Solution-Phase Affinity Selection of Potent Non-Canonical Inhibitors from Combinatorial Peptide Libraries
Technology #19988

Applications

This technology is a novel platform for protein-protein interaction drug discovery with applications in pharmaceutical R&D.

Problem Addressed

Nearly 85% of proteins are considered ‘undruggable’, meaning they cannot be inhibited using traditional small molecule drugs, and therapeutic targeting of these ‘undruggable’ proteins remains a major challenge in drug development. Therapeutic inhibition of protein-protein interactions (PPIs) is an attractive approach for drugging the undruggable since most proteins require specific interactions to function, however, targeting PPIs remains challenging. This technology is a novel drug discovery platform for identifying PPI inhibitors.

Technology

This technology uses iterative affinity selection to screen for protein-protein interaction inhibitors. First, a library of short amino acid sequences is generated by randomizing residues in a peptide known to bind to the target protein’s interaction region. Next, the library is mixed with the target protein and binders are isolated and identified with high-pressure size exclusion chromatography followed by LC-MS/MS. The short amino acid sequences that successfully bind the target protein then undergo another round of library synthesis, isolation, and identification. In this second selection round, the amino acid randomization step additionally includes non-canonical amino acids, which increases the structural diversity of the libraries and leads to identification of novel, more efficient inhibitors. Finally, the top candidates from the selection scheme can be macrocyclized, which greatly increases cell permeability. Using this scheme, the inventors successfully generated macrocyclic inhibitors of the MDM2-p53 interaction that efficiently penetrate the cell membrane and rapidly kill the osteosarcoma cell line SJSA-1 at micromolar concentrations in vitro.

Advantages

- Efficient generation of macrocyclic protein-protein interaction inhibitors
- Inclusion of non-canonical amino acids greatly increases the structural diversity of inhibitor libraries, leading to novel, more efficiently interacting peptides
- Macrocyclization boosts the cell permeability of the final amino acid sequences
- Proof of concept experiments generated efficient macrocyclic MDM2-p53 inhibitors

Categories For This Invention:

Life Sciences
Research Tools
Protein & Protein Chemistry
Screening Assays
Therapeutics
Peptide
Protein

Intellectual Property:
Solution-phase affinity selection of inhibitors from combinatorial peptide libraries
PCT
Solution-phase affinity selection of inhibitors from combinatorial peptide libraries
US Patent Pending

Inventors:
Bradley Pentelute
Faycal Touti

External Links:
Pentelute Lab
http://www.pentelutelabmit.com/