CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170797

Project Title:
The Preparation of Novel Phage-Displayed Macrocyclic Peptide Libraries for the Identification of Anticancer Agents

Award Mechanism:
High Impact/High Risk

Principal Investigator:
Liu, Wenshe

Entity:
Texas A&M University

Lay Summary:

The overall goal of this project is to build straightforward methods for the synthesis of phage-displayed macrocyclic peptide libraries and demonstrate their applications in the identification of macrocyclic peptides that can serve as anti-cancer agents. Phage display is a technique that allows rapid identification of target-interacting peptides. Its connection of peptides with phage genetic information that encodes them allows billions of unique peptides to be screened swiftly. However, current phage display techniques are mainly limited to the identification of linear peptides that are typically unstructured in solution and easy to be hydrolyzed proteolytically. There are two cysteine-based methods for the synthesis of phage-displayed macrocyclic peptide libraries. Both have significant limitations. In the past, our group has developed methods that expand the genetic code of E. coli for the genetic encoding of noncanonical amino acids (ncAAs). In this application, we propose to extend our methods to the synthesis of phage-displayed macrocyclic peptide libraries. Using E. coli with an expanded genetic code as a production system, we will integrate ncAAs with active functionalities into phage-displayed peptides. These active functionalities react or can be modified with other molecules that further react with adjacent cysteines for cyclizing phage-displayed peptides. More than 10 ncAAs will be tested to generate phage-displayed macrocyclic peptide libraries. Screening of these libraries for the identification of macrocyclic peptide inhibitors of a model protein, TEV protease will be carried out first to demonstrate the feasibility of our methods and further applications will be expanded to the identification of macrocyclic peptide inhibitors for deubiquitinases USP2 that is an anti-cancer target but notorious for drug design due to its fat binding interface with its substrates.