AACR Abstract #3945

Novel antagonists of TEAD palmitoylation inhibit the growth of Hippo-altered cancers in preclinical models

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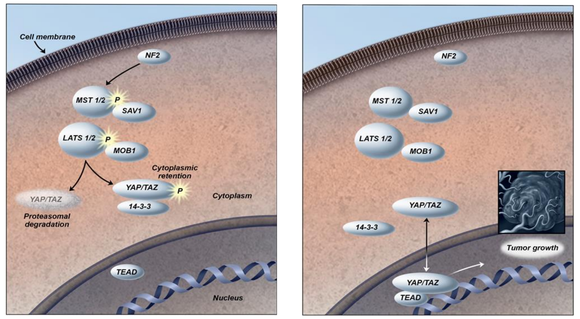
Introduction

The Hippo pathway is an evolutionarily conserved signaling cascade whose deregulation can promote excessive cell proliferation and tumor development. Pathway output is mediated by the YAP and TAZ transcriptional co-activators, which bind to TEAD family transcription factors to drive target gene expression[1]. Genomic aberrations in Hippo pathway components result in constitutive activation of YAP/TAZ, as seen with NF2 or LATS1/2 loss of function mutations in subsets of mesothelioma and other cancers[2]. Hyperactivation of YAP/TAZ has also been associated with resistance to a variety of targeted agents, including EGFR and MEK inhibitors, suggesting that targeting the pathway may be useful for rational combinations, in addition to genomically-informed monotherapy applications[3]. Activity of the YAP/TAZ-TEAD complex thus represents a compelling pharmacologic target, due to its essential role in the pathway, and the presence of a conserved druggable site in TEAD that is required for transcriptional function. Here, we identified novel pan-TEAD inhibitors that had *in vitro* and *in vivo* activity in Hippo mutant tumor models

Background

Hippo Pathway Active
YAP Inactive

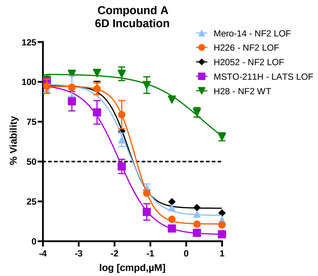
Hippo Pathway Inactive
YAP Active



- 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
- Multiple monotherapy and combination therapy opportunities guided by a biomarker-driven development approach

TEAD inhibitors antagonize proliferation of Hippo mutant tumor cells

- Potent and selective inhibitors of TEAD transcriptional output were generated and assessed by a TEAD-dependent reporter gene assay (RGA), with a HIF1 counter-screen
- Tumor cell lines harboring Hippo mutations are sensitive to TEAD inhibition, in contrast to Hippo WT cells



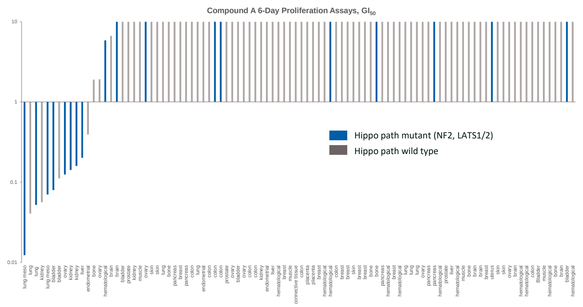
Compound	TEAD RGA IC_{50} (nM) HEK293	HIF1 RGA IC_{50} (nM) HEK293 (Negative Control)	Proliferation IC_{50} (nM) H226 (NF2-)	H2052 (NF2/ LATS2m)	MSTO-211H (LATS1/2 del)	Mero-14 (NF2 LOF)	H28 (WT) (Negative Control)
K-975	6	>3,000	60	40	59	16	>10,000
A	6	>3,000	47	29	13	24	>10,000
B	13	>3,000	47	28	25	NT	>10,000
C	3	>3,000	19	32	7	3	>10,000
D	15	>3,000	86	157	63	60	2,700
E	2	>3,000	30	>10,000	NT	NT	>10,000

Identification of pan-TEAD inhibitors that bind all isoforms

Compound	RGA IC_{50} (nM)	TEAD1 (°C)	TEAD2 (°C)	TEAD3 (°C)	TEAD4 (°C)
K-975	6	6.9	8.7	6.3	6.0
A	6	7.5	5.0	2.0	6.0
B	13	5.8	4.3	2.6	9.7
C	3	12.0	10.2	16.7	11.1
D	15	10.0	8.5	7.6	8.4
E	2	11.1	12.3	15.8	11.5

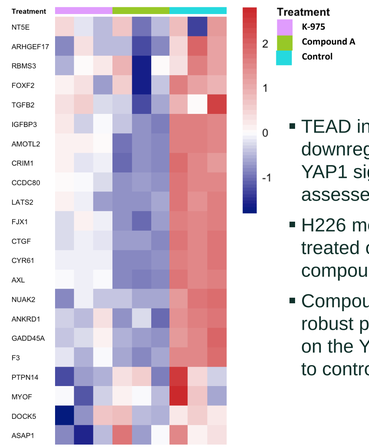
- Differential TEAD isoform expression in tumor cell lines (data not shown) suggests equipotent inhibition of all TEAD isoforms may be needed for optimal activity
- Several tested compounds show robust pan-TEAD binding via Thermal Shift Analysis, suggesting an attractive inhibitory profile
- T_m shift assessed following incubation with 10 µM of compound

Sensitivity to TEAD inhibitors is enriched in Hippo mutant tumor cell lines



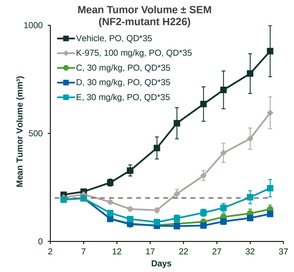
- Sensitivity to TEAD inhibition in a cancer cell line panel is enriched in cells with homozygous deletions of key Hippo pathway constituents
- Annotation of pathway mutations based on data available at cBioPortal

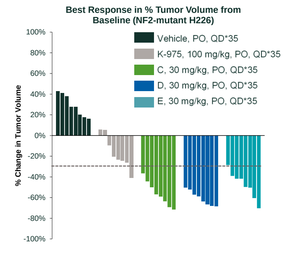
TEAD inhibitors downregulate transcription of YAP1 signature genes

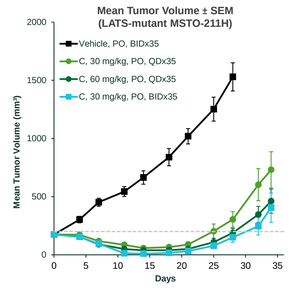


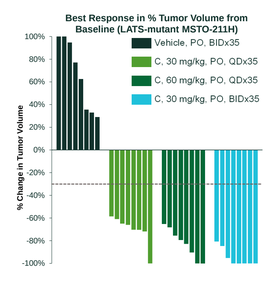
- TEAD inhibitors cause downregulation of a validated YAP1 signature gene set[4], assessed using RNAseq
- H226 mesothelioma cells were treated overnight with 100 nM of compound
- Compound A demonstrates a robust pharmacodynamic effect on the YAP1 signature relative to control and comparator K-975

TEAD inhibitors produce robust tumor regressions *in vivo*









- Tumor regressions seen at well-tolerated daily oral doses
- No effects on body weights observed (data not shown)

Conclusions

- We have discovered and optimized novel pan-TEAD inhibitors that bind all TEAD isoforms with low nanomolar potency
- TEAD inhibitors block *in vitro* tumor cell proliferation of Hippo mutant tumor cells and not wild-type Hippo tumor cells
- *In vivo* efficacy was demonstrated in two mesothelioma models (NF2 mutant and LATS mutant) at well-tolerated doses
- SpringWorks' TEAD inhibitors are being developed for both monotherapy and combination therapy use in Hippo mutant tumors guided by a biomarker-driven development approach

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References

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