

# Small Molecule Inhibitors as an Alternative to Antibody Blockade in Immunotherapy

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inhibits binding and release from the active site. This allows “primed” substrates that have accumulated in high levels to compete for the active site and become phosphorylated by GSK-3.

We have previously shown that inhibition of GSK-3 resulted in a down-regulation of *Pdcd1* (PD-1) transcription via upregulation of the transcription factor Tbet [26]. This led to enhanced cytotoxic functionality of CD8<sup>+</sup> T cells and increased levels of IFN- $\gamma$  and Granzyme B expression, promoting viral clearance [26]. Further to this our current work shows that inhibition of GSK-3 can control B16 and EL4 tumour growth and is as effective as PD-1 blockade [27].

We have shown *in vitro* inhibition of GSK-3 by SMIs or siRNA to act primarily in CD8<sup>+</sup> T cells reducing PD-1 expression. This inhibition has been shown further using SMIs *in vivo* in comparison to anti-PD-1 mAb treatment. T cells from GSK-3<sup>-/-</sup> mice also showed a reduction in PD-1 expression and B16 pulmonary metastasis was reduced to a similar extent in both *Pdcd1*<sup>-/-</sup> and GSK-3<sup>-/-</sup> mice. Both

17. Chen Y, Zhou C, Ji W, Mei Z, Hu B, et al. (2016) ELL targets c-Myc for proteasomal degradation and suppresses tumour growth. *Nat Commun* 7: 11057.
18. Gao J, Ward JF, Pettaway CA, Shi LZ, Subudhi SK, et al. (2017) VISTA is an inhibitory immune checkpoint that is increased after ipilimumab therapy in patients with prostate cancer. *Nat Med* 23: 551-555.
19. Koyama S, Akbay EA, Li YY, Herter-Sprie GS, Buczkowski KA, et al. (2016) Adaptive resistance to therapeutic PD-1 blockade is associated with upregulation of alternative immune checkpoints. *Nat Commun* 7: 10501.
20. Embi N, Rylatt DB, Cohen P (1980) Glycogen synthase kinase-3 from rabbit skeletal muscle. Separation from cyclic-AMP-dependent protein kinase and phosphorylase kinase. *Eur J Biochem* 107: 519-527.
21. Woodgett