COVALENT DEGRADER OF THE ONCOGENIC TRANSCRIPTION FACTOR CTNNB1

Tech ID: 33341 / UC Case 2024-044-0

PATENT STATUS

Patent Pending

BRIEF DESCRIPTION

Transcription factors are critical regulators of gene expression, but they have long been considered "undruggable" due to their lack of deep, well-defined binding pockets and their high degree of intrinsic disorder. To overcome this, UC Berkeley researchers have developed a new class of covalent monovalent degraders that utilize chemoproteomic platforms to target and eliminate these proteins. Unlike traditional inhibitors that must compete with natural ligands for a binding site, these compounds form a permanent covalent bond with specific, often disordered cysteine residues on the target transcription factor. This interaction induces structural destabilization of the protein, triggering its recognition and subsequent destruction by the cell's ubiquitin-proteasome system. This platform has already successfully produced potent degraders for major oncogenic drivers such as β-catenin (CTNNB1), MYC, and the androgen receptor variant AR-V7.

SUGGESTED USES

» Treatment of Intractable Cancers: Developing therapies for cancers driven by "undruggable" transcription factors, including colorectal, breast, lung, and prostate cancers.

» Autoimmune Disease Therapy: Applying the covalent degradation platform to immune regulatory factors such as IRF5 and IRF8 to dampen pro-inflammatory gene expression.

» Overcoming Resistance Mechanisms: Targeting mutated or truncated versions of transcription factors, such as AR-V7, that no longer respond to conventional hormone therapies.

» High-Throughput Drug Discovery: Using the established chemoproteomic handles to rapidly screen and optimize new covalent ligands for a wide array of high-value nuclear proteins.

» Precision Research Probes: Providing chemical biology tools that allow for the acute, dose-dependent depletion of specific proteins to study their function in complex signaling networks.

ADVANTAGES

» Targeting the "Undruggable": Accesses shallow or transient binding pockets on structurally flexible proteins that traditional small molecules cannot occupy.

» Destabilization-Mediated Degradation: By inducing a conformational flip that leads to degradation, these molecules bypass the need for the large, complex linkers found in traditional PROTACs.

» Superior Potency and Selectivity: Covalent binding ensures long-lasting target engagement and high potency, while chemoproteomic profiling allows for the fine-tuning of off-target profiles.

» Reduced Molecular Weight: Monovalent degraders are more compact than bivalent degraders, leading to significantly better drug-like properties, such as improved cellular permeability and potential for oral administration.

» Ablation of Scaffolding Functions: By completely removing the protein rather than just inhibiting an active site, these degraders eliminate the non-catalytic scaffolding roles that often contribute to disease progression.

RELATED MATERIALS

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

- 14-3-3 Covalent Molecular Glue Stabilizers
- Stereoselective Covalent Destabilizing Degradation of the Oncogenic Transcription Factor MYC
- Dcaf16-Based Covalent Handle For The Rational Design Of Monovalent Degraders

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OTHER INFORMATION

CATEGORIZED AS

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