CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP150245

Project Title:
EGFR Arginine Methylations: Biomarkers for Cetuximab Resistance in colon cancer

Award Mechanism:
Individual Investigator

Principal Investigator:
Hung, Mien-Chie

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

Lay Summary:

Epidermal growth factor receptor (EGFR) is a key enzyme that controls cell proliferation and growth, and is aberrantly activated in multiple human cancers. The EGFR inhibiting monoclonal antibody cetuximab (Erbitux) has been used to treat colorectal cancer (CRC) patients. Cetuximab alone or in combination with chemotherapy has shown efficacy in CRC treatment; however, significant numbers of patients exhibit resistance to cetuximab and the underlying mechanisms are not completely understood. Thus, it is extremely important to identify the subpopulation of EGFR-overexpressing CRC patients that will respond to treatment with cetuximab. In addition, understanding the mechanism of resistance for those patients whose tumors are resistant to cetuximab is important for the development of effective combination therapies to overcome the resistance. We aim to understand these important issues. We previously identified a novel mechanism of EGFR regulation, namely, methylation of EGFR. We recently obtained encouraging preliminary results suggesting that methylation of EGFR may confer resistance to cetuximab treatment. Thus, in this proposal, we will further dissect the molecular mechanisms of EGFR methylation regulation in CRC cells, and the role of EGFR methylation in drug resistance of CRC. Success of this proposal will identify relevant biomarkers for cetuximab resistance in CRC. Thus, we will be able to identify a sub-population of CRC patients who will benefit from this rational marker-guided EGFR targeted therapy. Furthermore, we plan to develop inhibitors for the enzymes responsible for protein methylation, and those inhibitors may be the attractive drugs to overcome resistance to cetuximab. Therefore, this proposal has high potential for immediate impacts on a subpopulation of CRC patients who will respond to cetuximab as well as long-term impacts on the development of rational combination therapy for the other subpopulation of CRC patients who is resistant to cetuximab.