iCADD: Next-generation Screening Platform for Identifying Small Molecular Glue Degraders

An efficient, high-throughput platform to rapidly identify protein degraders targeting undruggable proteins for therapeutic development.

Technology

The Pagano Lab has developed iCADD (iCasp9-Assisted Degrader Discovery), an innovative, high-throughput screening platform designed to identify small-molecule protein degraders, particularly molecular glues, for intracellular targets considered undruggable by conventional methods. iCADD addresses this limitation by cleverly fusing a “death switch” to the target protein of interest (POI) to create a phenotypic “survival-based” readout compatible with high-throughput, target protein degradation (TPD) compound libraries. The screen leverages an inducible caspase-based suicide system (i.e., iCasp9) that conditionally triggers apoptosis when homodimerized by small molecule agents (e.g., the commercially available tool compound Rimiducid). If a TPD compound from the library binds and degrades the target POI, then iCasp9 is also degraded, and the cell survives. Conversely, if no TPD compound from the library binds the target POI, then iCasp9 is not degraded, and in the presence of a dimerization agent, would induce apoptosis leading to cell death. Cellular phenotypes are measured in high-throughput 384-well plates using a luminescence-based cell viability assay, wherein each well is seeded with cells and then incubated with the TPD compound(s) followed by the dimerization agent.

In an unpublished proof-of-concept (POC) study, the research team screened approximately 3,800 FDA-approved compounds using the iCADD platform and successfully identified known degraders of the transcription factor Ikaros-ZF23. Additionally, in a large-scale screen using the ChemDiv Bioactive Library (~45,000 compounds), 14 candidate cyclin D1 degraders were identified, of which three were validated through orthogonal assays. One compound (cpd#10) selectively degrades cyclin D1 in an Ambra1-dependent manner and is advancing toward mechanistic and structural studies. This result demonstrates iCADD’s potential to both enable and accelerate the discovery of effective TPD agents for currently undruggable targets.

Background

Traditional drug discovery approaches fail to target over 80% of disease-related proteins, limiting treatment options for cancer, neurodegenerative, and infectious diseases. TPD has emerged as a promising strategy to “hit” these traditionally undruggable targets, but current approaches—such as PROTACs—face significant technical limitations. Specifically, they have large molecular size; their synthesis is often complex; and they rely on a limited set of E3 ligases, which could lead to compatibility issues. Molecular glues avoid many of the limitations associated with PROTACs, but their identification remains challenging. A major obstacle lies in the reliance on cell-based assays with long readout times, which slows down screening workflows. Thus, there is an unmet need for universalizable, high-speed screening platforms

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that reduce assay time, increase reliability, and expand molecular glue compatibility beyond known ubiquitin ligase systems.

Development Status

The iCADD platform has been validated in several screening studies and by the identification of early-stage degraders targeting cyclin D1.

Applications

High-throughput screening: Identification and development of TPD compounds for disease-related proteins, including currently undruggable targets

Advantages

- Target compatibility: Can identify degraders for numerous types of intracellular proteins, including currently undruggable targets
- Rapid and accurate: Provides a clear “survival-based” readout for fast and correct “hit” identification
- Customizable: Can incorporate various inducible cell suicide proteins in the target protein fusion construct
- Scalability: Enables high-throughput screening across diverse small molecule libraries

Intellectual Property

A U.S. provisional patent application has been filed covering the design of the iCADD platform; the compositions of both the inducible cell suicide protein and the fusion construct (the target POI-inducible cell suicide protein construct); and the application of the platform under various experimental conditions using different disease-causing target proteins, libraries, visual readouts.