

Project Title: Advancing Treatment for Pediatric Craniopharyngioma: Prospective Pilot Study Identifying Clinically Relevant Biological Targets for Medical Therapy

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Hypotheses and Specific Aims

Despite its benign histological features, pediatric adamantinomatous craniopharyngioma (CPA) is often a devastating tumor, resulting in an amalgamation of symptoms that significantly impair the patient's and family's quality of life. Current treatment regimens are largely limited to surgery and radiation therapy. Using 18 existing samples of CPA, we recently discovered highly elevated levels of a group of molecules that may represent therapeutic targets.

Through further studies, we identified highly upregulated levels of Epidermal Growth Factor signaling in CPA, and confirmed that most of these tumors harbor mutations in the β -catenin gene (CTNNB1). This coincided with recent work that revealed a higher than previously documented rate of mutation of the β -catenin gene in these tumors [1]. Confirmation of these findings and correlation with clinical characteristics of the patient's harboring these lesions could lead to the introduction of systemic antitumor therapies.

Hypothesis 1: Gene products of the Epidermal Growth Factor Receptor (EGFR) pathway (e.g. EGFR, Amphiregulin, and Ephrin A2); Sonic Hedgehog (SHH); and Matrix Metalloproteases 9 & 12 are upregulated in pediatric adamantinomatous CPA.

Hypothesis 1b: Mutation of the β -catenin gene (CTNNB1) will be identified in >90% of pediatric adamantinomatous CPA

Specific Aim 1: Identification of Potential Therapeutic Targets

Over a 36 month period, we will acquire and analyze 35 samples of snap frozen pediatric CPA using mRNA gene expression analysis, quantitative PCR and immunohistochemistry. A subset of these tumors will be examined using laser capture microdissection followed by DNA SNaPshot analysis and/or focused next generation sequencing (hot spot region of exome 3 for CTNNB1), in order to determine which components of the tumor are responsible for observed gene signatures. Tumor cells from a subset of tumors will also be grown in short term tissue culture for studies of inhibition of proliferation and migration.

Our recent laboratory findings demonstrate overexpression of a number of potentially druggable targets/pathways in CPA, when compared to normal brain and other CNS tumors. These include a 20-fold overexpression of AREG, a 127-fold overexpression of SHH, a 17-fold overexpression of EphrinA2, and 22-fold and 389-fold overexpression of MMP-9 and 12, respectively. AREG is known to be a potent growth inducer associated with poor prognosis and good response to EGFR therapy in some carcinomas [2-4]. As such, it may represent a rational target for CPA therapy using existing immunotherapy, such as Cetuximab. Similarly, SHH is believed to play a critical role in the proliferation pathway in medulloblastoma. The levels of SHH identified in CPA are higher than we have found in hedgehog dependent medulloblastoma. EphrinA2 is associated with elevated Epidermal Growth Factor signaling and is directly inhibited by Dasatinib. It has also been incorporated as an antigen for immunotherapy against pediatric gliomas [5]. Lastly, currently available inhibitors of the MMP-12 pathway have met with renewed interest, as demonstrated by the inclusion of the MMP-9/12 inhibitor AZD1236 in a recent NIH/ NCATS request for X02 grant applications ("Discovering New Therapeutic Uses for Existing Molecules"). Given the extraordinarily high levels of expression in our preliminary samples of CPA, MMP-12 inhibitors may become relevant anti-tumor therapies for CPA.

Hypothesis 2: Multicenter collaboration will successfully correlate biological and clinical tumor characteristics and demonstrate that electronic capture of data regarding academic and behavioral condition in pediatric CPA can be achieved.

Specific Aim 2: Correlation of Clinical Characteristics with Tumor Biology

Through a network of institutions, we will collect baseline and short-term (up to 1 year) follow-up data regarding the clinical, radiographic and behavioral condition of each patient. This data will then be correlated with the biological characteristics of the patient's tumor.

Through telephone and electronic contacts with the primary centers, the research staff at each site and/or CHCO/UC-AMC will populate our current REDCap database with data regarding presentation, and initial clinical management. Updates will be completed at 6 month intervals through 1 year of follow-up. If they choose to provide an electronic mail contact as a portion of the informed consent process, patients and families will be contacted electronically at 1 month and 12 months following surgical intervention in order to guide them through a brief online assessment of the patient's academic and behavioral condition. This contact will be undertaken by the research staff at the treating site or CHCO/UC-AMC, in accordance with the parameters and preferences of the institutional review board and treating team at the patient's site. These data will be applied to an initial analysis correlating clinical and biological characteristics of CPA as well as serving as proof of principle for the preparation of prospective trials of therapeutic interventions.