CENTER FOR DATA DRIVEN DISCOVERY IN BIOMEDICINE RESEARCH & ADMINISTRATIVE PROGRESS REPORT

Children's Hospital of Philadelphia
Center for Data Driven Discovery in Biomedicine

CONTENTS

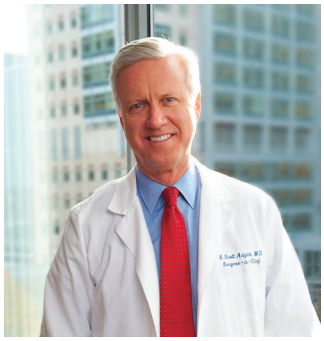
CHOP LEADERSHIP PERSPECTIVE

"The Center for Data Driven Discovery in Biomedicine (D³b) at Children's Hospital of Philadelphia is accelerating breakthroughs for children all over the world - and across a wide spectrum of diseases - by breaking down silos, fostering collaborations and empowering data-driven medicine, both at CHOP and throughout the world.

D³b's commitment to engage with patients as partners in the research process is supporting CHOP's rich tradition of innovation and quality care."

Madeline Bell, President and CEO
Children's Hospital of Philadelphia

"We are on the cusp of exciting breakthroughs in childhood medicine, thanks in part to the efforts of the Center for Data Driven Discovery in Biomedicine (D³b) at CHOP. D³b is a leader in collaborative science by empowering and providing the tools needed by clinicians and researchers to make meaningful discoveries. We are thrilled that the Division of Neurosurgery at CHOP is a vanguard of big data and precision medicine on behalf of children."



N. Scott Adzick, MD, Surgeon-in-Chief and Director
Center for Fetal Diagnosis & Treatment
Children's Hospital of Philadelphia

A MESSAGE FROM THE CHIEF SCIENTIFIC OFFICER

Behind every child treated at Children's Hospital of Philadelphia, you'll find a committed team of experts and professionals, all working together to provide the highest possible level of patient care. CHOP's innovative approach to research focuses on discovering breakthroughs for every child, every time, everywhere. The Center for Data Driven Discovery in Biomedicine (D³b) at CHOP understands this vision well and is tirelessly working to redefine the traditional research model in favor of personalized, targeted treatments for each and every patient.

D³b's multi-disciplinary team has reached a number of milestones throughout this past year by collaborating with leaders in the field and partner organizations, both here at CHOP and across the globe. The D³b Center's commitment to sharing data and resources with the research and patient communities has paved the way for new initiatives such as the National Institutes of Health Common Fund-supported Gabriella Miller Kids First Data Resource Center (DRC) and the continued growth of the Children's Brain Tumor Tissue Consortium (CBTTC).

Under the guidance of D³b co-directors Adam Resnick, PhD and Phillip "Jay" Storm, MD, these D³b-led initiatives have harmonized the diverse skills and understanding of many talented investigators to transparently share both data and expertise. In addition to their work to establish clinical and scientific collaborations, the D³b Center has been a champion of the patient community, working alongside more than 50 non-profit foundations and patient advocates. Solving the unique challenges of each of these communities is no small endeavor. The D³b Center is arming researchers with the knowledge and statistical power they need to rapidly develop new and more effective treatments for children.

It will take a team effort to advance our understanding of how to treat and prevent rare childhood diseases, and thanks to the work of the D³b Center, there's much to be excited about for breakthroughs yet to come.

Warmest regards,

Bryan Wolf, MD, PhD
Executive Vice President & Chief Scientific Officer
Children's Hospital of Philadelphia

WELCOME TO THE CENTER FOR DATA DRIVEN DISCOVERY IN BIOMEDICINE (D³b)

The directors of the Center for Data Driven Discovery in Biomedicine (D³b) are immensely proud to present the D³b Research and Administrative Progress Report. The D³b Center's achievements over the past year are evidence of the commitment and dedication shown by each member of the D³b Center to the mission of accelerating discoveries and breakthroughs on behalf of each and every patient and their families, every time and everywhere.

D³b represents the Department of Surgery's commitment, along with other partnered, supporting departments at CHOP, to a new model of scientific discovery defined by "convergence research." Traditionally, researchers, clinicians, and members of the patient community each worked and engaged within defined domains of expertise, in an attempt to solve the increasingly complex challenges of biomedical and translational research at their own laboratory, hospital, or institution. Under D³b's new research model and via its platforms, these communities are now working together, connecting leading experts and stakeholders across areas of expertise, across institutions, and across the globe to collaboratively generate the quantity and quality of information and drive the increased understanding and discoveries needed to accelerate discoveries and improve treatments for pediatric diseases. Children afflicted with these diseases simply cannot wait for the often lengthy process to develop therapies using the traditional research model. For these patients, every moment matters; underscoring the need for an agile, collaborative research model to speed the development of new therapeutics and improve scientific understanding of how to treat rare disease in children.

From its early beginnings as a pediatric brain tumor research program, D³b continues to expand and develop new, local, and global research collaborations, across the pediatric and adult research communities. Additionally, D³b has increased its impact in large-scale data generation and collection efforts across childhood cancers and other developmental childhood diseases. D³b has also expanded partnerships across oncology, neurology, and surgery programs at CHOP by utilizing new, data-driven technologies and cloud-based platforms. These collaborations and new technologies are allowing the D³b Center to translate 'big data' into new discoveries and breakthroughs.

D³b's trans-disciplinary pursuit of research excellence has resulted in national acknowledgement and grant support from the National Institutes of Health to establish the Gabriella Miller Kids First Data Resource Center (Kids First DRC), part of a 10-year commitment to childhood cancer and structural birth defects research. The Kids First DRC builds on D³b's existing innovative research programs, including the Children's Brain Tumor Tissue Consortium and partnered clinical trials consortia, which support over 60 collaborative scientific projects including a first-in-kind Pediatric Brain Tumor Atlas, the largest collection of non-embargoed, accessible, multi-omic, clinically annotated pediatric brain tumor dataset in the world.

We could not achieve this level of accelerated progress without the continued and timely support of CHOP's executive leadership, the CHOP Research Institute, the Department of Surgery's leadership and shared vision, our dedicated D³b Center unit teams, and especially the many patients and families who unwaveringly partner with us on behalf of a transformative vision for the future of children. On behalf of the entire D³b community, we look forward to many exciting breakthroughs yet to come.

Phillip "Jay" Storm, MD
D³b Director & Division Head
Neurosurgery

Adam Resnick, PhD
D³b Director & Stokes Investigator
Neurosurgery

Angela Waanders, MD, MPH
D³b Director & Attending Physician
Neuro-Oncology

Jena Lilly, MS, CCRC
D³b Director of Operations & Strategic Planning
Neurosurgery

Mateusz Koptyra, PhD, D³b Laboratory Director


ROBERTS CENTER
FOR PEDIATRIC RESEARCH

MESSAGE FROM THE BRAIN TUMOR BOARD OF VISITORS

Scott (left) and Sue (right) Perricelli address the audience as the presenting sponsors of the 2019 Cheers for CHOP, supporting childhood brain tumor research both at CHOP and across the globe.

Dear Colleagues,

On behalf of the Brain Tumor Board of Visitors at Children's Hospital of Philadelphia, we express our gratitude and continued partnership with the Center for Data Driven Discovery in Biomedicine (D^3b) at Children's Hospital of Philadelphia. We are excited by the incredible strides made by the D^3b Center in the three years since the D^3b Center's formation, specifically to advance collaborative pediatric medicine and provide the infrastructure needed to support innovative research projects.

We've witnessed tremendous growth within the D^3b Center over the past fiscal year, thanks in no small part to the dedicated team of clinicians, scientists, researchers, and professionals who are tirelessly working to provide more effective and less-toxic treatment alternatives for children diagnosed with brain tumors and other rare diseases. The expansion of D^3b's collaborative partnerships, including the Gabriella Miller Kids First Data Resource Center and the Children's Brain Tumor Tissue Consortium, is advancing research both locally at CHOP and across the globe. These partnerships enable the brilliant minds in the field of childhood medicine to work together and share their understanding of these rare and complex diseases.

As parents, family members, and advocates of children diagnosed with a brain tumor, we feel a tremendous sense of urgency to move the research forward and drive the discovery of more effective brain tumor treatments for affected children, a vision which is shared by each member of the D^3b team. Thanks to D^3b's commitment to excellence in research, we look forward to the upcoming year's efforts to provide breakthroughs for every child, every time, everywhere.

Sincerely,

Scott & Sue Perricelli, Co-chairs
CHOP Brain Tumor Board of Visitors

EXECUTIVE SUMMARY

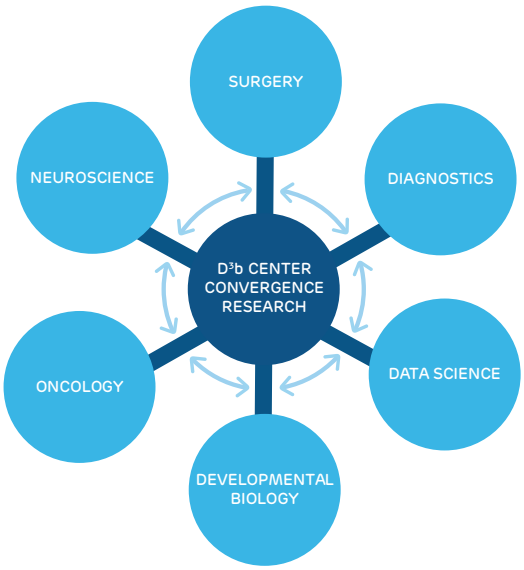
Members of the Center for Data Driven Discovery in Biomedicine during a D³b Center retreat.

The Center for Data Driven Discovery in Biomedicine's (D³b) research programs continue to drive innovation in translational research discoveries, clinical trials, and standards of care for children and adults diagnosed with devastating diseases. D³b's scientific expertise and diverse research platforms target pediatric cancers and diseases of childhood development, with pediatric brain tumors as a driving area of research emphasis.

Childhood brain tumors represent the leading cause of disease-related death in children, as those affected have had limited treatment options and often must endure toxic therapies, which have remained largely unchanged over the past 50 years. Although neurosurgical techniques continue to improve, surgery is often not curative or a viable option for many children.

Over the past three years, D³b has worked to develop a collaborative, translational and trans-disciplinary research methodology to support and align with CHOP Neurosurgery's research programs and objectives. The methodology is powered by newly-developed platforms that allow large-scale analytic computation, data harmonization, analysis, and visualizations, by collaborative and diverse sets of experts both at CHOP and across the globe.

Applying *D³b's Research Methodology*, the D³b Center and its partners are reducing the time to discovery, clinical trial delivery, and improved care for children. Tasks that once took researchers years to complete can now be completed in minutes, made possible through D³b's research platforms. These innovative platforms help to remove the current barriers to research within the Department of Surgery at CHOP, across the Research Institute, and throughout the entire scientific community. By breaking down silos, D³b is empowering and facilitating researchers everywhere to accelerate translational impact from the bench to the bedside.



D³b'S GLOBAL FOOTPRINT

INTERNATIONAL PARTNERS ACROSS FOUR CONTINENTS

One of the primary objectives of the D³b Center is to bring together expertise and connect resources from many of the world's leading scientists, clinicians, and researchers, from across a wide number of disciplines, disease areas, and functional research spaces.

Accumulating this shared knowledge and understanding has helped advance research programs at CHOP, and across an additional 60 laboratories from institutions around the world. To date, D³b has forged new and long-lasting collaborative efforts with more than 35 national and international organizations. Over the past year, our experts shared their research at over 30 major conferences and meetings across the U.S. and around the globe.

At the close of its third fiscal year, D³b was awarded 13 new grants for issuance in FY18/FY19; secured $13.5 million in funding; published more than 115 articles across more than 20 leading scientific journals; submitted one patent application; supported new precision medicine clinical trials; and became a national steward of the largest collection of pediatric genomic data in the world.

The D³b Center has seen an increase in secured funding of more than 70% compared to previous years, supporting over 20 new research initiatives across a diverse, yet synergistic landscape of research areas in pediatric brain tumors, other solid and liquid pediatric cancers, immunotherapy, and collaborative cloud-based, global biomedical research analytic platforms.

This expansive, cross-disease, convergence research is a key focus area within D³b's methodology. The D³b Center has expanded in size from just 13 full-time staff members in FY16, to more than 41 full-time staff members in FY18, with more than 20 additional matrix, supporting staff, students, and trainees.

A FOUNDATION OF PHILANTHROPY

The D³b Center is deeply grateful for the contributions of the many foundations and families who continue to support its innovative research projects, without which none of this progress would have been possible. These donations, including generous gifts of $1 million from the Abramson and Sislik families, as well as a $3 million gift from the Templeton Family, provided crucial funding to support the early stages of development for the D³b Center.

D³b KEY RESEARCH HIGHLIGHTS

new **precision therapeutic** strategies for pediatric low-grade gliomas and craniopharyngiomas

discoveries in **cancer fusion gene** mechanisms and their targeting and mechanisms of drug resistance in pediatric brain tumors

8
discoveries leading to clinical trials

8,000+
clinical research subjects enrolled

63,000+
biospecimen samples collected and available

3+
petabytes of pediatric genomic data generated and available

35+
institutional partners

40
biological models created and available

50
foundation partners

40
research projects across 11 programs at CHOP

60+
research projects with collaborating researchers

3
global data platforms launched

D³b CENTER ORGANIZATION

The D³b Center is organized into six functional units, each with unique, deep subject matter expertise, to support the D³b Center's translational and biomedical research programs and projects.

CLINICAL RESEARCH UNIT

The Clinical Research Unit (CRU) supports observational and interventional trials including the management of subject enrollment and consent, regulatory requirements, clinical data collection, and biospecimens. The CRU supports the Department of Surgery's partnered research across the rare disease space, with a specific focus in pediatric brain tumors, epilepsy, and fetal birth defects such as craniofacial abnormalities.

BIOSPECIMEN RESEARCH UNIT

In collaboration with the CHOP Biorepository Core and the Department of Pathology, under the leadership of Mariarita Santi, MD, PhD, the Biospecimen Research Unit (BRU) is responsible for the standardized collection, processing, management, and distribution of samples for research and discovery.

DATA ANALYTICS MANAGEMENT & ENGINEERING UNIT

The Data Analytics Management & Engineering Unit (DAMEU) empowers data-science approaches throughout the entire scientific and translational research process. The DAMEU unit is further structured into two main components, the Bioinformatics Team and the Data Engineering Team. The Bioinformatics team members focus on bioinformatics pipeline engineering, genomics data processing, downstream analysis, data integration and interpretation. The Data Engineering team members are responsible for designing, building, and operating software platforms and infrastructure for management, distribution, and scalable analysis of data.

PRECLINICAL LABORATORY RESEARCH UNIT

The Preclinical Laboratory Research Unit (PCLRU) supports the D³b Center's basic and translational research efforts. The PCLRU focuses its research on pediatric central nervous system and convergence research in Neuroscience. The primary goal of the PCLRU unit is to harness data-driven approaches on behalf of precision-based and targeted therapeutics using translational methodologies, including projects focused on the elucidation of cell signaling mechanisms of childhood development, oncogenesis, tumor progression, the creation and characterization of preclinical models, drug screening, development, and testing.

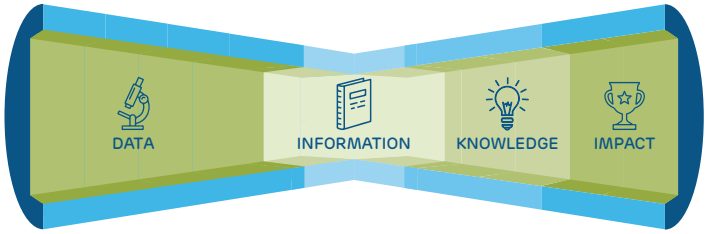
MOLECULAR DIAGNOSTIC RESEARCH UNIT

The Molecular Diagnostic Research Unit (MDRU) is directly partnered with the Department of Pathology's Division of Genomic Diagnostics, under the leadership of Marylin Li, MD. The MDRU focuses on the research and development of innovative clinical platforms and tests. The MDRU concentrates its efforts on the clinical harnessing of multimodal molecular data generation and analysis of biomarkers for direct clinical application. The MDRU works to develop new methods and workflows to improve and optimize disease prognosis, clinical diagnostic effectiveness and specificity, and patient risk and treatment stratification.

STRATEGIC COORDINATION UNIT

The Strategic Coordination Unit (SCU) provides key expertise in communications, business, financial and grant management, program and project management, strategic planning, operational infrastructure development, human resources, team development, and coordinates the execution of over 80 material transfer agreements, data disclosures, data use agreements, contracts, and agreements.

A DATA-DRIVEN DISCOVERY METHODOLOGY



D³b Center's vision and mission are supported through the ***D³b Data-Driven Discovery Methodology***, which defines the processes required to transform data into impact. Through the use of data-driven platforms and tools, which were developed using innovative design principles, the D³b Center is empowering convergent research. The *D³b Methodology* enables accelerated translational research and exponential growth and output in the number of data-driven discoveries, which, in turn, contribute to enhanced impact through improved patient outcomes. The *D³b Methodology* provides new routes to breakthroughs more rapidly than has ever been possible under previous processes and models of siloed research.

D³b DATA DRIVEN DISCOVERY MODEL

Since the completion of the first human genome at the turn of the 21st century, large-scale biomedical and genomic data generation have exponentially accelerated via new technologies, supporting the increased scale and diversity of molecular data generation, while lowering the costs of computation and data storage. To date, such "big data" efforts have primarily focused on data generation, while lacking the required infrastructure needed to translate discoveries into clinical impact during a child's lifetime.

We hypothesize that when processes and platforms support the rapid conversion of "big data" into information, or organized, harmonized datasets, which can be shared and accessed in real time for use by the worldwide scientific community, there will be exponential, accelerated growth in the discovery landscape and increased diversity of knowledge for disease mechanisms across pediatrics.

D³b's data platforms and tools are specifically designed to allow for collaborative team science. Each of these platforms are built to support the diversity and expertise of researchers everywhere. By continuing to scale and develop these platforms, D³b is supporting the research community's simultaneous translation to clinical impact.

FROM **DATA** TO **INFORMATION** TO **KNOWLEDGE** TO **IMPACT**

The model begins with and requires harnessing new technologies and resources that define the *Data Phase*, where large and continuously-growing collections of high-quality, multi-dimensional data are generated, localized, or connected, but exist in a raw format that is not yet useable or queryable for hypothesis-driven research. These raw data must be harmonized and structured to allow for the application of data science approaches, including modeling, mapping, and algorithmic processing during the *Information Phase*.

These harmonized data are next moved into the *Knowledge Phase*, where hypothesis-driven questions can be formulated on the harmonized dataset. Through iterative hypothesis testing, new data testing, and repeated scientific analysis of the data, information is distilled and further transitioned into scientific knowledge. During the *Knowledge Phase*, new knowledge of a disease type, potential therapeutics, mechanisms, patient populations, outcomes, predictions, and so much more is discovered. Once new knowledge is gained, it can be transformed and translated into the clinic via clinical trials, decision support, and novel therapeutic development for patient care, leading to the *Impact Phase*, and ultimately alleviating the suffering of children and their families.

RESEARCH DESIGN PRINCIPLES FOR PLATFORMS & TOOLS

To accelerate translational research and the processing of data using the *D³b Methodology*, new platforms, research environments, and tools are required, which must be built on the following design principles and accelerated impact requirements:

D³b PLATFORM DESIGN PRINCIPLES

- Must support discovery and knowledge creation as a non-local, information-driven, and collaborative global process
- Must maximize the number of information users and improve their secure access to data and information
- Must support and maximize a diversity of information users with varied interests, specialties, and expertise on behalf a convergence research process
- Must support and maximize connectivity and community building among such users and provide for the network's exponential growth
- Must prioritize frictionless flow of data and information via trusted connections, data federations, and user communities

D³b PLATFORM TECHNOLOGY & TOOLS REQUIREMENTS

- Scalable, secure, cloud-based compute and storage infrastructure and associated software platforms
- Data and information are accessible within a cloud-based computing environment, providing for real-time, shared analysis environment to support global collaboration
- Platforms for data federations that support NIH best practices and FAIR data principles
- Large-scale research, clinical, and biomedical information as harmonized genomic and molecular datasets, phenotypes, and metadata
- Authentication and authorization workflows for NIH and consortium-managed datasets that allow for data access, integration, and data security protocols
- User training and support resources for a diverse stakeholder community

D³b CONVERGENCE RESEARCH NETWORK REQUIREMENTS

- Maximized for connectivity, volume, and diversity including patients, clinicians, researchers, government, public and private partnerships, consortia, foundations, and healthcare data stakeholders which manage the use, access, distribution, and security practices of data

ACCELERATING RESEARCH THROUGH THE D³b PLATFORMS

Each of the platforms developed by the D³b Center, including the Gabriella Miller Kids First Data Resource Portal, Cavatica, and PedcBioPortal, provide access to newly-released, large-scale, pediatric genomic and clinical disease data, which empowers accelerated discovery efforts by enabling collaborative, cloud-based analyses across institutions and by researchers across the globe.

D³b's platforms allow investigators to securely access datasets from both NIH-sponsored research studies and newly-released data from other consortia-led efforts such as the Children's Brain Tumor Tissue Consortium and the Pediatric Neuro-Oncology Consortium.

RESEARCH DESIGN PRINCIPLES FOR PLATFORMS & TOOLS (*CONT.*)

Led by the Data Engineering Team of the D³b Data Analytics Management & Engineering (DAME) Unit, D³b's platforms and tools are developed with input from leading collaborators within CHOP and externally, to ensure leading-edge technology is included in the development and versioning of the tools.

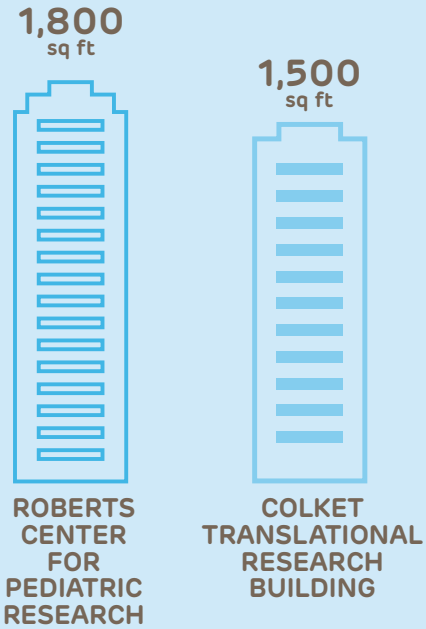
Partners include Children's Hospital of Philadelphia 's Department of Biomedical and Health Informatics (DBHi), the Ontario Institute for Cancer Research (OICR), the University of Chicago, Oregon Health and Science University (OHSU), Children's National Health System, CHU Sainte Justine, Seven Bridges, and the cBioPortal Consortium comprised of Children's Hospital of Philadelphia, Dana Farber Cancer Institute, Memorial Sloan Kettering Cancer Center, and Princess Margaret Cancer Centre.

By cross-supporting and developing an array of high-performing data-driven discovery platforms and data-science applications, D³b's DAME Unit has created a real-time, platform-based discovery ecosystem.

Miguel Brown, MA, a bioinformatics engineer in the Data Analytics Management & Engineering Unit, helps to develop and maintain analysis pipelines for collaborative projects within the D³b center and across the globe.

This environment allows users to easily move between different analytic views of the same data, perform analysis on the data in real-time with other researchers, and help improve the collaborative development of new tools, data processing workflows, and applications in the future.

D³b'S GROWING FOOTPRINT AT CHOP



At its founding in 2016, D³b was allocated over 1,500 sq. feet of wet and dry bench space at the Ruth and Tristram Colket, Jr. Translational Research Building at CHOP. D³b's Molecular Diagnostics Research and Preclinical Laboratory Research Units continue to occupy this space.

In 2018, due to its tremendous growth in staff and infrastructure, the D³b Center was granted over 1,800 sq. feet of work space for clinical research in the Roberts Center for Pediatric Research.

Currently, the D³b's Strategic Coordination, Clinical Research, Biospecimen Research, and Data Analytics Management and Engineering Units carry out their work at this location, with planned expansion in the coming years as CHOP grows its research footprint.

PLATFORM HIGHLIGHTS

GABRIELLA MILLER KIDS FIRST DATA RESOURCE CENTER

In June of 2017, the D³b Center was awarded a $14.8 million grant from the National Institutes of Health Common Fund, to develop the Gabriella Miller Kids First Data Resource Center (Kids First DRC). The Kids First DRC is a collaborative, pediatric research effort with the goal of understanding the genetic causes of and links between childhood cancer and structural birth defects.

D³b co-Director Adam Resnick, PhD, was named as the Kids First DRC's Principal Investigator and was tasked to bring together expert researchers and scientists from five additional participating institutions, including the Ontario Institute for Cancer Research (OICR), University of Chicago, Children's National Health System, Oregon Health & Science University (OHSU), and Seven Bridges.

With D³b leading the way, the Kids First DRC created a first-in-kind, centralized, cloud-based database, with collaborative analytic workspaces, and a discovery portal of well-curated, clinical, and genetically-sequenced data collected from dozens of childhood cancer and structural birth defect studies, comprising thousands of patients and their families.

FIRST YEAR MILESTONES

- Developed and deployed version 1.0 of the Kids First Data Resource Portal in partnership with OICR, which serves as the primary, public-facing resource for registered users to find data of scientific interest and utilized genomic files in Cavatica for analysis
- Received over 1.5 petabytes of whole genome, exome, and RNA-seq data from across five sequencing centers (HudsonAlpha Institute for Biotechnology, Broad Institute, Baylor College of Medicine, University of Washington, St. Jude Children's Research Hospital)
- Evaluated and performed initial harmonization of clinical and phenotypic data provided by 10 Kids First X01 Investigators
- Provided secure, yet collaborative, cloud-based access to the genomic data to seven Kids First X01 Investigators using Cavatica

GABRIELLA MILLER KIDS FIRST DATA RESOURCE CENTER (*CONT.*)

- In partnership with the University of Chicago, Kids First data is now available for researchers under the Bionimbus NIH Trusted Partnership, currently one of only six in operation
- Created an interoperable AWS cloud environment to securely support incoming sequencing data, automatically deploy applications, and reliably host all systems built to support the Kids First DRC
- Developed and optimized whole genome processing pipelines to harmonize all incoming Kids First genomic data on scalable cloud resources in partnership with Seven Bridges Genomics using the Cavatica platform. These pipelines will set the foundation for rapid, low-cost analysis of pediatric genomic data funded by NIH
- Developed and designed a data service to provide mechanisms of ingesting, modeling, and harmonizing clinical and phenotypic data from Kids First X01 investigators, as well as orchestration and synchronization of data across the Kids First DRC
- Designed and deployed a new data release coordinator that automates the flow of data for researchers
- Conducted and completed Kids First X01 Investigator listening tours and collaborated with 18 Kids First X01 Investigators across 17 institutions who were awarded sequencing grants to fully integrate their study data into the Kids First DRC
- Hosted the Kids First Data Resource Center Patient and Foundation Workshop, where the Kids First DRC met with 32 foundations to define patient and foundation interaction points and requirements for the Data Resource Portal
- Developed and implemented an outreach plan to promote the Kids First Data Resource Center to childhood cancer and structural birth defects research communities as well as the broader research community

DATA RESOURCE CENTER AT A GLANCE

Precision Approach
Data shared from the Data Resource Portal may help a patient's doctor to find treatments that are targeted to each child's needs based on their genetic characteristics

Patients as Partners
Patients and families can partner with researchers by participating in studies seeking cures for pediatric cancer and structural birth defects

Cross-Disease Research
Researchers will use the Data Resource Portal to perform complex data analyses to uncover new clues into causes of childhood cancer and structural birth defects

Genomic "Big Data"
Each patient's data is added to a database containing tens of thousands of patient DNA samples collected from blood, tissue, and saliva before it is sequenced and integrated with patient clinical data

Data Resource Portal
The Data Resource Portal provides a central location where researchers from all over the world can access genomic data from childhood disease patients and their families. This empowers researchers to share their findings and collaborate in real time

Safe & Secure
All of the personal information and data entered into the Data Resource Portal is de-identified and securely stored to maintain each patient's privacy

CAVATICA

Yuankun Zhu, BS, a bioinformatics engineer supervisor in the Data Analytics Management & Engineering Unit, points out the features of a cloud-based data portal.

In October of 2016, D³b launched Cavatica, an open-access, cloud-based, biomedical data-analysis platform created in partnership with Seven Bridges as part of the White House's launch of the Precision Medicine Initiative. Named after author E.B. White's character, Charlotte A. Cavatica, a spider in the children's story *Charlotte's Web*, Cavatica enables clinicians and scientists across CHOP and throughout the world to rapidly access large amounts of raw genomic data. Much like Charlotte, Cavatica is creating a "web," or diverse network, of information about pediatric diseases which is accessible in an individualized workspace environment. Cavatica provides researchers with a computation and storage environment where they can process, integrate, and analyze data in the cloud, reducing the time required to transform data into information and knowledge.

Cavatica enables researchers to analyze data through portable, shareable, and reproducible workflows to discover the shared mutations or characteristics across many different diseases. The data collectively represent contributions of more than 40 pediatric hospitals and covers a range of illnesses including cancer, congenital disorders, epilepsy, and autism.

Cavatica was created from the desire for secure platforms where large-scale data could be de-siloed and used collaboratively for research across institutions. Cavatica enables researchers to analyze data through harmonized and reproducible workflows to discover the shared characteristics or links across many different disease types.

Additionally, Cavatica interoperates with the Cancer Genomics Cloud, also powered by Seven Bridges, allowing approved researchers to securely access to National Cancer Institute datasets available through the Cancer Research Data Commons. This enables cancer data to interoperate across both adult and pediatric data, as well as across both NIH and consortia-based datasets, for the first time.

CAVATICA BY THE NUMBERS

- 17,000+ whole genome sequence (WGS) samples processed
- 1,100+ RNA-seq samples processed
- More than 1.5 petabytes of data processed
- 300,000+ pipeline executions completed
- Reduced costs from $35 to $15 to process each sample
- Optimized the time to process a whole genome sequence from 35 hours to just 15 hours per sample
- Increased total output from 33 to more than 300 samples per day
- Optimized the time to process an RNA sequence to just five hours per run

CAVATICA (*CONT.*)

Cavatica supports the Gabriella Miller Kids First Data Resource Center (Kids First DRC), and its associated portals which are expanding to include more than 25,000 patients and family members.

As part of the launch of the Kids First DRC, Cavatica was further integrated with the University of Chicago-managed *Bionimbus*, powered by the *Gen3* software platform, which provides authorization/authentication to users as a National Institutes of Health Trusted Partner. Cavatica and *Gen3* integration allow registered users to perform a variety of research tasks seamlessly, including the ability to: identify data of interest to them within the Kids First DRC; create a virtual cohort based on their search; request access to the files via dbGaP; and, upon access approval, immediately import the genomic files of interest into a new Cavatica project to perform further analysis.

Cavatica eliminates data transfer times that historically took days or weeks to complete, and allows instant access to approved users. Cavatica also provides the capacity for users to upload their own data and conduct analysis confidentially within controlled workspaces, while also working alongside the publicly available data.

Cavatica was awarded *Best-in-Show* at the 2017 Bio-IT World Conference and was a highlighted partner of the Biden Cancer Moonshot. Over the next year, Cavatica will expand and interoperate with other cloud providers, including the Google Cloud, in an effort to focus on integration opportunities with the NIH Data landscape and test deployments across additional, global, cloud environments.

PEDCBIOPORTAL

PedcBioPortal for Integrated Childhood Cancer Genomics

PedcBioPortal is an NIH-funded childhood cancer visualization tool modeled upon and partnered with the highly successful, adult-focused, cBioPortal, which was originally developed at Memorial Sloan-Kettering Cancer Center (MSK). PedcBioPortal provides access to high-level processed data types and supports the curation and cross-cancer integration of public, childhood cancer genomic information.

These 'open science' initiatives of consortia-based efforts include the Children's Brain Tumor Tissue Consortium (CBTTC), the Pacific Pediatric Neuro-Oncology Consortium (PNOC) and the St. Baldrick Pediatric Stand Up 2 Cancer Dream Team with the AACR Project Genie as an upcoming integration.

Since the beginning of FY18, an additional number of pediatric and adult cancer sets have been made available through PedcBioPortal, in conjunction with publications. The launch of the Pediatric Brain Tumor Atlas (PBTA) also prompted the release of somatic mutation data, copy number variations, and gene expression levels. This platform allows straight-forward visualization and analysis of the processed data, including the ability to view mutations and copy number aberrations along the genome, identifying correlations between gene expression profiles, and interacting with protein-protein networks.

AACR PROJECT GENIE

In May of 2018, D^{3}b was awarded a membership in the American Association for Cancer Research (AACR)'s Project GENIE. D^{3}b Co-director, Adam Resnick, PhD, is the CHOP PI for the project, with Marilyn Li, MD, of Pathology's Division of Genomics, and D^{3}b's MDRU serving on Project GENIE's executive board.

AACR Project GENIE, or Project Genomics Evidence Neoplasia Information Exchange, is a multi-phase, multi-year, international data-sharing project that accelerates breakthroughs in precision oncology. AACR is developing a regulatory-grade registry that links and brings together clinical-grade cancer genomic data, along with clinical outcomes from tens of thousands of cancer patients treated at multiple, international institutions.

The data collected through AACR Project GENIE includes nearly 19,000 de-identified, genomic records collected from patients who were treated at eight international institutions, making it among the largest fully-public, cancer genomic datasets released to date.

The release includes data from 59 major cancer types, including data from nearly 3,000 patients with lung cancer, more than 2,000 patients with breast cancer, and more than 2,000 patients with colorectal cancer.

DATA PHASE:

BIG DATA

Avi Kelman, MS (left) and Natasha Singh, MS (right), data engineers in the Data Analytics Management & Engineering Unit, discuss how data is transformed before it is ingested into the Gabriella Miller Kids First Data Resource ecosystem.

The D³b Center aims to help to inform the overall understanding of how childhood diseases develop and occur throughout the lifespan of patients. Providing access to significantly large collections of data, in addition to collecting diverse data types from across different ages and disease types, is crucial to the data-driven research process.

The D³b research model enables the generation, integration, collection, processing, harmonization, and sharing of data, including genomic whole-genome sequencing (WGS), RNA-seq and single-cell, proteomic, phospho and total, methylation, imaging, histology and radiology, as well as patients' clinical and phenotypic longitudinal data, with additional disease-specific categories of data also available. When harmonized and integrated, these diverse types of data provide opportunities to identify shared "signals" or pathways across different disease types, which could improve understanding of how and what to target to more effectively treat complex diseases of all types, throughout the lifespan of patients.

D³b is constantly seeking to identify existing collections of high-value data, in addition to generating new data from specimen collections, to further aid and inform the understanding of disease mechanisms for clinical impact.

D³b began with and has scaled its driver efforts in pediatric and adolescents/young adult (AYA) brain tumor (clinical and biospecimen efforts) for data generation and lifespan research, with five programs focused on the collection of samples throughout a child's development and maturity.

Additionally, pilot areas led by CHOP's Department of Surgery and its Divisions of Neurosurgery, Plastics, Cardiac, and Fetal Medicine are further expanding D³b's surgical, oncology, biospecimen, collection, and data generation efforts for cross-disease and developmental-biology research, along with additional support and partnership with the Departments of Biomedical Health Informatics, (DBHi), Pathology, and Pediatrics. D³b currently has more than 19 IRB-approved, single and multi-institutional observational research projects and programs, collecting the types of data and biospecimens listed above. The collection of this data is managed within the D³b Center by the CRU and BRU.

In addition to managing the 19 IRB-approved protocols over the past year, the CRU began study start-up activities on eight additional trials, supported three new trial concepts, and enrolled and followed over 8,000 total study participants.

DATA PHASE: BIG DATA (*CONT.*)

The CRU was also able to achieve a number of key milestones including the creation of more efficient operational processes and standards within CHOP (in partnership with the Pathology Core, Institutional Biobank, Radiology, DBHi, and externally with multi-international, consortium-member institutions) These standards provide the foundation for maintaining high-quality biospecimens and clinical data, allowing D³b to successfully scale to meet the volume of research trials needed. Relying on the proven success of collecting high-quality clinical data with paired biospecimens, D³b has secured external consortia grants including: the Chordoma Foundation Biobank, the launch and secured funding of a National Pediatric Brain Tumor Autopsy collection program, the CBTTC Operations Center, and new initiatives including the CPTAC III Tissue Source Site, the Corsica Consortium, and Project Hope with the National Cancer Institute.

The Biospecimen Research Unit (BRU), in collaboration with CHOP's Biorepository Core (BioRC) and the CHOP's Pathology Core, is responsible for the collection, management, and distribution of samples for research and discovery. This unit has collected a total of more than 63,000 biospecimen aliquots for use in collaborative research projects.

The BRU has also developed operational strategies and standards to manage the high-quality biospecimens needed for genomic and molecular research. These standards have enabled the BRU to collect samples of flash-frozen tissue, the collection method which poses the smallest risk of degradation in DNA and RNA. These procedures also ensure the best sequencing results using matched samples of either blood or saliva, providing researchers with a direct and comprehensive "snapshot" of each subject enrolled. The BRU team also works directly with the BioRC to create workflows for the extraction of DNA and RNA from bone, as required to study pediatric, craniofacial birth defects. In partnership with the Pathology Core, the BRU was able to obtain additional fresh tissue needed for the creation of biological models of subjects' tumors, as cell lines or animal models.

All of the collected samples are 2-D barcoded and managed through a Laboratory Information Management System (LIMS), called Nautilus, which is managed by CHOP's BioRC.

Mariarita Santi, MD, PhD, a neuropathologist in the Department of Neuropathology at CHOP, partners with the D³b Center to lead the biospecimen research efforts.

Nautilus allows for real-time location tracking, volume verification, aliquot management, shipping, testing and tracking of the specimens, while also linking each specimen to its associated clinical data via API (Application Programming Interface).

The BRU has transformed and improved upon the traditional biospecimen storage model for providing biospecimens to researchers. The improved workflows have served more than 40 research projects to date, both internally at CHOP and in support of external collaborators. To ensure the rapid use of each sample, while still maximizing the impact of these rare biospecimens, the BRU developed a transparent and efficient online scientific proposal process for the request of biospecimens by investigators, which is reviewed by a scientific committee.

This past year, the BRU achieved a significant milestone with the addition of the 2,000th biospecimen as part of the Pediatric Brain Tumor Atlas (PBTA). This is the first pediatric brain tumor effort to utilize high-quality, flash-frozen specimens with matched pairs for the generation of such a large and comprehensive data resource.

Looking forward, the BRU will integrate biospecimen collections obtained from interventional clinical trials and process them for genomic, epigenomic, transcriptomic, proteomic testing, and clinical diagnostics. These specimens will also be interoperable with D³b's partnered adult cancer initiatives.

RESEARCH HIGHLIGHTS

CHILDREN'S BRAIN TUMOR TISSUE CONSORTIUM (CBTTC)

The Children's Brain Tumor Tissue Consortium (CBTTC) is a collaborative, multi-institutional research program dedicated to the study and effective treatment of childhood brain tumors by supporting the research of new prognostic biomarkers and therapeutic approaches. As part of this research effort, the CBTTC has developed a network of informatics and data applications which allow researchers from across the globe to work together to discover cures. "Innovation through collaboration" is made possible by the state-of-the-art biorepository core at CHOP, as well as the expertise of leaders in the field of biomedicine.

As one of the CBTTC's founding institutions and home of the CBTTC Operations Center, D³b, in partnership with CHOP's Department of Pathology (under the leadership of neuropathologist, Mariarita Santi, MD, PhD), has been proud to support the CBTTC's growth, increases in scientific projects conducted, and the launch of the Pediatric Brain Tumor Atlas (PBTA).

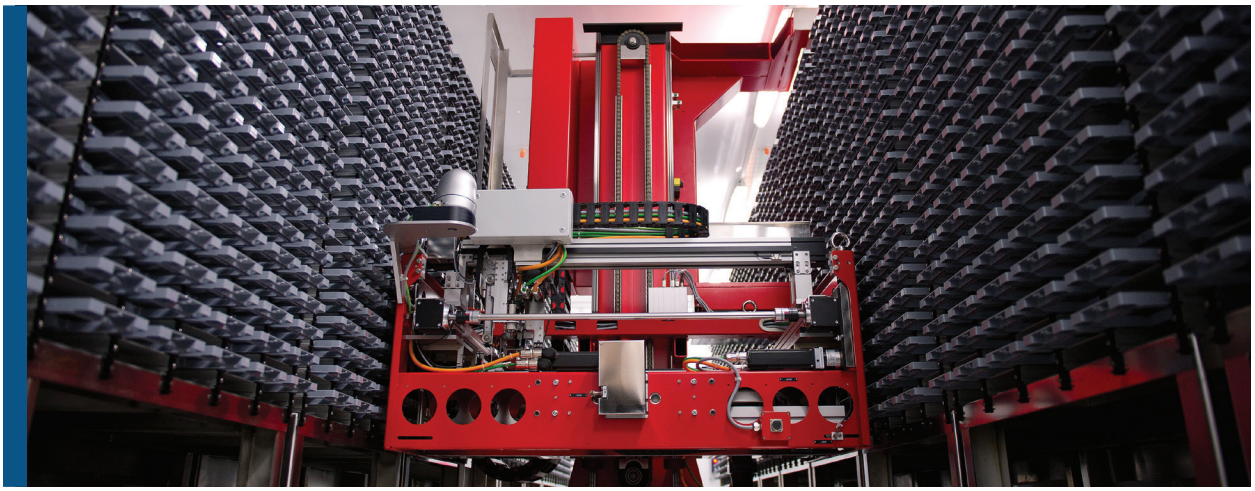
Within the first year of the PBTA's release, data from more than 1,000 patients, representing 30 different types of pediatric brain tumors, have been compiled. This data is now available for integration and processing on the Gabriella Miller Kids First Data Resource Portal, with raw genomic data deployed on the Cavatica platform, and processed data visualizations available on PedcBioPortal. Depending on individual needs, users can seamlessly move between applications and interact with the platforms, either individually or as a collaborative group.

Data types include those for matched tumor/normal samples, such as Whole Genome Sequencing (WGS), RNA-seq, proteomics, longitudinal clinical data, imaging data (MRIs and radiology reports), histology slide images, and pathology reports. To foster rapid and numerous discoveries, the PBTA was released without any embargo periods. To find out more about the PBTA visit cbttc.org/pediatric-brain-tumor-atlas

(From left) Angela Waanders, MD, MPH, Executive Chair of the CBTTC, Phillip "Jay" Storm, MD, Chief of the Division of Neurosurgery at CHOP, Adam Resnick, PhD, CBTTC Scientific Co-chair, and Yuankun Zhu, Bioinformatics Engineer Supervisor, view a project in Cavatica.

At the close of FY18, the CBTTC enrolled more than 2,500 patient subjects, collected over 30,000 biospecimens, initiated 45 scientific projects, and grew to include 16 member institutions globally. This collaborative effort has resulted in the largest collection of pediatric brain tumor whole genomes in the world.

CHILDREN'S BRAIN TUMOR TISSUE CONSORTIUM (*CONT.*)



The REMP mid-size store (MSS), a robotic sample management system located at CHOP, can accommodate more than 2 million biosamples in a carefully monitored -20°C temperature and humidity-controlled environment.

Due to the growth and expansion of biobanking and large-scale data generation, the increase of collaborative research efforts, a rising national profile, and additional research funding, the CBTTC's tremendous success and unprecedented molecular and genomic data generation efforts over the past year are meeting the objectives of the scientific research community, years ahead of what was initially envisioned.

Through the continuous financial support and tireless advocacy of patients and their families, the CBTTC was able to expand its existing infrastructure to house, process, and share biospecimens and molecular data across the globe. CBTTC also initiated the genomic sequencing of its entire biobank, and increased its international collaborations to include Tiantan Hospital in Beijing, The Chinese National Genebank, and The Hudson Institute of Medical Research in Australia.

The CBTTC is made possible solely through philanthropic support. In addition to a large number of individual supporters at CHOP, the consortium relies on a dedicated group of foundations that have come together to form the CBTTC Advisory Council.

CBTTC ADVISORY COUNCIL MEMBERS

- Children's Brain Tumor Foundation
- Christopher Brandle Joy of Life Foundation
- Dragon Master Foundation
- Grayson Saves Foundation
- Kortney Rose Foundation
- Kyle Daniel Kerpan Foundation
- Lilabean Foundation
- The Robert Connor Dawes Foundation
- The Ross K. MacNeill Foundation
- Smashing Walnuts
- Swifty Foundation
- Thea's Star of Hope
- Wylie's Day Foundation

To learn more about the Children's Brain Tumor Tissue Consortium, visit www.cbttc.org.

The Philadelphia Coalition for a Cure (PC4C) is a CHOP-led brain tumor initiative that supports translational research and clinical diagnostics across both adult and pediatric cancer populations at six major hospital systems in the Philadelphia area – Children's Hospital of Philadelphia, Cooper Medical Center of Rowan University, Drexel University Neurosciences Institute, Jefferson University Hospital, The Hospital of the University of Pennsylvania, and the Lewis Katz School of Medicine at Temple University, with D³b as the designated coordinating center.

PC4C arose from the Adult Brain Tumor Program, a collaborative effort between CHOP and the University of Pennsylvania Health System that began in 2014, and is made possible in part thanks to a generous commitment by the Templeton family of $3 million to establish the Templeton Family Coalition for a Cure Fund.

In 2016, the program expanded into PC4C, and has since facilitated the collection of unique brain tumor specimens from over 2,800 patient subjects. Through the efforts of the Hospital of the University of Pennsylvania, Penn Presbyterian Medical Center, Pennsylvania Hospital, and CHOP's Department of Neurosurgery and D³b, this coalition has supported 13 distinct scientific research projects.

In the spring of 2018, due to the success of PC4C, the National Cancer Institute (NCI) selected CHOP as a designated tissue-source site of the Clinical Proteomic Tumor Analysis Consortium (CPTAC), an effort sponsored by the NCI's Office of Cancer Clinical Proteomics Research. CPTAC is a comprehensive and coordinated program to accelerate the understanding of the molecular basis of cancer through the application of robust, quantitative, proteomic technologies and workflows.

The primary goal of CPTAC is to improve the capability to diagnose, treat, and prevent cancer. In its current phase, CPTAC member sites will be conducting proteomic analysis on selected cancer types (up to 10 cancer types, 200 cases each), in an effort to understand the molecular biology of each disease type.

CHOP is the first pediatric hospital to join CPTAC, and D³b, along with other PC4C member institutions, will support the Glioblastoma multiforme (GBM)-based tissue characterization efforts of the NCI.

PC4C GOALS & OBJECTIVES

PC4C's observational research trial is the first adult brain tumor genomic research initiative to integrate with and partner with the recently-launched Pediatric Brain Tumor Atlas Project initiative—the world's largest consortia-led effort for the comprehensive molecular and genomic characterization of all pediatric brain tumors.

In addition to initiating clinical research studies, PC4C institutions will work together to advance data-driven discovery through the rapid sharing and release of data to the entire research community through open science initiatives.

The goal of PC4C is to de-silo cancer research and precision medicine efforts. Patients enrolled in the study will have access to a comprehensive molecular profiling and diagnostics test, called GPS Cancer. This is a unique, comprehensive test to integrate DNA and RNA sequencing along with quantitative proteomics data, to provide oncologists with a comprehensive, molecular profile of a patient's cancer.

RESEARCH PROJECTS

FOCUS AREA: BRAIN TUMORS IN PEDIATRIC & ADOLESCENT/YOUNG ADULT (AYA) POPULATIONS

Pediatric brain tumor research serves as the life and blood driver research initiative for the D³b Center. Projects encompass all four stages of the D³b Methodology including large-scale data generation.

Program Title: **Children's Brain Tumor Tissue Consortium (CBTTC)**
PI(s): Angela Waanders, MD, MPH, Adam Resnick, PhD, Children's Hospital of Philadelphia; Javad Nazarian, PhD, MSc, Children's National Health System
Age: Pediatric/AYA
Status: Ongoing; +3,000 subjects, 40,000 biospecimens
Data types: Clinical (pathology, radiology, surgical, treatment, outcome)
Biospecimen types: Flash frozen tissue, blood, CSF, cell lines from subjects with paired parental saliva

Project Title: **Genomic Evaluation of Malignant Pediatric Cortical Tumors**
PI(s): Sarah Leary, MD, Seattle Children's Hospital; Angela Waanders, MD, MPH, Children's Hospital of Philadelphia
Age: Pediatric/AYA
Status: Complete and harmonized into PBTA
Data types: Clinical data with paired WGS/RNA-seq
Biospecimen types: Flash frozen tissue, blood

Project Title: **Comprehensive Molecular Analysis of Pediatric Thalamic Tumors**
PI(s): Javad Nazarian, PhD, MSC, Children's National Health System
Age: Pediatric/AYA
Status: Complete and harmonized added into PBTA
Data types: Clinical data with paired WGS/RNA-seq
Biospecimen types: Flash frozen tissue, blood

Project Title: **Whole Bank Sequencing**
PI(s): Adam Resnick PhD, Children's Hospital of Philadelphia
Age: Pediatric/AYA
Status: Complete and harmonized into PBTA
Data types: Clinical data with paired WGS/RNA-seq
Biospecimen types: Flash frozen tissue, blood

Project Title: **Kids First - CBTTC Proteogenomic Pilot Project**
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia; Brian Rood, MD, Children's National Health System
Age: Pediatric/AYA
Status: Complete and harmonized into PBTA
Data types: Clinical data with paired phospho and total proteomics WGS/RNA-seq generated in companion project
Biospecimen types: Flash frozen tissue

Project Title: **Whole Genome Sequencing of Low-grade Glioma and Ganglioglioma**
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia
Age: Pediatric/AYA
Status: Complete harmonized in PBTA used for research to identify BRAF fusion for diagnostic intervention
Data types: Clinical data with paired WGS/RNA-seq
Biospecimen types: Flash frozen tissue, blood

FOCUS AREA: BRAIN TUMORS IN PEDIATRIC & ADOLESCENT/YOUNG ADULT (AYA) POPULATIONS (*CONT.*)

Project Title: **Whole Genome Sequencing of Craniopharyngioma**
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia
Age: Pediatric/AYA
Status: Complete harmonized in PBTA used for research to identify BRAF fusion for diagnostic intervention
Data types: Clinical data with paired WGS/RNA-seq
Biospecimen types: Flash frozen tissue, blood

Project Title: **Whole Genome Sequencing of Medulloblastoma**
PI(s): Tom Curran, PhD, FRS, Children's Hospital of Philadelphia
Age: Pediatric/AYA
Status: Complete and harmonized into PBTA
Data types: Clinical data with paired WGS/RNA-seq
Biospecimen types: Flash frozen tissue, blood

Project Title: **Genomics of Human Medulloblastoma and AT/RT**
PI(s): Tom Curran, PhD, FRS, Children's Hospital of Philadelphia
Age: Pediatric/AYA
Status: Complete and harmonized into PBTA
Data types: Clinical data with paired WGS/RNA-seq
Biospecimen types: Flash frozen tissue, blood

Project Title: **Neurocytoma WGS and RNA-seq**
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia
Age: Pediatric/AYA
Status: Complete and harmonized into PBTA
Data types: Clinical data with paired WGS/RNA-seq
Biospecimen types: Flash frozen tissue, blood

Project Title: **CBTTC Tiantan Children's Hospital Medulloblastoma WGS Sequencing Project**
PI(s): Chunde Li, MD, Tiantan Children's Hospital;
Adam Resnick, PhD, Children's Hospital of Philadelphia
Age: Pediatric
Status: Ongoing - 100 subjects
Data types: Clinical data with paired WGS
Biospecimen types: Flash frozen tissue

Project Title: **Factors Associated with High Incidence of Pediatric Brain and Central Nervous System Tumors in Kentucky**
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia
Age: Pediatric
Status: Ongoing
Data types: Clinical data with paired genomic panel and WGS
Biospecimen types: FFPE

Project Title: **Proteomic Data Generation of AYA Brain Tumors**
PI(s): Brian Rood, MD, Children's National Health System;
Adam Resnick, PhD, Children's Hospital of Philadelphia
Age: AYA
Status: Ongoing
Data types: Clinical data with paired phospho and total proteomics paired with already-generated WGS/RNA-seq data
Biospecimen types: Flash frozen tissue

FOCUS AREA: BRAIN TUMORS IN PEDIATRIC & ADOLESCENT/YOUNG ADULT (AYA) POPULATIONS (*CONT.*)

Project Title: **Project HOPE: High-grade Glioma-Omics in Pediatric and AYA**
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia;
Michael Prados, MD, University of California San Francisco; Michelle Monje, MD, PhD, Stanford University; Mariella G. Filbin, MD, PhD, Dana Farber Cancer Center
Age: AYA
Status: Ongoing
Data types: CBTTC clinical data with paired single-cell sequencing, paired WGS/RNA-seq and proteomics generated in collaborative projects
Biospecimen types: Flash frozen tissue, blood

FOCUS AREA: SURGICAL ONCOLOGY CROSS-DISEASE RESEARCH & COMPARATIVE BIOLOGY INITIATIVES

In alignment with the D³b Center's research Design Principles and Methodology, D³b has established key strategic partnership projects that support biospecimen-based research through data-driven harmonization of workflows and processes. The focus is on integration in the data and information stages of research in support of cross-disease, cross-age and comparative biology studies that provide for shared knowledge creation and translational opportunities for impact.

Project Title: **Brain Tumors in Canines**
PI(s): Phillip "Jay" Storm, MD, Adam Resnick, PhD, Children's Hospital of Philadelphia;
Rebecca A. Packer, MS, DVM, DACVIM, Colorado State University
Age: Pediatric/AYA
Status: Ongoing
Data types: Clinical data with paired WGS/RNA-seq
Biospecimen types: Flash frozen tissue, blood

Program Title: **University of Pennsylvania Brain Tumor Biobank (Neurosurgery Tumor Tissue Bank)**
PI(s): Phillip "Jay" Storm, MD, Adam Resnick, PhD, Children's Hospital of Philadelphia;
Donald O'Rourke, MD, Hospital of the University of Pennsylvania
Age: Adult
Status: Ongoing +3,000 subjects, 40,000 biospecimens
Data type(s): Clinical data (pathology, radiology, surgical, treatment, outcome)
Biospecimen types: Flash frozen tissue, blood, CSF

Program Title: **PC4C CPTAC III**
PI(s): Phillip "Jay" Storm, MD, Adam Resnick, PhD, Children's Hospital of Philadelphia;
PC4C Consortium: Temple University Hospital, Hospital of the University of Pennsylvania, Jefferson University Hospital, Drexel University, Cooper Medical Center
Age: AYA/Adult
Status: Ongoing
Data types: Clinical data with phospho and total proteomics
Biospecimen types: Flash frozen tissue

Project Title: **Sinonasal Cancer Study to Evaluate Oncologic Outcomes and Quality of Life**
PI(s): Phillip "Jay" Storm, MD, Angela Waanders, MD, MPH, Adam Resnick, PhD, Children's Hospital of Philadelphia; Nithin Adappa, MD, University of Pennsylvania;
Corsica Consortium
Age: Pediatric/AYA/Adult
Status: Ongoing
Data types: Clinical data with paired WGS/RNA-seq
Biospecimen types: Flash frozen tissue

FOCUS AREA: CONTINUUM OF SURGICAL ONCOLOGY CROSS-DISEASE RESEARCH & COMPARATIVE BIOLOGY INITIATIVES (*CONT.*)

Project Title: **Oligo Nation Biorepository**
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia; Oligo Nation Foundation
Age: AYA/Adult
Status: Ongoing
Data types: Clinical data with paired WGS/RNA-seq
Biospecimen types: Flash frozen tissue, blood

Project Title: **Chordoma Foundation Biorepository**
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia; Chordoma Foundation
Age: AYA/Adult
Status: Ongoing
Data types: Clinical data with paired WGS/RNA-seq
Biospecimen types: Flash frozen tissue, FFPE tissue, blood

FOCUS AREA: PEDIATRIC SURGICAL BIOSPECIMEN CROSS-DISEASE RESEARCH PROGRAM

Harnessing the shared developmental biology and neuroscience research context of data-driven research has proven to be an accelerant for clinical translation and is the foundational mission of the at D³b-led Gabriella Miller Kids First Data Resource Center.

Project Title: **Shared Genetics Underlying Pediatric Congenital Craniofacial Pathologies**
PI(s): Jessie Taylor, MD, Phillip "Jay" Storm, MD, Adam Resnick, PhD,
Children's Hospital of Philadelphia
Age: Pediatric
Status: Ongoing
Data types: Clinical data with paired WGS/RNA-seq
Biospecimen types: Flash frozen tissue

Project Title: **Cardiac Birth Defect Pathologies**
PI(s): J. William Gaynor, MD, Phillip "Jay" Storm, MD, Adam Resnick, PhD,
Children's Hospital of Philadelphia
Age: Pediatric
Status: Ongoing
Data types: Clinical data with paired WGS/RNA-seq
Biospecimen types: Flash frozen tissue

Project Title: **The Epilepsy Genetic Research Project**
PI(s): Ben Kennedy, MD, Ingo Helbig, MD, Phillip "Jay" Storm, MD, Adam Resnick, PhD,
Children's Hospital of Philadelphia
Age: Pediatric/AYA
Status: Ongoing
Data types: Clinical data with paired WGS/RNA-seq
Biospecimen types: Flash frozen tissue

Project: **Pario Group - Congenital Birth Defect Biobanking for Genetic Research**
PI(s): Greg Heuer, MD, Phillip "Jay" Storm, MD, Adam Resnick, PhD,
Children's Hospital of Philadelphia
Age: Pediatric/AYA
Status: Planning
Data types: Clinical data with paired WGS/RNA-seq
Biospecimen types: Flash frozen tissue

INFORMATION PHASE: HARMONIZATION, TRANSFORMATION & MODELS

Phillip "Jay" Storm, MD, Chief of the Division of Neurosurgery (left) and Adam Resnick, PhD (right), Co-directors of the D³b Center, lead D³b's efforts to discover more effective therapeutic treatments for childhood brain tumors and other rare pediatric diseases.

Researchers everywhere need access to fundamental data and biological models to advance their knowledge and perform research experiments. Providing resources is an intensive endeavor requiring time, funding, and the staff to collect sufficient biological specimens and data required to transform that raw data into harmonized, processed datasets and biological models. These data are available for hypothesis generation and testing. D³b believes that by removing these barriers to research, resources, time and expertise can be spent translating this information into scientific understanding of disease.

Providing access to information and empowering the ability to query and integrate data in real-time is an important component of the *Convergence Research Model*. This model empowers a diverse community of researchers, each with unique expertise and interests, allowing them to access processed and harmonized data, accelerate discoveries, spawn new collaborations, and reduce the duplication of efforts across the scientific community.

D³b's process enhances the value of each dataset by allowing additional access to data, but is only valuable if the data is integrated and harmonized in ways that allow users to rapidly ask questions and test hypotheses. D³b strives to generate these fundamental resources to drive not only its own research, but aid all researchers. D³b collects and generates large-scale, raw data including, but not limited to: genomic data, proteomic data, methylation, abstracted, longitudinal, and clinical data from IRB-approved research protocols. This data may then be transformed, modeled, and harmonized to create information-rich datasets which are analyzed for scientific research.

To date, **D³b has generated the largest, accessible, pediatric brain tumor dataset released without embargo**. D³b has invested in the development of a large number of preclinical models, such as cell lines and animal models, with the largest set of HGG cell lines to be released, pre-publication, for researchers around the world during FY18. These efforts are reducing the timeline for researchers by providing everyone with access to the fundamental data and biological models required to perform targeted, high-quality research.

CLINICAL DATA HARMONIZATION

Currently, cross-disease clinical data harmonization is very difficult to implement in pediatric cancers and diseases of childhood development. To date, no "gold standard" exists for data collection or modeling, so numerous variations exist between different disease groups and areas of study. Clinical research data must be mapped to existing medical data standards, which are often not optimized to conform to the unique characteristics of pediatric diseases. Childhood conditions need allowances for unique data fields, as required by specific pediatric disease types and treatment contexts. In an effort to fully support the information phase, more effective data models and ontologies must be created and developed.

One of the key challenges in modeling clinical and phenotypic data harmonization is accounting for longitudinal treatments and outcome data, which is needed to help researchers understand each individual patient's treatment narrative across a period of time. A successful, longitudinal, clinical-data model has been established for pediatric brain tumors by the CBTTC. This model has been mapped to existing ontological models including the Observational Medical Outcomes Partnership (OMOP), the National Cancer Institute Thesaurus (NCIT), and the Human Phenotype Ontology (HPO), to allow for the cross-analysis of processed data with other collections of pediatric, brain tumor, cancer, developmental, and rare disease cohorts.

GENOMIC HARMONIZATION

To address the challenges of genomic harmonization, D³b's DAME Unit has developed and applied alignment and joint genotyping workflows, which follow the GATK Best Practice recommendations. These workflows help the D³b Center to be functionally equivalent with other current, large, genomic research efforts within the NIH.

The data processing in support of this effort is courtesy of the Cavatica platform hosted within an Amazon Web Services (AWS) environment. The final, harmonized data is stored in AWS and is searchable through the Kids First DRC Portal, with the ability to further analyze the data on Cavatica.

The D³b-developed Kids First DRC pipelines are optimized for speed and low-cost, and are available as open source workflows on Cavatica and further made available to the public via GitHub:

- Alignment workflow
- Joint genotyping workflow
- Genotype refinement workflow

The Data Analytics Management and Engineering Unit (DAME) works to ensure that data is empowered throughout the entire scientific and translational research process. The DAME unit is comprised of two functional teams, the Bioinformatics Team and the Data Engineering Team.

The Bioinformatics Team is focused on bioinformatics pipeline engineering, genomics data processing, downstream analysis, and interpretation. The Data Engineering Team members are responsible for designing, building, and operating software platforms and infrastructure for management, distribution, and scalable analysis of data.

The DAME team provides engineering expertise to accelerate discoveries by solving complex and challenging problems, while making the most of biomedical data as it becomes available in greater quantities than ever before. Additionally, several DAME members have been selected to participate in NIH external advisory committees, with the responsibility to inform NIH leadership on data-driven research and new platforms throughout the year.

Through its partnership with DBHi at CHOP, the DAME team helped secure a $14.8 million NIH grant to establish the Gabriella Miller Kids First Data Resource Center. The team has also played a key role in the development of the D³b-developed platforms such as Cavatica, PedcBioPortal, and the Kids First Data Resource Portal.

RESEARCH HIGHLIGHTS

PEDIATRIC BRAIN TUMOR ATLAS

As part of a highly-collaborative effort across D³b's units, the Data Analytics Management & Engineering (DAME) Unit supported the initial release of the Pediatric Brain Tumor Atlas (PBTA), which was launched in tandem with the Gabriella Miller Kids First Data Resource Portal (Kids First DRP). The Kids First DRP platform, which interoperates with platforms including Cavatica and Gen3, was selected to organize, manage, harmonize and ultimately release the first version of data of the PBTA. In addition to the genomic data stored in the atlas, the PBTA includes a number of clinical fields, pathology and radiology imaging, and associated reports, making it the most comprehensive data resource for pediatric brain tumors in the world.

Over the last year, the DAME unit has also helped to support a proteomics pilot project using PBTA samples, as part of the National Cancer Institute (NCI)'s Clinical Proteomic Tumor Analysis Consortium (CPTAC). This pilot is the first pediatric study to be included as part of CPTAC and will push innovation of new and emerging molecular characterizations and related data.

The foundational work of the DAME team to launch the PBTA during FY18 will allow additional, real-time releases of data for other projects, supporting increased integration into clinical trials, including those managed by the Pacific Pediatric Neuro-Oncology Consortium (PNOC), as well as in other disease-focused initiatives.

30 brain tumor types

Data from more than 1,000 patients

Releasing data in real-time

16 partner institutions

More than 50 foundation supporters

Nearly 3,000 RNASeq and whole genome sequence samples

HIGH-GRADE GLIOMA CELL LINE MODELS: DEVELOPMENTAL THERAPEUTICS UTILIZING PRECLINICAL MODELS FOR TESTING NEW THERAPIES

Preclinical models are used to test and develop therapies prior to testing in humans. However, there is a significant lack in the preclinical modeling available to pediatric patients. During FY18, the D³b Center's Preclinical Laboratory Research Unit focused on generating additional High-grade Glioma (HGG) cell lines, successfully evaluating and characterizing a large collection of cell lines, developed from HGG-patient tumors, to use as preclinical models. As a result of this and other efforts, D³b has the largest-available cohort of HGG cell lines available to clinical investigators in the world.

The HGG cell line generations was led by Kristina Cole, MD, PhD, of CHOP's Pediatric Neuro-Oncology Program, and her work with the Children's Brain Tumor Tissue Consortium. Although the effort is still ongoing, the D³b Center has worked extensively to ensure access to the generated data by investigators everywhere, including presenting this cell line cohort at the 2018 meeting of the International Society of Pediatric Neuro-Oncology (ISPNO). D³b's effort to meet the demand by researchers for data extracted from this precious cell-line cohort remains a top priority.

RESEARCH PROJECTS

DATA ANALYSIS PROJECTS

Shared access and collaborative analysis represent some of the most rapidly increasing areas of project growth in D³b, highlighting the power of platforms to advance research.

Project Title: **Pediatric Brain Tumor Atlas**
PI(s): Children's Brain Tumor Tissue Consortium
Dataset: 1,000 subjects, 30 histology types, WGS, RNA-seq, proteomics, imaging, longitudinal clinical data
Status: Genomic and clinical data harmonization complete and available Kids First Portal, Cavatica and PedcBioPortal portals

Project Title: **AACR Project Genomics Evidence Neoplasia Information Exchange (GENIE)**
PI(s): Marilyn Li, MD, Adam Resnick, PhD, Children's Hospital of Philadelphia
Dataset: 450 subjects, genomic & clinical panel data
Status: Clinical data and genomic data harmonization complete. Datasets available via the Kids First Portal, Cavatica and PedcBioPortal portals in Summer 2019

Project Title: **OPEN DIPG WGS/RNA-seq**
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia; Javad Nazarian, PhD, MSc, Children's National Health System
Dataset: Genomic and clinical data
Status: Genomic and clinical data harmonization pending - dataset availability through the Kids First DRC Portal, Cavatica and PedcBioPortal in Summer 2019

Project Title: **Comprehensive Genomic and Immune Signature Profiling of Ependymoma and Diffuse Intrinsic Pontine Glioma**
PI(s): Richard Wilson, PhD, Kathleen Schieffer, PhD, Stephanie LaHaye, PhD, Nationwide Children's Hospital
Dataset: Genomic and clinical data
Status: Pending

Project Title: **STAT3 Expression in Patients with Diffuse Intrinsic Pontine Glioma (DIPG)**
PI(s): David Daniels, MD, PhD, Liang Zhang, MD, Mayo Clinic
Dataset: Genomic and clinical data
Status: Pending

Project Title: **Gene Expression Analysis Platform Evaluation for FFPE Specimen Material Based Studies**
PI(s): Mateusz Koptyra, PhD, Children's Hospital of Philadelphia
Dataset: Genomic and clinical data
Status: Pending

PRECLINICAL MODELS: BRIDGING THE GAP TO CLINICAL TRANSLATION

In order to accelerate the translation of data to clinical impact, a critical gap often presents barriers to clinical trial development. In order to minimize potential harm to patients and define optimal therapeutic approaches, cell-and animal-based model systems provide a robust preclinical testing environment. To date, progress in clinical translation, across many pediatric diseases, has been hampered due to limited availability of preclinical disease models.

Project Title: **Developing a Novel Tumor Model to Screen for New Therapies for Spinal Ependymoma**
PI(s): Linda Resar, MD, Johns Hopkins University
Cell lines: 2
Status: Available

Project Title: **Development of Preclinical Models of Pediatric Ependymoma**
PI(s): Ching Lau MD, PhD, The Jackson Laboratory
Cell lines: 2
Status: Pending

Project Title: **High-grade Glioma Cell Line Models and PDX**
PI(s): Kristina Cole, MD, PhD, Adam Resnick, PhD, Mateusz Koptyra, PhD, Children's Hospital of Philadelphia
Cell lines: 26, PDX:1
Status: Available

Project Title: **OPEN DIPG Cell Line Model**
PI(s): Javad Nazarian, PhD, MSC, Children's National Health System; Adam Resnick, PhD, Children's Hospital of Philadelphia
Cell lines: 13
Status: Available

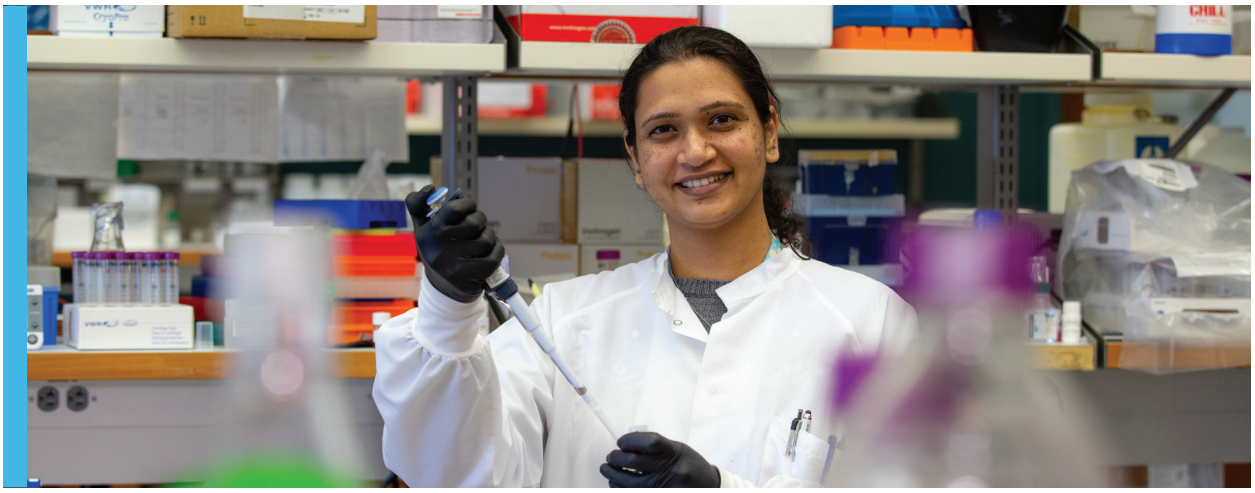
Project Title: **AT/RT Cell Line Models**
PI(s): Adam Resnick, PhD, Mateusz Koptyra, PhD, Children's Hospital of Philadelphia
Cell lines: 10
Status: Available

Project Title: **Chordoma Cell Line Models**
PI(s): Adam Resnick, PhD, Mateusz Koptyra, PhD, Children's Hospital of Philadelphia, Chordoma Foundation
Cell lines: 3, PDX: 1
Status: Available

Project Title: **Medulloblastoma Cell Line Models**
PI(s): Adam Resnick, PhD, Mateusz Koptyra, PhD, Children's Hospital of Philadelphia
Cell lines: 7, PDX: 1
Status: Pending

Project Title: **Tissue Derived Cell Line Models Generation for Rare Pediatric CNS Tumors**
PI(s): Adam Resnick PhD, Mateusz Koptyra, PhD, Children's Hospital of Philadelphia
Cell lines: 11 (choroid plexus, meningioma, orbital sarcoma, congenital glioblastoma, neurofibroma/plexiform, and more)
Status: Pending

KNOWLEDGE PHASE: HYPOTHESIS-DRIVEN RESEARCH



Poonam Sonawane, PhD, a scientist in D³b's Preclinical Laboratory Research Unit, generates cell line models for Neurofibromatosis type 1 (NF1) to test the effect of signaling pathway inhibitors.

Once data is transformed from a raw format into queryable and findable information, hypothesis generation and testing can occur internally at D³b/CHOP, as well as by external collaborators, such as consortia-led efforts including the CBTTC and other partners within the research community. The Preclinical Laboratory Research Unit (PCLRU) and the Molecular Diagnostic Research Unit (MDRU), which are supported by the bioinformatics team within the DAME unit, continue to generate new understanding of the disease landscape through hypothesis generation and testing to provide a foundation for new discoveries on behalf of clinical translation.

The PCLRU supports D³b's basic and translational research efforts. The PCLRU focuses on research of pediatric, central nervous system and solid tumors. Its primary goal is to harness data-driven approaches on behalf of precision-based and targeted therapeutics using translational methodologies, including projects focused on the elucidation of cell signaling mechanisms of childhood development, oncogenesis, tumor progression, the creation and characterization of preclinical models, and drug screening, development and testing.

The Molecular Diagnostic Research Unit (MDRU) represents a joint, strategic partnership with the Pathology Core and the Department of Surgery at CHOP, which builds on D³b's other existing foundational partnerships. Additionally, the D³b Center benefits from the support and partnership of the Division of Genomic Diagnostics at CHOP, led by Vice Chief Marilyn Li, MD, and the Director of Bioinformatics, Mahdi Sarmady, PhD. This research focuses on the development of novel diagnostic panels, tests, tumor biomarker discovery, and clinical genomics data generation for direct use in clinical applications.

Marilyn Li, MD, Vice Chief of the Division of Genomic Diagnostics

KNOWLEDGE PHASE: HYPOTHESIS-DRIVEN RESEARCH (*CONT.*)

In recent years, D³b investigators have achieved several key milestones related to the mechanisms of pediatric and adult cancers, which include novel discoveries in the mechanisms of pediatric and adult cancers, clinical trials based on the mechanistic discoveries, and new standards of care for children and adults diagnosed with devastating diseases. Other breakthroughs include:

- Improved immunotherapy techniques for pediatric brain tumors
- Research on the newly-released Pediatric Brain Tumor Atlas
- Early analysis of proteogenomic and single-cell data pediatric brain tumor data
- The development of new clinical diagnostic RNA-seq workflows, which aid investigators by connecting information in the genome to protein expressions (The mechanism in which drugs are targeted)
- Receiving proposals for more than 60 approved, CBTTC Scientific Projects, which utilize samples of biospecimens and data

RESEARCH HIGHLIGHTS

THERAPIES FOR GENE FUSION-DRIVEN PEDIATRIC TUMORS

Gene fusions are unique mutations that are found in several pediatric solid tumors, including brain tumors, sarcomas, and other childhood cancers. Gene fusions occur due to abnormal breaks in the chromosomes, resulting in the combination of two unrelated genes, or a portion of genes that would normally function separately, into a single "chimeric" gene. This process results in the generation of a new fusion protein, capable of driving abnormal growth and the proliferation of cancer cells.

Since these fusion proteins are only found in a patient's cancer cells, and not their healthy cells, they provide a unique and specific target for direct cancer therapies. Despite the potential curative effects on cancer therapeutics, very few gene fusion-specific therapies have been developed for use in children. To address this unmet need, D³b is working to identify and characterize the functional role and behavior of several gene fusions in pediatric brain tumor types. These gene fusions may inform the diagnosis, prognosis, and therapy of specific pediatric tumors.

The D³b Center strives to understand the underlying biology of these tumors, so that better, targeted therapies can be developed for patients who may be hosting these gene fusions.

Unique gene fusion events, which are specific to certain types of pediatric brain tumors, require a deeper understanding of the biology of gene fusions in order to result in a positive outcome for patients.

In order to achieve translatable results in real-time, the PCLRU collaborates with the Division of Genomic Diagnostics (DGD) at CHOP, which is host to all CHOP cancer patients undergoing molecular testing, to identify any targetable mutations in their tumors. After clinical work-up, the molecular pathologists at CHOP share any information from novel gene fusions that are identified in a child's brain tumor or other solid tumor with the PCLRU, so they can study these fusions in real-time in the lab.

After generating various cell and animal models in the lab to further investigate how the fusion gene functions, the PCLRU determines which cellular pathways the fusion gene product activates in the tumor, as well as the method to best target it with novel therapies. Based on this model, the PCLRU manages several ongoing projects to study the biological mechanisms of novel gene fusion events discovered in pediatric brain and solid tumors. By gaining a more complete understanding of how these tumors grow and develop, the PCLRU can more effectively translate these findings to patients.

ONGOING PCLRU PROJECTS

- Exploring the gene fusion landscape of Mixed Neuronal-Glial Tumors (MNGTs)
- Sclerosing epithelioid fibrosarcoma case with a novel EWSR1-CREB1L3 fusion
- A rare case of pediatric angiosarcoma harbors a novel and drug targetable Notch1-Ros1 fusion that activates distinct mechanisms
- Differential response of NTRK gene fusions to targeted drug therapy in pediatric solid tumors
- Identification and characterization of molecular mechanisms of ATG7-RAF1 and NRF1-BRAF fusions identified in pleomorphic xanthoastrocytoma
- Developing a fly (Drosophila melanogaster) model system for fusion genes to identify molecular mechanisms of oncogenesis (in collaboration with Yuanquan Song, PhD at CHOP)
- Gene fusion expression library and characterization pipeline

(See page 46, *Research Breakthroughs*, for more information on D³b's gene fusion efforts)

IMMUNOTHERAPY IN BRAIN TUMORS

Chimeric antigen receptor, or (CAR) T-cell therapy is a form of immunotherapy that involves taking a patient's own T-cells, programming the cells to attack a specific target on the tumor, and returning them back into the patient, where they seek out and kill the tumor. CAR T-cell therapy has produced tremendous success for relapsed and refractory B-cell leukemia, but has seen limited success to date in solid and brain tumors. Jessica Foster, MD, is leading D³b's efforts to create effective and safe CAR T-cell therapies for pediatric brain tumors using mRNA.

CHOP is a pioneer in CAR T-cell therapies, thanks in part to the hospital's Cancer Immunotherapy Program, which has the capability to manufacture complete T-cell in partnership with the University of Pennsylvania. Additionally, through D³b collaborations including the Pacific Pediatric Neuro-Oncology Consortium (PNOC) and Pediatric Cancer Immunotherapy Trials Network (Peds CITN), the D³b Center has improved the infrastructure needed to develop a viable clinical trial - available across multiple sites. D³b has successfully implemented this new therapy with its participating in a CD19 CAR T-cell trial.

D³b's mRNA approach addresses concerns about the effects of off-target toxicity, allowing for relatively accelerated IRB and FDA testing approval. By combining D³b's institutional experience along with this project's preclinical affirmation of mRNA CAR T-cells, D³b is creating an unparalleled opportunity to advance CAR T-cell therapy in pediatric brain tumors.

HOW DOES CAR T-CELL THERAPY (IMMUNOTHERAPY) WORK?

The form of CAR T-cell therapy developed through a collaboration of Children's Hospital of Philadelphia and the Hospital of the University of Pennsylvania was FDA-approved for use in children with relapsed B-cell acute lymphoblastic leukemia in 2017.

In this cancer treatment, immune cells called T-cells are taken from a patient's own blood. These cells are genetically modified to express a protein which will recognize and bind to a target called CD19, which is found on cancerous B-cells.

T-cells, a type of white blood cell, are designed to kill disease cells. Cancerous B-cells often look like your own normal, healthy cells, so T-cells don't go after them.

Millions of T-cells are collected from the patient, then reprogrammed in a lab so they can now identify the cancerous B-cells and grab onto a substance that is found only on the surface of B-cells.

When the reprogrammed T-cells are put back into the patient, they flow throughout the body and begin locating cancerous B-cells.

As the reprogrammed T-cells attach to and destroy the rapidly dividing cancerous B-cells, they also multiply in the body and can remain in the body long after to continue fighting any new cancerous B-cells. They will also kill the healthy B-cells. A patient who undergoes this therapy will not have any B-cells in their immune system.

RESEARCH PROJECTS

CBTTC-APPROVED BIOSPECIMEN SCIENTIFIC PROJECTS

To date the CBTTC has approved the following biospecimen projects : 19 projects studying Medulloblastoma, 17 projects studying High-grade Gliomas, 10 projects focusing on sPNET, eight Ependymoma projects, seven projects focused on Low-grade Gliomas, five AT/RT projects, four Ganglioglioma projects, four Craniopharyngioma projects, and four DIPG-focused projects. This diverse collection of tumor types is helping to provide researchers throughout the world with the information they need to understand the behavior of specific tumor types. Varied data types from different populations, ages, and stages of development are crucial to providing a more targeted understanding of how brain tumors can be treated.

Project Title: **Proteogenomic Identification of Structural Variations**
PI(s): Brian Rood, MD, Children's National Health System

Project Title: **Integrated Genomic Analysis to Elucidate the Role of PIKC3A and 10q LOH as Unique Drivers and Cooperating Events in Pediatric High-grade Gliomas**
PI(s): Ian Pollack, MD, Sameer Agnihotri, PhD, Children's Hospital of Pittsburgh

Project Title: **Integrative Functional Genomics of Recurrent Childhood Medulloblastoma**
PI(s): Javad Nazarian, PhD, MSC, Brian Rood, MD, Children's National Health System; Paul Northcott, PhD, St. Jude Children's Research Hospital

Project Title: **Choroid Plexus Tumor (CPT) Therapies Based on Patient Derived Cell Culture Resources**
PI(s): Mark Souweidane, MD, Uday Maachani, PhD, Weill Cornell Medicine

Project Title: **Identifying Tumor Cell Vulnerabilities in Human Medulloblastomas by Single-Cell RNA-Sequencing and Preclinical Modeling**
PI(s): Ninib Baryawno, PhD, Harvard University

Project Title: **Understanding Developmental Cell Lineage in Childhood Medulloblastoma Using Single-Cell DNA Sequencing Technology**
PI(s): Jessica Tsai, MD, PhD, Christopher Walsh, MD, PhD, Children's Hospital of Boston

Project Title: **Utility of Cerebrospinal Fluid Cell-Free DNA in Pediatric Brain Tumors**
PI(s): Jessica Tsai, MD, PhD, Christopher Walsh, MD, PhD, Children's Hospital of Boston

Project Title: **Cracking the Histone Code: Characterizing Pediatric Brain Tumor Epigenetics Using Cerebrospinal Fluid**
PI(s): Amanda Saratsis, MD, Rishi Lulla, MD, Ann & Robert H. Lurie Children's Hospital of Chicago

Project Title: **Gpc2 as an Immunotherapeutic Target in Medulloblastoma and Other Pediatric Brain Tumors**
PI(s): Kristopher Bosse, MD, Jessica Foster, MD, Children's Hospital of Philadelphia

Project Title: **Interactions Between Astrocytes and Tumor Cells Are Critical For Medulloblastoma Growth**
PI(s): Zeng-Jie Yang, MD, PhD, Fox Chase Cancer Center

CBTTC-APPROVED DATA SCIENTIFIC PROJECTS

Currently, the CBTTC is managing more than 20 projects which are utilizing a pan-brain tumor approach, to look across all available histologies of childhood brain tumors. An additional six projects focus on researching High-grade Gliomas, five projects with medulloblastoma, four projects in ependymoma, two projects studying DNET tumors, and additional projects focused on other histologies represented in the CBTTC, including but not limited to: Diffuse Intrinsic Pontine Gliomas (DIPG), Low-grade Gliomas and AT/RT tumors.

Project Title: **Immunotherapy: DIPG and Other Primary Pediatric Brain Tumors**
PI(s): Hideho Okada, MD, PhD, University of California, San Francisco

Project Title: **Proteogenomic Identification of Structural Variations**
PI(s): Brian Rood, MD, Samuel Rivero-Hinojosa, PhD, Children's National Health System

Project Title: **Analysis of Chromatin Pathways as Regulators of High-grade Glioma Gene Expression Patterns**
PI(s): Jamie Anastas, PhD, Boston Children's Hospital

Project Title: **Derek Wainwright, PhD on IDO1 Expression With All CBTTC RNA-Seq Data**
PI(s): Derek Wainwright, PhD, Northwestern University Feinberg School of Medicine

Project Title: **Telomere Maintenance Across Multiple Brain Tumors**
PI(s): Gonzalo Lopez Garcia, PhD, Children's Hospital of Philadelphia

Project Title: **Multi-Tensor Decompositions for Personalized Pediatric Glioma Diagnostics and Prognostics**
PI(s): Sri Priya Ponnapalli, PhD, Eigengene, Inc.

Project Title: **In Silico Neo-antigen Detection in High-grade Pediatric Brain Tumors Utilizing RNA-seq and WGS**
PI(s): Peter Madsen, MD, Children's Hospital of Philadelphia

Project Title: **Spatial Evolution and Somatic Mutations Spectrum of Gliomatosis Cerebri**
PI(s): Birra Taha, MD, Weill Cornell Medicine

Project Title: **Malignant Cortical Tumors**
PI(s): Sarah Leary, MD, Seattle Children's Hospital, Annie Huang, MD, PhD, Angela Waanders, MD, MPH, Children's Hospital of Philadelphia

Project Title: **Defining the Mutational Landscape of Pediatric Brain Tumors**
PI(s): Sharon Diskin, PhD, Children's Hospital of Philadelphia

Project Title: **Fusion Analysis in CBTTC RNA-seq Data**
PI(s): Rohan Bareja, MS, Weill Cornell Medicine

Project Title: **Cooperating Mutations in Brain Tumors of Patients with NF1**
PI(s): Thomas De Raedt, PhD, Children's Hospital of Philadelphia

Project Title: **Identification of Non-coding Drivers From Brain Tumour Genomes**
PI(s): Shimin Shuai, Ontario Institute for Cancer Research

Project Title: **Molecular Analysis of the Cellular Ecosystem of Childhood Ependymoma**
PI(s): Pablo González Cámara, PhD, University of Pennsylvania

CBTTC-APPROVED DATA SCIENTIFIC PROJECTS (*CONT.*)

Project Title: **Treehouse Childhood Cancer Initiative: Identification of Therapeutic Leads for Individual Pediatric Cancer Patients via Pan-cancer Analysis**
PI(s): David Haussler, PhD, University of California, Santa Cruz

Project Title: **Genomic Landscape of Mixed Glial Neuronal Tumors**
PI(s): Lea Surrey, MD, Children's Hospital of Philadelphia

Project Title: **Identify Novel Therapeutic Targets and Biomarkers in Non-coding Genome of Pediatric Cancers**
PI(s): Lihua Zou, PhD, Northwestern University Feinberg School of Medicine

Project Title: **Children's Brain Tumor Tissue Consortium Pediatric Brain Tumor Proteomics Pilot**
PI(s): Brian Rood, MD, Children's National Health System;
Adam Resnick, PhD, Children's Hospital of Philadelphia

Project Title: **Immunogenomic Landscape of Pediatric Cancers**
PI(s): Trevor Pugh, PhD, FACMG, University Health Network

Project Title: **Genetic Polymorphisms and Neurocognitive Outcomes in Pediatric Brain Tumor Survivors**
PI(s): Julie Baran, MS, Children's Hospital of Philadelphia

Project Title: **Comparison of Clinical Targeted Next Generation Sequencing (NGS) in FFPE With Whole Genome Sequencing (WGS) of Snap-frozen Pediatric Brain Tumors**
PI(s): Bonnie Cole, MD, Seattle Children's Hospital

Project Title: **Cancer Predisposition in Pediatric Brain Tumors**
PI(s): Suzanne MacFarland, MD, Children's Hospital of Philadelphia

Project Title: **Cracking the Histone Code: Characterizing Pediatric Brain Tumor Epigenetics Using Cerebrospinal Fluid**
PI(s): Daphne Li, MD, FAAP, Ann & Robert H. Lurie Children's Hospital of Chicago

Project Title: **Identifying New Cell Surface Targets for Immunotherapy Treatment of Poor Prognosis Pediatric Brain Tumors**
PI(s): Misty Jenkins, BSc, PhD, Walter and Eliza Hall Institute of Medical Research

Project Title: **Detection of Cooperative and Mutually Exclusive Genetic Alterations in Pediatric Cancer**
PI(s): Patrick Kemmeren, PhD, Princess Máxima Center for Pediatric Oncology

Project Title: **Characterizing the Prevalence of ETMR by Molecular Signature**
PI(s): Derek Hanson, MD, Hackensack University Medical Center

Project Title: **Deciphering the Molecular Characteristics of Pediatric Meningiomas**
PI(s): Nadia Dahmane, PhD, Weill Cornell Medicine

Project Title: **Integrative Functional Genomics of Recurrent Childhood Medulloblastoma**
PI(s): Javad Nazarian, PhD, MSc, Children's National Health System

Project Title: **Comprehensive Genomic and Immune Signature Profiling of Ependymoma and Diffuse Intrinsic Pontine Gliom**a
PI(s): Katherine Schieffer, PhD, Stephanie LaHaye, PhD, Nationwide Children's Hospital

PCLRU RESEARCH PROJECTS

Project Title: **Liquid Biopsy in Monitoring and Prognosis for Pediatric Brain Tumors**
PI(s): Mateusz Koptyra, PhD, Adam Resnick, PhD, Children's Hospital of Philadelphia

Project Title: **Identifying and Elucidating the Function of Novel Gene Fusion Mutations Prevalent in Pediatric Solid Cancers along with Development of Potent Therapies Against Gene Fusion-driven Pediatric Brain and Other Solid Tumors**
PI(s): Payal Jain, PhD, Adam Resnick, PhD, Children's Hospital of Philadelphia

Project Title: **Understanding the Mechanism of Co-existing Mutations in the Development and Tumorigenesis of Neurofibromatosis (NF1) Associated Pediatric Low-grade Gliomas**
PI(s): Poonam Sonawane, PhD, Adam Resnick, PhD, Children's Hospital of Philadelphia

Project Title: **Functional Characterization and Effective Targeting of NRF1-BRAF and ATG7-RAF1 Fusions Identified in Anaplastic Pleomorphic Xanthoastrocytoma Patients Without BRAF p.V600E Mutation**
PI(s): Poonam Sonawane, PhD, Adam Resnick, PhD, Children's Hospital of Philadelphia

Project Title: **Immunotherapy in Brain Tumors**
PI(s): Jessica Foster, MD, and Adam Resnick, PhD, Children's Hospital of Philadelphia

DAMEU ANALYSIS PROJECTS

Project Title: **AACR Project Genomics Evidence Neoplasia Information Exchange (GENIE)**
PI(s): Marilyn Li, MD, Adam Resnick, PhD, Children's Hospital of Philadelphia
Analysis Team: Mahdi Sarmady, PhD, Pichai Raman, PhD, Yuankun Zhu, Bo Zhang, Children's Hospital of Philadelphia

Project Title: **OPEN DIPG WGS/RNA-seq Analysis of Midline Glioma and DIPG**
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia;
Javad Nazarian, PhD, MSC, Children's National Health System
Analysis Team: Pichai Raman, PhD, Yuankun Zhu, Bo Zhang, Children's Hospital of Philadelphia

Project Title: **GPC2 as an Immunotherapeutic Target in Medulloblastoma and Other Pediatric Brain Tumors**
PI(s): Kristopher Bosse, MD, Jessica Foster, MD, Children's Hospital of Philadelphia
Analysis Team: Pichai Raman, PhD, Yuankun Zhu, Bo Zhang, Children's Hospital of Philadelphia

Project Title: **Children's Brain Tumor Tissue Consortium Pediatric Brain Tumor Proteomics Pilot**
PI(s): Brian Rood, MD, Children's National Health System;
Adam Resnick, PhD, Children's Hospital of Philadelphia
Analysis Team: Pichai Raman, PhD, Yuankun Zhu, Children's Hospital of Philadelphia

Project Title: **Pediatric Medulloblastoma Cell Lines: Using WGS Sequencing to Understand How the Mutation Landscape Changes Between a Primary Tumor Sample and a Derived Cell Line**
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia
Analysis Team: Pichai Raman, PhD, Yuankun Zhu, Bo Zhang, Children's Hospital of Philadelphia

DAME UNIT ANALYSIS PROJECTS (*CONT.*)

Project Title: **PNOC 003 Diffuse Intrinsic Pontine Glioma Clinical Feasibility: Analyzing the Difference Between Whole Exome Data Generated as Part of a Clinical Trial with the Research of Whole Genome and RNA-seq to Evaluate the Potential Benefits of Utilizing Whole Genome and RNA-seq as Part of a Clinical Trial**
PI(s): Sabine Mueller, MD, PhD, University of California, San Francisco;
Adam Resnick, PhD, Children's Hospital of Philadelphia
Analysis Team: Pichai Raman, PhD, Komal Rathi, MS, Yuankun Zhu, Bo Zhang,
Children's Hospital of Philadelphia

Project Title: **TERT Analysis: Work with Kristina Cole on Analysis of Telomerase and its Role in Pediatric Cancers, Specifically Glioma**
PI(s): Adam Resnick, PhD, Kristina Cole, MD, PhD, Children's Hospital of Philadelphia
Analysis Team: Pichai Raman, PhD, Krutika Gaonkar, MS, Yuankun Zhu, Bo Zhang,
Children's Hospital of Philadelphia

Project Title: **22q Deletion Syndrome Data Analysis: Work with the Center of Mitochondrial and Epigenomic Medicine (CMEM) on the WGS Germline Analysis of 500 Patients with 22.11q Deletion Syndrome. Developed a Customized Mitochondrial Analysis Pipeline for This Study**
PI(s): Stewart Anderson, MD, Adam Resnick, PhD, Children's Hospital of Philadelphia
Analysis Team: Pichai Raman, PhD, Larry Singh, PhD, Yuankun Zhu, Bo Zhang,
Children's Hospital of Philadelphia

Project Title: **Mutation Detection for NF1 Patients: Work with Preclinical Unit to Identify Common and Top Mutations and Gene-fusions from NF1 Patients**
PI(s): Adam Resnick, PhD, Michael Fisher, MD, Children's Hospital of Philadelphia
Analysis Team: Pichai Raman, PhD, Komal Rathi, MS, Children's Hospital of Philadelphia

Project Title: **Pediatric Brain Tumor Atlas**
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia
Analysis Team: Pichai Raman, PhD, Yiran Guo, PhD, Larry Singh, PhD, Yuankun Zhu,
Children's Hospital of Philadelphia

Project Title: **Circulating Tumor DNA: Evaluating Somatic Mutations and Copy Number Alterations by Comparing the Plasma WGS data with Tumor WGS Data**
PI(s): Adam Resnick, PhD, Mateusz Koptyra, PhD, Children's Hospital of Philadelphia
Analysis Team: Pichai Raman, PhD, Children's Hospital of Philadelphia

Project Title: **Neoantigen Workflow and Data Analysis: Based on the Current CBTTC Somatic Mutations and Structural Variations, Generate the Changed Peptide Sequence to Predict Patient-specific Neoantigens**
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia
Analysis Team: Pichai Raman, PhD, Children's Hospital of Philadelphia

Project Title: **RNA-Seq fusion studies: An RNA-Seq Fusion Pipeline and an Annotation/ Ranking System for the Fusion Candidates**
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia
Analysis Team: Pichai Raman, PhD, Komal Rathi, MS, Nick Chimicles, Payal Jain, PhD
Children's Hospital of Philadelphia

DAMEU ANALYSIS PROJECTS (*CONT.*)

Project Title: **Open DIPG/Tumor Extension/Thalamic: Bringing Together DIPG and Closely Related Brain Tumors with Sequencing Analysis to Gain Better Insight into DIPG**
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia;
Javad Nazarian, PhD, MSC, Children's National Health System
Analysis Team: Pichai Raman, PhD, Krutika Gaonkar, MS, Children's Hospital of Philadelphia

Project Title: **HDAC Inhibitors**
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia
Analysis Team: Pichai Raman, PhD, Children's Hospital of Philadelphia

Project Title: **Disease Express: miRNA Analysis Establishing a Common mRNA Analytic Platform**
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia
Analysis Team: Pichai Raman, PhD, Yiran Guo, PhD, Larry Singh, PhD, Mateusz Koptyra, PhD, Children's Hospital of Philadelphia

Project Title: **The Role of ACVR1 in DIPG**
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia
Analysis Team: Pichai Raman, PhD, Abby Menschik, Children's Hospital of Philadelphia

Project Title: **Mates - Medulloblastoma Classifier**
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia
Analysis Team: Pichai Raman, PhD, Children's Hospital of Philadelphia

Project Title: **Proteomics/CPTAC: Clustering Transcriptome and Proteomics Data and Correlating to Disease, Genetic Lesions**
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia
Analysis Team: Pichai Raman, PhD, Children's Hospital of Philadelphia

Project Title: **DGD Tumor Pan Cancer Analysis**
PI(s): Adam Resnick, PhD, Mahdi Sarmady, PhD, Children's Hospital of Philadelphia
Analysis Team: Pichai Raman, PhD, Komal Rathi, MS, Children's Hospital of Philadelphia

Project Title: **Immune Component of Medulloblastoma Tumors**
PI(s): Adam Resnick, PhD, Mai T. Dang, MD, PhD, Children's Hospital of Philadelphia
Analysis Team: Pichai Raman, PhD, Krutika Gaonkar, MS, Children's Hospital of Philadelphia

Project Title: **ERAP1/TAP1**
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia; Robert Wechsler-Reya, PhD, University of California, San Diego
Analysis Team: Pichai Raman, PhD, Children's Hospital of Philadelphia

Project Title: **IDO1 Analysis Across Pediatric and Adult Tumors**
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia; Derek Wainwright, PhD, Ann & Robert H. Lurie Children's Hospital of Chicago
Analysis Team: Pichai Raman, PhD, Krutika Gaonkar, MS, Komal Rathi, MS, Children's Hospital of Philadelphia

DAME UNIT ANALYSIS PROJECTS (*CONT.*)

Project Title: **Target Identification and Modeling of NF1-associated Low-Grade Glioma**
PI(s): Michael Fisher, MD, Children's Hospital of Philadelphia

Project Title: **Evaluation of Immunosignature Profile in Medulloblastoma**
PI(s): Mateusz Koptyra, PhD, Children's Hospital of Philadelphia

Project Title: **Targeting Replicative Stress in Pediatric Brain Tumors with ALT**
PI(s): Kristina Cole, MD, Children's Hospital of Philadelphia

Project Title: **Development of the Ganglioside GD2 as a Biomarker and Clinical Trial Endpoint for Childhood Cancers**
PI(s): Frank Balis, MD, Children's Hospital of Philadelphia

Project Title: **Molecular Analysis of the Cellular Ecosystem of Childhood Ependymoma**
PI(s): Pablo González-Cámara, PhD, University of Pennsylvania

Project Title: **Exploration of IDO1 as a Therapeutic Target in Pediatric Central Nervous System Tumors**
PI(s): Rishi Lulla, MD, Ann & Robert H. Lurie Children's Hospital of Chicago

Project Title: **Epigenetic Basis of Gender Differences in Pediatric GBM**
PI(s): Sheng Li, PhD, Weill Cornell Medicine

Project Title: **Immune Component of Medulloblastoma Tumors**
PI(s): Mateusz Koptyra, PhD, Children's Hospital of Philadelphia
Analysis Team: Pichai Raman, PhD, Krutika Gaonkar, MS, Mai T. Dang, MD, PhD, Children's Hospital of Philadelphia

Project Title: **ENT Data Analysis**
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia
Analysis Team: Pichai Raman, PhD, Children's Hospital of Philadelphia

IMPACT PHASE: DISCOVERIES AND NEW CLINICAL THERAPEUTICS

Zamiyha, 23, was diagnosed at age 4 with a very rare, aggressive brain tumor called an atypical teratoid rhabdoid tumor (AT/RT). Then, as a young adult, with a toddler of her own, she was diagnosed with a bone marrow cancer — and she once again came to CHOP for treatment.

D³b is harnessing the speed and volume at which knowledge is gained through the *D³b Research Methodology*, by applying these methods to each collaborative research project conducted in the D³b Center.

This process spans across different data types, diseases, and ages, to allow for accelerated impact in the care of children diagnosed with cancer and other diseases throughout the world. In the brief three year history since the launch of the D³b Center, D³b has constructed the necessary foundation and framework to accelerate translational impact, while continuing to gain a more complete understanding of disease mechanisms across each unique brain tumor type.

The projects listed in this section provide a high-level cross-section of D³b's current translational focus areas and provide insights into the accelerated volume of discoveries made possible by the recently-launched data of the PBTA and platforms for worldwide, collaborative research.

Highlighted in this section, D³b's research programs are improving clinical impact for disease types including Low-grade Gliomas, High-grade Gliomas, Diffuse Intrinsic Pontine Gliomas, and Craniopharyngiomas, in addition to other pediatric conditions. The data generated from samples of these tumors are paired with the information collected from hypothesis-driven research, which results in a more comprehensive knowledge of how to treat and target disease in children.

From this knowledge, D³b is working to deliver new clinical trials and potential therapeutics to ease suffering and save lives of children. Through partnerships within the healthcare community, as well as pharmaceutical, government, industry, foundations, and patients/families, this impact is being amplified and felt across the globe.

RESEARCH HIGHLIGHTS

PEDIATRIC LOW-GRADE GLIOMA (LGG) RESEARCH PROGRAM

A DATA-DRIVEN APPROACH: GENE FUSIONS

Low-grade Astrocytomas are the most common cancer of the central nervous system in children. They represent a heterogeneous group of tumors that can be discovered anywhere within the brain or spinal cord. Although surgical removal may be curative, up to 20% of children still suffer from the effects of a tumor, which may result in higher rates of morbidity and mortality. The available treatment options for children are limited in recurrent and/or disseminated, or circulated tumors, as well as those with tumors not suited for surgical removal. To date, this significant, un-met need for more effective, targeted therapeutics for children with unremovable or progressive Astrocytomas has not yet been satisfied.

Early Low-grade glioma research efforts at D³b began with the generation and integration of genomic and molecular data for the identification of molecular markers found in these particular tumor types. The processed data and information were then used within the laboratory to understand the biological mechanisms of Low-grade Gliomas. This is a new, collaborative approach to develop new therapies and initiate new clinical trials based upon improved therapeutic strategies for children with Low-grade Gliomas.

The D³b laboratory's efforts led by Adam Resnick, PhD, Angela Waanders, MD, MPH, Shih-Shan Lang Chen, MD and Payal Jain, PhD, made progress in utilizing this model by producing results in the identification of novel gene-fusion therapeutic targets. One active clinical trial was initiated, with an additional two in development. These clinical trials are providing an outlined therapeutic strategy for patients diagnosed with a Low-grade Glioma based on their molecular profile, providing the first, early steps towards a precision medicine approach for Low-grade Gliomas. The data collected from these trials is being used to create the largest-available, paired-omic dataset, with available biospecimens now accessible through the Kids First, Cavatica, and PedcBioPortal platforms.

These efforts in LGG research, which have spanned across ten years, emphasize the need to uncover more effective solutions to accelerate

Lamiya Tauhid, MS, a research technician in the D³b Preclinical Laboratory Research Unit, transports biospecimen samples for further analysis in the lab.

discoveries into clinical impact. Through these large-scale, collaborative endeavors, the D³b Center is optimizing CHOP's resources and strategic initiatives to benefit more than a single laboratory at a time. Thanks to pioneering efforts like the CBTTC, collaborations have resulted in a multi-institutional initiative to collate clinical data, biospecimens and generated multi-omics data, and then share that data to empower researchers across the globe. The foundational efforts of the CBTTC are providing researchers to the resources, data, and biospecimens they need to allow them to form and test hypotheses with immediacy, significantly reducing the years of work and funding that were previously required to generate data using the traditional research model. Researchers can now access rich collections of "multi-omics" data, along with curated clinical/phenotypic datasets.

Through the *D³b Research Methodology*, translational laboratory efforts are rapidly expanding into molecularly based clinical trials, like those performed by the Pacific Pediatric Neuro-Oncology Consortium (PNOC). In addition, the continued development of tools such as the Gabriella Miller Kids First Data Resource Portal, Cavatica, and PedcBioPortal are empowering researchers to accomplish more than was previously possible. These platforms support collections of large-scale, raw and harmonized, clinical, and genomic data within a cost efficient, secure, analytic, cloud-based, collaborative environment for cross-disease research.

D³b's Low-grade Glioma Program has produced a number of novel discoveries, by improving the processes used to identify new therapeutic targets in pediatric Low-grade Gliomas. This work has resulted in precision therapies such as MAPK-targeted inhibition (as a standard of care), as well as defining treatment approaches which may inadvertently harm children who possess certain gene fusions; being treated with drugs such as Sorafenib and Vemurafenib. These developments underscore the importance of Low-grade Glioma research, which will remain a focus for D³b-led research projects and preclinical research initiatives.

AVAILABLE LOW-GRADE GLIOMA DATA AND BIOSPECIMENS

Includes 256 CBTTC-enrolled Low-grade Glioma subjects with 3,063 files/88.35 Terabytes of 60x whole-genome sequencing with paired RNA-seq, with a subset of total and phospho proteomics, clinically annotated with treatment and outcome data with matched available biospecimens. Additional non-CBTTC Low-grade Glioma data from collaborating investigators available on PedcBioPortal.

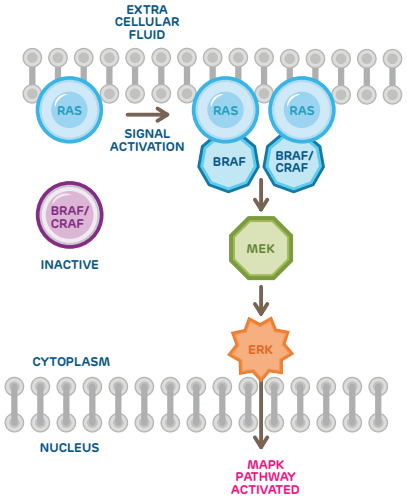
View & query LGG clinical and omic data on the Kids First Portal

View & Analyze data PedcBioPortal:

View & Analyze raw genomic data on Cavatica:

Apply for raw genomic access via the CBTTC Data Access Form

BRAF AND CRAF ACTIVATE THE MAPK PATHWAY VIA DIMERIZATION



PNOC CLINICAL TRIALS

PNOC 001: **Phase II Study of Everolimus for Recurrent or Progressive Low-grade Gliomas in Children**
Status: Available

PNOC Concept: **Combinatorial Targeting of MEK & mTOR in Pediatric Low-grade Gliomas**
Status: In development at Children's Hospital of Philadelphia & Children's National Health System

PNOC Concept: **Type-2 BRAF Inhibitors as Potent Inhibitors for BRAF-fusions in Low-grade Gliomas**
Status: In development by Dana Farber Cancer Institute

BIOSPECIMEN PROJECTS INCLUDING LOW-GRADE GLIOMA

Project 0001: **Whole Genome Sequencing of Low-grade Glioma and Ganglioglioma**
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia

Project 0005: **Exploration of IDO1 as a Therapeutic Target in pCNS Tumors**
PI(s): Rishi Lulla, MD, Ann & Robert Lurie Children's' Hospital of Chicago; Derek Wainwright, PhD, Craig M. Horbinski, MD, PhD, Northwestern University Feinberg School of Medicine

Project 0010: **Target Identification and Modeling of NF1-associated Low-grade Glioma**
PI(s): Michael Fisher, MD, Children's Hospital of Philadelphia

Project 0012: **Pediatric Brain Tumor Atlas Initiative**
PI(s): Children's Brain Tumor Tissue Consortium

Project 0016: **Comprehensive Molecular Analysis of Pediatric Thalamic Tumors**
PI(s): Heloisa Moser, MD Susanne Yoon, MD, Madhuri Kambhampati, MS, Sridevi Yadavilli, MD, PhD, Children's National Health System, Angela Waanders, MD, MPH, Adam Resnick, PhD, Children's Hospital of Philadelphia, Roger Packer, MD, Javad Nazarian, PhD, MSc, Children's National Health Center

Project 0023: **Kids First – CBTTC Proteogenomic Pilot Project**
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia, Brian Rood, MD, Children's National Health System

D³b COLLABORATIVE RESEARCH

Kentucky Cancer Census Brain Tumor Project in Low-grade Glioma
PI(s): Eric Durbin, DrPH, MS, Tom Badgett, MD, PhD, W. Jay Christian, PhD, MPH Chunyan He, ScD, Bin Huang, DrPH, Jong Cheol Jeong, PhD, Thomas C. Tucker, PhD, University of Kentucky

DATA PROJECTS INCLUDING LOW-GRADE GLIOMA

Project 0004: **IDO1 Expression With All the CBTTC RNA-Seq Data**
PI(s): Derek Wainwright, PhD, Northwestern University Feinberg School of Medicine

Project 0012: **Defining the Mutational Landscape of Pediatric Brain Tumors**
PI(s): Sharon Diskin, PhD, Children's Hospital of Philadelphia

Project 0014: **Fusion Analysis in CBTTC RNA-seq Data**
PI(s): Rohan Bareja, Weill Cornell Medicine

Project 0015: **Cooperating Mutations in Brain Tumors of Patients with NF1**
PI(s): Thomas De Raedt, PhD, Children's Hospital of Philadelphia

D³b CENTER LOW-GRADE GLIOMA PUBLICATIONS

Based on collaborative efforts to identify novel therapeutic targets through preclinical research. A full publication list can be found in the appendix of this report.

Bandopadhayay, Pratiti, Lori A. Ramkissoon, **Payal Jain**, Guillaume Bergthold, Jeremiah Wala, Rhamy Zeid, Steven E. Schumacher, Laura Urbanski, Ryan O'Rourke, William J. Gibson, Kristine Pelton, Shakti H. Ramkissoon, **Harry J. Han**, **Yuankun Zhu**, **Namrata Choudhari**, Amanda Silva, **Katie Boucher**, Rosemary E. Henn, Yun Jee Kang, David Knoff, Brenton R. Paolella, Adrianne Gladden-Young, Pascale Varlet, Melanie Pages, Peleg M. Horowitz, Alexander Federation, Hayley Malkin, Adam A. Tracy, Sara Seepo, Matthew Ducar, Paul Van Hummelen, **Mariarita Santi**, Anna Maria Buccoliero, Mirko Scagnet, Daniel C. Bowers, Caterina Giannini, Stephanie Puget, Cynthia Hawkins, Uri Tabori, Almos Klekner, Laszlo Bognar, Peter C. Burger, Charles Eberhart, Fausto J. Rodriguez, D. Ashley Hill, Sabine Mueller, Daphne A. Haas-Kogan, Joanna J. Phillips, Sandro Santagata, Charles D. Stiles, James E. Bradner, Nada Jabado, Alon Goren, Jacques Grill, Azra H. Ligon, Liliana Goumnerova, **Angela J. Waanders**, **Phillip B. Storm**, Mark W. Kieran, Keith L. Ligon, Rameen Beroukhim, and **Adam C. Resnick**. 2016. 'MYB-QKI rearrangements in angiocentric glioma drive tumorigenicity through a tripartite mechanism', *Nature Genetics*, 48: 273-82.

Jones, D. T. W., M. W. Kieran, E. Bouffet, S. Alexandrescu, P. Bandopadhayay, M. Bornhorst, D. Ellison, J. Fangusaro, M. J. Fisher, N. Foreman, M. Fouladi, D. Hargrave, C. Hawkins, N. Jabado, M. Massimino, S. Mueller, G. Perilongo, A. Y. N. Schouten van Meeteren, U. Tabori, K. Warren, **A. J. Waanders**, D. Walker, W. Weiss, O. Witt, K. Wright, **Y. Zhu**, D. C. Bowers, S. M. Pfister, and R. J. Packer. 2018. 'Pediatric Low-grade Gliomas: next biologically driven steps', *Neuro-oncology*, 20: 160-73.

Jain, Payal, Lea F. Surrey, **Joshua Straka**, Minjie Luo, Fumin Lin, Brian Harding, **Adam C. Resnick**, **Phillip B. Storm**, Anna Maria Buccoliero, **Mariarita Santi**, **Marilyn M. Li**, and **Angela J. Waanders**. 2018. 'Novel FGFR2-INA fusion identified in two low-grade mixed neuronal-glial tumors drives oncogenesis via MAPK and PI3K/mTOR pathway activation', *Acta Neuropathologica*, 136: 167-69.

Jain, P., T. M. Fierst, **H. J. Han**, **T. E. Smith**, A. Vakil, **P. B. Storm**, **A. C. Resnick**, and **A. J. Waanders**. 2017. 'CRAF gene fusions in pediatric Low-grade Gliomas define a distinct drug response based on dimerization profiles', Oncogene, 36: 6348.

Jain, P., A. Silva, **H. J. Han**, S. S. Lang, **Y. Zhu**, **K. Boucher**, **T. E. Smith**, A. Vakil, **P. Diviney**, **N. Choudhari**, **P. Raman**, C. M. Busch, T. Delaney, X. Yang, A. K. Olow, S. Mueller, D. Haas-Kogan, E. Fox, **P. B. Storm**, **A. C. Resnick**, and **A. J. Waanders**. 2017. 'Overcoming resistance to single-agent therapy for oncogenic BRAF gene fusions via combinatorial targeting of MAPK and PI3K/mTOR signaling pathways', *Oncotarget*, 8: 84697-713.

Jain, Payal, Tamara Fierst, **Harry Han**, **Tiffany Smith**, **Phillip B. Storm**, **Angela J. Waanders**, and **Adam C. Resnick**. 2017. 'PDTM-40. Pediatric Low-grade Gliomas with craf gene fusions are therapeutically distinct from braf-fusions based on dimerization mediated by n-terminal fusion partner', Neuro-oncology, 19: vi198-vi98.

Liu, Kevin X., Sabine Mueller, Rogier Dik, Xiaodong Yang, Steven DuBois, **Angela J. Waanders**, **Adam C. Resnick**, William A. Weiss, and Daphne Haas-Kogan. 2017. 'EXTH-58. Effects of Torc1/2 Inhibitor mln0128 Alone and in Combination with Mek Inhibition in BRAF Mutated Glioma Models in Vitro and in Vivo', Neuro-oncology, 19: vi85-vi86.

Han, Harry J., **Payal Jain**, and **Adam C. Resnick**. 2018. 'Shared ACVR1 mutations in FOP and DIPG: Opportunities and challenges in extending biological and clinical implications across rare diseases', Bone, 109: 91-100.

LOW-GRADE GLIOMA PUBLICATIONS (*CONT.*)

Touat, Mehdi Touat, Nadia Younan, Philipp Euskirchen, Maxime Fontanilles, Karima Mokhtari, Caroline Dehais, Patrick Tilleul, Amithys Rahimian-Aghda, **Adam Resnick**, Anne-Paule Gimenez-Roqueplo, Helene Blons, Khˆe Hoang-Xuan, Jean-Yves Delattre, Ahmed Idbaih, Pierre Laurent-Puig, and Marc Sanson. 'Successful Targeting of the RAF1 Gene Fusion in Anaplastic Pleomorphic Xanthoastrocytoma With Leptomeningeal Dissemination', JCO Precision Oncology. Pending review, February 2019.

Talk Title: **'Targeted Therapy Approaches and Resistance Mechanisms for Pediatric Low-grade Gliomas with Activated RAF Gene Fusions'**
Presenter Author: Payal Jain, PhD
Meeting: 14th Asian Society for Neuro-Oncology (ASNO), October 28-31, 2017. Osaka, Japan

Abstract: **'Pediatric Low-Grade Gliomas with CRAF Gene Fusions are Therapeutically Distinct from BRAF-fusions Based on Dimerization Mediated by N-terminal Fusion Partner'**
Presenting Author: Payal Jain, PhD, Children's Hospital of Philadelphia
Meeting: Neuro-Oncology Meeting (SNO), November 16-17, 2017, San Francisco, CA

CBTTC LOW-GRADE GLIOMA RESEARCH: ABSTRACTS AND PUBLICATIONS

Title: **'Comprehensive Molecular Analysis of Pediatric Thalamic Tumors'**. *Cancer Research*, 77 2017. Heloisa H. Moser, Susanne Yoon, Madhuri Kambhampati, Sridevi Yadavilli, Angela J. Waanders, Adam Resnick, Roger J. Packer and Javad Nazarian (CBTTC Project 016)

Abstract: **'Pediatric Brain Tumor Atlas (CBTTC Project 001, 0012)'**
Authors: Pichai Raman, PhD, Javad Nazarian, PhD, MSC, Rishi Lulla, Adam Resnick, PhD, Angela Waanders, MD, MPH, Phillip B. "Jay" Storm, MD
Meeting: AACR 2019, In review

Abstract: **'Kids First – CBTTC Proteogenomic Pilot Project (CBTTC Project 023)'**
Meeting: Peds SNO 2019 Publication: Pending Submission

Abstract: Lenzen, Alicia, Derek Wainwright, Erik Ladomersky, Kristen Lauing, Lijie Zhai, Komal Rathi, Pichai Raman, Rishi Lulla, and Rintaro Hashizume. 2018. **'PDTM-10. Novel RNA-targeting Strategy for Treating T-cell Driven Immunosuppression in Human Diffuse Intrinsic Pontine Glioma'**, *Neuro-Oncology*, 20: vi205-vi06.

LOW-GRADE GLIOMA SPONSORED RESEARCH

NIH R01 NS085336-05 07/01/14-04/30/19 $1,837,500
Pediatric Low-grade Glioma: Biology and Molecular Targeting
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia

NIH R01 NS091620-03 09/30/15-07/31/20 $904,343
Precision Medicine for Pediatric Low-grade Gliomas
PI(s): Daphne Haas-Kogan, MD, Boston Children's Hospital; Adam Resnick, PhD, Children's Hospital of Philadelphia

Children's Tumor Foundation 12/01/15-05/13/19 $466,299
Synodos Low-grade Glioma
PI(s): Michael Fisher, MD, Angela Waanders, MD, MPH, Adam Resnick, PhD, Children's Hospital of Philadelphia

LOW-GRADE GLIOMA SPONSORED RESEARCH (*CONT.*)

NIH HHS N261200800001E 04/01/18-09/25/20 $55,342
CPTAC III Proteomics in AYA and Adult LGG (opening)
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia

NCI CPTAC Proteomics Pilot 07/01/17-07/31/18 $50,000
The goal of this project is to generate proteomics data in the pediatric brain tumor population - 250 subjects with matched WGS/RNAseq data were selected to have proteomics data generated
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia

NIH 3U2C HL138346-01S2 09/26/17-05/31/19 $1,800,000
U2C Kids First Admin Supplement – cloud-based data storage and compute
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia

NIH 3U2C HL138346-02S2 09/01/18-05/31/19 $957,570
U2C Kids First Admin Supplement – cloud resources
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia

Thea's Star of Hope - $30,000
• Title: Identifying and Elucidating the Function of Novel Gene Fusion Mutations Prevalent in Pediatric Solid Cancers Along with Development of Potent Therapies Against Gene Fusion-driven Pediatric Brain and Other Solid Tumors.
• Title: Understand the Role of NF1 Mutations in Pediatric Optic Gliomas
• Title: Understand the Mechanism of Co-existing Mutations in the Development and Tumorigenesis of Neurofibromatosis (NF1)-Associated Pediatric Low-grade Gliomas

Genuardi Family Foundation - $50,000
Low-grade Glioma (LGG) Research Fund

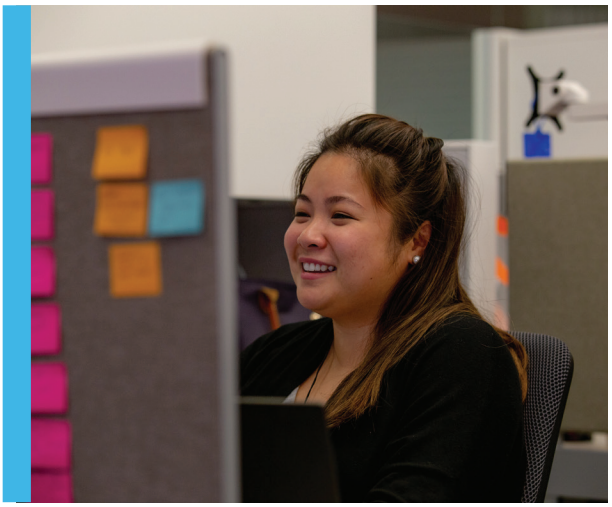
HIGH-GRADE GLIOMA PHILANTHROPIC RESEARCH SUPPORT

High-grade Gliomas (HGG) in children nearly always result in a dismal prognosis. Although novel therapeutic approaches are currently in development, preclinical testing has been limited, due to a lack of pediatric-specific HGG preclinical models. These models are needed to help test the effectiveness of different drug types in the laboratory.

Medical advances over the last 40 years have increased the survival rates for many types of childhood cancers. However, the prognosis for patients diagnosed with a Diffuse Intrinsic Pontine Glioma (DIPG) has not improved. These highly-aggressive brain tumors defy treatment and have a 98% mortality rate, typically within nine months of a diagnosis. Located in the area of the brainstem that controls a child's breathing, blood pressure, heart rate, and other vital functions, DIPG tumors cannot be removed through surgery.

Project Open DIPG, led by Drs. Adam Resnick PhD of D³b and Javad Nazarian PhD, MSC of Children's National Health System, is a global collaboration supported by the Pacific Pediatric Neuro-Oncology Consortium (PNOC) and the Children's Brain Tumor Tissue Consortium (CBTTC), to empower discovery of improved treatments for children diagnosed with Diffuse Intrinsic Pontine Gliomas (DIPG). Open DIPG is targeting these highly-aggressive brain tumors through a system of data-driven clinical trials and innovative research techniques. The project is also leveraging the strength of these two consortia' combined-global network of 37 member institutions to race toward discoveries, innovations, and effective treatment strategies for this difficult-to-treat form of cancer.

Using a "team science" approach, Project Open DIPG is building upon PNOC's expanding clinical portfolio and CBTTC's expertise in collecting and analyzing biospecimen-driven research data.



Judy Palma, BS, a clinical research coordinator in the Clinical Research Unit, supports multiple, investigator-initiated, clinical research protocols and studies.

The project is collating and releasing newly-generated, DIPG-omic and clinical data, including liquid profiling of cerebrospinal fluid (CSF) and plasma, DNA methylation, copy-number variation (CNV), proteomics, whole-genome sequencing (WGS), whole-exome sequencing (WES), and RNA-seq from individual investigator labs and consortia efforts on a rapid, pre-embargo release cycle. To date, 838 clinical research subjects have been enrolled with corresponding biospecimens collected.

The D³b High-grade Glioma Program, in partnership with PNOC, has identified several novel discoveries of new therapeutic targets, including four active clinical trials. This largest-available collection of High-grade Glioma data includes clinical, paired-omic data, and biospecimen samples, and is available through the Kids First Data Resource Portal, Cavatica, and PedcBioPortal platforms. HGG research will remain a focus for D³b through the implementation of CBTTC and preclinical research projects.

AVAILABLE HIGH-GRADE GLIOMA DATA & SPECIMEN SAMPLES

CBTTC High-grade Glioma subjects with 1,390 files/35.18 Terabytes of 60x whole genome sequencing harmonized to 38 with paired RNA-seq, with a subset of total and phospho proteomics clinically annotated with treatment and outcome data with matched available biospecimens. 26 HGG cell lines. Additional non-CBTTC HGG data from collaborating investigators and TCGA harmonized available on PedcBioPortal.

⦿ View & Query LGG Clinical and Omic Data on the Gabriella Miller Kids First Portal

⦿ View & Analyze data on PedcBioPortal

⦿ View & Analyze raw genomic data on Cavatica

⦿ Applying for Raw Genomic Access

AVAILABLE DIPG DATA & SPECIMEN SAMPLES

CBTTC Diffuse Intrinsic Pontine Glioma subjects with 140 files / 2.84 Terabytes of 60x whole genome sequencing harmonized to 38 with paired RNA-seq, with a subset of total and phospho proteomics clinically annotated with treatment and outcome data with matched available biospecimens. 13 cell lines from collaborators. Additional non-CBTTC DIPG data from collaborating investigators and TCGA harmonized available on PedcBioPortal.

⦿ View & Query LGG clinical and omic data Kids First Portal

⦿ View & analyze data on PedcBioPortal

⦿ View & analyze raw genomic data on Cavatica

⦿ Apply for raw genomic access via the CBTTC Data Access Form

HIGH-GRADE GLIOMA & DIPG CLINICAL TRIALS

PNOC 003: Molecular Profiling for Individualized Treatment Plan for DIPG

PNOC 008: A Pilot Trial Testing the Clinical Benefit of Using Molecular Profiling to Determine an Individualized Treatment Plan in Children and Young Adults with High-grade Glioma (Excluding Diffuse Intrinsic Pontine Glioma)

PNOC 015: MTX110 by Convection-Enhanced Delivery in Treating Participants With Newly-Diagnosed Diffuse Intrinsic Pontine Glioma

PNOC 017: BGB-290 and Temozolomide in Treating Isocitrate Dehydrogenase (IDH) ½-Mutant Grade I-IV Gliomas

CBTTC BIOSPECIMEN RESEARCH PROJECTS

Project 0003 a,b,d: Genomic Evaluation of Malignant Pediatric Cortical Tumors

Project 0005: Exploration of IDO1 as a Therapeutic Target in pCNS Tumors

Project 0006: Epigenetic Basis of Gender Differences in Pediatric GBM

Project 0011: Targeting Replicative Stress in Pediatric Brain Tumors with ALT

Project 0012: Pediatric Brain Tumor Atlas

Project 0013 a,b: Gene Expression Analysis Platform Evaluation for FFPE Specimen Material-Based Studies

CBTTC BIOSPECIMEN RESEARCH PROJECTS (*CONT.*)

Project 0016: Comprehensive Molecular Analysis of Pediatric Thalamic Tumors

Project 0017: Integrated Genomic Analysis to Elucidate the Role of the PIK3CA and 10q LOH as Unique Drivers and Cooperating Events in Pediatric High-grade Gliomas

Project 0018: Development of the Ganglioside GD2 as a Biomarker and Clinical Trial Endpoint for Childhood Cancers

Project 0023: Kids First – CBTTC Proteogenomic Pilot Project

Project 0027: Cracking the Histone Code: Characterizing Pediatric Brain Tumor Epigenetics Using Cerebrospinal Fluid

Project 0028 - GPC2 As an Immunotherapeutic Target in Medulloblastoma and Other Pediatric Brain Tumors

CBTTC DATA RESEARCH PROJECTS

Project 0003 a,b,d: Analysis of Chromatin Pathways as Regulators of High-grade Glioma Gene Expression Patterns

Project 0005: Telomere Maintenance Across Multiple Brain Tumors

Project 0007: In Silico Neo-Antigen Detection in High-Grade Pediatric Brain Tumors Utilizing RNA-seq and WGS

Project 0011: Malignant Cortical Tumors

Project 0012: Pediatric Brain Tumor Atlas Initiative

Project 0016: Identification of Non-coding Drivers from Brain Tumour Genomes

Project 0017: Integrated Genomic Analysis to Elucidate the Role of the PIK3CA and 10q LOH as Unique Drivers and Cooperating Events in Pediatric High-grade Gliomas

Project 0023: Comparison of Clinical Targeted Next Generation Sequencing (NGS) in FFPE with Whole Genome Sequencing (WGS) of Snap-frozen Pediatric Brain Tumors

Project 0027: Identify Novel Therapeutic Targets and Biomarkers in Non-coding Genome of Pediatric Cancers

Project 0028: High-grade Glioma Cell Lines

HIGH-GRADE GLIOMA & DIPG-SPONSORED RESEARCH

NIH P30 CA016520-42S3 09/01/18-08/31/20 $399,877
Project HOPE: High-grade Glioma-Omics in Pediatric and AYA
Project Lead: Adam Resnick, PhD, Children's Hospital of Philadelphia

Kortney Rose Foundation 10/01/14-09/30/17 $100,000
Shared ACVR1 Mutations in FOP and DIPG: Opportunities and Challenges in Extending Biological and Clinical Models in Overcoming Resistance to Single-agent Therapy for Oncogenic BRAF Gene Fusions via Combinatorial Targeting Implications Across Rare Diseases

NIH HHS N261200800001E 04/01/18-09/25/20 $55,342
CPTAC III Proteomics in AYA and Adult
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia

NCI CPTAC Proteomics Pilot 07/01/17-07/31/18 $50,000
The goal of this project is to generate proteomics data in the pediatric brain tumor population - 250 subjects with matched WGS/RNAseq data were selected to have proteomics data generated
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia

CBTTC Advisory Council $5,000
HGG Defining Molecular Events Driving Biological Variation in Preclinical Models
PI: Mateusz Kopyrta, PhD, Children's Hospital of Philadelphia

PHILANTHROPIC SUPPORT: PROJECT OPEN DIPG INITIATIVE

Kortney Rose Foundation 10/01/15-ongoing $388,000
DIPG Multi-Institutional Collaborative PNOC/CBTTC
PI: Adam Resnick, PhD, Children's Hospital of Philadelphia

Dragon Master Foundation 07/01/17-06/30/20 $300,000
PNOC/CBTTC DIPG Clinical Trial
PI: Adam Resnick, PhD, Children's Hospital of Philadelphia

Pediatric Brain Tumor Foundation 04/15/18-04/14/19 $100,000
A Multidisciplinary Approach for the Development of New Therapeutic Strategies for DIPG and HGG in Children.
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia; Javad Nazarian, PhD, MSC, Children's National Health System; Benjamin A. Garcia, PhD, University of Pennsylvania; Eric Raabe, MD, PhD, Johns Hopkins University

Musella Foundation 02/01/17-08/31/18 $100,000
Comprehensive Genomic Characterization of DIPG Through a Shared Biorepository Architecture for Biospecimen collection and Curation.
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia; Javad Nazarian, PhD, MSC, Children's National Health System

PHILANTHROPIC HIGH-GRADE GLIOMA RESEARCH SUPPORT

CBTTC Advisory Council Research Projects $10,000

Templeton Family Fund
In support of the D³b Center's strategic research initiatives

D³b INVESTIGATOR RESEARCH PUBLICATIONS

Hoffman, Mary, AH Gillmor, DJ Kunz, M Johnston, A Nikolic, K Narta, M Zarrei, J King, K Ellestad, NF Dang, FMG Cavalli, MM Kushida, FJ Coutinho, **Y Zhu***, B Luu, Y Ma, AJ Mungall, R Moore, MA Marra, MD Taylor, TJ Pugh, PB Dirks, D Strother*,L Lafay-Cousin, **AC Resnick**, S Scherer, DL Senger, BD Simons, JA Chan, AS Morrissy, Marco Gallo. 2019. 'Intratumoral genetic and functional heterogeneity in pediatric glioblastoma'. Manuscript in press at *Cancer Research.*

Mueller, Sabine, **Payal Jain**, Winnie S. Liang, Lindsay Kilburn, Cassie Kline, Nalin Gupta, Eshini Panditharatna, Suresh N. Magge, **Bo Zhang**, **Yuankun Zhu**, John R. Crawford, Anu Banerjee, Kellie Nazemi, Roger J. Packer7, Claudia K. Petritsch, Nathalene Truffaux, Alison Roos, Sara Nasser, Joanna J. Phillips, David Solomon, Annette Molinaro, **Angela J. Waanders**, Sara A. Byron, Michael E. Berens, John Kuhn, Javad Nazarian, Michael Prados, **Adam C. Resnick** . 'Genomics Driven Feasibility Trial to Guide a Precision Medicine Approach for Children With Diffuse Intrinsic Pontine Glioma – A Report from the Pacific Pediatric Neuro-Oncology Consortium (PNOC).' Manuscript in press at *International Journal of Cancer*, February, 2019.

Hwang, Eugene, Javad Nazarian, Lindsay Kilburn, Roger Packer, Annette Molinaro, Anu Banerjee, Michael Prados, Nalin Gupta, Sabine Mueller, Theodore Nicolaides, **Adam Resnick**, Kellie Nazemi, Michael Berens, Sara Byron, Winnie Liang, John Kuhn, and John Crawford. 2018. 'DIPG-76. PNOC-003: Precision medicine trial for children with diffuses intrinsic pontine glioma: preliminary experience with multi-agent personalized therapy recommendations', *Neuro-Oncology*, 20: i64-i64.

Mackay, Alan, Anna Burford, Diana Carvalho, Elisa Izquierdo, Janat Fazal-Salom, Kathryn R. Taylor, Lynn Bjerke, Matthew Clarke, Mara Vinci, Meera Nandhabalan, Sara Temelso, Sergey Popov, Valeria Molinari, **Pichai Raman**, **Angela Waanders**, **Harry Han**, Saumya Gupta, Lynley Marshall, Stergios Zacharoulis, Sucheta Vaidya, Henry C. Mandeville, Leslie R. Bridges, Andrew J. Martin, Safa Al-Sarraj, Christopher Chandler, Ho-Keung Ng, Xingang Li, Kun Mu, Saoussen Trabelsi, Dorra H'mida-Ben Brahim, Alexei N. Kisljakov, Dmitry M. Konovalov, Andrew S. Moore, Angel Montero Carcaboso, Mariona Sunol, Carmen de Torres, Ofelia Cruz, Jaume Mora, Ludmila I. Shats, João N. Stavale, Lucas T. Bidinotto, Rui M. Reis, Natacha Entz-Werle, Michael Farrell, Jane Cryan, Darach Crimmins, John Caird, Jane Pears, Michelle Monje, Marie-Anne Debily, David Castel, Jacques Grill, Cynthia Hawkins, Hamid Nikbakht, Nada Jabado, Suzanne J. Baker, Stefan M. Pfister, David T. W. Jones, Maryam Fouladi, André O. von Bueren, Michael Baudis, **Adam Resnick**, and Chris Jones. 2017. 'Integrated Molecular Meta-Analysis of 1,000 Pediatric High-Grade and Diffuse Intrinsic Pontine Glioma', *Cancer Cell*, 32: 520-37.e5

Panditharatna, Eshini, Lindsay B. Kilburn, Mariam S. Aboian, Madhuri Kambhampati, Heather Gordish-Dressman, Suresh N. Magge, Nalin Gupta, John S. Myseros, Eugene I. Hwang, Cassie Kline, John R. Crawford, Katherine E. Warren, Soonmee Cha, Winnie S. Liang, Michael E. Berens, Roger J. Packer, **Adam Resnick**, Michael Prados, Sabine Mueller, and Javad Nazarian. 2018. 'Clinically Relevant and Minimally Invasive Tumor Surveillance of Pediatric Diffuse Midline Gliomas Using Patient-Derived Liquid Biopsy,' *Clinical Cancer Research*, 24: 5850-59.

Mackay, Alan, Anna Burford, Valeria Molinari, David T. W. Jones, Elisa Izquierdo, Jurriaan Brouwer-Visser, Felice Giangaspero, Christine Haberler, Torsten Pietsch, Thomas S. Jacques, Dominique Figarella-Branger, Daniel Rodriguez, Paul S. Morgan, **Pichai Raman**, **Angela Waanders**, **Adam Resnick**, Maura Massimino, Maria Luisa Garrè, Helen Smith, David Capper, Stefan M. Pfister, Thomas Würdinger, Rachel Tam, Josep Garcia, Meghna Das Thakur, Gilles Vassal, Jacques Grill, Tim Jaspan, Pascale Varlet, and Chris Jones. 2018. 'Molecular, Pathological, Radiological, and Immune Profiling of Non-brainstem Pediatric High-grade Glioma from the HERBY Phase II Randomized Trial', *Cancer Cell*, 33: 829-42.e5.

Pal, Sharmistha, David Kozono, Xiaodong Yang, Wojciech Fendler, Whitney Fitts, Jing Ni, John A. Alberta, Jean Zhao, Kevin X. Liu, Jie Bian, Nathalene Truffaux, William A. Weiss, **Adam Resnick**, Pratiti Bandopadhayay, Keith L. Ligon, Steven G. DuBois, Sabine Mueller, Dipanjan Chowdhury, and Daphne A. Haas-Kogan. 2018. 'Dual HDAC and PI3K Inhibition Abrogates NFkB- and FOXM1-Mediated DNA Damage Response to Radiosensitize Pediatric High-grade Gliomas', *Cancer Research*, 78: 4007-21.

D³b INVESTIGATOR RESEARCH PUBLICATIONS (*CONT.*)

Gröbner, Susanne N., Barbara C. Worst, Joachim Weischenfeldt, Ivo Buchhalter, Kortine Kleinheinz, Vasilisa A. Rudneva, Pascal D. Johann, Gnana Prakash Balasubramanian, Maia Segura-Wang, Sebastian Brabetz, Sebastian Bender, Barbara Hutter, Dominik Sturm, Elke Pfaff, Daniel Hübschmann, Gideon Zipprich, Michael Heinold, Jürgen Eils, Christian Lawerenz, Serap Erkek, Sander Lambo, Sebastian Waszak, Claudia Blattmann, Arndt Borkhardt, Michaela Kuhlen, Angelika Eggert, Simone Fulda, Manfred Gessler, Jenny Wegert, Roland Kappler, Daniel Baumhoer, Stefan Burdach, Renate Kirschner-Schwabe, Udo Kontny, Andreas E. Kulozik, Dietmar Lohmann, Simone Hettmer, Cornelia Eckert, Stefan Bielack, Michaela Nathrath, Charlotte Niemeyer, Günther H. Richter, Johannes Schulte, Reiner Siebert, Frank Westermann, Jan J. Molenaar, Gilles Vassal, Hendrik Witt, ICGC PedBrain-Seq Project, ICGC Mmml- Seq Project, Birgit Burkhardt, Christian P. Kratz, Olaf Witt, Cornelis M. van Tilburg, Christof M. Kramm, Gudrun Fleischhack, Uta Dirksen, Stefan Rutkowski, Michael Frühwald, Katja von Hoff, Stephan Wolf, Thomas Klingebiel, Ewa Koscielniak, Pablo Landgraf, Jan Koster, **Adam Resnick**, Jinghui Zhang, Yanling Liu, Xin Zhou, **Angela Waanders**, Danny A. Zwijnenburg, **Pichai Raman**, Benedikt Brors, Ursula D. Weber, Paul A. Northcott, Kristian W. Pajtler, Marcel Kool, Rosario M. Piro, Jan O. Korbel, Matthias Schlesner, Roland Eils, David T. W. Jones, Peter Lichter, Lukas Chavez, Marc Zapatka, and Stefan M. Pfister. 2018. 'The landscape of genomic alterations across childhood cancers', *Nature*, 555: 321.

CRANIOPHARYNGIOMA INITIATIVE

Craniopharyngiomas are a rare type of brain tumor derived from embryonic tissue in the pituitary gland that occurs most commonly in children, but also affect adults. The D³b Craniopharyngioma Program is currently focusing on the identification of new therapeutic targets for active clinical trials in adults.

Data collected from these tumor types is key to helping the D³b Center to better understand the biology of Craniopharyngiomas, and is leading to the development of additional, minimally-invasive surgical techniques. These innovative developments have resulted in a new standard of care for patients, by using BRAF inhibitors for Papillary Craniopharyngioma in combination with new surgical approaches.

AVAILABLE CRANIOPHYARYNGIOMA AND BIOSPECIMEN DATA

40 CBTTC craniopharyngioma subjects with 472 files/13.72 terabytes of 60x whole genome sequencing harmonized to 38 with paired RNA-seq, clinically annotated with treatment and outcome data with matched available biospecimens.

⦿ View & query Craniopharyngioma clinical and omic data on the Kids First Portal

⦿ View & analyze data on PedcBioPortal

⦿ View & analyze raw genomic data on Cavatica

⦿ Apply for raw genomic access via the CBTTC Data Access Form

CLINICAL TRIALS

Vemurafenib and Cobimetinib are currently being tested to treat patients diagnosed with a BRAF V600E Mutation, testing positive for a Craniopharyngioma.

D³b Co-director Phillip "Jay" Storm, MD, Chief of the Division of Neurosurgery at CHOP, pioneered new surgical techniques for the removal and treatment of craniopharyngiomas in children.

CBTTC BIOSPECIMEN RESEARCH PROJECTS

Project 0002: Genomic Investigation of Craniopharyngioma

Project 0012: Pediatric Brain Tumor Atlas Initiative

Project 0023: Kids First – CBTTC Proteogenomic Pilot Project

CBTTC DATA RESEARCH PROJECTS

Project 0012: Pediatric Brain Tumor Atlas Initiative

Project 0029: Children's Brain Tumor Tissue Consortium Pediatric Brain Tumor Proteomics Pilot

D³b INVESTIGATOR COLLABORATIVE RESEARCH PUBLICATIONS

Brastianos, Priscilla K., Amaro Taylor-Weiner, Peter E. Manley, Robert T. Jones, Dora Dias-Santagata, Aaron R. Thorner, Michael S. Lawrence, Fausto J. Rodriguez, Lindsay A. Bernardo, Laura Schubert, Ashwini Sunkavalli, Nick Shillingford, Monica L. Calicchio, Hart G. W. Lidov, Hala Taha, Maria Martinez-Lage, **Mariarita Santi**, **Phillip Storm**, John Y. K. Lee, James N. Palmer, Nithin D. Adappa, R. Michael Scott, Ian F. Dunn, Edward R. Laws Jr, Chip Stewart, Keith L. Ligon, Mai P. Hoang, Paul Van Hummelen, William C. Hahn, David N. Louis, **Adam Resnick**, Mark W. Kieran, Gad Getz, and Sandro Santagata. 2014. 'Exome sequencing identifies BRAF mutations in papillary craniopharyngiomas', *Nature Genetics*, 46: 161.

Douglas, Jennifer E., Bobby A. Tajudeen, Edward C. Kuan, Marvin Bergsneider, Marilene B. Wang, John Y. K. Lee, James N. Palmer, Nithin D. Adappa, and **Phillip Storm**. 2017. 'Outcomes of Pediatric Craniopharyngioma Resections after Open versus Expanded Endonasal Surgical Approach', *Journal of Neurological Surgery* Part B, 78: A035.

Tong, Charles C., Edward C. Kuan, Seerat K. Poonia, Michael A. Kohanski, Justina L. Lambert, **Phillip Storm**, James N. Palmer, and Nithin D. Adappa. 2018. 'Posttreatment Rhinosinusitis Following Endoscopic Resection of Pediatric Craniopharyngioma', *Journal of Neurological Surgery* Part B, 79: P034.

PHILANTHROPIC RESEARCH SUPPORT

Templeton Family Fund
In support of the D³b Center's strategic research initiatives

PEDIATRIC BRAIN TUMOR IMMUNOTHERAPY RESEARCH

Recently-developed immunotherapies, including the pioneering efforts of the Cancer Immunotherapy Program at CHOP, have led to incredible breakthroughs in the treatment of pediatric leukemias over the past five years. D³b's efforts in this area have focused on translating the currently-available treatment methods for leukemias into therapies for solid tumors, including pediatric brain tumors.

Over the past two years, D³b's data-driven efforts, led by the PCLRU, have focused on the identification of promising targets derived from available pediatric brain tumor data, as well as initiating preclinical research models in the lab to identify mechanisms and confirm targets in solid tumors. These, along with other efforts, have led to a clinical trial concept currently being vetted through the Pacific Pediatric Neuro-Oncology Consortium (PNOC).

Crystal Griffin, BS, a research technician in D³b's Preclinical Laboratory Research Unit, supports wet bench research efforts in the development of immunotherapies for brain tumors

CURRENTLY-AVAILABLE DATA

DiseaseXpress is a dataset that contains 21,000 harmonized RNA-seq samples from pediatric and adult cancers, which enable researchers to define new immunotherapeutic targets.

CBTTC BIOSPECIMEN RESEARCH PROJECTS

Project 0005: Exploration of IDO1 as a Therapeutic Target in pCNS Tumors

Project 0014: Evaluation of Immunosignature Profile in Medulloblastoma

Project 0028: GPC2 As an Immunotherapeutic Target in Medulloblastoma and Other Pediatric Brain Tumors

Project 0029: Molecular Analysis of the Cellular Ecosystem of Childhood Ependymoma

CBTTC DATA RESEARCH PROJECTS

Project 0001: Hideho Okada on DIPG and Other Primary Pediatric Brain Tumors

Project 0004: Immunotherapeutically – Targeting IDO1 in Pediatric High-grade Glioma

Project 0007: In Silico Neo-Antigen Detection in High-Grade Pediatric Brain Tumors Utilizing RNA-seq and WGS

Project 0030: Immunogenomic Landscape of Pediatric Cancers

Project 0031: Identifying New Cell Surface Targets for Immunotherapy Treatment of Poor Prognosis Pediatric Brain Tumors

Foster Jessica, **Choudhari Namrata**, Perazzelli Jessica, Storm Julie, Hofmann Ted J., **Jain Payal**, **Storm Phillip**, Pardi Norbert, Weissman Drew, **Waanders Angela**, Grupp Stephan A., Karikó Katalin, **Resnick Adam**, and Barrett David M. 2019. 'Purification of mRNA Encoding Chimeric Antigen Receptor Is Critical for Generation of a Robust T-Cell Response', *Human gene therapy*, 30: 168-78

Foster, Jessica, **Namrata Choudhari**, **Adam Resnick**, and David Barrett. 2017. 'Abstract 5614: Novel mRNA Purification Method with RNaseIII Improves Efficacy of RNA Chimeric Antigen Receptor T-cells', *Cancer Research*, 77: 5614-14.

Campbell, Brittany B., Nicholas Light, David Fabrizio, Matthew Zatzman, Fabio Fuligni, Richard de Borja, Scott Davidson, Melissa Edwards, Julia A. Elvin, Karl P. Hodel, Walter J. Zahurancik, Zucai Suo, Tatiana Lipman, Katharina Wimmer, Christian P. Kratz, Daniel C. Bowers, Theodore W. Laetsch, Gavin P. Dunn, Tanner M. Johanns, Matthew R. Grimmer, Ivan V. Smirnov, Valérie Larouche, David Samuel, Annika Bronsema, Michael Osborn, Duncan Stearns, **Pichai Raman**, Kristina A. Cole, **Phillip Storm**, Michal Yalon, Enrico Opocher, Gary Mason, Gregory A. Thomas, Magnus Sabel, Ben George, David S. Ziegler, Scott Lindhorst, Vanan Magimairajan Issai, Shlomi Constantini, Helen Toledano, Ronit Elhasid, Roula Farah, Rina Dvir, Peter Dirks, Annie Huang, Melissa A. Galati, Jill Chung, Vijay Ramaswamy, Meredith S. Irwin, Melyssa Aronson, Carol Durno, Michael D. Taylor, Gideon Rechavi, John M. Maris, Eric Bouffet, Cynthia Hawkins, Joseph F. Costello, M. Stephen Meyn, Zachary F. Pursell, David Malkin, Uri Tabori, and Adam Shlien. 2017. 'Comprehensive Analysis of Hypermutation in Human Cancer', *Cell*, 171: 1042-56.e10.

SPONSORED IMMUNOTHERAPY RESEARCH

NIH R03 CA230366-01 07/05/18-6/30/20 $344,000
Discovering the Genetic Basis of Neuroblastoma Initiation and Progression
PI(s): Sharon Diskin, PhD, University of Pennsylvania

NIH P30 CA016520-42S3 09/01/18-08/31/20 $399,877
Project HOPE: High-grade Glioma-Omics in Pediatric and AYA
Project Lead: Adam Resnick, PhD, Children's Hospital of Philadelphia

NIH U2C CA233285-01 09/30/18-8/31/23 $2,645,037
Center for Pediatric Tumor Cell Atlas
PI(s): Kai Tan, PhD, Stephen Hunger, MD, Children's Hospital of Philadelphia
Co-Investigator: Adam Resnick, PhD, Phillip "Jay" Storm, MD, Angela Waanders, MD, MPH
Children's Hospital of Philadelphia

NIH U54 CA232568-01 $2,162,140
Discovery and Development of Optimal Immunotherapeutic Strategies for
Childhood Cancers
PI(s): John Maris, MD, Crystal Mackall, MD, Children's Hospital of Philadelphia
Co-Investigator: Adam Resnick, PhD, Jessica Foster, MD, Children's Hospital of Philadelphia

St. Baldrick's SU2C-AACR-DT1113 07/01/13-12/31/21 $2,000,000
Immunogenomics to Create New Therapies for Pediatric Cancers
PI(s): John Maris, MD, Crystal Mackall, MD, Children's Hospital of Philadelphia

PHILANTHROPIC IMMUNOTHERAPY RESEARCH SUPPORT

Kortney Rose Foundation $60,000

Grayson Saves Foundation $35,000

Patriarch Family Foundation $35,000

Emily's Smiles Foundation $35,000

Wylie's Day Foundation $25,000

CBTTC Advisory Council Research Projects $5,000

PLATFORMS TO ACCELERATE COLLABORATIVE RESEARCH

D³b Co-director, Phillip "Jay" Storm, MD, (left) and Director of Clinical Research, Angela Waanders, MD, MPH (right), review a de-identified image of a brain scan.

D³b successfully developed and launched three powerful analytic platforms to help accelerate breakthroughs by researchers all over the world. These efforts are directly linked to increased efforts to remove the barriers to pediatric brain tumor and other pediatric cancer, developmental, and rare-disease research efforts, enabling large-scale research in a way never before possible. Today, researchers located anywhere in the world can log in, explore, analyze, and compute massive collections of high-quality data. D³b-developed platforms are helping redefine the traditional research model by improving collaboration across institutions and removing the primary barriers to research.

Launched in September of 2018, the NIH-funded Gabriella Miller Kids First Data Resource Portal (DRP) is a platform designed to help accelerate the worldwide discovery of precision-based treatments for pediatric disorders, including childhood cancer and structural birth defects. The DRP contains more than 30,000 files of clinical and genomic data, accessible in a way in which allows any researcher to query across harmonized data and request access to raw genomic data through the NIH's dbGaP authentication or via consortia-specific access agreements.

The DRP allows users to import genomic files into a Cavatica project, a compute area where they can analyze the raw genomic data using an existing project pipeline, or create their own project spaces. Cancer-focused researchers can also link their Kids First account to virtual cohorts in PedcBioPortal to visualize RNA-seq data.

COLLABORATIVELY-DEVELOPED D³b PLATFORMS

Through key collaborations, D³b makes several research platforms available to the community. The D³b collaborative research platforms are accessible through a Google authentication method. Additionally, cloud resource grants available are available to researchers. To learn more, email support@kidsfirstdrc.org

- Kids First Data Resource Portal
- Cavatica
- PedcBioPortal

D³b INVESTIGATOR ABSTRACTS

INTERNATIONAL SYMPOSIUM ON PEDIATRIC NEURO-ONCOLOGY (ISPNO 2018)

June 29 - July 3, 2018, Denver, Colorado

Abstract: **'PedcBioPortal, a Cancer Data Visualization Tool for Integrative Pediatric Cancer Analyses'**
Presenting author: Adam Resnick, PhD

Abstract: **'DiseaseXpress, a Cancer Data Analytics and Visualization Tool for Identifying Immunotherapeutic Targets in Pediatric Brain tumors and Other Cancers'**
Presenting author: Adam Resnick, PhD

Abstract: **'Gabriella Miller Kids First Data Resource Center - Advancing Genetic Research in Childhood Cancer and Structural Birth Defects Through Large-scale, Integrated, Data-driven Discovery and Cloud-based Platforms for Collaborative Analysis'**.
Presenting author: Adam Resnick, PhD

D³b INVESTIGATOR PUBLICATIONS

Raman, Pichai, **Angela Waanders**, **Phillip Storm**, **Jena Lilly**, **Jennifer Mason**, **Allison Heath**, **Alex Felmeister**, Anthony Cros, **Yuankun Zhu**, Leonard Sender, Michael Prados, Sabine Mueller, Rishi Lulla, Javad Nazarian, and **Adam Resnick**. 2017. 'GENE-15. CAVATICA - A Pediatric Genomic Cloud Empowering Data Discovery Through the Pediatric Brain Tumor Atlas', *Neuro-Oncology*, 19: iv21-iv21.

Resnick, Adam, **Phillip Storm**, **Angela Waanders**, **Jena Lilly**, Rishi Lulla, Sabine Mueller, Michael Prados, Leonard Sender, **Allison Heath**, **Alex Felmeister**, Anthony Cros, **Yuankun Zhu**, and **Pichai Raman**. 2017. 'Abstract LB-008: The Pediatric Brain Tumor Atlas: Building an Integrated, Multi-platform, Data-rich Ecosystem for Collaborative Discovery in the Cloud', *Cancer Research*, 77: LB-008-LB-08.

Gao, Jianjiong, Ersin Ciftci, **Pichai Raman**, Pieter Lukasse, Istemi Bahceci, Adam Abeshouse, Hsiao-Wei Chen, Ino de Bruijn, Benjamin Gross, Zachary Heins, Ritika Kundra, Aaron Lisman, Angelica Ochoa, Robert Sheridan, Onur Sumer, Yichao Sun, Jiaojiao Wang, Manda Wilson, Hongxin Zhang, James Xu, Andy Dufilie, Priti Kumari, James Lindsay, Anthony Cros, **Karthik Kalletla**, Fedde Schaeffer, Sander Tan, Sjoerd van Hagen, Jorge Reis-Filho, Kees van Bochove, Ugur Dogrusoz, Trevor Pugh, **Adam Resnick**, Chris Sander, Ethan Cerami, and Nikolaus Schultz. 2017. 'Abstract 2607: The cBioPortal for Cancer Genomics: an open source platform for accessing and interpreting complex cancer genomics data in the era of precision medicine', *Cancer Research*, 77: 2607-07.

Gibson, Kristin McDonald, Addie Nesbitt, Kajia Cao, Zhenming Yu, Elizabeth Denenberg, Elizabeth DeChene, Qiaoning Guan, Elizabeth Bhoj, Xiangdong Zhou, Bo Eric Marsh, Elaine Zackai, Nancy Spinner, Ian Krantz, Matt Deardorff, and Avni Santani. Zhang, Chao Wu, Holly Dubbs, Alisha Wilkens, Livija Medne, Emma Bedoukian, Peter S. White, Jeffrey Pennington, Minjie Lou, Laura Conlin, Dimitri Monos, **Mahdi Sarmady**, 2017. 'Novel Findings with Reassessment of Exome Data: Implications for Validation Testing and Interpretation of Genomic Data', *Genetics In Medicine*.

Volchenboum, SL, SM Cox, **A Heath**, **A Resnick**, SL Cohn, and R Grossman. 2017. 'Data Commons to Support Pediatric Cancer Research.' In *American Society of Clinical Oncology Educational Book*. American Society of Clinical Oncology. Meeting, 746-52.

Wilson, Shane, Michael Fitzsimons, Martin Ferguson, **Allison Heath**, Mark Jensen, Josh Miller, Mark W. Murphy, James Porter, Himanso Sahni, Louis Staudt, Yajing Tang, Zhining Wang, Christine Yu, Junjun Zhang, Vincent Ferretti, and Robert L. Grossman. 2017. 'Developing Cancer Informatics Applications and Tools Using the NCI Genomic Data Commons API', *Cancer Research*, 77: e15-e18.

D³b INVESTIGATOR PUBLICATIONS (*CONT.*)

Christini, Amanda, **Angela J. Waanders**, Joost B. Wagenaar, **Alex S. Felmeister**, **Mariarita Santi**, Nitin R. Wadhwani, **Jennifer L. Mason**, **Mateusz P. Koptyra**, **Jena V. Lilly**, Jeffrey W. Pennington, Rishi R. Lulla, and **Adam C. Resnick**. 2017. 'Abstract 2593: Accelerating Pediatric Brain Tumor Research Through Team Science Solutions', *Cancer Research*, 77: 2593-93.

Felmeister, A. S., **T. J. Rivera**, A. J. Masino, **A. C. Resnick**, and J. W. Pennington. 2015. "Scalable Biobanking: A Modular Electronic Honest Broker and Biorepository for Integrated Clinical, Specimen and Genomic Research." In *2015 IEEE International Conference on Bioinformatics and Biomedicine* (BIBM), 484-90.

Felmeister, Alex, Aaron Masino, **Tyler Rivera**, **Adam Resnick**, and Jeffrey Pennington. 2016. 'The Biorepository Portal Toolkit: An Honest Brokered, Modular Service-oriented Software Tool Set for Biospecimen-driven Translational Research', *BMC Genomics*, 17: 434.

SPONSORED DATA PLATFORM RESEARCH

NIH U24 CA220457-01 08/01/17-07/31/22 $93,407
The cBioPortal for Cancer Genomics
PI(s): Nikolaus Schultz
Co-Investigator: Adam Resnick, PhD, Pichai Raman, PhD, Children's Hospital of Philadelphia

American Association for Cancer Research 11/01/18-12/31/23 $185,260
Project Genomics Evidence Neoplasia Information Exchange (GENIE)
PI(s): Marilyn Li, MD, Adam Resnick, PhD, Children's Hospital of Philadelphia

European Commission 01/01/19-12/31/20 $216,788
IndividualizedPaediatricCure: Cloud-based Virtual-patient Models for Precision Paediatric Oncology
Consortium Site PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia

NIH U2C HL138346-02 06/25/17-5/31/22 $14,822,538
Innovation Through Collaboration at the Intersection of Childhood Development and Cancer: a platform for the Gabriella Miller Kids First Pediatric Data Resource Center
PI(s): Adam Resnick, PhD, Allison Heath, PhD, Deanne Taylor, PhD, Hakon Hakonarson, MD, PhD, Children's Hospital of Philadelphia, Vincent Ferretti, PhD, Lincoln Stein, PhD, Ontario Institute for Cancer Research, Robert Grossman, PhD, Samuel Volchenboum, MD, PhD, MS, University of Chicago, Brandi Davis-Dusenbery, PhD, Seven Bridges

NIH 3U2C HL138346-01S2 09/26/17-05/31/19 $1,800,000
U2C Kids First Admin Supplement – cloud-based data storage and compute
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia

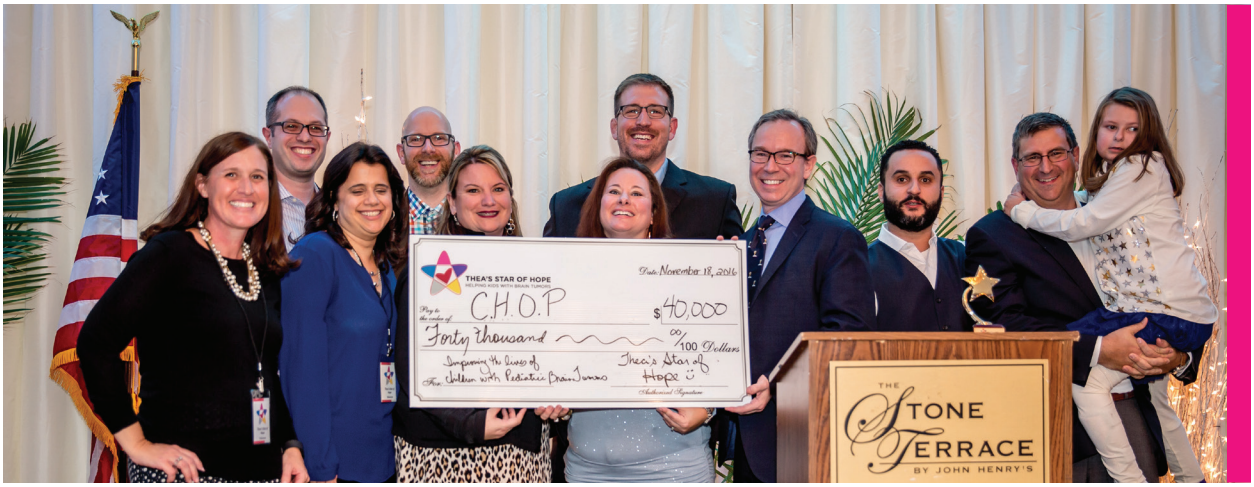
NIH 3U2C HL138346-02S2 09/01/18-05/31/19 $957,570
U2C Kids First Admin Supplement – cloud resources
PI(s): Adam Resnick, PhD, Children's Hospital of Philadelphia

PHILANTHROPIC RESEARCH SUPPORT

Christopher Court Foundation $107,000

Templeton Family Fund
In support of the D³b Center's strategic research initiatives

A STAR OF HOPE



Thea's Star of Hope presents a check to fund pediatric Low-grade Glioma research at CHOP. Pictured from left: Kari Forwood, Craig Fishman, Marie Valentino, Scott Coakley, Stacy Reh, Trisha Danze, Josh Walker (CHOP Foundation), Jay Storm (D³b), Mike Carpenter, Jeff Danze, Thea Danze

When our 4-month-old daughter was diagnosed with a brain tumor, we could never have fathomed how much we would all go through. Many of the treatments and side effects have been devastating. She has suffered so much in her short 10 years. Thea is now 11 and it is amazing how far we have come. But she has also grown. For that, we could not be more thankful.

When she was first diagnosed, none of the targeted therapies were even available. There are now more options for treatment than there have ever been for her tumor type. I don't worry as much as I used to about her tumor growing because I know that there is hope.

Thea's brain tumor journey led to us establish Thea's Star of Hope. Our search for what research to support led us here. Our second home. CHOP, the CBTTC and the Center for Data Driven Discovery in Biomedicine. We were immediately in love with the concept. YES! Collaboration amongst institutions. Why wasn't this already happening! How can we help! That idea of collaboration has driven every single project we have worked on.

Partnering combines resources and consolidates efforts. It makes us all much more efficient. It has led us to new discoveries. It has led to amazing relationships. It has led to awareness. It has led to hope.

Our story does not end here. In fact, this is really just the beginning. With the support of families and foundations, this effort will lead to a cure for kids with brain cancer.

Trisha Danze
Thea's Mom & Founder, Thea's Star of Hope

A LOOK AHEAD

D³b Co-directors Phillip "Jay" Storm, MD and Adam Resnick, PhD, demonstrate the loading process for samples stored in a tank of liquid nitrogen, located in CHOP's biorepository. CHOP's facility can safely store more than 2 million samples of fluids, DNA, RNA, tissue samples, cells, and additional types of biospecimens.

D³b will continue to drive the acceleration of translational, convergence-based research. Drawing upon the D³b Center's expertise in cross-disease data generation, D³b is poised to further accelerate and continuously deliver new discoveries, providing new knowledge on disease mechanisms and their potential for therapeutic impact.

In the coming year, D³b will continue to harness, expand, and refine the new translational *D³b Research Methodology* by applying it directly to its local, core infrastructure of neuroscience research, and across the CHOP Department of Neurosurgery's multi-disciplinary programs of surgical oncology, neuroscience, developmental biology, and structural birth defects.

By working together with these core programs, D³b is positioned to continue expanding its collaborative partnerships across the Department of Surgery, including relationships with the Division of Cardiothoracic Surgery, the Division of Plastic Surgery, the Division of Fetal Surgery and the Craniofacial Program, as well as enhanced partnerships with the Division of Neurology, the Department of Pathology and Laboratory Medicine, and the Department of Radiology, across multimodal data integration and diagnostics.

This cross-functional, convergence-research support helps to define D³b's commitment to cancer, developmental biology, and neuroscience research, and positions the D³b Center for the exponential acceleration of discoveries that lay ahead. Over the coming year, D³b's key research objectives will focus on cross-disease analyses of cancer, neuroscience, and developmental biology.

Additionally, D³b will maintain its focus on the generation and analysis of new types of data from emerging genomic and molecular profiling techniques, including single-cell sequencing and proteomics. The D³b Center will also leverage newly-established, preclinical models to identify disease-based mechanisms to conduct drug and target identification screens.

In addition to expanded efforts in the *Data* and *Information* phases of our efforts, dedicated efforts will focus on translation to impact by testing and implementing new immunotherapeutic approaches for pediatric brain tumors to leverage newly-generated datasets and preclinical models in the development of new disease specific clinical trial concepts development along with consortia partners.

STRATEGIC INITIATIVES & PROGRAMS

Focusing on translational research, D3b has identified the need to study cancers along the continuum of research - which tries to understand the biology of a disease across a patient's lifespan and across multiple disease types. This strategy provides key opportunities for novel knowledge generation to improve D3b's understanding of the development of these diseases.

D3b seeks to bridge the current discovery gap across pediatrics, adolescents, and adult cancers, with a focus on the underrepresented areas of young adults, as well as for diseases with no curative standard of care. D3b's current and future collaborative research programs are underpinned by the D3b Center's commitment to redefine the traditional research model and provide solutions across the entire lifespan of each child diagnosed with a pediatric disease.

In the coming months, D3b looks forward to the launch of additional projects to serve populations from adolescent/young adult (AYA), adult brain tumors, ear, nose & throat (ENT) tumors, chordomas, and oligodendrogliomas, through the consortia-led efforts of the Philadelphia Coalition for a Cure (PC4C) in brain tumors, the Corsica Sinonasal Cancer Consortium, the Chordoma Foundation, and Oligo Nation initiatives.

Within the next two years, D3b will fully integrate these programs into the *D3b Methodology* to generate the required data to understand and accelerate translational impact in these areas.

Through the integration of disease research across ages and disease types, D3b is complementing the Department of Surgery's approach to surgical division and disease treatment. These and other D3b-led partnerships are guiding biospecimen-driven research for novel, cross-disease research. Surgical programs also build upon CHOP Neurosurgery's areas of emphasis which span across disciplines including oncology, neurology/epilepsy, vascular and fetal, congenital birth defects, and data-driven programs in cardiac and craniofacial birth defects.

In the coming year, in addition to local partnerships at CHOP and the nationally-partnered Gabriella Miller Kids First Data Resource Center, D3b will support the growth of additional molecularly-based, clinical trials for pediatric brain tumors and the creation of an international, data-driven infrastructure throughout the European Union, Australia, India, and China.

D3b INVESTIGATOR PUBLICATIONS

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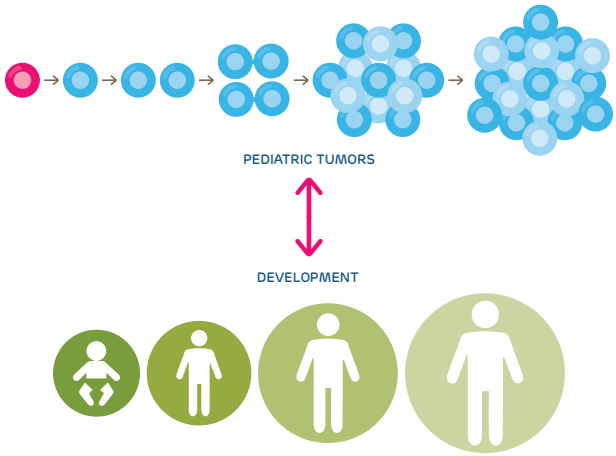
RESEARCH PLATFORMS & ANALYTICS

D³b will continue to expand the development of selected platform features, allowing the D³b-developed platforms to support and interoperate with other global research initiatives. Looking forward, new features will be added to D³b's platforms, such as the Gabriella Miller Kids First Data Resource Portal, to integrate and maximize the use of longitudinal and clinical data.

The ability of D³b's platforms to connect and interoperate with other data efforts, including the NIH data landscape, will further facilitate the cross-disease analysis and analytic research needed to discover more effective treatments for diagnosed children. Cavatica will expand internationally into Australia and the European Union, under new initiatives that will launch in the coming year, including the Australia Data Commons and the European Union iPC.



WITH GRATITUDE

Through collaboration and a deep commitment to improving care for children diagnosed with pediatric brain tumors and rare diseases, the D³b Center is grateful for its team members, leadership, patients, foundations, the research community, and each partnership, dedicated to accelerating translational research to help patients.

Philanthropy has played a critical role in the recent growth of D³b. The Abramson, Templeton, and Sislik families each provided crucial support by providing the early foundations of the D³b Center, with the Abramson and Sislik family each generously committing $1 million in 2016.

These gifts opened the door for new research possibilities, and in 2017, D³b took another giant step forward when the Templeton family made a generous commitment of $3 million to establish the Templeton Family Coalition for a Cure Fund. It is thanks to the generosity of these families that D³b has been able to make potentially life-saving breakthroughs in only a few short years.

While the gifts above have played a crucial role in establishing D³b, it has also been the loyal support from a wide-range of donors that has helped to sustain the D³b Center. Like the research D³b empowers, these fundraising efforts have been largely collaborative.

From the Brain Tumor Research Board of Visitors at CHOP, to the CBTTC Advisory Council, groups of individual donors, foundations, and patient families have rallied together to make the success of D³b inevitable.

It is only through this continued support and partnership with collaborators across the globe that D³b can look forward to leading and driving additional collaborations to **accelerate breakthroughs for every child, every time, everywhere.**

Jaxson, (cover, pictured above), was diagnosed with an Atypical Teratoid Rhabdoid Tumor (ATRT) brain tumor at age 1. Through the D³b Center's collaborative, data-driven research model, new therapies are on the horizon for all children diagnosed with a brain tumor or other rare disease."

PUBLICATION & CONFERENCE UPDATES

EXECUTIVE SUMMARY

Due to sustained achievements in their respective fields of expertise, D³b team members have received acknowledgments from institutions and collaborators across the globe. Our experts were published more than 115 times in over 20 different scientific journals, with seven more awaiting approval. We presented our work at over 30 conferences and symposia, with oral and poster presentations. In addition, Adam Resnick, PhD and Allison Heath, PhD were invited to serve as Chairs for several international conferences. Members of the D³b Center filed one patent application, received nine major honors from foundations and institutions, and were covered by nine online, print, and broadcast media outlets.

PUBLICATIONS

D³b Center members published 116 articles in renowned scientific journals. Key focus areas spanned basic research, bioinformatics, and clinical and translational research (organized alphabetically by first author).

Bandopadhayay, Pratiti, Lori A. Ramkissoon, **Payal Jain**, Guillaume Bergthold, Jeremiah Wala, Rhamy Zeid, Steven E. Schumacher, Laura Urbanski, Ryan O'Rourke, William J. Gibson, Kristine Pelton, Shakti H. Ramkissoon, **Harry J. Han**, **Yuankun Zhu**, **Namrata Choudhari**, Amanda Silva, **Katie Boucher**, Rosemary E. Henn, Yun Jee Kang, David Knoff, Brenton R. Paolella, Adrianne Gladden-Young, Pascale Varlet, Melanie Pages, Peleg M. Horowitz, Alexander Federation, Hayley Malkin, Adam A. Tracy, Sara Seepo, Matthew Ducar, Paul Van Hummelen, **Mariarita Santi**, Anna Maria Buccoliero, Mirko Scagnet, Daniel C. Bowers, Caterina Giannini, Stephanie Puget, Cynthia Hawkins, Uri Tabori, Almos Klekner, Laszlo Bognar, Peter C. Burger, Charles Eberhart, Fausto J. Rodriguez, D. Ashley Hill, Sabine Mueller, Daphne A. Haas-Kogan, Joanna J. Phillips, Sandro Santagata, Charles D. Stiles, James E. Bradner, Nada Jabado, Alon Goren, Jacques Grill, Azra H. Ligon, Liliana Goumnerova, **Angela J. Waanders**, **Phillip B. Storm**, Mark W. Kieran, Keith L. Ligon, Rameen Beroukhim, and **Adam C. Resnick**. 2016. 'MYB-QKI Rearrangements In Angiocentric Glioma Drive Tumorigenicity Through A Tripartite Mechanism', *Nature Genetics*, 48: 273-82.

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Vasilevsky, Nicole A., Erin D. Foster, Mark E. Engelstad, Leigh Carmody, Matt Might, Chip Chambers, Hugh J. S. Dawkins, Janine Lewis, Maria G. Della Rocca, Michelle Snyder, Cornelius F. Boerkoel, Ana Rath, Sharon F. Terry, Alastair Kent, Beverly Searle, Gareth Baynam, Erik Jones, Pam Gavin, Michael Bamshad, Jessica Chong, Tudor Groza, David Adams, **Adam C. Resnick, Allison P. Heath**, Chris Mungall, Ingrid A. Holm, Kayli Rageth, Catherine A. Brownstein, Kent Shefchek, Julie A. McMurry, Peter N. Robinson, Sebastian Köhler, and Melissa A. Haendel. 2018. 'Plain-language Medical Vocabulary for Precision Diagnosis', *Nature Genetics*, 50: 474-76

Volchenboum, SL, SM Cox, **A Heath, A Resnick**, SL Cohn, and R Grossman. 2017. "Data Commons to Support Pediatric Cancer Research." In *American Society of Clinical Oncology educational book. American Society of Clinical Oncology. Meeting*, 746-52.

Wilson, Shane, Michael Fitzsimons, Martin Ferguson, **Allison Heath**, Mark Jensen, Josh Miller, Mark W. Murphy, James Porter, Himanso Sahni, Louis Staudt, Yajing Tang, Zhining Wang, Christine Yu, Junjun Zhang, Vincent Ferretti, and Robert L. Grossman. 2017. 'Developing Cancer Informatics Applications and Tools Using the NCI Genomic Data Commons API', *Cancer Research*, 77: e15-e18.

Workman, Alan D., Ivy W. Maina, Vasiliki Triantafillou, James N. Palmer, Nithin D. Adappa, **Phillip B. Storm**, and Jordan T. Glicksman. 2018. 'Cerebrospinal Fluid Leak Repaired with Nasoseptal Flap in a 2-Week-Old Neonate', *Journal of Neurological Surgery Part B*, 79: P141.

Wu, M., L. S. Chong, D. H. Perlman, **A. C. Resnick**, and D. Fiedler. 2016. 'Inositol Polyphosphates Intersect with Signaling and Metabolic Networks Via Two Distinct Mechanisms', *Proc Natl Acad Sci USA*, 113: E6757-e65.

Zaghloul, K. A., G. G. Heuer, M. D. Guttenberg, E. M. Shore, F. S. Kaplan, and **P. B. Storm**. 2008. 'Lumbar Puncture And Surgical Intervention in a Child with Undiagnosed Fibrodysplasia Ossificans Progressiva', *J Neurosurg Pediatr*, 1: 91-4.

CONFERENCES AND ABSTRACTS

The D³b Center directors and staff were invited to either present, participate, or chair 28 conferences during fiscal year 2018. Below are highlights of the meetings:

Englander Institute for Precision Medicine Seminar Series at Weill Cornell Medicine/
New York-Presbyterian Hospital.
August 1, 2017 - New York, NY,
Title: *"Innovation through Collaboration: How an Emerging Pediatric Cancer Data Discovery Landscape is Changing the Way We Do Research"*
Presenter: Adam Resnick, PhD

Kids First Technical Meeting
August 16-17, 2017 - Philadelphia, PA
Presenters: Allison Heath, PhD, Jena Lilly, MS, CCRC, Pichai Raman, PhD, MS, Adam Resnick, PhD

Kids First Pediatric Research Program First Annual Meeting
September 6th-7th, 2017 - Johns Hopkins University
Presenters: Allison Heath, PhD, Pichai Raman, PhD, MS, Adam Resnick, PhD

Kids First Patient User Group Workshop
November 14th- Philadelphia. PA
Presenters: Jena Lilly, MS, CCRC and Pichai Raman, PhD, MS

BloodPAC Quarterly Meeting
September 26th, New York, NY
Presenters: Allison Heath, PhD, Mateusz Koptyra, PhD

Pediatric Brain Tumor Autopsy Conference
September 28th-29th, Chicago, IL
Presenters: Jennifer Mason, Angela Waanders, MD, MPH

Cancer Informatics for Cancer Centers (CI4CC)
October 23rd-25th, 2017. La Jolla, CA
Title: *"Innovation Through Collaboration: Emerging Models in Pediatric for Data Driven Healthcare Ecosystem"*
Chairs: Allison Heath, PhD, Adam Resnick, PhD

Global Alliance for Genomics and Health (GA4GH) 5th Plenary Meeting
October 15-17, 2017
Presenter: Allison Heath, PhD

The 12th International Conference on Genomics (ICG)
October 26-27, 2017. Shenzhen, China
Presenters: Marilyn Li, MD, Adam Resnick, PhD

Neurosurgery Conference - TianTan Hospital Beijing China
October, 2017. Beijing, China
Presenter: Phillip "Jay" Storm, MD

14th Asian Society for Neuro-Oncology, (ASNO)
October 28-31, 2017. Osaka, Japan
Poster Title: "*CBTTC: Empowering Pediatric Brain Tumor Research Through Collaboration*".
Talk Title: "*Targeted Therapy Approaches and Resistance Mechanisms for Pediatric Low-grade Gliomas with Activated RAF Gene Fusions*"
Presenter: Payal Jain, PhD

CONFERENCES AND ABSTRACTS

2017 IEEE International Conference on Bioinformatics and Biomedicine (BIBM)
November 13-16, 2017, Kansas City, MO.
Abstract: "*Preliminary Exploratory Data Analysis of Simulated National Clinical Data Research Network for Future Use in Annotation of a Rare Tumor Biobanking Initiative*"
Presenter: Alex Felmeister, MS

Pacific Pediatric Neuro-Oncology Consortium (PNOC) Fall Investigators Meeting
November 15, 2017, San Francisco, CA.
Presenters: Adam Resnick, PhD, Angela Waanders, MD, MPH

Society for Neuro-Oncology Meeting (SNO)
November 16-17, 2017, San Francisco, CA
Abstract: "*Pediatric Low-grade Gliomas with CRAF Gene Fusions are Therapeutically Distinct from BRAF-fusions Based on Dimerization Mediated by N-terminal Fusion Partner.*"
Presenter: Payal Jain, PhD

Workshop: Tissue Microarray and Quantitative Digital Proteomics in Pathology
November 17, 2017, Philadelphia, PA
Title: "*New Models for an Integrated Data-driven Healthcare Ecosystem*"
Presenter: Adam Resnick, PhD

LGG Consensus Meeting
December 4-6, 2017, Toronto, Canada
Presenter: Angela Waanders, MD, MPH

NIH Data Commons External Panel of Consultants
December 7-8, 2017- Bethesda, MD
Title: "*Platforms for FFPE: Pediatric Brain Tumor Specimens*"
Presenter: Adam Resnick, PhD

Childhood Cancer Research Symposium
February 7, 2018, Clayton, Australia

a) Title: "*The Children's Brain Tumour Tissue Consortium (CBTTC): The CBTTC Vision and Goals With a Focus on the Autopsy Program*"
Presenter: Angela Waanders, MD, MPH

b) Title: "*Innovation Through Collaboration: New Models for an Integrated Data-driven Healthcare Ecosystem"*
Presenter: Adam Resnick, PhD

c) Title: "Paediatric Neurosurgical Case Review at the Children's Hospital of Philadelphia
Presenter: Phillip "Jay" Storm, MD

Meeting with BioNTech for Immunotherapy Project
February 20 - 22, 2018, Mainz, Germany
Presenters: Jessica Foster, MD and Adam Resnick, PhD

21st Annual Update on Pediatric and Congenital Cardiovascular Disease
February 21 - 25, 2018, Scottsdale, Arizona
Presenter: Phillip "Jay" Storm, MD

CONFERENCES AND ABSTRACTS (*CONT.*)

2nd Pediatric Precision Oncology Conference
March 4-7, 2018, Scottsdale, Arizona

a) Abstract: "*Gabriella Miller Kids First Data Resource Center: Advancing Genetic Research in Childhood Cancer and Structural Birth Defects Through Large-scale Integrated Data-driven Discovery and Cloud-based Platforms for Collaborative Analysis*"
Presenter: Adam Resnick, PhD

b) Abstract: "*Functional Characterization and Effective Targeting of NRF1-BRAF and ATG7-RAF1 Fusions Identified in Anaplastic Pleomorphic Xanthoastrocytoma Patients Without BRAF p.V600E Mutation*"
Presenter: Poonam Sonawane, PhD

The Kids First Data Resource Center, NIH Platform Demo Day
March 13, 2018, Bethesda, MD
Presenters: Jena Lilly, MS, CCRC, Allison Heath, PhD, Pichai Raman, PhD, MS, Adam Resnick, PhD

ISNOCON 2018, 10th Annual Conference of the Indian Society of Neuro-Oncology
April 6-8, 2018, New Delhi, India
Abstract: "*CBTTC: Empowering Pediatric Brain Tumor Research Through Collaboration*"
Presenter: Payal Jain, PhD

AACR Annual Meeting 2018
April 16, 2018, Chicago, Illinois
Abstract: "*Empowering Rare Disease Cohort Biomarker Discovery via Comparative Assessments of Gene Expression Analysis Platforms for FFPE pediatric brain tumor specimenss*"
Presenter: Mateusz Koptyra, PhD

23rd Neuro-Tumor Club Meeting
April 16, 2018, Chicago, IL
Abstract: "*High Grade Glioma Cell Line Cohort as an Example of Children's Brain Tumor Tissue Consortium Tumor Specimen Processing Pipeline*"
Presenter: Mateusz Koptyra, PhD

2018 International Chordoma Research Workshop
March 22-23, Boston, MA
Talk Title: New Models for an Integrated Data Driven Healthcare Ecosystem
Presenter: Adam Resnick, PhD

CONFERENCES AND ABSTRACTS (*CONT.*)

International Symposium on Pediatric Neuro-Oncology (ISPNO 2018)
June 29 - July 3, 2018, Denver, Colorado

a) Abstract: "*PedcBioPortal, A Cancer Data Visualization Tool for Integrative Pediatric Cancer Analyses"*
Presenter: Adam Resnick, PhD

b) Abstract: "*DiseaseXpress, A Cancer Data Analytics and Visualization Tool for Identifying Immunotherapeutic Targets in Pediatric Brain Tumors and Other Cancers".*
Presenter: Adam Resnick , PhD

c) Abstract: "*Gabriella Miller Kids First Data Resource Center Advancing Genetic Research in Childhood Cancer and Structural Birth Defects Through Large-scale Integrated Data-driven Discovery and Cloud-based Platforms for Collaborative Analysis*".
Presenter: Adam Resnick, PhD

d) Abstract: "*Functional characterization and effective targeting of NRF1-BRAF and ATG7-RAF1 fusions identified in anaplastic pleomorphic xanthoastrocytoma patients without BRAF p.V600E mutation*"
Presenter: Poonam Sonawane, PhD

e) Abstract: "*Novel FGFR2 fusions drive oncogenesis via MAPK and PI3K/mTOR pathway activation in dysembryoplastic neuroepithelial tumors"*
Presenter: Payal Jain, PhD

Brain Tumors 2018 meeting
Warsaw Poland, June 21-23, 2018
Title: "Collaborative Consortium-Based Brain Tumor Research "
Presenter: Angela Waanders, MD, MPH

POSTERS

Five scientific posters, showcasing the research work of the D³b Center, were accepted for presentation during FY18:

Pichai Raman, Komal Rathi, Karthik Kalletla, Yuankun Zhu, Bo Zhang, Nikolaus Schultz, Ethan Cerami, Alan Mackay, Chris Jones, Sabine Mueller, Javad Nazarian, John M Maris, **Phillip B Storm, Angela J Waanders, Adam C Resnick**; 'TBIO-29. PedcBioPortal, A Cancer Data Visualization Tool for Integrative Pediatric Cancer Analyses'. *Neuro-Oncology*, Volume 20, Issue suppl_2, 22 June 2018, Pages i186

Ijaz, Heba; Dilley, Robert; **Koptyra, Mateusz**; Garcia, Gonzalo; **Zhu, Yuankun; Zhang, Bo; Baubet, Valerie; Mason, Jennifer; Resnick, Adam; Gaonkar, Krutika**. 2018. 'HGG-33. Patient Derived Cell Lines To Study Atrx And Alt In Pediatric Brain Tumors', *2018 Oxford University Press US*.

Gao, Jianjiong; Mazor, Tali; Ciftci, Ersin; **Raman, Pichai**; Lukasse, Pieter; Bahceci, Istemi; Sigaras, Alexandros; Abeshouse, Adam; de Bruijn, Ino; Gross, Benjamin. 'The cBioPortal for Cancer Genomics: An Intuitive Open-source Platform for Exploration, Analysis and Visualization of Cancer Genomics Data'. *2018 American Association for Cancer Research*.

Heath, Allison P; Raman, Pichai; Zhu, Yuankun; Lilly, Jena V; Taylor, Deanne; **Storm, Phillip B; Waanders, Angela J**; Volchenboum, Sam; Stein, Lincoln; Ellrott, Kyle; 'TBIO-27. Gabriella Miller Kids First Data Resource Center Advancing Genetic Research in Childhood Cancer and Structural Birth Defects Through Large Scale Integrated Data-driven Discovery and Cloud-based Platforms for Collaborative Analysis'. *2018 Oxford University Press*.

Raman, Pichai; Rathi, Komal; Kalletla, Karthik; Zhu, Yuankun; Zhang, Bo; Cros, Anthony; Nazarian, Javad; **Waanders, Angela J**; Mueller, Sabine; **Storm, Phillip B**; 'TBIO-28. Diseasexpress, A Cancer Data Analytics and Visualization Tool for Identifying Immunotherapeutic Targets in Pediatric Brain Tumors and Other Cancers'. *2018 Oxford University Press*.

PATENT APPLICATIONS

US Patent Application No. PCT/US2017/015448 filed 1/27/2017; Entitled: Compositions and Methods for Screening Pediatric Gliomas and Methods for Treatment Thereof

International Patent Publication Number: WO 2017/132574 Al; International Application Published Under The Patent Cooperation Treaty (PCT) at the World Intellectual Property Organization, International Bureau; International Publication Date 3 August 2017 (03.08.2017); Entitled: Compositions And Methods For Screening Pediatric Gliomas And Methods Of Treatment Thereof

URL: https://patents.google.com/patent/WO2017132574A1/en

AWARDS & RECOGNITION

BGI Visiting Professor, Beijing Genomics Institute
Adam Resnick, PhD, July 2017

2017 CHOP Research Annual Report, Innovation Section
Cavatica

NIH Data Commons External Advisor
Adam Resnick, PhD , October 2017

2017 iFellows Doctoral Fellowship, Andrew W. Mellon Foundation
Alex Felmeister, MS

Chordoma Foundation Scientific Committee
Adam Resnick, PhD (selected), August 2017

PNOC Scientific Leadership Award
Adam Resnick, PhD, November 2017

Pediatric Oncology Conference, Trainee Award
Poonam Sonawane, PhD, March 2018

2018 Columbia Softball Pediatric Award, American Association of Neurological Surgeons (AANS) Annual Scientific Meeting,
Peter Madsen, MD, May 2018

2018 Young Investigator Grant, Hyundai Hope on Wheels
Jessica Foster, MD, September 2018

MEDIA COVERAGE

This list showcase some of the media coverage the D³b Center had during this year:

Children's Hospital of Philadelphia. (2017, August 15). Children's Hospital of Philadelphia to Lead New Pediatric Data Resource Center for Research in Childhood Cancer and Structural Birth Defects. Retrieved from *PRNewswire* http://www.prnewswire.com/news-releases/childrens-hospital-of-philadelphia-to-lead-new-pediatric-data-resource-center-for-research-in-childhood-cancer-and-structural-birth-defects-300504528.html

Thinkstock. (2017, August 23). Big Data Analytics Resource Center Takes Aim at Pediatric Cancer. Retrieved from *Health IT Analytics* https://healthitanalytics.com/news/big-data-analytics-resource-center-takes-aim-at-pediatric-cancer

Children's Hospital of Philadelphia Research Institute. (2017, August 25). D³b Leads Data Collaboration for Cancer and Structural Birth Defects. Retrieved from *Cornerstone* https://blog.research.chop.edu/kids-first-data-center-drc-chop%E2%80%99s-health-hero-concussions-on-air-coping-for-parents-madeline-bell

APP network. (2017, September 3). Kortney's Challenge spreads hope for pediatric brain tumor research. Retrieved from *Asbury Park Press* https://www.app.com/story/life/2017/09/03/kortneys-challenge-pediatric-brain-tumor-research/105118096/

MEDIA COVERAGE (*CONT.*)

Children's Hospital of Philadelphia. (2017, October 3). Kids First Data Resource Center Aims to Explain Links between Childhood Cancers and Birth Defects. Retrieved from *ClinicalOmics*. https://clinicalomics.com/articles/kids-first-data-resource-center-aims-to-explain-links-between-childhood-cancers-and-birth-defects/1272

Children's Hospital of Philadelphia. (2017, October 16). Biology of childhood brain tumor subtypes offers clues to precision treatments: Researchers reveal differences among gene fusions in low-grade pediatric brain tumors. Retrieved from *ScienceDaily* www.sciencedaily.com/releases/2017/10/171016190313.htm

PR Newswire. (2017, November 2). Blackfynn extends position as the leading data platform for neuroscience through funding, partnerships, product launch and team. Retrieved from *Business Insider* http://markets.businessinsider.com/news/stocks/blackfynn-extends-position-as-the-leading-data-platform-for-neuroscience-through-funding-partnerships-product-launch-and-team-1006601624

Children's Hospital of Philadelphia Research Institute. (2017, November 3). Distinctions in Tumor Biology Provide Insights for Precision Treatments. Retrieved from *Cornerstone* https://blog.research.chop.edu/in-the-news-weight-CHD-tumor-biology-iact-grant-mitochondrial-disease-guidelines

PRNewswire. (2018, February 12) Blood Profiling Atlas in Cancer Consortium (BloodPAC) Announces Milestone in Accelerating Development of Liquid Biopsy for Cancer: Initial Release of Open Data. Retrieve from *PRNewswire* .http://www.prweb.com/releases/2018/02/prweb15194915.htm

The Center for Data Driven Discovery in Biomedicine (D³b) is a transformative healthcare discovery ecosystem at Children's Hospital of Philadelphia (CHOP) Research Institute, one of the largest pediatric research institutes in the U.S.

D³b's multi-disciplinary team brings together experts in basic science, precision medicine, bioinformatics, and genomic research to provide innovative and personalized care for children through collaborative, data-driven science.

Learn more at **d3b.center**

Children's Hospital of Philadelphia
Center for Data Driven Discovery in Biomedicine