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Mezigdomide Overcomes CRBN Mutations Emerging Post-IMiD Therapy

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ASH 2025, Abstract #436

CELMoD agents were purposefully developed from deep scientific understanding of CRBN and MM biology

IMiD® agents

CELMoD agents

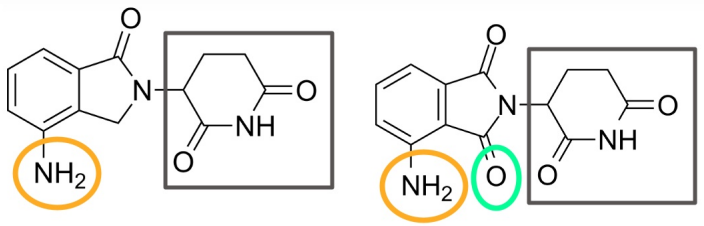
Lenalidomide (2002)[1]

Pomalidomide (2004)[2]

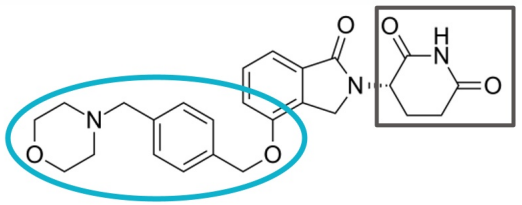
CRBN identified as being bound by IMiD agents (2010)[7,8]

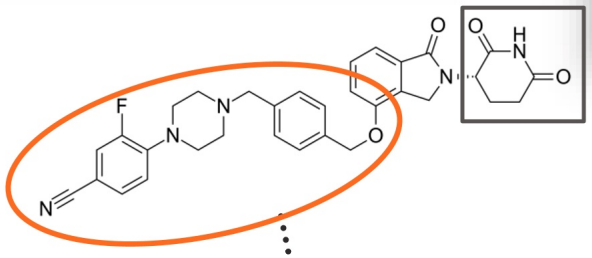
Iberdomide (2019)[9]

Mezigdomide (2020)[10]



LEN and POM transformed MM treatment, but the mechanism of action was unknown[3-6]





- Greater binding with CRBN
- More than 10x higher affinity

This journey from IMiDs to CELMODs showcases how scientific discovery fuels innovation leading to potential therapies with greater specificity and potency against multiple myeloma

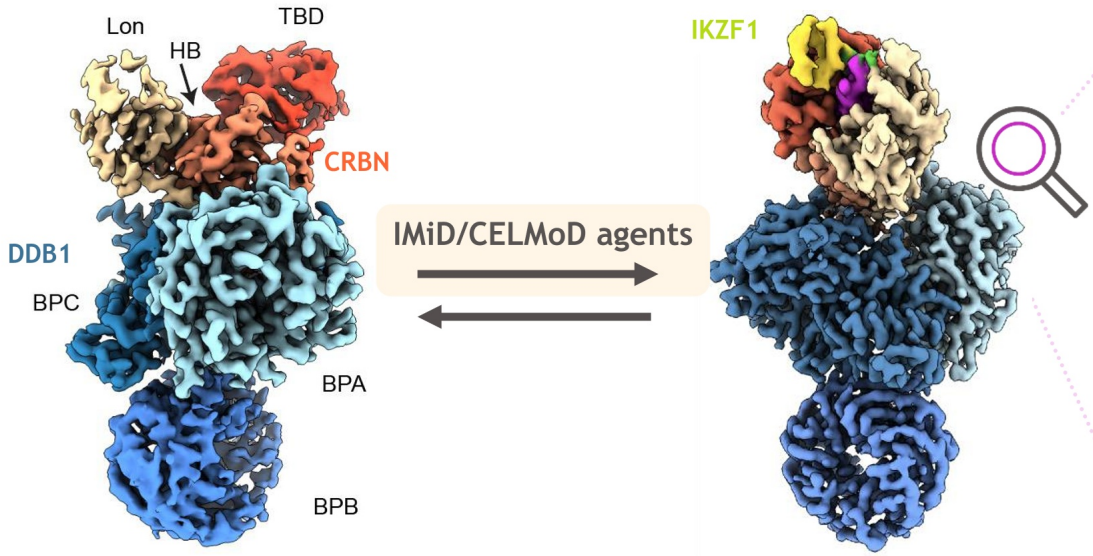
IBER and MEZI are investigational products, currently not approved by any regulatory agency.

Dates refer to first publication of the asset. CRBN, cereblon; IBER, iberdomide; IMiD, immunomodulatory drug; LEN, lenalidomide; MEZI, mezigdomide; MM, multiple myeloma; POM, pomalidomide.

1. Richardson PG, et al. *Blood* 2002;100:3063-3067; 2. Galustian C, et al. *J Immunother* 2004;27:S50; 3. Chen C, et al. *Br J Haematol* 2009;146:164-170; 4. Fotiou D, et al. *Ther Adv Hematol* 2022;13:1-17; 5. Krönke J, et al. *Science* 2014;343:301-305; 6. Lu G, et al. *Science* 2014;343:305-309; 7. Ito T, et al. *Science* 2010;327:1345-1350; 8. Chamberlain PP, Cathers BE. *Drug Discov Today Techno* 2019;31:29-34; 9. Lonial S, et al. *Blood* 2019;134(suppl 1). Abstract 3119; 10. Wong L, et al. *Blood* 2020:136(suppl 1). Abstract 2295.

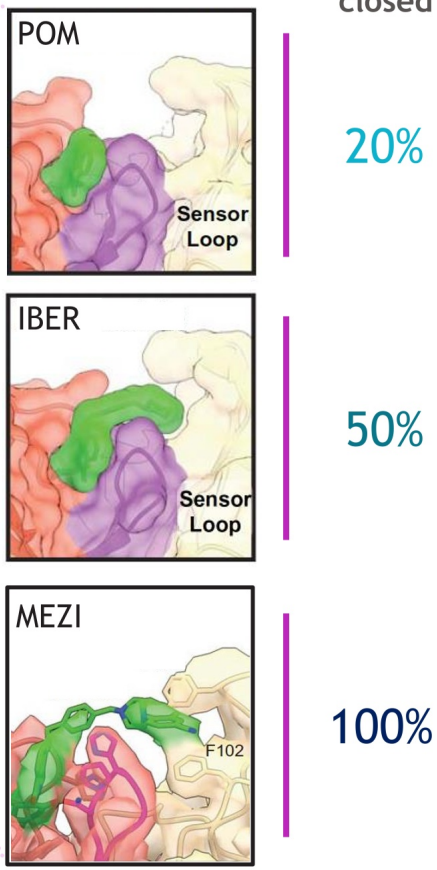
CELMoD agents bind CRBN with distinct features that affect degradation efficiency

CELMoD agents promote conformational changes in CRBN



Open/Inactive state
No Ikaros/Aiolos recruitment

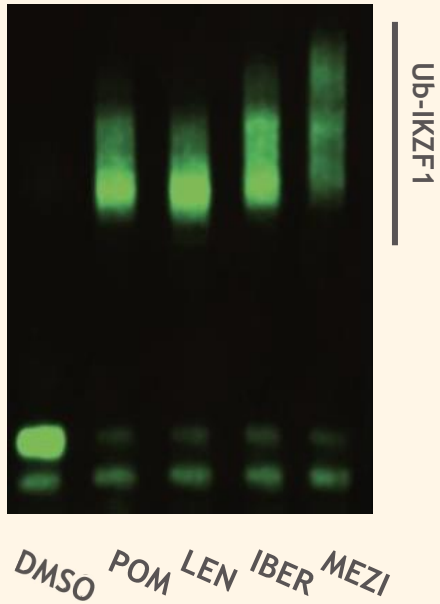
Closed/Active state
Ikaros/Aiolos recruitment
Essential for ubiquitination



Binding to CRBN and inducing a closed/active conformation leads to substrate degradation

Adapted from Watson ER, et al. *Science* 2022;378:549-553.

Substrate ubiquitination assay[1]



More efficient ubiquitin elongation

Purposefully designed CELMoDs like mezigdomide are being investigated clinically in RRMM patients

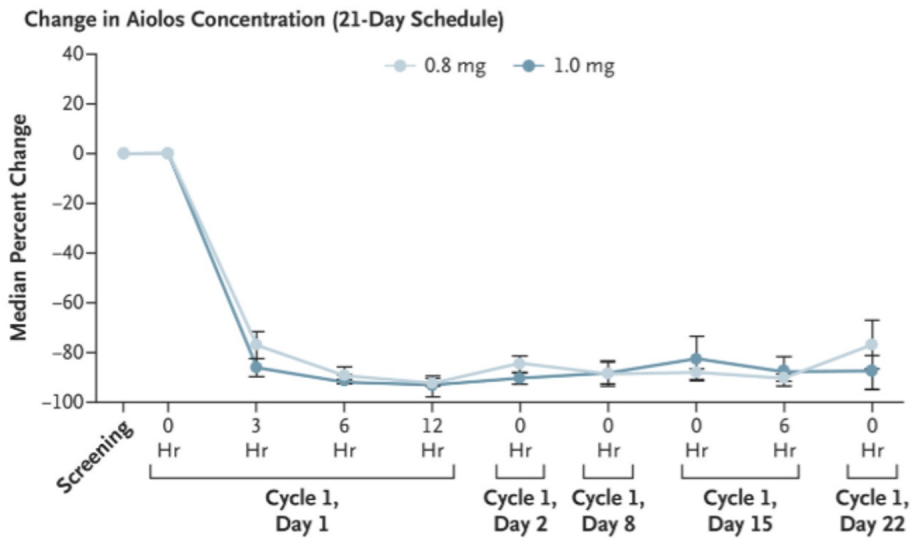
Clinical development plan for mezigdomide in multiple myeloma

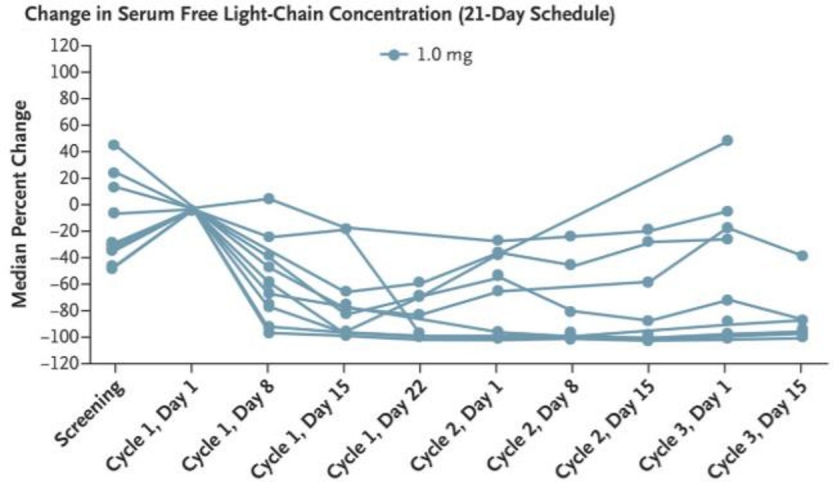
Phase 1/2 Studies

CC-92480-MM-001: Dose Escalation and Expansion of Mezi + Dex in RRMM	Mezi mono Mezi-dex
CC-92480-MM-002: Dose Escalation and Expansion of Mezi + SOC in RRMM	Mezi-Vd Mezi-Dd Mezi-Kd Mezi-Ed
CA057-003: Dose Escalation and Expansion of Mezi + Novel Therapies in RRMM	Novel-Novel Combinations Mezi-d + TAZE (EZH2i) Mezi-d + BMS-986158 (BETi) Mezi-d + TRAM (MEKi)

Registrational Ph3 Studies

SUCCESSOR-1: Mezi-Vd vs Pom-Vd in 1-3L RRMM	Len exposed; not refractory to PI; Pom naïve
SUCCESSOR-2: Mezi-wKd vs biwKd in ≥ 1L RRMM	≥ 1 prior line including Len and anti-CD38 mAb, K naïve



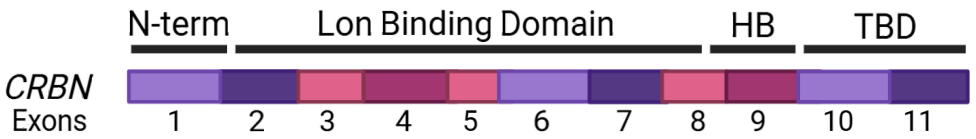


Is there rationale to believe that newer generation CELMoDs will be effective in patients previously treated with traditional immunomodulatory agents?

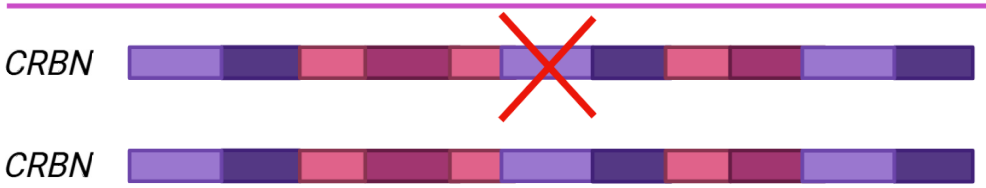
1. Richardson PG, et al. *NEJM* 2023;389:1009-1022

Profiling of post-IMiD treated MM patients suggest potentially different mechanisms of resistance

IMiD-REFRACTORY MECHANISM OF ACTION ABERRATION CATEGORIES

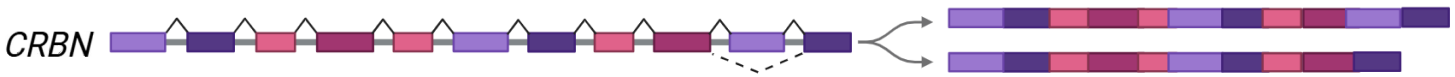


CRBN Dysregulation ~40% — **All**

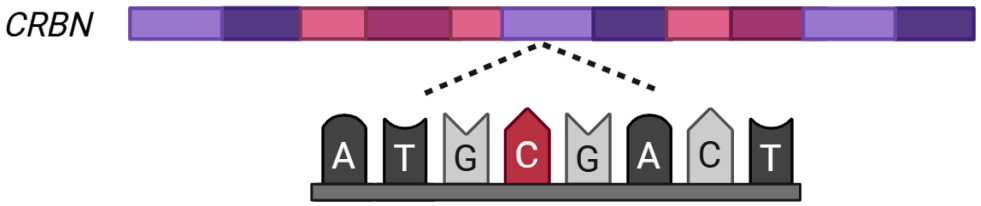


CRBN Copy Loss ~30% — **Deletions Structural Variants**

CRBN Destabilization
COPS Signalosome Loss ~ 18% — **2q Deletions COPS7Bdel COPS8del**



CRBN Alternative Splicing ~14% — **CRBNdel10**

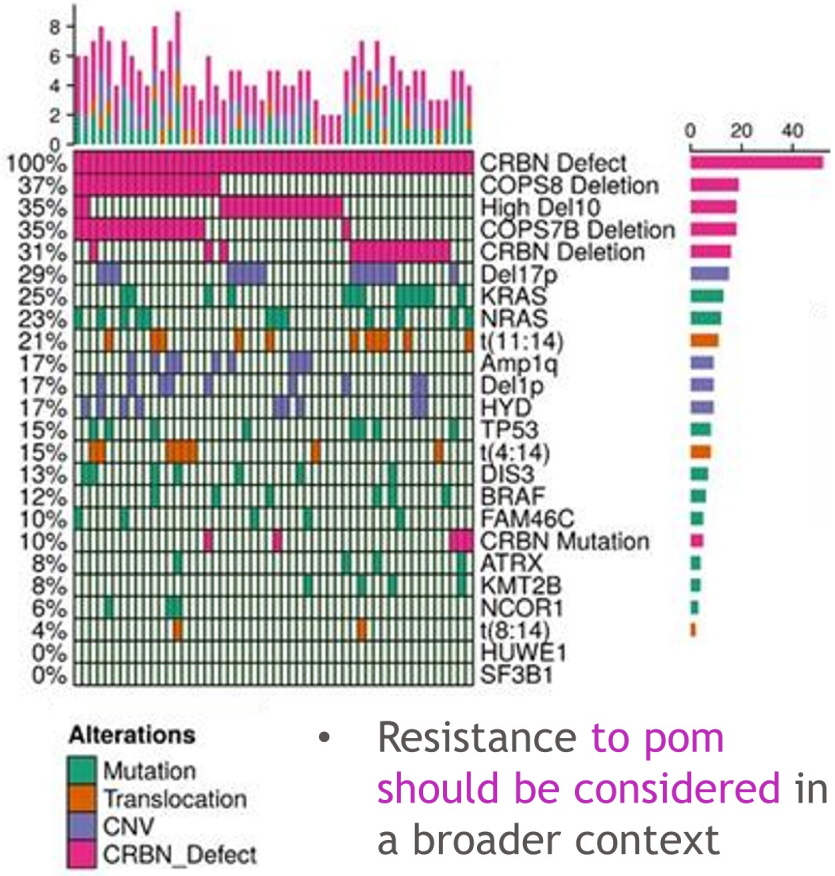


What does CRBN dysregulation look like in pomalidomide-treated patients?

CRBN Mutations ~5% — **POTENTIAL:**
Open/Closed Loop Destabilization
E3 Ligase Complex Destablization
Drug Interface Disruptions

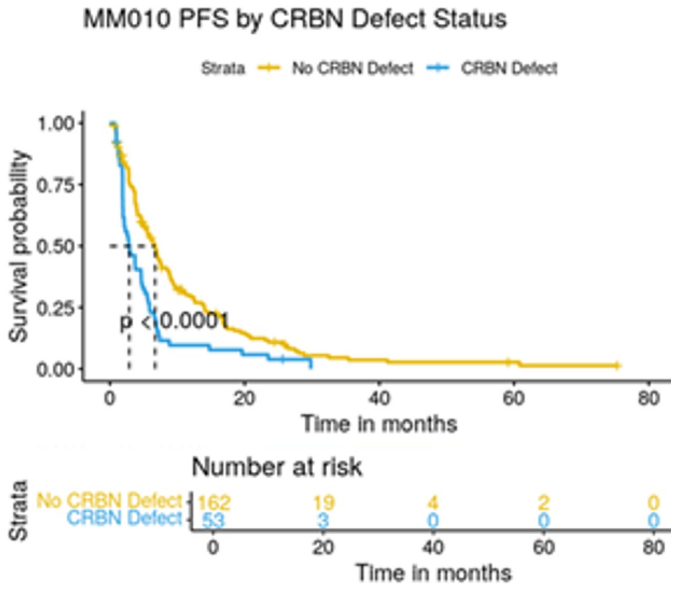
CRBN dysregulation is complex and may contribute to inferior clinical responses

- Distribution and co-genomic features of patients with *CRBN* dysregulation treated with pomalidomide

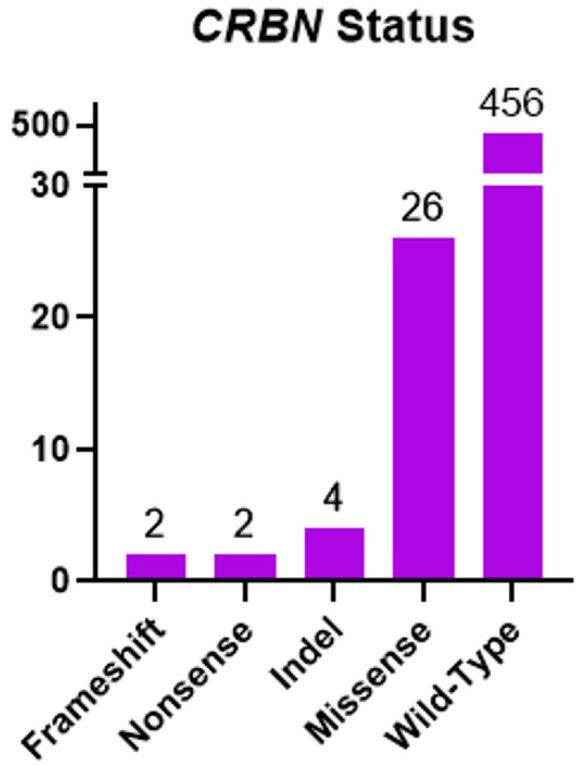


- Resistance to pom should be considered in a broader context

- Presence of *CRBN* dysregulation have an inferior response compared to non *CRBN* defect in pomalidomide treated MM patients

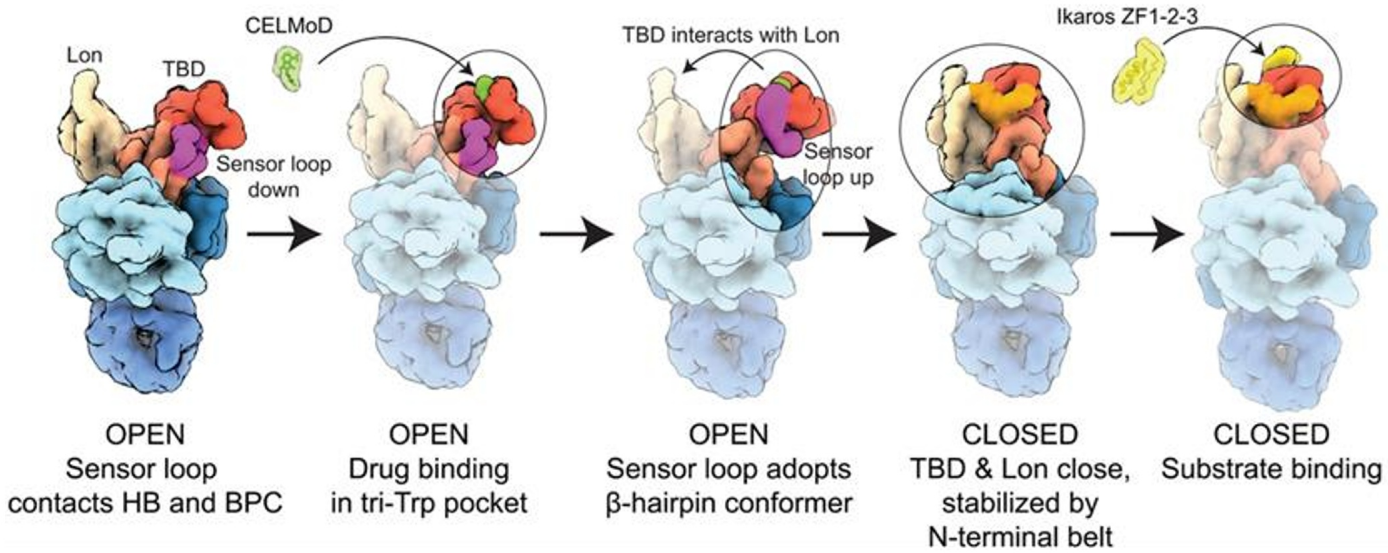


- Analysis of nearly 500 patients post-pomalidomide studies reveals distinct *CRBN* mutations

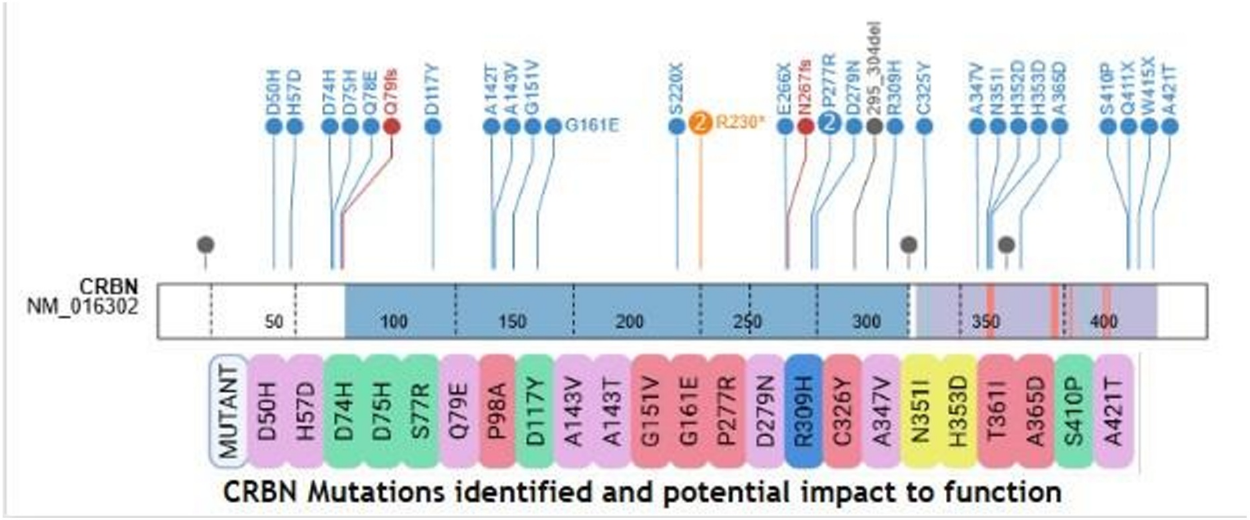


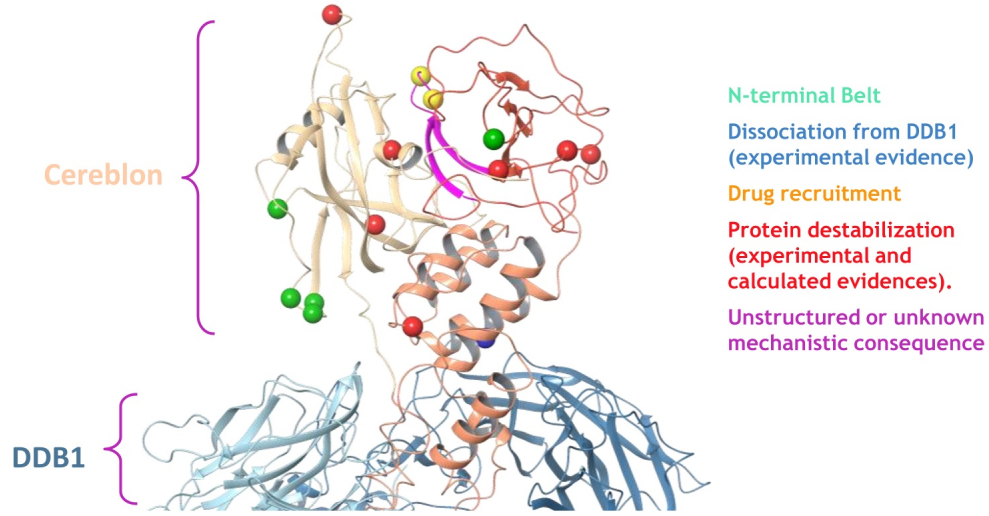
How do we leverage our mechanistic understanding of the mechanism of action of these agents to understand these mutations on the potential impact of resistance in the clinic?

Leveraging structural insights of cereblon mutants and their potential functional consequences



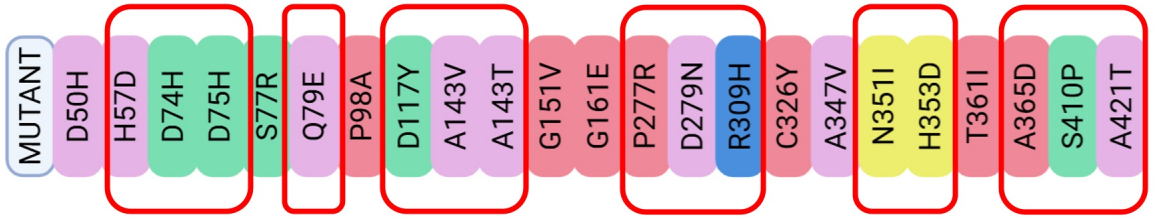
- CELMoDs act as allosteric regulators of CRBN conformation to promote recruitment of neosubstrates for Ub and downstream degradation
- CELMoDs need to be able to favor the closed conformation of CRBN for neosubstrate recruitment and better degraders may favor more closed state conformation





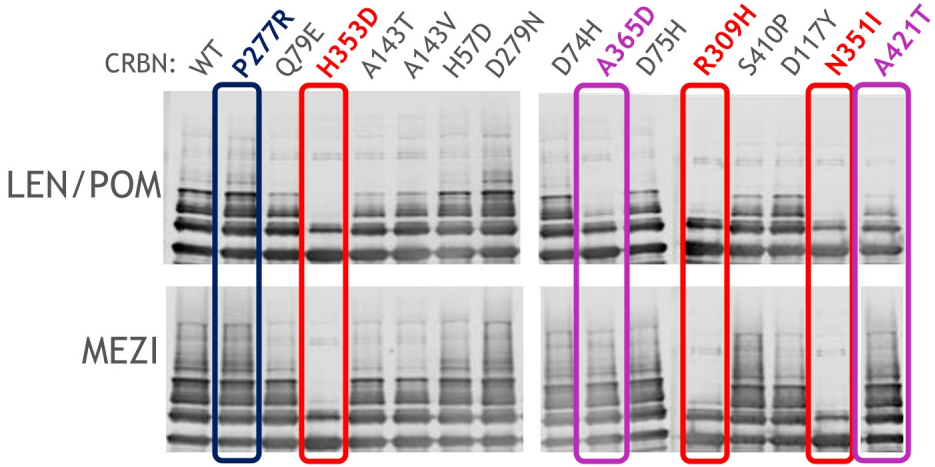
Direct evidence of mutant CRBN effect

1) Selection of mutants with potential functional impact on CRBN modulators



2) Bacculovirus expression and purification of mutant CRBN/DDB1 complexes

3)Assay mutants for enzymatic Ub'n activity



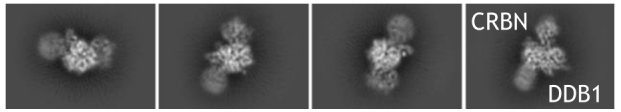
No effect on either IMiDs/CELMoDs – **10/15**

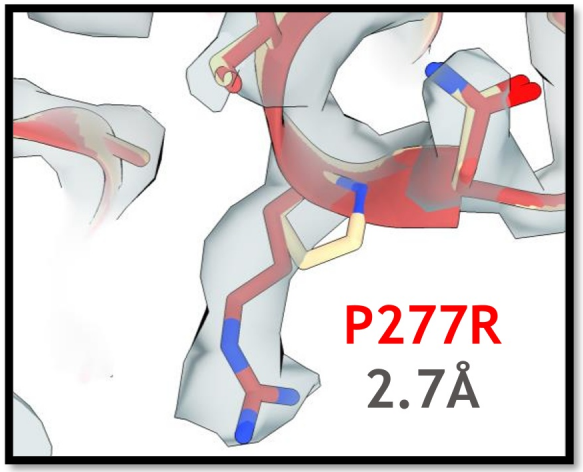
Critical for all compounds (N351I, H353D, R309H) – **3/15**

Mezigdomide overcomes IMiD deficiency (A365D) - **2/15**

4) CryoEM structural interrogation of relevant mutants

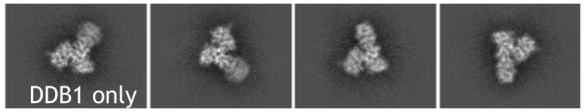
P277R mutant CRBN

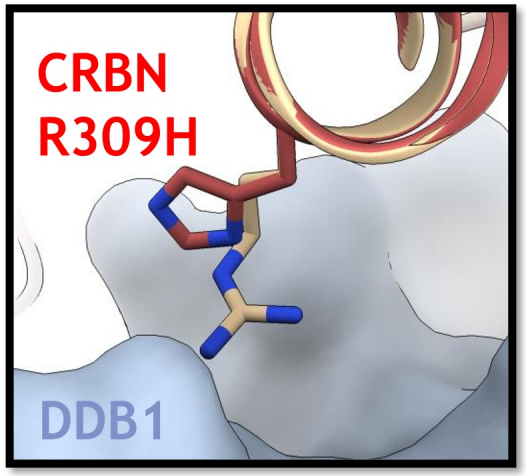




Obvious sidechain density, no effect

R309H mutant CRBN



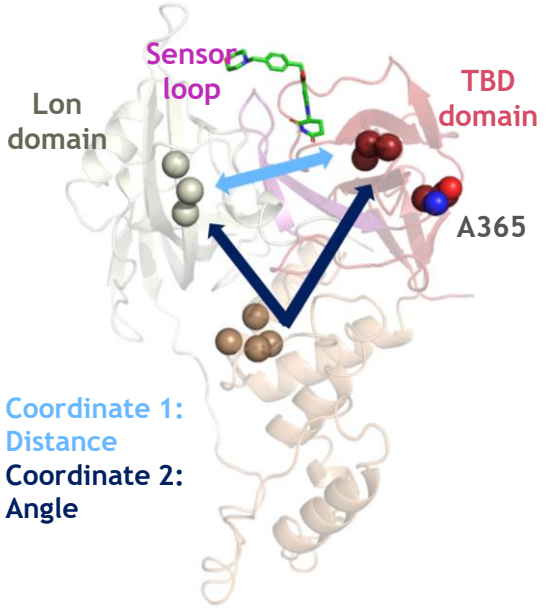


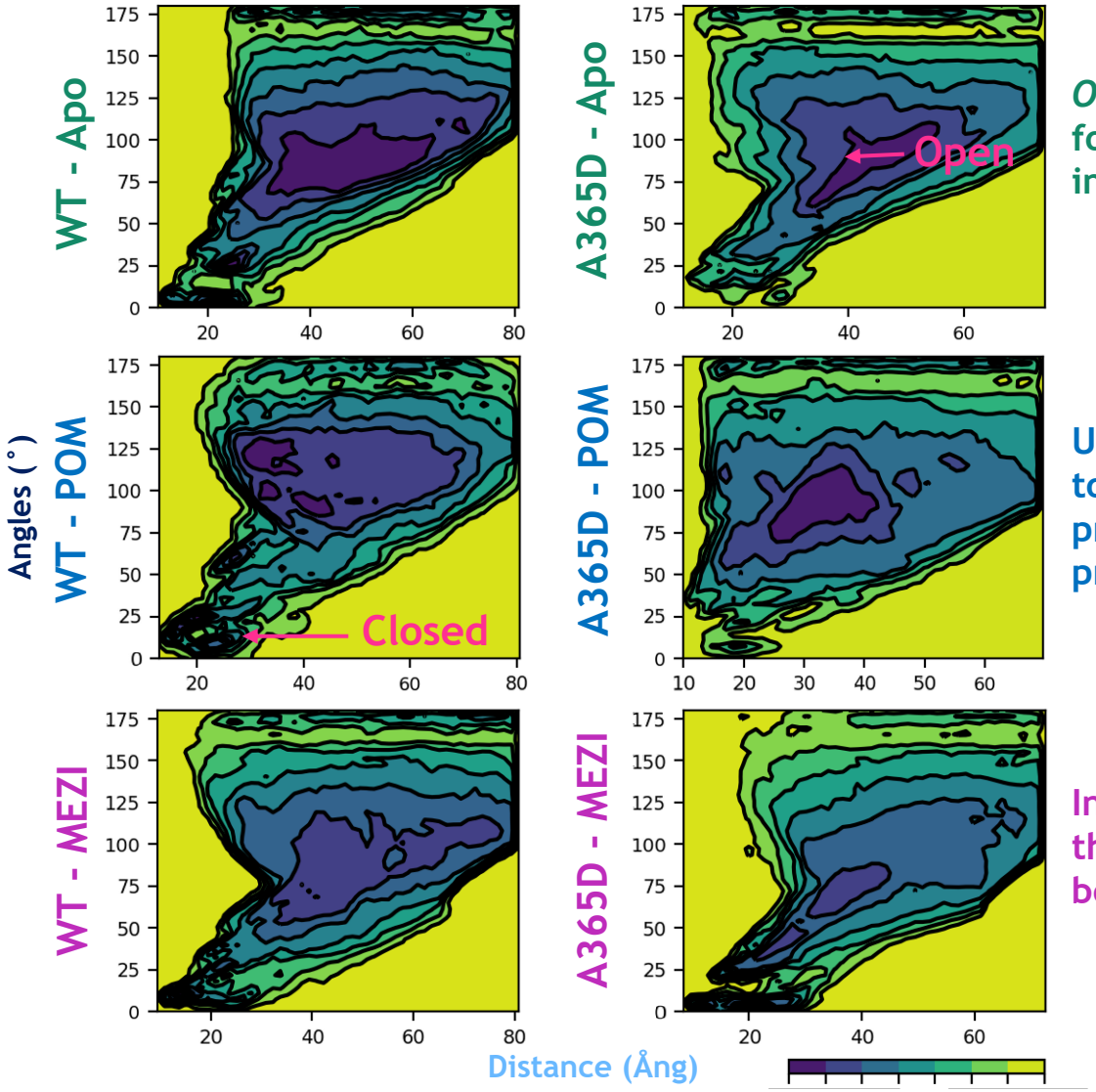
Interface mutant disrupts CRBN-DDB1

- In the P277R mutant, mezigdomide can faithfully associate with CRBN, secure the closed, active confirmation and recruit Ikaros for ubiquitination
- The R309H mutation, sits at the interface of CRBN and DDB1 causing complex dissociation explaining the harsh effect in the ubiquitination experiment

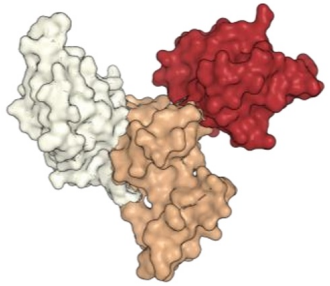
Metadynamics simulations series predict stabilization of closed state of the CRBN A365D mutant in the presence of mezigdomide

Metadynamics simulations help explore the energy landscapes for transition between open and closed conformations of CRBN

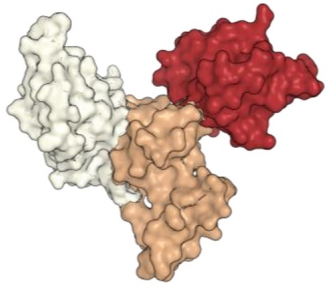




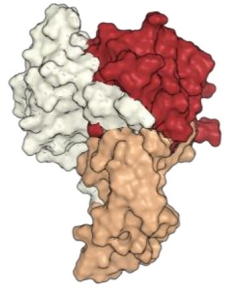
Open state is preferred for both WT and A365D in the apo condition



Unlike WT which shifts to closed state, A365D prefers *open* state in the presence of POM

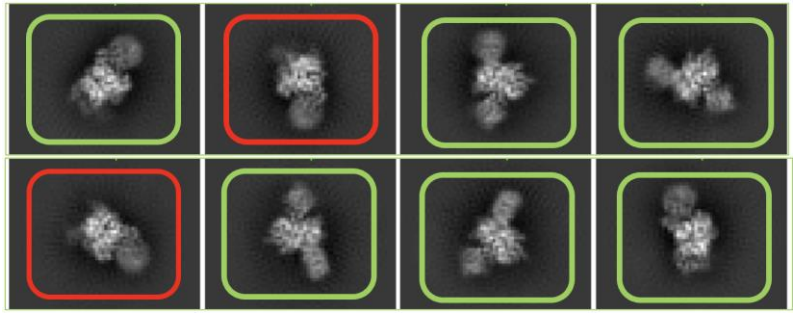


In the presence of MEZI, the *closed* conformation becomes stabilized

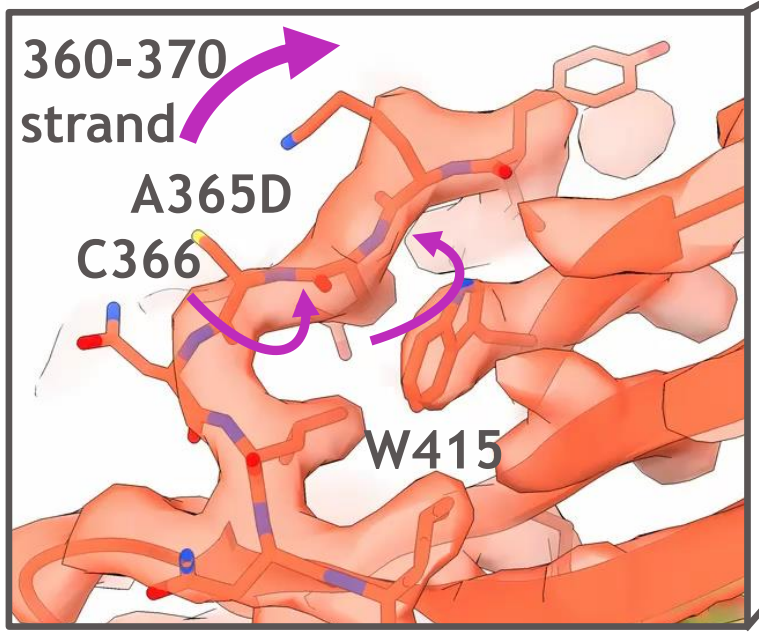


2.8Å cryoEM of A365D CRBN reveals dynamic reassembly

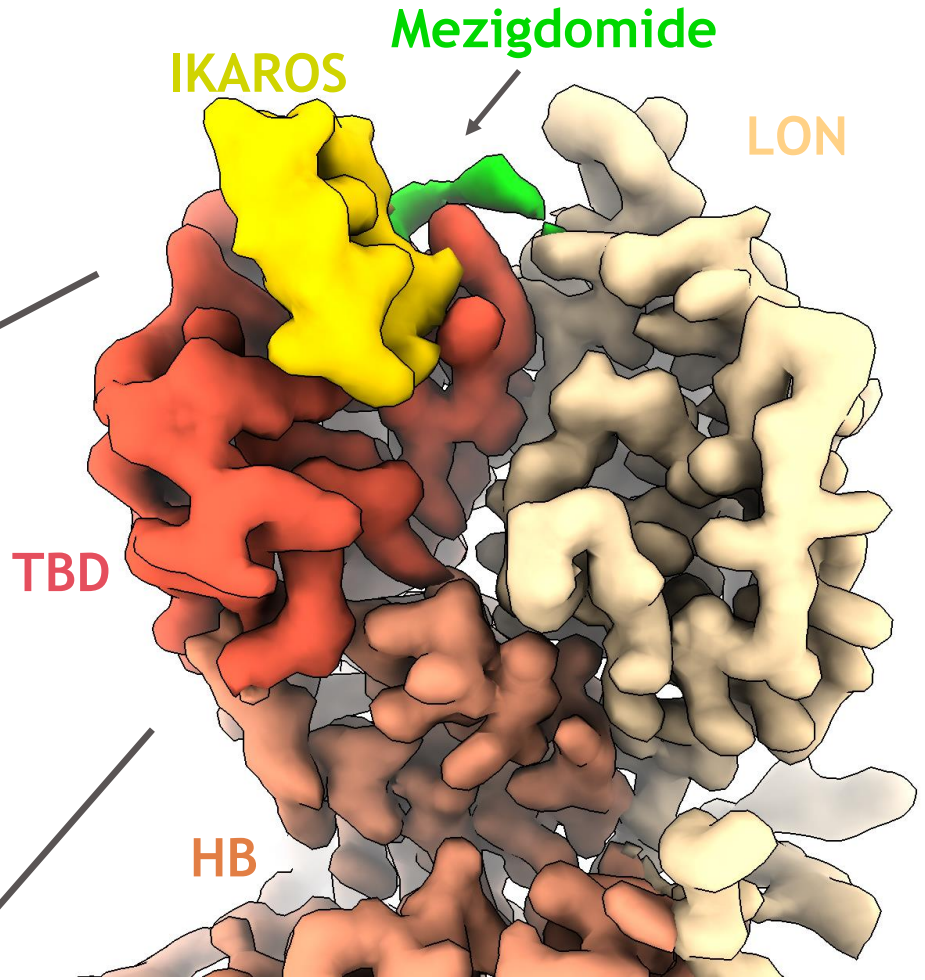
A365D mutant CRBN - mild "open"

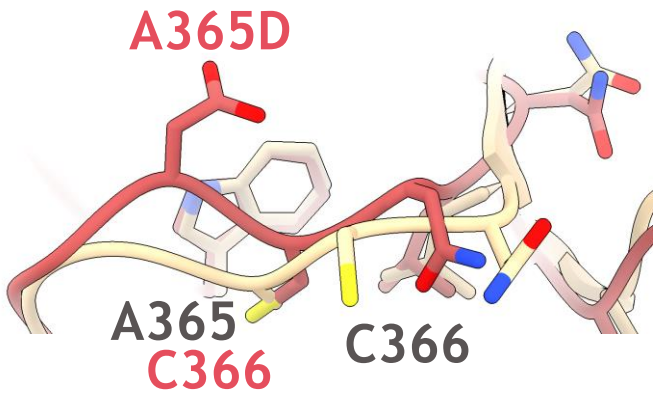


Dynamic reassembly movie



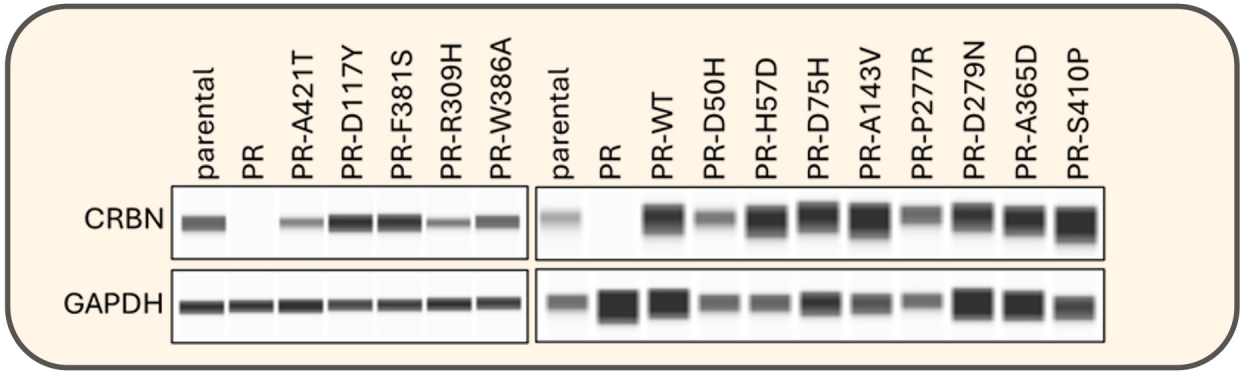
2.8Å CryoEM structure
A365D + Mezi + Ikaros

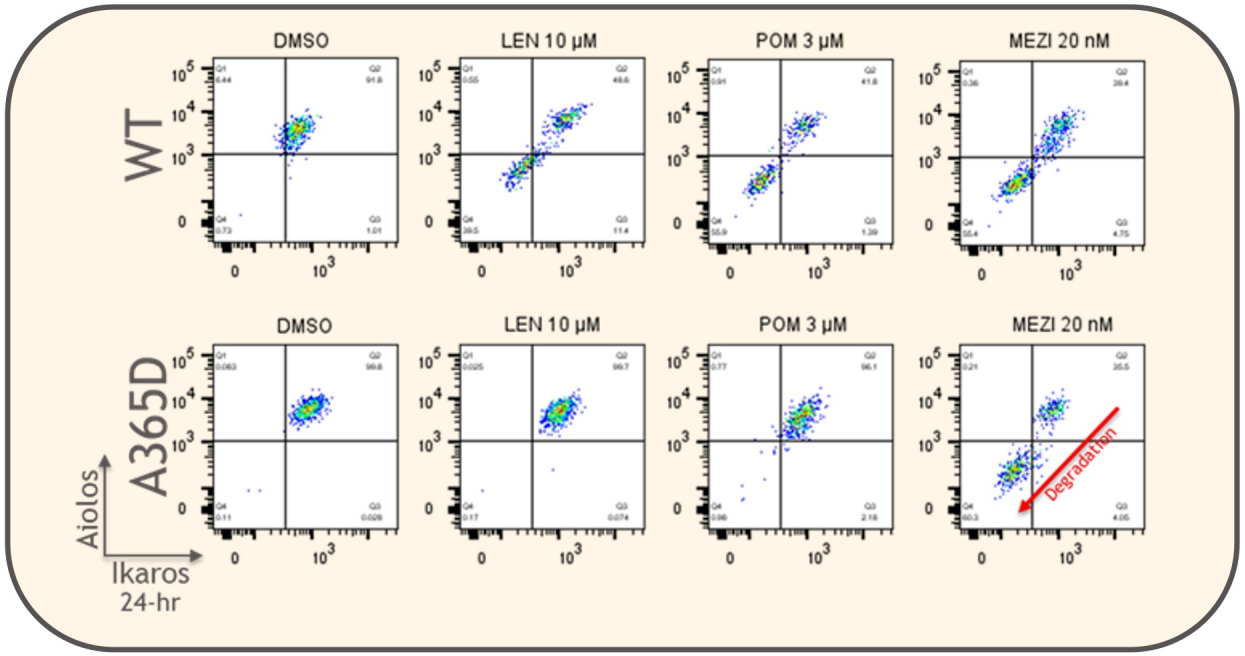


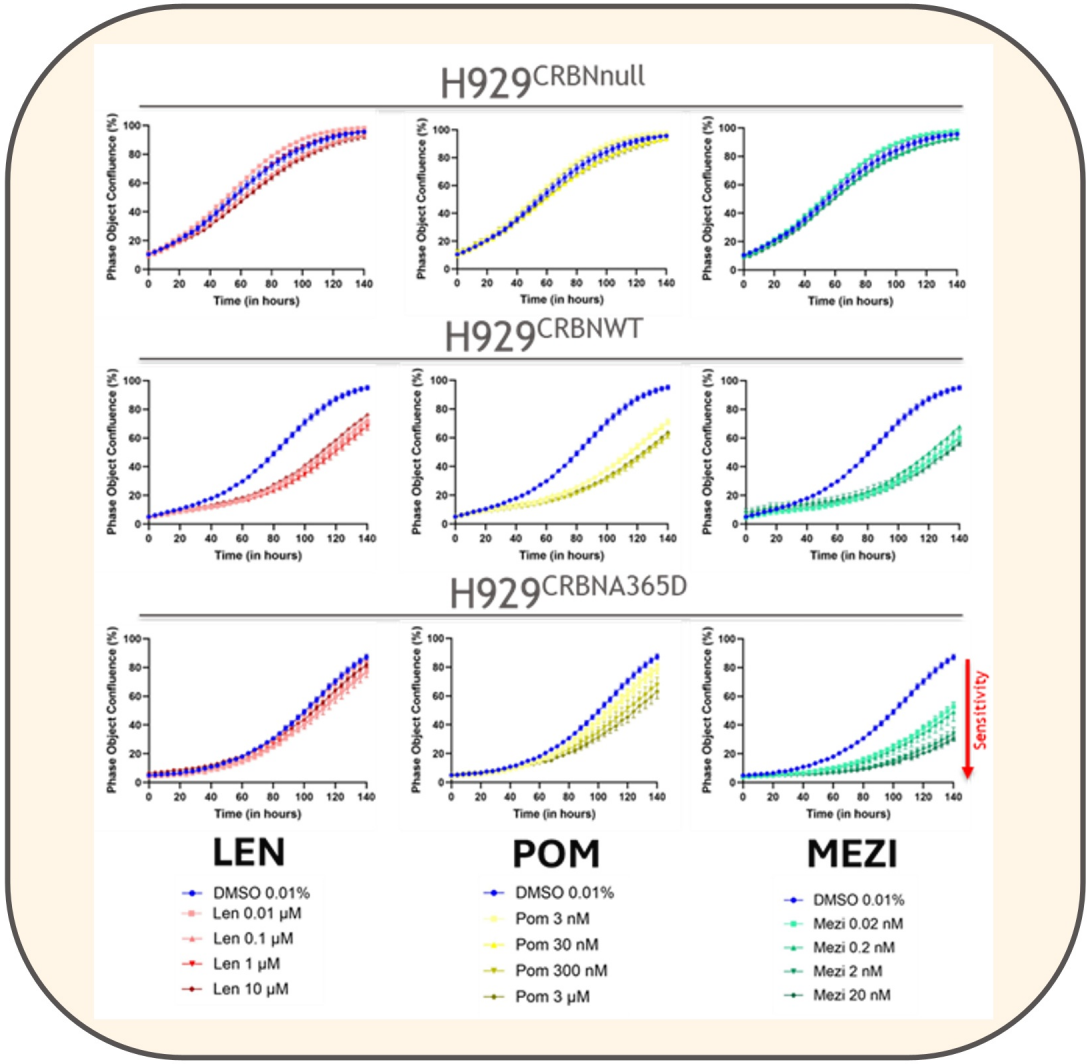


- A365D mutation is incompatible with the standard alanine placement in a small hydrophobic pocket – leading to reassembly to accommodate C366
- Mezigdomide largely drives assembly of active "closed" conformation
- **Mezigdomide associates with *compromised* cereblon and stabilizes the active form when the mutant is distal to the compound binding site.**

Mezigdomide maintains antitumor cytotoxicity in CRBN mutant models





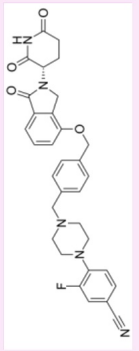


These observations collectively suggest that mezigdomide may overcome certain CRBN mutations where IMiDs may be ineffective

Summary and Conclusions

CELMoD agents have been designed based on a deep understanding of cereblon and MM biology

- These agents have shown superior anti-myeloma activity and immune modulation



CRBN dysregulation incidence increases over prior clinical exposure to IMiD agents

CRBN mutations are rare and heterogenous (no hotspots)

- In silico, biochemical and structural modelling of *CRBN* mutations reveals distinct classes of potential functional impact
- Most mutations have no functional impact on IMiD/CELMoD MoA
- Rare mutations can render all *CRBN* binding molecules inactive
- Mezigdomide can overcome certain *CRBN* mutations where IMiD agents show no activity

Immunomodulatory activity may still be present with deleterious *CRBN* mutations in the tumor