Award ID:
RP130266

Project Title:
Rational Redox-Driven Non-Toxic Therapeutic Strategies For Pediatric Brain Cancers (Carson Leslie Award)

Award Mechanism:
Individual Investigator

Principal Investigator:
Srivenugopal, Kalkunte S

Entity:
Texas Tech University Health Sciences Center

Lay Summary:

Each year, about 4,300 children are diagnosed with a brain tumor in the United States. Childhood brain cancers are deadly and rank as number two killer among pediatric patients. The last 20 years have seen some marked improvements in the survival of patients with mild medulloblastomas, however, the outlook for malignant gliomas, high risk medulloblastomas, and diffuse brainstem gliomas in children has changed very little. Every brain tumor patient goes through chemotherapy using alkylating agents. However, the treatment fails mainly because of 3 reasons. First, there is inadequate delivery of anticancer drugs to the tumor. Second, a DNA repair protein called MGMT which removes the DNA damage is present at higher levels in pediatric brain tumors, and this reduces tumor cell killing. Finally, the patients experience high levels of bone marrow toxicity which results in discontinuance of therapy. This project will undertake multipronged approaches for improving the pediatric brain tumor therapy. Based on the biochemical properties of MGMT protein, we will focus on new ways to curtail the DNA repair activity of MGMT using a drug called nitroaspirin. Nitroaspirin can be given to patients in large amounts with no toxicities. Studies will be performed in cancer cell lines and tumor bearing mice to dissect nitroaspirin's specific effects on MGMT. Further, we will design methods to deliver the alkylating agents directly to the brain through nasal inhalation. The nasal route delivers drugs at high concentrations to the brain within minutes, is safe and children compliant as well. More importantly, the bone marrow toxicity associated with oral ingestion or injectable drugs can be reduced. We will sequentially administer or combine the DNA repair inhibitors with temozolomide in nasal formulations and determine the extent of brain tumor killing. Our efforts represent a major step forward in pediatric brain tumor management and should encourage new clinical trials.