Novel Dual Small molecule Inhibitor Targeting LSD1 and HDAC6/8

S. Dhanalakshmi*, R. Sridharan*, S. Nair, B. Dehingia, Basavaprabhu, Venkatesha V., A.K. Singh, R.Kar, A. Siddiqui, S. J. Tantry, Hari Prakash, Sopan D.G., S. Ingle, M. Zainuddin, G. Rudresh, D. Prashanthi ., S. Rajagopal

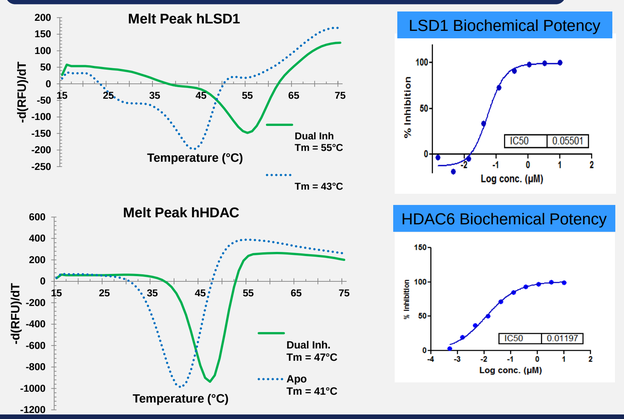
Jubilant Biosys Ltd., Bangalore India; *Jubilant Therapeutics Ltds., NJ, USA

Abstract Control #1290

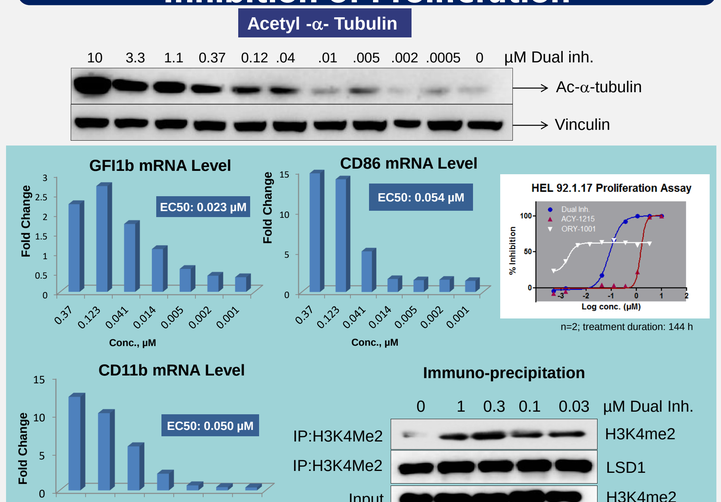
Summary

Cross-talk between LSD1 and HDAC and their distinct roles in carcinogenesis has clearly been proved 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 dual inhibitors of LSD1 and HDAC6 that inhibit both LSD1 and HDAC6/8. Dual inhibitor shows stronger activity on a sub-set of AML as compared to single agents. HDAC6 as well as LSD1 inhibition was confirmed by modulation of tubulin acetylation with a concomitant increase in mRNA levels of GFI1b, CD86 and CD11b. Dual inhibitor shows reasonable oral exposure and showed strong dose-dependent efficacy in Erythroleukemia as compared to single agent LSD1 or HDAC6 inhibitors. Further, LSD1 and HDAC6 inhibition lead to immune modulation, leading to dsRNA mediated stress (up-regulation of IFN-α, IFN-β, MDA5 and IL-28) and modulation of immune-suppression (IL-4) in a syngeneic model. Dual inhibitor also shows much stronger tumor growth inhibition in combination with anti-PD-L1 in syngeneic tumor models. Single dose MTD for the dual inhibitor was > 1000 mg/kg. Pre-clinical and advanced studies are warranted for this molecule to be developed as a clinical candidate for a subset of AML as well as an immunomodulatory agent for solid tumors.

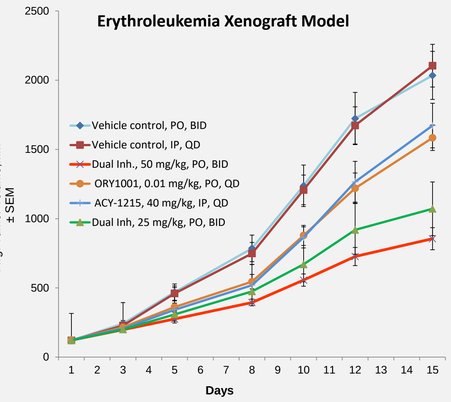
In vitro Potency

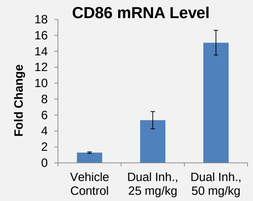


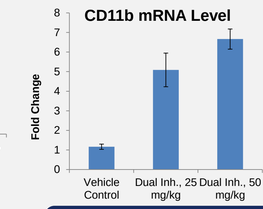
Strong Biomarker Modulation Leading to Inhibition of Proliferation

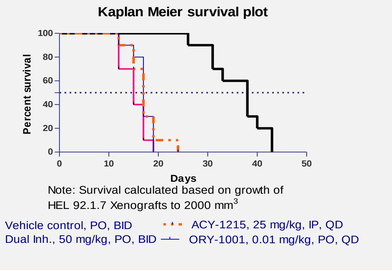


Stronger Efficacy and Enhances Survival in Erythroleukemia Model









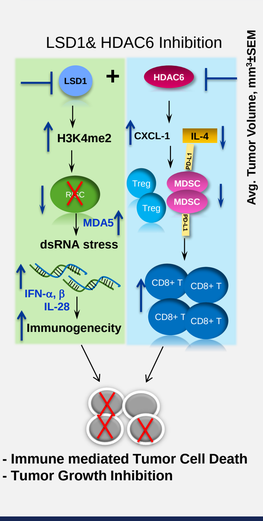
Dual inhibitor shows strong efficacy in erythroleukemia by oral dosing as compared to single agents

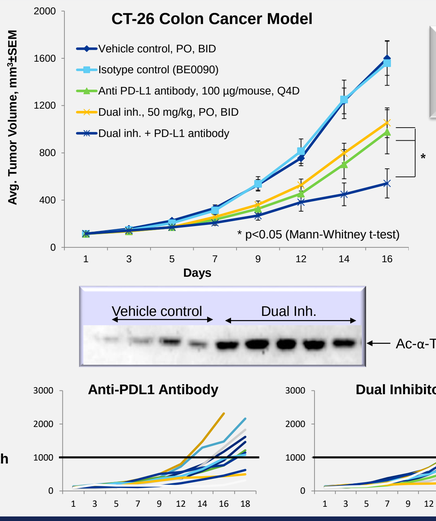
	Vehicle control, IP, QD	ACY-1215, 25 mg/kg, IP, QD	Vehicle control, PO, BID	Dual Inh., 50 mg/kg, PO, BID	ORY-1001, 0.01 mg/kg, PO, QD
Median survival, days	15	17	15	**38**	17

ADME/PK and Safety

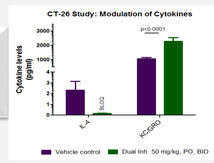
Properties	Dual Inhibitor
ADME/PK	
PBS sol , μM	>100
HLM/MLM/DLM (%rem @ 30 min.)	57-80
Caco2(10^{-6} cm/s) A2B/B2A/ER	3.3/16.4/4.9
Stability across pH's	83-96% stable
PK in mice/rat/dog, DRC, gender effect, food effect in mice	Reasonable bioavailability across species and good dose proportionality ; no gender or food effects
Off Target	
hERG IC_{50} (μM) Qpatch	>30
AMES test	Negative
CYP inhibition 3A4, 2D6, 2C9 and 2C19 (% Inhibition at 10μM)	< 20% for 3A4, 2C9 and 2C19, 60 % for 2D6
Toxicity studies	
MTD in Mice	>1000 mg/Kg
14 day Repeat dose toxicity in Mice	No adverse effects; mechanism based changes observed
MW/PSA/cLogP	[redacted]/77/1.6

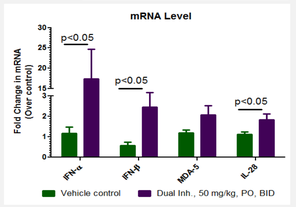
Efficacious in Syngeneic Model and Shows Superior activity with checkpoint Inhibitors





Tumor Exposure:
HDAC6 IC50: >35 fold
LSD1 IC50: > 7 fold
No direct cytotoxicity in CT-26 **(EC50: >5 μM)**





Conclusions

- LSD1-HDAC6/8 dual inhibitor has strong potency on LSD1, HDAC6 and HDAC8, while exhibiting excellent selectivity against other HDACs.
- Showed a strong TGI in HEL92.1.7 xenograft model as compared to single agents.
- In 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 a subset of AML and for other solid tumors as an immune modulatory agent.

Contact: dhanalakshmi.sivanandhan@jubilanttx.com