KDDF
Korea Drug Development Fund

Asset #36
Dana-Farber Cancer Institute

Small molecules that Block Proteasome-Associated Ubiquitin Receptor RPN13 Function

Therapeutic Area	Oncology	**Indications**	Multiple Myeloma
Modality	Small Molecule	**Development Stage**	Pre-clinical

Overview

Background

- Proteasome inhibition is a successful approach for treating multiple myeloma (MM), but targeting specific parts of the ubiquitin-proteasome system (UPS) remains a challenge.
- The ubiquitin receptor Rpn13 has been identified as a crucial factor in MM cell growth and survival through RNA interference studies. However, developing methods to selectively degrade Rpn13 has been lacking.

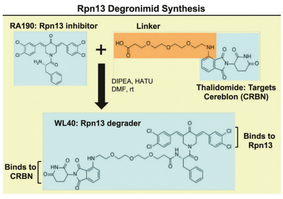
Technology Advantages

- This innovatively introduces WL40, the first degrader targeting proteasome-associated ubiquitin receptor Rpn13.
- The fusion of a covalent inhibitor (RA190) with thalidomide leads to Rpn13 degradation, effectively reducing multiple myeloma cell viability, even in bortezomib-resistant cells.
- This strategy showcases the potential of targeted UPS component degradation and utilizes covalent inhibitors for potent degrader development.

Key Data

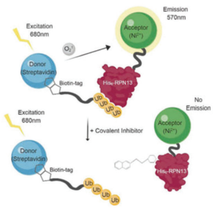
WL40, created by linking RA190 to thalidomide with a short PEG linker, showed promising activity as a potent degrader

A



WL40 was created by linking the Rpn13 inhibitor RA190 to the IMiD thalidomide as a ligand for the CRBN E3 ligase via a PEG linker

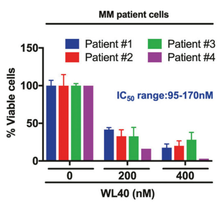
B



The novel AlphaScreen assay to measure the binding activity of inhibitor with RPN13 proteins

WL40, created by linking RA190 to thalidomide with a short PEG linker, showed promising activity as a potent degrader

C



Purified CD138+ patient MM cells were treated with DMSO control or WL40 at indicated concentrations for 48 h, followed by assessment for cell viability using the CellTiter-Glo assay (mean ± SD of triplicate cultures; $p < 0.001$)

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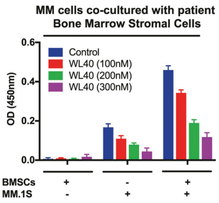
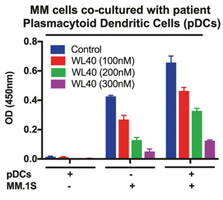


MM.1S cells were cultured with or without patient BMSCs in the presence or absence of WL40 for 48 h, and cell proliferation was measured by the WST assay (mean ± SD; n = 3; $p < 0.0001$)

E



MM.1S cells were cultured with or without patient plasmacytoid dendritic cells (pDCs) in the presence or absence of WL40 for 48 h, and cell proliferation was measured by the WST assay (mean ± SD; n = 3; $p < 0.0001$)

IP Status & Publication(s)

Intellectual Property

Patent Number
US 11702402 B2 (2023.07.18)

Patent Family
PCT, US, EP, JP, CA, AU

Publication(s)

- Song at el. (2019) Development and preclinical validation of a novel covalent ubiquitin receptor Rpn13 degrader in multiple myeloma. Leukemia