CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP120840

Project Title:
P1: Enhancing the Identification of Markers and Potential Therapeutic Targets for Improving Tumor Response via MIRNA and DNA Methylation Analysis

Award Mechanism:
Individual Investigator

Principal Investigator:
Story, Michael D

Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

Prior work from our group and others showed that epidermal growth factor receptor (EGFR) expression was associated with radiation resistance, and that adding cetuximab (anti-EGFR antibody) to radiotherapy improved outcomes in patients with locally advanced head and neck squamous cell cancer (HNSCC). However, many patients still experienced local relapse. The goal of this project is to identify markers of tumor resistance and new molecular pathways for selective radiation sensitization. We hypothesize that by systematically investigating these molecular pathways and validating them using tumor specimens from phase III clinical trials, novel markers of response and rational approaches for overcoming resistance can be developed. To do this we propose the following aims. In Aim 1, we will expand on our pilot genome-wide analysis of microRNA and DNA methylation profiling for therapeutic response with emphasis on human papilloma (HPV)-negative HNSCC treated by radiation-platinum regimens. Markers identified here will be expanded to include published potential markers. In addition, we will test these samples for gene fusion products via RNAseq. These will be refined in order to reduce the number of potential markers. In Aim 2, this final list of markers will be tested in samples from two large clinical trials, RTOG 0129, which compares accelerated or standard fractionation with concurrent cisplatin, and RTOG 0522, where radiation-cisplatin with or without cetuximab is being compared. These data will be used in conjunction with gene expression and proteomic data being studied through a R01 grant (PI: John Heymach, co-co-PI: Michael Story). Some of these potential markers may represent molecular pathways that can be targeted to overcome resistance. This notion will be investigated in Aim 3 where in vitro functional validation studies (e.g., by pharmacologic blockade, knockdown, and over?expression) of these potential therapeutic targets using 3-dimensional tissue culture of our panel of HNSCC and NSCLC cell lines. The validated markers and targets that emerge from these studies will be addressed in human xenografts through projects 2 and 3. Together, these efforts will serve to streamline cancer therapy by logical selection of tumor-specific treatment. Such individualization of therapy will reduce overall treatment toxicity and diminish the financial burden to patients and society.