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ABSTRACT #573

Novel Multifunctional Degraders of EP300/CBP and IKZF1/3 with Potent Anti-Myeloma Activity

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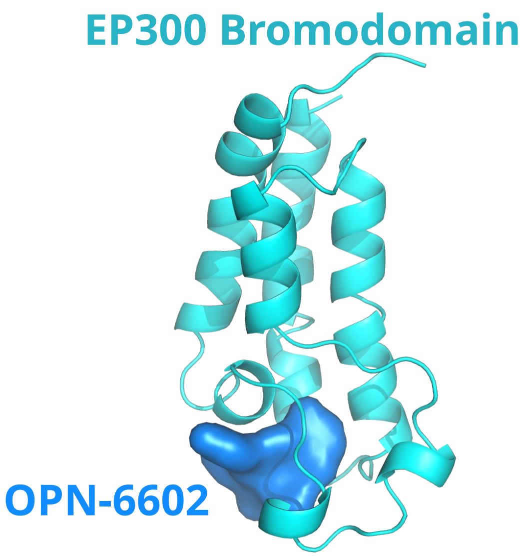
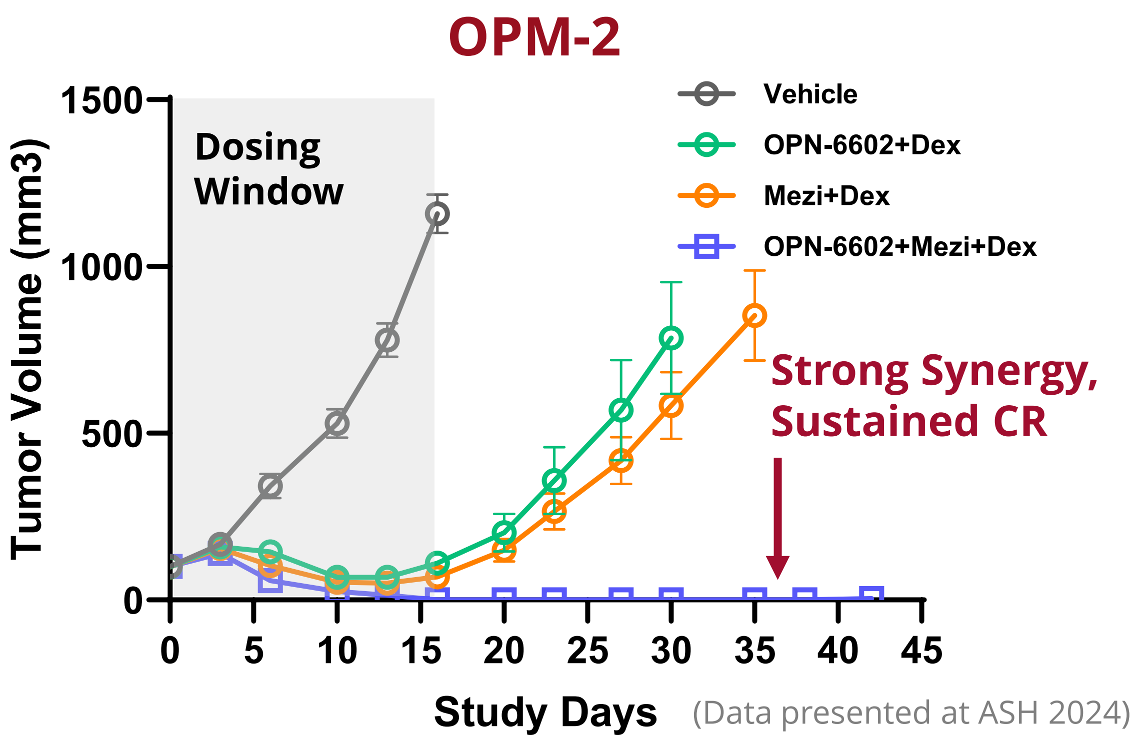
Opna Bio

OPN-6602 and IMiDs Downregulate Key Multiple Myeloma (MM) Drivers, IRF4 and MYC

- IMiDs cause degradation of IKZF1/IKZF3 (Ikaros/Aiolos) and consequently downregulate IRF4 and MYC
- EP300/CBP inhibition can overcome resistance to IMiDs by orthogonally blocking IRF4 and MYC
- OPN-6602 is an oral small molecule EP300/CBP bromodomain inhibitor
  - Currently being evaluated in a Phase 1 study (NCT06433947) in patients with relapsed/refractory MM

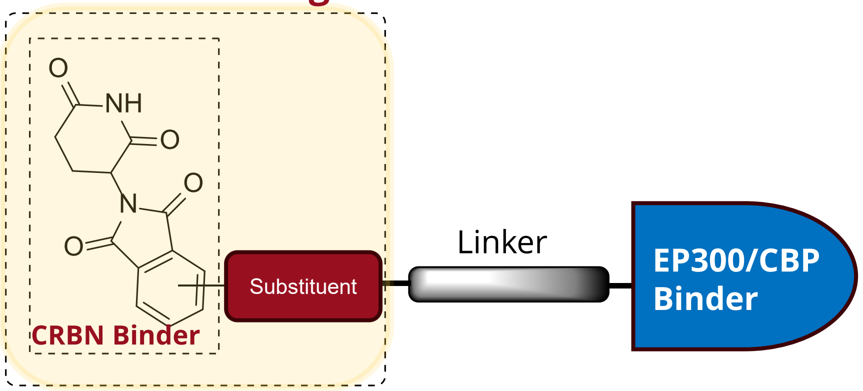


OPN-6602 and Mezigdomide Exhibit Strong *In Vivo* Synergy in MM Models



- **Hypothesis:** Combining both activities in one compound will achieve potent <u>single agent anti-tumor activity</u>

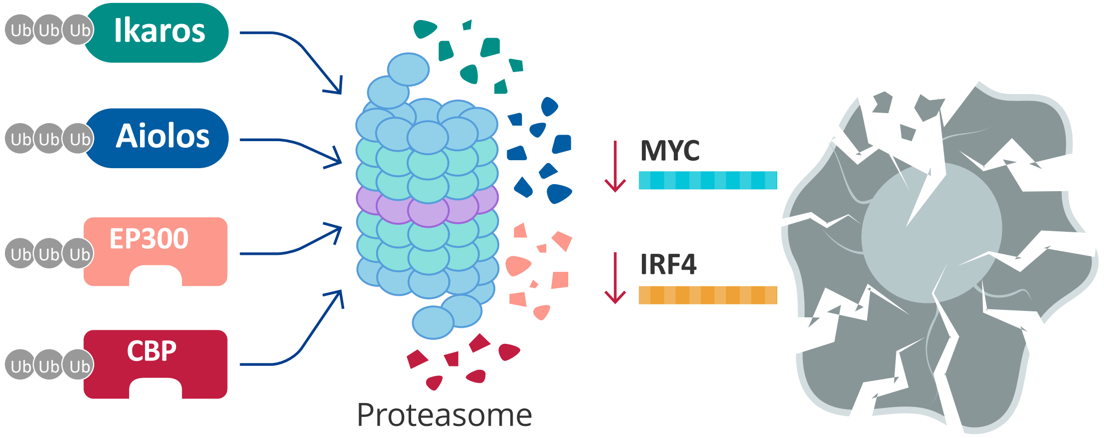
Multifunctional Degraders Concurrently Target EP300/CBP and Ikaros/Aiolos ➔ Potent Single Agent Anti-Tumor Activity



IMiD-like Warhead
Degrades Ikaros/Aiolos

OPN-6602-like Warhead
Degrades EP300/CBP

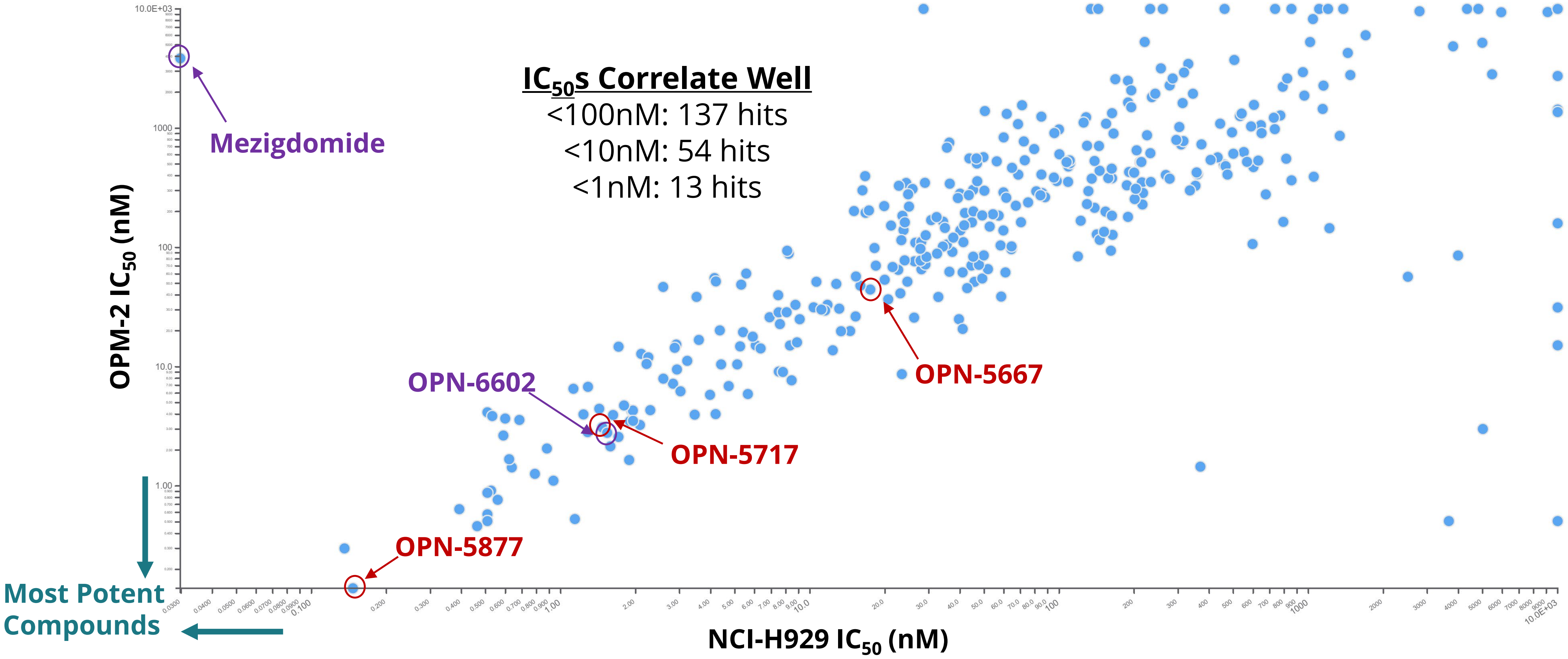
Single Agent Hyperactive Anti-Myeloma Drug



Cancer Cell Death

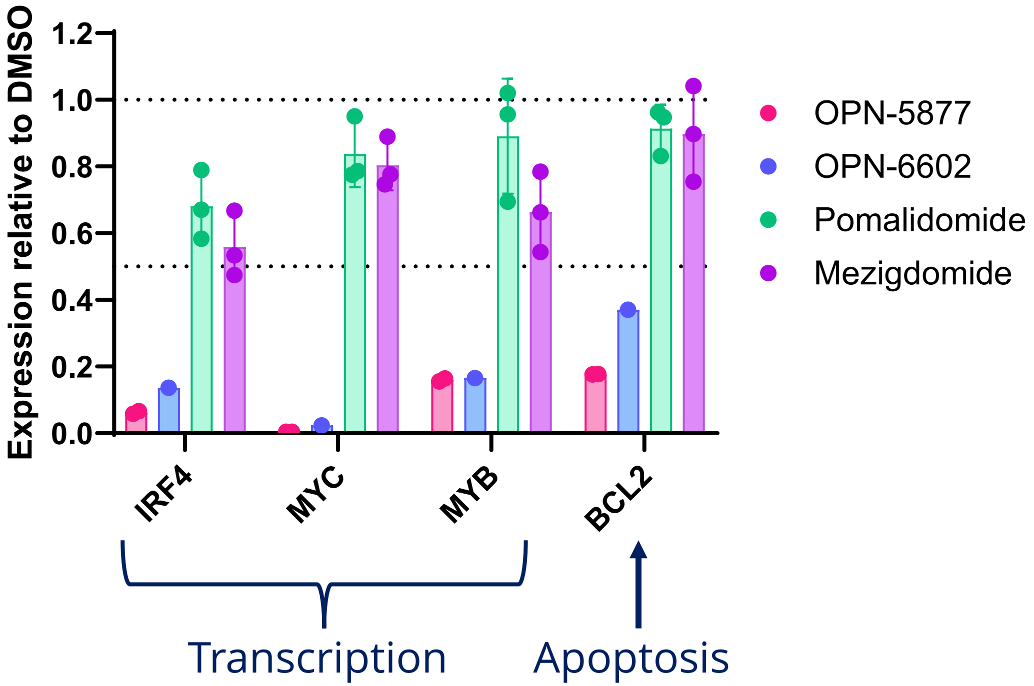
Potent Degraders Impair OPM-2 and NCI-H929 MM Cell Proliferation

- 370 compounds profiled to date

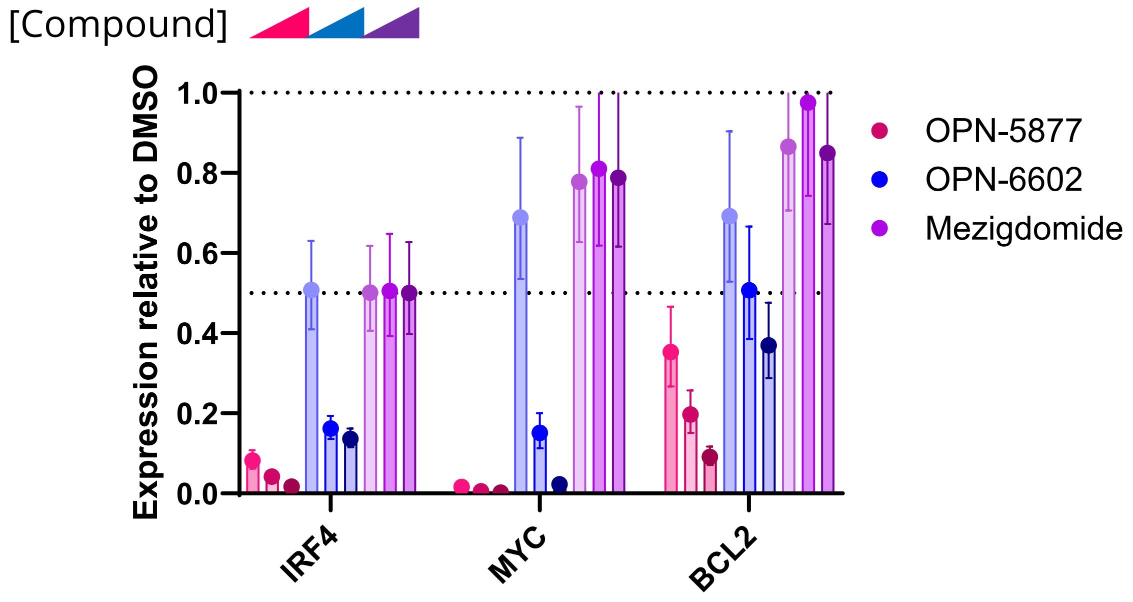


OPN-5877 Exerts Differentiated Transcriptional Effects on *IRF4*, *MYC*, *MYB*, and *BCL2*

Effects on Target Genes at 100 nM

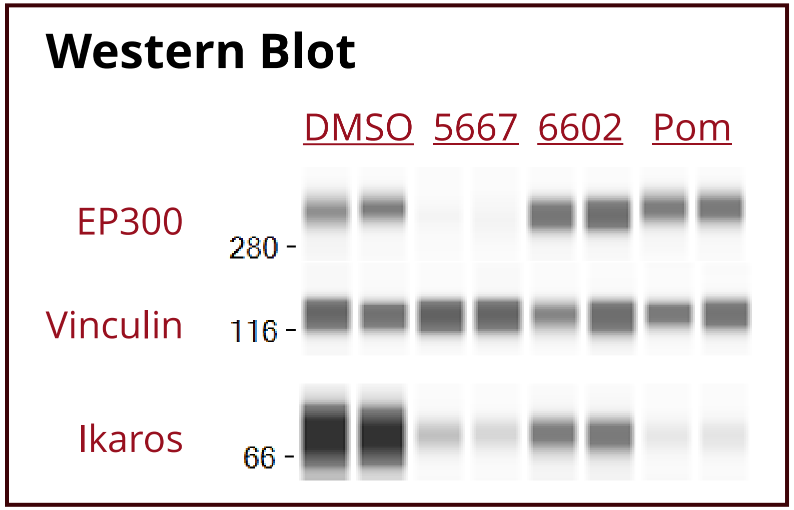


Dose Response: 1, 10, 100 nM

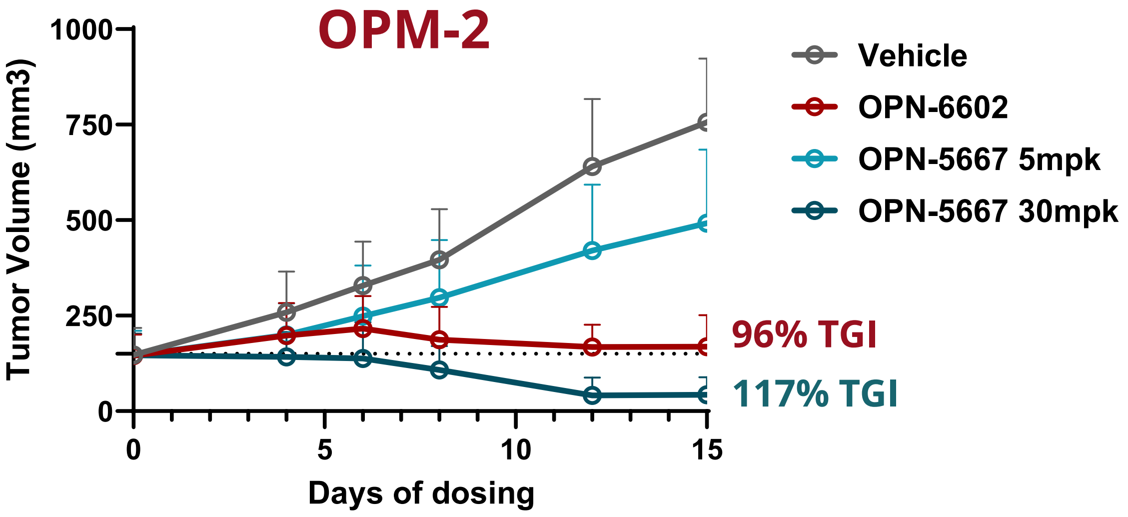


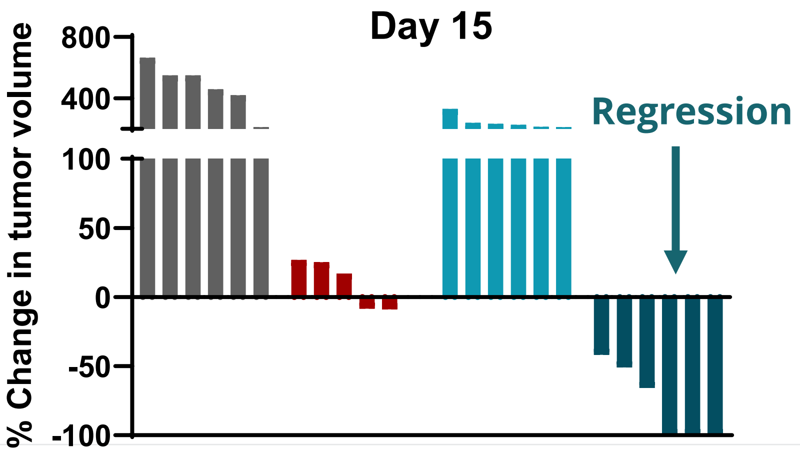
OPM-2, 6hr treatment

OPN-5667 Results in Xenograft Tumor Regression



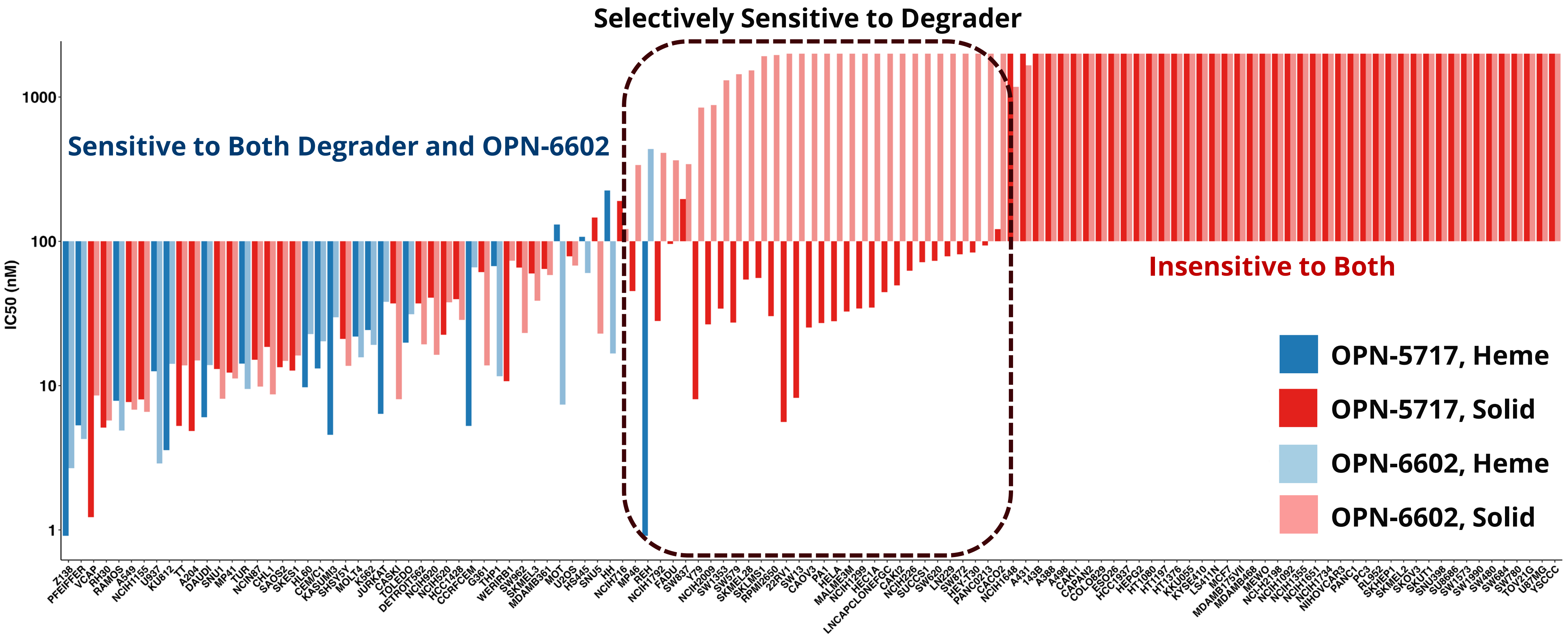
Jurkat, 100nM, 24hr





OPN-5717 Shows Broader Cellular Activity Compared to OPN-6602

- 20 heme and 99 solid tumor cell lines



Chemistry Improves Potency, Oral Bioavailability, and Tolerability *In Vivo*

Potency

Compound	OPM-2 IC50 (nM)	EP300 HiBiT DC50 (nM)	Ikaros HiBiT DC50 (nM)	PBMC IC50 (nM)	*In Vivo*	Oral
OPN-0001	<0.5	0.4	0.02	>10e3	Moderate	-
OPN-0002	<0.5	0.4	0.04	>10e3	TBD	-
OPN-5877	0.1	7	0.1	>10e3	Toxic	+
OPN-0003	0.3	10	1.0	40	Toxic	-
OPN-0004	0.8	32	1	>10e3	Active	-
OPN-0005	0.9	15	0.7	24	Moderate	+
OPN-0006	1	31	0.8	6	Toxic	+
OPN-0007	1	15	1	135	Active	+
OPN-6602	2.8	>1e3	50	>10e3	Active	+
OPN-0008	3	>313	2	>10e3	Moderate	-
OPN-0009	8	183	5	>10e3	TBD	-
OPN-0010	21	16	65	>10e3	Moderate	-
OPN-5667	35	15	20	>10e3	Active	-

TBD: To Be Determined

Multifunctional Degraders Summary

- Concurrently degrade EP300/CBP and Ikaros/Aiolos in the same cancer cell
- Achieve potent single agent anti-myeloma activity
- Exert differentiated transcriptional effects on *IRF4*, *MYC*, and *BCL2*
- Demonstrate activity in solid tumor cell lines
- Medicinal chemistry campaign to improve pharmacological properties is in progress
    - Lead candidate selection mid-2026

Acknowledgement

Opna Bio Team

Discovery and Preclinical

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Slides will be available on opnabio.com