OPN-6602, a dual EP300/CBP bromodomain inhibitor modulates androgen-driven transcription in mCRPC

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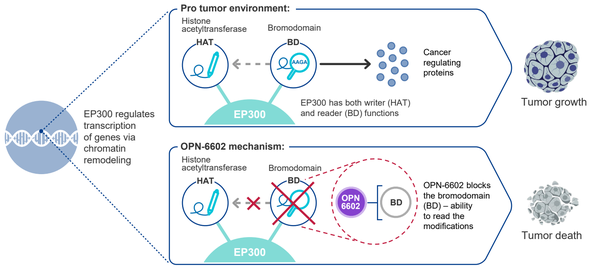
OPN-6602 and OPN-6742 downregulate the androgen receptor (AR) pathway



OPN-6602 and OPN-6742 are potent, orally active small molecule dual E1A Binding Protein P300 (EP300) and CREB Binding Protein (CBP) inhibitors. OPN-6602 and OPN-6742 regulate gene transcription via chromatin remodeling. Histone acetyltransferase (HAT) EP300 is a transcriptional coactivator of androgen receptor (AR). EP300 bromodomain (BRD) inhibition partially blocks its HAT activity, reducing AR-mediated gene expression and tumor growth.

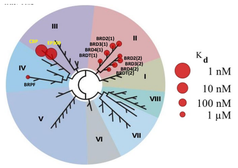
Mechanism of Action in metastatic Castration-Resistant Prostate Cancer (mCRPC): EP300 is an attractive target in mCRPC as it mediates AR-dependent and -independent transcription factor function. OPN-6602 and OPN-6742 abrogate persistent AR signaling in mCRPC by modulating H3K27 acetylation and the recruitment of EP300, AR-FL, and AR-v7 to AR response elements. OPN-6602 and OPN-6742 inhibit EP300 bromodomain activity leading to downregulation of the AR pathway and to anti-tumor effects in AR dependent mCRPC.

Potent EP300/CBP AR-dependent inhibition and selectivity against other bromodomains with OPN-6602 and OPN-6742

Compound	Biochemical (nM)			Cellular				
				Acetylation (nM)	Proliferation (nM)			
	EP300	CBP	Selectivity BRD4	LK2 H3K27Ac	VCaP	LNCaP	22rV1	DU145
OPN-6742	13	18	277	51	146	392	2,663	5,425
OPN-6602	28	31	>286	7	6	6	940	>10,000

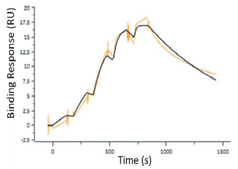
Dual EP300/CBP BRD inhibition by OPN-6602 and OPN-6742 based on biochemical screens using AlphaScreen technology. Cell viability was measured using CellTiter Glo. Both compounds show an AR-selective mode of action with anti-proliferative activity in AR-dependent prostate cancer cell lines (e.g. VCaP, LNCaP, and 22Rv-1) but are inactive against AR-negative prostate cancer cell lines (e.g. DU145).

OPN-6602 BROMOscan



DiscoverX TREESpot of OPN-6602 evaluated against 40 BRDs. Selectivity for EP300/CBP against BRD2, 3, and 4 is >100-fold.

OPN-6602 Sensorgram

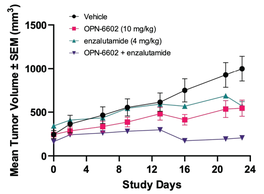


Compound	OPN-6602
Koff (1/s)	1.3E-03
KD (nM)	0.87
Residence Time (mins)	13
T1/2 (mins)	8.8

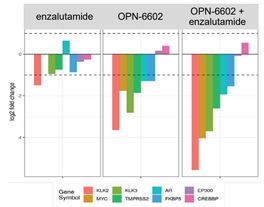
OPN-6602 sensorgram from surface plasmon resonance (SPR) analysis. OPN-6602 displayed high affinity for EP300 bromodomain (KD = 0.87 nM) as a result of having a fast on-rate and slow off-rate.

RESULTS

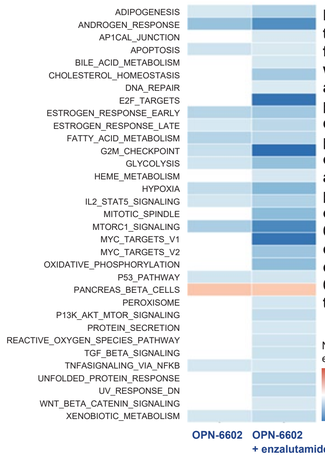
Synergy between OPN-6602 and enzalutamide in mCRPC PDX with corresponding pharmacodynamic responses



Patient-derived xenograft (PDX) of CRPC post-ADT treatment, AR-V7+, combination of OPN-6602 (10mg/kg) + enzalutamide (4mg/kg) resulted in strong efficacy with 3 out of 5 mice having tumor regressions (>100% TGI) at day 23. Single agent groups, OPN-6602 (10 mg/kg) and enzalutamide (4 mg/kg) resulted in ~55% TGI at day 23.

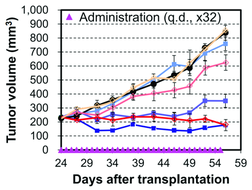


OPN-6602 caused significant downregulation of AR signature genes (KLK2, KLK3, FKBP5, and TMPRSS2) with strongest alteration in the OPN-6602 + enzalutamide combination group. Alterations of AR pathway genes with enzalutamide single-agent treatment were not observed.



RNA-seq analysis of tumor samples collected from the CRPC PDX study with gene enrichment analysis on hallmark pathways. Significant downregulation of AR pathway genes was observed. More cell cycle and metabolism related pathway alterations occurred with the OPN-6602 + enzalutamide combination treatment compared to the OPN-6602 single-agent treatment.

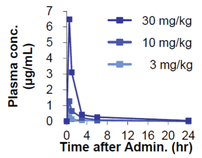
Dose-dependent anti-tumor activity in VCaP xenograft model with OPN-6602 and OPN-6742



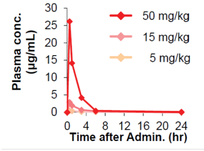
Compd.	Dose (mg/kg)	TGI (%)	TGIn (%)
Control	-	-	-
OPN-6602	3	9	13
	10	58	81
	30	79	108
OPN-6742	5	-2	-3
	15	26	36
	50	79	109

OPN-6602 and OPN-6742 treatment resulted in dose-dependent antitumor activity in a VCaP Xenograft in castrated mice.

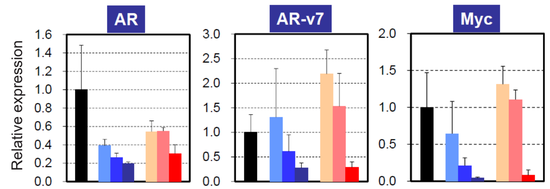
OPN-6602



OPN-6742



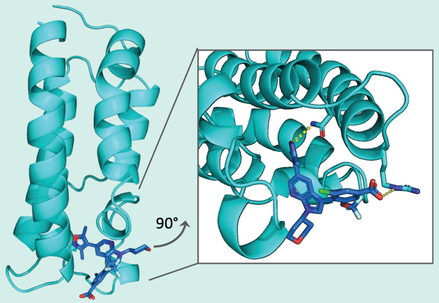
Pharmacokinetic profiles show a high Cmax and short half-life following oral administration of OPN-6602 and OPN-6742 in mice.



PD biomarker response 6 hrs after final administration showed reduction of gene expression of AR, AR-v7, Myc and

AR-regulated genes with both OPN-6602 and OPN-6742 treatments.

Crystal structure of OPN-6742 bound EP300



The crystal structure of EP300 BRD (residues 1047-1161) bound to OPN-6742 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 in the binding pocket.

CONCLUSIONS:

- OPN-6602 and OPN-6742 are orally bioavailable, highly potent and selective EP300/CBP inhibitors.
- Based on safety, PK, and preclinical animal model data, OPN-6602 is favored for oral once daily dosing.
- In the preclinical human mCRPC models OPN-6602 suppresses tumor growth.
- RNA profiling shows a marked, dose-dependent, pharmacodynamic response indicative of EP300/CBP inhibition.
- Further development of OPN-6602 as a single agent and in combination with other agents in mCRPC and other oncology indications is planned.
- A first-in human study of OPN-6602 in cancer patients is scheduled to start in 2024.

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