Project Title: Establishment of an International Diffuse Intrinsic Pontine Glioma (DIPG) Registry

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Section 2: Executive Summary

Brainstem gliomas account for up to 20% of all CNS tumors in children with a median age at presentation of 6-7 years.[1] Diffuse intrinsic pontine gliomas (DIPG) comprise 80% of all brainstem gliomas. In North America and Europe, approximately 300 children develop brainstem gliomas per year.[2] Prognosis for patients with DIPGs remains dismal with a median survival of less than 1 year. Although radiotherapy does improve neurological function and survival by 2-3 months, no effective chemotherapeutic regimens are currently available.[1,2] Achieving cure for all children with DIPG remains a major goal of pediatric neuro-oncology. In this application, **we propose the establishment of an International Diffuse Intrinsic Pontine Glioma Registry to provide a comprehensive database of clinical, radiologic and pathologic data linked to a bioinformatics repository of molecular data of patients.** The specific aims include: a) To recruit patients diagnosed with DIPG in the International DIPG Registry; b) To provide a repository of clinical and demographic, radiological, pathologic data for patients with DIPG enrolled on the registry and maintain annual follow-up on all cases; c) To develop a bioinformatics repository of existing molecular data on DIPGs that can be linked to patient information in the registry; d) To establish collaborations among investigators for hypothesis-driven research studies through the registry that will ultimately lead to better classification and more effective treatment of patients with DIPG. The first two projects proposed for specific aim 4 are a comprehensive study of long-term DIPG survivors based on data (clinical, radiographic, molecular and pathologic) captured in the registry, as well as an epidemiological study to assess the incidence patterns of DIPG in North America. **Our long-term goal is to establish and maintain a highly collaborative, international, hypothesis-driven research infrastructure that can support a wide spectrum of interdisciplinary and translational projects in DIPGs for all investigators**. The data collected form a research continuum from basic biology to clinical practice that will ultimately address our primary goals of a) understanding the biology of DIPGs, b) developing more effective therapies and c) developing new approaches to diagnosis, response assessment and multidisciplinary treatment and follow-up that will improve patient outcome.

Section 3: Description of Research Proposal

Brainstem gliomas account for up to 20% of all CNS tumors in children with a median age at presentation of 6-7 years.[1] In North America and Europe, approximately 300 children develop brainstem gliomas per year.[2] Prognosis for patients with diffuse intrinsic pontine gliomas (DIPGs) is poor, with a median survival of less than 1 year. Although radiotherapy does improve neurological function and survival by 2-3 months, an effective chemotherapeutic regimen has remained elusive.[1,2] Achieving cure for all children with DIPG remains a major goal of pediatric neuro-oncology. Following the successful International DIPG symposium that was sponsored by Cure Starts Now and other agencies in March 2011 in Cincinnati, the investigators and sponsors concluded that an essential need that remained unfulfilled in DIPG research was a multinational focus on developing uniform criteria for diagnosis, classification, disease assessment, and treatment for patients with DIPGs using a collaborative approach to a) delineate the biology of this disease and b) to develop novel agents and treatment paradigms, in order to improve treatment outcomes and to avoid duplicative studies.

To that end, many of the participants of that symposium have banded together to propose the establishment of an International Diffuse Intrinsic Pontine Glioma Registry to provide a data base of demographic, clinical (including treatment, outcome, toxicities, progression, survival), radiologic and pathologic data as well as a bioinformatics repository of molecular data of patients. Our long-term goal is to establish and maintain a hypothesis-driven research infrastructure that can support a wide spectrum of interdisciplinary and translational projects in DIPGs for all investigators. The data collected form a research continuum from basic biology to clinical practice that will ultimately address our primary goals of a) understanding the biology of DIPGs, b) developing more effective targeted therapies and c) developing novel approaches to uniform diagnosis, classification, response assessment and multidisciplinary treatment and follow-up that will improve patient survival and care.

Hypothesis: The establishment of the International DIPG registry will be the basis of a novel international research infrastructure for interdisciplinary and translational studies in DIPGs that will lead to a better understanding of this disease and lead to the development of more uniform and effective therapies through strong multinational collaborations among basic, translational and clinical investigators.

1.1 To recruit patients diagnosed with DIPG in the International DIPG Registry.
1.2 To provide a repository of clinical and demographic, radiological, pathologic data for patients with DIPG enrolled on the registry and maintain annual follow-up on all cases.
1.3 To develop a bioinformatics repository of existing molecular data on DIPGs that can be linked to patient information in the registry.
1.4 To establish collaborations among investigators to develop hypothesis-driven research studies through the registry that will ultimately lead to a better classification and more effective treatment of patients with DIPG.

B. Background and rationale for the proposed research project

Brainstem gliomas account for up to 20% of all CNS tumors in children less than 15 years of age with a median age at presentation of 6-7 years.[1] Diffuse intrinsic brainstem gliomas comprise 80% of all brainstem gliomas and are typically AA, GBM or Grade 2 lesions. In North America and Europe, approximately 300 children develop pontine gliomas per year.[2]

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Prognosis for patients with diffuse intrinsic brainstem gliomas is poor with a median survival of less than 1 year. [1,2] Standard therapy consists of conventional local field radiotherapy to a dose of 54-60 Gy for 6 weeks. Without radiotherapy, median survival is approximately 20 weeks. [1,3] Radiotherapy leads to improved neurological function for a few months and improves overall survival by approximately 2-3 months. Studies that have explored the efficacy of increasing the dose of RT beyond 60Gy with the use of hyperfractionation using total doses of up to 78 Gy delivered twice daily in smaller dose fractions have demonstrated no significant improvement in survival with 2 year progression free survival of less than 20%. [4]

No trials have ever shown benefit of chemotherapy for management of patients with DIPG. In North America, the Children's Cancer Group (CCG) conducted a trial between 1977-1980 to assess the potential benefit of adding chemotherapy to irradiation for children with newly diagnosed brainstem gliomas. Patients were randomized to receive either involved field radiotherapy or irradiation with concomitant vincristine followed by cycles of pCV. No difference between the two arms were observed and 5 year survival was about 20%.[5]
CCG 9941 randomized between pre-irradiation use of cyclophosphamide and cisplatin vs ifosfamide and Carboplatin. Both regimens led to few objective responses and high progression rates prior to irradiation with no improvement in overall survival. POG 8833 showed no benefit with the use of pre- irradiation chemotherapy followed by hyperfractionated irradiation at 6600 cGy.[6]

Korones et al reported the results of POG 9836 study using a combination of irradiation at 54 Gy with two 28 day cycles of vincristine, oral VP 16 starting concurrently with irradiation and continuing for ten cycles post irradiation. Of the 30 eligible patients, overall survival at one year was 27% ±7% and at 2 years was 3±2%. The median survival was 9 months (range 3-36 months). Hematological toxicity was significant.[4]
Several other studies have similarly demonstrated no survival benefit for patients with DIPG[7]. Marrow ablative chemotherapy (consisting of thiotepa and busulfan, thiotepa and etoposide with BCNU or Carboplatin, or thiotepa and cyclophosphamide did not demonstrate any survival advantage over radiotherapy alone. [8,9,10]Most recently, the Children's Oncology Group and the Pediatric Brain tumor consortium evaluated the efficacy of a variety of radiosensitizing agents (gadolinium texaphyrin) and biologic agents (farnesyl transferase inhibitors, platelet derived growth factor inhibitors and epidermal growth factor antagonists). So far, none of published reports have demonstrated improvements in outcome for children with DIPG[11,12,13].

In the US and Canada, the role of surgery has been limited to biopsy of cases where the diagnosis of DIPG is questionable and other histologies (low grade gliomas, PNETs or ependymoma) have been considered based on imaging characteristics of the tumor. Although these tumors are not resectable, the relatively high morbidity rates that have been previously reported have led to a general reluctance to biopsy these lesions unless there is a specific question regarding the diagnosis. However, more recent studies from Europe have questioned the wisdom of this approach and have advocated biopsy using more modern techniques such as stereotactic biopsies and have argued that such surgical approaches have very little morbidity and may help guide therapy in patients with a presumed diagnosis of DIPG. Recently, In Europe, tumor biopsies are routinely done at several centers based on data from Roujeau et al who reported very little morbidity associated with surgery in patients with presumed DIPG. Among 24 patients with imaging characteristics of an infiltrative diffuse pontine glioma, all underwent a suboccipital transcerebellar stereotactic biopsy. Two patients suffered deficits consisting of transient (< 2 months) new cranial nerve palsy and one of the patients also experienced an exacerbation of a preoperative hemiparesis. No patients died during the perioperative period. Twenty-two patients had a malignant infiltrative astorcytoma; one patient had a JPA and one patient had a low grade glioma. The diagnosis of the latter two affected the initial treatment after biopsy. Thus, this study demonstrated that stereotatic biopsy sampling is safe, with little morbidity and a high diagnostic yield. [14]

In recent years, our understanding of the biology of DIPGs has advanced considerably because of a concerted effort by North American oncologists to collect, and the willingness of families to donate autopsy materials for study. The biological data obtained from autopsies can ultimately be compared to the European data

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obtained from biopsy specimens. Zargooni and Hawkins have shown that gains in platelet derived growth factor receptor alpha occurred in 36% of patients with DIPGs and all showed PDGFR alpha expression. Low level gains in poly (ADP-ribose) polymerase (PARP)-1 were identified in approximately 25% of cases. [15]

We propose the establishment of an International Diffuse Intrinsic Pontine Glioma Registry to provide a repository of demographic, clinical (including epidemiologic, treatment, outcome, progression, survival, toxicities), radiologic, pathology data as well as a bioinformatics repository of molecular data of patients. Our long-term goal is to establish and maintain a hypothesis-driven research infrastructure that can support a wide spectrum of interdisciplinary and translational projects in DIPGs for all investigators. The data collected forms a research continuum from basic biology to clinical practice that will ultimately address our primary goals of a) improving our understanding of the biology of DIPGs, b) developing effective therapies and classification systems for DIPGs based on clinical, biological or imaging parameters of importance and c) developing new approaches that will impact patient care.

C. RESEARCH DESIGN AND METHODS

Hypothesis: The establishment of the International DIPG registry will be the basis of a novel international research infrastructure for interdisciplinary and translational studies in DIPGs that will lead to a better understanding of this disease and lead to the development of more uniform and effective therapies through strong multinational collaborations among basic, translational and clinical investigators.

1.1 To recruit patients diagnosed with DIPG in the International DIPG Registry.

A website will be created to inform patients/families/physicians of the International DIPG registry. The website will have separate links to the European and North American Registries. Drs. Dannis Van Vuurden and Dr. Maryam Fouladi will work together to ensure that the European and North American Registries collect the same clinical, radiologic and pathologic data to ensure that patient information in both registries can be pooled for research purposes. Given that the European collaborators in this grant are already working on different systems for their registry and imaging repository, we have decided to develop the two registries in close parallel to one another. Research projects described in the grant, as well as future research endeavors requiring registry data will be embarked on jointly using both registries' data. Both registries will use the same central review panel for pathology and radiology review. In addition, both registries have committed to supporting the bioinformatics data repository led by Dr. Jones in the UK.

1.1.1. Recruitment and Consent

Cincinnati Children's Hospital Medical Center (CCHMC) IRB approval of the web content regarding recruitment will be obtained prior to activation. Participating investigators, other referring physicians or pathologists may refer patients or patient cases (in the event the patient is deceased) to the Registry. With verbal permission of the patient/guardian, the physician or pathologist may provide their contact information to Registry personnel in accordance with all applicable FDA and NCI requirements for Human Subjects Protections. Subjects may also self-refer to the Registry. Registry personnel will then contact the patient/guardian to obtain consent. All consenting and data completion for the North American DIPG registry will be performed by delegated study staff at CCHMC. A telephone consent process will be used to obtain written consent. An attempt will be made to obtain all consent signatures on the same date. If this is not feasible, the patient/guardian may mail the consent form back to CCHMC. Upon receipt, the member of the study staff who obtained consent will sign the returned consent form. Deceased patients are eligible for inclusion in the registry. A waiver of the consent process is requested from the CCHMC IRB to allow this process.

1.1.2. Eligibility Criteria

All patients of any age who have/had a DIPG are eligible. Unless the patient is deceased, all patients and their parents or legal guardians must provide written informed consent as well as HIPAA/release of information consent.

1.1.3. Other Human Subjects Protections

CCHMC-IRB approval will be maintained by the Registry. If required at any other institution, any other institutional or IRB

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requirements will be the responsibility of the local physician/investigator. In such cases, after obtaining IRB approval, FAX an officially signed copy of the IRB approval form to Fax number to the attention of the DIPG Registry. All institutional, FDA, and NCI requirements for human studies must be met.

1.1.4. Registration

Physicians with patients to refer or patients who wish to register on the International DIPG Registry may call the International DIPG Registry Office Monday through Friday 7:30-4:00 pm EST (513-636-2799). Once a referral has been obtained, the DIPG registrar will obtain the appropriate consents for living patients from patients/legal guardians.

1.1.5. Website

An International Registry website (DIPG.org) will be developed and maintained to facilitate patient education, registry recruitment and enrollment, and to update the target audience on registry research and accomplishments. The patient education section will include information on DIPG as well as links to other DIPG oriented web-based information, including those of collaborators and funding organizations for the Registry. The recruitment and enrollment section will include links to the North American and the European Registry (led by Dr. Dannis Van Vuurden, Netherlands), a sample consent/HIPAA release for review, a description of study procedures and data collection/storage, as well as a process to initiate enrollment. The registry research section will update the audience on research projects and publication using data, samples, and images collected by the Registry. The registry will also enable parents/patients or physicians to seek a case review and second opinion from the investigators leading the registry. Additional enhancements will likely occur in subsequent funding years. The set up will involve purchase of the domain name DIPG registry.org and contract with a hosting provider (e.g. godaddy.com) which will house the HTML and related files displayed on the website. Specified functionality will include emailing functions, cascading menus, searchable meta keywords etc.

1.2 To provide a repository of clinical and demographic, radiological, pathologic data for patients with DIPG enrolled on the registry and maintain follow-up on all cases.

1.2.1 Data Collection

Clinical data, imaging studies and pathology specimens may be submitted to the Registry, or designated pathologists (see section 1.2.4) by the treating/referring physician or by the local pathologist.

Upon receiving all clinical material, personal identifiers are stripped from all pieces of data. A unique Registry number is assigned to each case. A separate list kept under a special password connects the Registry number with the personal identifiers. Access to this list is restricted to the Registry designated CRA and the Medical Director.

The process of obtaining registered patients' medical information, radiographic imaging, and pathological material has been developed specifically to minimize work load burden at the referring institutions. In North America, Cincinnati Children's Hospital Medical Center (CCHMC) will be the main site to which referring physicians from outside institutions and self-referring patients will be directed. All regulatory and IRB approvals will be obtained and maintained at CCHMC. In general, outside physicians who wish to refer their patients to the registry will not need to have the registry protocol approved by their respective institutions' IRBs. Once patients have been referred to the DIPG Registry by their physicians or other care team members, the CCHMC DIPG Registry coordinator will contact the family to obtain written informed consent. Following consent, the CCHMC DIPG Registry coordinator will work with an identified designee from the referring center to obtain pertinent source documentation including medical records, radiographic imaging on CD-ROM, and pathological material (if available). All records and imaging will be submitted using a FedEx account number supplied by the Registry. All data will be abstracted from the medical record by the CCHMC DIPG Registry coordinator, who will be solely responsible for all CRF completion in the registry database. Images submitted on CD-ROM will be uploaded, de-identified, and stored in the research PACS system housed at CCHMC.

1.2.1.1 Clinical data to be collected include:

Demographic data, date of diagnosis, symptoms and signs at diagnosis, laboratory data, detailed treatment data (e.g. types and dates of surgeries (if any)) and treatment (chemotherapy, radiotherapy), best response to treatment, dates of progression,

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types of progression (local or metastatic), relevant severe toxicities associated with therapy, long term sequelae and follow-up, quality of life data (if available), epidemiological data (family, environmental, infection and pregnancy history).

1.2.2 Data Management

Patient, imaging and tissue data will be recorded and maintained by The International DIPG Registry. The North American Registry will utilize Oncore®, a clinical trials management software system that has obtained a BIG™ Bronze Compatibility Certification from the NCI. Requests for data for research studies must be approved by the Registry Leadership Committee and will be subject to usual IRB guidelines. For any additional studies requiring additional patient information or tissue for living subjects, the patient or his legal guardian will be approached for a separate consent process. When permission has been granted by the subject or his/her surrogate, patient contact information may be released to investigators only for purposes of obtaining agreement to participate in further approved research projects.
Results of research studies on specific specimens will not be released to patients. However, results of actual studies generated from the Registry are in the public domain, and will be posted to the Registry website. Demographic, clinical, radiographic, and pathology data will be abstracted into the database using the Registry number. Reports, manuscripts and information in the website cannot be traced to individual patients, as they are supplied as statistical data only.

1.2.3. Imaging Data collection and Review

Imaging data will be submitted by physicians on CDs that will be de-identified at the time of receipt. The radiology department has a dedicated research server for the storage of de-identified research images. It is **2 terabytes** in size, expandable. It is accessible by password on the hospital network, viewed with the Amicas PACS software. The hospital should be able to grant VPN access to the outside neuroradiologists to enable them to log onto the server and view the de-identified studies. This system is being donated by the radiology research group at CCHMC. An international central neuroimaging review panel has been assembled to conduct imaging review of submitted cases on a semiannual basis. The central neuroradiologists are Dr. Blaise Jones, (CCHMC), Dr. James Leach (CCHMC) and Dr. Dawn Saunders (Great Ormond Street, UK). Consultants include Dr. Tina Young Poussaint (Boston Children's), Dr. Gilbert Vezina (Children's National Medical Center) who will review films only if there are discrepancies among the central neuroradiologists. Neuroimaging Data to be collected include: MRIs at the following time points: at diagnosis, at baseline prior to each therapeutic intervention, best response to each therapy, at time of progression with each therapeutic.
Although there is a general consensus regarding the radiographic appearance of classic vs. atypical DIPGs, no specific definitions exist. One of the goals of this registry is to learn more accurately the distinguishing features of these lesions and to come up with radiographic guidelines for the diagnosis and response assessments of DIPGs.

1.2.4. Pathology Material Submission and Review

In patients for whom biopsy or autopsy specimens are available, pathology material (see below) and reports should be sent for central pathology review to:
For North American patients: *Dr. Cynthia Hawkins,* The Hospital for Sick Children, Toronto, Canada; *Dr. Lili Miles*, Cincinnati Children's Hospital Medical Center, Cincinnati, USA.
For European patients: *Dr. Pieter Wesseling*, Radboud University Nijmegen Medical Centre, The Netherlands; *Dr. Thomas Jacques*; Great Ormond Street Hospital for Children; London, England; *Dr. Pascale Varlet,* Hospital Sainte Anne, Paris, France.

Pathology material:

Retrospective: If pathology (biopsy or autopsy) materials are available, review will be requested at the time of enrollment but is not mandatory for enrollment. Requested material:
Snap Frozen Tissue: If available, submit as many ~100-mg/ 5mm^2 pieces of tumor and normal brain tissue as possible. Wrap each piece of tissue in sterile foil and snap freeze in liquid nitrogen.
*Paraffin Blocks/ slides**: Submit representative paraffin embedded tissue blocks containing tumor. Please label blocks or slides with the institutional surgical pathology number and the patient's Registration Number. If

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blocks are unavailable, send the following slides: Two (2) H&E stained slide of each block, Five (5) unstained slides of each block.
Pathology Reports: Write the patient's Registration Number on the reports.
-Institutional pathology report; photographs of representative gross lesions, if available, specimen transmittal form (with each shipment).

Prospective: If there is prospective collection of samples at autopsy the following protocol is recommended:

1. The time of death and time of autopsy should be recorded (ie post-mortem interval)
2. Cerebrum, cerebellum and brainstem are removed from the skull, brain weight is recorded and external photographs taken (if available)
3. The brainstem is separated from the cerebrum by a transverse cut at the level of the superior colliculi
4. Transverse sections are made through the brainstem aiming for levels identified as containing tumor based on the most recent imaging. Gross photos of the transverse sections of the brainstem should be taken, if available. Tumor tissue is sampled as follows:
    i. 4 samples in cryotubes and snap frozen in liquid nitrogen for DNA/RNA extraction
    ii. samples from adjacent regions for formalin fixation and paraffin embedding

    Samples should be at least 1 cm^3 and the region of origin described on the tube as precisely as possible.
5. Macroscopically normal brain tissue (usually from frontal lobe and/or occipital lobe, depending on extent of tumor involvement) should also be sampled as for tumor tissue (#4 above).
6. The remainder of the brain can be fixed in formalin and blocked at a later date by either the referring center or the central review pathologist. Samples to be taken for paraffin embedding should include: brainstem (at least three levels), thalamus (bilateral), frontal cortex, periventricular white matter, basal ganglia, occipital cortex, hippocampus, and cerebellum.

*Paraffin blocks will be retained at the central review site at least until the Pathology Central Review Panel diagnosis is completed. For cases requiring urgent return of paraffin blocks to the primary institution, the referring institution should contact the central review pathologist to request that initiation of the review process be expedited or blocks be returned immediately after completion of central review.

Pathology Digital Repository

The Division of Pathology and Laboratory Medicine at CCHMCwill be responsible for archiving digitized pathology cases. The division has a well-established morphology research core that is fully staffed and supported by the Division of Pathology. The core lab has been in existence for more than ten years and has provided a broad range of morphology based research support to investigators including multi-institutional based studies supported by the NIH. This support service includes access to digital slide scanner by Aperio to archive pathology cases and to review slides with specialists in other institutions. The microscope is supported by a fully trained technician who will be responsible for scanning the slides and maintaining the digital files. The SCANSCOPE XT program is for most slides (H&E, special stains and immunohistochemistry stains), and the SCANSCOPE FL program is for fluorescence. Some of the features of the **XT** include automated scanning of 60 or 120 slides at a time at 20x and 40x scanning magnification capabilities. The program can rapidly create seamless and high resolution slide scans. The software also includes comprehensive morphometric analysis capabilities for investigators. The management of digital slides is simple and most importantly adherent with HIPPA regulations. The slides will be labeled with barcodes, but a data base is associated with the barcodes for all searches. The data is stored on a server, which is maintained and housed by the institutional IT service. This server is backed up by the IT service and currently has capacity for 4 terabytes of data which is expandable. This system is designed to support multi-user, multi-site, or laboratory workflow-integrated deployments.
Each neuropathologist on the panel will have an account created, and have instructions on how to login and use the software which runs right inside their web browser. A specific user would only have access to the data group (s)he is authorized to access (i.e. DIPG pathology repository), all other data is protected.

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1.3 To develop a bioinformatics repository of existing molecular data on DIPGs linked to other patients information in the registry

Molecular data including, but not restricted to, genome-wide DNA copy number, karyotyping, expression profiling (mRNA and miRNA), methylation analysis and somatic mutations will be collated into an International DIPG Bioinformatics Repository (Chris Jones). Data will be gathered retrospectively through a systematic review of published literature in DIPG, carried out according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Newly-generated data will also be incorporated by continual literature/database evaluation.

Researchers with publications identified by this systematic review will be invited to contribute any relevant data in addition to that which may be found in the published literature or databases. Investigators known to have unpublished data will be approached to either contribute pre-publication or to provide information as to when this will be possible. Data may be held in this context in a non-public (password-controlled) area.

The repository will hold data from any DIPG sample identified worldwide, and will be hosted independently to the International DIPG Registry. Sample identifiers will be linked (anonymized) to those which appear in the Registry allow for the correlation of molecular and clinicopathological variables. The repository will be held at the genomic data facility at the Institute of Molecular Life Sciences, University of Zurich (Michael Baudis). Both original raw data and processed files will be requested, and can be uploaded along with annotation files to a secure ftp site.

The repository will be built using the array Map structure (www.arraymap.org), powered by the Progenetix platform (www.progenetix.org). A separate web resource and domain will be constructed specifically for the DIPG repository, with password-controlled login to allow authorized researchers to access the full database, with a restricted public interface also available for appropriate levels of online data analysis. The Progenetix platform uses cross-platform integration and standardization algorithms to allow for comparison across datasets Password-controlled access will allow for the download of individual raw and processed data files for researchers to perform their own data integration strategies, as required. Data which include genotype calls must be held according to a confidentiality agreement in order to further protect patient confidentiality.

We intend that by combining these data we will generate a comprehensive, accessible database of the molecular profiles of DIPG for the academic community. Initial collaborative analyses will be undertaken as part of this project (Andre von Beuren, Joachim Gerss), with the following goals:

- create a low-resolution fully integrated dataset to define the frequencies of chromosomal alterations
- retain the original platform-specific data to accurately map amplification/deletion breakpoints
- compare the data with publicly available paediatric and adult high-grade glioma datasets
- investigate any retrospective clinicopathological correlations of the genetic aberrations identified
- better define the intrinsic subgroups of the disease based upon gene expression signatures
- integrate expression and genetic/epigenetic data with the copy number studies

Data generated from biospecimens contributed to the Registry, and submitted as part of the Pathology Review, will also be incorporated into the repository in a prospective manner, with due consideration given to the most appropriate platforms for data generation and integration with the repository.

1.4 To establish collaborations among investigators to develop hypothesis-driven research studies through the registry that will ultimately lead to more effective treatment of patients with DIPG.

The primary co-investigators on this grant will form a Working Group which will develop and maintain the resources to conduct interdisciplinary research and establish collaborations with external investigators. This Working Group will develop all instruments for data and imaging collection, protocols for biospecimen collection, include uniform procedures and questionnaires for data and biospecimen collection and processing. Research proposals from internal and external investigators will be evaluated by an advisory committee from among the group for scientific merit and appropriate use of resources before approval.

The following two studies will be conducted through the registry at the end of year 1.

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1.4.1: To describe the clinical, radiographic, pathological and biologic characteristics of long-term survivors with DIPG and correlate key variables with outcome.

1.4.1.1 Background: Although patients with DIPG have a dismal prognosis, long-term survivors have been reported in the literature, including in the context of clinical trials with robust inclusion/exclusion criteria. There have been very few reports specifically analysing long-term survivors due to the rarity of such patients. Apart from very young age, it is unclear whether these patients differ from other DIPG patients in terms of baseline characteristics, clinical presentation, imaging, tumour biology and treatment regimens. The establishment of an International DIPG registry (bringing together comprehensive data from multiple clinical trials and national registries) would allow the study of long-term DIPG survivors.

1.4.1.2 Methods: All patients registered in the International DIPG registry will be eligible for study. In order to be eligible for this study cases must fulfil pre-defined DIPG diagnostic criteria based on clinical and radiological data (i.e. minimum MRI images will be required) plus, if available, pathology data. Cases who have an overall survival of greater than 2 years will be studied. Data collection will include: demographics (age, gender, ethnicity, relevant past medical history & family history), symptoms & signs at diagnosis and their duration, MRI features at diagnosis and during disease (including if available advanced imaging techniques), treatment regimen and (clinical and radiological) response to treatment. Radiology will be reviewed by a panel of independent neuroradiologists to confirm the diagnosis of DIPG and documented response. Biology: If a biopsy has been performed, the material will be collected and reviewed by a panel of independent neuropathologists for histological diagnosis. In cases of long-term survivors who ultimately have succumbed to their illness, any autopsy samples will also be reviewed by the panel. If tumour tissue has already had molecular analysis or there is available tissue there will be further analysis of the underlying molecular pathology of the long term survival cases.

1.4.1.3 Statistics: The data from long-term survivors will be compared to matched historical cohorts. Multivariate regression analyses will be performed to compare the outcome variables.

1.4.2 An epidemiological study to determine incidence patterns of DIPG in North America 2000-2010.

1.4.2.1 Background: Currently, there are no epidemiologic data on the incidence patterns and trends of DIPG. Most information on the incidence comes from limited institutional series. The Canadian Pediatric Brain Tumor Consortium has representation from all the Canadian university-affiliated teaching hospitals where close to 100% of the children with brain tumors are being treated (the exception are some teenagers referred to adult services), and therefore, a true cross-Canada epidemiologic survey is feasible. In the US, we will approach all the Pediatric Brain Tumor Consortium Institutions as well as other large volume pediatric neuro-oncology programs (e.g. Boston, Seattle, Atlanta, Children's Hospital of Los Angeles) to garner support for enrollment of patients on the registry. This approach should provide us access to the vast majority of patients with DIPG in the US. We propose to study the epidemiology of DIPG across Canada and the US between 2000 and 2010. We will study the annual incidence (variation, trend), the seasonal variations in incidence, clusters (by collecting postal codes/ZIP codes), and geographical distribution. 1.4.2.2 Inclusion Criteria: All patients diagnosed with DIPGs between the ages of 0-21 who are in the registry will be included. Proven pathologic diagnosis is not required and we do not expect pathology to be available in the majority of patients.

1.4.2.3 Method: Clinical, radiologic data on patients with DIPG will be sent to the registry as described previously. The registry personnel will enroll the patients and enter all data into the registry. The data required for this study (see appendix A) will be extracted from the registry data base by the registry personnel. The central neuroradiology panel will review at least two MRI sequences at diagnosis including 1 Axial T2 or FLAIR picture of the tumor in the area of largest dimension and 1Sagittal T2 or Flair picture of the tumour in

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the area of largest dimension. All imaging studies will be reviewed centrally by the neuroradiology panel to further classify as focal or diffuse pontine glioma.

1.4.2.4 Statistical Design: Descriptive statistics and incidence trends will be calculated.

1.4.2.5 Relevance to Patients with DIPG: Information regarding epidemiology of diffuse pontine glioma is scant. The understanding of the incidence of these tumors is necessary in planning future strategies and protocol development. Furthermore, identifying clinical features that may be associated with prognosis would be important in future clinical trials.

1.4.2.5 Possible Pitfalls: The registry will not capture all patients with DIPG in North America.

D. Use of Human Subjects

D.1. Patient Characteristics: Patients living or deceased with DIPG who meet the eligibility criteria can enroll. No patient will be refused enrollment on the registry on the basis of race, religion, ethnic background, physical or mental disability. Patients will be enrolled on this registry indefinitely.

D.2. Recruitment and Informed Consent: Patients with DIPG can be referred for enrollment. These procedures are outlined in sections 1.1.1-1.1.3 of the application. Copies of all signed documents will be provided to patients and/or legal guardians. Institutional policies for obtaining assent will be followed.

D.3 Potential Risks and Procedures for Minimizing Potential Risk: This is not a therapeutic protocol; so there are no potential risks associated with therapy. One risk is the inadvertent release of information from health records or information from biological material. The registry will make every effort within the limits imposed by technology and the law to protect the records so that patients' identifying data are kept private. All patient data will be deidentified prior to being entered onto the registry. The DIPG registry data base, where this information would be held, is compliant with all U.S. Department Health and Human Services requirements for the maintenance of confidential patient information. The chance that this information will be given to someone else, besides researchers, by mistake is very small. All biological material if available, is deidentified prior to entry in to the repository. Access to the pathologic and molecular biology bioinformatics repository will be password protected and limited to the investigators.

D.4 Anticipated Benefits to Patients and knowledge to be gained: Patient data in this registry will be used to better understandthe biology of DIPGs, developing novel approaches to uniform diagnosis, classification, response assessment and multidisciplinary treatment and follow-up for DIPGs and ultimately to assist us in developing scientifically rational and effective targeted therapies that will improve patient survival and care.

D5. Women and Minority Inclusion for Research Involving Human Subjects. Entry onto the registry will not depend on the sex or race of the patients.

E. Disease Impact and Innovation

The outcome for children with diffuse intrinsic pontine gliomas (DIPGs) remains dismal with no curative treatment options. Since the number of children diagnosed with DIPGs is small, our proposal to establish an International Diffuse Intrinsic Pontine Glioma Registry that captures linked clinical, radiologic, pathologic and molecular data will provide a highly collaborative, hypothesis-driven research infrastructure that can support a wide spectrum of interdisciplinary and translational projects in DIPGs for investigators. During the first year, we propose to conduct two studies. The first study will describe the clinical, treatment, radiographic,

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pathological and biologic characteristics of long-term survivors with DIPG and will correlate variables of interest with survival. If certain characteristics are found to correlate with better outcome, we may succeed in classifying subgroups of patients who, based on their pathological, molecular or clinical characteristics have better survival or respond better to agents targeting specific pathways. Such findings may quickly pave the way to the development of more effective therapy for a subgroup of patients. The second is an epidemiological study to determine the incidence patterns of DIPG in North America that may delineate the etiology of DIPGs and characteristics associated with prognosis.

The data collected in this registry will form a research continuum from basic to clinical practice that will ultimately address our primary goals of a) understanding the biology of DIPGs, b) developing more effective targeted therapies and c) developing novel approaches to uniform diagnosis, classification, response assessment and multidisciplinary treatment and follow-up that will improve patient survival and care.

F. Update on Current Status: (June 2015)

The International DIPG Registry is now the largest and most comprehensive collection of data from a diverse cohort of DIPG patients available to researchers in the world. With the generous support of a coalition of pediatric brain tumor foundations from the DIPG Collaborative, and collaborations with more than 40 academic medical centers in the US, Canada and Australia, the registry is growing exponentially. To date, 405 patients have been enrolled; with more than 500 additional patients committed from participating institutions. Data are fully abstracted on all 405 patients. The radiology repository contains over 1731 studies on 270 patients. Each diagnostic MRI is being centrally reviewed by two neuroradiologists. The pathology repository contains tissue on 24 patients, 212 specimens. However, approximately 30% of patients have had either biopsies or autopsies performed, and we hope to expand the tissue acquisition efforts. To date, 13 autopsies have been performed for tumor donation to the DIPG Registry and several have been coordinated for families at sites across the country through the efforts of the DIPG Registry.

DIPG Registry staff members continue to work on the frontlines of DIPG research. In an effort to rapidly increase enrollment, they have traveled to sites including Seattle Children's, Children's National, and Children's Hospital of Philadelphia to retrieve patient records, neuroimaging and tumor samples directly. Our regulatory expert has worked with sites to assist in ensuring sites can successfully participate and fulfil their obligations for their Institutional Research Board. The DIPG Registry has presented its work at the International Society for Pediatric Neuro-Oncology (ISPNO, 2014) conference in Singapore and at the AACR/Pediatric Society of Neuro-Oncology (SNO, 2015) conference in San Diego, as well as at DIPG Symposium in Chicago.

The DIPG Registry now has 4 studies that have been approved by the Scientific Advisory Committee and are in various stages of conduct and analysis.

a) **To describe the clinical, radiographic, pathological and biologic characteristics of long-term survivors with DIPG and correlate key variables with outcome. Oral presentation by Dr. Lindsey Hoffman, at Peds AACR/SNO 2015**

Children with diffuse intrinsic brainstem glioma (DIPG) have a median survival of less than 1 year despite radiation ± chemotherapy. The International DIPG Registry, a collaborative effort among

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researchers in North America and Australia has enrolled 395 patients with data for over 900 patients committed from 35 institutions. Among the 395 patients, 32 long-term survivors (LTS) (overall survival [OS] $\geq$ 2 years) have been identified. Preliminarily, we report clinical, radiographic, and histologic data for 112 of 395 patients, including the 32 LTS and 80 in the comparison (C) group. On central radiographic review, 5 were deemed not to represent DIPG (3 LTS and 2 C). Median age at diagnosis for LTS and C groups was 5.8 and 6.4 years, respectively. Fifty-seven percent of LTS had > 6 weeks between onset of symptoms and diagnosis versus 28% for the comparison group ($p<0.05$). Incidence of signs and symptoms at diagnosis (cranial nerve, cerebellar, or pyramidal) was similar in both groups. All patients, except 3 LTS, underwent radiation at diagnosis; all but 6 received adjunct chemotherapy. Median OS was 28.4 and 10.8 months for the LTS and C groups, respectively. Two patients (1 LTS) had an H3.3K27M mutation and 2 (1 LTS) had an H3.1K27M mutation. Biology data from 25 other patients from autopsy (n=12) or biopsy (n=13) are under analysis. Presence of enhancement on diagnostic imaging was associated with poorer survival ($p=0.02$). There was no significant difference in radiographic evidence of hemorrhage, necrosis, diffusion restriction, or tumor size between LTS and C groups. Predictors of longer term survival in patients with DIPG include absence of cranial nerve palsies and pyramidal signs, absence of necrosis on diagnostic imaging and low grade histology.

b) **An epidemiological study to determine incidence patterns of DIPG in North America 2000-2010.** Our Canadian collaborators have presented the Canadian epidemiology in the past year and we hope to be able to validate their data with ours in the next year.

Two other studies that have been approved in 2015 involving the use of tissue repository resources:

c) **Establishment of *in vitro* and *in vivo* Models (Michelle Monje, Xiao-Nan, Li). Tissue from two autopsies have already been shared with these investigators to establish models.**

d) **Comprehensive Molecular and Genomic Study of DIPG (Becher, Hawkins, Nazarian, Drissi)**

Another study under consideration is the validation of the survival prediction model, developed within a cohort of European DIPG patients (Sophie Veldhuijzen van Zanten, Danis Van Vuurden)

Two registry manuscripts are in preparation in 2015, focusing on the establishment of the DIPG registry and long-term survivors. We hope to also receive SAC approval for the two validation studies outlined above and publish our findings.

In 2015, Dr. Cynthia Hawkins, who is already directing the DIPG tissue repository in Canada, took over the leadership of the International DIPG Registry bioinformatics/genomics repository, since the European Registry will have parallel efforts led by Dr. Chris Jones. Preliminary data from the registry demonstrate that approximately 30% of patients have undergone a biopsy or autopsy and may have tissue available. Many of these patients have had their tumors profiled and their data have been included in recent publications. An important goal of the registry is to attempt to link anonymized genomics data from published studies to the clinical, neuroimaging and pathological data on these patients. In addition, the study approved by the DIPG

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Registry SAC to conduct a comprehensive molecular and genomic study of DIPG tissues in the registry (Becher, Hawkins, Nazarian, Drissi) will allow us to conduct these studies and link data from these studies to patients enrolled on the registry in an anonymized manner. One critical goal will be to establish the infrastructure for this genomics/bioinformatics repository over the next year.

In the next 3 years, Registry investigators will promote robust collaborative research projects on all aspects of DIPG, and will continue to make Registry data available to external investigators after review of the proposed research by SAC. In an effort to support innovative research, we plan to grow the Registry cohort to greater than 1,000 patients and expanding internationally to Japan and New Zealand with whom we have already had some discussions. We are also considering a later expansion to the other countries in the Middle East, China, Central and South America. Another important area of focus is the development of supplemental educational materials for families and medical teams.

Finally, our website continues to serve as a resource to families and medical professionals, providing international consultations, answering questions and providing education and updates about the latest research in DIPG. In 2015, the website will undergo a redesign, which should be re-launched this summer 2015 with updated and improved content, and research updates.

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Section 4: BUDGET: 2016, 2017, 2018

A. PERSONNEL: $508,955

Neuro-oncologist (Maryam Fouladi)-Principal Investigator: 5% salary support **$34,506**

Neuro-oncologist (Lindsey Hoffman) – Co-investigator: DIPG Registry research project support: 5% salary support **$29,481**

Project Manager (Josh Baugh) at CCHMC: The project manager will have primary responsibility for:

- Building the operational and data management processes to make the registry a success. This includes development of case report forms in the registry database.
- Managing all of the regulatory approvals and ongoing compliance needs for the registry.
- Identifying potential participants, consenting participants, completing enrollment in the registry, requesting medical records, imaging, and tissue samples, in addition to abstracting data into the registry database and completing all follow up data. (North American and Australian patients)
- Work closely with personnel at referring institutions to maximize enrollment, data quality/timeliness.
- Coordinate the central review of pathology and imaging to ensure data quality. Managing the registry website and any other approved recruitment methods.

Salary requested is **$34,000** (Year 1), **$35,020** (Year 2), **$36,071** (Year 3) Fringe requested is **$8,670** (Year 1) **$8,930** (Year 2) **$9,198** (Year 3). Total: Salary $105,091 + Fringe $26,798= **$131,889**

Research Coordinator/Data Technician (Brooklyn Hacker) at CCHMC: The coordinator will have responsibilities for:

- Abstracting data into the registry database and assisting with follow up data. (North American and Australian patients)
- Will provide coverage for the lead coordinator and assist with the management of the Registry as needed.

Salary requested is **$33,000** (Year 1), **$33,990** (Year 2), **$35,010** (Year 3) Fringe requested is **$8,415** (Year 1) **$8,667** (Year 2) **$8,928** (Year 3). Total: Salary $102,000 + Fringe $26,010= **$128,010**

Regulatory Specialist (Renee Doughman) for IRB support and ethics consultation both at CCHMC and with external institutions: 15% salary support **$46,462**

DIPG Genomics Repository: Bioinformatician: (Pawel Buczkowicz) Sick Kids-for WES pipeline development, database maintenance, sample processing and support: 25% salary support = **$75,000**

Radiology Central Reviewers: 2 central reviewers at CCHMC (Drs. Leach and Jones) will be reviewing all imaging for patients enrolled on the registry and ensuring upload into the PACS research system; 2% salary support **$11,697** for Dr. Leach, **$13,803** for Dr. Jones.

Radiology Technician (Rose Martin) in charge of uploading all imaging into research PACS system: 7% salary support **$8,772**

Central Neuropathologist *at CCHMC* (TBD) who will review pathology for all patients submitted to CCHMC. She will also be responsible for overseeing digitization and archiving of all pathology cases received from other central neuropathologists from North America and Europe in order to establish a digital pathology repository for the registry: 2% salary support **$11,697**

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Pathology technician (Janette Fellows) to digitize, archive and keep track of all slides that are submitted: 5% salary support **$6,000**

Statistician (Adam Lane) for data mining (clinical, radiology, pathology for projects 1 and 2), data analysis and ensuring integrity of the data in the database: 3% salary support **$11,638**

B. TECHNOLOGY: $ 76,780

Information Database: Unified Registries Management module, donated to this project by Forte Research Systems, Madison, Wisconsin;

Imaging Database: Research PACS donated to this project to Cincinnati Children's Hospital Medical Center, Imaging Research Center. Fee Per Patient- $100.00 x 250 patients = $25,000 per year x 3= **$75,000**

Includes:

- Object storage and management
- Use of visualization software
- Metadata anonymization
- Cross referencing

DIPG Genomics Repository: (Sick Kids)

1-year data storage of 1 exome (BAM and vcf files ~10GB, $4/exome)...if paired (tumour/normal) ~$8.
Year 1: 50 samples paired (tumour/normal) $400/year
Year 2: 70 samples paired (tumour/normal) $560/year
Year 3: 90 samples paired (tumour/normal) $720/year
Total data storage cost for 3-years assuming 90 paired WES samples over 3 years = **$1,680.00**

Website Domain: **$300.00**

Website Development and Maintenance: The Information Systems team within the Cancer & Blood Diseases Institute of Cincinnati Children's Hospital Medical Center will provide the website development and maintenance support for the registry at no additional cost to the Registry project.

C. TRAVEL: $30,000

Trips to retrieve retrospective patient data and to conferences for 2 people- $10,000 per year x 3=**$30,000**

D. SUPPLIES/SHIPPING: $84,000

Supplies and shipping cost = Year 1 ($120/patient x 150 patients): $18,000
Year 2 ($120/patient x 150 patients): $18,000
Year 3 ($120/patient x 150 patients): $18,000
Total: **$54,000**

Includes:

- CDs, copies, fax machine, shipping supplies for tissue samples, slides, cutting of slides by other institutions' pathologists (both locally and to support costs from other institutions who submit data)

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- Shipping of Records/Imaging/Pathology from referring institutions
- Shipping Images to NeuroImaging central reviews (remote viewing likely capable in Year 2 of project)

Autopsies: ($1,000/patient x 10): $10,000 x 3 years= **$30,000**

- Includes cost of transportation and pathology cost.

Budget requested is $699,935 total for 2016, 2017, 2018

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Conflict of Interest Statements

b. P.I. must include a statement in this section that discloses any potential conflicts of interest regarding the research project or its funding by The Cure Starts Now. The P.I. must sign this conflict of interest statement (no stamps accepted). A potential conflict of interest is a situation in which a reviewer or individual involved in a funding decision, a family member, a friend, or other associate is in a position to gain or lose personally or professionally by the foundation's funding of the program.

PI was a co-organizer of the DIPG symposium organized by Cure Starts Now and other agencies.

Maryam Fouladi, MD

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