CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP180457

Project Title:
Tumor Activated Enzyme Inhibitors for the Treatment of Cancer

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

Ideal treatments for cancers kill tumor cells but not normal tissues. Traditional chemotherapies do not meet this ideal because they injure both cancer cells and normal cells. Agents like cisplatin help shrink tumors but cause peripheral pain due to toxicity to nerve tissues. Similarly, many chemotherapies cause nausea because they damage the stomach and intestines. The poor selectivity of traditional therapies not only causes debilitating side effects. It also reduces the effectiveness of drugs because it limits the tolerable dose.

In this application, we describe technology that can limit the systemic toxicity of cancer treatments. We discovered that certain cancer types express metabolic enzymes that can activate a drug within the tumor. Thus, specific cytochrome P450 enzymes can convert an inert molecule into an inhibitor of unsaturated fatty acid synthesis. Specifically, Cyp4F11 converts our pro-drug to an active inhibitor of stearoyl CoA desaturase. Cancer cells require large amounts of unsaturated fatty acids to support rapid growth and to maintain their membranes. Blocking the synthesis of unsaturated fatty acids is toxic to cancer cells, leading to cancer cell death. We show that our compounds are potent enzyme inhibitors, that they block tumor growth in mice, and that that are less toxic than conventional inhibitors.

To develop our targeted agents further, we plan to 1) characterize the interaction between our inhibitors and stearoyl CoA desaturase, 2) develop optimized inhibitors, and 3) test optimized enzyme inhibitors in mouse models of cancer. Successful completion of these objectives will validate our enzyme target and the tumor-targeted mechanism of activation. Moreover, the proposed research will provide advanced drug leads with validated activity and safety profiles. Analysis of human tumor samples indicates that 15-25% of lung, breast, prostate and clear-cell renal cell cancer patients could benefit from this approach.