



CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP100406

Project Title:
Investigation of Highly Potent Benzosuberene Analogs as Novel Anticancer Agents

Award Mechanism:
High Impact/High Risk

Principal Investigator:
Pinney, Kevin G

Entity:
Baylor University

Lay Summary:

The discovery and development of new small-molecule anticancer agents remains an important approach in the fight against cancer. Recent studies in the laboratories of the co-PIs (Pinney and Trawick, Baylor University) resulted in the discovery of a small molecule benzosuberene-based phenolic compound with remarkable in vitro cytotoxicity (picomolar range) against a number of human cancer cell lines. It is extremely rare to identify new cancer treatment agents that demonstrate picomolar cytotoxicity against human cancer cell lines in vitro. This compound is also a potent inhibitor of tubulin assembly into microtubules which are essential elements of cellular architecture. The studies described in this proposal are designed to rapidly advance this benzosuberene lead in preclinical development as an anticancer agent while also further investigating its mode of action. Specifically, the parent benzosuberene alcohol and the corresponding amine, plus their water-soluble phosphate and amine salts, will be synthesized. Several deactivated bioreductive prodrugs of the target benzosuberenes will be prepared to localize these compounds to tumors by targeting the hypoxic microenvironment. These prodrugs will be evaluated for differential cytotoxicity under both anoxic and normoxic conditions. Competitive binding assays will provide information on tubulin binding site specificity. Bioluminescence imaging with a breast cancer cell line in mice will be carried out in collaboration with Drs. Liu and Mason at UT Southwestern. These studies will assess antitumor activity and determine whether these benzosuberenes function as vascular disrupting agents (VDAs) which selectively disrupt the tumor blood vessels. Molecular mechanism of action studies will focus on the ability of the benzosuberenes to affect intracellular cell signaling. Intracellular cell signaling has implications for both vascular damage and programmed cell death. New cancer treatment agents that ultimately prove successful in patients have a major impact both in the field of cancer research and importantly in the lives of cancer patients.