Novel, small molecule PRMT5 inhibitors for treatment of cancer

D. Sivanandhan*, S. Rajagopal*, M.N. Sadhu* G. Chandru*, S. Vadivelu, T. Natarajan, I.N. Swamy, S. Vishwakarma, A.Siddiqui , S. wahid, M. Zainuddin*, G. Rudresh, P. Daram, R. Gosu, D. Tiagaraj, S. Garapaty, S. Nair, N. Kapoor. * Jubilant Therapeutics, Bedminster, NJ, Jubilant Biosys Limited, Bangalore, India

Jubilant Therapeutics, Bedminster, NJ

Poster # 1128

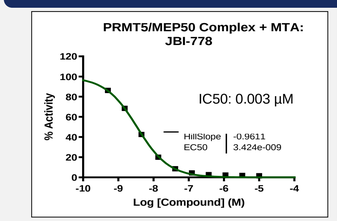
Abstract Control # 1683

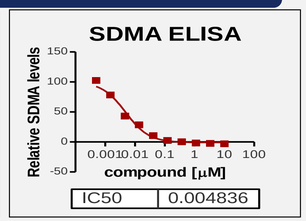
SUMMARY

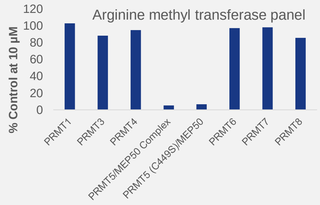
PRMT5, the major modulator of symmetric dimethylation of arginine (SDMA) has emerged as an attractive therapeutic strategy in various cancer types. PRMT5 over-expression (shown in several cancers including lymphoid, lung, breast, glioblastoma, gastric etc.) is thought to be an important factor in its tumorigenicity due to its repressive function on tumor suppressor gene expression. Therefore, inhibitors selectively targeting PRMT5 could be of high clinical value.

Structure based drug design was used to identify novel PRMT5 inhibitors. FlashPlate® methylation assays, long term cell proliferation assays and symmetric dimethylation of known cellular protein SmD3 were used to assess *in vitro* potency and functional effect of PRMT5 inhibition. A number of compounds from two different series showed strong *in vitro* potency against PRMT5 and good ADME properties. Multiple co-crystal structures have been solved in-house and extensively used in optimization of these novel scaffolds. Our lead PRMT5 inhibitor, JBI-778 exhibited a low nM potency both *in vitro* and cell based assays . A broad panel of lymphoma cell lines as well as a number of solid tumor cells lines (PDAC, SCLC and GBM) were sensitive to JBI-778. The compound exhibited good *in vitro* ADME properties in terms of aqueous solubility and metabolic stability and excellent oral bioavailability in mouse pharmacokinetics. It was clean in terms of off target activity and CYP liability and AMES negative. In Z-138 xenograft model, oral administration of JBI-778 at 50 mg/kg resulted in complete (>90%) tumor growth inhibition with an ED50 of < 10 mg/Kg. In addition, JBI-778 showed excellent sustained exposure in brain covering and also showed significant tumour growth inhibition in orthotopic model, translating into substantial survival advantage. IND-enabling studies is underway to develop JBI-778 as a clinical candidate.

In vitro characterization of JBI-778

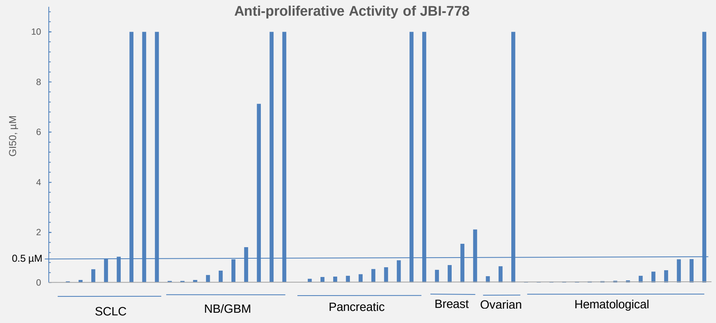






JBI-778 is potent and highly selective for PRMT5 in the panel of Arginine methyl transferases

Phenotypic effect of JBI-778 across multiple cancer cell lines



Indicated cell lines were treated with JPRMT5i for 8-11 days; the viability was assessed by Cell Titer Glo®.

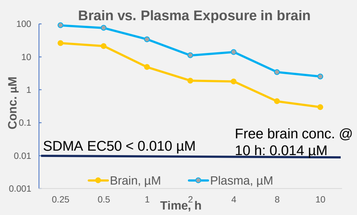
Note: Cell line panel profiling performed at Eurofins

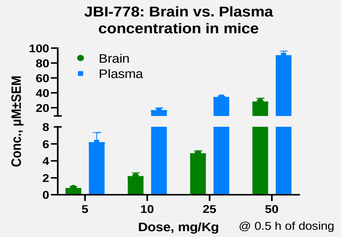
Strong inhibition of proliferation in lymphoma/leukemia cell lines as well as in multiple solid tumors

ADME/PK and Off-target

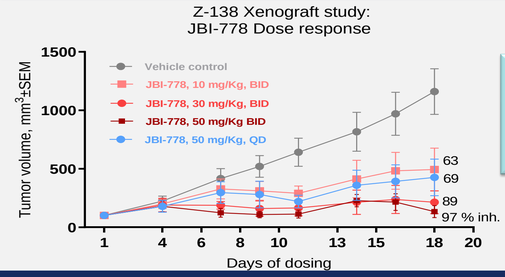
Parameters	JBI-778
ADME/PK	
PBS sol (µM)	217
HLM/MLM/RLM/DLM (%rem)	>50%
Caco2(10^{-6} cm/s) ER	1.02
Stability across pH	≥90% stable
PPB mouse (mice/rat/human) % unbound	4-5%
Oral availability in mice/rat/dog, %F	66/52/47
Off Target	
Cardiac profiler	Clean
Cerep Panel-44 toxicity panel	Clean
AMES test	Negative
CYP inhibition 3A4, 2D6, 2C9, 2C19 and 1A2 (% Inhibition at 10µM)	<50%

High and sustained brain exposure



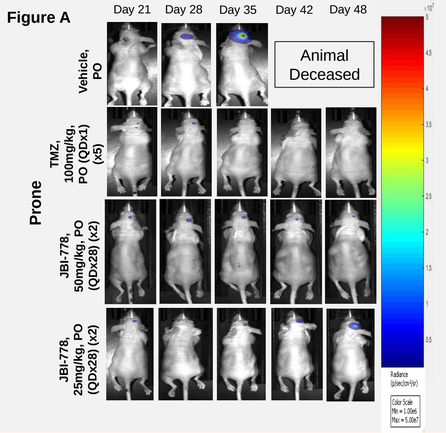


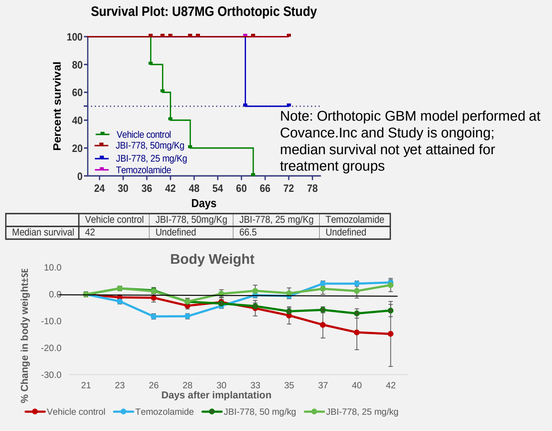
In vivo anti-tumor efficacy of JBI-778 in Z-138 xenografts



- JBI-778 showed excellent dose response in Z-138 xenograft model.
- Showed superior efficacy at 50mg/kg, BID with complete tumor growth inhibition (97%).

JBI-778 Efficacious and provides significant survival advantage in an Orthotopic GBM model





Note: Orthotopic GBM model performed at Covance.Inc and Study is ongoing; median survival not yet attained for treatment groups

	Vehicle control	JBI-778, 50mg/Kg	JBI-778, 25 mg/Kg	Temozolamide
Median survival	42	Undefined	66.5	Undefined

Nude mice bearing orthotopic U-87MG tumors were dosed orally with vehicle or JBI-778 (25 or 50mg/kg) ,BID. The survival, body weight and tumor growth were assessed. Figure A: Representative median BLI images of mice bearing orthotopic images

Conclusions

JBI-778 is a potent PRMT5 inhibitor that is selective against other PRMTs; JBI-778 is highly potent against a number of cancers, in terms of anti-proliferative activity.

Oral administration of JBI-778 leads to sustained brain exposure, which translates into strong inhibition of orthotopic GBM model and substantial survival advantage; Similar strong efficacy is also observed in MCL model by oral administration with an ED50 of <10 mg/Kg

Given the therapeutic importance of PRMT5 in Glioblastoma, JBI-778 will be extremely valuable in treating this cancer either as standalone therapy or in combination with other standard of care agents.

Contact: dhanalakshmi.sivanandhan@jubilanttx.com