Thongon N, Castiglioni I, Zucal C, Latorre E, D'Agostino VG, Bauer I, Pancher M, Ballestrero A, Feldmann G, Nencioni A, Provenzani A. The GSK3β inhibitor BIS I reverts YAP-dependent EMT signature in PDAC cell lines by decreasing SMADs expression level. *Oncotarget* Mar 28 2016. [Epub ahead of print].

The Yes-associated protein, YAP, is a transcriptional co-activator, mediating the Epithelial to Mesenchymal Transition program in pancreatic ductal adenocarcinoma (PDAC). With the aim to identify compounds that can specifically modulate YAP functionality in PDAC cell lines, we performed a small scale, drug-based screening experiment using YAP cell localization as the read-out. We identified erlotinib as an inducer of YAP cytoplasmic localization, an inhibitor of the TEA luciferase reporter system and the expression of the bona fide YAP target gene, Connective Tissue Growth Factor CTGF. On the other hand, BIS I, an inhibitor of PKCδ and GSK3β, caused YAP accumulation into the nucleus. Activation of β-catenin reporter and interfering experiments show that inhibition of the PKCδ/GSK3β pathway triggers YAP nuclear accumulation inducing YAP/TEAD transcriptional response. Inhibition of GSK3β by BIS I reduced the expression levels of SMADs protein and reduced YAP contribution to EMT. Notably, BIS I reduced proliferation, migration and clonogenicity of PDAC cells in vitro, phenocopying YAP genetic down-regulation. As shown by chromatin immunoprecipitation experiments and YAP over-expressing rescue experiments, BIS I reverted YAP-dependent EMT program by modulating the expression of the YAP target genes E-cadherin, vimentin, CTGF and of the newly identified target, CD133. In conclusion, we identified two different molecules, erlotinib and BIS I, modulating YAP functionality although via different mechanisms of action, with the second one specifically inhibiting the YAP-dependent EMT program in PDAC cell lines.