CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP140515

Project Title:
CDK Inhibitors as Adjunctive to 5-FU and/or Radiation in Esophageal Adenocarcinoma- Assessment of Efficacy and Predictive Biomarkers

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
The University of Texas M.D. Anderson Cancer Center

Lay Summary:

Patients with esophageal adenocarcinoma localized to esophagus and surrounding lymph nodes are treated with chemotherapy and radiation followed by surgical resection of esophagus. In spite of this aggressive therapy, 5 year survival is poor (20-25%). There is a dire need to increase sensitization of tumor to chemoradiotherapy to improve survival of these patients. Cyclin dependent kinase 9 is a critical enzyme for maintenance of several proteins which affect cell death (apoptosis). We propose to study the utility of cyclin dependent kinase (CDK) inhibitors with CDK 9 inhibitory activities in increasing sensitivity of esophageal carcinoma to commonly used chemotherapeutic agent 5-Fluouracil (5-FU) and radiation. We will assess the effects of CDK inhibitor with and without 5-FU and radiation in esophageal adenocarcinoma cell lines grown in tissue culture. We will assess sensitivity of CDK inhibitors in reducing cell growth in tumor grown in mice from human esophageal cancer cell lines (xenografts). We will test treatment efficacy in patient derived tumor xenografts (PDXs) of esophageal adenocarcinoma by implanting biopsy samples from patient into mice. PDXs of esophageal adenocarcinoma are non-existent (in our knowledge) and it will be a major asset for researchers interested in esophageal adenocarcinoma. We will also test role of MCL-1; a protein which prevents cell death (apoptosis) and likely to be a common target of CDK inhibitor, 5-FU and radiation; in mediating enhancing cytotoxic effects of CDK inhibitor in EAC cell lines, xenografts, PDX and retrospectively collected patient samples. We will also test other CDK 9 targets which are modified by the CDK inhibitor and are candidate markers of resistance to 5-FU and/or radiation in EAC cells, xenografts, PDXs and patient samples. We will use the efficacy and biomarker information about CDK inhibitor to design future clinical trial combining CDK inhibitor with chemoradiation in esophageal adenocarcinoma.