OPN-6602, an Orally Bioavailable EP300/CBP Bromodomain Inhibitor, Targets Multiple Myeloma through Suppression of IRF4 and MYC

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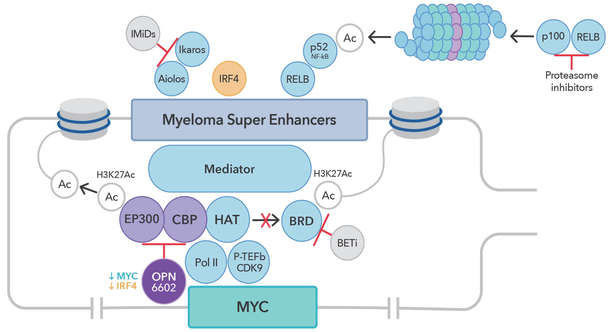
Publication number: 1908

OPN-6602 downregulates IRF4 and MYC in Multiple Myeloma cells



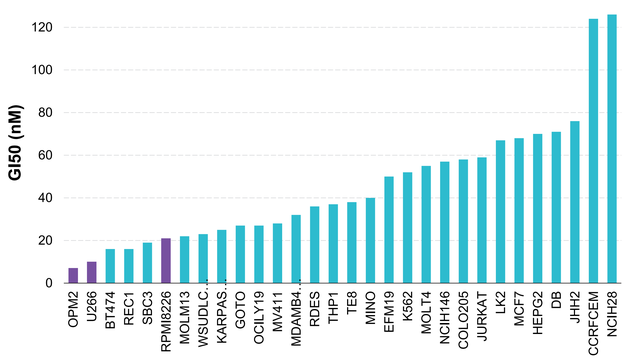
E1A Binding Protein P300 (EP300) and CREB Binding Protein (CBP) are transcriptional co-activators that contain both epigenetic 'writer' histone acetyltransferase (HAT) and 'reader' bromodomains (BRD) that regulate transcription of genes via chromatin remodeling. EP300/CBP inhibition causes cell cycle 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[2,3]. 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 in MM and has the potential to combine with other therapeutic agents.

[2] de Matos Simoes et al., *Nat Cancer* 2023; [3] Welsh et al., *Blood Cancer Discov* 2024

Multiple Myeloma cell lines are highly sensitive to OPN-6602

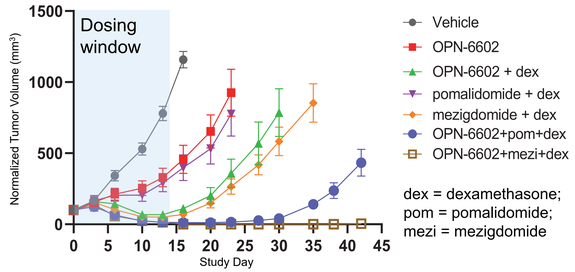
Drug sensitivity (GI50) to OPN-6602 highlighting most sensitive among 91 cell lines tested
<250nM- sensitive (16 of top 30 represent Heme Malignancies)

3 of top 6 are Multiple Myeloma cells



RESULTS

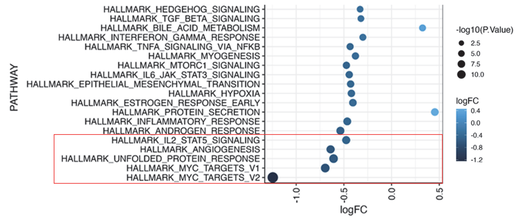
Synergy observed between OPN-6602 and dexamethasone, pomalidomide, or mezigdomide in MM OPM-2 xenograft model



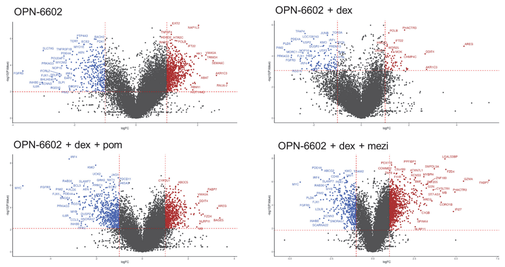
dex = dexamethasone; pom = pomalidomide; mezi = mezigdomide

In the OPM-2 xenograft model, OPN-6602 as a single agent suppressed tumor growth (71% tumor growth inhibition(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+dex mezi 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 out to 42 days, when the study was concluded.

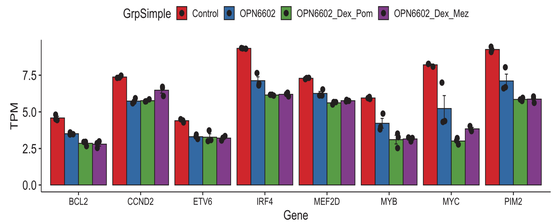
RNA-seq analysis of OPM-2 tumors reveals significant downregulation of MYC, IL2-STAT5 signaling, and androgen response following treatment with OPN-6602



Significant global transcriptome changes with OPN-6602



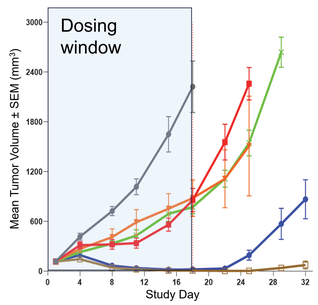
OPN-6602 cooperates with pomalidomide and mezigdomide to down-regulate key genes including *MYC*, *IRF4*, and *MYB in OPM-2 tumors*



The expression changes in response to OPN-6602 treatment and its combination with pom or mezi were further investigated. Genes such as *BCL2, CCND2, ETV6, IRF4, MEF2D, MYB, MYC*, and *PIM2* exhibited reduced expression following OPN-6602 treatment, with even greater downregulation observed when combined with pom or mezi. The significant downregulation of these genes following OPN-6602 treatment suggests that these genes play a critical role in the treatment response. The further downregulation observed with combination therapies indicates a potential synergistic effect.

Synergy, including complete regressions, observed between OPN-6602 and dexamethasone and/or mezigdomide in the MM1.S xenograft model[3]

MM1.S xenograft

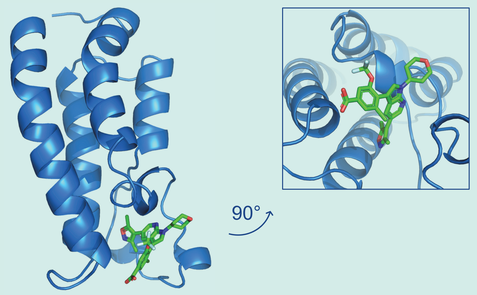


Treatment	%TGI on day 18	Tumor Regression
Vehicle	0	NA
OPN-6602	65	0/6
mezi	64	1/6
mezi +dex	69	0/6
OPN-6602+mezi	105	6/6
OPN-6602+dex+mezi	105	6/6

During the 18-day dosing period OPN-6602 in combination with mezi+dex increased anti-tumor activity, resulting in 100% TGI with 6/6 animals having tumor regressions. Duration of response was substantially increased in groups with both OPN-6602 and mezi. The results were comparable in the absence of dex and tolerability was improved.

[3] Study conducted in collaboration with Translational Drug Development (Scottsdale, AZ)

Co-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.

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 down-regulation of key genes such as MYC, IRF4, MYB, PIM2, MEF2D, ETV6, BCL2, CCND2 in the OPM-2 xenograft model
- In 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 in combination with other standard-of-care agents in multiple myeloma is planned
- OPN-6602 phase 1 clinical trial in patients with multiple myeloma is currently enrolling (NCT06433947)

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