CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP180875

Project Title:
Cyanine-Conjugated Kinase Inhibitors (Cy-KIs) as Potential Glioblastoma Theranostics

Award Mechanism:
High Impact/High Risk

Principal Investigator:
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Entity:
Texas A&M University System Health Science Center

Lay Summary:

Drugs called “kinase inhibitors” (KIs) are extremely effective in treating several cancers, but notable exceptions are brain cancers, including the most common and deadly adult brain tumor, glioblastoma (GBM). KIs have been unsuccessful for treating GBM because they do not effectively reach the brain due to limited permeability though the blood-brain barrier (BBB), which separates the blood system from the brain. Additionally, drugs that can cross the BBB tend to be actively pumped back out. Another obstacle to effectively treating GBMs is the difficultly in complete surgical removal due to their aggressive invasion into healthy brain tissue. Indeed, the high invasiveness of GBMs is a major factor underlying the strong tendency for these tumors to become resistant to KIs and other chemotherapy.

Cyanine dyes (Cys) have been shown to cross the BBB and accumulate in tumors, but not normal brain cells. These Cys have been attached to various therapeutic compounds, and there is evidence that these modified drugs can efficiently reach the brain. However, no previous studies have evaluated the therapeutic efficacy of Cys attached to a KI.

This proposal will test the hypothesis that conjugation of Cy to KIs (Cy-KI) will generate novel cancer therapy agents that localize intracranially to GBM tumors more effectively than the unmodified, parent KIs, and have increased potency in diminishing GBM growth and invasion. Three KIs were carefully chosen for their potential to undermine GBM pathogenesis at different cellular/biochemical steps. Since Cys glow intensely when excited by light, we predict that administering these compounds prior to brain surgery will “light up” tumor tissue that is surgically amenable and can be excised.

Therefore, completion of this proposal will establish novel Cy-KIs as robust theranostic agents (i.e. therapeutics that also allow sensitive tumor imaging) and facilitate the development of new treatment paradigms to improve GBM patient survival.