CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170696

Project Title:
Targeting Cathepsin L as a Selective Mechanism for the Release of Potent Anticancer Agents from Drug-Linker Conjugates

Award Mechanism:
High Impact/High Risk

Principal Investigator:
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Entity:
Baylor University

Lay Summary:

The discovery and development of new, targeted therapeutic regimens for the treatment of cancer is crucial for realization of the promise afforded by the future of precision oncology. Pancreatic cancer is among the most deadly cancers in which patient survival is low and treatment options remain limited. In this proposal, the synthesis and biological evaluation of drug-linker conjugates is described that are designed to be activated (cleaved) by a specific enzyme (cathepsin L) that is found in increasingly high levels in and around pancreatic cancer cells as the disease progresses. Cleavage of these drug-linker conjugates will release very potent, small-molecules that were discovered by the research teams of the PI and co-PI and demonstrate remarkable cytotoxicity (sub-nM to pM) against human cancer cell lines including those of pancreatic cancer. These studies represent the first example (to the best of our knowledge) of specifically targeting cathepsin L as a trigger for the selective (tumor-specific) release of highly potent, small-molecule anticancer agents from suitable drug-linker conjugates. The linker portion of the drug-linker conjugates will consist of selective dipeptides or promising inhibitors of cathepsin L that resulted from a collaborative research project of the PI and co-PI. If successful, these studies have the potential to provide a new paradigm for the selective delivery of a wide-range of therapeutic agents to tumors with increased levels of cathepsin L. Pancreatic cancer is one example for which new treatment modalities are urgently needed.