Nuove prospettive future nei linfomi

L’aspetto farmacologico

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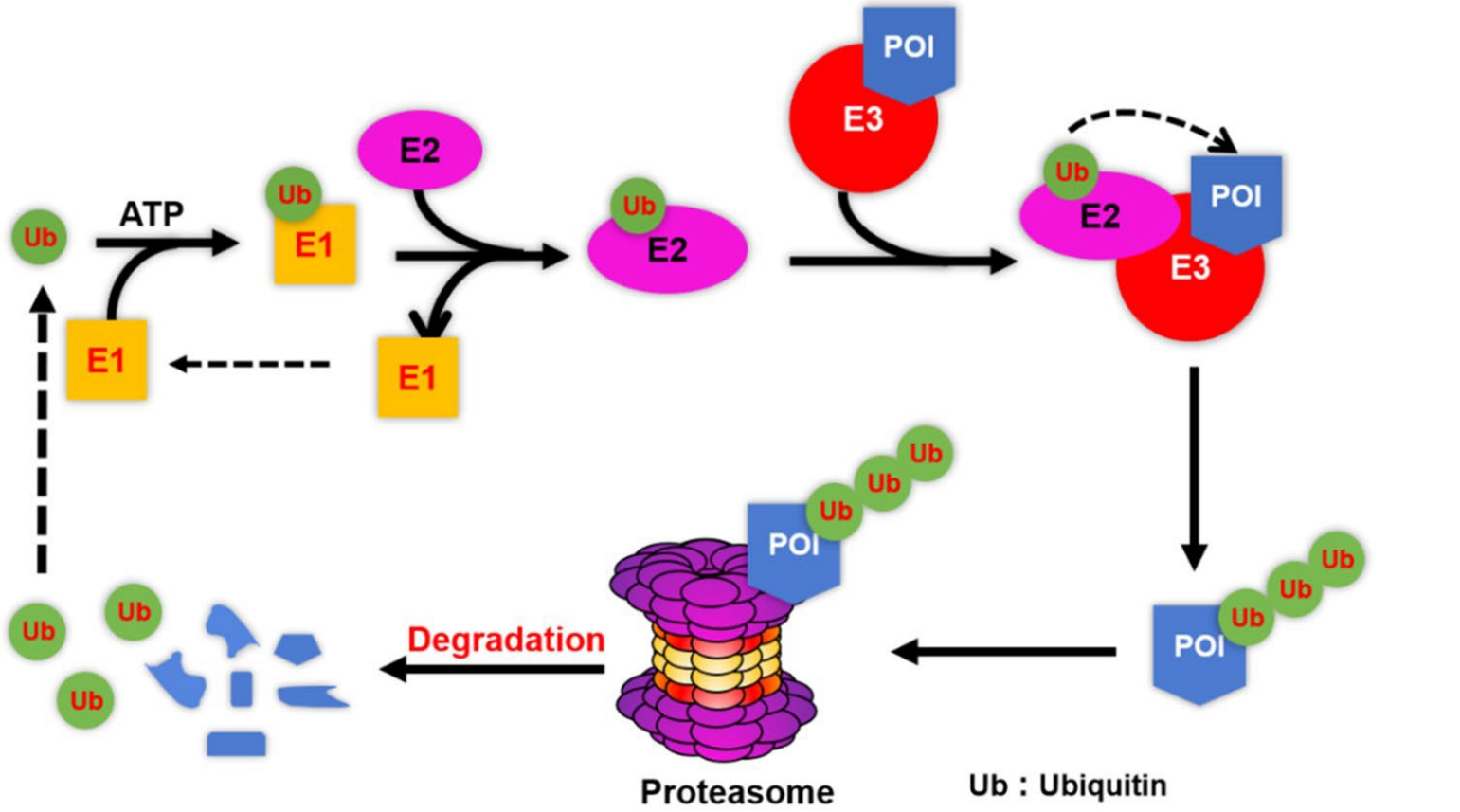
Disclosures of Romano Danesi

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
MSD			X		X		
Eisai			X		X	X	
AstraZeneca	X		X		X	X	
BeiGene					X		
Janssen	X		X		X		
Novartis			X		X		
Lilly			X		X		
Incyte			X		X		
AB Science			X				

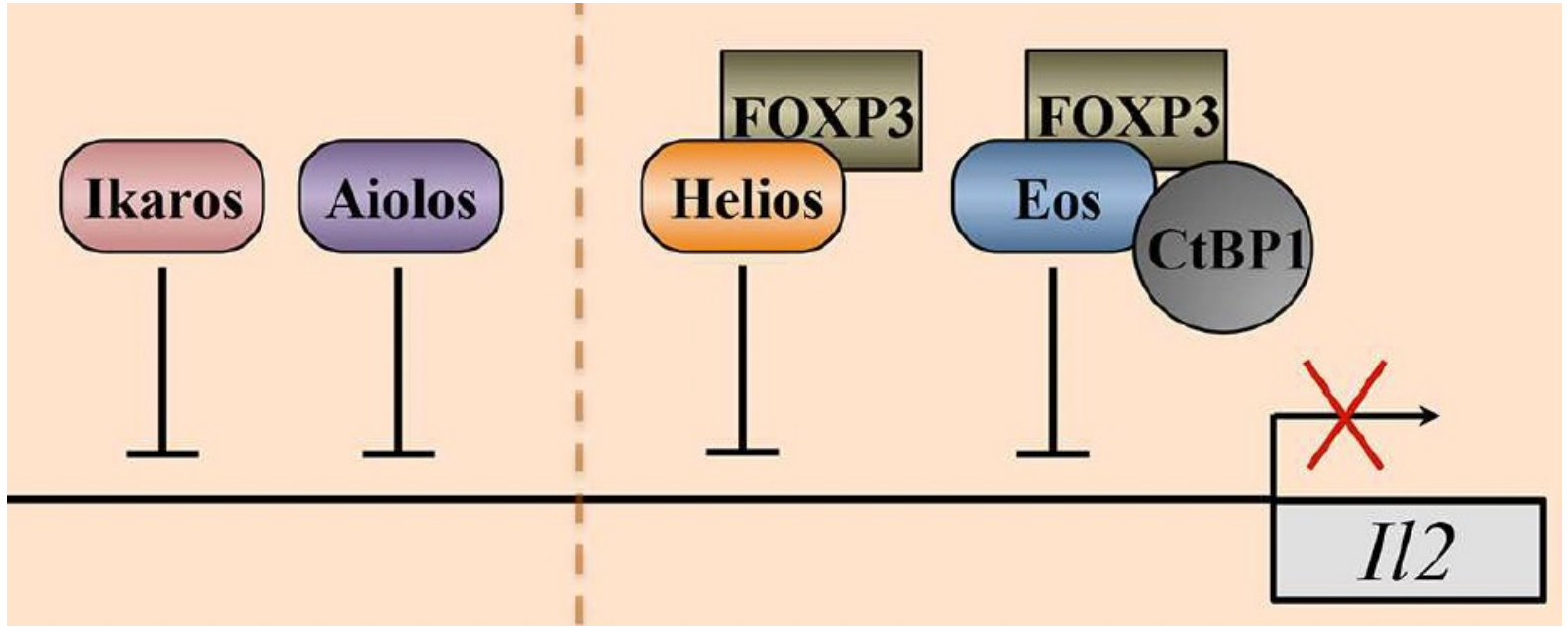
The ubiquitin-proteasome pathway

The ubiquitin proteasome pathway



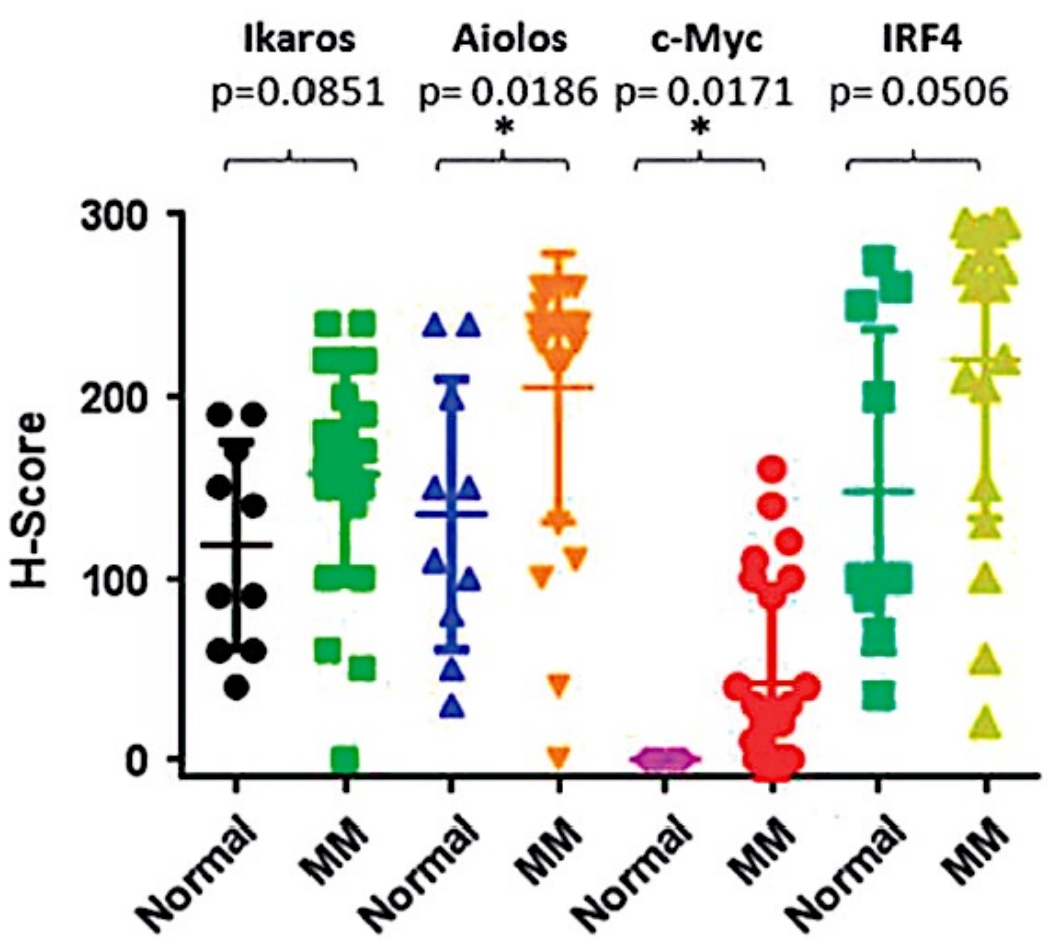
Na Yang et al. Mol Divers 202315;1-25

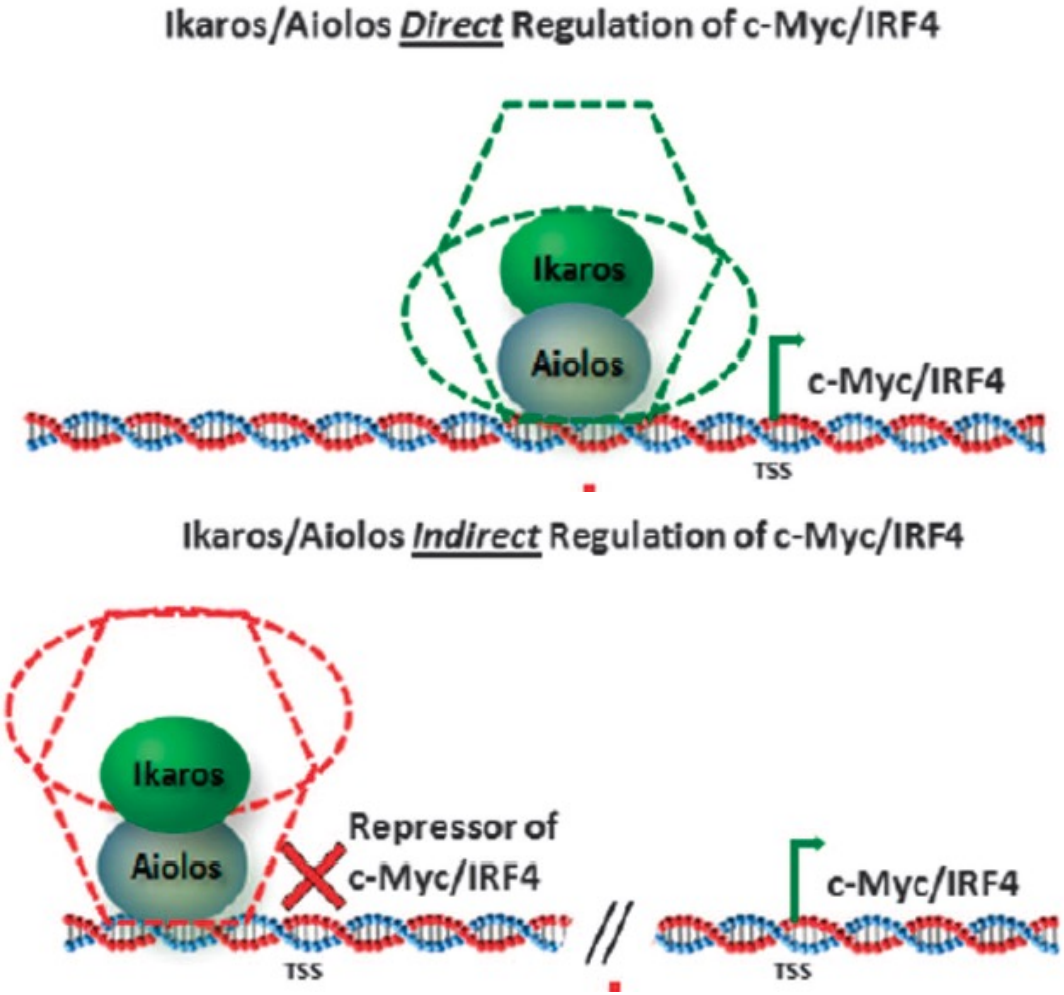
The cereblon substrates Aiolos and Ikaros zinc-finger proteins inhibits IL-2 gene transcription



Powell MD et al. Front Immunol 2019;10:1299

Ikaros, Aiolos, c-Myc and IRF4 are upregulated in MM samples compared with normal bone marrow





CC Bjorklund et al. Blood Cancer Journal (2015) 5, e354

Evolution of Cereblon-Mediated Protein Degradation as a Therapeutic Modality

CELMoDs are next generation IMiDs

The molecular “glue” degrader landscape in 2022

- Since the 2014 discoveries that thalidomide-like compounds “glue” together the cereblon (CRBN) unit of the ubiquitin E3 ligase complex and certain immune cell transcription factors, molecular glue degraders have attracted much attention.
- These monomeric small molecules induce protein-protein interactions and catalytically destroy their molecular targets.
- Recent breakthroughs in understanding of the chemistry and biology of these molecules have created numerous opportunities for drugging previously underexplored targets.

Molecular glues and induced proximity - cas.org/moleculargluе

IMiDs and CELMoDs: only difficult to pronounce (or remember)?

IMiDs: Cereblon-targeting **I**mmuno**M**odulatory **i**mide **D**rug**s**

CELMoDs: **C**ereblon **E**3 **L**igase **Mo**dulator **D**rug**s**

IMiDs

- Thalidomide, a first generation IMiD, is associated with significant toxicity in older patients.
- Lenalidomide is a more potent second generation IMiD with fewer adverse events than thalidomide.
- Pomalidomide is a third generation IMiD 10 times more potent than lenalidomide.
- Cereblon modulators like lenalidomide bind to Cereblon and modify its surface to create a new interface for target substrate binding. Target substrates bind CRBN with Cereblon modulator, allowing a substrate lysine side chain to attack the E2–ubiquitin bond and leading to ubiquitin transfer from E2 to substrate.

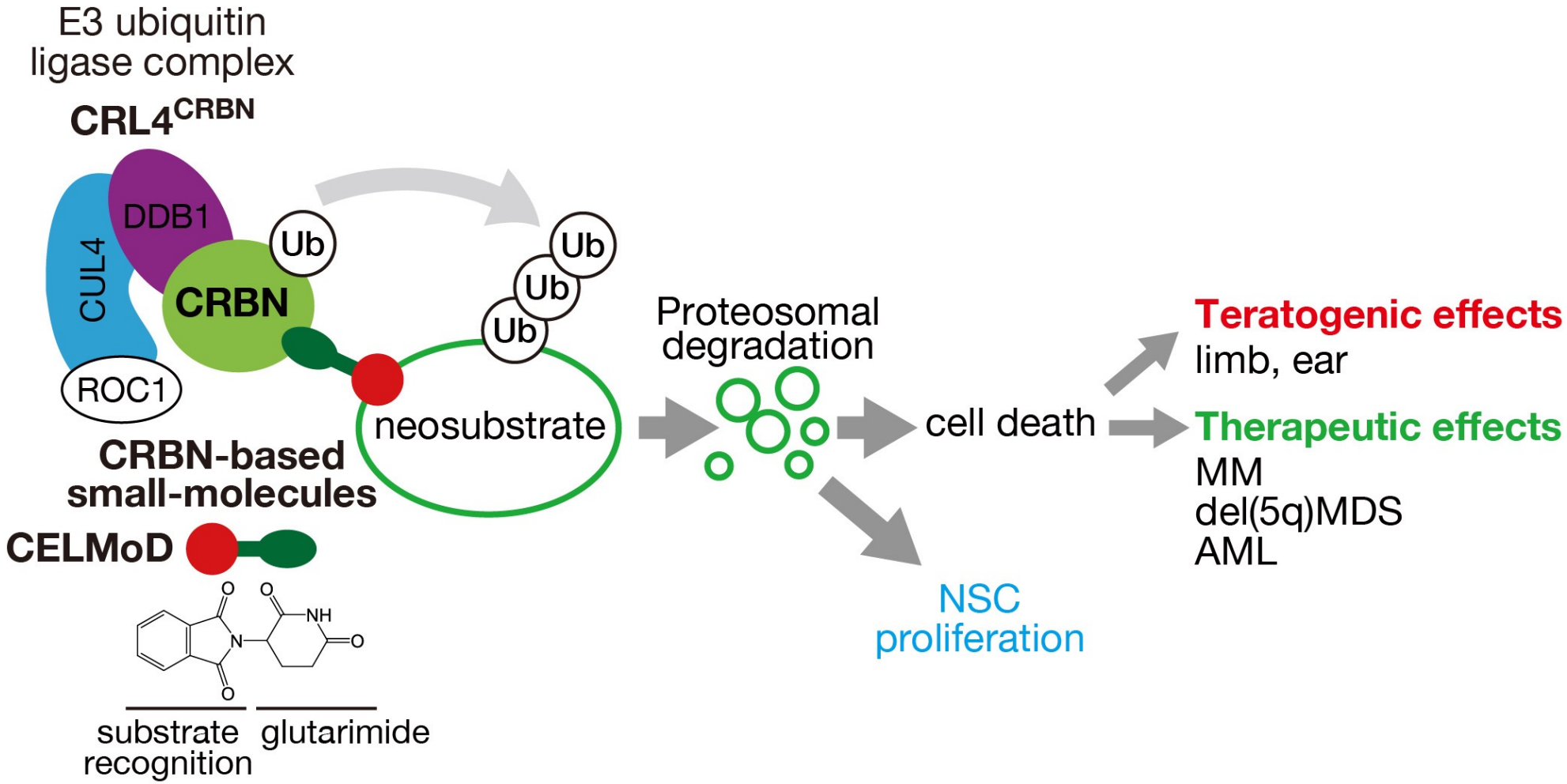
Chamberlain PP et al. ACS Med. Chem. Lett. 2019, 10, 1592−1602

CELMoDs

- New-generation IMiDs include avadomide, golcadomide, iberdomide, CC-885, eragidomide, mezigdomide, CFT7455, BTX-1188, CC- 91633, CC-647, and CC-3060.
- Their half maximal inhibitory concentration (IC50) is nanomolar compared to lenalidomide (1.5 µM) and pomalidomide (1.2 µM). Published IC50 values vary in different publications, because they are dependent on the type and conditions of a binding assay.
- The potency of CELMoDs in the induction of Ikaros degradation is in comparison with classical IMiDs: golcadomide > iberdomide > avadomide > pomalidomide > lenalidomide.

Fuchs O. Blood Reviews 57 (2023) 100994

Degradation of a protein of interest via the ubiquitin-proteasome system using a molecular glue bound to the ubiquitin ligase $CRL4^{CRBN}$ complex



Differentiation of IMiDs and CELMoDs

- CELMoDs bind CRBN and trigger recruitment, polyubiquitination and degradation of substrates.
- IMiDs and CELMoDs share glutarimide rings for binding to the tri-tryptophan pocket of cereblon, and isoindolinone rings that interact with cereblon and substrates (e.g. Ikaros, Aiolos, etc.).
- However, CELMoD structures are extended relative to those of IMiDs, containing additional phenyl and morpholino moieties enabling enhanced interactions with CRBN or substrates.

Anjan Thakurta et al. Oncotarget, 2021, 12:1555-1563

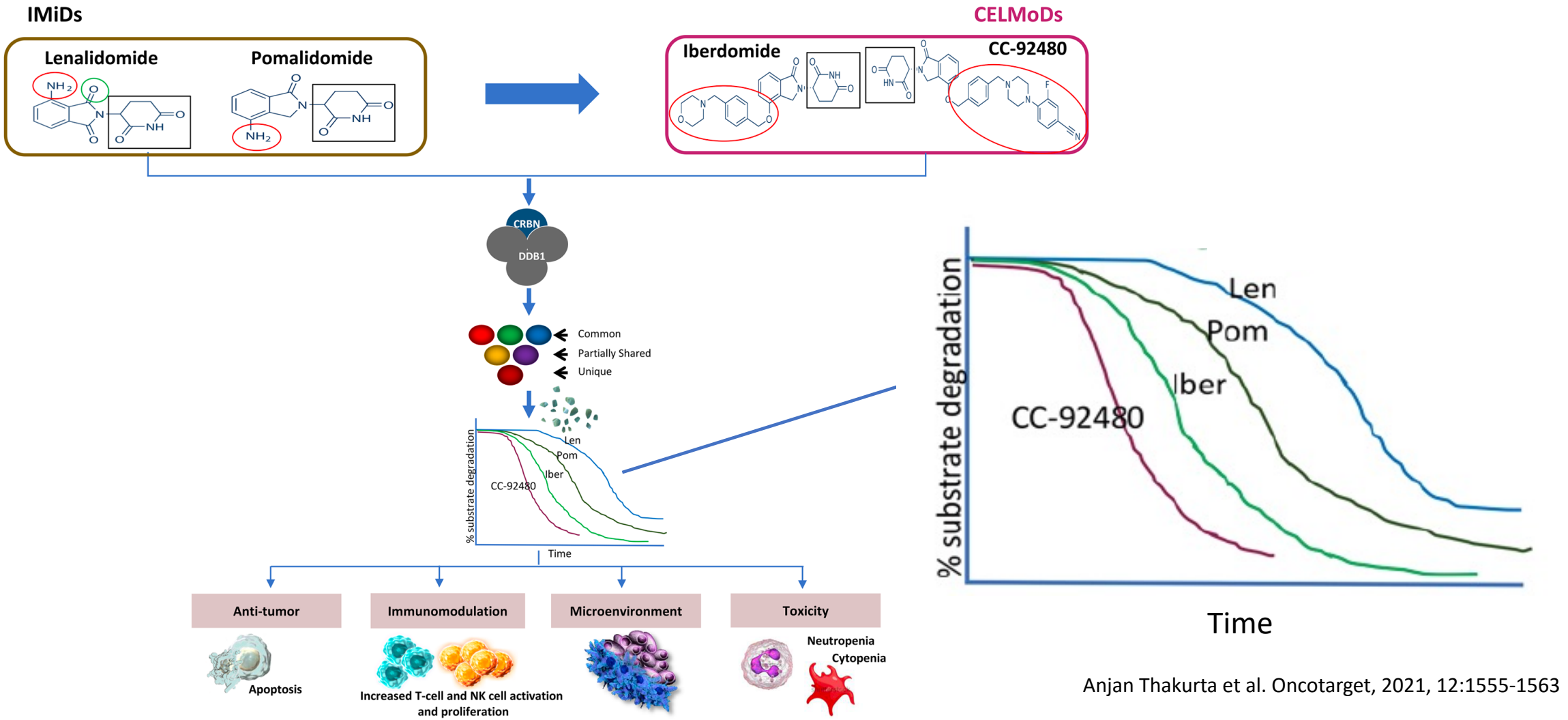
Differentiation of IMiDs and CELMoDs

- While both lenalidomide and pomalidomide bind CRBN with similar affinity (Kd~1.0–1.5 uM), iberdomide and golcadomide bind CRBN with ~10-20-fold higher affinity and potency (~ 10-100 fold) and more efficiently degrade Ikaros and Aiolos.

- The superior CRBN-binding affinity of CELMoDs compared to IMiDs is a key feature that differentiates these compounds.

Anjan Thakurta et al. Oncotarget, 2021, 12:1555-1563

Differentiation of IMiDs and CELMoDs



Anjan Thakurta et al. Oncotarget, 2021, 12:1555-1563

Therapeutic applications of molecular glues inducing protein degradation

Types of protein degradation	Description
E3 ligase utilizing targeted protein degraders	
Transcription factors IKZF1 and IKZF3 degradation	Lymphocyte lineage transcription factors - key regulators for survival of malignant plasma cell in multiple myeloma - considered undruggable due to lack of druggable binding pockets.
Cyclin K and CDK12 degradation	Drug targets to treat cyclin E1-overexpressing tumors of human tumorigenesis.
Casein kinase 1α (CK1α) degradation	Member of CK1 family of proteins that regulate various signaling pathways involving autoimmune diseases, neurodegenerative diseases, and cancer.
G1 to S phase transition protein 1 (GSPT1) degradation	Translation termination factor GSPT1 is overexpressed and oncogenic in several cancers.
Sal-like protein 4 (SALL4) degradation	SALL4, a spalt-like developmental transcription factor, is important for limb development. Thalidomide and derivatives induce degradation of SALL4 - likely reason for the observed birth defects.
RNA-binding motif protein 39 (RBM39) degradation	RNA-binding protein involved in transcriptional co-regulation and alternative RNA splicing.
β-catenin degradation	Oncogenic transcription factors remain extremely challenging proteins to target, despite being implicated in multiple diseases.
Tumor protein p53 stabilization and activation	Acts as a tumor suppressor - regulates cell division by keeping cells from growing and proliferating in an uncontrolled way.
BCL6 protein degradation	Targeting BCL6 protein is an effective therapeutic approach for treating diffuse large B-cell lymphoma (DLBCL).

Molecular glues and induced proximity
cas.org/moleculargluе

Examples of CELMoDs

Iberdomide (CC-220)

- Iberdomide is a CELMoD with enhanced antimyeloma activity in comparison with lenalidomide or pomalidomide.
- Iberdomide binds much more tightly to CRBN in the RING E3 ubiquitin ligase CRL4CRBN, changes its specificity, and induces more potent and faster polyubiquitination and subsequent degradation of the transcription factors Ikaros and Aiolos in tumor cells.
- Preclinical studies demonstrated higher antiproliferative and proapoptotic activity of iberdomide (0.1 µM) than pomalidomide (1.0 µM) in both lenalidomide-sensitive (H929) and lenalidomide-resistant cells (H929/LR).
- A IC_{50} of 60 nM was determined for iberdomide in comparison with the IC50 for lenalidomide (1.5 µM) and pomalidomide (1.2 µM).

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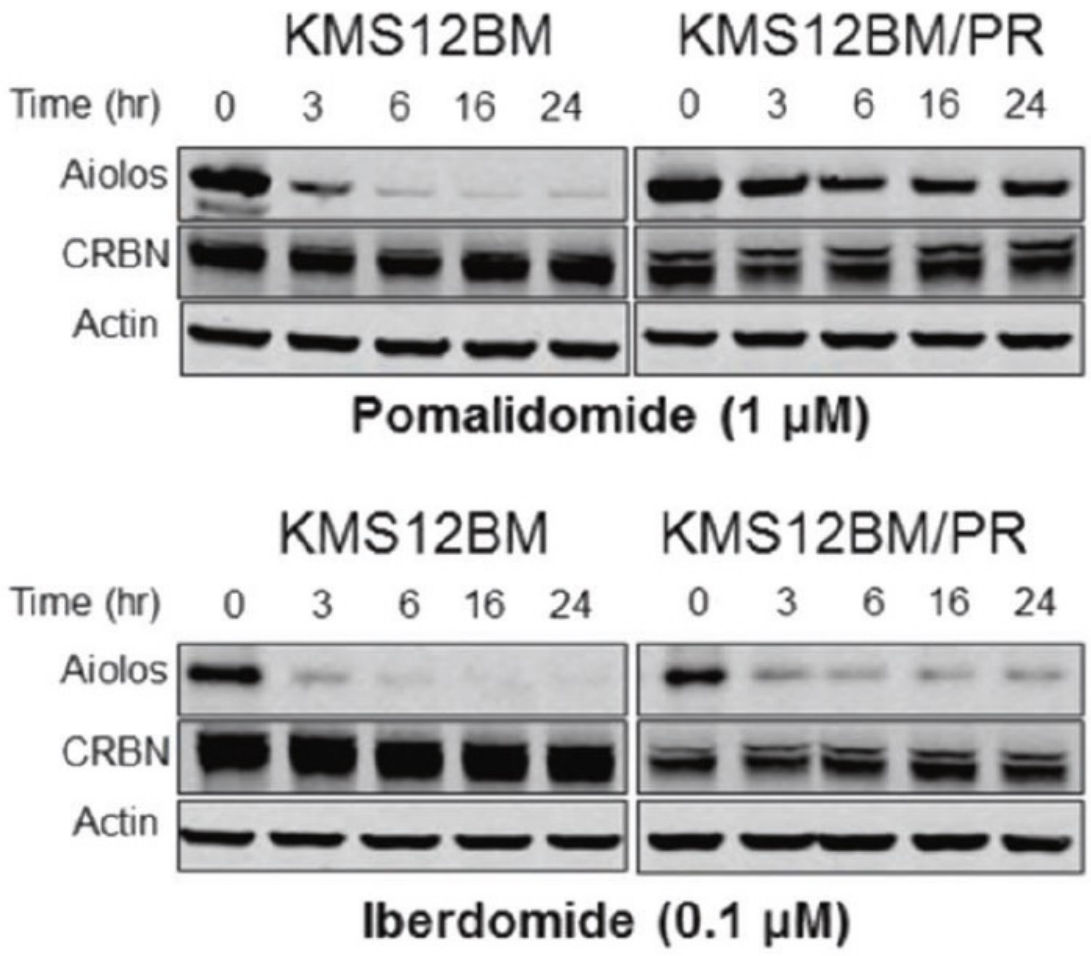
Iberdomide (CC-220)

- The interaction of itraconazole and rifampin with iberdomide was studied in healthy subjects (NCT02820935), similar to avadomide. A single oral avadomide dose of 0.6 mg alone or with itraconazole or rifampin is well tolerated.
- Changes in plasma iberdomide concentration during treatment by combinations of iberdomide with itraconazole or rifampin are more pronounced than in the case of avadomide.
- Caution must be taken in cases of iberdomide coadministration with itraconazole, and the combination of iberdomide with rifampin is not advised.

Fuchs O. Blood Reviews 57 (2023) 100994

Western blot analysis showing the effects of pomalidomide or iberdomide on the degradation kinetics of Aiolos



Chad C. Bjorklund et al. Leukemia (2020) 34:1197–1201

Golcadomide (CC-99282)

- CC-99282 showed 10- to 100-fold enhanced antiproliferative activity compared with lenalidomide independent of subtype or chemoresistance of DLBCL cells.
- CC-99282 induced extensive and prolonged degradation of the transcription factors Ikaros and Aiolos, which correlated with the induction of the expression of IFN-inducible genes (IRF7, IFIT3, and DDX58) and derepression of cyclin-dependent kinase (CDK) inhibitors.
- CC-99282 induced activation of caspases and cleavage of poly(ADP-ribose) polymerase-1 (PARP1) and decreased the levels of the important oncogenic factors c-myc and IRF4.
- Substantial antitumor activity was also detected in various lymphoma xenograft models.
- CC-99282 induced the secretion of IL-2 and effector cytokines and chemokines (GM-CSF, IFNγ, and TNFα) that correlated with Ikaros and Aiolos degradation.
- Complete tumor regression was achieved with a combination of CC-99282 and rituximab in xenograft models

Conclusions

- The ligand-directed protein–protein interaction approach of CELMoDs, offers the possibility of recruiting and degrading proteins for which there are no ligands.
- Given the ~600 ubiquitin ligases in the genome and the potential for both tissue- and organelle-specific ubiquitin ligases, there remains great potential for diversity in targeting options.
- These approaches in the emerging modality of targeted protein degradation should be expected to considerably expand the “druggable proteome” to provide countless new therapeutic opportunities.
- Combination of CELMoDs, anti-CD38 and CAR-T cells in the future?

Chamberlain PP et al. ACS Med. Chem. Lett. 2019, 10, 1592−1602