CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170207

Project Title:
BBB-penetrating redox-responsive smart drugs and exploiting the MGMT-driven S-phase checkpoint for chemotherapy of childhood brain cancers

Award Mechanism:
Individual Investigator Research Awards for Cancer in Children and Adolescents

Principal Investigator:
Srivenugopal, Kalkunte S

Entity:
Texas Tech University Health Sciences Center

Lay Summary:

Each year, about 4,300 children are diagnosed with brain tumors 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 because, these tumors have multiple genetic abnormalities, and malignant cells can escape the cytotoxic effects of drugs and develop resistance. Chemo-drugs for brain cancers are few and have changed little. There is a need for new and effective drugs; those that hit multiple targets simultaneously will be useful. There is also 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. We are a bioorganic chemistry laboratory and have synthesized a small molecule called KSS-72, which gets into the brain, acts through increasing the oxidative stress, affects multiple targets and kills glioblastoma cells in cultures and in animals. We will engineer KSS-72 to selectively deliver DNA damaging agents to brain cancers. Further, the MGMT repair protein has been found to have non-repair functions in the DNA replication process. Inhibition of the MGMT activity with O6-benzylguanine reduced the extent of DNA synthesis. This finding provides us a new strategy of combining the MGMT inhibitors with DNA synthesis curtailing drugs to achieve brain tumor regression. We will synthesize brain penetrating S-phase specific drugs and test all compounds in cell culture and brain cancer animal models. Our efforts represent a major step forward in pediatric brain tumor management and encourage new clinical trials.