

The Andrew Christian Bryce Pediatric Grant for PNET Research

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Harnessing Apoptosis for Medulloblastoma Therapy

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Abstract

Medulloblastoma (MB) is a highly malignant pediatric brain tumor and while current treatment using surgery, chemotherapy and radiation has increased survival rates, survivors often face life-long endocrine, intellectual and social problems. Since the biology of childhood tumors is significantly different from adult tumors, it is imperative that pediatric cancers be treated differently from CNS cancers of adults. Targeted therapy based on molecular features of the disease may be an avenue that needs to be evaluated. Apoptosis or programmed cell death is critical for tumor cell response to chemotherapy, however, a number of studies have shown that MB cells develop mechanisms to evade apoptosis by epigenetically repressing gene expression. Since epigenetic aberrations are potentially reversible, use of drugs that target specific enzymes involved in the modulation of the epigenome has emerged as an effective and valuable approach to chemotherapy. Histone deacetylases (HDACs) are enzymes that remodel chromatin and play an important role in gene silencing. We have demonstrated that HDAC inhibitors (HDACIs) as mono agents alter gene expression and induce cell death *in vitro* and in pre-clinical models of MB. However, since brain tumors are complex diseases and cancer cells are inherently genetically unstable, they often develop resistance to single agents. We have tested the efficacy of HDACIs in conjunction with conventional chemotherapeutic agents such as etoposide and demonstrated a dramatic synergy in induction of apoptosis in MB cells and in animal models. Mechanistically, this involves transcriptional up regulation of genes that monitor genomic integrity such as 53BP1 and γ -H2AX as well as pro-apoptotic genes such as FAS, DR4, DR5, and Caspase-8. An application for a clinical trial for pediatric neural tumors has been submitted to the institutional review board (IRB), based on this study. The purpose of the proposed project is to evaluate if HDACI-mediated up regulation of the death receptors, DR4 and DR5 expression can be used synergistically with TRAIL, the ligand for these death receptors, to promote apoptosis in human MB cells and murine xenograft models. Findings from the proposed project will be used to design a phase I clinical trial in patients with MB.