Homo-PROTACs for the Chemical Knockdown of Cereblon

Stefanie Lindner

60th ASH Annual Meeting and Exposition
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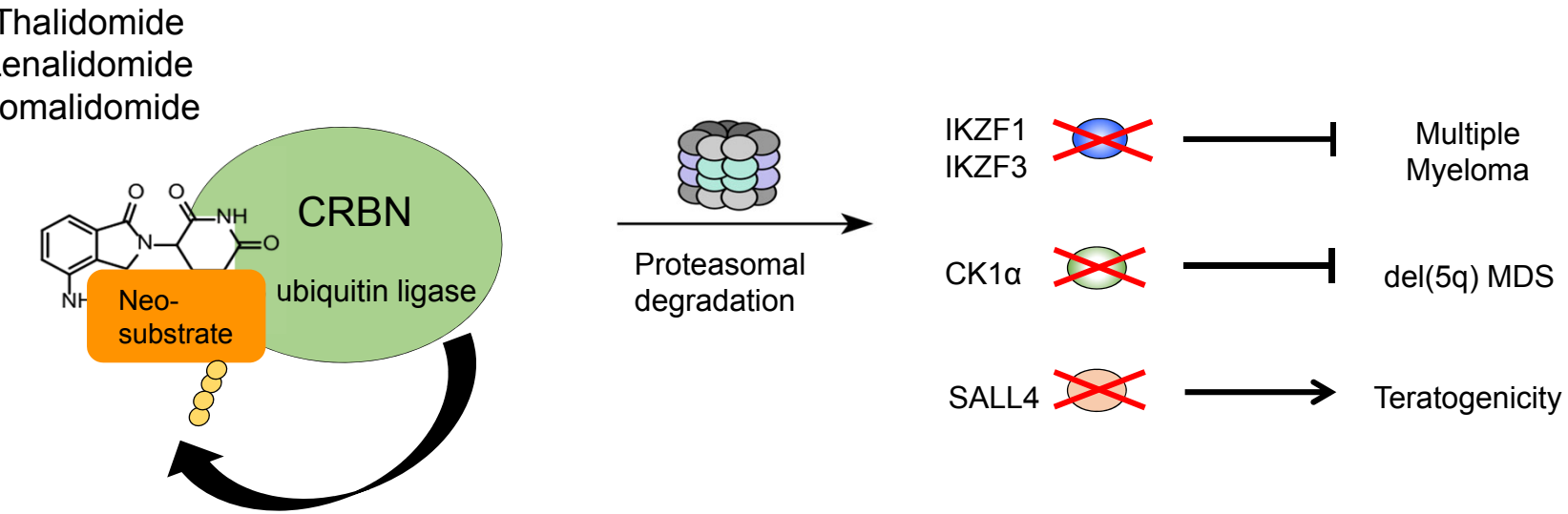
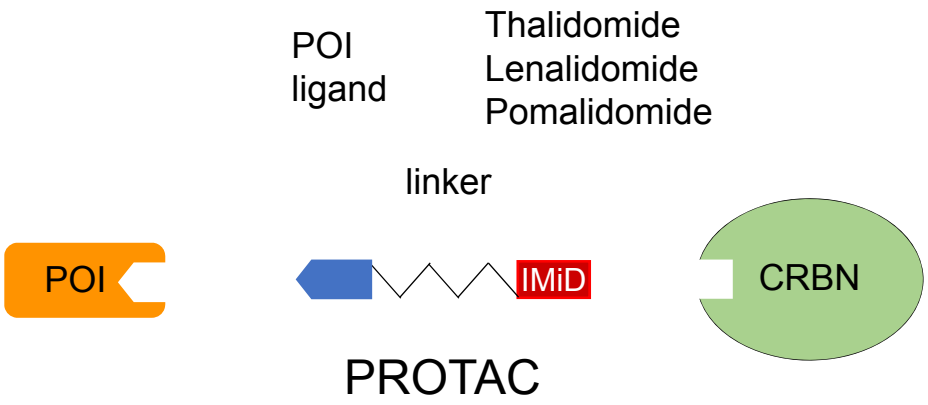
IMiDs modulate substrate specificity of the CRBN E3 ligase



Ito *et al.*, **2010**, *Science*
Krönke *et al.*, ***2014*** *Science*
Lu *et al.*, ***2014***, *Science*
Krönke *et al.*, **2015**, *Nature*
Donovan *et al.*, **2018**, *Elife*
Matyskiela *et al.*, **2018**, *Nat Chem Biol.*

Proteolysis ***Ta***rgeting ***C***himeras (PROTACs)

Bifunctional molecules for degradation of proteins of interest (POI)



Sakamoto *et. al*, **2001**, *PNAS*
Schneekloth *et. al*, **2004**, *J Am Chem Soc*.
Lu *et al.*, **2015**, *Chem Biol*
Winter *et al.*, **2017**, *Mol Cell*.

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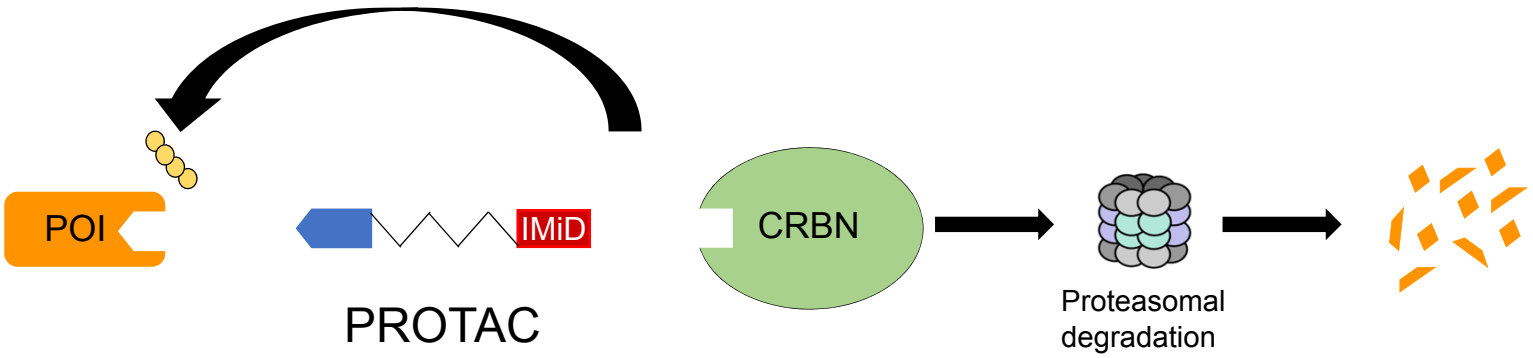

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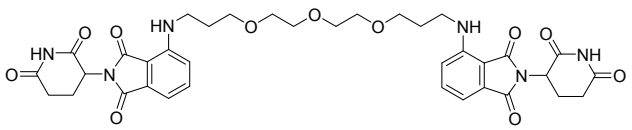
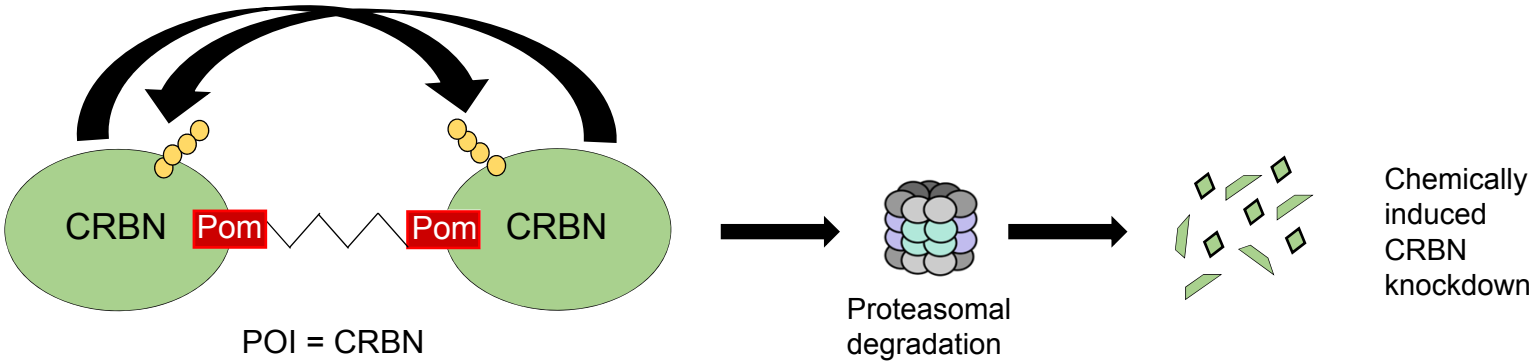
Homodimeric pomalidomide-based PROTACs

Linker (size X)



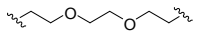
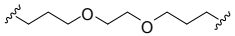
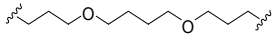
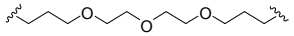
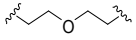
Pomalidomide Pomalidomide

Homo-bifunctional molecules

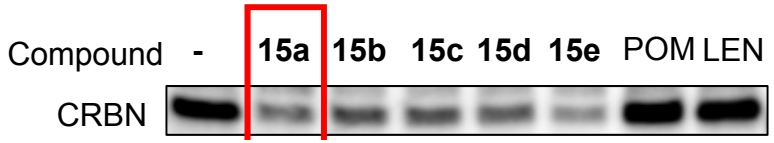


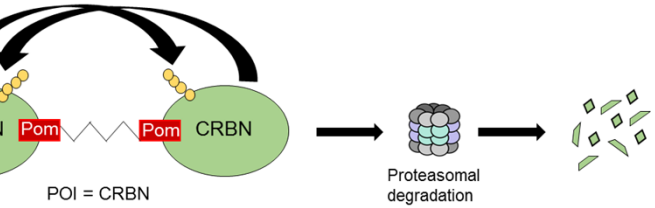
Homodimeric pomalidomide-based PROTACs

corresponding linker substructures

Linker	No. of linear linker atoms	CRBN degradation	IKZF1 degradation
	8	++	+
	10	+	++
	12	+	++
	13	+	++
	5	++	+

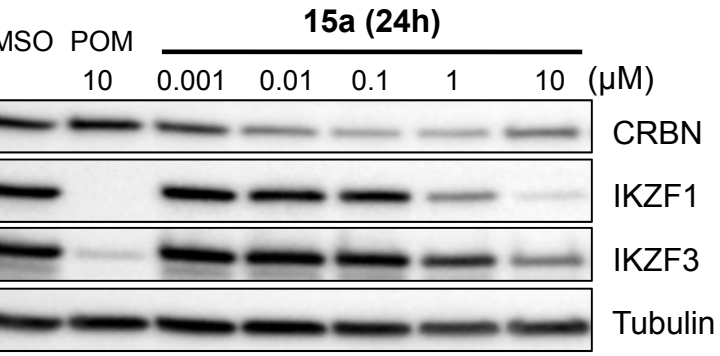
multiple myeloma cell line MM1S

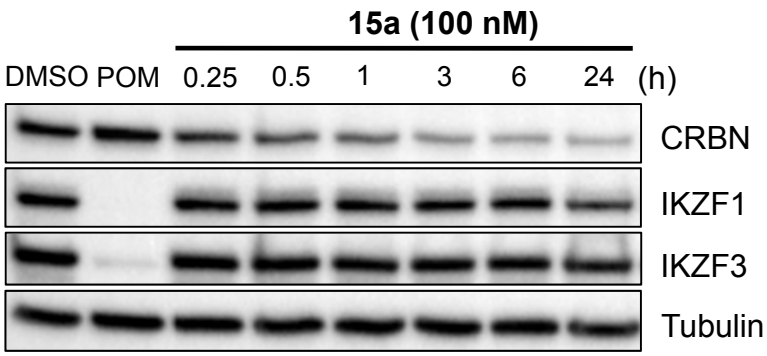


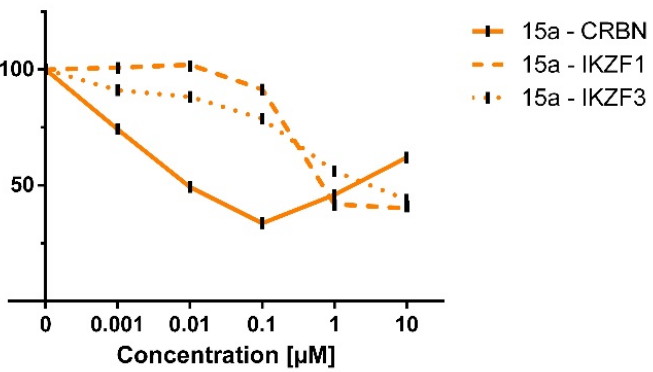


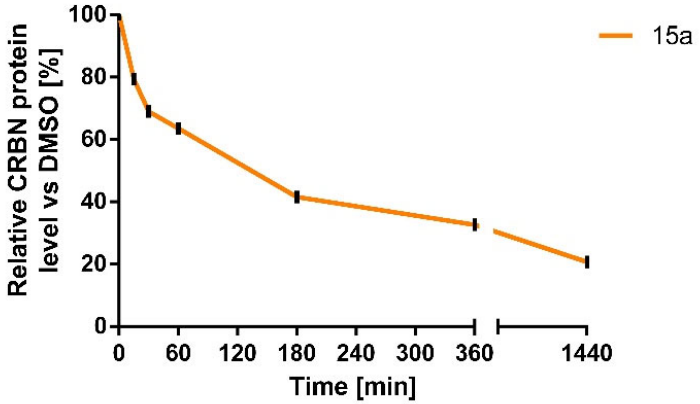
LEN: Lenalidomide
POM: Pomalidomide

Pomalidomide-based Homo-PROTACs induce degradation of CRBN





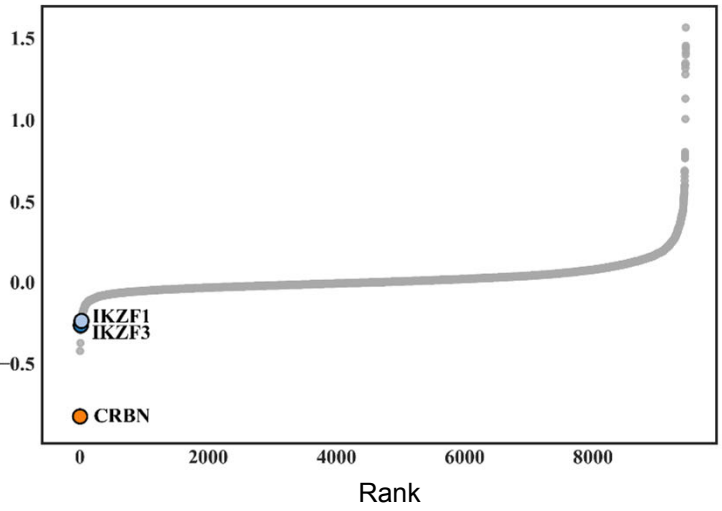




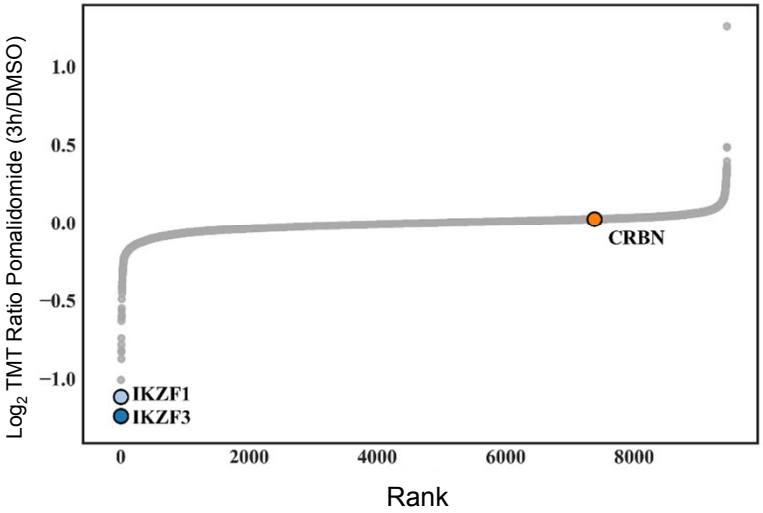
Impact of Homo-PROTAC 15a on the cellular proteome

- based quantitative proteomics in MM1S cell line
centration: 100nM
bation: 3h

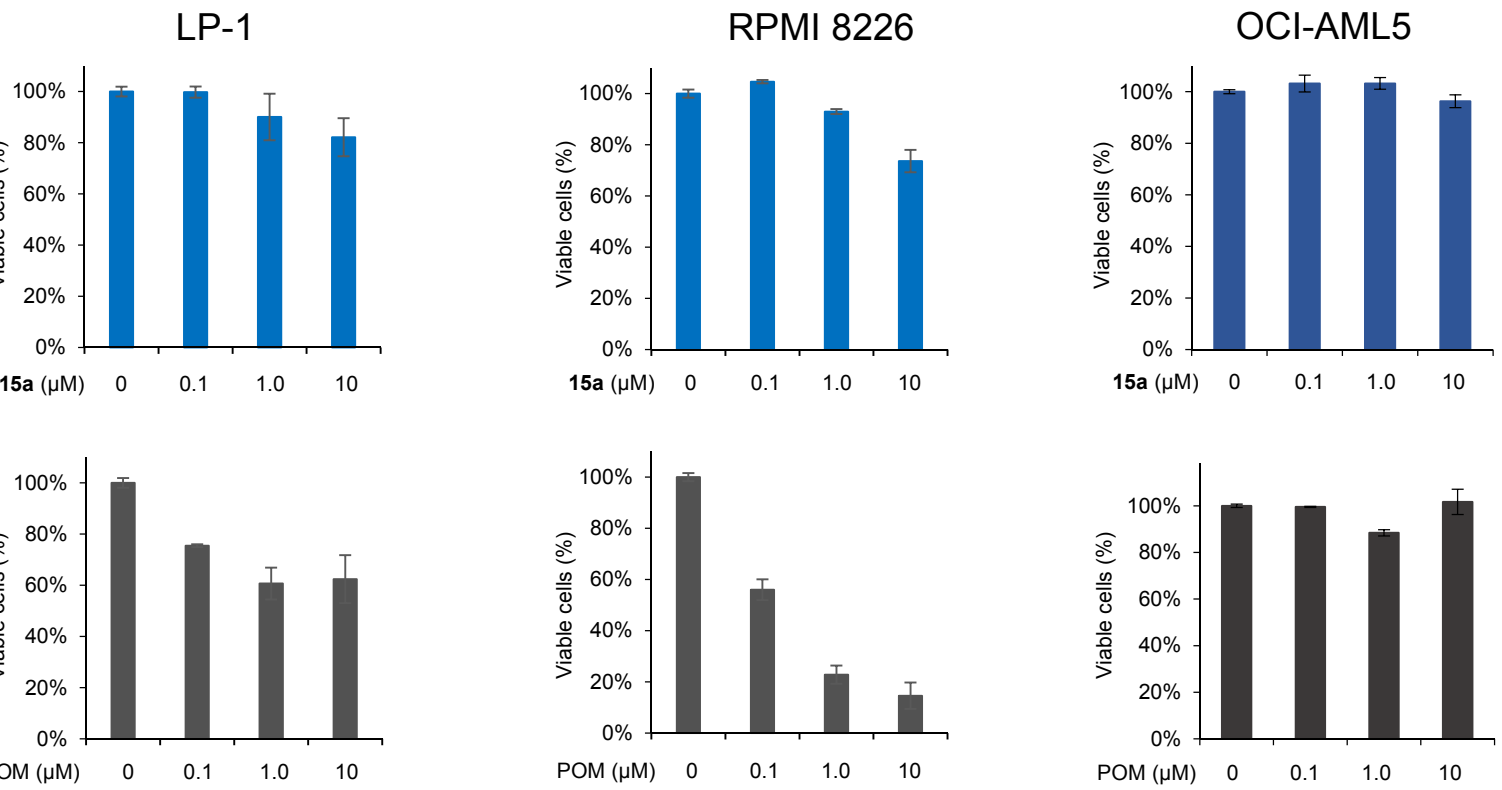
Homo-PROTAC 15 vs. DMSO (3h)



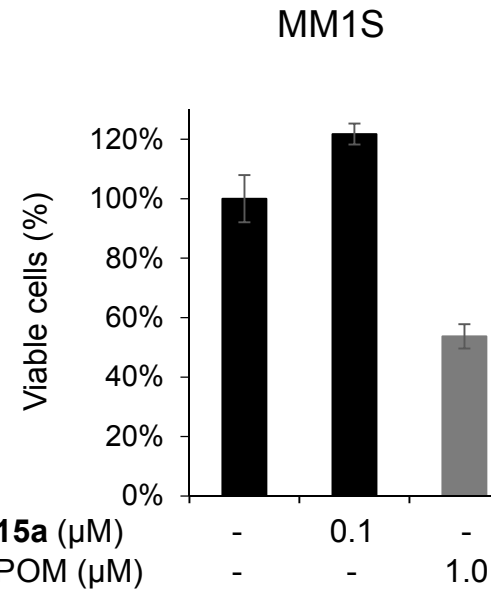
Pomalidomide vs. DMSO (3h)

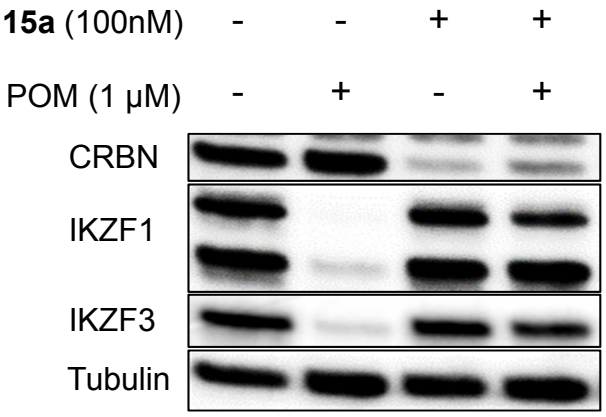


CRBN knockdown has no effect on cell proliferation



npound 15a antagonizes the effects of IMiDs on multiple myeloma cells



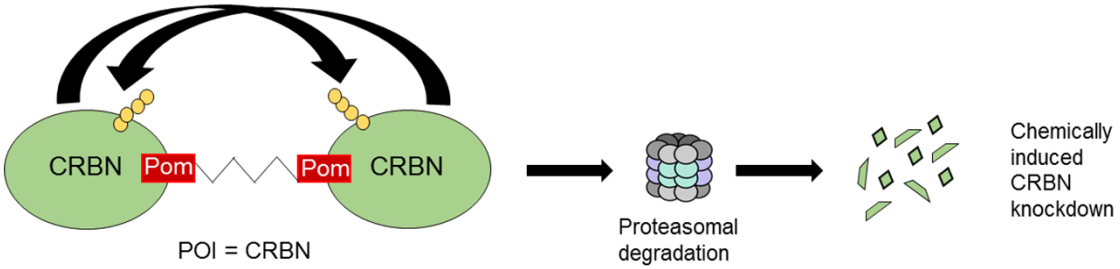


Conclusions

IMiD-based Homo-PROTACs induce specific CRBN ubiquitination and degradation

Chemical CRBN degradation had no effect on cancer cell proliferation

Homo-PROTAC abrogates IMiD effects in multiple myeloma



Homodimeric pomalidomide-based compounds may help to:

- Identify CRBN‘s endogenous substrates and physiologic function
- Investigate the molecular mechanism of IMiDs
- Potential clinical application in obesity (Lee *et al*., 2013, *Diabetes*)

Acknowledgment

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