AACR Abstract #4964

SW-682: a novel TEAD inhibitor for the treatment of cancers bearing mutations in the Hippo signaling pathway

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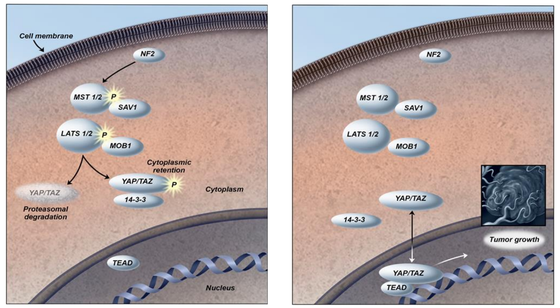
Abstract

Many cancers harbor mutations in the Hippo pathway that lead to constitutive activation of the transcriptional co-activators YAP/TAZ that then bind the transcription factor TEAD and drive aberrant transcription of target genes involved in cell proliferation and tumor progression[1]. Hyperactivation of YAP/TAZ has also been associated with resistance to targeted therapies, including MAPK pathway inhibitors[3]. To target cancers that bear mutations in the Hippo pathway or are resistant to therapies due to YAP/TAZ activation, we developed SW-682, a pan-TEAD small molecule inhibitor that blocks TEAD-dependent transcription by binding to the palmitoylation pocket. *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[4], as measured by RNA-seq analysis. SW-682 has a favorable PK profile with good oral bioavailability in mouse and was well tolerated with no adverse effects noted or body weight loss throughout the study period. To test the hypothesis that TEAD inhibition can overcome YAP-driven resistance mechanisms, we explored SW-682 in combination with MEK inhibitors *in vitro* in tumor cell lines that carry Hippo pathway mutations. In summary, SW-682 is a potent and selective investigational TEAD inhibitor which demonstrated anti-tumor effects in mouse models harboring aberrant expression of the Hippo pathway, suggesting therapeutic potential in multiple Hippo-mutant solid tumors.

Background

Hippo Pathway Active
YAP Inactive

Hippo Pathway Inactive
YAP Active

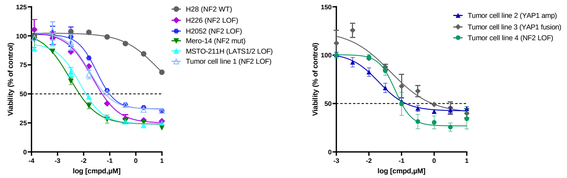


- Hippo pathway is genetically altered in approximately 10% of cancers and is generally associated with poor patient outcomes[2]
- TEAD inhibition represents a rational target given its central position in integrating Hippo pathway signaling
- TEAD palmitoylation is required for transcriptional activity and can be antagonized with potent and selective small molecules
- Targeting TEAD offers multiple monotherapy and combination therapy opportunities guided by a biomarker-driven development approach

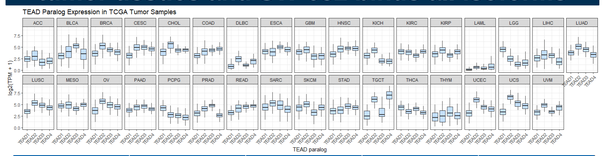
SW-682 causes potent and selective inhibition of proliferation of Hippo-mutant tumor cell lines

Compound	TEAD RGA IC_{50} (nM) HEK293	HIF1 RGA IC_{50} (nM) HEK293 (Negative Control)	Proliferation IC_{50} (nM) H226 (NF2 LOF)	H2052 (NF2/ LATS2m)	MSTO-211H (LATS1/2 del)	Mero-14 (NF2m)	H28 (WT) (Negative Control)
SW-682	3	>3,000	19	32	7	3	>10,000

- SW-682 displays low nanomolar inhibition in TEAD-dependent reporter gene assay (RGA) and not in a HIF1 RGA counter-screen
- Mesothelioma cell lines harboring Hippo mutations are sensitive to SW-682, in contrast to Hippo-WT cells (HT28)
- SW-682 also inhibits the proliferation of non-mesothelioma tumor cell lines that carry Hippo pathway gene mutations



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

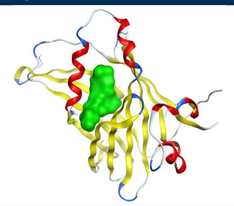


Compound	TEAD1 (°C)	TEAD2 (°C)	TEAD3 (°C)	TEAD4 (°C)
SW-682	12.0	10.2	16.7	11.1

- Differential TEAD isoform expression in TCGA tumor samples suggests equipotent inhibition of all TEAD isoforms may be needed for optimal activity
- SW-682 showed robust TEAD binding to all TEAD isoforms, suggesting an attractive inhibitory profile
- Compound binding to TEAD isoforms was measured by Thermal Shift Analysis following incubation with 10 µM of SW-682; binding was also confirmed by AlphaScreen P-pocket competition assay (data not shown)

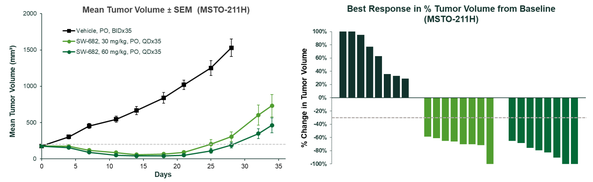
SW-682 is a potent, drug-like, pan-TEAD inhibitor

- MW < 400
- TPSA < 90
- Pan-TEAD binder
- hERG blockade IC50 > 10 µM
- No CYP IC50 < 10 µM (7 isoforms)
- Binding mode confirmed by high-resolution co-crystal structure (TEAD1)

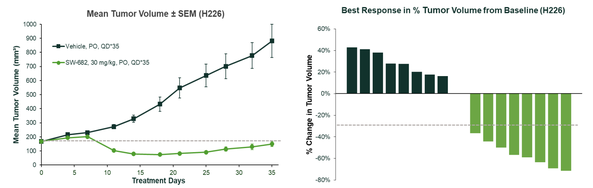


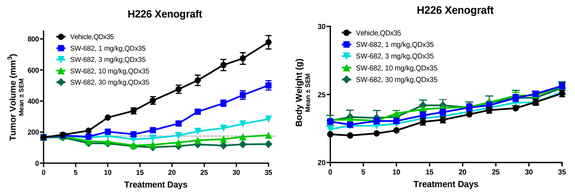
SW-682 demonstrates robust anti-tumor activity in mesothelioma xenograft models *in vivo*

MSTO-211H (LATS1/2 del)



H226 (NF2 del)

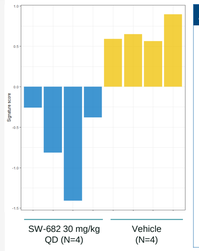




- Tumor regressions observed with SW-682 at well-tolerated daily oral doses with no effects on body weight
- SW-682 exhibits rapid absorption and good oral bioavailability in mouse models (data not shown)

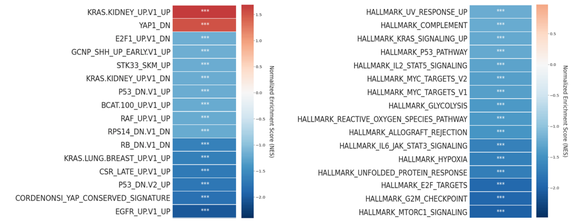
SW-682 significantly down-regulated YAP/TAZ target genes in H226 mesothelioma model

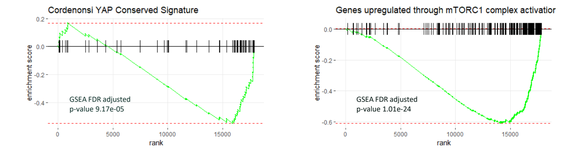
- HT226 mesothelioma xenograft, dosed for 35 days
- YAP signature[4] score for each sample was calculated as the mean of the z-values for each gene across all samples.
- YAP/TAZ target genes were significantly downregulated in SW-682-treated groups, indicating on-target activity in inhibiting YAP/TAZ signaling in H226 tumors



Gene Name	Log Fold Change	P-value	Adjusted p-value
IGFBP3	-4.87	2.37E-46	5.43E-44
NT5E	-3.85	3.12E-47	7.62E-45
F3	-3.57	2.33E-21	6.75E-20
CCN1	-2.32	1.39E-41	2.32E-39
NUAK2	-1.90	5.95E-27	3.05E-25
ANKRD1	-1.87	1.32E-16	2.39E-15
AXL	-1.67	1.56E-32	1.29E-30
GADD45A	-1.52	5.29E-21	1.46E-19
TGFB2	-1.34	9.31E-07	4.60E-06
CCN2	-1.31	3.75E-15	5.84E-14
AMOTL2	-0.72	2.77E-10	2.32E-09
LATS2	-0.60	9.35E-10	7.29E-09
FJX1	-0.54	2.05E-05	7.78E-05
DOCK5	-0.50	4.54E-06	1.94E-05
MYOF	-0.39	2.85E-07	1.51E-06
FOXF2	-0.37	0.002	0.006
CRIM1	-0.23	0.008	0.017

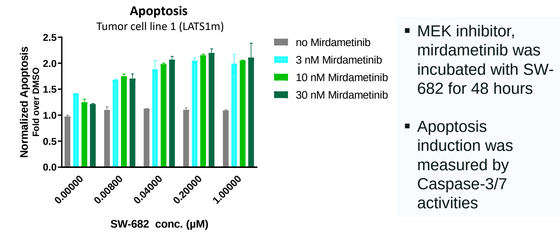
Down-regulation of cell proliferation and cell survival signatures in H226 tumors by SW-682





- Gene set enrichment analysis demonstrated down-regulation of cell cycle, MYC, 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 increased apoptosis in Hippo-mutant tumor cells



- MEK inhibitor, mirdametinib was incubated with SW-682 for 48 hours
- Apoptosis induction was measured by Caspase-3/7 activities

Conclusions

- SW-682 is a novel pan-TEAD inhibitor that inhibits TEAD-dependent gene transcription with low nanomolar potency
- SW-682 blocks *in vitro* cell proliferation of Hippo-mutant tumor cells but not wild-type Hippo tumor cells
- SW-682 is efficacious *in vivo* in two mesothelioma models and caused dose-dependent tumor regression in xenograft model
- Treatment with SW-682 led to significant down-regulation of YAP/TEAD target gene expression and cell proliferation and survival signatures in tumor cells
- SW-682 is orally bioavailable and demonstrated favorable tolerability in GLP toxicology studies
- Combination of SW-682 with a MEK inhibitor, mirdametinib, increased apoptosis in Hippo-mutant cell lines *in vitro*

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References

1. Sanchez-Vega et al., 2018, *Cell* 173:321-337.
2. Zanconato et al., 2016, Cancer Cell 29:783-803
3. Barry et al., 2021, *Cells* 10:2515.
4. Wang et al., 2018, *Cell Reports* 25:304-1317.