STRONG CHILDREN'S RESEARCH CENTER

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Name: Zoe Kory

School: University of Rochester

Mentor: Nina F. Schor, M.D. Ph.D., Xingguo Li, Ph.D.

ABSTRACT

Title: PRMT1 as a Novel Therapeutic Target in Chemoresistant Neuroblastoma

Background: Neuroblastoma (NB) is one of the most common childhood cancers, stemming from the neural crest,and most often diagnosed in or before the second year of life. High-risk or chemoresistant incidences account for a large percentage of cases and are a significant obstacle to clinical treatment. There are several key oncogenes which have been linked to the development of NB and the poorer prognoses, including MYCN (22% of NB) and ALK (10%).

Amplified MYCN activity has been linked to consistently worse patient outcomes through a complex pathway involving several geneprotein and protein-protein interactions. MYCN is a transcription factor and is therefore difficult to target directly, but a recent paper has shown it has several target genes which are much more feasible therapeutic targets, such as protein arginine methyltransferase 1 (PRMT1). PRMT1 is highly conserved and commonly expressed in mammalian cells, resulting in a multitude of functions in normal and abnormal cells. PRMT1 is primarily responsible for signal transduction, cotranscriptional recruitment, and post-translational modification. Loss of PRMT1 in normal cells leads to the suppression of cell growth, induced cell death, and increased sensitivity to chemotherapeutic agents. It has been further shown in leukemia cell lines that PRMT1 inhibition suppresses cell proliferation.

Eyes Absent 1 (EYA1), a transcriptional co-activator found in a diverse range of normal tissues, is responsible for cell mobility and motility during normal development and has key functions in the cell survival pathway. We have demonstrated that PRMT1 forms a complex with EYA1 and activates EYA1 through arginine methylation. We believe the PRMT1-EYA1 complex recruits critical components to the DNA damage repair system and thereby increases tumor cell survival by directing the cell to enter repair pathways instead of apoptotic pathways in response to DNA damage.

Objectives: Determine the effect of PRMT1 inhibition on cell behavior and growth. Determine if treatment with PRMT1 inhibitors increases sensitivity to genotoxic drugs. Correlate co-expression of PRMT1, EYA1, and methyl-EYA1 in patient samples with patient treatment and outcomes.

Results: We examined PRMT1 inhibition in three NB cells lines, two with amplified *MYCN* and one with non-amplified *MYCN*. Treatment with specific PRMT1 inhibitors suppressed cell growth, decreased viability, and induced cell death in both *MYCN* amplified lines but not the *MYCN* non-amplified line. We also investigated the effects of PRMT1 inhibition on sensitivity to etoposide over a short timeframe. We found possible synergistic effects of PRMT1 inhibitors and etoposide and clear potential for enhancing the therapeutic effects of genotoxic agents in NB through the use of PRMT inhibitor drugs, primarily in *MYCN* amplified cells.

Conclusion: While PRMT1 may still have a role in preserving cell viability in the *MYCN* non-amplified cells, it is not to the critical degree as seen in *MYCN* amplified lines. These results are in line with existing research which has demonstrated a clear link between amplified *MYCN*, high expression of PRMT1, and poor patient response to chemotherapeutic treatment. PRMT1 inhibitors are therefore potentially of clinical importance if effective disruption of the PRMT1-EYA1 complex blocks the cell survival pathway during treatment with DNA damage inducing agents.