A Novel Method to Generate Specific and Permanent Macromolecular Covalent Inhibitors

Tech ID: 27411 / UC Case 2016-162-0

INVENTION NOVELTY

UCSF researchers have invented a novel method to generate covalent macromolecular inhibitors. This strategy allows a peptide inhibitor to bind to its target protein specifically and irreversibly through proximity-enabled bioreactivity.

VALUE PROPOSITION

Covalent inhibitors are rationally designed drugs that form precisely directed permanent bonds with their targets. Compared to non-covalent drugs, covalent inhibitors generally show improved binding affinity and efficacy, reduced patient burden due to smaller dosage, and lower chance of drug resistance because of sustained inhibition. While small molecule covalent inhibitors have been widely explored, macromolecular covalent inhibitors are more difficult to design and implement. Due to increased molecular weight and bulk, macromolecules such as peptide inhibitors usually cannot reach the active site of target proteins but only gain access to protein surface or protein-protein interacting interface, where catalytic residues are often lacking for covalent bond formation. This invention provides a strategy to enable a peptide to bind to its target protein covalently via proximity-enabled bioreactivity at mild conditions.

The current invention provides the following advantages:

- The first validated method to generate macromolecular covalent inhibitors
- Higher specificity toward the target protein due to larger interaction interface than small molecular covalent inhibitors
- Permanent linkage prevents dissociation and improves peptide inhibition efficiency
- Easily adapted to develop novel treatments for various diseases

TECHNOLOGY DESCRIPTION

Researchers at University of California, San Francisco have developed a novel technology that couples an aryl sulfonyl fluoride moiety-containing unnatural amino acid with a macromolecular peptide. When brought together in close proximity, lysine residues on the surface of the target protein react with the aryl sulfonyl fluoride moiety to form a permanent covalent link. The investigators have validated this method *in vitro* by disrupting the interaction between p53 and Mdm4 through a covalent peptide inhibitor of Mdm4. Upon binding to p53, Mdm4 blocks the transcriptional activity of p53 and contributes to tumor development and malignant progression. This novel strategy enables the designed peptide inhibitor to form a covalent bond with Mdm4, improving its activity of inhibiting the p53-Mdm4 interaction by 10-fold for treatment of cancer. This strategy is highly adaptable to other macromolecular

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OTHER INFORMATION

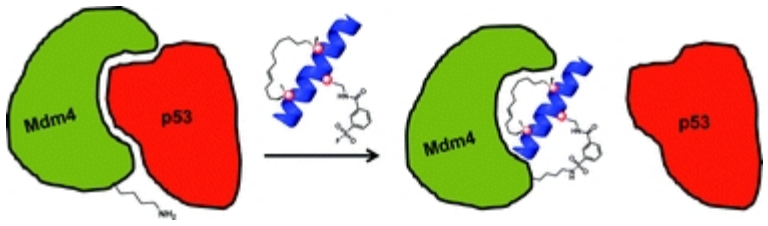
KEYWORDS

Macromolecular drugs, Covalent peptide inhibitors, Cancer, p53-Mdm4 interaction

CATEGORIZED AS

- **Medical**
  - Disease: Autoimmune and Inflammation
  - Disease: Cancer
  - Disease: Cardiovascular and Circulatory System
  - Disease: Central Nervous System

covalent inhibitors to develop treatments for different disorders and diseases.



LOOKING FOR PARTNERS

To develop and commercialize the technology as a tool to develop effective therapeutics in cancers, infections, gastrointestinal disorders, central nervous system diseases, cardiovascular diseases, inflammation and other illnesses.

STAGE OF DEVELOPMENT

Pre-Clinical

RELATED MATERIALS

▶ Hoppmann C, Wang L. Proximity-enabled bioreactivity to generate covalent peptide inhibitors of p53-Mdm4. Chem Commun (Camb). 2016 Apr 14;52(29):5140-3.

DATA AVAILABILITY

Under CDA / NDA

PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Issued Patent	11,884,612	01/30/2024	2016-162

▶ Disease: Digestive System

▶ Disease: Infectious Diseases

▶ New Chemical Entities, Drug Leads

▶ Therapeutics

RELATED CASES

2016-162-0

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