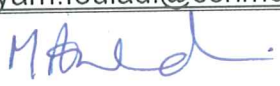


## SECTION 1: CONTACT INFORMATION

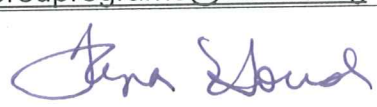
**Institute:** Children's Hospital Medical Center

**Title:** A study of Radiotherapy and concurrent Bevacizumab± Temozolomide followed by Bevacizumab, Irinotecan±Temozolamide in patients with newly diagnosed high grade gliomas and diffuse Intrinsic Pontine Gliomas

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## Section 2: Executive Summary

Five-year overall survival in children with high-grade glioma (HGG) and diffuse, intrinsic brainstem glioma (DIPG) are approximately 25% and 10%, respectively<sup>1-3</sup>. Achieving cure for all children with HGG and DIPG remains a major goal of pediatric neuro-oncology. DIPGs are infiltrative gliomas, and have typically been found to be high-grade in histology<sup>1,3</sup> when tissue confirmation has been available. HGGs are highly vascularized and infiltrative tumors. They are dependent on endothelial cell proliferation regulated by proangiogenic cytokines, especially vascular endothelial growth factor [VEGF]. In fact, VEGF expression has been shown to correlate with worse prognosis in patients with HGG<sup>4,5</sup>. Furthermore, in a xenograft model, antibodies to VEGF have inhibited the growth of GBM<sup>6</sup>. Recently, the targeting of VEGF signaling, with bevacizumab in patients with recurrent HGG has led to unprecedented rates of durable responses both clinically and radiographically, with a tolerable toxicity profile among recurrent malignant glioma patients<sup>7</sup>. We propose targeting of VEGF signaling as a potential therapeutic target for pediatric HGG and DIPG. Pre-clinical and clinical studies with VEGF targeting agents have demonstrated *in vitro* and *in vivo* activity of these agents in HGG.<sup>8-11</sup> The most effective and well-studied drug targeting VEGF signaling is bevacizumab, a VEGF-specific recombinant, humanized monoclonal antibody. Bevacizumab + irinotecan has led to response rates of 60% and 6 month progression-free survival rates of 46% in adults with recurrent HGG. In this application, we propose a pilot study, designed to assess feasibility, tolerability, molecular activity and therapeutic potential of bevacizumab and irinotecan±temozolomide (TEM) in children with newly diagnosed HGG and DIPG. Data from this pilot study will be used in the rational design of future studies to stratify patients for targeted therapy and improve the clinical and functional outcome in children with these poor prognosis tumors.

### **Hypothesis 1: The treatment regimens proposed (bevacizumab± temozolomide and concurrent radiotherapy followed by bevacizumab and irinotecan ± temozolomide) are feasible, well-tolerated and efficacious in children with newly diagnosed HGG and DIPG tumors**

- 1.1 To determine the proposed regimen's feasibility and toxicities in patients with HGG and DIPG.
- 1.2 To determine the one year EFS, median PFS and median OS in newly diagnosed patients with HGG treated with radiotherapy and concurrent temozolomide, bevacizumab followed by bevacizumab, irinotecan and temozolomide for 12 courses.
- 1.3 To determine the 1-yr EFS, median PFS and OS in newly diagnosed patients with DIPG undergoing radiotherapy and concurrent bevacizumab followed by bevacizumab, irinotecan for 12 courses.

### **Hypothesis 2: Children with HGG and DIPG have characteristic molecular and radiographic features that correlate with response and PFS.**

- 2.1 To estimate the incidence of VEGF expression and pathway activation in tumor as well as blood of patients with HGG and DIPG (blood only) and at different time points
- 2.2 To document changes in MR perfusion and diffusion within 24-48 hours after the 2<sup>nd</sup> dose of bevacizumab during radiotherapy and correlate functional changes in tumor with responses to treatment
- 2.3 To conduct gene expression profiling, CGH and SNP arrays in tumor and blood of patients
- 2.4 To assess telomerase activity, *hTert* expression, and telomere length in patients' blood and tumor
- 2.5 To correlate the results of the biology studies in serum or tumor with PFS

### **Hypothesis 3: The proposed treatment in children with HGG and DIPG will lead to better quality of life and functional outcomes**

- 3.1 To assess the health related quality of life of patients by parent report, and when possible, patient report at key points in therapy
- 3.2 To assess functional abilities and level of independence of patients during and following treatment.

**Statistical Considerations:** The primary objective of the study is to assess the safety and feasibility of the study regimen. Stopping rules have been defined. We will estimate event-free-survival and overall survival for patients by each stratum using Kaplan-Meier curves. Descriptive statistics will be used to investigate the secondary objectives. We will estimate the frequency of the laboratory marker/indicator and perform exploratory analysis to correlate them with the survival outcomes

### Section 3: Research Plan

#### A. Specific Aims

Five-year overall survival in children with high-grade glioma (HGG) and diffuse, intrinsic brainstem glioma (DIPG), are approximately 25% and 10%, respectively<sup>1-3</sup>, and the outcome for patients with recurrent disease is dismal. Thus, achieving cure for all children with HGG and DIPG remains a major goal of pediatric neuro-oncology. DIPGs are infiltrative gliomas, and have typically been found to be high-grade in histology<sup>1,3</sup> when tissue confirmation has been obtained at diagnosis or autopsy. HGG are highly vascularized and infiltrative tumors. They are dependent on endothelial cell proliferation regulated by proangiogenic cytokines, especially vascular endothelial growth factor [VEGF]. In fact, VEGF expression has been shown to correlate with worse prognosis in patients with high grade gliomas<sup>4,5</sup>. Furthermore, in a GBM xenograft model, antibodies to VEGF have inhibited the growth of tumor<sup>6</sup>. Recently, the targeting of VEGF signaling, with bevacizumab, in patients with recurrent malignant gliomas has led to unprecedented rates of durable responses both clinically and radiographically, with a tolerable toxicity profile among recurrent malignant glioma patients<sup>7</sup>. We propose targeting of VEGF signaling as a potential therapeutic target for pediatric HGG and DIPG. Pre-clinical and clinical studies with VEGF targeting agents have demonstrated *in vitro* and *in vivo* activity of these agents in HGG.<sup>8-11</sup> The most effective and well-studied drug targeting VEGF signaling is bevacizumab, a VEGF-specific recombinant, humanized monoclonal antibody. The combination of bevacizumab + irinotecan has led to response rates of 60% and 6 month progression-free survival rates of 46% in adults with recurrent HGG<sup>7</sup>. In this application, we propose to investigate the molecular activity and therapeutic potential of bevacizumab and irinotecan±Temozolomide (TEM) in children with newly diagnosed HGG and DIPG.

The primary aims of this proposal are a) To determine the toxicities and feasibility of this treatment regimen in patients with HGG and DIPG b) To determine the one year EFS, median PFS and OS in newly diagnosed patients with HGG treated with radiotherapy and concurrent temozolamide, bevacizumab followed by bevacizumab, irinotecan and TEM for 12 courses c) To determine the one year EFS, median PFS and median OS in newly diagnosed patients with DIPG treated with radiotherapy and concurrent bevacizumab followed by bevacizumab and irinotecan for 12 courses. The secondary aims of this study are to a) To estimate blood levels of VEGFR2 related signaling pathways; c) To conduct gene expression profiling, CGH and SNP arrays in patients, d) To assess the role of telomerase in patients with HGG and DIPG e) To assess quality of life and functional abilities of patients with HGG and DIPG during and following treatment.

Data from this pilot study will be used in the rational design of future studies to stratify patients for targeted therapy and to improve the clinical and functional outcome in children with these poor prognosis tumors.

#### **Hypothesis 1: The bevacizumab combination treatment regimens proposed are feasible, well-tolerated and efficacious in children with newly diagnosed HGG and DIPG tumors**

- 1.4 To determine the proposed regimen's feasibility and toxicities in patients with HGG and DIPG.
- 1.5 To determine the one year EFS, median PFS and median OS in newly diagnosed patients with HGG treated with radiotherapy and concurrent temozolamide, bevacizumab followed by bevacizumab, irinotecan and temozolimde for 12 courses.
- 1.6 To determine the 1-yr EFS, median PFS and median OS in newly diagnosed patients with DIPG undergoing radiotherapy and concurrent bevacizumab followed by bevacizumab, irinotecan for 12 courses.

#### **Hypothesis 2: Children with HGG and DIPG have characteristic molecular and radiographic features that correlate with response and PFS.**

- 2.6 To estimate the incidence of VEGF expression and pathway activation in tumor as well as blood of patients with DIPG ( blood only) and HGG at different time points
- 2.7 To document changes in MR perfusion and diffusion within 24- 48 hours after the 2<sup>rd</sup> dose of bevacizumab during radiotherapy and correlate functional changes in tumor with responses to treatment
- 2.8 To conduct gene expression profiling, CGH and SNP arrays in tumor and blood of patients
- 2.9 To assess telomerase activity, *hTert* expression, and telomere length in patients' tumor and blood
- 2.10 To correlate the results of the biology studies in serum or tumor with PFS

**Hypothesis 3: The proposed treatment in children with HGG and DIPG will lead to better quality of life and functional outcomes**

- 3.1 To assess the health related quality of life of patients by parent report, and when possible, patient report at key points in therapy
- 3.2 To assess functional abilities and level of independence of patients during and following treatment.

**B. Background and Significance**

**B1. Rationale for the use of the proposed combination**

Diffuse intrinsic brainstem gliomas are infiltrative gliomas, and have typically been found to be high-grade in histology<sup>1,3</sup> when tissue confirmation has been obtained at diagnosis or autopsy. High-grade gliomas are highly vascularized and infiltrative tumors. They are dependent on endothelial cell proliferation regulated by proangiogenic cytokines, chief among them vascular endothelial growth factor [VEGF]. In fact, VEGF expression has been shown to correlate with worse prognosis in patients with HGG.<sup>14</sup> and antibodies to VEGF have inhibited the growth of GBM in a xenograft model<sup>6</sup>.

Bevacizumab is a VEGF-specific recombinant, humanized monoclonal antibody that binds directly to all four VEGF isoforms with high affinity and specificity and inhibits VEGF from binding to its receptors.

Bevacizumab has been approved by Food and Drug Administration for usage for first- or second-line treatment in combination with chemotherapy in adults with colorectal carcinoma. The most significant adverse events include hypertension, proteinuria, thrombosis and bleeding. However, in large randomized studies with and without bevacizumab there does not appear to be a statistically significant increase in venous thrombotic events.

The Children's Oncology Group has completed a pediatric phase I study of bevacizumab in patients with refractory solid tumors. Three dose levels (5 mg/kg, 10 mg/kg and 15 mg/kg every 2 weeks intravenously) were studied in a total of 18 evaluable patients. No dose-limiting toxicities were observed. PK studies revealed increased serum exposure with dose. No objective responses were observed. Five patients had disease stabilization for > 3 months.<sup>12</sup> Bevacizumab has demonstrated synergy with several chemotherapeutic agents including cisplatin, camptothecins and cyclophosphamide in preclinical xenograft models and has decreased vascular permeability and increased cellular apoptosis in GBM xenograft models.<sup>13</sup>

Recent studies using bevacizumab ±irinotecan in adults with recurrent HGG has led to unprecedented rates of durable responses, both clinically and radiographically, with a tolerable toxicity profile. Vredenburgh<sup>7</sup> et al evaluated this combination in patients with recurrent advanced HGG in a phase II trial. Bevacizumab was administered at 10mg/kg IV q14d. Irinotecan dose for patients on EIACD was 340 mg/m<sup>2</sup>, compared to 125 mg/m<sup>2</sup> for those without. Objective responses (OR) were noted in 63%. The 6 month PFS was 38%. Three patients developed a DVT or pulmonary emboli and one patient had an arterial ischemic stroke. Cloughesy et al reported the interim results of a randomized phase II trial using bevacizumab vs bevacizumab/irinotecan in patients with recurrent high grade glioma in which 167 patients were randomized to receive bevacizumab (n=85) or bevacizumab + irinotecan (n=82), every 2 weeks. 6-month PFS was 35.6% for bevacizumab (ORR=21.2%) and 51% for bevacizumab/CPT-11 (ORR=34.1%), based on independent radiological review<sup>14</sup>. A pediatric study of irinotecan and bevacizumab in patients with recurrent HGG and DIPG is currently being conducted by the Pediatric Brain Tumor Consortium. The combination has been found to be tolerable and feasible. (Gururangan et al, personal communication). Efficacy data are pending.

**Bevacizumab during RT**

Gorski et al demonstrated that irradiation of tumor cells induced increased VEGF expression. Pre-treatment of GBM xenografts *in vivo* with anti-VEGF therapy, had a greater than additive effect when combined with subsequent radiation.<sup>15</sup> Lee et al demonstrated that anti-VEGF mAB exposure induced reduction of tumor vascular density and a reduction of tumor interstitial fluid pressure by 74%. Combined treatment with radiation yielded greater than additive tumor growth delay, suggesting that anti-VEGF therapy mitigated the impact of hypoxic conditions in this GBM model *in vivo*.<sup>16</sup> An orthotopically placed U87 glioblastoma mouse was treated with anti-VEGR2, DC101, therapy. Maximum tumor oxygenation occurred by day 5 following drug exposure,

and decreased again by day 8. Radiation exposure days 4-6 following DC101 exposure yielded synergistic effects, whereas alternative schedules had no more than additive effects.<sup>17</sup>

Batchelor et al reported that anti-VEGF therapy normalized the tumor vasculature and alleviates edema in glioblastoma patients. In their report of 16 glioblastoma patients treated with the anti-VEGF agent AZD2171, the onset of vascular normalization was rapid and sustainable, but reversible by 28 days following cessation of drug therapy.<sup>18</sup> Gonzalez et al similarly reported the MD Anderson experience with 15 patients with malignant glioma, 8 of whom were diagnosed with radiation necrosis. Bevacizumab anti-VEGF therapy either alone or in combination with chemotherapy reduced radiation necrosis by decreasing capillary leak and associated brain edema in all 8 patients demonstrated by MRI performed 8 weeks following therapy initiation.

Mohile et al conducted a study in patients with recurrent HGG, who received bevacizumab 10 mg/kg iv q 2 weeks and stereotactic intensity modulated IMRT: 30 Gy in 5 fractions over 15 days. 12 patients with HGG received a median of 5.5 cycles of therapy. Grade 3 events occurred in 10 patients, including hypertension, headache, neutropenia, seizures, hyponatremia and hypophosphatemia. There were no grade 4 or 5 events, no DLTs and no intracranial hemorrhage. 7/12 patients had objective responses (3 CR, 4 PR). Estimated 6 month PFS was 76%. MR perfusion imaging demonstrated a decrease in mean perfusion values after 1 cycle of bevacizumab.<sup>19</sup> Cloughesy et al are conducting a frontline study in patients with newly diagnosed HGG, in which bevacizumab and temozolamide are given concurrently with RT followed by bevacizumab and temozolamide. Preliminary results demonstrate feasibility and tolerability of this combination in newly diagnosed patients with HGG. (Cloughesy et al, personal communication)

#### Rationale for Irinotecan and temozolomide

Irinotecan is a water-soluble chemical derivative of camptothecin, which inhibits topoisomerase I, an enzyme necessary for DNA replication. Irinotecan has shown marked single agent activity against adult and pediatric GBM models. And objective response rates of up to 15%<sup>20</sup> in adult and 44% in children with refractory HGG.<sup>21</sup> In addition to the single-agent activity and non-overlapping toxicity profiles, irinotecan and TEM is an attractive combination because of significant therapeutic synergy demonstrated by Houghton et al. in preclinical experiments.<sup>22</sup> Activity is greatest when TEM is given before irinotecan.<sup>23</sup> Studies in adults have demonstrated up to a 28% RR and a 6 month PFS of 39% with this combination.<sup>24</sup> Pediatric trials with this combination have also proven to be tolerable.<sup>25</sup> No pharmacokinetic interactions were observed.

#### **Rationale for the combination of bevacizumab, irinotecan and Temozolomide**

Maron et al reported the early results of a phase II trial of bevacizumab and temozolomide in patients with recurrent GBM. The treatment had acceptable toxicity: 1 patient had grade 4 hemorrhagic pancreatitis, and 1 had grade 5 PCP. There was no > grade 3 hematologic toxicity, and no CNS hemorrhages. Of 32 patients, 12 (37.5%) had a PR.<sup>26</sup> The combination of bevacizumab, irinotecan and TEM is currently being used in adults with newly diagnosed HGG at Duke University (Dr. Sri Gururangan, personal communication). Although no large reports have been published on the 3 drug regimen in HGG, there are anecdotal reports of its tolerability and efficacy published<sup>27</sup>. Furthermore, the fact that these three drugs do not have overlapping toxicities and are potentially synergistic<sup>28</sup> makes this combination of great interest in pediatric HGGs

*The current proposal will be the first pediatric study of the proposed regimen in patients with newly diagnosed HGG and DIPG, in which the feasibility and tolerability of this regimen will be elucidated. This study will also assess the efficacy of this regimen in inhibiting a variety of molecular targets in blood and in leading to a better event-free survival in patients with newly diagnosed HGG and DIPG.*

#### **B2. Molecular correlates of activity of antiangiogenic agents**

**Evaluation of blood levels of VEGF, BFGF, TSP-1, I-CAM, v-CAM and circulating endothelial cells in patients and subsequent detection of proteome-wide biomarkers.** Sathornsumetee et al reported that in patients with recurrent malignant astrocytomas treated with bevacizumab and irinotecan, VEGF, VEGF receptor-2, CD31, hypoxia-inducible carbonic anhydrase 9 (CA9), and hypoxia-inducible factor-2alpha were

semiquantitatively assessed by immunohistochemistry. Radiographic response and survival outcomes were correlated with these angiogenic and hypoxic markers. Of 45 patients, 26 (58%) had at least partial radiographic response. High VEGF expression was associated with increased likelihood of radiographic response ( $P = .024$ ) but not survival benefit. Survival analysis revealed that high CA9 expression was associated with poor survival outcome ( $P = .016$ ).<sup>29</sup>

We therefore are proposing to measure these markers and to extend our analyses to other candidate biomarkers reflective of tumor load, tumor biological activity, and blood cell responses to antiangiogenic therapies.

### **To conduct genome-wide gene expression profiling and genomic DNA integrity analyses using high density SNP/CNV arrays in patients with high grade gliomas**

Faury et al recently published data on 32 pediatric GBM and seven adult GBM samples which they investigated using biochemical and transcriptional profiling. Ras and Akt pathway activation was assessed through the phosphorylation of downstream effectors, and gene expression profiles were generated using the University Health Network Human 19K cDNA arrays. Results were validated using real-time polymerase chain reaction and immunohistochemistry and compared with existing data sets on aGBM. At least two subsets of pGBM were distinguishable. One subset, associated with Ras and Akt pathway activation, has very poor prognosis and exhibits increased expression of genes related to proliferation and the adoption of a neural stem-cell phenotype, similar to findings in aggressive GBM. This subset was molecularly distinguishable from aGBM using either unsupervised or supervised expression profiles analyses indicating its strong distinction from a second subset that had a better prognosis and was not associated with activation of Akt and Ras pathways. Tumors with these characteristics may originate from astroglial progenitors, and their markers do not overlap with those of aGBM that have either a better or worse outcome. However, both subsets of pGBM show overexpression of Y-box-protein-1 that may help drive oncogenesis in this tumor. This small study of gene expression profiles in pGBM provides both valuable insight into their active pathways, suggest new targets in a cancer with minimal survival, and suggests that these tumors cannot be understood exclusively through studies of adult GBM.<sup>30</sup>

### **To assess telomerase activity, *hTert*, *hTERC* expression, and telomere length in patients with HGG**

Telomerase is a ribonucleoprotein complex that elongates telomeric DNA and appears to play an important role in cellular immortalization and cancers. Because telomerase is expressed in the vast majority of malignant gliomas but not in normal brain tissues, it is a logical target for gliomaspecific therapy. Telomerase adds hexameric repeats of 5'-TTAGGG-3' to the ends of telomeres to compensate for the progressive loss with each cell division<sup>31-33</sup>. Telomerase activity, which is generally undetectable in normal somatic cells, is expressed in approximately 90% of tumors.<sup>34-36</sup> In malignant gliomas, telomerase activity is very often detected<sup>37 38,39 40 41 42 43 44 45 46 47 48 49,50</sup>. In Grade I or II of gliomas, telomerase activity is detected in 0% and 0 to 33%, respectively. In malignant gliomas, telomerase is positive in 10 to 100% of anaplastic astrocytomas and in 26 to 100% of GBM. Although the ratio of telomerase-positive cells in gliomas varies, most of the reports show that the incidence of telomerase expression is closely correlated with the malignancy, and telomerase is detected in the vast majority of malignant gliomas. By contrast, normal brain tissues do not express telomerase activity<sup>38,44,48,50</sup>, while telomerase is detectable only in human embryonic neural precursor cells at low levels<sup>51</sup>.

Boldrini et al examined telomerase activity in 42 gliomas.<sup>52</sup> A significant association between telomerase activity and *hTERT* mRNA expression was found (chi2 test;  $p < 0.0001$ ). At univariate analysis, advanced age as well as high telomerase activity and *hTERT* mRNA levels were seen to be significant predictors of worse prognosis regarding both overall survival ( $p = 0.007$ ,  $p = 0.007$ ,  $p = 0.04$ , respectively) and disease-free interval ( $p = 0.008$ ,  $p = 0.008$ ,  $p = 0.04$ , respectively). These variables had a significant independent prognostic role in multivariate analysis. GRN163, a telomerase inhibitor, led to significant growth delay in GBM xenografts<sup>53</sup>

#### **2.1.10 Rationale for Imaging Correlative Studies**

Using MRI techniques, Batchelor et al showed that normalization of tumor vessels in recurrent glioblastoma patients by daily administration of AZD2171-an oral tyrosine kinase inhibitor of VEGF receptors-has rapid onset, is prolonged but reversible, and has the significant clinical benefit of alleviating edema. Reversal of

normalization began by 28 days, though some features persisted for as long as four months. Basic FGF, SDF1alpha, and viable circulating endothelial cells (CECs) increased when tumors escaped treatment, and circulating progenitor cells (CPCs) increased when tumors progressed after drug interruption. This study suggests that the timing of combination therapy may be critical for optimizing activity against this tumor.<sup>18</sup> T2\*-weighted perfusion MRI, a method based on the rapid intravenous administration of Gd-DTPA, has been used for the assessment of treatment response to antiangiogenic agents in adults with recurrent high-grade gliomas.<sup>54 55</sup> In the referenced studies, the variations observed during therapy using this sequence seemed to correlate with the clinical response experienced by the patients. A third study used this sequence in adults with newly diagnosed HGG and demonstrated its usefulness to assess angiogenesis and microvascular leakage, two characteristics associated with the malignant potential of these tumors.<sup>56</sup>

*The overall goal for the biological correlative studies is to obtain directly measurable blood sample and tumor status characteristics from each patient and tumor ( in patients with HGG only) that can be subsequently correlated to response to therapy, rates of tumor progression, functional MRI imaging characteristics, clinical outcome, and potentially be used to predict novel therapeutic approaches most suitable for individual patient tumors. To do this, we propose to systematically collect a sample of tumor at primary resection stages for DNA, RNA, and protein analysis; and a series of small blood samples from patients at presentation, resection, treatment, and recurrence. We will also perform Affymetrix gene expression profile analysis of tumor samples to determine the impact of ERBB signal blockade on genome-wide expression patterns and identify potential novel determinants of disease response to this treatment regimen.*

### **B3. Rationale for Quality of Life and Functional Outcome Studies**

**Quality of life** Tracking the health-related quality of life for participants in this clinical trial is important in measuring treatment and disease related effects on emotional well-being and functioning, which may undergo significant short-term changes over the course of treatment and post-treatment survival<sup>57 58,59</sup>. In addition, recent reports from adults have documented a decreased use of steroids while on bevacizumab based therapy,<sup>60,62</sup> and have demonstrated an improvement in patient functional status while on therapy.<sup>30</sup> Gonzalez et al reported that bevacizumab can reduce radiation necrosis by decreasing capillary leakage and the associated brain edema. Such attenuation of the effects of radiation necrosis and brain edema may improve quality of life for patients, and may decrease the diagnosis of pseudoprogression (radiation-induced tumor inflammation) frequently noted in the first months following chemoradiotherapy in approximately 15% of patients.<sup>60,61</sup> The PedsQL and the various modules being proposed are in common use in pediatric cancer research<sup>62,63</sup> and have established reliability and validity<sup>64 65 66</sup>. They can be completed in less than 5 minutes each and administered over short intervals so as to track short-term changes. For most of the ages represented in this protocol, there are both parent report and child self-report versions available. The Functional Assessment of Cancer Therapy – Brain (FACT-Br) is a measure of health-related quality of life that has established reliability and validity for use in adult brain tumor patients  $\geq 18$  years of age<sup>67</sup>. It is a self-report measure that can be completed in 10 to 15 minutes, and has been shown to be sufficiently brief to support repeated assessment over short intervals without a high refusal or patient attrition rate. It includes subscales measuring physical, social/family, emotional, and functional well-being as well as an additional brain scale and a scale assessing the patient's perceived relationship with his/her physician. Domains assessed are comparable to those being assessed by the PedsQL in the pediatric groups included in this protocol. The Conners' Continuous Performance Test (CPT) is a computerized vigilance task designed for children  $\geq 5$  years of age. It can be administered over short intervals with an administration time of 14 minutes. The CPT is included in order to assess short-term fluctuations in attention, arousal, and alertness. The CPT is currently being used in our ongoing research with children with brain tumors

### **Functional Outcome Studies**

Functional independence during and following treatment are areas of concern for patients, families and physicians. Tumor location, surgical resection, intensive multi-agent chemotherapy and radiation all have the potential to affect gross motor, fine motor and balance skills thus having implications on functional

independence. Limited physical functioning in children followed in the CCSS has been demonstrated to be associated with limitations in graduation from high school, less likely to be employed and more likely to have difficulties attaining financial independence.<sup>68</sup> Rehabilitation programs are being incorporated more often in the care of cancer patients.<sup>69-72</sup> Assessment of functional independence during and following treatment will assist in identifying specific therapeutic needs that can be met through rehabilitation medicine physicians and physical and occupational therapist interventions to optimize functional independence outcomes. The Bruininks-Oseretsky Test of Motor Proficiency, Second Edition (BOT-2) is a standardized, norm-referenced measure used by physical therapists and occupational therapists as a measure of fine and gross motor skills of children and youth, 4 through 21 years of age.<sup>73</sup> The Functional Rehabilitation Evaluation of Sensori-Neurologic Outcomes (FRESNO) will be used to measure functional skill competence. It is a reliable and valid functional measurement for children between the ages of 15 months through 18 years with physical, neurological, sensory, communicative, and/or cognitive deficits and is designed to provide rehabilitation programs with a method of tracking functional recovery across time.<sup>74</sup>

*The current proposal will be the first to comprehensively assess the functional outcome and quality of life of patients with HGG receiving the current regimen. The information gathered will be helpful in a) developing an optimal quality of life assessment tool for these vulnerable patients, b) implementing interventions that may ameliorate the quality of life and functional outcome of children with such poor prognosis tumors*

### **C Research Design and Methods**

The target sample size is 20 for the HGG stratum and 15 for the DIPG stratum, to allow a preliminary assessment of the safety and feasibility of this regimen. We anticipate 3-5 eligible patients per year for each stratum. The study will be completed within 40-48 months.

#### **Power Analysis and Statistical Analysis Plan including Stopping Rules**

The primary safety endpoints are the incidence of toxic deaths and grade 3 or 4 hemorrhages. We will separately monitor the rate of toxic death and that of grade 3 or 4 hemorrhages for each radio-sensitizer during RT. We will stop the study and conclude the treatment regimen unsafe, if more than 2 toxic deaths or more than 2 grade 3 or 4 hemorrhages are observed among the proposed sample of 35 patients. The stopping rule will be triggered about 3% (44.8%) of the time if the true incidence rate is 2% (7%). Based on a simulation study, we anticipate about 65%~89.6% power to stop the study if the true incidence rate is 7% and the incidences of toxic deaths and those of grade 3 or 4 hemorrhages are correlated with the correlation  $\leq 0.3$ . The probability of falsely concluding the treatment regimen unsafe is controlled at 6% or less if the true incidence rate is 2% or less. We will similarly monitor the safety of the maintenance therapy using the same stopping rule.

The primary feasibility endpoints are the incidence of significant delays (> 2 weeks) in the completion of RT and that of significant delays (> 2 weeks) in the start of any course of maintenance. A review of treatment and patient safety will be undertaken and we will conclude the study regimen unfeasible if we observe more than 4 significant delays during RT. The rule will be met about 3% (62%) of the time if the true incidence rate of delay is 5% (15%). Similar action will be taken if more than 4 significant delays are observed during the maintenance therapy. Based on a simulation study, we anticipate about 78%~88% power to conclude the study regimen unfeasible overall if the true incidence of significant delays is  $\geq 12\%$  during either therapy and delay incidences during RT and the maintenance therapy are correlated with the correlation  $\leq 0.5$ . The probability of falsely concluding the infeasibility of the treatment regimen is controlled at 6% or less if the true incidence rate is 5% or less. Because the number of total maintenance courses cannot be easily estimated (as patients may not all complete 12 courses), a statistics-driven boundary is not feasible and the monitoring will just be based on the marginal incidence. We will estimate event-free-survival, progression-free survival and overall survival for patients by each stratum using Kaplan-Meier curves. Frequency tables will be used to summarize toxicities by stratum. Descriptive statistics will be used to investigate the secondary objectives. We will estimate the frequency of the laboratory marker/indicator and perform exploratory analysis to correlate them with the survival outcomes. The standard error (precision) of the frequency estimate assuming 100% complete data or 75% complete data for various frequencies are shown in the table below. The 95% CI is the estimate  $\pm 2S.E.$ . The precision (S.E.) of the estimated frequency.

Sample size	p*: Frequency of the marker/indicator
-------------	---------------------------------------

	10%	30%	50%
35	5.1%	7.7%	8.5%
35*75%=26	5.9%	9.0%	9.8%

If  $p > 50\%$ , the S.E. is the same as that for 1-p.

We will monitor rates of toxic death during XRT and during maintenance. We will also monitor significant delays in completion of XRT or in the start of maintenance courses. Statistical monitoring rules will not be used. A careful review of treatment and patient safety will be undertaken whenever observed rates nominally exceed the maximum acceptable rate (5%), or when there is a large observed difference in these rates between the strata. Cumulative incidence of toxic deaths and that of significant delays during therapy will be computed.

### Statistical Section for Biology Studies

For genome allelotype analysis, LOH data generated in this study will be binary (loss of one allele or retain of both alleles). To distinguish the biologically significant changes from the random changes, we will compute the frequency of allelic loss (FAL) statistic. FAL for a cytoband is the number of tumors that exhibit LOH at the SNP loci divided by the number of tumors in which at least on SNP loci is informative. The expected FAL between tumors of different covariates will be tested using Fisher's exact test or a chi-squared test. SNP loci will be ranked based on the FAL statistics and LOH will be validated by PCR amplification and direct sequencing analysis. SNP with copy number changes will be validated by quantitative real-time PCR. Validated SNP markers will be subject to Kaplan-Meier analysis. The log rank test will be used to test for association between PFS and prognostic factors and genetic alterations. Similar analysis will be done with expression profiles data. Differential gene expression will be validated by real-time quantitative RT-PCR.

**Hypothesis 1: The treatment regimens proposed (bevacizumab± TEM and concurrent radiotherapy followed by bevacizumab and irinotecan ± TEM) are feasible, well-tolerated and efficacious in children with newly diagnosed HGG and DIPG tumors**

**1.1 To determine the proposed regimen's feasibility and toxicities in patients with HGG and DIPG.**

**1.2 To determine the one year EFS, median PFS and OS in newly diagnosed patients with HGG treated with radiotherapy (RT) and concurrent temozolomide, bevacizumab followed by bevacizumab, irinotecan and temozolomide for 12 courses.**

**1.3 To determine the 1-yr EFS, median PFS and median OS in newly diagnosed patients with DIPG undergoing RT, concurrent bevacizumab followed by bevacizumab, irinotecan for 12 courses.**

1.1.1 Eligibility: Patients must be  $\geq 3$  years and  $\leq 30$  years with a newly diagnosed non-metastatic HGG (stratum 1) or DIPG (stratum 2), no prior therapy. Standard eligibility criteria will be used (e.g. adequate organ function, Karnofsky score  $\geq 50$ ). Certain potent CYP3A4 inhibitors and inducers are prohibited as they may interfere with the metabolism. Patients with new intracranial hemorrhages, greater than punctuate size are excluded as are patients with previous thromboembolic phenomena, non healing wound, on anticoagulants. Patients with HGG must agree to submitting tumor tissue for biology studies.

1.1.2 Treatment: HGG patients will receive bevacizumab 10 mg/kg, TEM 90 mg/m<sup>2</sup> daily for 42 days with concurrent RT. Maintenance therapy will begin 4 weeks after completion of RT with irinotecan 125 mg/m<sup>2</sup>/day IV q 2 weeks, bevacizumab 10 mg/kg q 2 weeks and TEM, 150 mg/m<sup>2</sup>/day days 1-5. DIPG patients will receive exactly the same regimen without TEM Each course is 28 days. A maximum of 12 courses of maintenance therapy can be given.

1.1.3 Collection of tumor and blood specimens for molecular studies. Fresh-frozen tissue will be collected from all patients with HGG to characterize the relevant cell signal network in pediatric HGG and identify molecular determinants of tumor sensitivity to the proposed combination and correlate with outcome

1.1.4 Dose-Modifying Toxicity is defined in section 5. Adverse events will be monitored and graded according to the CTC version 3.

1.1.5 Response Criteria: Patients will be evaluated with standard 3 dimensional MRI to assess response before treatment, prior to maintenance chemotherapy, and every 2 courses thereafter. Complete response:

disappearance on MRI of all enhancing tumor or mass effect; partial response is  $\geq 50\%$  reduction in tumor size by bidimensional measurement. Progressive disease: progressive neurological abnormalities not explained by causes unrelated to tumor progression, or  $\geq 25\%$  increase in bidimensional diameter, or appearance of a new lesion or increasing doses of steroids required to maintain stable neurological condition; stable disease:

**1.4 Expected Results** Preliminary results from Cloughesy et al show that a similar regimen is tolerable and feasible in newly diagnosed adults; the PBTC is also completing a study with bevacizumab and irinotecan in patients with recurrent CNS malignancies without untoward toxicity. At CCHMC, we have treated 9 patients with recurrent HGG/DIPG with this regimen with 3 OR documented and long term tolerability of the regimen confirmed.(up to 90 weeks). Thus, we expect that this regime will prove feasible, tolerable, but efficacious.

**1.5 Potential Problems** It is possible that this regimen will prove too toxic and lack feasibility. We have incorporated a de-escalation and very explicit dose modifying criteria as well as stopping and monitoring rules in the protocol to address unforeseen toxicities associated with the administration of this regimen. We will assess downstream targets of VEGF in tumor and in blood (obtained before and during therapy) to assess pharmacodynamic endpoints and correlate those changes to changes in imaging. Finally, this regimen can prove to be less effective than standard therapy. If that is the case the study will be closed. However, given the secondary biological objectives, we hope to gain a much better understanding of the biology of these tumors, which would assist us in the rationale design of future studies.

**1.5 Future Directions** If the feasibility and tolerability of this regimen is established, this regimen will form the basis of the next national study to test the efficacy of this regimen in newly diagnosed patients

## **Hypothesis 2: Children with HGG and DIPG have characteristic molecular and imaging features that correlate with response and PFS.**

### **2.1 To estimate the incidence of VEGF expression and pathway activation in tumor as well as blood of patients with HGG and DIPG at different time points**

These studies will: characterize the VEGFR cell signal network in pediatric HGG and DIPG; determine how bevacizumab treatment impacts the activity of this network, and identify molecular determinants of tumor sensitivity to bevacizumab. Both fresh frozen tissue from diagnosis and serial blood samples prior to and during therapy will be used to correlate changes with response and outcome. **Fresh frozen tumor material:** Fresh frozen tumor material is the ideal source for the extraction and analysis of high quality protein, RNA and DNA. Therefore, we will use snap frozen primary tumor material to accurately delineate the expression and activity of the VEGF receptor network by western blotting..

### **2.2 To document changes in MR perfusion and diffusion within 24- 48 hours after the 2<sup>nd</sup> dose of bevacizumab during radiotherapy and correlate functional changes in tumor with responses to treatment**

### **2.3 To conduct gene expression profiling, CGH and SNP arrays in tumor and blood of patients**

### **2.4 To assess telomerase activity, *hTert* expression, and telomere length in patients with HGG**

### **2.5 To correlate the results of the biology studies in serum or tumor with PFS**

### **2.6 Expected Results**

Published data in pediatric HGG implicate VEGF signaling in the biology of these diseases; *in vitro* and *in vivo* models have demonstrated the therapeutic potential of small molecule inhibitors of VEGFR. We anticipate that a large proportion of patients' tumor specimens will prospectively be shown to overexpress VEGF. Furthermore, we expect that bevacizumab concentration in the plasma and tumor tissue will be adequate to inhibit the VEGF in patients' tumors and peripheral blood mononuclear cells. We anticipate that clinical response to this regimen will correlate with a subgroup of patients who overexpress VEGF and who demonstrate inhibition after therapy with bevacizumab. Through the expression profile analysis, we hope to identify unique determinants of response to bevacizumab at the RNA expression level. We expect that telomerase activity, *hTert* expression will be an important determinant of response, PFS and prognosis.

### **2.7. Potential Problems**

**2.7.1 Collection of tumor samples** may be difficult. However, since consent to tumor sample is required as part of the eligibility criteria, compliance should be high.

**2.7.2 Specimen Analysis for Biology Studies** Since the techniques have been validated, have high sensitivity and specificity and have been routinely performed, we do not anticipate that the analysis of the collected specimens using the techniques described in the application will be problematic.

**2.7.3 No VEGF overexpression of pathway inhibition detected:** Although pre-clinical and clinical data clearly demonstrate that bevacizumab inhibits the VEGF pathway, it is possible that we may not detect any inhibition of the VEGF pathway during the study. This may reflect several problems including a) lack of VEGF expression in the tumor samples, b) inadequate plasma concentrations of drug achieved c) inadequate blood-brain-barrier penetration of the drug or d) inadequate tumor penetration of the drug.

**2.7.4: Inadequate number of clinical responses reported:** If no activity is detected in patients enrolled on this trial, it may reflect problems with inadequate plasma or tumor tissue concentration, as described above, lack of overexpression of VEGF in tumor samples. Also, similar to the explanation recently offered for the discrepancy between ERBB1 overexpression and gefitinib response, gene sequence studies in the patients may delineate a small responsive subgroup of patients who may have unique features that would explain the lack of response in a larger population who overexpress VEGF. There may be other unique determinants of response to bevacizumab that may be more important than the VEGF pathway, that may be delineated through expression profile analysis of the tumors of treated patients. Finally, the inhibition of VEGF pathway may not be sufficient to lead to tumor response, especially in the setting of patients with large residual tumor burden.

## **2.8 Future Directions**

We hope that the proposed study will elucidate the activity, mode of action and determinants of sensitivity of bevacizumab. The molecular studies proposed may assist in identifying subgroups of patients who can most benefit from the use of this regimen and identify other pathways for which molecular targeted therapies are available that may be successfully combined with antiangiogenic therapies.

## **Hypothesis 3: The proposed treatment in children with HGG and DIPG will lead to better quality of life and functional outcomes**

**3.1 To assess the health related quality of life of patients with high grade gliomas by parent report, and when possible, patient report at key points in therapy**

**3.2 To assess functional abilities and level of independence of patients during and following treatment**

**3.3 Expected Results:** Recent reports from adults have documented a decreased use of steroids while on bevacizumab based therapy,<sup>60,62</sup> and have demonstrated an improvement in patient functional status while on therapy.<sup>30</sup> We believe that children will have a better quality of life and functional outcome while on this study

**3.4 Potential Problems:** If this regime proves more toxic than expected, there may be a higher number of serious adverse events that may adversely affect quality of life and functional outcome. Of particular concern are thromboembolic, hemorrhagic events, severe hypertension and difficulties with wound healing.

**3.5. Future Directions:** The information gathered will be helpful in a) developing an optimal quality of life assessment tool for these vulnerable patients, b) implementing interventions that may ameliorate the quality of children with such poor prognosis tumors

## **D. Human Subjects Research.**

### **D.1. Patient Characteristics**

Patients (3-30 years) with newly diagnosed HGG or DIPG who meet the eligibility criteria can enroll. No patient will be refused therapy on the basis of race, religion, ethnic background, physical or mental disability. We anticipate that patients will be enrolled on this protocol over a 4-year period.

### **D.2. Recruitment and Informed Consent**

Children with newly diagnosed HGG and DIPG who are referred specifically for phase I therapy. Consent for protocol enrollment will be obtained by study PI or her representatives. Informed consent will follow the institutional and federal guidelines which include the discussion of procedures, methods, risks and benefits involved. 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**

The primary aim of this clinical trial relates to administration of a bevacizumab containing regimen, and obtaining of blood, and tumor specimens. The risks of serious side effects should be no greater than seen in previous chemotherapy protocols conducted through the cooperative groups. Chemotherapeutic procedures and related surgical procedures are in accord with current accepted standards. Minimizing of risks is accomplished by having experts in pediatric oncology supervise the conduct of this trial. Active monitoring and auditing of study results will be conducted.

D.3.1 Surgery Pain, discomfort, bleeding, infection, potential damage to organs and tissues, hypotension or shock during anesthesia.

D.3.2 Treatment Regimen side-effects:: nausea, vomiting, anorexia, abdominal bloating, indigestion, constipation, diarrhea, mucositis, early satiety, facial flushing, fatigue, flu-symptoms, headaches, rash, insomnia. Myelosuppression, fever, taste changes, edema of hands and feet, liver dysfunction, thromboemboli, hemorrhage, hypertension, proteinuria, poor wound healing

#### D.4 Procedures for Minimizing Potential Risks

Each patient's general state of health and tolerance of therapy will be monitored closely. Alternations in therapy based on the tolerance will be outlined in the treatment documents. Other supportive care services are available and provided if needed. These include nutritional, psychosocial, rehabilitation, and other subspecialty services. Patients will be followed on a regular basis for periods defined by institutional policies to detect acute and long-term effects of treatment; medical treatment for these effects will be provided when necessary. Minimal volumes of blood (adjusted to age/weight) are obtained for pharmacokinetic studies.

D.5 Anticipated Benefits to Patients: The major potential benefit for participating patients is to reduce disease burden and prolong survival.

#### D.6. Importance of Knowledge to Be Gained

This will be the first pediatric trial of a bevacizumab+ irinotecan regimen to be used in newly diagnosed patients with HGG and DIPG and will determine feasibility and tolerance in the pediatric population, and will provide a comprehensive assessment of the molecular and clinical activity of this bevacizumab-based regimen among children with recurrent or refractory MB, HGG, or EP.

#### D.7. Women and Minority Inclusion for Research Involving Human Subjects.

Entry onto the study will not depend on the sex or race of the patients, except in the rare instances that there is a very compelling patient safety or scientific reason to do so (e.g., pregnancy may be an exclusion criterion). For most childhood cancers, no treatment has proven superior for one gender or ethnic group. Thus, studies are not generally adjusted to ensure high power to detect differences in outcome in groups defined by gender and race.

### **E. Disease Impact and Innovation**

Children with DIPG and HGG have a very poor prognosis. No chemotherapy has proven of any benefit. RT is currently the only therapy that has proven to be of any benefit. Recently, the targeting of VEGF signaling with bevacizumab in adults with recurrent malignant gliomas has led to unprecedented rates of durable responses both clinically and radiographically, with a tolerable toxicity profile. The current proposal will be the first pediatric study of a bevacizumab-based combination regimen in children with newly diagnosed HGG and DIPG. In this study, we will assess the feasibility, tolerability and efficacy of this regimen. The aim of the molecular studies proposed is to identify subgroups of patients who can most benefit from the use of antiangiogenic agents, and identify other pathways for which molecular targeted therapies are available that may be successfully used to improve the prognosis for these vulnerable children.

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## Section 4: BUDGET

### Personnel: \$4,870

*Rachid Drissi, PhD (co-investigator)*. Dr Drissi is an Assistant Professor of Pediatrics at CCHMC. His laboratory focuses on the role of telomeres and telomerase in cancer. Dr Drissi is an expert in the basic biology of telomeres and telomerase as it pertains to pediatric cancers and has also published on the role of telomerase, *hTert* expression and their prognostic significance in pediatric cancers. Dr. Drissi's will be responsible for all the studies related to telomerase activity on this protocol. 5% effort. Salary requested is \$3,850. Fringe requested is \$1,020

### Supplies: \$150,542.80

#### Costs for the functional outcomes: \$54,957.80

Test and Measures (1.75hrs) \$658.63 x 3 x 20 patients = \$39,517.80

BOT-2 Test kits \$772.00 x 20 patients = \$15,440

BOT-2 Examinee Booklet & record form sets \$78.00 x 20 patients = \$1,560

#### Costs for Neurocognitive outcomes: \$2,835

3 modules of Peds QL (\$1,150)

CPT II (\$685)

Laptop (\$1,000)

#### Costs for Microarray Analysis: \$87,500

DNA and RNA analysis (\$2,500 x 35 patients = \$87,500)

#### Costs for Telomerase: \$5,250

Telomerase (\$150 x 35 patients = \$5,250)

Total budget is \$155,412.80

### Budget requested is \$80,000

Remaining costs will be paid from division of Hematology/Oncology and other sources of funding we will be applying for.

## Section 5: Collaborations and Conflict of Interest

*Maryam Fouladi MD, MSc. (PI)* Dr. Fouladi is an Associate Professor of Pediatrics and Medical Director of Neuro-oncology at Cincinnati Children's Hospital Medical Center. She has extensive experience and expertise in the development and conduct of phase I and II trials in patients with recurrent solid and CNS malignancies, and has been the PI of a number of national phase I/II trials at the COG, PBTC and CERN. She is currently Chair of the COG CNS-New Agents Subcommittee and is a member of the COG Brain Tumor Steering Committee. Dr. Fouladi is also leading the next national COG study for newly diagnosed patients with high grade gliomas.

*Rachid Drissi, PhD (co-investigator)*. Dr Drissi is an Assistant Professor of Pediatrics at CCHMC. His laboratory focuses on the role of telomeres and telomerase in cancer. Dr Drissi is an expert in the basic biology of telomeres and telomerase as it pertains to pediatric cancers and has also published on the role of telomerase, *hTert* expression and their prognostic significance in pediatric cancers. Dr. Drissi's laboratory will be responsible for all the studies related to telomerase activity on this study.

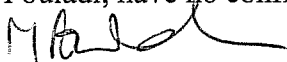
*Bruce Aronow, Ph.D. (Co-Investigator)*. Dr. Aronow is a molecular geneticist and is a Professor and Director of Genome Informatics core at the University of Cincinnati College of Medicine. He has expertise in analyzing and interpreting genomic and functional genomic data using a variety of advanced bioinformatics tools. He also has expertise in designing user interface and group-accessible Bioinformatics tools and databases for regulatory and pathway relationships. His input will be particularly important in experimental design, and he will work with the bioinformatics analyst for data integration and analysis.

*Douglas Ris, PhD (co-investigator)*. M. Douglas Ris, PhD, is a Professor of Pediatrics at Cincinnati Children's Hospital Medical Center and the University of Cincinnati College of Medicine. He founded and directs the Neuropsychology Program and the Neuropsychology Postdoctoral Fellowship. Dr. Ris is a diplomate of the American Board of Clinical Neuropsychology (ABCN) of the American Board of Professional Psychology (ABPP). He has authored more than 50 scientific papers and book chapters related to the neurobehavioral effects of various medical conditions including sickle cell anemia, brain tumors, metabolic disorders and environmental toxins. His research into the neurobehavioral late effects of pediatric brain tumors is sponsored by the National Cancer Institute, and he has also received funding as Principal Investigator from the National Institute of Environmental Health Sciences for research on the developmental effects of environmental lead. Dr. Ris and Dr. North will be in charge of conducting and analyzing the quality of life assessments on this protocol

*Marsha Nortz, PhD (co-investigator)*. Dr. Nortz joined the CCHMC faculty as an Assistant Professor of Clinical Pediatrics in September, 2002. She is a staff psychologist with a specialization in pediatric neuropsychology, and she serves as the consulting clinical neuropsychologist to the Neuro-oncology Program at CCHMC. Her primary clinical and research interests are in the neuropsychology of pediatric brain tumors and clinical outcomes in pediatric neuro-oncology. Dr. Nortz is also active in CCHMC's training programs as a faculty supervisor and Co-director of the Postdoctoral Residency in Pediatric Neuropsychology. Dr. Ris and Dr. North will be in charge of conducting and analyzing the quality of life assessments on this protocol.

*David Pruitt, MD (co-investigator)* is an Assistant Professor of Pediatrics in the Division of Physical Medicine and Rehabilitation. Dr. Pruitt is part of the Multidisciplinary Neuro-oncology Clinic and follows all patients who require PM&R services. His research focus is functional outcomes in children with head injuries and CNS malignancies. He will supervise the conduct and analysis of the functional outcomes objectives of this protocol.

I, Maryam Fouladi, have no conflict of interest regarding this research project or its funding by The Cure Starts Now.



## BIOGRAPHICAL SKETCH

NAME Maryam Fouladi	POSITION TITLE
eRA COMMONS USER NAME	Associate Professor

EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
University of Toronto, Toronto, Canada	Pre-Med	1985-87	Human Biology
University of Toronto, Toronto, Canada	M.D.	1991	Medicine
Institute of Medical Science, University of Toronto	M.Sc.	2002	

**A. Positions and Honors.** List in chronological order previous positions, concluding with your present position. List any honors. Include present membership on any Federal Government public advisory committee.

### PROFESSIONAL APPOINTMENTS:

- 1991-1992 Chief Intern, Scarborough General Hospital, Scarborough, Ontario, Canada
- 1992-1995 Pediatric Resident, The Hospital for Sick Children, Toronto, Ontario, Canada
- 1995-1996 Clinical Fellow, Division of Hematology/Oncology, The Hospital for Sick Children, Toronto, Ontario, Canada
- 1996-1997 Chief Fellow, Division of Hematology/Oncology, The Hospital for Sick Children, Toronto, Ontario, Canada
- 1997-2002 Clinician Investigator Program, Royal College of Physicians and Surgeons of Canada
- 1997-1998 Clinical Research Fellow, New Agents and Innovative Therapy Program, Division of Hematology/Oncology, the Hospital for Sick Children, Toronto, Ontario, Canada
- 1998 Neuro-Oncology Fellow, Division of Neuro-Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee
- 1999 Postdoctoral Fellow, Molecular Pharmacology, St. Jude Children's Research Hospital, Memphis, Tennessee
- 2000-2005 Assistant Member, Division of Neuro-Oncology, Department of Hematology/Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee
- 2005- 2007 Associate Member, Division of Neuro-Oncology, Department of Hematology/Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee
- 2008-present Associate Professor, Division of Hematology/Oncology. Medical Director of Neuro-Oncology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

### HONORS AND AWARDS:

- 1997 Terry Fox Clinician Scientist Research Fellowship
- 1997 John H. Crookston Travel Award, Canadian Society of Hematology
- 1997 American Society of Hematology Travel Award
- 1997 Seventh Cooley's Anemia Symposium Travel Award
- 1997 Berlex Oncology Foundation Award for Workshop in Epidemiology and Clinical Trial Design
- 1995 The Hospital for Sick Children Foundation Humanitarian Award
- 1995 Fredrick F. Tisdall Award for Excellence in Research
- 1986-1987 Faculty Scholar for Academic Standing with High Distinction
- 1985 J.W. Billes Admission Scholarship, University of Toronto

### PROFESSIONAL SOCIETY MEMBERSHIPS:

- 1996 Fellow of the Royal College of Physicians and Surgeons of Canada
- 2002 American Society of Clinical Oncology
- 2000 Children's Oncology Group
- 2000 Pediatric Brain Tumor Consortium

**B. Selected peer-reviewed publications (in chronological order).** Do not include publications submitted or in preparation.

1. **Fouladi M**, Baruchel S, Chan H, Grant R, Malkin D, Weitzman S, Greenberg ML. Use of Adjuvant ICE Chemotherapy in the Treatment of Anaplastic Ependymomas. *Child's Nerv Syst* 14:590-595, 1998.
2. **Fouladi M**, Grant R, Baruchel S, Chan H, Malkin D, Weitzman S, Greenberg ML. Comparison of Survival Outcomes in Patients with Intracranial Germinomas Treated with Radiation Alone Versus Reduced-Dose Radiation and Chemotherapy. *Child's Nerv Syst* 14:596-601, 1998.

3. **Fouladi M**, Macmillan MI, Nisbet-Brown E, Klein N, Barlas J, Waye JS, Olivieri NF. Hemoglobin E/ $\beta$  Thalassemia: the Canadian Experience. *Ann N Y Acad Sci* 850: 410-411, 1998.
4. MacMillan ML, **Fouladi M**, Nisbet-Brown E, Waye JS, Olivieri NF. Treatment of Two Infants with Cooley's Anemia with Sodium Phenylbutyrate. *Ann N Y Acad Sci* 850:452-4, 1998.
5. Gajjar A, **Fouladi M**, Walter AW, Thompson SJ, Reardon DA, Merchant TE, Jenkins JJ, Liu A, Boyett JM, Kun LE, Heideman RL. Comparison of Lumbar and Shunt Cerebrospinal Fluid Specimens for Cytologic Detection of Leptomeningeal Disease in Pediatric Patients with Brain Tumors. *J Clin Oncol* 17:1825-1828, 1999.
6. Fouladi M, Heideman R, Langston JW, Kun LE, Thompson SJ, Gajjar A. Infectious Meningitis Mimicking Recurrent Medulloblastoma on Magnetic Resonance Imaging. *J Neurosurg* 91:499-502, 1999.
7. **Fouladi M**, Gajjar A, Boyett JM, Walter AW, Thompson SJ, Merchant TE, Jenkins JJ, Langston JW, Liu A, Kun LE, Heideman, RL. Comparison of CSF Cytology and Spinal Magnetic Resonance Imaging in the Detection of Leptomeningeal Disease in Pediatric Medulloblastoma or Primitive Neuroectodermal Tumor. *J Clin Oncol* 17:3234-3237, 1999.
8. **Fouladi M**, Langston J, Mulhern R, Jones D, Xiong X, Yang J, Thompson S, Walter A, Heideman R, Kun LE, Gajjar A. Silent Lacunar Lesions Detected by Magnetic Resonance Imaging of Children with Brain Tumors: a Late Sequela of Therapy. *J Clin Oncol* 18:824-31, 2000.
9. **Fouladi M**, Herman R, Rolland-Grinton M, Jones-Wallace D, Blanchette V, Calderwood S, Doyle J, Halperin D, Leaker M, Saunders EF, Zipursky A, Freedman MH. Improved Survival in Severe Acquired Aplastic Anemia of Childhood. *Bone Marrow Transplant*. 26:1149-56, 2000.
10. **Fouladi M**, Stempak D, Gammon J, Klein J, Grant R, Greenberg ML, Koren G, Baruchel S. Phase I Trial of a Twice-daily Regimen of Amifostine with Ifosfamide, Carboplatin, and Etoposide Chemotherapy in Children with Refractory Carcinoma. *Cancer* 92:914-23, 2001.
11. **Fouladi M**, Jenkins J, Burger P, Langston J, Merchant T, Heideman R, Thompson S, Sanford A, Kun LE, Gajjar A. Pleomorphic Xanthoastrocytoma: Favorable Outcome After Complete Surgical Resection. *Neuro-oncol* 3:184-92, 2001.
12. Crews KR, Stewart CF, Jones-Wallace D, Thompson SJ, Houghton PJ, Heideman RL, **Fouladi M**, Bowers DC, Chintagumpala MM, Gajjar A. Altered Irinotecan Pharmacokinetics in Pediatric High-grade Glioma Patients Receiving Enzyme-inducing Anticonvulsant Therapy. *Clin Cancer Res*. 8:2202-9, 2002.
13. Leggas M, Stewart CF, Woo MH, **Fouladi M**, Cheshire PJ, Peterson JK, Friedman HS, Billups C, Houghton PJ. Relation Between Irofulven (MGI-114) Systemic Exposure and Tumor Response in Human Solid Tumor Xenografts. *Clin Cancer Res* 8:3000-7, 2002
14. **Fouladi M**, Wallace D, Langston JW, Mulhern R, Rose SR, Gajjar A, Sanford RA, Merchant TE, Jenkins JJ, Kun LE, Heideman RL. Survival and Functional Outcome of Children with Hypothalamic/chiasmatic Tumors. *Cancer* 97:1084-92, 2003.
15. Wilimas JA, Donahue N, Chammas G, **Fouladi M**, Bowers LJ, Ribeiro RC. Training Subspecialty Nurses in Developing Countries: Methods, Outcome, and Cost. *Med Pediatr Oncol* 41:136-40, 2003.
16. **Fouladi M**, Hunt DL, Pollack IF, Dueckers G, Burger PC, Becker LE, Yates AJ, Gilles FH, Davis RL, Boyett JM, Finlay JL. Outcome of Children with Centrally Reviewed Low-grade Gliomas Treated with Chemotherapy with or without Radiotherapy on Children's Cancer Group High-grade Glioma Study CCG-945. *Cancer* 98:1243-52, 2003.
17. Panetta JC, Kirstein MN, Gajjar A, Nair G, **Fouladi M**, Heideman RL, Wilkinson M, Stewart CF. Population Pharmacokinetics of Temozolomide and Metabolites in Infants and Children with Primary Central Nervous System Tumors. *Cancer Chemother Pharmacol* 52:435-41, 2003.
18. Panetta JC, Kirstein MN, Gajjar AJ, Nair G, **Fouladi M**, Stewart CF. A Mechanistic Mathematical Model of Temozolomide Myelosuppression in Children with High-grade Gliomas. *Math Biosci* 186:29-41, 2003.
19. **Fouladi M**, Helton K, Dalton J, Gilger E, Gajjar A, Merchant T, Kun LE, Newsham I, Burger P, Fuller C. Clear Cell Ependymoma: a Clinicopathologic and Radiographic Analysis of 10patients. *Cancer* 98:2232-44, 2003.
20. Stewart CF, Iacono LC, Chintagumpala M, Kellie SJ, Ashley D, Zamboni WC, Kirstein MN, **Fouladi M**, Seele LG, Wallace D, Houghton PJ, Gajjar A. Results of a Phase II Upfront Window of

- Pharmacokinetically Guided Topotecan in High-risk Medulloblastoma and Supratentorial Primitive Neuroectodermal Tumor. *J Clin Oncol* 22:3357-65, 2004.
21. **Fouladi M**, Chintagumpala M, Laningham FH, Ashley D, Kellie SJ, Langston JW, McCluggage CW, Woo S, Kocak M, Krull K, Kun LE, Mulhern RK, Gajjar A. White Matter Lesions Detected by Magnetic Resonance Imaging After Radiotherapy and High-dose Chemotherapy in Children with Medulloblastoma or Primitive Neuroectodermal Tumor. *J Clin Oncol* 22:4551-60, 2004.
  22. Helton KJ, **Fouladi M**, Boop FA, Perry A, Dalton J, Kun LE, Fuller C. Medulloblastoma: a Radiographic and Clinicopathologic Analysis of Six Cases and Review of the Literature. *Cancer* 101:1445-54, 2004.
  23. Tekautz TM, Fuller CE, Blaney S, **Fouladi M**, Broniscer A, Merchant TE, Krasin M, Dalton J, Hale G, Kun LE, Wallace D, Gilbertson RJ, Gajjar A. Atypical Teratoid/rhabdoid Tumors (ATRT): Improved Survival in Children 3 Years of Age and Older with Radiation Therapy and High-dose Alkylator-based chemotherapy. *J Clin Oncol* 23:1491-9, 2005.
  24. Broniscer A, Iacono L, Chintagumpala M, **Fouladi M**, Wallace D, Bowers DC, Stewart C, Krasin MJ, Gajjar A. Role of Temozolomide After Radiotherapy for Newly Diagnosed Diffuse Brainstem Glioma in Children: Results of a Multi-institutional Study (SJHG-98). *Cancer* 103:133-9, 2005.
  25. Hinds P, Drew D, Oakes L, **Fouladi M**, Spunt S, Welborn D, Furman W. End-of-life Care Preferences of Pediatric Patients with Cancer. *J Clin Oncol* 36: 9146 -54, 2005.
  26. **Fouladi M**, Gilger E, Kocak M, Wallace D, Buchanan G, Reeves C, Robbins N, Merchant T, Kun LE, Khan R, Gajjar A, Mulhern R. Intellectual and Functional Outcome of Children 3 Years Old or Younger Who Have CNS Malignancies. *J Clin Oncol* 28: 7152-60, 2005.
  27. Bai F, Freeman B, Fraga C, **Fouladi M**, Stewart C. Determination of Lapatinib (GW572016) In Human Plasma by Liquid Chromatography Electrospray Tandem Mass Spectrometry (LC ESI-MS/MS) *Biomed Life Sci* 831: 169-75, 2005.
  28. Graham V, Tucker C, Creech J, Favours E, Billups C, Liu T, **Fouladi M**, Freeman B, Stewart C, Houghton PJ Evaluation of the Antitumor Efficacy, Pharmacokinetics and Pharmacodynamics of the Histone Deacetylase Inhibitor Depsipeptide in Childhood Cancer Models in Vivo. *Clin Cancer Res* 1: 223-34, 2006.
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  32. **Fouladi M**, Furman WL, Chin T, Freeman B, Stewart CF, Krailo M, Houghton PJ, Wright J, Adamson P, Blaney SC. A Phase I Trial and Pharmacokinetic Study of Depsipeptide in Pediatric Patients with Refractory Solid Tumors: A Children's Oncology Group Study. *J Clin Oncol* 24 (22):3678-85, 2006.
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  34. Merchant T, **Fouladi M**. Ependymoma: New Therapeutic Approaches Including Radiation and Chemotherapy. *J Neuro Oncol* 3:287-99, 2005.
  35. **Fouladi M**. Histone Deacetylase Inhibitors. *Cancer Invest* 5:521-7, 2006.
  36. **Fouladi M**, Blaney S, Young Poussaint T, Freeman B, McLendon R, Fuller C, Adesina A, Hancock M, Danks M, Ivy P, Stewart C, Gajjar A. A Phase II Study of Oxaliplatin in Children with Recurrent or Refractory Medulloblastoma (MB), Supratentorial Primitive Neuroectodermal Tumors (SPNET) and Atypical Teratoid Rhabdoid Tumors (ATRT): A Pediatric Brain Tumor Consortium Study. *Cancer* (107)2291-2297,2006.
  37. Helton K, Weeks J, Phillips N, Zou P, Kun LE, Khan R, Gajjar A, **Fouladi M**, Broniscer A, Li CS, Ogg, R. Diffusion Tensor Imaging of Brainstem Tumors: Axonal Degeneration of Motor and Sensory Tracts. *J. Neuro Oncol (in press)*

38. Gajjar A, Chintagumpala M, Ashley D, Kellie S, Kun LE, Merchant TE, Woo S, Wheeler G, Ahern V, Krasin MJ, **Fouladi M**, Broniscer A, Krance R, Hale GA, Stewart CF, Dauser R, Sanford RA, Fuller C, Lau C, Boyett JM, Wallace D, Gilbertson RJ. Risk-adapted Craniospinal Radiotherapy Followed by High-dose Chemotherapy and Stem-cell Rescue in Children with Newly Diagnosed Medulloblastoma (St Jude Medulloblastoma-96): Long-term Results from a Prospective, Multicenter Trial. *Lancet Oncology*, 813-820, 2006.
39. Haas-Kogan DA, Kocack M, Banerjee A, Prados, M, Geyer, R; **Foualdi M**, McKnight T, Poussaint T-Y, Broniscer A, Blaney SM, Boyett JM, Kun LE: Phase I Trial of Tipifarnib in Pediatric Patients with Newly Diagnosed non-Disseminated Intrinsic Brainstem Gliomas. *Neuro-Oncology (Neuro-oncology, in press)*
40. Morris B, Gajjar A, Okuma J, Yutaka Y; Wallace D; Kun LE; Merchant, T; **Fouladi, M**; Broniscer, A; Robison L; Hudson M. Survival and Late Mortality in Long-term Survivors of Pediatric Central Nervous System Tumors. *J Clin Oncol*: 25 (12):2535-2541, 2007.
41. **Fouladi M**, Laningham F, Wu J, O'Shaughnessy M, Molina K, Broniscer A, Spunt SL, Stewart CF, Houghton PJ, Gilbertson RJ, Furman, WL. Phase I Study of Everolimus (RAD001) in Pediatric Patients with Refractory Solid Tumors. *J Clin Oncol.*, 25(30): 4806-12, 2007.
42. **Fouladi M**, Nicholson S, Zhou T, Laningham F, Helton K, et al. A Phase II Study of the Farnesyl Transferase Inhibitor, Tipifarnib, in Children with Recurrent or Progressive High Grade Glioma, Medulloblastoma/PNET or Brainstem Glioma: A Children's Oncology Group Study. *Cancer* 107(9):2291-2297, 2007.
43. Shih C, Hale GA, Gronewold L, Tong X, Gilger EA, Srivastava DK, Kun LE, Gajjar A, **Fouladi M**. High-Dose Chemotherapy with Autologous Stem Cell Rescue for Children with Recurrent Malignant Brain Tumors. *Cancer Epub ahead of print, Jan 25, 2008*
44. **Fouladi M**, Chintagumpala M, Ashley D, Kellie S, Gururangan S, Hassall T, Stewart CF, Gronewold L, Wallace D, Broniscer A, Hale GA, Kasow K, Merchant TE, Morris B, Krasin M, Kun LE, Boyett JM, Gajjar A. Amifostine Protects Against Cisplatin-Induced Ototoxicity in Children with Average-Risk Medulloblastoma. *J Clin Oncol*, 2008.
45. Laughton S, Merchant TE, Sklar C, **Fouladi M**, Broniscer A, Morris EB, Sanders R, Kun LE, Krasin M, Shelso J, Xiong Z, Wallace D, Gajjar A. Endocrine Outcomes For Children With Embryonal Brain Tumors Following Risk-Adapted Cranio-Spinal And Conformal Primary Site Irradiation And High-Dose Chemotherapy With Stem-Cell Rescue On The Sjmb-96 Trial. *J Clin Oncol*, 2008.
46. McGregor L, Spunt SL, Santana V, Stewart CF, Ward DA, Watkins A, Laningham FL, IvyP, Furman W, **Fouladi M**. Phase I Study of an Oxaliplatin–Etoposide Regimen in Pediatric Patients with Recurrent Solid Tumors. *Cancer* 2008, in press.
47. **Fouladi, M**, Gururangan, S, Moghrabi, A, Phillips P, Gronewold L, Wallace D, Sanford RA, Gajjar A, Kun LE, Heideman R. Carboplatin-Based Primary Chemotherapy For Infants And Young Children With CNS Tumors. *Cancer*, submitted.

### C. Research Support.

U01 CA81457 (Boyett) 04/01/08-03/31/09  
 NIH/St. Jude  
 The Pediatric Brain Tumor Consortium (PBTC)

U01 CA097452 (Adamson) 08/01/07-07/31/08  
 NIH/National Childhood Cancer Foundation

No number assigned (Gajjar) 08/01/08-07/31/13 per patient  
 Collaborative Medical Research /St. Jude  
 Collaborative Ependymoma Research  
 Network (CERN)

## BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Bruce J. Aronow		POSITION TITLE Professor, Divisions of Biomedical Informatics, Developmental Biology, Departments of Pediatrics, Biomedical Engineering	
eRA COMMONS USER NAME baronow			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Stanford University, Stanford CA	BS	1976	Chemistry, Physics
University of Kentucky, Lexington, KY	Ph.D.	1986	Biochemistry, Genetics

### A. Positions and Honors

1986-present	Cincinnati Children's Hospital, Depts. of Pediatrics, Biomedical Informatics, Developmental Biology, Biomedical Engineering, College of Medicine: University of Cincinnati Ohio, USA (Post Doc /Assist Prof -1990 /Assoc. Prof w/tenure -1995 / Prof - 2006)
2000-present	Director; HHMI Genome Bioinformatics Shared Core, Univ. of Cincinnati College of Medicine and Children's Hospital Research Foundation;
Feb. 2004-Present	Scientific Director; State of Ohio Third Frontier Center for Computational Medicine
<u>Awards/Honors:</u>	
1983 – 1985	University Fellow, University of Kentucky
1984	Sigma Xi Annual Graduate Research Award, University of Kentucky
1987-1989	National Research Service Award
1997	Leo Prize for "Regulation of Clusterin" Villars-sur-Ollon, Switzerland
1998 - 1999	Member, Chair, Mammalian Genome SBIR Biotechnology Study Section
2000 – 2006	Board of Scientific Advisors "Critical Assessment of Microarray Data Analysis" CAMDA at Duke Univ.
1998 – 2002	Member, NIH Physiological Chemistry Study Section
2004 – 2006	Genomics Consultant for United States Environmental Protection Agency
2003 – Present	Bioinformatics and Systems Biology Committees, NCI/NIH Mouse Models of Human Cancer Consortium
2004 – Present	Assoc. Editor, Physiological Genomics
2006 – Present	Program and Meetings Committees: American Medical Informatics Assoc.
2005 – Present	Intl. Society for Computational Biology
Aug 2007	Member, Ohio State University Comprehensive Cancer Center; Scientific Program Committee Chair, OCCBio2007 Statewide Bioinformatics Conference
Present	Steering Committee OCC Bio 2008

### B. Selected peer-reviewed publications (in chronological order)

- Blanchard C, Wang N, Stringer KF, Mishra A, Fulkerson PC, Abonia JP, Jameson SC, Kirby C, Konikoff MR, Collins MH, Cohen MB, Akers R, Hogan SP, Assa'ad AH, Putnam PE, Aronow BJ, Rothenberg ME. Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. *J Clin Invest.* 2006 Feb 1;116(2):536-547.
- Imhof A, Charnay Y, Vallet PG, Aronow B, Kovari E, French LE, Bouras C, Giannakopoulos P. Sustained astrocytic clusterin expression improves remodeling after brain ischemia. *Neurobiol Dis.* 2006 Feb 9; [Epub ahead of print] PMID: 1647351
- Xu J, Gong NL, Bodi I, Aronow BJ, Backx PH, Molkenin JD. MEF2A and MEF2C induce dilated cardiomyopathy in transgenic mice. *J Biol Chem.* 2006 Feb 9; [Epub ahead of print] PMID: 16469744
- Miller SJ, Rangwala F, Williams J, Ackerman P, Kong S, Jegga AG, Kaiser S, Aronow BJ, Frahm S, Kluwe L, Mautner V, Upadhyaya M, Muir D, Wallace M, Hagen J, Quelle DE, Watson MA, Perry A, Gutmann DH, Ratner N. Large-scale molecular comparison of human schwann cells to malignant peripheral nerve sheath tumor cell lines and tissues. *Cancer Res.* 2006 Mar 1;66(5):2584-91.

- Oka T, Maillet M, Watt AJ, Schwartz RJ, Aronow BJ, Duncan SA, Molkentin JD. Cardiac-specific deletion of *Gata4* reveals its requirement for hypertrophy, compensation, and myocyte viability. *Circ Res*. 2006 Mar 31;98(6):837-45. Epub 2006 Mar 2.
- Schwab K, Hartman HA, Liang HC, Aronow BJ, Patterson LT, Potter SS. Comprehensive microarray analysis of *Hoxa11/Hoxd11* mutant kidney development. *Dev Biol*. 2006 Mar 31;
- Lowy AM, Clements WM, Bishop J, Kong L, Bonney T, Sisco K, Aronow B, Fenoglio-Preiser C, Groden J. beta-Catenin/Wnt signaling regulates expression of the membrane type 3 matrix metalloproteinase in gastric cancer. *Cancer Res*. 2006 May 1;66(9):4734-41
- McGraw DW, Fogel KM, Kong S, Litonjua AA, Kranias EG, Aronow BJ, Liggett SB. Transcriptional response to persistent beta<sub>2</sub>-adrenergic receptor signaling reveals regulation of phospholamban which alters airway contractility. *Physiol Genomics*. 2006 Jul 18; [Epub ahead of print]
- Gerber LK, Aronow BJ, Matlib MA. Activation of a novel long-chain free fatty acid export system in mitochondria of diabetic rat hearts. *Am J Physiol Cell Physiol*. 2006 Jul 19; [Epub ahead of print] PMID: 16855217
- Fink D, Fazli L, Aronow B, Gleave ME, Ong CJ. Clusterin is not essential for androgen-regulated involution and regeneration of the normal mouse prostate. *Prostate*. 2006 Jul 24; [Epub ahead of print]
- P Rajan S, Williams SS, Jagatheesan G, Ahmed RP, Fuller-Bicer G, Schwartz A, Aronow BJ, Wiczorek DF. Microarray analysis of gene expression during early stages of mild and severe cardiac hypertrophy. *Physiol Genomics*. 2006 Aug 1 [Epub ahead of print]
- Bosco EE, Wang Y, Xu H, Zilfou J, Knudsen KE, Aronow BJ, Lowe SW, Knudsen ES. The retinoblastoma tumor suppressor modifies breast cancer therapeutic response. *J Clin Invest*. 2007 Jan 2;117(1):218-228.
- Jegga AG, Chen J, Gowrisankar S, Deshmukh MA, Gudivada R, Kong S, Kaimal V, Aronow BJ. GenomeTrafac: a whole genome resource for the detection of transcription factor binding site clusters associated with conventional and microRNA-encoding genes conserved between mouse and human gene orthologs. *Nucleic Acids Res*. 2006 Dec 18; [Epub ahead of print] PMID: 17178752
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- Wong HR, Shanley TP, Sakthivel B, Cvijanovich N, Lin R, Allen GL, Thomas NJ, Doctor A, Kalyanaraman M, Tofil NM, Penfil S, Monaco M, Tagavilla MA, Odoms K, Dunsmore K, Barnes M, Aronow BJ. Genome level expression profiles in pediatric septic shock indicate a role for altered zinc homeostasis in poor outcome. *Physiol Genomics*. 2007 Mar 20
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- Jeong JW, Lee KY, Han SJ, Aronow BJ, Lydon JP, O'malley BW, Demayo FJ. The p160 Steroid Receptor Coactivator 2, SRC-2, regulates murine endometrial function and regulates progesterone independent and dependent gene expression. *Endocrinology*. 2007 Jun 14
- Liang, Y, Geiger, H, Aronow, B and G Van Zant. The quantitative trait gene, *Latexin*, influences the size of the hematopoietic stem cell population in mice. *Nature Genetics*, In Press 2007
- Deane NG, Manning HC, Foutch AC, Washington MK, Aronow BA, Bornhop DJ, Coffey RJ. Targeted imaging of colonic tumors in *smad3*<sup>-/-</sup> mice discriminates cancer and inflammation. *Mol Cancer Res*. 2007 Apr;5(4):341-9.
- Oka T, Xu J, Kaiser RA, Melendez J, Hambleton M, Sargent MA, Lorts A, Brunskill EW, Dorn GW 2nd, Conway SJ, Aronow BJ, Robbins J, Molkentin JD. Genetic Manipulation of Periostin Expression Reveals a Role in Cardiac Hypertrophy and Ventricular Remodeling. *Circ Res*. 2007 Jun 14
- Kaiser S, Park YK, Franklin JL, Halberg RB, Yu M, Jessen WJ, Freudenberg J, Chen X, Haigis K, Jegga AG, Kong S, Sakthivel B, Xu H, Reichling T, Azhar M, Boivin GP, Roberts RB, Bissahoyo A, Gonzales F, Bloom

GL, Eschrich S, Carter SL, Aronow JE, Kleimeyer J, Kleimeyer M, Ramaswamy V, Settle SH, Boone B, Levy S, Graff JM, Doetschman T, Groden J, Dove WF, Threadgill DW, Yeatman TJ, Coffey RJ Jr, Aronow BJ. Transcriptional recapitulation and subversion of embryonic colon development by mouse colon tumor models and human colon cancer. *Genome Biol.* 2007 Jul 5;8(7):R131

Mayhew CN, Carter SL, Fox SR, Sexton CR, Reed CA, Srinivasan SV, Liu X, Wikenheiser-Brokamp K, Boivin GP, Lee JS, Aronow BJ, Thorgeirsson SS, Knudsen ES. RB Loss Abrogates Cell Cycle Control and Genome Integrity to Promote Liver Tumorigenesis. *Gastroenterology.* 2007 Sep;133(3):976-84. Epub 2007 Jun 20.

Shanley TP, Cvijanovich N, Lin R, Allen GL, Thomas NJ, Doctor A, Kalyanaraman M, Tofil NM, Penfil S, Monaco M, Odoms K, Barnes M, Sakthivel B, Aronow BJ, Wong HR. Genome-level longitudinal expression of signaling pathways and gene networks in pediatric septic shock. *Mol Med.* 2007 Jun 11; [Epub ahead of print]

Liu X, Jessen WJ, Sivaganesan S, Aronow BJ, Medvedovic M. Bayesian hierarchical model for transcriptional module discovery by jointly modeling gene expression and ChIP-chip data. *BMC Bioinformatics.* 2007 Aug 3;8(1):283

Deichmann A, Hacein-Bey-Abina S, Schmidt M, Garrigue A, Brugman MH, Hu J, Glimm H, Gyapay G, Prum B, Fraser CC, Fischer N, Schwarzwaelder K, Siegler ML, de Ridder D, Pike-Overzet K, Howe SJ, Thrasher AJ, Wagemaker G, Abel U, Staal FJ, Delabesse E, Villeval JL, Aronow B, Hue C, Prinz C, Wissler M, Klanke C, Weissenbach J, Alexander I, Fischer A, von Kalle C, Cavazzana-Calvo M. Vector integration is nonrandom and clustered and influences the fate of lymphopoiesis in SCID-X1 gene therapy. *J Clin Invest.* 2007 Aug;117(8):2225-32.

### **C. Research Support**

#### **Ongoing Research Support**

**UO1 CA084291** PI: Groden 04/01/2004-03/31/2009  
NCI/NIH

“Mouse Models of Human Cancer Consortium”

This multi-university consortium seeks to develop mouse models of human cancer for improved understanding of molecular mechanisms and the development of effective cancer therapeutics. The goals of the bioinformatics core are to aid investigators in the design and analysis of experiments that will shed light into the molecular basis of cancer processes, aid in the organization and analysis of microarray, genetic, and proteomic cores in the organization and management of tracking and reference data for samples, pathways, gene structures, and to generate web accessible databases that will allow public access to genes, pathways, gene expression data and detailed gene annotation information.

**1P30-DK078392-01** PI: Cohen 08/01/2007-05/31/2012  
NIH/NIDDK

Cincinnati Digestive Health Center: Bench to Bedside Research in Pediatric Digestive Disease

The overall goal is to promote research that will yield insights into the fundamental processes and pathogenic mechanisms of digestive disease in children and generate innovative treatment to restore digestive health. The aims of our DHC are to foster research and promote interdivisional and interdepartmental collaboration to achieve an even greater critical mass in digestive disease research and to focus on translational research opportunities.

**ODD TECH 04-042** PI: Boat 07/01/2004-06/30/2009

State of Ohio Biomedical Research Development w/University of Cincinnati

“Center for Computational Medicine”

The long-term objectives of the CCM are to- develop and commercialize computational systems that facilitate the integration of genetics and genomics into clinical medicine; thus, enabling improved understanding, prevention, diagnosis, treatment, and amelioration of disease.

**P01 AR048929** PI: Glass 08/22/2003-7/31/2008  
NIH

“Gene Expression in Pediatric Arthritis”

This program project grant application focuses on the use of DNA micro array (gene chip) technology to detect differential expression of genes in children with pediatric arthritis.

**R01 DK074055**

PI: Crombleholme

10/01/2005-09/30/2009

NIH

“Endothelial Progenitor Cell Biology in Type 1 Diabetes”

Our overall objective is to understand the mechanisms by which EPCs are mobilized and recruited to a target tissues in wound healing and in response to ischemia and understand how these mechanisms are impaired by type I diabetes.

**U01DK070251**

PI: Potter

09/30/2004-07/31/2009

NIH

“Global Gene Expression Atlas of the Developing Kidney”

The objective is to create a global gene expression atlas of the developing kidney. The central thesis is that a combination of laser capture microdissection and microarrays can be used to efficiently achieve this goal. Microarrays with essentially complete gene representation can be used to rapidly determine the expression levels of every gene in laser capture microdissected elements of the developing kidney. Analysis of the complex orchestrations of gene expression will provide deeper insight into the genetic basis of the development of the distinct parts of the nephron.

**U19AI070235**

PI: Hershey

09/15/2006-08/31/2011

NIH

“Epithelial Genes in Allergic Inflammation”

The focus of this Center proposal is to dissect the role of allergy-driven epithelial genes in allergic disorders of childhood. Specifically, this Center proposal includes 3 projects, each focusing on epithelial-derived genes and gene products. The genetic, phenotypic, and health outcome data generated in each project will be integrated by a central core and analyzed independently and in conjunction with each of the other projects to identify potential genetic, biologic, and environmental interactions. The public health impact of this study will be significant. Through the results of this study, we will be able to provide information regarding: 1. mechanisms by which epithelial cells drive the development of allergic disease; 2. the relevant epithelial genes with regard to allergic disorders of childhood; 3. genotypes to identify children that are at greater risk for severe asthma; 4. genetic biomarkers of childhood asthma; and 5. novel targets for therapeutic intervention for allergic disorders.

**R01HL076458**

PI: von Kalle

04/01/2004-03/31/2009

NIH

“Vector Insertion and Mutagenesis in Human Hematopoiesis”

To gain substantial additional insight into the identity, significance, and impact of retroviral insertions in gene corrected progenitor cells. The overall aim of this proposal to determine the frequency of retrovirus insertion into the vicinity of the LMO2 locus in human repopulating cell clones and to track their fate in vivo (Aim 1), to understand the frequency of insertions into other critical cellular genes and gene structures (Aim 2), and to map the clonal composition of the inventory of genetically corrected hematopoietic cells in typical patients of the X-SCID gene therapy trials (Aim 3) in order to develop safe and efficient dosage and side effect prevention strategies for future gene therapy trials. Results from these studies of insertion sites in the human genome, and the role of LMO2 overexpression on the evolution of a lymphoproliferative phenotype will have great significance for the field.

**W81XWH0410273**

PI: Ratner

02/01/2004-02/28/2009

DOD

“Therapeutic Targets for Neurofibromatosis: Identification”

## BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Rachid Drissi	POSITION TITLE		
eRA COMMONS USER NAME	Assistant Professor		
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
University of Rouen, France	B.S.	1983	Biochemistry
University of Rouen, France	M.S.	1984	Organic Chemistry
University of Paris VI, France	M.S.	1988	Biochemistry
University of Paris VI, France	Ph.D.	1994	Molecular Biology

**A. Positions and Honors.** List in chronological order previous positions, concluding with your present position. List any honors. Include present membership on any Federal Government public advisory committee.

### PROFESSIONAL APPOINTMENTS:

- 1994-1996 Postdoctoral Research Associate, St. Jude Children's Research Hospital, Memphis TN, USA. Department of Virology and Molecular Biology. "Regulation of DNA Replication induced by UV-DNA damage," laboratory of Dr. Suk-Hee Lee.
- 1996-2000 Postdoctoral Research Associate, St. Jude Children's Research Hospital, Memphis TN, USA. Department of Biochemistry. "c-Myc function in myeloid cell proliferation and apoptosis," laboratory of Dr. John L. Cleveland.
- 2000-2004 Research Associate Investigator, St. Jude Children's Research Hospital, Memphis TN, USA. Department of Hematology-Oncology. "Role of Telomerase/Telomeres in Immortalization and Cancer," laboratory of Dr. Jeffrey S. Dome.
- 2004-2007 Research Associate Investigator, St. Jude Children's Research Hospital, Memphis TN, USA. Department of Hematology-Oncology. "Role of ATM in Mitochondrial DNA Damage Pathway," laboratory of Michael B. Kastan.
- 2007-Present Assistant Professor, Cincinnati Children's Hospital Medical Center, Cincinnati OH, USA. Division of Hematology-Oncology "Telomeres, Telomerase and Cancer"

### MEMBERSHIP IN PROFESSIONAL ORGANIZATIONS:

Member of American Association for Cancer Research

**B. Selected peer-reviewed publications (in chronological order).** Do not include publications submitted or in preparation.

1. Miyakawa I, **Drissi R**, Dinouel N, Rousset S, Viola A-M, Sor F, Fukuhara H. Linear mitochondrial DNAs of yeasts. *Yeast* 8(S407):9-11A, 1992.
2. Fukuhara H, Sor F, **Drissi R**, Dinouel N, Miyakawa I, Rousset S, Viola A-M. Linear mitochondrial DNAs of yeasts: Frequency of occurrence and general features. *Mol Cell Biol* 13:2309-2314, 1993.

3. Dinouel N, **Drissi R**, Miyakaya I, Sor F, Rousset S, Fukuhara H. Linear mitochondrial DNAs of yeasts: Closed-loop structure of the termini and possible linear-circular conversion mechanisms. *Mol Cell Biol* 13:2315-2323, 1993.
  4. **Drissi R**, Sor F, Fukuhara H. DNA sequences coding for the ribosomal small subunit RNA and Valyl tRNA from the linear mitochondrial genome of the yeast *Williopsis mrakii*". *Nucleic Acids Res* 21(12):2947, 1993.
  5. **Drissi R**, Sor F, Nosek J, Fukuhara H. Genes of the linear mitochondrial DNA of *Williopsis mrakii*: Coding sequences for a maturase-like protein, ribosomal protein var1 homolog, cytochrome oxidase subunit 2 and methionyl tRNA. *Yeast* 10:391-398, 1994.
  6. Lee S-H, Kim DK, **Drissi R**. Human *Xeroderma pigmentosum* group A protein interacts with human replication protein A and inhibits DNA Replication. *J Biol Chem* 270:21800-21806, 1995.
  7. Lee S-H, Kuchta RD, Kim DK, **Drissi R**. Use of in vitro eukaryotic DNA Replication system as tool to develop anti-viral drug, nucleotide analog. *Proceedings of KSEA Symposium, Alexandria, VA*, pp 68-75, 1996.
  8. **Drissi R**, Lee S-H. In vitro analysis of UV-damage-induced inhibition of replication. *Biochem J* 330:181-187, 1998.
  9. Stigger E, **Drissi R**, Park M, Lee SH. Functional analysis of human replication protein A in nucleotide excision repair. *J Biol Chem* 273:9337-9343, 1998.
  10. **Drissi R**, Zindy F, Roussel MF, Cleveland JL. c-Myc-mediated regulation of telomerase activity is disabled in immortalized cells. *J Biol Chem* 276:29994-30001, 2001.
  11. **Drissi R\***, Bakkenist CJ\*, Wu J, Kastan MB, Dome JS. Disappearance of the telomere dysfunction-induced stress response in fully senescent cells. *Cancer Res* 64:3748-3752, 2004. (\*equal contribution).
  12. Sanders RP, **Drissi R**, Billups CA, Daw NC, Valentine MB, Dome JS. Telomerase expression predicts unfavorable outcome in osteosarcoma. *J Clin Oncol* 22(18):3790-3797, 2004.
- C. Research Support.** List selected ongoing or completed (during the last three years) research projects (federal and non-federal support). Begin with the projects that are most relevant to the research proposed in this application. Briefly indicate the overall goals of the projects and your role (e.g. PI, Co-Investigator, Consultant) in the research project. Do not list award amounts or percent effort in projects.

None

## BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME <b>Nortz, Marsha J.</b>	POSITION TITLE  Assistant Professor of Pediatrics		
eRA COMMONS USER NAME			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
University of Rochester; Rochester, NY	B.S.	1994	Neuroscience
University of Rochester; Rochester, NY	B.A.	1994	Psychology
Washington University, St. Louis. MO	M.A.	1996	Clinical Psychology
Washington University, St. Louis, MO	Ph.D.	2000	Clinical Psychology (Neuropsychology specialization)

### A. Positions and Employment

#### Positions and Employment

- 1999-2000 Full Time Internship in Neuropsychology, Clinical Psychology (Neuropsychology specialization), University of Oklahoma Health Science Center, Oklahoma City, OK,
- 2000-2002 Full Time Fellowship in Pediatric Neuropsychology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH
- 2002-present Assistant Professor of Pediatrics, Division of Psychology, Cincinnati Children's Hospital Medical Center
- 2002-2005 Associate Director, Postdoctoral Program in Pediatric Neuropsychology, Cincinnati Children's Hospital Medical Center
- 2005-present Co-Director, Postdoctoral Program in Pediatric Neuropsychology, Cincinnati Children's Hospital Medical Center

#### Honors

- 1990-1994 University of Rochester, Bausch and Lomb Scholarship
- 1990 University of Rochester, Phi Beta Kappa
- 1994 University of Rochester, Summa Cum Laude, B.A. Psychology
- 1994 University of Rochester, Summa Cum Laude, B.S. Neuroscience
- 1992 University of Rochester, deKiewet Summer Research Fellowship
- 1994 University of Rochester, Jane Howell Clark Prize
- 1994-2000 Washington University, The Mr. & Mrs. Spencer T. Olin Fellowship for Women
- 1997 Washington University, Subject Matter Orals (Clinical), Pass with Distinction
- 2002-present Appointment to the Medical & Dental Staff, CHMC
- 2003-present Ad Hoc Reviewer for select professional journals

### B. Selected peer-reviewed publications (past 10 years).

1. Banich, M.T., Passarotti, A.M., White, D.A., **Nortz, M.J.**, & Steiner, R.D. (2000). Interhemispheric interaction during childhood: II. Children with early-treated phenylketonuria. Developmental Neuropsychology, 18(1), 53-71.
2. White, D.A., **Nortz, M.J.**, Mandernach, T., Huntington, K., & Steiner, R. (2001). Deficits in memory strategy use related to prefrontal dysfunction during early development: Evidence from children with phenylketonuria. Neuropsychology, 15(2), 221-229.
3. White, D.A., **Nortz, M.J.**, Mandernach, T., Huntington, K., & Steiner, R.D. (2002). Age-related working memory impairments in children with prefrontal dysfunction associated with phenylketonuria. Journal of the International Neuropsychological Society, 8(1), 1-11.

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4. Ammerman, R.T., **Nortz, M.J.**, Ris, M.D., Walz, N.C., & Oppenheimer, S.G (2007). Psychological functioning in children and adolescence with spina bifida. In S.G. Oppenheimer (Ed.), Neural Tube Defects, pp. 61-78. Marcel Dekker, NY.
  5. **Nortz, M.J.**, Hemme-Phillips, J.M., & Ris, M.D. (2007). Neuropsychological sequelae in children treated for cancer. In S. J. Hunter & J. Donders (Eds.), Pediatric Neuropsychological Intervention: A Critical Review of Science & Practice, pp. 112-132. Cambridge University Press, NY.
  6. Ris, M.D. & **Nortz, M.** (2008). Nonverbal learning disorders. In J. Morgan and J. Ricker (Eds.), Textbook of Clinical Neuropsychology, pp. 346-359. Swets & Zeitlinger Publishers, Netherlands.

### **C. Research Support**

#### **Ongoing Research Support**

N/A

#### **Completed Research Support (in past three years)**

N/A

## BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME David William Pruitt, MD	POSITION TITLE		
eRA COMMONS USER NAME	Assistant Professor		
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
University of Notre Dame	B.S.	1994	Biology
Loyola University of Chicago	MD	1998	

**A. Positions and Honors.** List in chronological order previous positions, concluding with your present position. List any honors. Include present membership on any Federal Government public advisory committee.

### Academic Appointment:

June 2004-May 2005      Clinical Instructor, Pediatrics, Loyola University Medical Center, Maywood, Illinois  
Feb 2004-May 2005      Assistant Professor, Physical Medicine & Rehabilitation, Adjunct Faculty, Pediatrics Rush University Medical Center, Chicago, Illinois  
Sept 2003-May 2005      Attending Physcician, Pediatric Rehabilitation, Marianjoy Medical Group, Wheaton, Illinois  
June 2005 – present      Assistant Professor, Clinical Physical Medicine & Rehabilitation and Clinical Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

### Awards and Honors

June 2003      Adolescent Medicine Award – Cincinnati Children's Hospital Medical Center

### Professional Memberships

American Academy of Pediatrics  
American Academy of Physical Medicine and Rehabilitation  
American Academy of Cerebral Palsy and Developmental Medicine  
Children's Oncology Group

**B. Selected peer-reviewed publications (in chronological order).** Do not include publications submitted or in preparation.

Michaud LJ, Reid SR, McMahon MA and **Pruitt DW**. *Rehabilitation of the Child with Cancer*. In: DG Poplack, PA Pizzo (eds.): *Principles and Practice of Pediatric Oncology, 5<sup>th</sup> Edition*. Philadelphia: Lippincott-Raven, 2006, p1399-1413.

McMahon MA, **Pruitt DW** and Vargus-Adams JN. Cerebral Palsy. In: DJ Matthews and M Turk (eds.) *Essential Pediatric Rehabilitation Medicine*. (In preparation)

Spierre LZ, **Pruitt DW** and Mehlman, CT. Rehabilitation of the Child With Multiple Injuries. In: NE Green, MF Swiontkowski (eds.): *Skeletal Trauma in Children, 4<sup>th</sup> Edition*. Philadelphia, Saunders, 2003. (In preparation)

**Pruitt, DW** and Nagarajan R. *Rehabilitation in Pediatric Cancer*. In: M Stubblefield and M O'Dell (eds.): *Principles and Practice of Cancer Rehabilitation*. (In preparation)

**C. Research Support.** List selected ongoing or completed (during the last three years) research projects (federal and non-federal support). Begin with the projects that are most relevant to the research proposed in this application. Briefly indicate the overall goals of the projects and your role (e.g. PI, Co-Investigator, Consultant) in the research project. Do not list award amounts or percent effort in projects.

None

## BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.  
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Ris, M. Douglas	POSITION TITLE  Professor of Pediatrics		
eRA COMMONS USER NAME RISDOU			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Michigan State University, East Lansing, MI	B.S.	1976	Psychology
Texas A & M University, College Station, TX	M.S.	1978	Psychology
Wayne State University, Detroit, MI	Ph.D.	1982	Clinical Psychology

### A. Positions and Employment

#### Positions and Employment

1980-1981	Full Time Internship in Neuropsychology, Division of Neuropsychology, Henry Ford Hospital
1981-1982	Full Time Internship in Clinical Psychology, College of Human Medicine, Michigan State Univ.
1983-1985	Staff Psychologist, Department of Psychology, Cincinnati Children's Hospital Medical Center
1985-1995	Assistant Professor of Clinical Pediatrics
1991-present	Director, Postdoctoral Program in Pediatric Neuropsychology, Cincinnati Children's Hospital Medical Center
1993-1995	Assistant Professor, University of Cincinnati Department of Psychology
1995-2001	Associate Professor of Clinical Pediatrics
1996-present	Associate Professor, University of Cincinnati Department of Psychology
2000-present	Director, Behavioral Core of the General Clinical Research Center, Cincinnati Children's Hospital Medical Center
2001-present	Professor of Pediatrics

#### Honors

1978 & 1979	Graduate Tuition Scholarships, Wayne State Univ.
1981	Henry Ford Hospital In-House Grant for Doctoral Dissertation
1989	Diplomate, American Board of Clinical Neuropsychology (ABCN), American Board of Professional Psychology (ABPP)
1990-1999	Children's Cancer Group appointments to: Psychology Steering committee; CCG 9892 (PNET) Study Committee; CCG 9891 (Low Grade Astrocytoma) Study Committee; Brain Tumor Strategy Committee.
1992-1997	Founding Member & Member of the Board of Directors, Association of Postdoctoral Programs in Clinical Neuropsychology (APPCN)
1992-present	Ad Hoc Reviewer for numerous professional journals
1994-present	Appointment to the Medical & Dental Staff, CHMC
1994-present	Appointment to the CHMC Institutional Review Board
1997-1999	Vice President, APPCN
1999-2004	Board of Directors, American Board of Clinical Neuropsychology
2003-present	Editorial Boards of <i>The Clinical Neuropsychologist</i> & <i>Child Neuropsychology</i>
2004-2006	Co-Chair, Institutional Review Board

### B. Selected peer-reviewed publications (past 10 years).

1. Ris MD, Weber A, Hunt MM, Berry HK, Williams SE, Leslie N. Adult psychosocial adjustment in early-treated phenylketonuria. *J Inher Metab Dis* 1997;20:499-508.
2. Williams SE, Ris MD, Ayyangar R, Schefft BK, Berch D. Recovery in Pediatric Brain Injury: The use of Psychostimulant Medication. *J Head Trauma Rehabil* 1998;13:73-81.
3. Chase-Charmichael CA, Ris MD, Weber AM, Schefft BK. The neurologic validity of the Wisconsin Card Sorting Test with a pediatric population. *Clin Neuropsychol* 1999;13:405-13.
4. Packer RJ, Goldwein J, Nicholson S, Vezina LG, Allen JD, Ris MD, Muraszko K, Rorke LB, Wara WM, Cohen BH, Boyett JM. Treatment of children with medulloblastomas with reduced-dose craniospinal

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- radiation therapy and adjuvant chemotherapy: A children's cancer group study. *J Clin Oncol*, 1999;17:2127-36.
5. Yeates KO, Ris MD, Taylor HG. *Pediatric Neuropsychology, Theory, Research, and Practice*. New York: Guilford Publications, Inc. 2000.
  6. Ris MD, Grueneich R. *Neuropsychology of Sickle Cell Disease*. In K.O. Yeates, M.D.Ris, &H.G. Taylor (Eds.), *Pediatric Neuropsychology, Theory, Research, and Practice*. New York: Guilford Publications, Inc. 2000.
  7. Beebe DW, Ris MD, Dietrich KN. The relationship between CVLT-C rocess scores and measures of executive functioning: Lack of support among community-dwelling adolescents. *J Exp Clin Neuropsychol* 2000;22:779-792.
  8. Noll R, Stith L, Gartstein MA, Ris MD, Grueneich R, Vannatta K, Kalinyak K, Noll RB. Neuropsychological functioning of youth with sickle cell disease: Comparison with non-chronically ill peers. *J Pediatr Psychol* 2001;26:69-78.
  9. Ris MD, Packer R, Goldwein J, Jones-Wallace D, Boyett JM. Neurocognitive outcome following reduced-dose radiation therapy plus adjuvant chemotherapy for medulloblastoma: A Children's Cancer Group Study. *J Clin Oncol* 2001;19: 3470-76.
  10. Dietrich KN, Ris MD, Bornchein RL, Berger OG, Succop PA. Early exposure to lead and juvenile delinquency in middle to late adolescence. *Neurotoxicol Teratol* 2001;23:511-18.
  11. McDonough-Ryan P, DelBello M, Shear PK, Ris MD, Soutullo C, Strakowski S. Academic and cognitive abilities in children of parents with bipolar disorder: A test of the nonverbal learning disability model. *J Clin Exp Neuropsychol* 2002;24:280-85.
  12. Cavallo A, Good WV, Ris MD, Succop P. Dose response to melatonin treatment for disordered sleep rhythm in a blind child. *Sleep Med* 2002;3:159-61
  13. Cavallo A, Jaskiewicz J, Ris MD. Impact of night float rotation on sleep, mood, and alertness: The resident's perception. *Chronobiol Int* 2002;19:893-902
  14. Coscia JM, Ris MD, Succop P, Dietrich KN. Neurodevelopment of lead exposed children from ages 6 to 15 years: An application of growth curve analysis. *Child Neuropsychol* 2003;9:10-21.
  15. Ris MD. Casual inference in lead research: Introduction to the Special Section on the neurobehavioral effects of environment lead. *Child Neuropsychol* 2003;9:1-9.
  16. Dunn TM, Shear PS, Howe SA, Ris MD. Detecting Neuropsychological Malingering: Effects of coaching and information. *Arch Clin Neuropsychol* 2003;18:121-34.
  17. Cavallo A, Ris MD, Succop, P. The night float paradigm to decrease sleep deprivation: Good solution or a new program. *Ergonomics* 2003;46:653-63
  18. Grueneich R, Ris MD, Ball W, Kalinyak K, Noll R, Vannatta K, Wells R. Relationship of structural MRI, MR perfusion and other disease factors to neuropsychological outcome in sickle cell disease. *J Pediatric Psychol* 2004;29:83-92.
  19. Beebe DW, Ris MD, Brown TM, Dietrich KN. Executive functioning and memory for the Rey-Osterreith Complex Figure task among community adolescents. *Appl Neuropsychol* 2004;11:91-98.
  20. McSweeny AJ, Ris MD, Ricker JH, Westerveld M. Board certification in clinical neuropsychology: A response to Rohling et al. *Clin Neuropsychol* 2004;18:494-508.
  21. Ris MD, Dietrich KN, Succop PA, Berger OG, Bornschein RL. Early exposure to lead and neuropsychological outcome in adolescence. *J Int Neuropsychol Soc* 2004;10:261-270.
  22. Beebe DW, Ris MD, Armstrong FD, Fontanesi J, Mulhern R, Holmes E, Wisoff JH. Cognitive and adaptive outcome in low-grade pediatric cerebellar astrocytomas: evidence of diminished cognitive and adaptive functioning in National Collaborative Research Studies. *J Clin Oncol* 2005;23:5198-204.
  23. Cavallo A, Ris MD, Succop P, Jaskiewicz J. Melatonin treatment for adaptation to night shift work. *Ambul Pediatr* 2005;5(3):172-7.
  24. Ris MD, McDonough RP, Lamba M, Brenemen J, Cecil K, Succop P, Ball WS. An improved methodology for modeling neurobehavioral late-effects of radiotherapy in pediatric brain tumors. *Pediatr Blood Cancer* 2005;44(5):487-493.
  25. Yuan W, Holland SK, Cecil KM, Dietrich KN, Wessel SD, Altaye M, Hornung RW, Ris MD, Egelhoff JC, Lanphear BP. The impact of early childhood lead exposure on brain organization: A functional magnetic resonance imaging study of language function. *Pediatrics* 2006;118:971-977.
  26. Ris, M.D. Lessons in pediatric neuropsychology: What we've learned since Johnny Gunther. *Journal of Pediatric Psychology*. 2007 Oct;32(9):1029-37. Epub 2007 Apr 9. PMID: 17426043

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### **C. Research Support**

#### **Ongoing Research Support**

R01 CA112182-01 Ris (PI)

03/22/05 – 02/28/10

NIH/NCI

Neurobehavioral Late-Effects in Pediatric Brain Tumors

The goals of this study are to improve our knowledge and prediction of radiation-related late-effects, which in turn will guide further improvements in RT techniques. It will also provide important information about the development of vulnerable neurobehavioral functions, how they might be protected/preserved, and where to focus early interventions to limit functional morbidity.

GCRC Grant # M01 RR08084 Boat/Heubi (PIs)

12/01/01 – 11/30/11

General Clinical Research Center Grant

Inpatient unit at Children's Hospital with outpatient, scatter bed, and Core Laboratory facilities. Major areas of research: pediatric liver disease, cholera challenge study, diabetes mellitus, cystic fibrosis-gene therapy, bone disease, growth hormone, Gaucher disease, cancer prevention and treatment, and transplantation immunology.

R01 ES015559 Cecil (PI)

06/01/07 – 03/31/12

NIH/NIEHS

Early Lead Exposure, ADHD and Persistent Criminality: Role of Genes and Environment

The goals of this study is to examine the prevalence of adult ADHD and persistent criminality in a population with childhood lead exposure. Determine correlates with neuroanatomical and functional features.

#### **Completed Research Support (in past three years)**

R-82938901 Lanphear (PI)

11/01/01 – 10/31/06

EPA

Center for Children's Environmental Health and Disease Prevention Research

Early Exposure to Lead and Adult Antisocial Outcome (Project 4)

The major goal of this study is to research early exposure to environmental lead and its' association with increased risk for delinquency and whether or not this increased risk extends into adulthood. In addition research will be performed to get a clear understanding of what neurobehavioral factors mediate the relationship between lead and antisocial behavior.

P01 ES011261 Lanphear (PI)

09/01/01 – 08/31/06

NIH/NIEHS

Center for Children's Environmental Health and Disease Prevention Research

Study of Prevalent Neurotoxicants in Children

The major goals of this study is to conduct a cohort study to examine the effect of low-level exposures to prevalent neurotoxicants. A randomized controlled trial to test the efficacy of lead hazard controls on the development of adverse neurobehavioral effects will be performed. If funded further research will test the efficacy of an intervention for the primary prevention of lead toxicity.