IK-930 is a Novel TEAD Inhibitor for the Treatment of Cancers Harboring Mutations in the Hippo Signal Transduction Pathway

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Disclosure Information

Jeffrey Ecsedy

I have the following relevant financial relationships to disclose:

Employee of: Ikena Oncology

Consultant for: Cytoimmune Sciences

Ikena Disclosure

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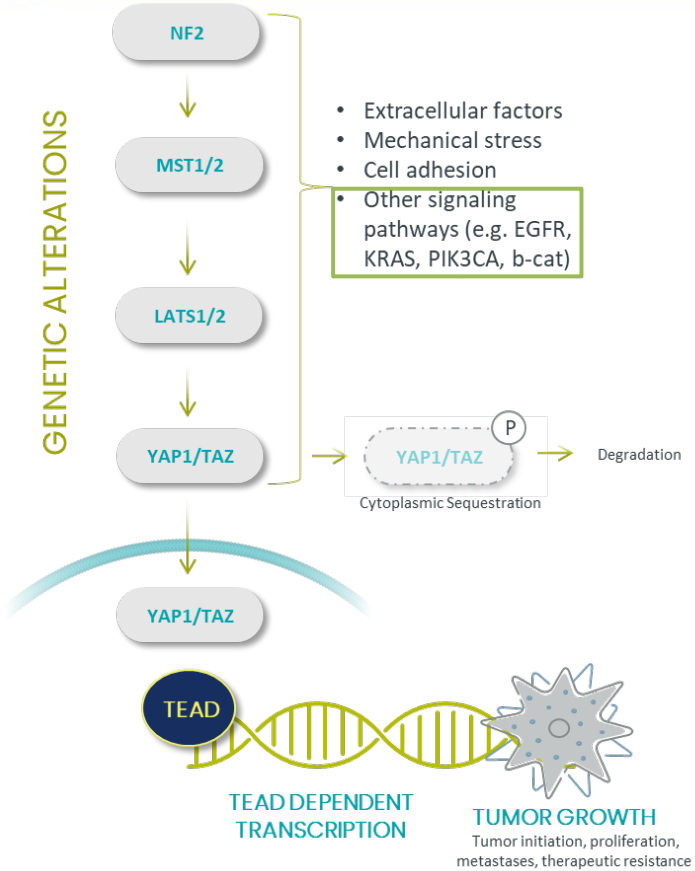
Hippo Signal Transduction Pathway in Cancer



- Multiple activating signals drive
  YAP/TAZ nuclear localization ⇢ TEAD binding ⇢ gene expression of proliferation / pro-survival pathways
- TEAD transcription dysregulated in many cancers
  Numerous tumor suppressor / oncogenes lead to TEAD activation
  Increased nuclear YAP1/TAZ, TEAD activity associated with poor outcome
- Key mechanism of therapeutic resistance

Genetic Alterations in Hippo Signal Transduction Pathway Drive Oncogenesis in Patients Across Multiple Indications

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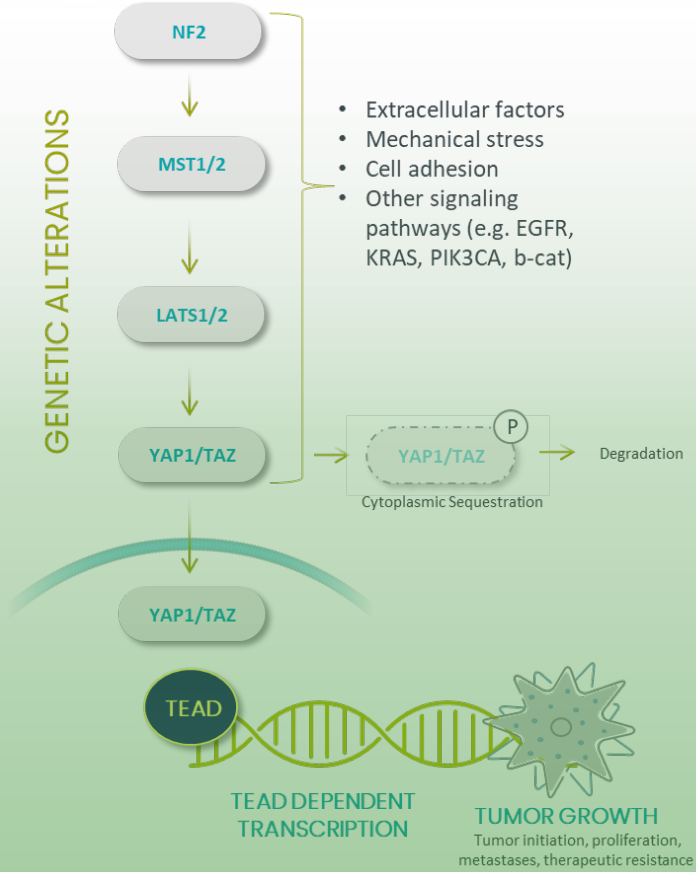
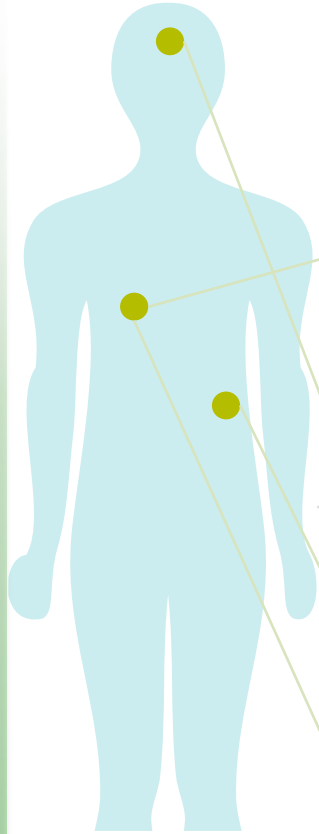




~125,000 Newly Diagnosed Cancer Patients (US Only / Year) with Deregulated Hippo Pathway

Malignant Mesothelioma
- ~**40%** have NF2 loss of function mutations
- Associated with poor patient prognosis
- In both epitheliod and sarcomatoid/byphasic

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

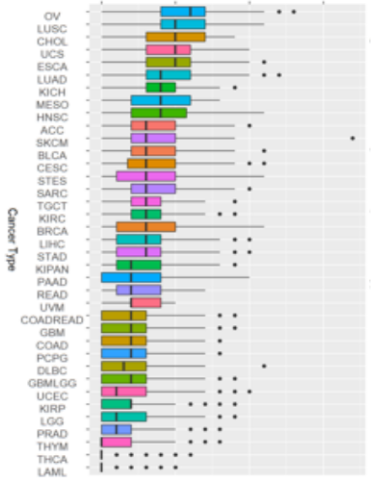
Soft Tissue Sarcoma
- **~90%** of epithelioid hemangioendothelioma, or EHE, have TAZ-CAMTA1 fusions
- 10% of EHE have YAP1-TFE3 fusions

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

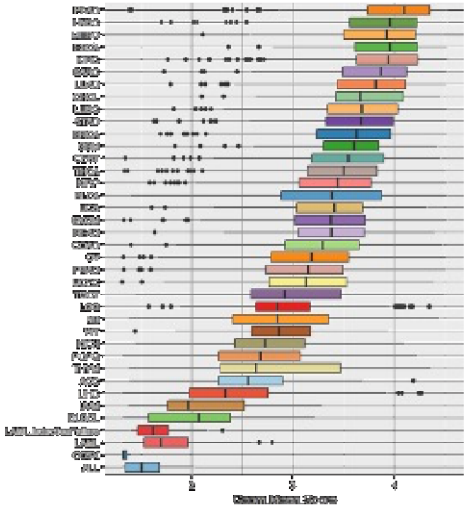
Translational Data to Drive Indication Selection

Bioinformatics Analyses

NF2, YAP1, TAZ, LATS1/2, MST1/2, BAP1 Alterations



YAP1/TAZ Activity Score*

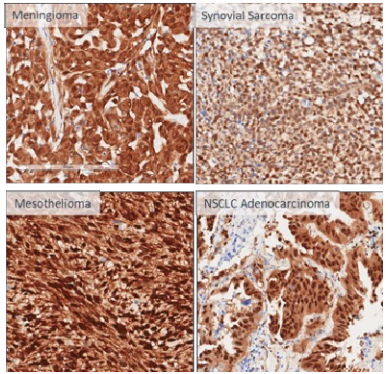


Indications of Interest

MESO, HNSCC, CHOL, NSCLC, Pancreatic

Signature derived from Pham et al 2021

YAP/TAZ Nuclear Localization



High YAP1 nuclear protein expression indicative of pathway activation in select indications

	%YAP1 +2 +3	%TAZ +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

IK-930 is an Oral, Selective, Potent TEAD Inhibitor

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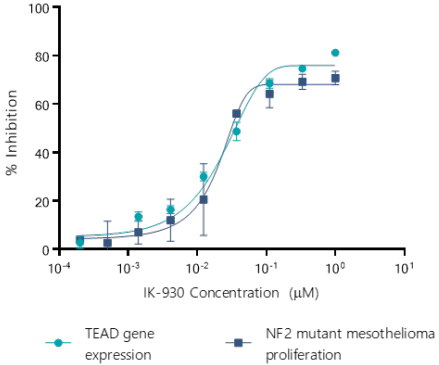
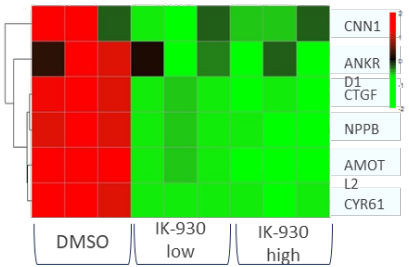
Binding the Central Lipid Pocket of TEAD

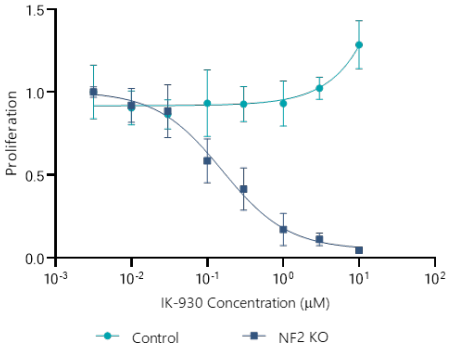
Potent TEAD Inhibition



Robust Inhibition TEAD Target Gene Expression



Selective Activity in Hippo-Mutated Cells



IK-930 Demonstrated Anti-Tumor Activity in Tumor Models with Hippo Pathway Mutations

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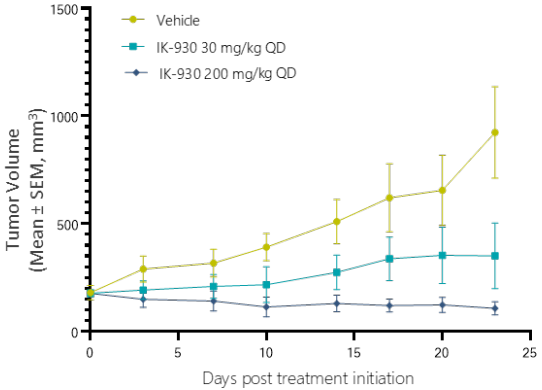
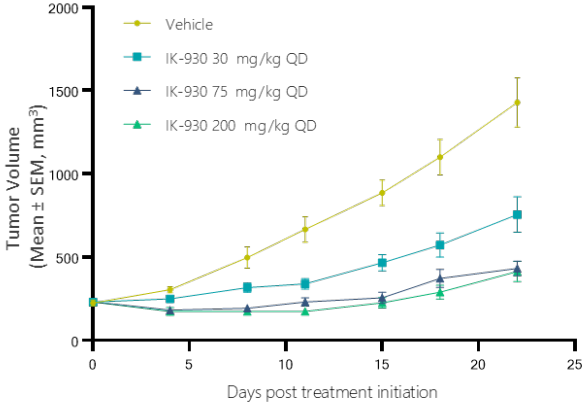
Potential for Monotherapy Across Genetic Mutations

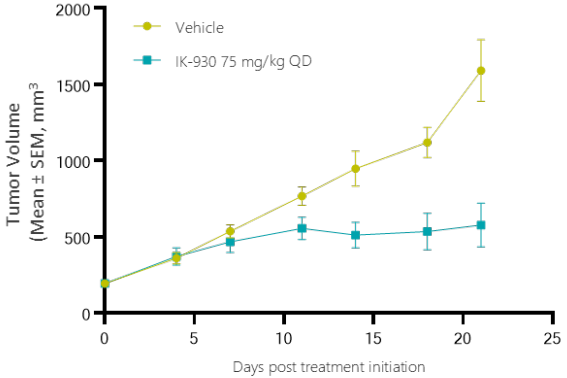
NF2 Deficient Mesothelioma Model



LATS1/LATS2 Mutated Mesothelioma Model



YAP1 Amplified HNSCC Model



IK-930 has Favorable ADME/PK Profile

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Cyp, hERG and Safety Panel Profiling Suggest Low Risk for Drug-drug Interaction

CYP Inhibition, IC_{50}	
Cyp1A2	>10 uM
Cyp2B6	>10 uM
Cyp2C9	>10 uM
Cyp2C19	7.6 uM
Cyp2D6	>10 uM
Cyp3A4-M	9.0 uM
Cyp3A4-T	>10 uM

Plasma protein binding, free fraction	
Mouse	2.8%
Rat	1.7%
Dog	2.1%
Monkey	2.3%
Human	4.3%

Nonclinical PK Summary		
Mouse	T1/2	1.6 h
	Vd	2.7 L/kg
	Oral bioavailability	55%
Rat	T1/2	1.7 h
	Vd	2.8 L/kg
	Oral bioavailability	56%
Dog	T1/2	1.8 h
	Vd	3.1 L/kg
	Oral bioavailability	52%
Monkey	T1/2	2.2 h
	Vd	2.8 L/Kg
	Oral bioavailability	49%

- ✓ Highly selective across a receptor, enzyme, ion channel safety panel (> 50 fold over H226 IC_{50})
- ✓ Minimal inhibition of hERG in automated patch clamp assay (IC_{50} > 200 fold over H226 IC_{50})
- ✓ Minimal Cyp inhibition - low potential to drug-drug-interactions
- ✓ Not a substrate of P-gp or BCRP transporters
- ✓ Moderate and similar plasma protein binding across species
- ✓ Very good oral bioavailability in mouse, rat, dog, and monkey
- ✓ Brain penetrant

Role of Hippo Pathway in Therapeutic Resistance; Multiple Opportunities for Combination with IK-930

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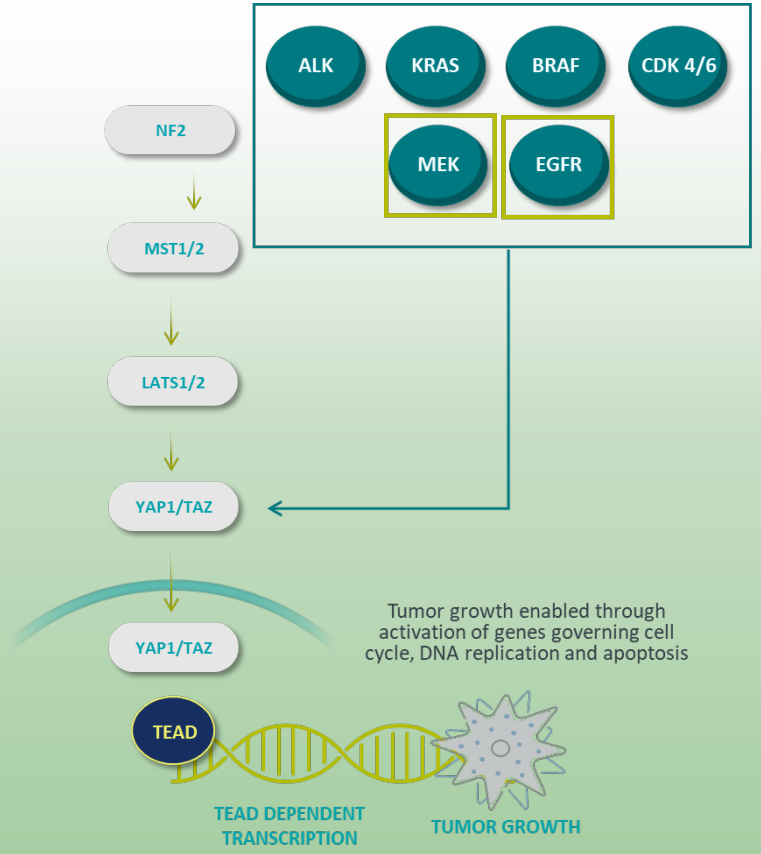
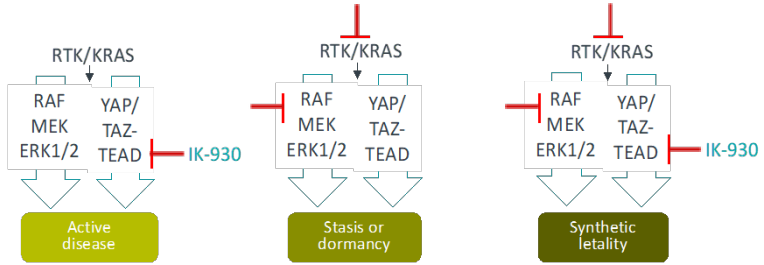


Screens identifying Hippo-mediated resistance

Cancer	Condition	Hit	Format	Reference
Melanoma	BRAFi	NF2	CRISPR	Shalem, O. et al. (2014) Science, 343, 84
Melanoma	BRAFi	EMICERI*	CRISPR	Joung, J. et al. (2017) Nature, 548, 343
BRAF mut lung	BRAFi	YAP	shRNA	Lin, et al., (2015) Nat Genet, Mar; 47(3): 250
Kras mut CRC	Kras KD	YAP	cDNA	Shao et al., (2014) Cell, 3;158(1):171
PDAC	Kras KO	YAP amp	GEMM	Kapoor, A. et al. (2014) Cell, 158, 185
NSCLC	EGFRi	TEAD Gene signature	RNASeq	Kurppa, K et al. (2020) Cell, 37 (104-22)
NSCLC	EGFRi	NF2	CRISPR	Zeng, H. et al (2019 Elife, 8:e50223

* EMICERI : Increase MOB3B (component of MST1/2 and LATS1/2 inhibitor complex) expression

Combined TEAD and RTK or KRAS / MAPK inhibition synthetically lethal in BRAF- and KRAS mutant tumors



Adapted from Lin, et al., (2015) Nat Genet, Mar; 47(3): 250

MEK Inhibitor Induces YAP1 Nuclear Localization and TEAD Dependent Transcription

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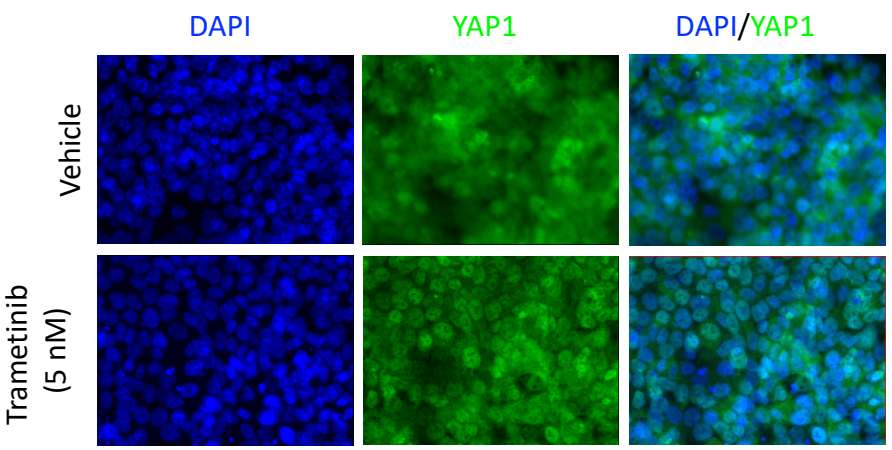
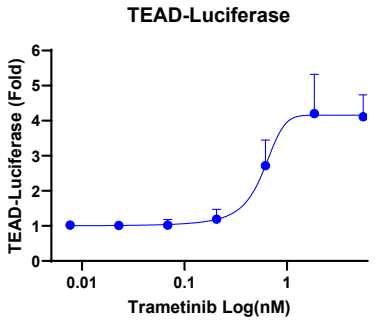
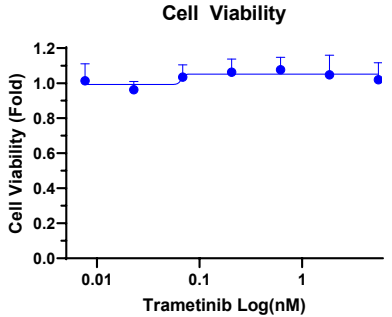
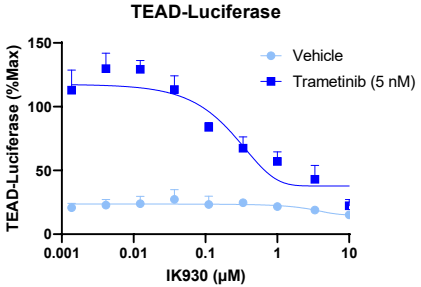
HCT116 cells (KRAS G13D)

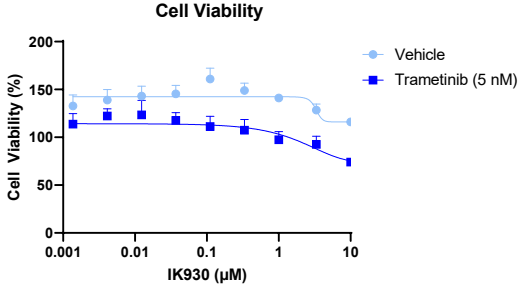


HCT116 cells (KRAS G13D)









IK-930 Enhances Apoptosis in MEK Inhibitor -Treated KRAS Mutant Cells

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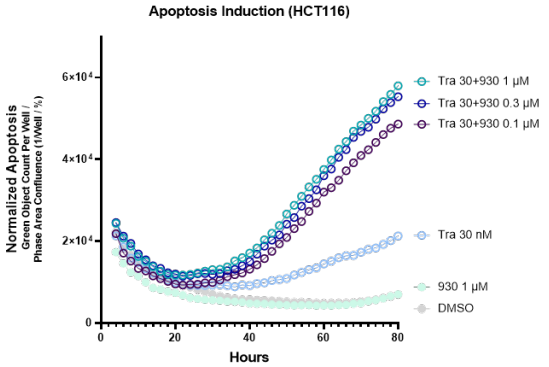
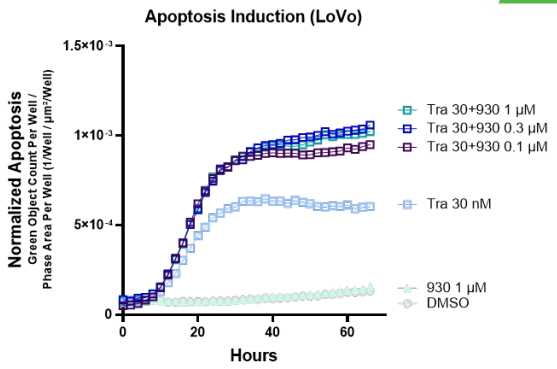
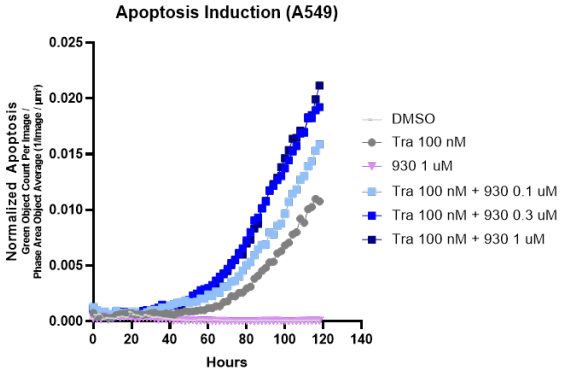
HCT116: KRAS G13D CRC Model



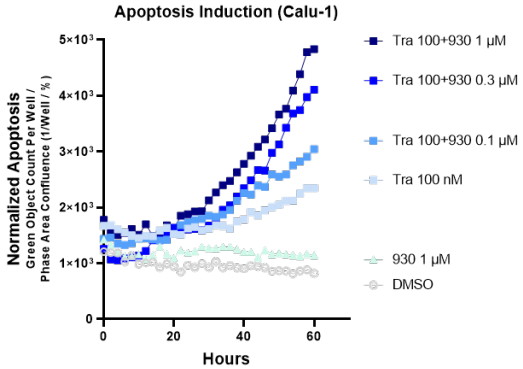
LOVO: Human KRAS G13D CRC Model



A549: KRAS G12S NSCLC Model



Calu-1: KRAS G12C NSCLC Model



Increased Anti-Tumor Effect of IK-930 in Combination with MEK Inhibitor in KRAS Mutant Tumors In Vivo

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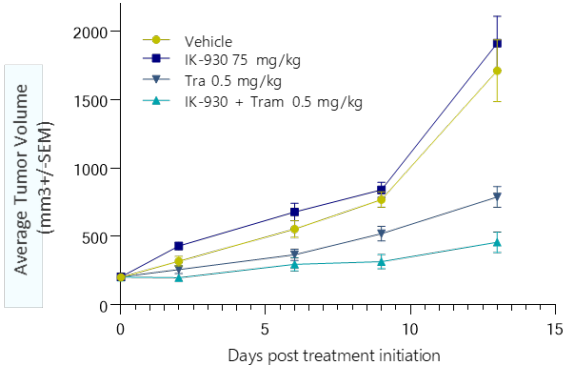
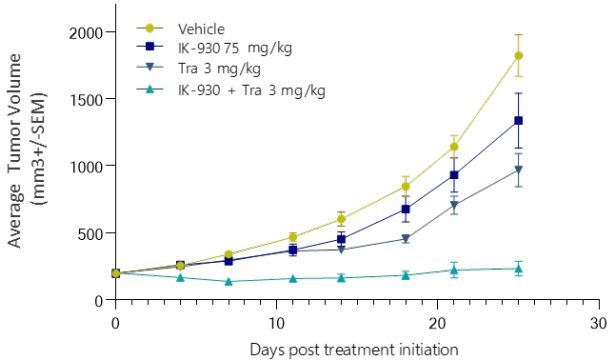
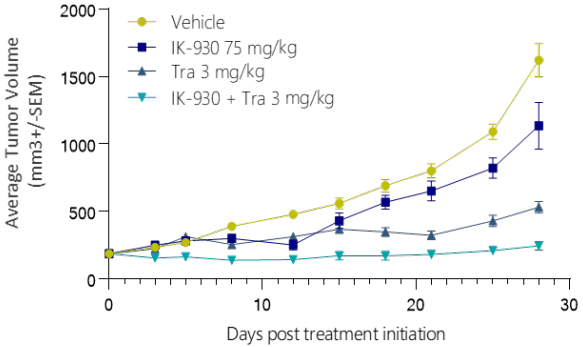
Impact Across Tumor Models for KRASm CRC and NSCLC



HCT116: KRAS G13D CRC Model



A549: KRAS G12S NSCLC Model



LOVO: Human KRAS G13D CRC Model

Model	HCT116	A549	Lovo
In vivo TGI Combination	83% (1mg/kg MEKi)	78% (0.5mg/kg MEKi)	75% (1mg/kg MEKi)

Developing First-in-Class TEAD Inhibitor for Genetically Altered Cancers and Therapeutic Resistance

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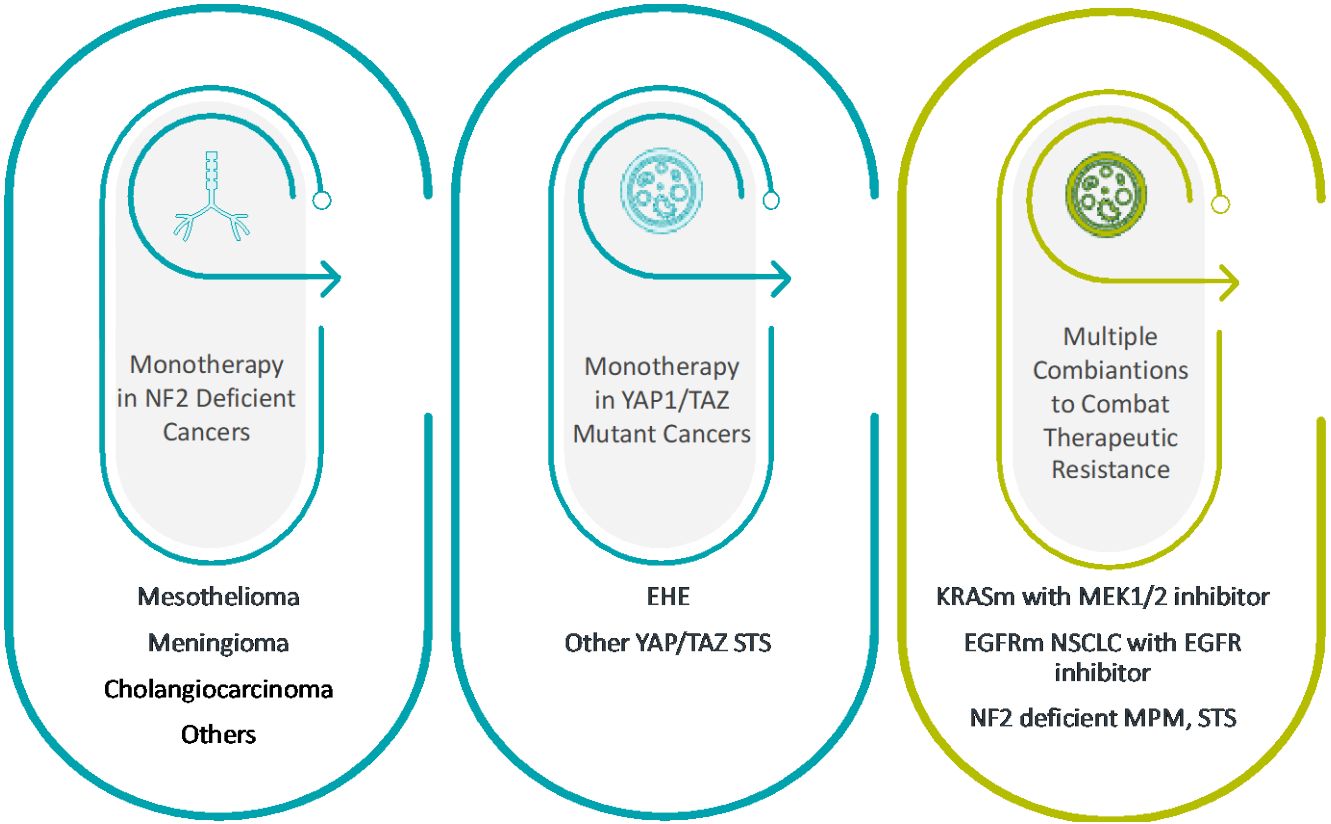

Monotherapy strategy focused on NF2- deficient orphan indications including NF2 deficient MPM, EHE and other solid tumors with prevalent NF2 and YAP/TAZ fusion genes

Combination strategy to explore multiple with targeted agent combos to reverse mechanism of resistance in broader indications

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