Precision Immuno-Oncology for Pediatric Brain Tumors

Pediatric brain tumors are the leading cause of disease-related death in children. Gliomas constitute the most common brain tumor type in children. High-grade gliomas (HGG), including anaplastic astrocytomas (AA) and glioblastomas (GBM), are the most aggressive gliomas with 5-year survival rates of less than 20% in the pediatric population. If these tumors occur within the pons – diffuse intrinsic pontine glioma (DIPG) - outcome is even worse with a median survival of approximately 9 months and all children die of their disease. Despite several decades of research, outcomes and treatment strategies for these children have not significantly changed. For children with HGG no standard treatment has been established although most children are treated with surgical resection followed by focal irradiation. Once HGG recurs or progresses, there are very few treatment options and most children die of their disease within a very short timeframe on the order of months.

The need for new and less toxic therapies for pediatric brain tumors is especially salient as existing standard therapies such as radiation are exceedingly harmful to the developing central nervous system, leaving children who may survive the cancer with life-altering morbidities and a reduced quality of life. Even when a targeting therapeutic is identified, brain tumor precision medicine approaches have the additional challenge of poor penetration of the blood-brain-barrier of many small molecule compounds, limiting efficacy of targeted approaches in the central nervous system. Furthermore, the more limited overall repertoire of mutations in the pediatric cancer contexts provides for a more limited small molecule targeting platform for pediatric brain tumors as compared to adults. The emergence and successful implementation of immunotherapeutic approaches in pediatric cancers, combined with the institutional expertise and highly developed research and clinical platforms the applicant collaborative team comprises, positions the following proposed collaborative efforts for a first-in-kind implementation of a precision immuno-oncology research platform previously unavailable to the the pediatric brain tumor research and clinical community.

In developing novel, precision immunotherapeutic approaches for pediatric brain tumors that can be positioned for rapid translation to safe and efficacious clinical care, the field faces a number of key challenges. First, in contrast to other pediatric cancers (e.g. Therapeutically Applicable Research to Generate Effective Treatments, TARGET) for which large scale genomic characterization has been supported by NIH initiatives, the pediatric brain tumor genomic data landscape has yet to be supported by coordinated, NIH-led initiatives that provide accessibility to large-scale data. As such, access to a centralized resource for large-scale pediatric brain tumor data and associated clinical/phenotypic annotation has been limited. Second, while immunotherapeutic strategies such as chimeric antigen receptor T cell (CAR-T) therapies in hematologic malignancies have had remarkable and demonstrable success, achieving specificity and safety for such immunotherapeutics in the context of pediatric brain tumors will remain challenging. Third, the implementation of immunotherapeutic approaches for pediatric brain tumors in the clinical setting will require additional biomarker-based development and preclinical modeling yet to have been initiated for pediatric brain tumors.

Hypothesis and goals: Accelerated development and implementation of novel, efficacious and safe approaches for newly developed immune-based therapies for pediatric high grade gliomas and diffuse intrinsic pontine gliomas can be achieved through emergent, integrated genomics analysis platforms that utilize next generation sequencing and proteomics workflows. These, combined with robust, tissue-based and preclinical-modeling resources being developed within leading large-scale consortia-based biorepositories and clinical trial networks will serve for the rapid translation, integration, and implementation of novel, precision immuno-oncology therapeutics in pediatric brain tumor clinical trials for high grade gliomas and diffuse intrinsic pontine gliomas.

Specific Aims:

1) Identification and prioritization of high-confidence gene targets and neo-antigens for immunotherapeutic-based interventions in pediatric high-grade gliomas and diffuse intrinsic pontine gliomas.
2) Validation and targeting of high-confidence gene targets in existing patient- and clinical-trial-derived models of high-grade gliomas and diffuse intrinsic pontine gliomas.
3) Translation of target identification into novel immunotherapeutic approaches and correlative analyses to be implemented and evaluated in ongoing and emergent clinical trials.

Research Plan:

Over the past five years, the applicant investigators have collaborated to (1) lead the world's largest data-driven brain tumor initiative in the context of the Children's Brain Tumor Tissue Consortium (CBTTC.org); (2) Centralized the largest existing dataset cohorts and associated preclinical model collection for pediatric gliomas and DIPGs (Mackay et. al, Cancer Cell, i*n press*) further developed in the context of the Pacific Pediatric Neuro-Oncology Consortium (PNOC.us) and associated clinical trials and correlative studies; (3) Initiated the development of the world's largest pediatric and rare disease collaborative cloud-based genomic discovery environment (cavatica.org), under further development via the recently announced Kids First Program (kidsfirst.d3b.center); and (4) have demonstrated the applicability of novel immunotherapeutic discovery workflows, pipelines, and workflows in support of the identification and development of novel, high confidence immunotherapeutic approaches for solid tumors (Bosse et. al, Cancer Cell 2017).

Preliminary Data and Workflows:

A) **Identification of oncogenes and candidate immunotherapeutic targets in solid and brain tumors.**
Developing novel, precision immunotherapeutic approaches for pediatric brain tumors that can be translated to safe and efficacious clinical care faces a number of key challenges. A major hurdle for the development of new and effective immune-based therapies is the identification of tumor-specific cell surface molecules with limited expression on normal childhood tissues or other brain-specific cell types. Ideally these differentially expressed cell surface molecules are also required for tumor survival--this ensures long-lasting tumor cytotoxic effect in the absence of

immune escape. To identify and prioritize antigens for CAR-T, antibody drug conjugate (ADC), and monoclonal antibody (mAB) based therapies we developed a data analytics and harmonized sequencing platform (DiseaseXpress) that overcomes a number of these challenges. First, we compare our large-scale RNA sequencing based mRNA expression between tumors and a compendium harmonized normal mRNA (GTEx) to determine genes which are significantly differentially expressed overall or in a meaningful molecular subtype. We then couple this unbiased RNA sequencing-based discovery platform with the comprehensive validation of differential protein expression and tumor cell functional dependency. Together, these workflows and associated clinical trials provide for ultimate translation to a potently efficacious immunotherapeutic.

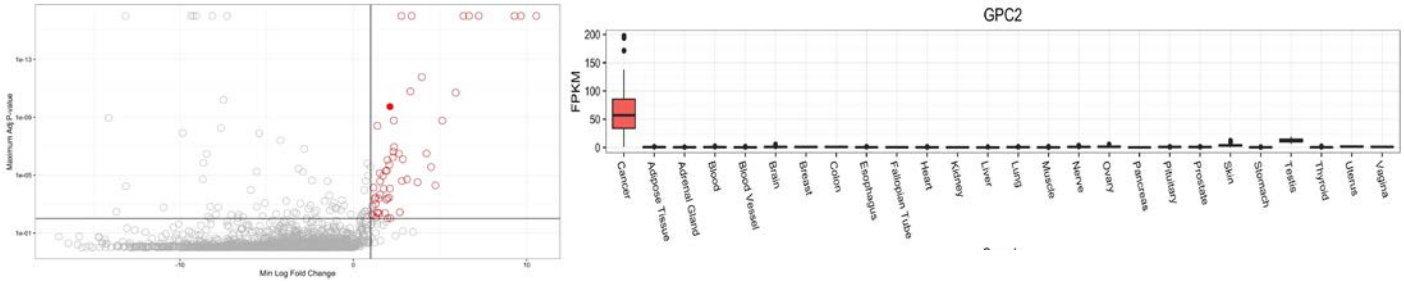

Fig. 1. Identification of GPC2 as a novel target in solid tumors using DiseaseXpress.

B) Validation of immunotherapeutic targets in patient derived xenograft (PDX) models

Using our vast number of patient samples through CBTTC and PNOC, we will validate the immunotherapeutic targets identified by immunohistochemical staining of tumor samples. We will also investigate if these targets are necessary for tumor survival using cells grown in culture, and prioritize targets for which this is true.

C) Creation and testing of immunotherapeutics

Using collaborations we have established with the National Cancer Institute (NCI) and Ganymed (pharmaceutical company), we will create CAR-T, ADC, and mAB based therapies using our prioritized targets. These will be tested and vetted both in cell cultures and mouse xenograft models of HGG and DIPG. To overcome the obstacles of the blood-brain barrier, we will investigate if delivery of these therapeutics directly into the tumor bed itself will improve efficacy.

D) Translation to clinical trial

Our position in PNOC make us well poised to translate our findings from the bench to the bedside…

Conclusion:

Our highly-specialized team has the optimal dataset and tools to navigate the pediatric brain tumor landscape, and identify novel immunotherapeutic targets which will be tested pre-clinically and brought to clinical trials for these devastating tumors.

Multi-Institutional Management and Administration:

This study, while lead by CHOP, is a CBTTC research project and will benefit from multi-institutional collaborative efforts, with the goal of speeding up the discovery of new therapies for children with brain tumors.

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