Novel Dual Small Molecule Inhibitor Targeting LSD1 and HDAC6

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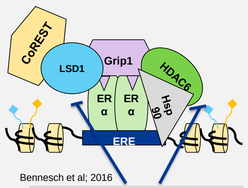
Summary

Cross-talk between LSD1 and HDAC and their distinct roles in carcinogenesis has clearly been proven in literature. Also, combined inhibition of LSD1 and HDAC has been shown to be more efficacious in inhibiting cancer. In this regard, we have developed a dual inhibitor JBI-802 that inhibits both LSD1 and HDAC6. JBI-802 showed stronger anti-proliferative activity on select AML, CLL, SCLC, sarcoma and multiple myeloma cell lines as compared to single agents. HDAC6 as well as LSD1 inhibition was confirmed by dose and time dependent modulation of tubulin acetylation and differentiation markers (CD11b). Further we also observed strong upregulation of pro-inflammatory and M1 macrophage markers (CD80, CD64 and CD86). JBI-802 inhibitor showed excellent dose-dependent efficacy in erythroleukemia as compared to single agent LSD1 or HDAC6 inhibitors with an ED50 of ~6.25 mg/kg, BID by oral administration. JBI-802 inhibitor also showed much stronger tumor growth inhibition in combination with anti-PD-1/PD-L1 antibodies in syngeneic tumor model. JBI-802 is well tolerated as observed by exploratory toxicology studies. Further pre-clinical IND enabling studies are underway for this molecule to be developed as a clinical candidate for AML as well as for other solid tumors.

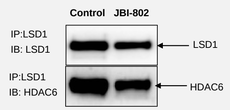
LSD1 and HDAC6 function in a complex

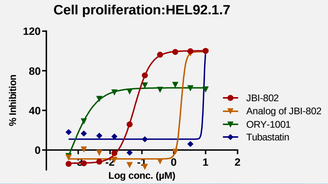


Bennesch et al; 2016

JBI- 802
LSD1- HDAC6 dual inhibitor

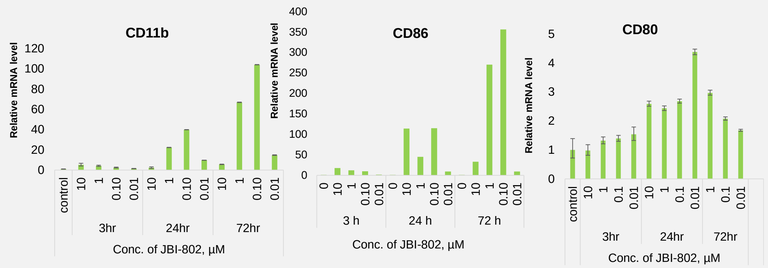
	Biochemical Potency		HEL92.1.7 Cellular IC_{50} µM
	LSD1, IC_{50}, µM	HDAC6 IC_{50} µM	
JBI-802	0.055	0.011	0.058
Analog of JBI - 802	1.3	0.018	1.7
Tubastatin	NA	0.015	5.8
ORY-1001	0.016	NA	0.001 (Top-61%)

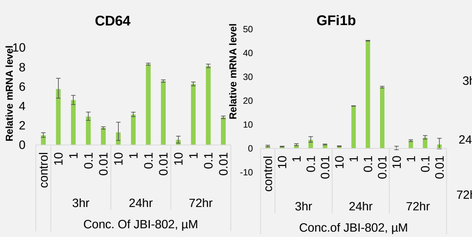




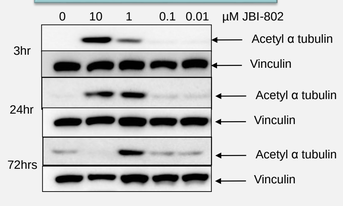
- JBI-802 is potent against LSD1 and highly selective (~77 fold) against HDAC6

Clear Biomarker Modulation



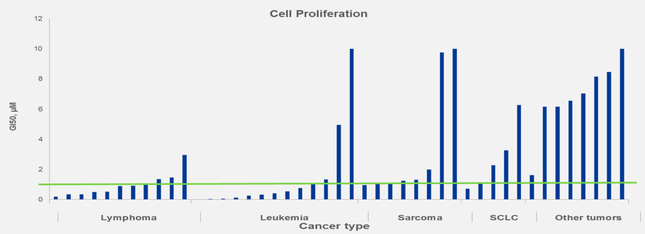


HDAC6 biomarker: Acetyl Tubulin



- Sustained activation of differentiation as well as M1 macrophage markers (CD11b, CD86,CD64 and CD80) was observed.
- The strong upregulation of GFi1b mRNA levels shows that the interaction between the LSD1 and GFi1b is disrupted leading to trans differentiation from erythroid lineage to granulomonocytic lineage.
- Dose and time dependent increase in tubulin acetylation.
- Note: HEL.92.1.7 cells treated with JBI-802 at different concentrations (µM) for 3 to 72hrs.

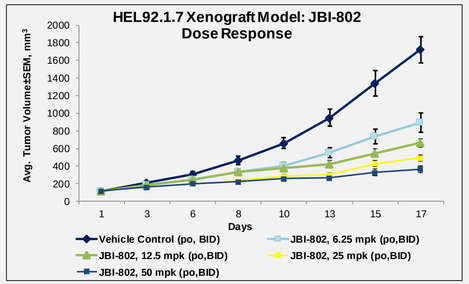
Strong Anti-Proliferative activity

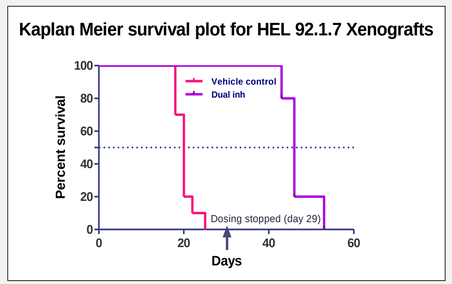


Note: Cell line panel profiling performed at Eurofins

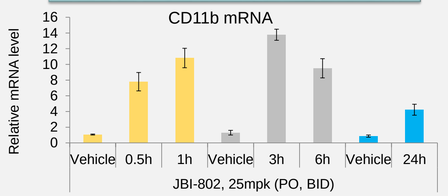
- JBI-802 was screened in a panel of cell lines where it showed strong anti-proliferative activity on select AML, CLL, Lymphoma and also in certain solid tumors such as SCLC, sarcoma.

Stronger Efficacy in Erythroleukemia Model leading to Enhanced Survival





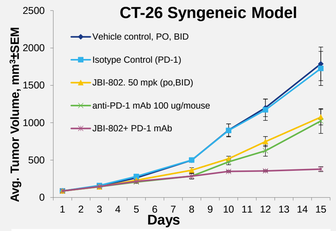
Sustained biomarker modulation upto 24hrs

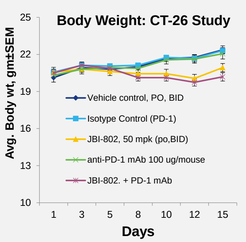


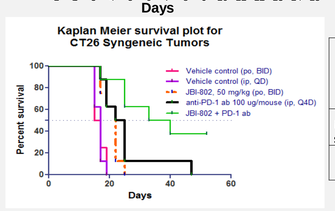
Treatment	Median in Days	% ILS	P Value (Mantel-Cox) Test
Vehicle control, PO, BID	20	NA	NA
JBI-802, 50 mg/kg, PO, BID	46	130	< 0.0001

- JBI-802 prolonged survival of mice bearing HEL 92.1.7 tumors.
- Showed excellent dose response in HEL model and ED50 is 6.25 mpk/BID
- Showed superior efficacy as compared to single agents

Superior efficacy with Checkpoint inhibitors in Syngeneic model







	Vehicle control, PO	Vehicle control, IP	JBI-802	anti-PD-1 ab	JBI-802 + PD-1 ab
Median survival	16	17	22	23.5	**36.5**
% ILS			38	38	**115**

ILS: Increase in Life span

- ~80% tumor growth inhibition observed in the combination of JBI-802 with anti-PD-1 mAb; combination was tolerated well
- 3 out of 8 mice showed complete tumor regression

Conclusions

- JBI-802 has strong potency on LSD1 and HDAC6 while exhibiting excellent selectivity against other HDACs.
- Showed a strong tumor growth inhibition in erythroleukemia and multiple other haematological tumors as compared to single agents.
- Syngeneic models showed single agent activity with unique mechanism of action and it can be combined with checkpoint inhibitors safely.
- Shows favourable tolerability profile at efficacious doses.
- Is currently being developed as a clinical candidate for treating AML and other solid tumors.

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