#2615

Antitumor Activity of a Dual PI3K and HDAC Inhibitor in Hematologic Cancer Models

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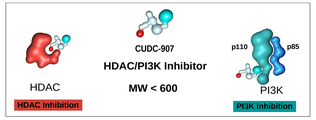
Rationale and Design of Single Molecule HDAC-PI3Ki

- Multiple signaling pathways are de-regulated in cancer. Extensive cross-talk and redundancy exist. Therefore, network disruption is needed to achieve maximum efficacy.
- Blocking PI3K can up-regulate other survival signaling pathways which in turn can be overcome by HDAC inhibition via epigenetic regulation.
- Synergistic effects can be achieved by inhibition of both HDAC and PI3K in cancer cells as reported previously.



CUDC-907 Potency

- Enzymatic activity against PI3K isoforms (IC50, nM)

PI3Kα	PI3Kα H1047R	PI3Kα E545K	PI3Kβ	PI3Kδ	PI3K γ	mTOR
19	73	93	167	39	333	>2000

- Enzymatic activity against HDAC subtypes (IC50, nM)

Class	I				II						IV
HDAC	HDAC1	HDAC2	HDAC3	HDAC8	HDAC4	HDAC5	HDAC6	HDAC7	HDAC9	HDAC10	HDAC11
	1.7	5.0	1.8	191	409	674	27	426	554	2.8	5.5

CUDC-907 Potently Inhibits Proliferation of Hematologic Cancer Cell Lines in Vitro

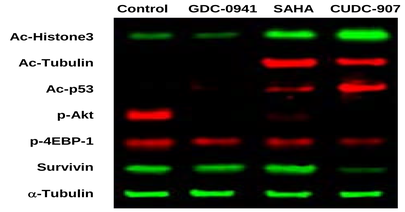
IC50 (μM)

Cancer Type and Cell Line		SAHA	GDC-0941	CUDC-907
ALL	MOLT-4	0.29	0.99	0.006
	SUP-B15	0.42		0.0007
AML	HL-60	0.7	0.71	0.007
	U937	0.41	1.17	0.007
	THP-1	>20	3.5	0.03
	MV-4-11	0.34	1	0.003
NHL	Pfeiffer	>20	0.41	0.009
	Raji	0.9	>20	0.03
	Daudi	>20	>20	0.012
CML	K562	>20	>20	0.44
	MEG-01	>20	>20	0.058
Multiple Myeloma	RPMI-8226	0.42	>20	0.007
	OPM-2	0.64	0.65	0.001
	ARH77	1.31	>20	0.018
Mouse LL	L1210	>20	>20	0.014
Mouse Lymphoma	P388 D1	>20	1.64	0.011

Reference compounds:
HADC inhibitor: SAHA (suberoylanilide hydroxamic acid)
PI3K inhibitor: GDC-0941

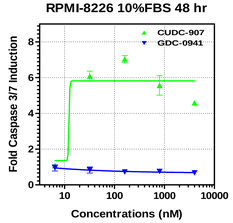
CUDC-907 Inhibits Both PI3K and HDAC, and Induces Apoptosis in Vitro

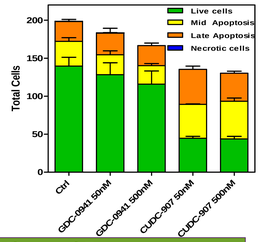
- Western blot analysis of Daudi (NHL), 16 Hrs of treatment, 1uM



- Flow cytometry analysis of multiple myeloma cell, 48 hrs of treatment

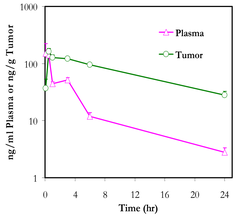
RPMI-8226 10%FBS 48 hr





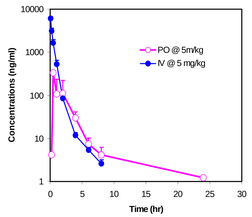
CUDC-907 PK in Mice and Dogs

PK in tumor-bearing mice 50mg/kg, PO



Parameters	Units	Plasma	Tumor
Half-Life	hr	5.9	10.1
Cmax	ng/ml	186	154
AUC	ng/ml*hr	478	2126
Bioavailability	%	7.8	14.8

PK in Beagle dogs 5 mg/kg, iv, PO

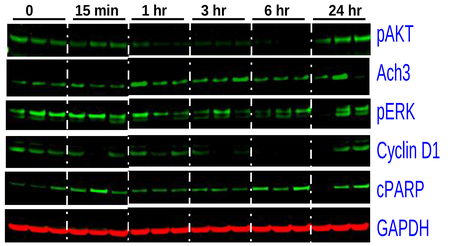


Parameters	Units	iv	PO
Half-Life	hr	1.85	4.88
Cmax	ng/ml	6156.16	312.1
AUC	ng/ml*hr	2977.47	450.04
Bioavailability	%		15.1

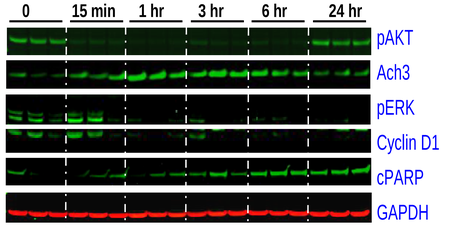
CUDC-907 Inhibits HDAC, PI3K, MEK-ERK Pathways and Induces Apoptosis in NHL Daudi Tumor Xenografts

- Western blot analysis of tumors collected at various time points following CUDC-907 treatment

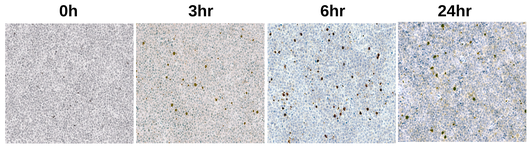
50 mg/kg, PO



100 mg/kg, PO

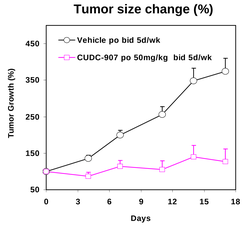


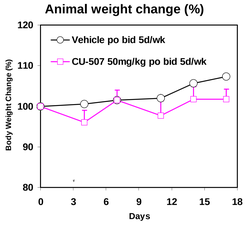
- IHC staining of cleaved caspase-3 in Daudi tumor after single dose CUDC-907 treatment (100 mg/kg, PO)



CUDC-907 Inhibits Tumor Growth in Daudi NHL Models

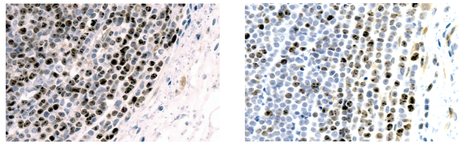
- Efficacy study in Daudi subQ xenografts





Pretreatment tumor size:341±112mm3

- IHC staining of Ki-67 in CUDC-907 treated Daudi tumor



Conclusions

- CUDC-907 is a dual inhibitor of HDAC and PI3K. It not only inhibits the PI3K-AKT pathway, but also suppresses other vital signaling pathways, and induces apoptosis in cancer cells via epigenetic modification.
- CUDC-907 displays greater anti-proliferation potency against human hematologic cancer cell lines than reference compounds.
- CUDC-907 is orally bioavailable in animals, and displays antitumor activity in PD and efficacy studies in hematologic cancer models with favorable safety profile.
- CUDC-907 disrupts cancer signaling networks, which therefore may overcome limitations of other PI3K-mTOR or HDAC single target inhibitors.
- CUDC-907 was selected as a development candidate.