C3 / Padres Pedal the Cause 2018

“Targeting a Therapeutic Vulnerability in PTEN-Deficient Brain Tumors”

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SCIENTIFIC ABSTRACT

Glioblastoma (GBM) represents the most lethal type of human brain cancer. The US Central Brain Tumor Registry states that primary brain tumor incidence is ~ 40 cases per 100,000, but the five-year survival is among the lowest of all cancers. One of the most common genetic alterations in GBM (30-40%) occurs in the tumor suppressor gene PTEN (phosphatase and tensin homolog), where loss of function has been mechanistically linked to invasion, and lack of radio- and chemo-therapy response. We previously discovered a synthetic growth defect mediated by DAXX inhibition in the context of PTEN-deleted brain cancers. DAXX disruption specifically restores Histone 3.3 (H3.3) chromatin binding, suppresses tumor growth, and extends animal survival in preclinical GBM models. We hypothesize that DAXX-H3.3 protein-protein interaction (PPI) is a potential therapeutic intervention target for PTEN-deleted cancers. We propose to investigate this hypothesis by generating synthetic peptides based on mapped DAXX:H3.3 interaction domains and test their ability to disrupt DAXX-H3.3 interaction complex in living cells. We will accomplish this goal by building cell-based DAXX-H3.3 PPI reporter cell lines using the ReBiL (recombinase enhanced bimolecular luciferase complementation) platform due to its ability to accurately assess on-target/off-target effects of peptide antagonist candidates in living cells. The ReBiL assay also provides cell permeability assessment of candidate peptide antagonists. Peptides disrupting DAXX-H3.3 complexes will be tested for biological effectiveness in GBM-patient derived cultures. Results from this platform will serve as the foundation for small molecule screens with the goal of developing new therapies specific for patients with PTEN-null GBMs.

LAY ABSTRACT

Glioblastoma (GBM), the most common primary brain tumor in adults, is a highly invasive neurologically destructive tumor with a survival range of 12-15 months, despite aggressive treatment efforts. Like most cancers, gain of function of oncogenes and/or loss of function of tumor suppressor genes are common in GBM, and in addition to bestowing enhanced growth to the tumor, these genetic alterations create collateral dependencies on cellular processes, otherwise known as synthetic vulnerabilities, that can be targeted for cancer therapy. A gene associated with the aggressive nature of GBM is the PTEN tumor suppressor gene, which is affected in ~40% of patients. This proposal aims to leverage this information by establishing a new molecular-based platform designed to rapidly identify molecules able to inhibit the growth of PTEN-deficient GBMs. By focusing on this genetically distinct class

of GBMs, this proposal represents a unique personalized therapeutic approach to target an Achilles heel that arises as a consequence of a specific gene mutation.