JBI-802: Novel LSD1/HDAC6 inhibitor with a unique mechanism of action

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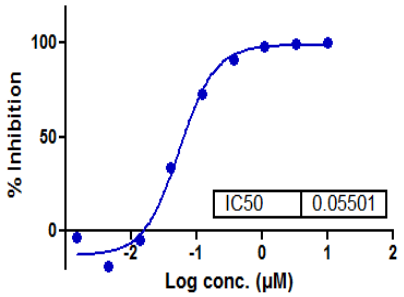
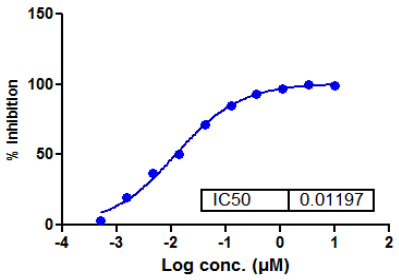
JBI-802: Dual LSD1/HDAC6 inhibitor

JBI-802	**IC50, nM**
LSD1	55
HDAC6	**11.9**

LSD1 Inhibition

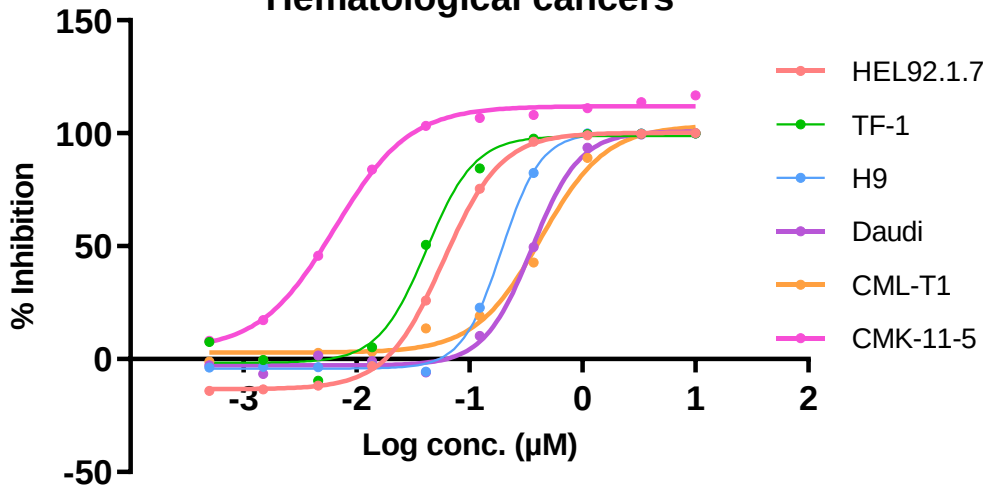


HDAC6 Inhibition



HDAC Isoform	JBI-802 IC_{50} nM
HDAC1	923
HDAC2	1560
HDAC3	1220
HDAC4	7840
HDAC5	4450
HDAC6	11.9
HDAC7	1720
HDAC8	98.3
HDAC9	5710
HDAC10	2220
HDAC11	1330

Cell proliferation: Hematological cancers



	HEL92.1.7	TF-1	H9	Daudi	CML-T1	CMK-11-5
IC50	0.05889	0.04183	0.1920	0.3573	0.4264	0.006441

- JBI-802 is a novel small molecule inhibitor of LSD1 and HDAC6; shows high selectivity against class I HDACs
- Highly efficacious in multiple hematological cancers

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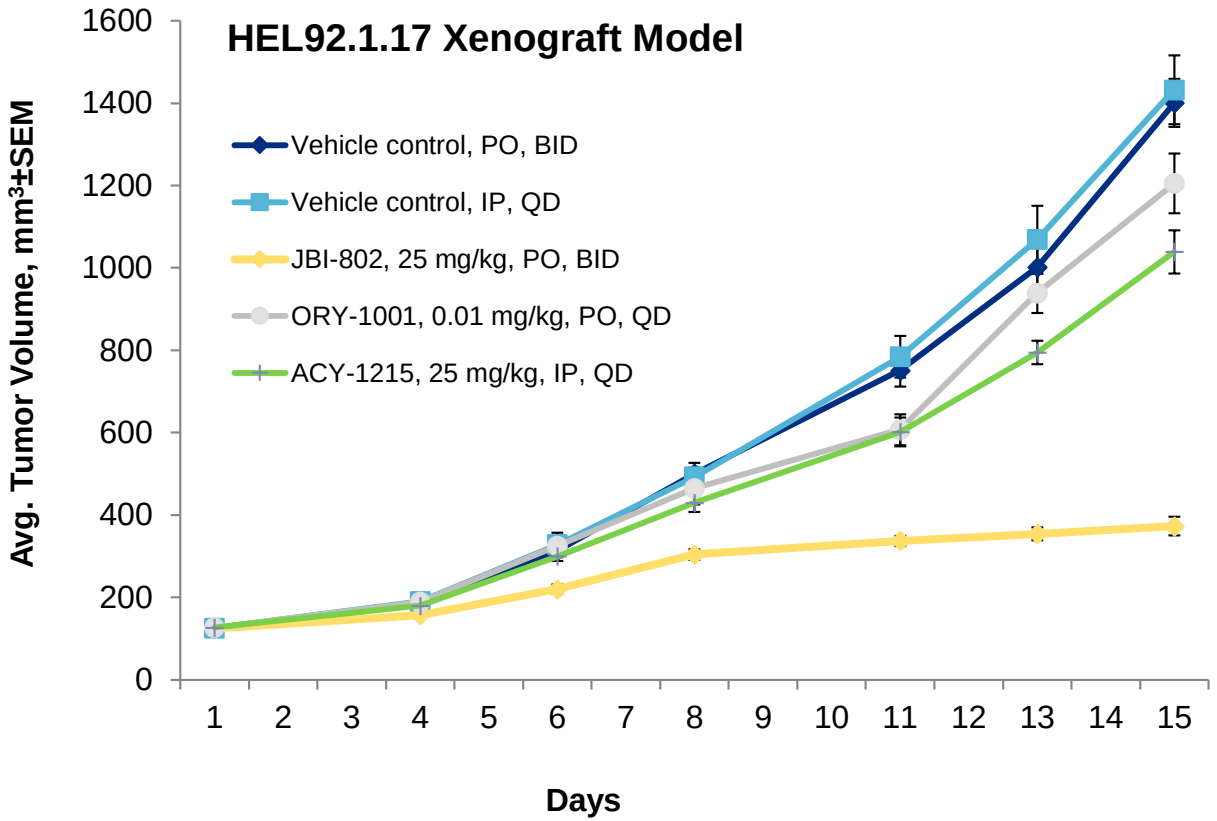
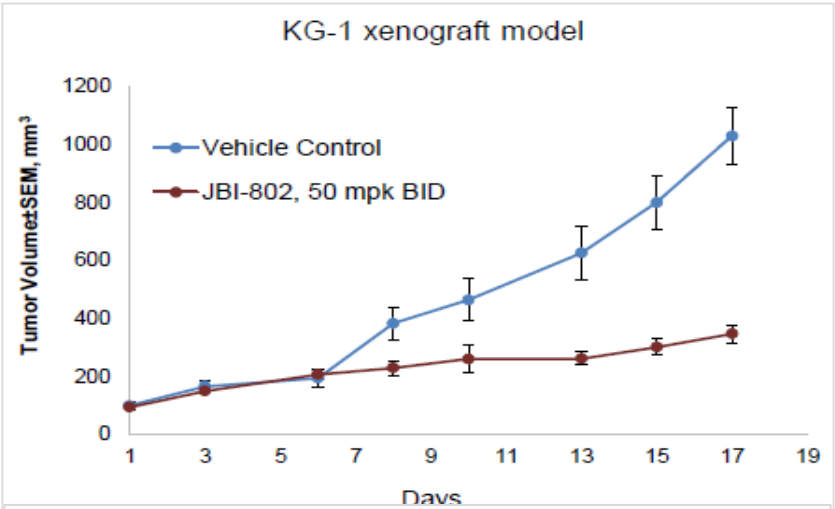
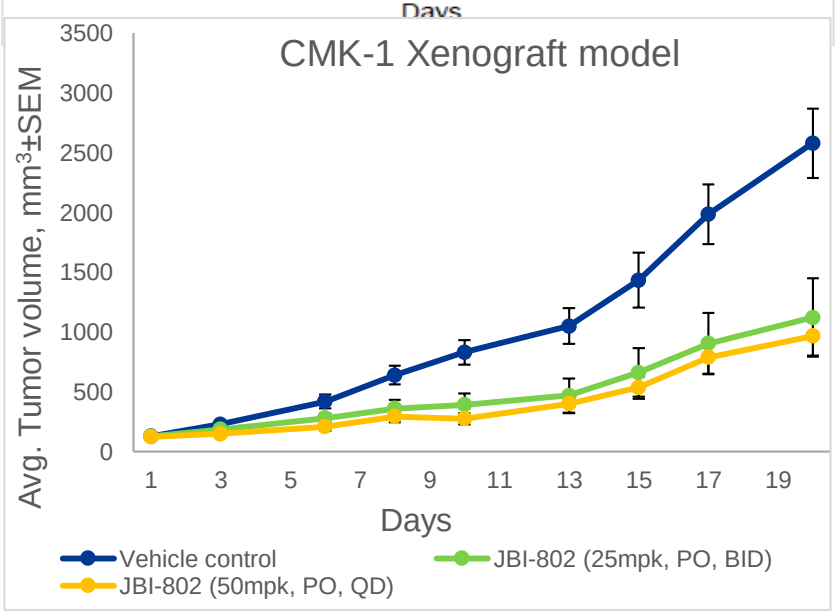
Efficacious in multiple models of leukemia

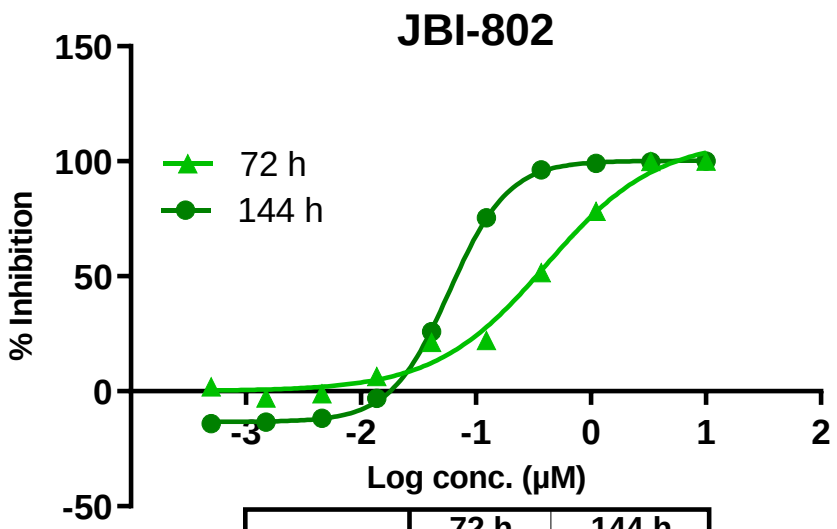




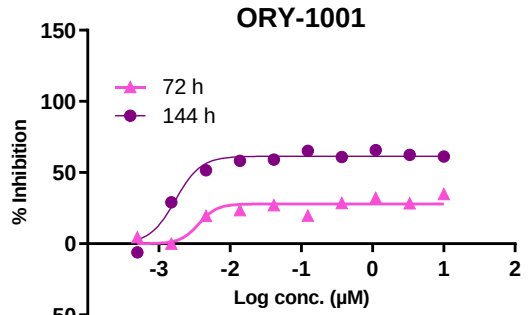


Both LSD1 and HDAC6 mechanisms are operational

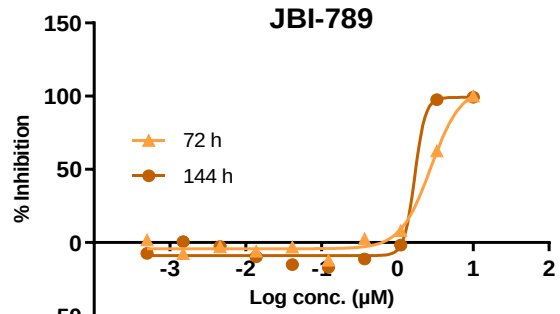
Compound	LSD1 (nM)	HDAC6 (nM)
JBI-789 Analog of JBI-802	1342	18.9
JBI-802	55	11.9
Tubastatin	NA	6
ORY-1001	16	NA



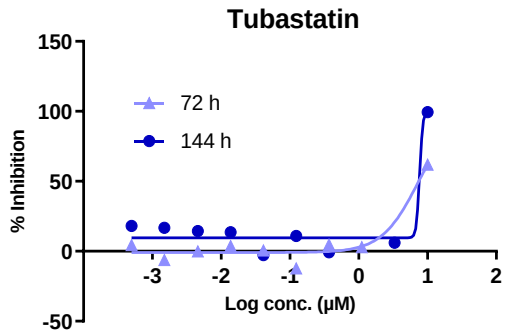
	72 h	144 h
IC50	0.4073	0.05889
Span	109.4	113.6



	72 h	144 h
IC50	0.003640	0.001711
Span	= 27.92	= 61.43



	72 h	144 h
IC50	2.764	1.696
Span	110.7	108.1



	72 h	144 h
IC50	7.361	~ 7.660
Span	= 100.9	= 90.45

- Inhibition of LSD1 alone translates into anti-proliferative effect at only 144 h and does not cause 100% inhibition
- HDAC6 inhibition shows moderate anti-proliferative effect that is comparable at 72 and 144 h
- Dual inhibition shows stronger effect and enhanced potency at 144h compared to 72 h

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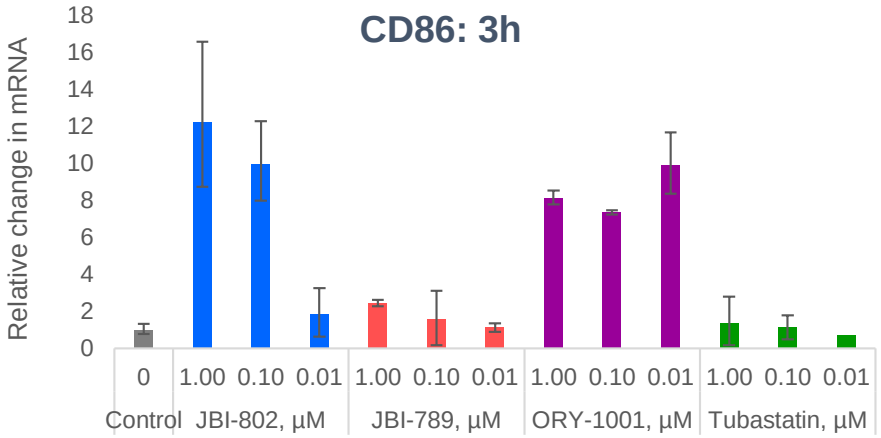
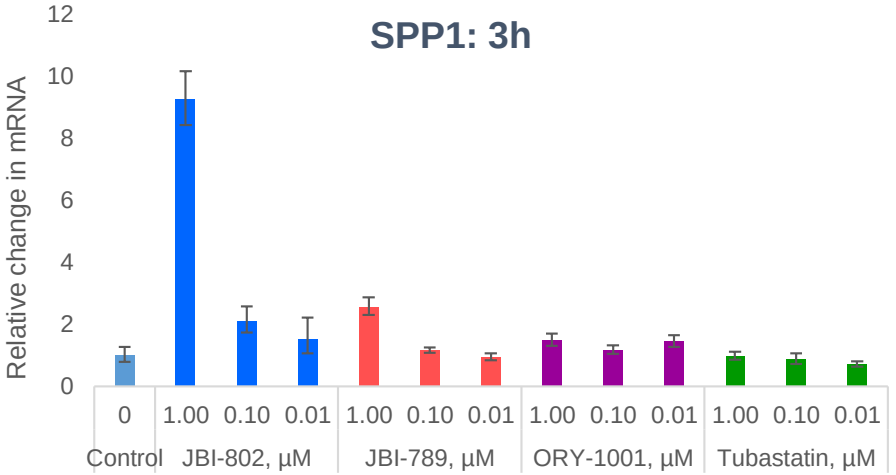
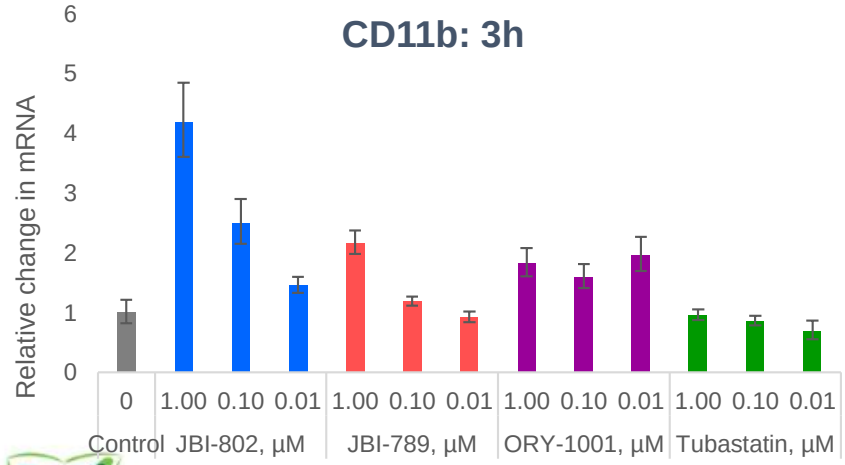
Modulation of LSD1 and HDAC6 specific biomarkers







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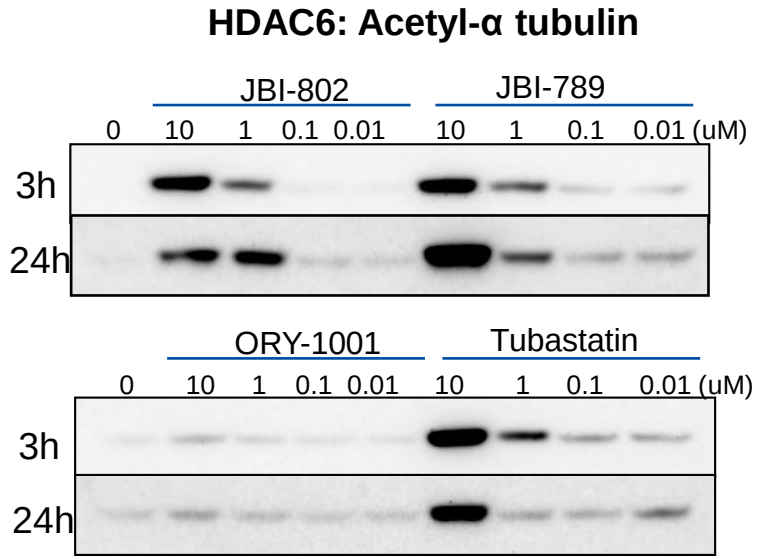
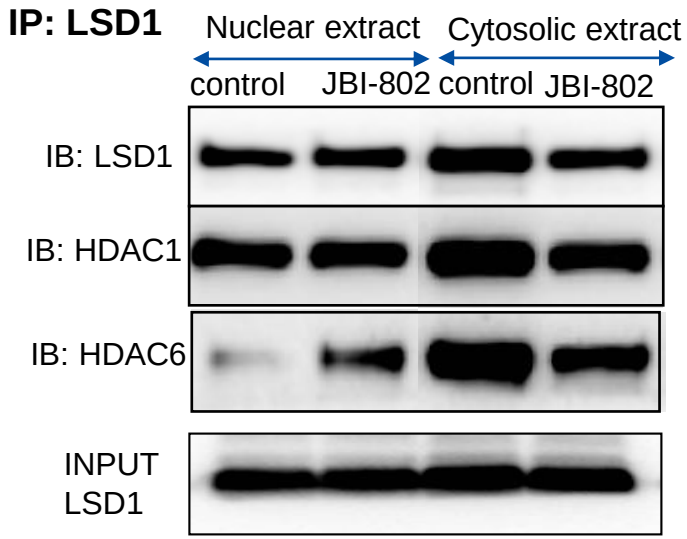
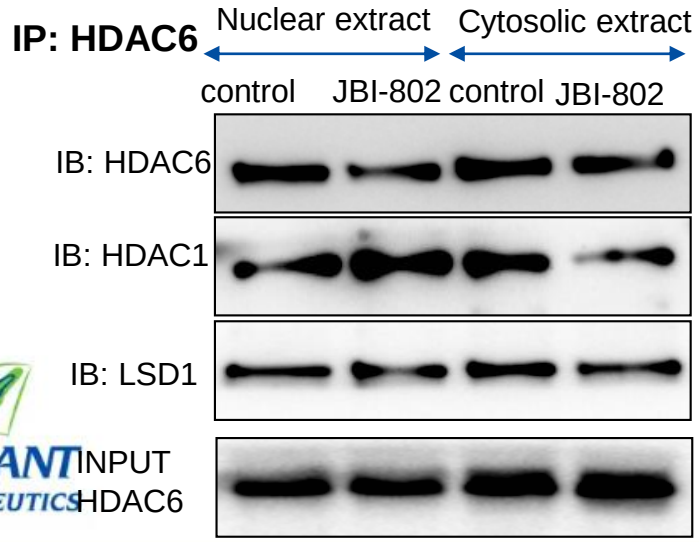


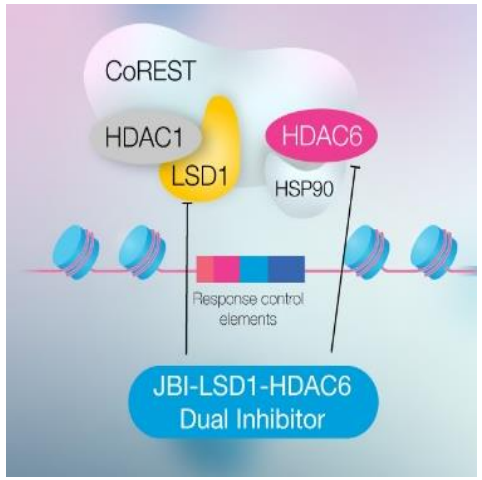
- LSD1 and HDAC6 selective biomarkers are modulated by the dual inhibitor
- Stronger modulation observed with dual inhibitor

LSD1, HDAC6 and HDAC1 are part of a complex in sensitive cells

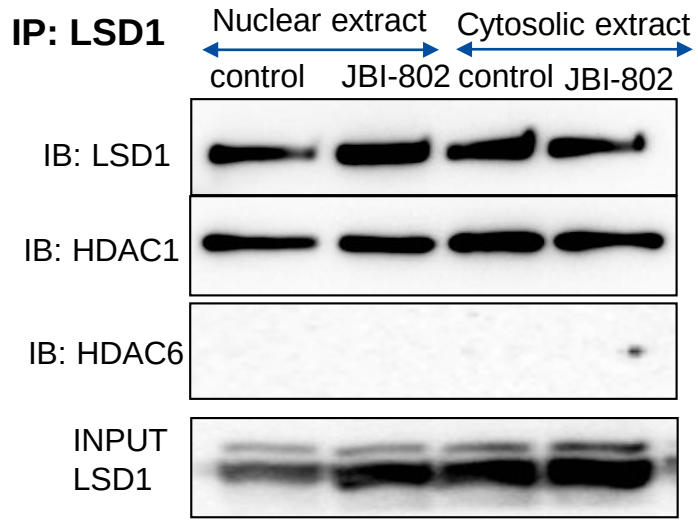
Sensitive cell line

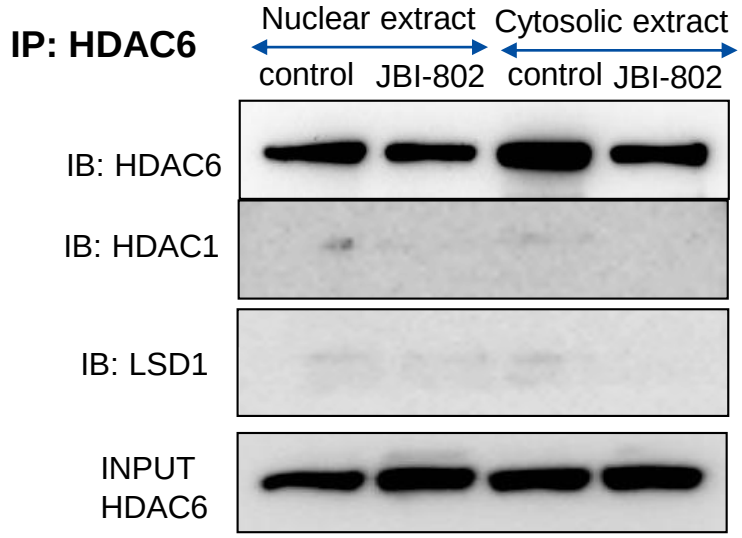






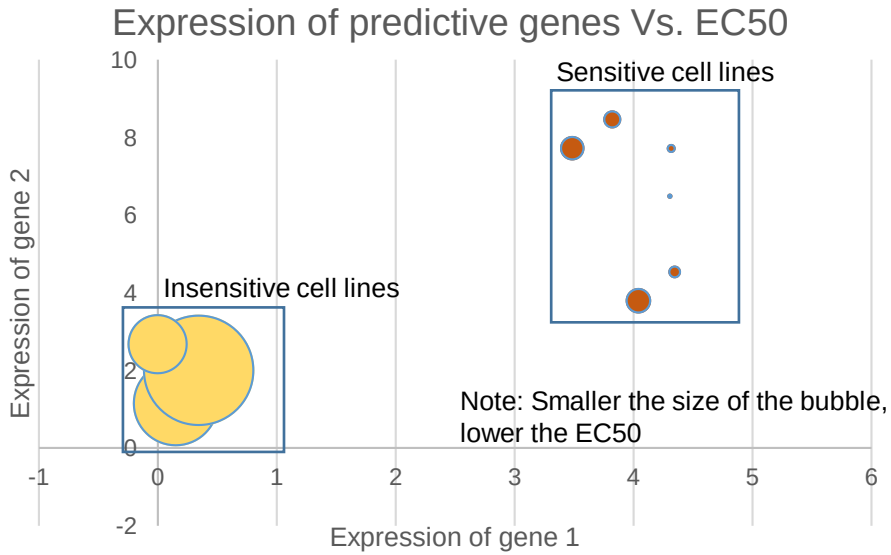
Insensitive cell line



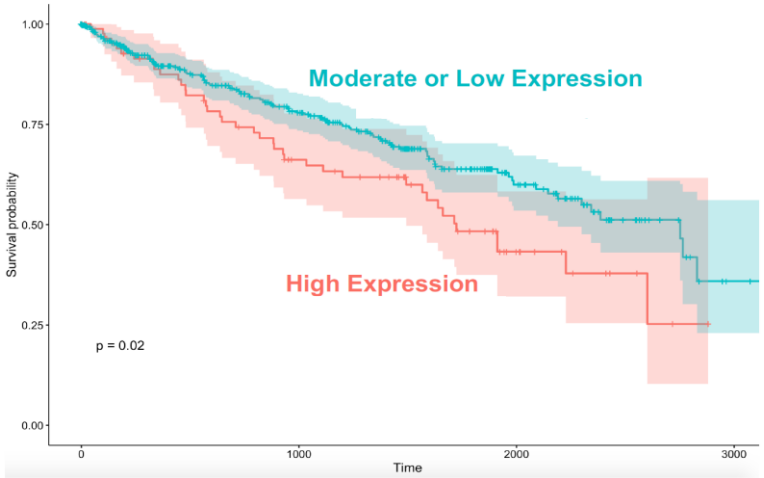


AI studies identify potential biomarker for patient stratification

- 2 potentiation biomarkers identified to help patient stratification; Sensitive cell lines clearly show the higher expression of the predicted biomarkers
- Sensitive cells have higher expression of pro-inflammatory genes and those specifically involved in macrophage polarization.
- A subset of solid tumors proposed to be sensitive to the dual inhibitor, where higher expression of these markers has shown to have a prognostic value

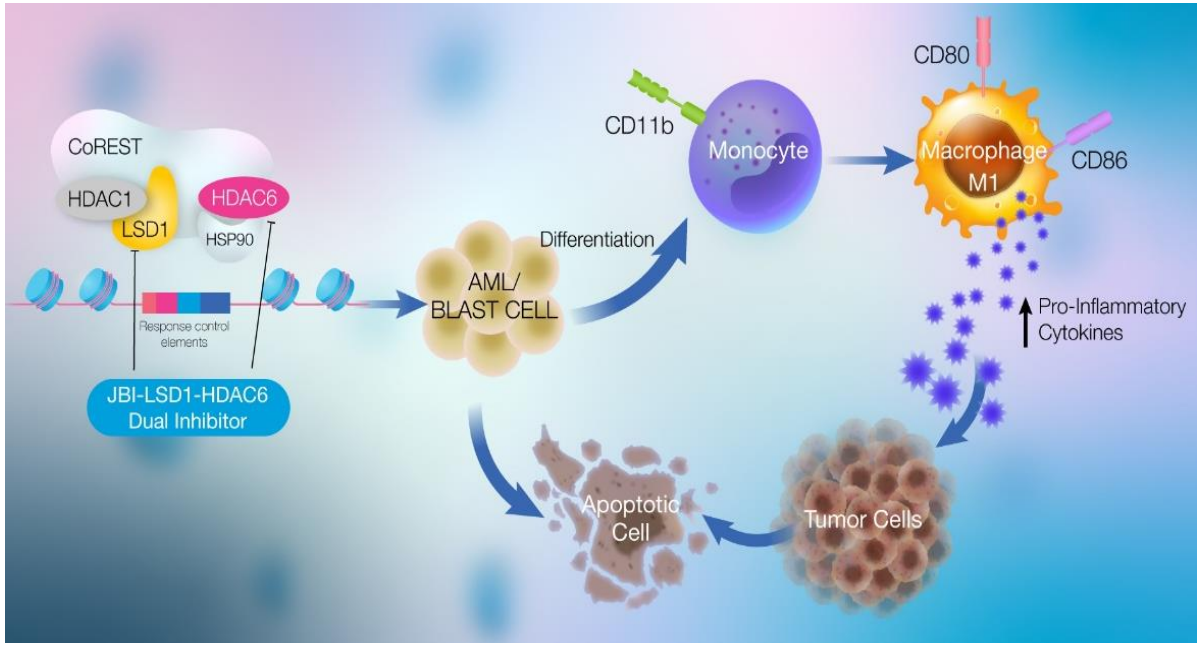


Expression of gene 1 and 2 and prognosis



These analyses were carried out at ONETHREE BIOTECH

LSD1 and HDAC6 are part of gene modulation complex in sensitive cell lines



- Inhibition of LSD1 and HDAC6 in a subset of cell lines leads to stronger anti-proliferation and efficacy
- In such cell lines, both LSD1 and HDAC6 are in a complex and lead to stronger gene modulation
- Dual inhibition leads to modulation of unique set of genes as compared to inhibition of LSD1 or HDAC6 alone
- Potential biomarkers for patient stratification identified and these biomarkers are strongly upregulated in sensitive cell lines
- These studies clearly pave way for the clinical strategy of the dual inhibitor. Currently IND enabling studies are being carried out to progress into clinical trial by 2nd half of 2020

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Thank You

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