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"Tissue-specific role of SMARCB1 in pediatric rhabdoid tumors"

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SCIENTIFIC ABSTRACT
Cancers of the brain and central nervous system (CNS) are one of the most common types of pediatric cancers, comprising 20-30% of pediatric cases. Atypical teratoid rhabdoid tumors (ATRT) are particularly challenging pediatric cancers, associated with a less than 20% 5 year survival rate in patients less than 12 months of age. ATRT and rhabdoid tumors of the kidney are both associated with inactivation of the SMARCB1 gene in nearly all cases, and few other recurrent mutations have been identified. Given that SMARCB1 is a major subunit of the chromatin remodeling SWI/SNF complex, we hypothesize that its transcriptional targets are influenced by tissue lineage. To address this hypothesis, we will generate a cell- based model of pediatric rhabdoid brain and kidney tumors by inducibly silencing SMARCB1 expression in human induced pluripotent stem cells (iPSCs) and comparing the effect of SMARCB1 silencing in both neural and kidney progenitor cells. We will validate our model against patient-derived rhabdoid cultured cell lines as well as publicly available gene expression data from clinical samples and use gene expression profiling to identify pathways which are commonly or differentially regulated by SMARCB1 in the different lineages. We will investigate the ability of control and SMARCB1-silenced cells to undergo differentiation. Finally, we will quantify the impact of SMARCB1 silencing on tumor growth of orthotopically-engrafted cells. Successful generation of this cell-based system will serve as a platform for extramural funding aimed at addressing the unmet need of effective therapeutics targeting these lethal childhood tumors.

LAY ABSTRACT
This project aims to identify the mechanisms underlying initiation of pediatric rhabdoid tumors of the kidney and atypical teratoid rhabdoid tumors (ATRT) of the brain, which result from deletion of the SMARCB1 gene. To determine why SMARCB1 deletion initiates tumors only in certain tissues and developmental stages the project will investigate differences in the effect of eliminating SMARCB1 expression on cells of different tissue types and attempt to identify potential therapeutic targets which could aid in the treatment of patients with these lethal childhood tumors, which currently have very limited therapeutic options.