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Systems biology-guided indication selection to inform the clinical development of a novel TEAD inhibitor

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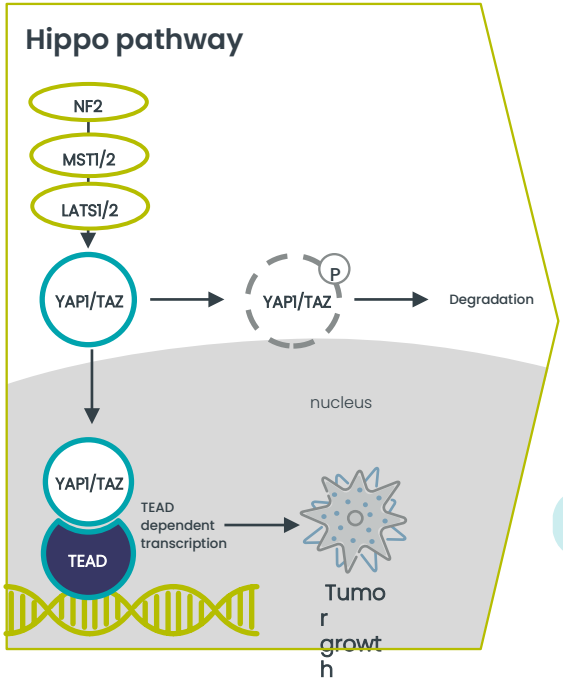
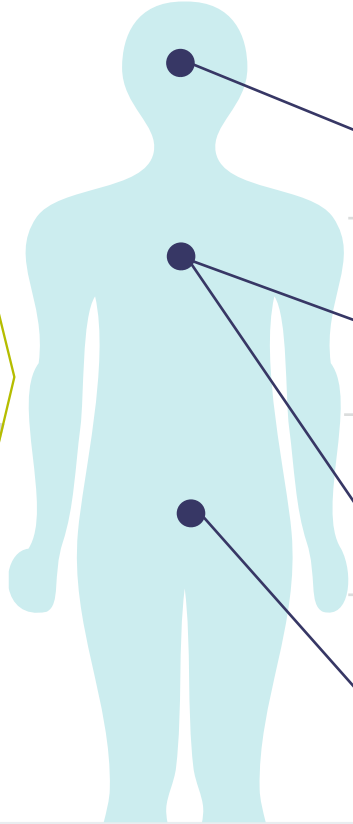
Genetic Alterations in Hippo Pathway are Prevalent in Multiple Cancer Types





Meningioma
- High frequency of NF2 deficiency
- Most common CNS tumor, accounting for ~one-third of primary CNS tumors

Non-small Cell Lung Cancer (Squamous and adenocarcinoma)
- **6%** YAP1 and **29%** TAZ amplification
- Drives resistance to EGFR therapies

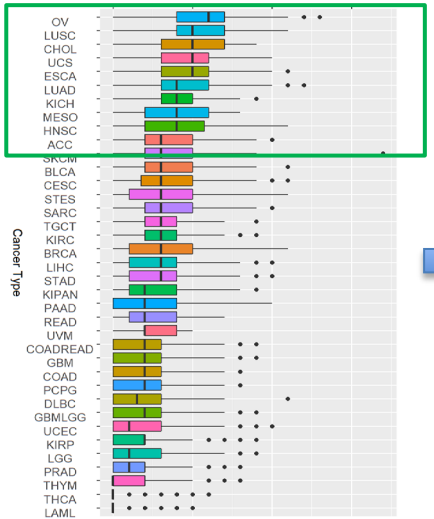
Malignant Mesothelioma
- **~40%** have NF2 deficiency
- Associated with poor patient prognosis

Soft Tissue Sarcoma
- **~90%** of epithelioid hemangioendothelioma, or EHE, have TAZ-CAMTA1 fusions
- 10% of EHE have YAP1-TFE3 fusions

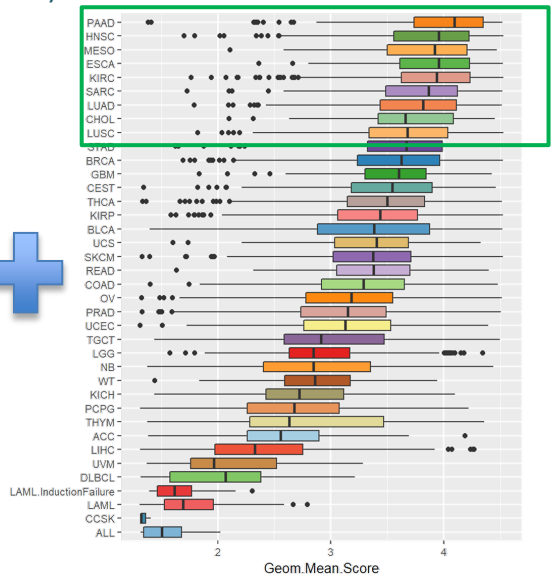
A Genetic & Transcriptional Signature Identifies Cancers with High YAP/TAZ/TEAD Activity

- Genetic and transcriptional analysis of Hippo pathway dependency identifies a common subset of cancers:
  - Mesothelioma (MESO), Cholangiocarcinoma (CHOL) with high prevalence of NF2 deficiency
  - NSCLC and HNSCC characterized by YAP1 or TAZ amplifications

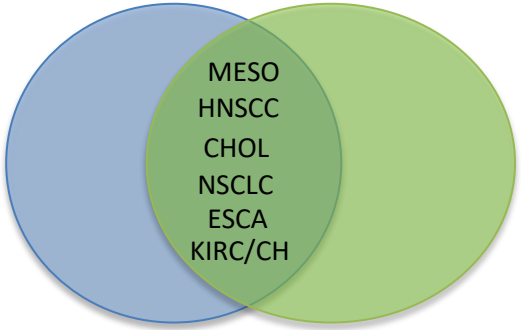
Alterations in Hippo pathway components (NF2, YAP1, TAZ, LATS1/2, MST1/2, BAP1)



YAP1/TAZ activity score*



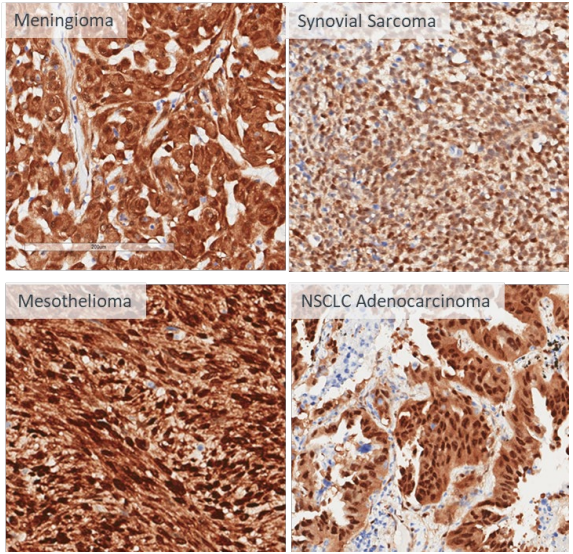
Overlapping tumor types



*Signature derived from Pham et al 2021

IHC of YAP/TAZ in the Nucleus Measures YAP/TAZ/TEAD Activity in Tumor Tissues

Tumor types with Hippo pathway alterations or high YAP1/TAZ gene signature show high YAP1 nuclear protein expression indicative of pathway activation

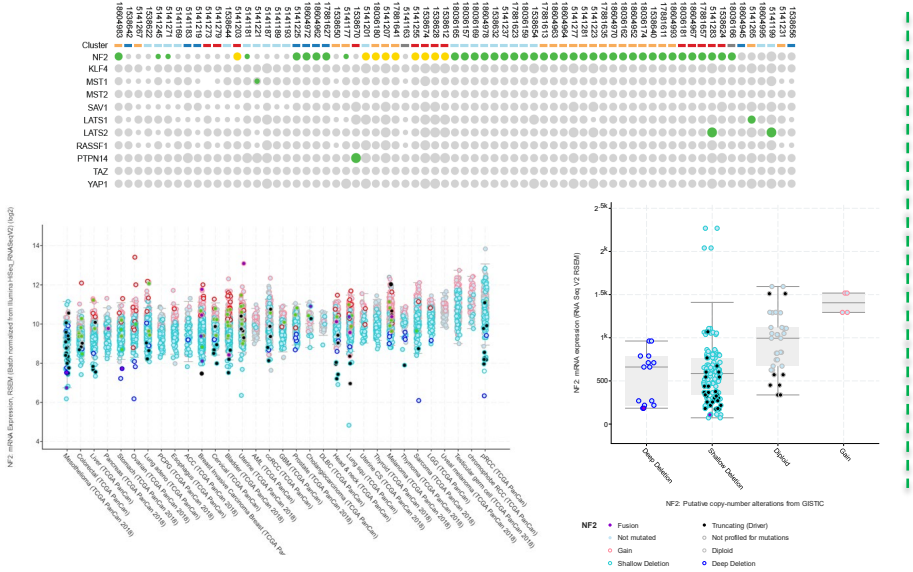


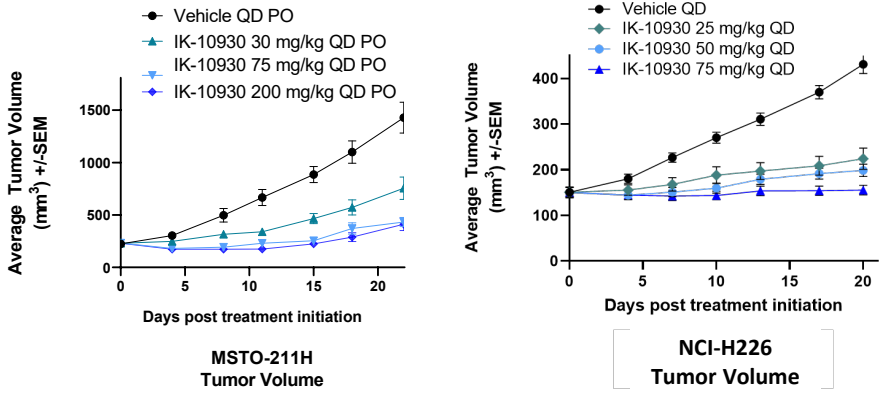
	%YAP1 Nuc +2 +3	%TAZ Nuc +2 +3
Meningioma	76	8
Sarcoma	56	11
Mesothelioma	46	19
Cholangiocarcinoma	31	4
NSCLC	25	10
Pancreas	20	4
Thymoma	10	5
Liver/Hepatocellular	3	1

+2 and +3 denote the highest intensity staining by manual pathology

NF2-Deficient Mesothelioma is a Clinical Development Opportunity For TEAD Inhibitors

- NF2 loss of function mutations, gene copy and chromosome losses are recurrent in mesothelioma (>40%)[1,2]
- Mesothelioma is the tumor type with lowest NF2 expression
- NF2 deficiency has been associated with poor prognosis[3]
- TEAD inhibition drives anti-tumor responses in murine Mesothelioma models *in vivo*

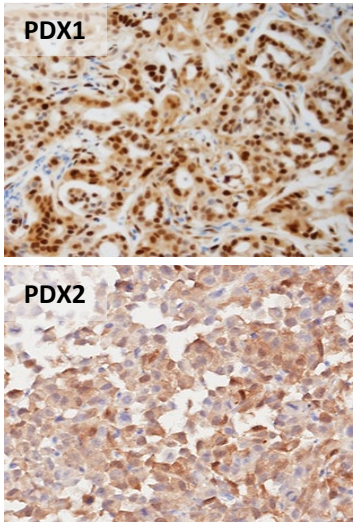


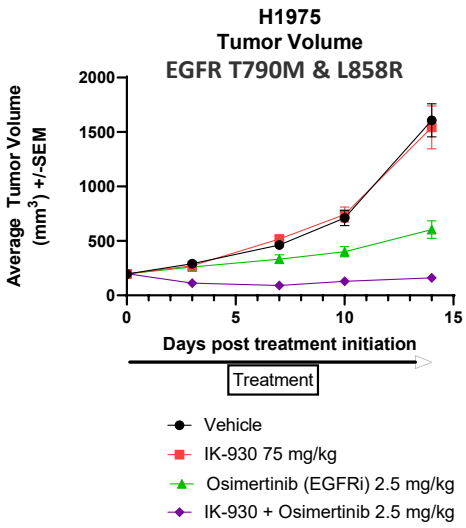


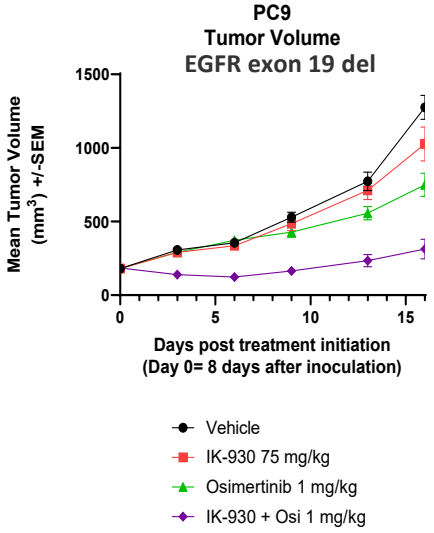
[1]Sato *2018; Bueno, 2016*
[2]*De Rienzo 2016; Neragi-Miandoab 2009; Fletjer 1989*
[3]*Singi 2015; Quetel 2020*

YAP1 Activation Provides A Mechanism Of Resistance To EGFR Inhibitors: Opportunity For Combinations

- YAP1 activation has been described as a mechanism of resistance to multiple targeted therapies such as MEK and EGFR inhibitors in KRAS or EGFR mutant tumors [1,2 (Amidon's P216 EORTC AACR)].
- TEAD inhibitor in combination with Osimertinib shows potent anti-tumor effect in EGFR mutant NSCLC models *in vivo*
- PDX models from patients with acquired resistance to EGFR inhibitors show high YAP1 nuclear expression indicative of active signaling which can be used as a biomarker for patient selection







[1]Kurppa 2020; Bratch 2019
[2]BBRC. 2016 May 20;474(1):154

Conclusions

- NF2 deficient Mesothelioma is the most relevant indication for clinical development of Ikena's TEAD inhibitor as monotherapy, based on genetic, transcriptional, tissue based and pharmacological profiling.

- Our comprehensive bioinformatics analyses of cancer genomics and transcriptomics, and tissue-based screens have identified additional clinical opportunities for TEAD inhibitors as monotherapy and in combination with other agents.

- Biomarkers of elevated YAP/TAZ/TEAD activity could guide combination opportunities for TEAD inhibitors in the clinic, such as with EGFR inhibitors

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