical Tumors. Dr. Sarah Leary from Seattle Children's Hospital aims to describe genomic alterations and tumor subtypes within a large cohort of well characterized supratentorial malignant pediatric brain tumors. She also aims to evaluate the association between genetically determined subtypes and standard clinical factors such as histology, location, metastatic status, survival and prioritize molecular alterations which warrant further study as potential biomarkers.

Project 6. *Diffuse Intrinsic Pontine Gliomas and FOP: A Genetic Crossroads for Therapeutic Targeting. The project focuses on identifying the mechanisms of actions underlying mutations found in DIPGs and the opportunities of therapeutically targeting affected genes shared by Fibrodysplasia ossificans progressiva (FOP) and DIPGs. This project is supported by the Kortney Rose Foundation.*

Project 7. *Medulloblastoma resistance to SMO Inhibitors: Rare variant tumor cells in treated Medulloblastoma (MB) escape elimination by SMO inhibitors, either by activating downstream signaling events in the HH pathway, or by recruiting alternative oncogenic pathways. We propose that these alterations can be targeted effectively using existing drugs. This project is supported by the Munoz Family in honor of their son Alex Munoz through the Kortney Rose Foundation.*

Informatics

In September of 2013, the CBTTC Data and Inventory platform based on the CHOP Center for Bioinformatics (CBMi) Harvest interface was launched allowing researchers at member sites to enroll subjects, prepare samples for shipment to the CBTTC OC, enter longitudinal clinical data and query de-identified data for scientific research. During the next reporting period we will continue to plan additional functionality for integrations with NGS Variant Analysis to provide researchers with next generation sequencing results, tissue slides images and file capabilities for online collaborative analysis.

Screen shot of the CBTTC Data and Inventory Tool

Operations

The roles of the CBTTC OC at CHOP includes receiving, processing, storing and performing quality control on specimens and clinical data submitted from the current CBTTC member sites. Additionally, the CHOP OC oversees all applicable regulations allowing for specimen collection and use; provides access for participating institutions to analyzed data via the online CBTTC Data and Specimen Inventory System; hosts monthly, quarterly and yearly CBTTC meetings; maintains a public CBTTC website to educate and inform the general public; and communicates CBTTC progress with our supporters by means of written progress reports.

CHOP is committed to this program with over twenty institutional leaders and personnel contributing to the project. This team is led by Tom Curran PhD, FRS, Deputy Scientific Director, Peter Phillips M.D., Director of CHOP's Pediatric Neuro-Oncology Program, Adam Resnick PhD, Assistant Professor of Neurosurgery and Phillip (Jay) Storm M.D., Chief of the Division of Neurosurgery. CHOP has also invested significant institutional funding in equipment, informatics and building a state-of-the-art specimen storage and processing facility to support the future of these efforts.

The Children's Hospital of Philadelphia
CBTTC Operations Center

This dedication is matched on a national and international level through our consortium partners. At each of these sites, a compliment of researchers, clinicians, coordinators, pathologists and support staff are energized and committed to realizing our *shared* vision. Our partners are the Children's Hospital of Pittsburgh, led by Ian Pollack M.D., the Ann and Robert Lurie Children's Hospital of Chicago, led by Stewart Goldman M.D., Seattle Children's Hospital, led by Russ Geyer M.D., Sarah Leary M.D., and the Meyer Children's Hospital in Florence, Italy, led by Anna Maria Buccoliero M.D. PhD.


Children's Hospital of Pittsburgh


Seattle Children's Hospital


The Ann and Robert Lurie
Children's Hospital of Chicago

During this reporting period, the CHOP CBTTC OC completed all activities for specimens, data management, regulatory compliance and reporting. To achieve the collection and submission of clinical data, a data analyst was added to the CHOP CBTTC OC team. This addition allowed the CBTTC to meet the objective of complete clinical data submission per protocol for all subjects enrolled in the CBTTC. The data analyst also performs quality control activities to ensure the highest level of data accuracy, integrity and completeness.

Looking Forward: CBTTC 2015

The CBTTC has accomplished the development of a collaborative, open access, consortium complete with high quality biospecimens with annotated clinical data. Looking forward, we are excited to not only continue our successful operations but also expand. This will be accomplished by adding on new member institutions to the consortium and turning focus to analysis of the specimens collected. Our aim is to sequence all of the specimens within the repository and create an open access platform to facilitate data sharing and analysis of the resulting genomic data. This will directly result in a large increase of researchers around the world with access to this critical data in hopes of accelerating findings for new potential targeted therapies.

The Children's Hospital of Philadelphia®
RESEARCH INSTITUTE

CHILDREN'S BRAIN TUMOR TISSUE CONSORTIUM (CBTTC)

3501 Civic Center Blvd.
Philadelphia, PA 19104