

Curebound Discovery Spring 2022

High throughput-screen for inhibitors of pediatric ependymoma

Michael Jackson, PhD (Scripps)
Lukas Chavez, PhD (SBP)



Scientific Abstract:

Ependymoma (EPN) is the third most common pediatric brain tumor and a leading cause of death in childhood cancer patients. Intracranial ependymomas are segregated on the basis of anatomical location and further divided into distinct molecular subgroups that reflect differences in the age of onset, gender, and response to therapy. The most common and aggressive subgroup, posterior fossa ependymoma group A (PFA), occurs almost exclusively in young children. PFA EPN patients account for 74% of all posterior fossa ependymomas and have a 10-year progression free survival rate of only 24%. Despite great progress in the molecular characterization and subtyping of ependymomas, the standard treatment remains surgery with adjuvant radiation therapy. To identify novel therapeutic leads for improved treatment of PFA ependymoma patients, we propose a drug screen by leveraging recently derived PFA ependymoma cell lines and rich drug libraries available at the SBP Medical Discovery Institute. In addition, we aim to validate drug hits identified in our preliminary screen in additional PFA ependymoma lines and to dissect their mechanisms of action by epigenetic and transcriptional profiling of untreated and treated samples. We expect that our study will identify new drugs for the treatment of PFA ependymoma patients, dissect their mechanisms of action, and thus reveal new therapeutic approaches for an improved treatment of this deadly disease in children.

Lay Abstract:

Brain and other tumors of the central-nervous system (CNS) are the most common cancers in children aged 0- 14 years in the USA. Ependymoma (EPN) is the third most common pediatric brain tumor and a leading cause of death in childhood cancer patients. The most common and aggressive subgroup, posterior fossa ependymoma group A (PFA), occurs mainly in young children and frequently leads to recurrences. Here we propose to screen patient derived PFA EPN samples with drugs already approved by the FDA for various other conditions and diseases. These compounds are safe to administer to humans and as such provide the quickest path to identifying drugs that could be rapidly deployed to ependymoma patients in the medium term. We will prioritize drugs that can access the brain and will test for agents that are effective only against ependymoma, and not normal healthy brain cells, to avoid eventual toxicity. Once active drugs have been identified we will also investigate their mechanisms of action. By investigating changes in gene expression after treatment we will identify specific genes and downstream pathways that are involved in cell death and survival of ependymoma cells, potentially allowing further targeting of this deadly childhood disease.