A Powerful Platform for Ubiquitin Modulators Drug Discovery (Ramot)

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The Technology

A modular system, facilitating the straightforward production of ubiquitylated proteins

- System I – Produces large quantities of highly pure ubiquitylated-proteins for downstream biophysical / biochemical characterization

- System II – A split reporter gene allows selection of ubiquitylated protein in bacteria (E2:E3, E3:Substartes, substrate:DUB interactions; mutant screening; drug screening)

The Need

Blocking protein-protein interactions is a swiftly emerging therapeutic strategy. Ubiquitylation is an enzymatic process in which the C-ter of Ub is covalently attached to lysine residue on the protein surface. ~7,000 out of 21,000 proteins of the human proteome are modified by ubiquitylation. Since Ub is key in numerous aspects of cellular processes, aberrations in the Ub system result in numerous pathologies, including various forms of cancer such as breast cancer, neurodegenerative diseases such as Parkinson's and Alzheimer's diseases, infectious diseases such as AIDS, and others. Therefore, there is a critical need for simple screening procedures that would facilitate the development of drugs for the Ub system. Although there have been significant advances in our understanding of the ubiquitylation process, a knowledge gap persists in studies that links E3s, Ub receptors and DUBs to their substrates, and in developing of highly specific inhibitors that targeted these proteins. Filling these technical and knowledge gaps is important since in the Ub system, specificity is critical to ensure tight control and regulation. Thus, this new tool promises to yield important therapeutic benefits. The expected significance of the research is to enable specific pharmacologic manipulation of the Ub system.

Potential Application

A simple screening system for functional activity of the ubiquitin cascade in bacteria: The system facilitates the screening for drugs that blocks specific E3-ligase and ubiquitin- (Ub) receptors (Ub binding domain containing proteins). Moreover, it may facilitate the identification and characterization of E3s, deubiquitylating enzymes and their cognate substrates.

Using such a screen with potential drugs (small molecule) array predicted to provide inhibitors for variety of diseases linked to a specific E3-ligase, deubiquitylating enzyme or Ub-receptor such as cancers, mental and metabolic disorders or viral and bacterial infections. Potential drugs that will be found in the screen will be subjected to downstream characterization by xray crystallography and biophysical measurements of affinity using SPR and ITC, to improve the specificity and IC50.

Stage of Development

POC

Patents

Pending

Supporting Publications

EMBO J. 2011 Nov 11;31(2):378-90.

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