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Inhibition of HDAC3 Induces BRCAness and Potent Synergy with PARP Inhibition in Neuroendocrine Prostate and Small Cell Lung Cancers

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Translational Drug Development (TD2)

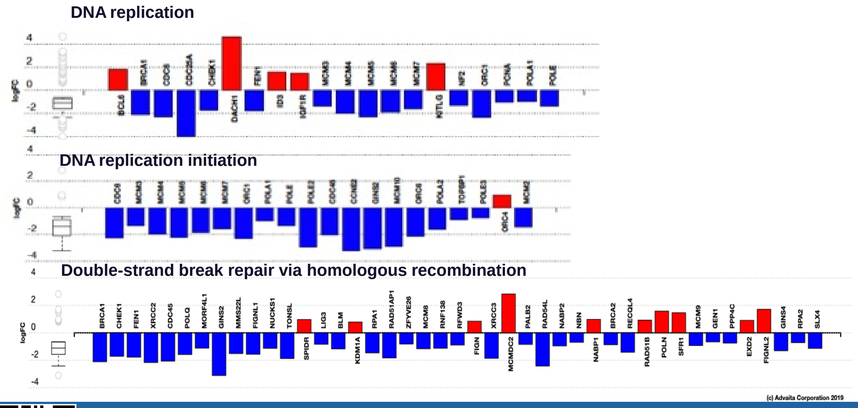
ABSTRACT

HDAC3 is essential for transcriptional repression and is required for the activity of NCOR1 & SMRT co-repressors complexes. Inhibition of HDAC3 results in the suppression of genes responsible for DNA damage repair and maintenance of genomic stability. HDAC3/NCOR1 also play critical roles in tumor metabolism and immune cell biology. GB-3103 is a novel and potent inhibitor of HDAC3 with an IC_{50} of 0.56nM that was tested for activity against human neuroendocrine prostate (NEPC) and small cell lung cancers (SCLC). RNA-seq analysis of GB-3103 treated human tumor cells revealed induction of BRCAness, inhibition of genes from DNA repair pathways and inhibition of PI3K-AKT1, MYC and p53 signaling. GB-3103 showed potent in vitro anticancer activity against the human H660 NEPC line, with an IC_{50} of 28nM, and 21nM against the murine PNEC30 line and potent IC_{50} of 16nM against NCI-H209 human lung neuroendocrine cancer. Because of the potent induction of BRCAness we used zero interaction potency (ZIP) model to test the activity of the combination of GB-3103 with a PARP inhibitor against human H660 and murine PNEC30 cell lines. These experiments revealed synergy for the combination of PARPi with GB-3103 in NEPC. GB-3103 was subsequently tested alone and in combination with olaparib in a xenograft model of H660. GB-3103 (TGI=3%) showed minimal activity at the selected dose against H660 compared to single agent olaparib (TGI=67%). However, when combined with olaparib, GB-3103 revealed potent synergy (TGI=96%, p<0.01). In the NCI-H209 human lung neuroendocrine xenograft model, GB-3103 showed robust activity as a single agent (TGI=83%) compared to single agent olaparib (TGI=33%) and single agent talazoparib (TGI=69%). When combined with olaparib, GB-3103 induced synergistic antitumor effect (TGI=99%, p<t0.001) when compared to olaparib treatment alone. When combined with talazoparib, GB-3103 induced synergistic antitumor effect (TGI >100%, p<0.001) when compared to talazoparib treatment alone. Taken together, these data confirm the important role of HDAC3 in neuroendocrine prostate and small cell lung cancers and suggest HDAC3 inhibition by GB-3103 could be an effective approach for patients with neuroendocrine cancers particularly when combined with inhibitors of PARP.

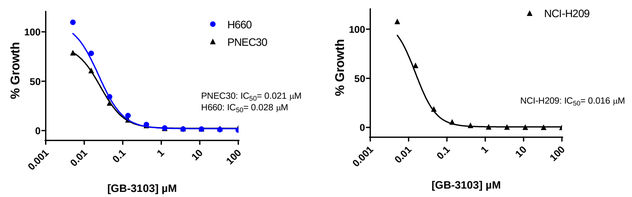
GB-3103 – Potent Selective Inhibitor of HDAC3

Compound	HDAC1 IC_{50} nM	HDAC2 IC_{50} nM	HDAC3 IC_{50} nM	HDAC4 IC_{50} 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-3103	1	5.27	**0.5645**	138	73.5	0.706	34.5	133	187	2.03	5780

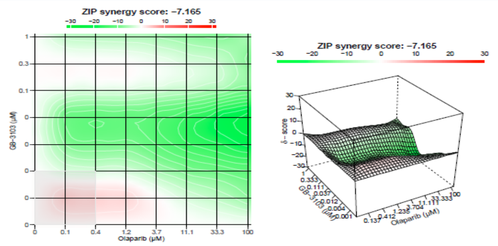
GB-3103 – RNA-seq Broad Effects on DNA Replication and Repair



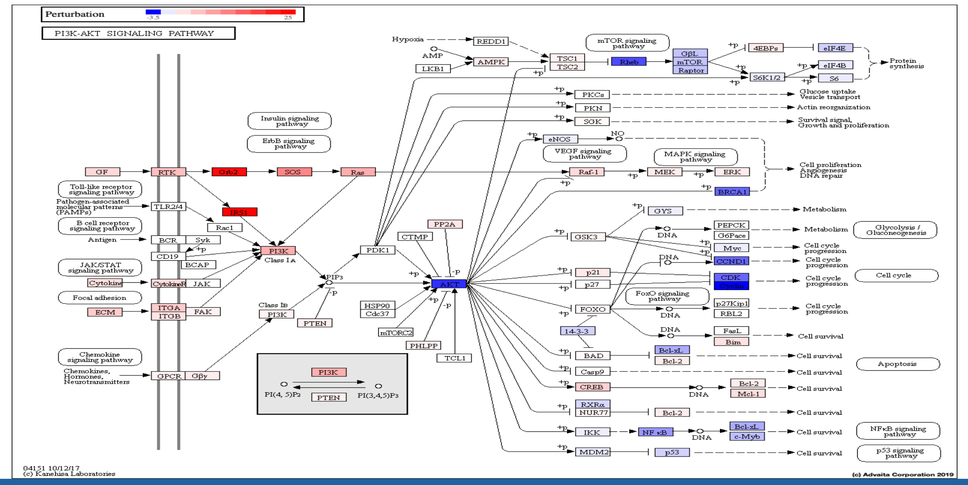
GB-3103 – In Vitro Activity in NEPC and SCLC



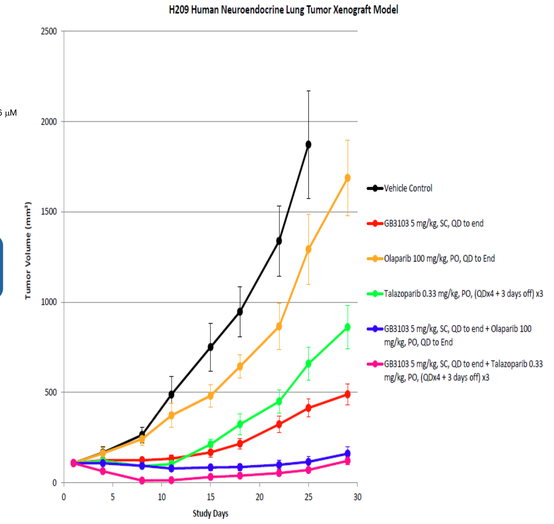
GB-3103 and Olaparib –Targeted Concentrations Show Potential for Synergy in NEPC

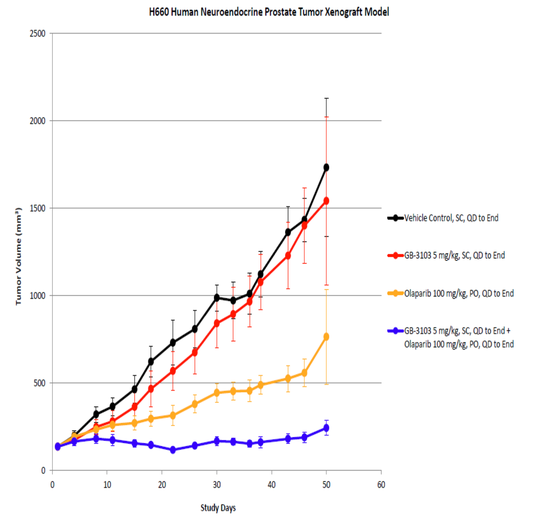


GB-3103 – Pathway Perturbation Plot Reveals Suppression of AKT



GB-3103 – Acting Synergistically with PARP Inhibitors in Xenograft Models of Human Neuroendocrine and SCL Cancers





CONCLUSIONS

- GB-3103 is a subnanomolar HDAC3 inhibitor.
- RNASeq analysis shows GB-3103 inhibits DNA repair pathway genes, inducing BRCAness, as well as PI3K-AKT1, MYC and p53 genes.
- GB-3103 elicits potent single agent anticancer activity in vitro against human and murine neuroendocrine tumor cell lines.
- Combination of GB-3103 with a PARP inhibitor against neuroendocrine cell lines revealed synergy in targeted concentrations using in vitro screens.
- GB-3103 is synergistic with PARP inhibitors in vivo, resulting in significant tumor growth inhibition in H660 neuroendocrine prostate and NCI-H209 small cell lung xenograft models.
- Potent HDAC3 inhibition by GB-3103 could be an effective approach for patients with neuroendocrine cancers
- Given the potent inhibition of DNA repair pathways, GB-3103 will have utility in enhancing PARP inhibitor activity in homologous repair proficient tumors or in overcoming PARP inhibitor resistance in homologous repair deficient tumors.