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DEVELOPMENT OF NOVEL HISTONE DEMETHYLASE INHIBITOR AGAINST DIPG

Translational
DIPG, Childhood (Brain Cancer)
Affiliation: The Cure Starts Now
Requested Funding: $100,000 (Minimum Funding: $50,000)

EXECUTIVE SUMMARY

Diffuse intrinsic pontine glioma (DIPG) is one of most the devastating pediatric brain tumors, and virtually all patients die within two years after diagnosis. Recent discovery of oncogenic histone gene mutations in DIPG has dramatically improved our understanding of disease pathogenesis, and has

stimulated the development of novel therapeutic approaches to target epigenetic regulators. We have shown that targeted inhibition of JMJD3 demethylase activity by GSK-J4 results in restored K27 methylation and a significant delay of tumor progression and prolonged animal survival in intracranial DIPG patient-derived xenograft (PDX) models. Because of its promising anti-tumor activities, GSK-J4 has been used to treat many kinds of tumors in preclinical models including leukemia, lymphoma, neuroblastoma, prostate and gastric cancer, and DIPG; however, GSK-J4 is not yet in clinical development. The major challenge for GSK-J4 in clinical development is that GSK-J4 is a prodrug and is rapidly converted *in vivo* to the active drug GSK-J1, which has restricted cellular and brain permeability. We developed a novel alcohol derivative of GSK-J1, UR-8, as a lead anti-cancer agent through our screening and drug development activities. UR-8 has demonstrated selective cytotoxic activity against human K27M DIPG cells *in vitro* and apparently transported the brain to a useful extent based on its *in vivo* biodistribution and effectiveness. UR-8 showed greater anti-tumor activity and survival benefit than that obtained by GSK-J4 treatment in intracranial DIPG PDX models. Based on the observation of this lead compound, UR-8, we will further develop new alcohol and related GSK-J4/J1 analogs to optimize the potency, specificity, and transport features. Our synthetic effort will be closely guided by molecular modeling studies using the crystal structure of JMJD3 with the GSK-J1: CO_2H binding site to identify highly potent JMJD3 inhibitors. We will also explore prodrug and formulation strategies to further enhance the transport features of this series. We will test *in vitro* cytotoxicity and assess safety and tolerability of selected potent analogs in DIPG PDX models**.** Our long-term goal is to use new GSK-J4/J1 analogs in combination with radiation which is used routinely for the treatment of DIPG. We will treat DIPG PDX with a new GSK-J4/J1 analog alone or in combination with radiation. By studying the biological effects of the GSK-J4/J1 analogs in DIPG cells and xenografted animal models in association with genetic and epigenetic analysis, we will elucidate the molecular basis for anti-tumor activity of novel GSK-J4/J1 analogs. Identification of highly efficient and selective agents will ultimately lead to the generation of investigational new drug (IND) candidates for clinical testing in pediatric brain cancer patients. Our basic drug discovery, in combination with preclinical therapeutic testing, in turn, will therefore provide insights for testing a novel therapeutic approach for treating currently incurable pediatric brain tumors.