Potent small molecule TEAD inhibitors targeting the Hippo pathway exhibit anti-proliferation in vitro and anti-tumor effect in vivo

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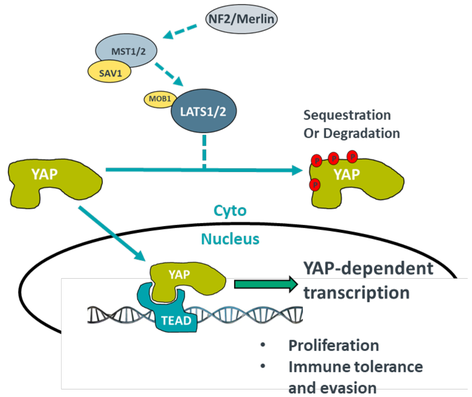
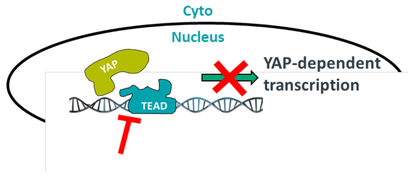
Poster #2474

Hippo pathway overview



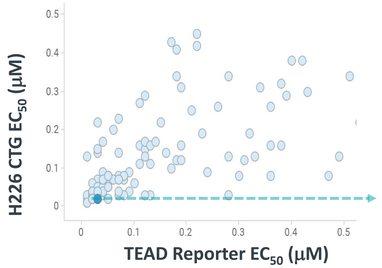
- Important signaling pathway for modulating cell growth and survival; often promiscuously activated by oncogenes to promote tumor growth.
- Highly mutated pathway across many indications in cancer; pathway activation is correlated with overall poor patient outcome.
- Multiple layers of regulation control the pathway by restricting nuclear translocation of YAP or TAZ, including sequestration and proteasome-dependent degradation.
- YAP/TAZ interaction with a member of the TEAD family of co-transcription factors drives essential gene transcription.
- Dysregulation can be induced by different mechanisms, such as loss-of-function mutations in upstream regulatory proteins of YAP/TAZ-TEAD, miRNA leading to loss of upstream gene translation, or loss of post-translational modifications of YAP/TAZ.

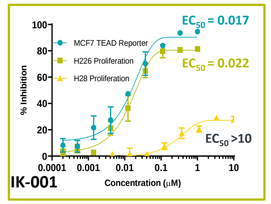


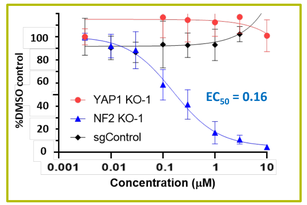
Ikena TEAD Inhibitors

- Novel compounds bind in the central lipid (palmitate) binding pocket of TEAD family members.
- Small molecule inhibitors disrupt YAP-TEAD dependent transcription.

Cell based activity demonstrates potency and selective anti-proliferative effects dependent on Hippo dysregulation







- Inhibition of TEAD-dependent reporter activity (MCF7, NF2 WT) correlates with inhibition of cell proliferation in H226 cells (NF2-deficient)
- Effect of IK-001 on cell proliferation is dependent on presence of Hippo/NF2 mutation (H28 cell line is NF2 wildtype)
- NF2 knockout in H28 cells confers sensitivity to TEAD inhibition

Co-crystal structures demonstrate compounds bind to lipid pocket

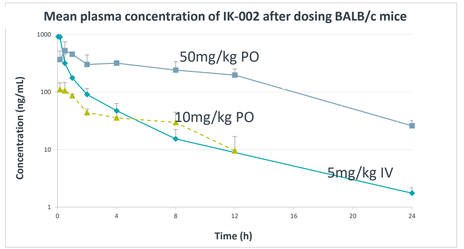
- Multiple high quality TEAD2 co-crystal structures with Ikena compounds
- Co-crystal structures with Ikena's irreversible and reversible inhibitors bound in central lipid pocket
- Observed binding interactions are consistent with established SAR

Anti-proliferation pilot cell line screen reveals additional candidate models of sensitivity for in vivo testing

A2058	*STK11/PTEN*	HT-1080	*IDH1/NRAS*	NCIH2452	*EGFR*
A2780	*PIK3CA/PTEN*	JHH4	*p53*	NCI-H28	*VHL*
A549	*KRAS/STK11*	LN-229	*ERBB2/TEAD2*	NCI-H292	*NF2*
ACHN	*EPHA2/NF2*	LOVO	*KRAS/FBXW7*	NCIH647	*KRAS*
AM-38	*BRAF*	MDAMB231	*KRAS/NF2/(atypicalBRAF)*	OE33	*p53*
ASPC1	*p53/KRAS/CDK2NA*	MDA-MB-468	*p53*	NCI-H2172	*P53/EGFR/FBXW7*
BxPC-3	*p53*	MKN74	*APC*	OVMANA	*PIK3CA*
Caki-1	*NF2*	MSTO211H	*LATS1-PSEN*	PANC-1	*p53/KRAS*
CALU1	*KRAS*	NCI-H1299	*NRAS*	SK-HEP-1	*BRAF/NF2*
Caov-3	*p53*	NCIH1563	*STK11*	SKOV-3	*p53/PIK3CA/FBXW7*
CFPAC1	*p53/KRAS*	NCIH1568	*p53*	SNU182	*p53*
COV362	*EGFR*	NCI-H1650	*EGFR*	SW1353	*CDKN2A/IDH2*
Daoy	*p53*	NCI-H1703	*CDKN2A*	SW1573	*KRAS/STK11*
DETROIT562	*p53/PIK3CA*	NCIH196	*p53/PTEN*	SW579	*p53*
DMS153	*p53/NOTCH1*	NCI-H1975	*P53/EGFR/PIK3CA/CDKN2A*	T24	*HRAS*
DMS53	*p53/STK11*	NCI-H2030	*p53/KRAS*	TE1	*p53/Rb*
DU145	*STK11/NF2*	NCIH2052	*NF2*	U251	*p53/PTEN*
DU4475	*BRAF*	NCIH2085	*p53*	U87MG	*PTEN*
HCC1143	*p53*	NCI-H2228	*p53*	YD8	*p53*
HCC827	*p53/EGFR*	NCI-H226	*NF2*	ZR751	*PTEN*
HCT116	*PIK3CA/KRAS/CDKN2A*				

- Cell lines were chosen based on the Cancer Dependency Score (https://depmap.org/portal/achilles/) and sampling of known interacting oncogenes
- Anti-proliferative effects of IK-001 were evaluated in a 3-day Cell TiterGlo™ assay. Cell lines with an EC_{50} <0.2µM or <1.0µM are indicated
- Analysis is ongoing to explore in vitro to in vivo correlation as well as TEAD-specific expression profiles

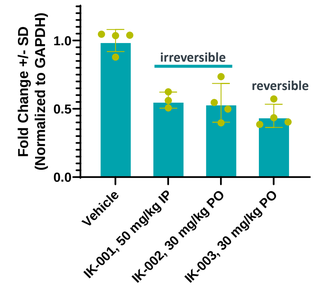
Ikena compounds demonstrate good ADME/PK properties



$T_{1/2}$ = 4.4 h
V_d = 17 L/kg
Oral bioavailability = 26%

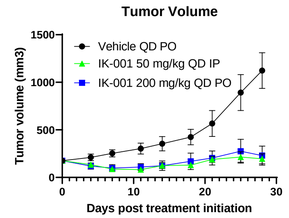
- Plasma levels of IK-002 were quantified from mice after receiving a single administration of compound

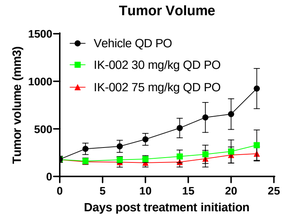
Ikena compounds display TEAD-dependent pharmacodynamic effects



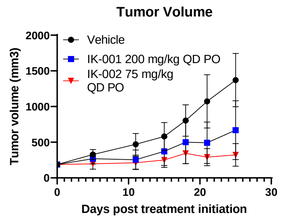
- NCI-H226 tumor bearing mice were dosed for 3 consecutive days and tumors were collected and process 4h after the last dose. RNA was isolated and expression of TEAD-dependent genes was assessed by qPCR.
- Similar effects noted on CYR61, AMOTL2

Antitumor Activity in H226 Xenograft





Antitumor Activity in MSTO-211H Xenograft



- ✓ Robust efficacy with Ikena compounds at well tolerated daily oral doses
- ✓ No effect on body weight or organ damage throughout studies
- ✓ Dose response efficacy studies with advanced leads are in progress

Conclusions and Future Steps

- Ikena identified novel and selective small molecule inhibitors of TEAD with different modes of inhibition (reversible and irreversible) with low nanomolar potency and good oral bioavailability
- Co-crystal structures demonstrate inhibitors bind in central lipid binding pocket
- Oral administration leads to suppression of TEAD-dependent transcription in H226 tumors
- Efficacy was demonstrated in two mesothelioma xenograft models at well tolerated doses
- Ikena's TEAD inhibitors are being developed for cancer therapy in selected cancer patients with Hippo driven tumors
- A development candidate is expected in the second half of 2020

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