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Exploiting Metabolic Defects with NAMPT Inhibitors in DIPG

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DIPG is a devastating pediatric cancer that develops in the pons, the area of the brain responsible for the control of breathing, involuntary actions (reflex), chewing, swallowing, sensations such as hearing, taste, and balance, and communication among the different areas of the brain. The pons is essential in the control of life-sustaining functions, so damage resulting from either the tumor itself or its treatment has tremendous repercussions. As a result, and because DIPG cells spread out between normal brain cells, surgical removal of these tumors is not an option. Dismal survival statistics reflect the incredible challenges associated with treating DIPG, the most common brainstem tumor in children. Patients generally live less than one year after being diagnosed, with fewer than 1% surviving after five years.

Dr. Muraleedharan's project has immense potential to move quickly into the clinic and offers the possibility for the first effective therapy for DIPG. It consists of a comprehensive series of studies testing specific targeted inhibitors, in combination with radiation therapy and DNA damaging therapies that are already used in the clinic for glioma treatment.

As a postdoctoral associate at Yale University, Dr. Muraleedharan performed a focused synthetic lethal drug screen in a collection of DIPG cell lines. Synthetic lethality is the identification of two genes that depend upon one another so that, when the functions of both genes are disrupted, the result is cell death. As a result, he identified the nicotinamide phosphoribosyl transferase (NAMPT) inhibitor as a potent killer of histone-mutant DIPG. Based on this exciting identification, Dr. Muraleedharan then took things a bit further. He determined that the inhibitor was capable of killing DIPG neurospheres. A neurosphere is a free-floating cluster of neural stem cells and is an accurate model in a cell culture dish. The inhibitor halted growth of neurospheres, further supporting its potential therapeutic role in DIPG. Based on preliminary data, Dr.



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Muraleedharan hypothesizes that a NAMPT inhibitor-based treatment strategy will be effective against histonemutant DIPG. This project has enormous clinical relevance, because it has the potential to establish DIPG-associated histone-specific mutations as a potential biomarker for inhibitor-based therapeutics. Based on the findings of this project, Dr. Muraleedharan will focus on developing a clinical trial.