OPN-6602, a potent dual EP300/CBP bromodomain inhibitor, targets multiple myeloma through concomitant suppression of IRF4 and MYC

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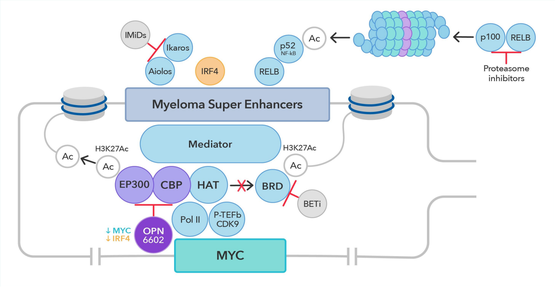
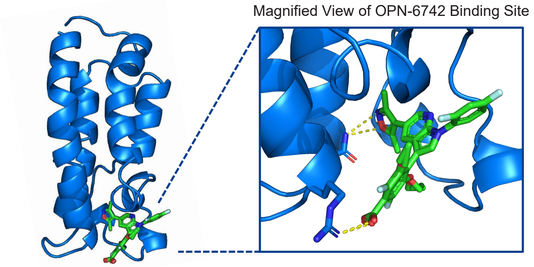
OPN-6602 downregulates IRF4 and MYC in Multiple Myeloma Cells



E1A Binding Protein P300 (EP300) and CREB Binding Protein (CBP) are transcriptional co-activators that contain both epigenetic writer histone acetyltransferase (HAT) and reader bromodomains (BRD) that regulate transcription of genes via chromatin remodeling. EP300/CBP inhibition causes cell cycle arrest and apoptosis in multiple myeloma (MM) cells through suppression of interferon regulatory factor 4 (*IRF4*) and concomitant repression of *MYC*, highlighting the rationale for targeting EP300/CBP as a novel target for MM[a,b]. OPN-6602 is a potent, orally active small molecule EP300 and CBP inhibitor. OPN-6602 demonstrates potent in vitro and in vivo anti-MM activity. As a potent inhibitor of EP300/CBP, OPN-6602 has the potential to overcome standard-of-care resistance mechanisms of MM and has great potential to combine with other therapeutic agents.

[a] de Matos Simoes et al., *Nat Cancer* 2023; [b] Welsh et al., *Blood Cancer Discov* 2024

Crystal Structure of OPN-6742 bound to EP300

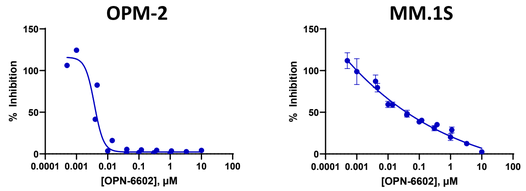


The crystal structure of EP300 BRD (residues 1047-1161) bound to OPN-6742 (analog of OPN-6602) was solved to 1.7Å resolution. OPN-6742 binds a predominantly hydrophobic pocket distal to the N- and C-termini and formed by three helices. Two key polar interactions were identified, Asn1132 and Arg1137, which help to anchor OPN-6742 and OPN-6602 in the binding pocket.

RESULTS

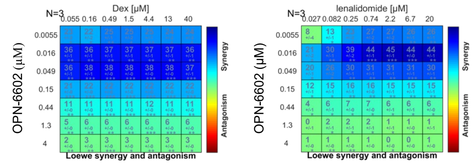
OPN-6602 as a dual EP300/CBP inhibitor for MM

Compound	Biochemical IC_{50} (nM)			Proliferation (nM)	
	EP300	CBP	BRD4	OPM-2	MM.1S
OPN-6602	27	31	>8000	4.1	47



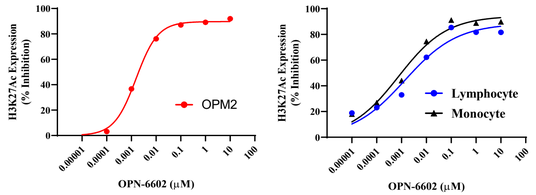
OPN-6602 was evaluated for the ability to inhibit the binding of acetylated histone peptides by the BRDs of EP300 and CBP in a protein-ligand interaction assay. OPN-6602 has low nanomolar activity against EP300/CBP with >200-fold less activity against BRD4 (IC50 >8000 nM) and potently inhibits MM1.S and OPM2 cell growth. By SPR, the Kd is 870 pM, with a fast on-rate and slow off-rate yielding a residence time of 13 min (data not shown).

Combination of OPN-6602 with dexamethasone or lenalidomide exhibits synergy in MM1.S growth inhibition



Dexamethasone (dex) and lenalidomide (len) as a monotherapies have limited effects in inhibiting the growth of these cells. Maximal growth inhibition reached 60–75% following dex treatment and only reached 30–40% following len treatment. A significant proportion of cells could survive dex or len treatment even when compounds were used at high concentrations. OPN-6602 in combination with dex or len demonstrated strong synergism in MM .1S cells.

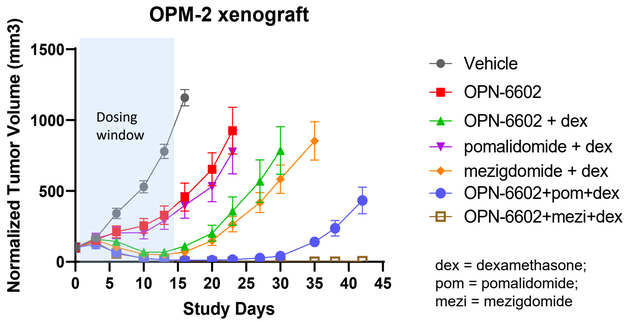
OPN-6602 inhibits H3K27Ac in OPM-2 and PBMCs



Assay	Cells	IC50 (nM)
H3K27Ac Flow Cytometry	OPM-2	1.6
	Monocyte	0.75
	Lymphocyte	1.4

The effect of OPN-6602 in regulating H3K27Ac expression, a marker of histone acetylation, was evaluated in the OPM-2 human MM cell line and human peripheral blood mononuclear cells (PBMCs) isolated from a healthy blood donor. OPN-6602 demonstrated potent inhibition of H3K27Ac in all of these cells.

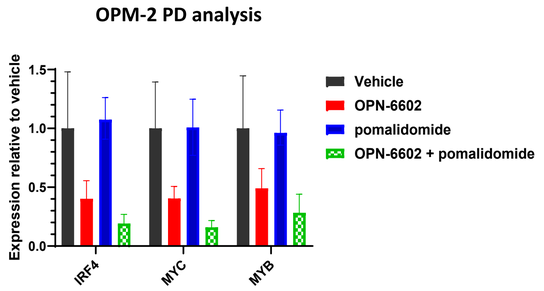
Synergy observed between OPN-6602 and dexamethasone, pomalidomide, or mezigdomide in MM OPM-2 xenograft model



dex = dexamethasone;
pom = pomalidomide;
mezi = mezigdomide

OPN-6602 synergistic effects are observed in the OPM2 xenograft model. OPN-6602 as a single agent suppressed tumor growth (71% TGI). The combination of OPN-6602+dex resulted in increased anti-tumor activity (>100% TGI) with 3 out of 6 mice having tumor regressions. OPN-6602+dex+pom and OPN-6602+mezi+dex exhibited increased anti-tumor activity with 6 out of 6 mice having tumor regressions (>100% TGI). Dosing for all groups was stopped on day 13 to monitor the duration of response. The triplet of OPN-6602+pom+dex resulted in a sustained duration of response up to day 30, whereas the OPN-6602+mezi+dex exhibited a longer sustained duration of response > 42 days.

OPN-6602 exhibits down-regulation of *MYC*, *IRF4*, and *MYB*



In the OPM-2 xenograft model, the pharmacodynamic analysis of tumors harvested 4 hours after 3 days of dosing reveals significant down-regulation of *MYC*, *IRF4*, and *MYB* following OPN-6602 treatment. No significant effects were observed with 2.5 mg/kg pomalidomide treatment. Synergistic effects with further reduction in *MYC*, *IRF4* and *MYB* gene expression was observed with the OPN-6602+pomalidomide combination.

CONCLUSIONS:

- OPN-6602 is an orally bioavailable small molecule dual EP300/CBP inhibitor with antitumor activity in multiple myeloma (MM)
- OPN-6602 is highly potent and selective, enabling notable combinability with other agents
- OPN-6602 is highly efficacious in reducing MM cell growth through the inhibition of bromodomain and subsequent inhibition of histone acetylation
- In the preclinical human derived MM models OPN-6602 suppresses tumor growth with synergistic effects observed in combination with dexamethasone, pomalidomide, and mezigdomide
- Further development of OPN-6602 as a single agent and in combination with other standard-of-care agents in multiple myeloma and other oncology indications is planned
- A first-in human study of OPN-6602 in multiple myeloma patients is scheduled to start in 2024

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