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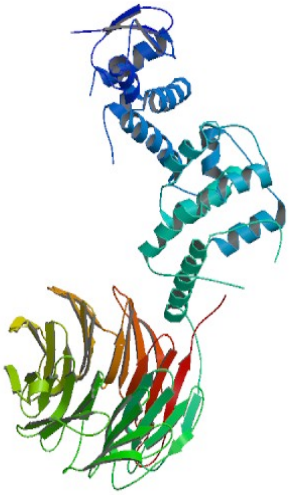

SCREENING PLATFORM

Drugging E3 Ubiquitin Ligases as Cancer Therapeutics

Brief Description of Technology

Screening platform to identify small molecules therapeutics.

BUSINESS OPPORTUNITY
Exclusive license
Sponsored research
Start-up

TECHNOLOGY TYPE
Immuno-oncology
Protein/peptide
Small molecule
Target vector

STAGE OF DEVELOPMENT
Preclinical *in vitro*

PATENT INFORMATION
Drafting patent application

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Technology Overview

The ubiquitin-proteasome system (UPS) controls protein dynamics and regulates complex cellular processes such as protein degradation, protein-protein interactions, and cell cycle progression. When this system goes awry, this leads to many diseases, including cancer and neurodegeneration. E3 ligases are the matchmakers that bring the UPS complex to the target protein so it can be tagged with ubiquitin and marked for destruction. Dr. Clurman's team developed a high-throughput assay to identify E3 ligase agonists in order to restore native function to mutated E3 ligases and supercharge wild-type versions for increased activity. Proof of concept of this method was performed with Fbw7, a well-studied and characterized E3 ligase found mutated in 10% of cancers. The screening pipeline is validated and shows the ability to narrow a starting library of ~700,000 compounds down to 41 compounds as potentially selective activators. The lab also generated cell-based screens in human cell lines to validate hits.

Applications

- Screening platform to identify novel small molecule agonists to E3 ligases

Advantages

- Leverages structural insights of E3 ligases and docking of target substrates
- Allows for targeting of previously undruggable targets

Market Overview

The global market for ubiquitin proteasome research and development was $2.8 million in 2013 and is expected reach $5.6 million by 2018. To date, only a handful of drugs targeting the ubiquitin system have been approved by the FDA. The UPS was largely considered undruggable using traditional small molecule approaches due to the lack of readily identifiable enzymatic catalytic pockets and the dynamic rearrangement of multiple protein-protein interactions. The ability to screen and identify small molecule E3 ligase agonists and restore protein homeostasis has the potential to treat not only cancer, but other UPS-dysregulated indications.