1359

Selective HDAC6 Inhibition By GB-1101 Revokes Tumor Immune Privilege and Synergizes with Immune Checkpoint Therapies to Induce Tumor Regressions

K. Kotlarczyk, M. Murray, M. Sepulveda, T. Wang, PhD, P. Gonzales, S. Gately, PhD

Translational Drug Development (TD2)

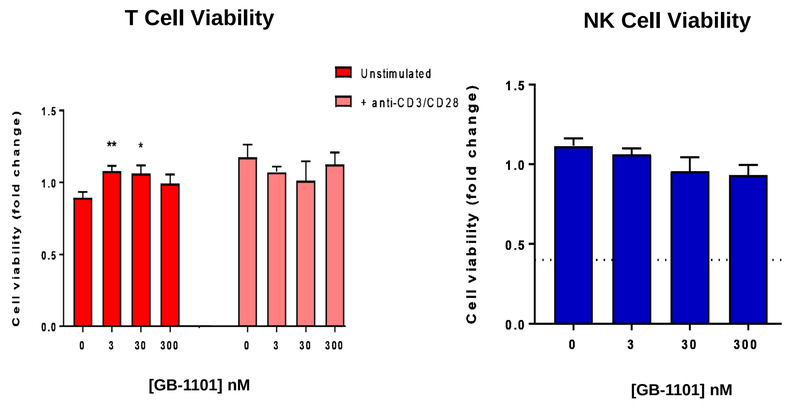
ABSTRACT

HDAC6 is a cytoplasmic class IIB HDAC isoenzyme that is involved in the deacetylation of cytoplasmic proteins. HDAC6 also binds ubiquitinated proteins, facilitating the formation of the aggresome, to remove misfolded proteins. Previously, HDAC6-selective inhibitors were shown to decrease immunosuppression and enhance immune function of melanoma patient T-cells demonstrating an important role for HDAC6 inhibition for cancer immunotherapy. GB-1101 is a novel, orally bioavailable, nanomolar potent inhibitor of HDAC6. GB-1101 tested in vitro did not induce direct cytotoxicity to CD4/CD8 or NK cells at concentrations up to 300 nM. RNA-seq on GB-1101 exposed MHC-null human MSS colon cancer cell lines reveal potent induction of MHC Class I/II genes and expression numerous cancer neoantigens. To test the activity of GB-1101 in vivo, we established large (~450mm3) 4T1-luc syngeneic tumors and initiated treatment of GB-1101 given orally once daily alone and combined with anti-PD1, anti-CTLA4, and anti-PD1/anti-CTLA4 combination. The activity of anti-PD1 in this model was minimal (TGI: 3%); GB-1101 as a single agent showed more potent anti-tumor activity (TGI: 50%) compared to anti-PD1. We observed synergistic benefit when GB-1101 was combined with anti-PD1 (Combination TGI: 78%). GB-1101 showed comparable anti-tumor activity to single agent anti-CTLA4 (TGI: 43%) but revealed significant tumor regressions of large and well-established tumors when combined with anti-CTLA4 (Combination TGI: >100%). As a single agent, GB-1101 was superior to anti-PD1+anti-CTLA4 (TGI: 7%) and induced significant tumor regressions when combined with anti-PD1+anti-CTLA4 (Triple Combination TGI: >100%). In the TC-1, HPV-positive syngeneic model, GB-1101 reprogrammed the tumor immune microenvironment reducing the number of M-MDSC and TReg cells and increase the numbers of CD4/CD8 and NK cells. Taken together, these data support GB-1101 as an important new targeted epigenetic immunomodulator able to revoke immune privilege to enhance the clinical activity of immune checkpoint therapies.

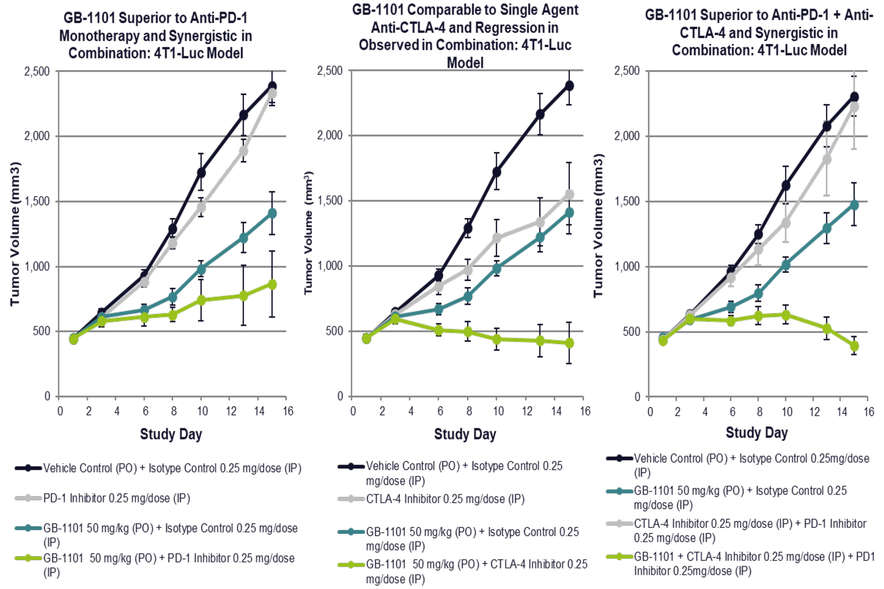
GB-1101 – Potent Selective Inhibitor of HDAC 6

Compound	HDAC1 IC_{50} nM	HDAC2 IC_{50} nM	HDAC3 IC_{50} nM	HDAC4 IC50 nM	HDAC5 IC_{50} nM	HDAC6 IC_{50} nM	HDAC7 IC_{50} nM	HDAC8 IC_{50} nM	HDAC9 IC_{50} nM	HDAC10 IC_{50} nM	HDAC11 IC_{50} nM
GB-1101	103	503	19	8820	6840	**6.44**	3670	791	10100	137	4220

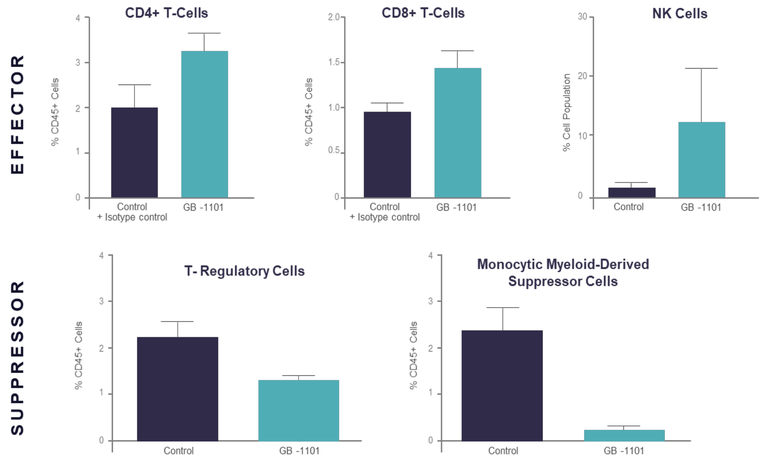
GB-1101 – Tolerated by Immune Effector Cells



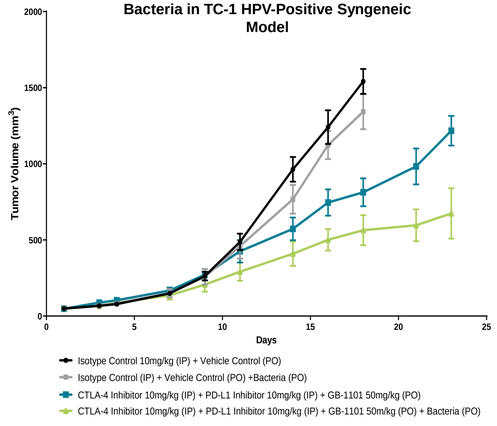
GB-1101 – Potent Combination Interaction with Immune Checkpoint mAbs in Syngeneic Mouse Tumor Models



GB-1101 – Reprograms the Tumor Microenvironment



GB-1101 Synergizes with Checkpoint Inhibitors in Combination with Commensal Bacteria in TC-1 HPV-Positive Syngeneic Model



GB-1101 – Orally Bioavailable Small Molecule

PK Parameters	GB-1101	
	1.0 mg/kg IV	5.0 mg/kg PO
Half life (hr)	1.05	1.52
Tmax (hr)		1.00
Cmax (ng/mL)		1619.19
C0 (ng/mL)	1058.71	
$AUC_{0\text{-last}}$ (hr*ng/mL)	601.72	8120.57
$AUC_{0\text{-inf}}$ (hr*ng/mL)	605.89	8120.74
AUC %Extrap	0.69	0.00
Vss (L/Kg)	1.69	
Vz/ F obs (L/Kg)		1.35
Cl/ F obs (L/hr/Kg)	1.65	0.62
MRTinf_obs (hr)	1.02	3.01
%F		>100%

CONCLUSIONS

- GB-1101 is a single digit nanomolar inhibitor of HDAC6.
- In sharp contrast with pan-HDAC inhibitors, isoform restricted HDAC inhibition revokes tumor immune privilege.
- GB-1101 is an orally bioavailable structurally rigid compound with a %F of 100%.
- RNASeq analysis of GB-1101 exposed human cancer cells reveal potent induction of MHC Class I/II genes and re-expression of multiple cancer neoantigens.
- Unlike pan-HDAC inhibitors, GB-1101 is not cytotoxic to human immune effector cells even at exaggerated concentrations.
- GB-1101 acts synergistically with immune checkpoint inhibitors eliciting tumor growth inhibition in two syngeneic mouse models.
- GB-1101 dramatically increases $CD4^+$, $CD8^+$ T Cells and NK Immune Effector cells in the tumor microenvironment.
- GB-1101 significantly decreases T-Regulatory and Myeloid-Derived Suppressor cells in the tumor microenvironment.
- GB-1101 is progressing toward IND-enabling studies and P1 clinical development