Differential TEAD isoform expression in TCGA tumor samples suggests YAP/TAZ target genes were SWP35 at well binding was also 1 25 Pan15 30 rational target given its central position in 10:2515. MW < 400 SW was hERG blockade IC50 > 10 μM TEAD palmitoylation is required for transcriptional activity and can be "cell proliferation of Hippo 15

References
2. Deconinck et al., 2016, Cancer Cell 29:783-803

Conclusion
1. SW-682 is a novel pan-TEAD inhibitor that inhibits TEAD-dependent gene expression with low nanomolar potency
2. SW-682 blocks in vitro cell proliferation of Hippo tumor cells but not wild-type Hippo tumor cells
3. SW-682 is efficacious in vivo in mesothelioma models and caused dose-dependent tumor regression in xenograft model
4. Treatment with SW-682 led to significant down-regulation of YAP/TAZ target gene expression and cell proliferation and survival signatures in tumor cells
5. SW-682 is orally bioavailable and demonstrated favorable tolerability in GLP toxicity studies
6. Combination of SW-682 with a MEK inhibitor, mitametinib, increased apoptosis in Hippo tumor cell lines in vitro

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Abstract
Many cancers harbor mutations in the Hippo pathway that lead to constitutive activation of the transcriptional co-activators YAP/TAZ that in turn drive aberrant proliferation and survival. To understand the impact of these mutations on YAP/TAZ function and to develop appropriate therapeutic strategies, we performed a comprehensive analysis of the TEAD isoform expression across multiple Hippo-mutant cell lines and tumor samples. In vitro, SW-682 inhibited the proliferation of human Hippo-mutant mesothelioma cells with nanomolar potency, with little to no effect on Hippo-wildtype tumor cells. SW-682 down-regulated TEAD-dependent reporter gene expression in a dose-dependent manner, while having no effect on reporters monitoring other pathways. In vivo, daily oral administration of SW-682 in tumor-bearing mice resulted in tumor regression in Hippo-mutant mesothelioma models and caused decreased expression of the TEAD-dependent genes CCN1 and CCN2 and a YAP gene signature in mesothelioma models and caused decreased expression of the TEAD-dependent genes CCN1 and CCN2 and a YAP gene signature. In summary, SW-682 causes potent and selective inhibition of TEAD transcription with low nanomolar potency, and in combination with a MEK inhibitor, it causes cell death and regression of mesothelioma xenografts in vivo.

Background
Hippo Pathway active YAP inactive YAP active

TEAD isoforms are differentially expressed in tumor tissues and SW-682 binds all isoforms

Components

- SW-682 down-regulates TEAD-dependent reporter gene assay (RGA) and is not a RGA reporter counter-screen
- Mesothelioma cell lines harboring Hippo mutations are sensitive to SW-682, in contrast to Hippo-WT cells (HT26)
- SW-682 also inhibits the proliferation of normal-mesothelioma cell tumor cell lines that carry Hippo pathway gene mutations

Down-regulation of cell proliferation and cell survival signatures in H226 tumors by SW-682

Combination of SW-682 with a MEK inhibitor increased apoptosis in Hippo-mutant tumor cells

Conclusions

- Gene set enrichment analysis demonstrated down-regulation of cell cycle, mTORC, KRAS and growth factor related signatures in SW-682 treated H226 tumors compared to vehicle-treated group
- Combination of SW-682 with a MEK inhibitor, mitametinib, increased apoptosis in Hippo-mutant cell lines in vitro

References
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