#C-70

Antitumor Activity of CUDC-907, a Single Small Molecule Inhibitor That Targets Both Pi3K and HDAC, in Hematologic Cancer Models

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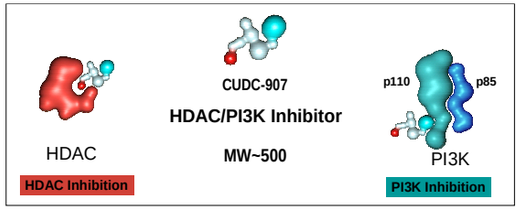
Rationale for a Single Molecule Targeting Hematological Cancers and, Design

- Both HDAC and PI3K are validated targets in hematological cancers.
- HDAC inhibition may overcome signaling pathway up-regulation following PI3K blockade by single target PI3K inhibitors.
- Therefore, inhibiting both targets achieves synergistic anti-tumor effects.

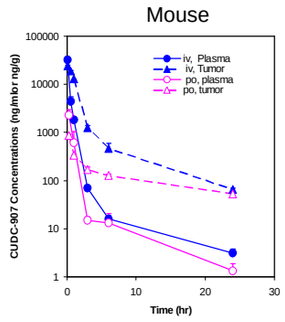


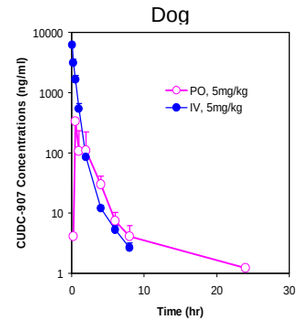
CUDC-907 Potently Inhibits Proliferation of Hematological Cancer Cell Lines in Vitro

IC50 (μM)

Cancer Type	Cell Line	IC50 (uM) SAHA	GDC-0941	SAHA + GDC-0941	CUDC-907	CAL-101	Known mutations
B cell lymphoma	Granta 519 (MCL)	3.02	>20	0.59	0.007	>20	
	DOHH2 (Follicular)	0.57	0.025	0.013	0.001	0.055	p16INK4
	RL (DLBCL)	0.94	1.34	0.15	0.002	>20	p53
	Pfeiffer (DLBCL)	2.73	0.55	0.37	0.004	ND	
	SuDHL4 (DLBCL)	1.15	0.45	0.25	0.003	9.73	
	Daudi (Burkitt's)	1.23	>20	0.89	0.015	>20	p53
	Raji (Burkitt's)	3.56	>20	3.9	0.009	>20	p53
Myeloma	RPMI8226	1.01	>20	0.69	0.002	>20	p53, k-Ras, EGFRT751I
	OPM-2	0.43	0.05	0.11	0.001	ND	PTEN
	ARH77	1.42	14.79	0.83	0.005	ND	p53

CUDC-907 is Orally Bio-Available in Preclinical Animal Studies

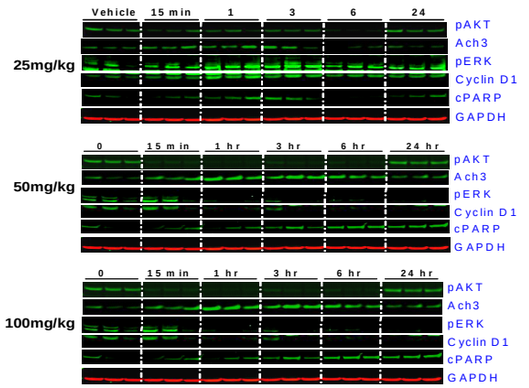




Parameters	Units	100 mg/kg, iv Plasma	100 mg/kg, iv Tumor	100 mg/kg, po Plasma	100 mg/kg, po Tumor
Cmax	ng/g	33673.1	26985.7	2285.4	1044.7
T1/2	hr	5.0	7.9	7.7	12.6
AUC	ng/g*hr	11455.3	35022.6	1899.3	3973.6
Vz	L/kg	3.0	-	-	-
CL	L/hr/kg	8.7	-	-	-
Bioavailability	%	-	-	16.6	-

Parameters	Units	5 mg/kg IV	5 mg/kg PO
Cmax	ng/ml	6156.2	312.1
T1/2	hr	1.9	4.9
AUC	ng/ml/hr	2977.5	450.4
Vz	L/kg	4.5	-
CL	L/hr/kg	1.7	-
Bioavailability	%	-	15.1

CUDC-907 Dose-Dependently Disrupts Signaling Networks, Induces Apoptosis in NHL Tumor Xenografts



CUDC-907 Potency Against PI3K Isoforms and HDAC Subtypes

•Enzymatic activity against PI3K isoforms (IC50, nM)

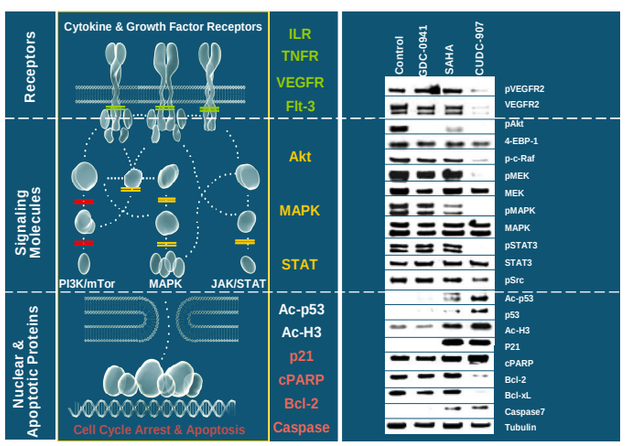
Compound	PI3Kα	PI3Kβ	PI3Kγ	PI3Kδ	PI3Kαh1 047R	PI3Kα E545K
Vorinostat/SAHA	NA	NA	NA	NA	NA	NA
GDC-0941	8	31	55	4	12	4.4
BEZ235	3	ND	7	11	ND	ND
Cal-101	354	108	31	18	1641	565
CUDC-907	19	54	311	39	73	62

•Enzymatic activity against HDAC subtypes (IC50, nM)

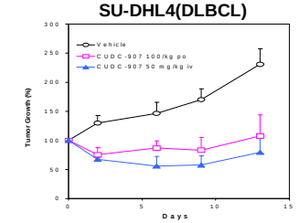
Class		I				II						IV
HDACs		HDAC1	HDAC2	HDAC3	HDAC8	HDAC4	HDAC5	HDAC6	HDAC7	HDAC9	HDAC10	HDAC11
Compound	SAHA	42.5	156	33.1	113	NA	NA	21.6	NA	NA	68.4	51.3
	LBH 589	1.4	6.8	1.5	26.7	196	124	8.2	1864	922	2.1	1.6
	CUDC-907	1.7	5.0	1.8	191	409	674	27	426	554	2.8	5.4

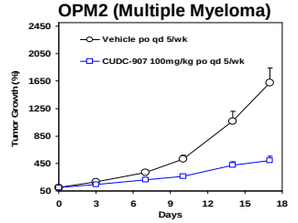
Reference compounds:
HADC inhibitor: SAHA (suberoylanilide hydroxamic acid), LBH-589
PI3K inhibitor: GDC-0941, BEZ235, CAL-101

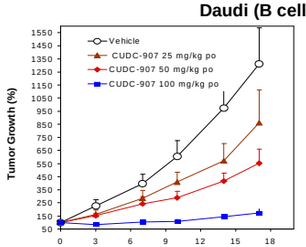
MOA: CUDC-907 Disrupts Signaling Networks in Hematological Cancer Cell lines

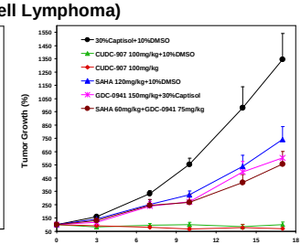


CUDC-907 Inhibits Tumor Growth in NHL and Multiple Myeloma Models with Better Activity Than References









Conclusions

- CUDC-907 is a dual inhibitor of HDAC and PI3K which inhibits PI3K-AKT as well as 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 (with a favorable safety profile) in efficacy studies in hematologic cancer models.
- 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 candidate for clinical development.