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IK-930 mediated TEAD inhibition decreases and delays tumor growth and enhances targeted apoptosis in lung and colon cancer xenografts when combined with MEK or EGFR inhibitors

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TEAD Transcription is a Tumor Driver and Key Node for Therapeutic Resistance

Multiple activating signals drive

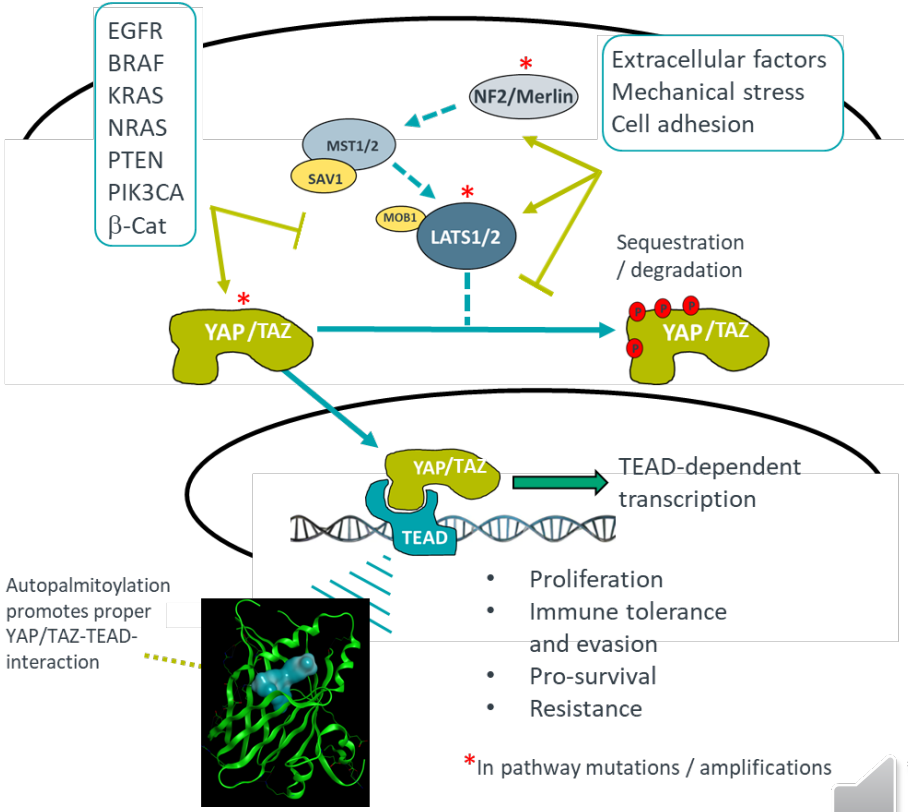
- YAP/TAZ nuclear localization ⇢ TEAD binding ⇢ gene expression of proliferation / pro-survival pathways

TEAD transcription is dysregulated in many cancers

- Numerous tumor suppressor / oncogenes lead to TEAD activation
- Increased nuclear YAP associated with poor outcome

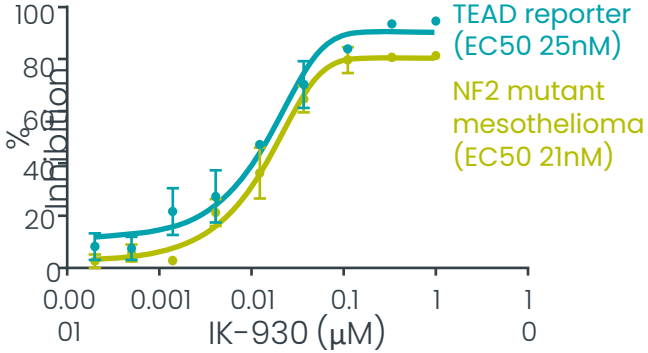
Mechanism of therapeutic resistance

- IDed in multiple genome-wide resistance screens
- Functions in parallel with RAF/MEK or EGFR in regulation of anti-apoptotic genes conferring resistance
- Inhibition downstream of KRAS triggers upregulation and resistance

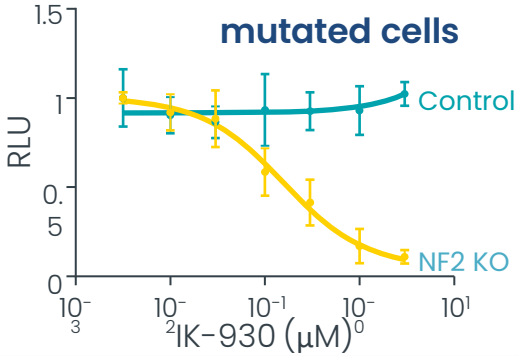


IK-930 is a Potent and Selective TEAD Inhibitor

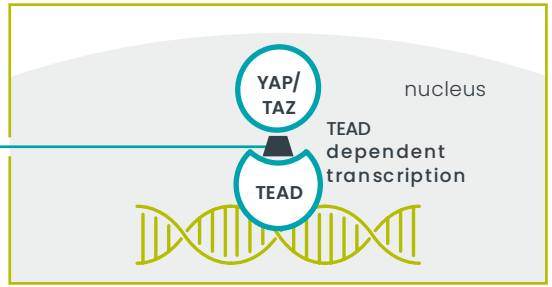
IK-930 is a potent TEAD inhibitor



IK-930 selectively active in Hippo pathway mutated cells



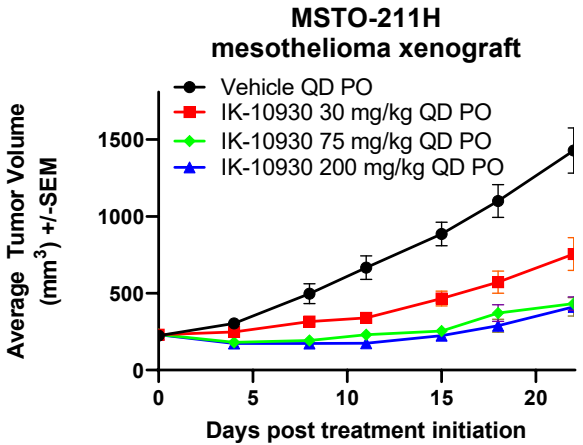
IK-930 binds in central lipid pocket of TEAD



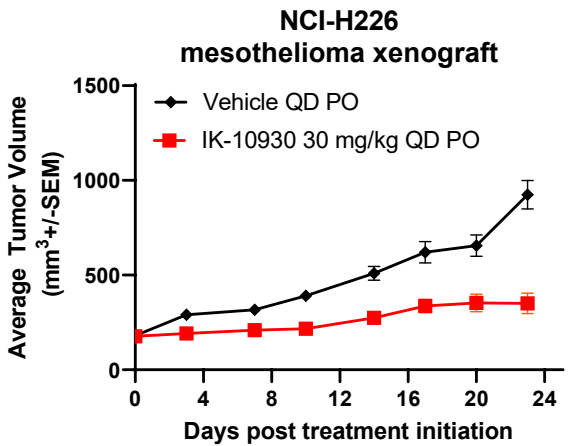
Cyp, hERG and safety panel profiling suggest low risk for drug-drug interaction and off target activity

IK-930 Possesses Single Agent Anti-tumor Activity

Maximum efficacy in H226 and MSTO-211H xenograft models at 75 mg/kg QD



LATS mutations



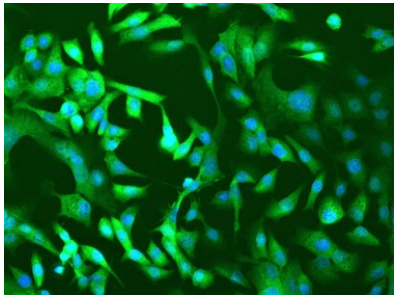
NF2 mutant

Mesothelioma tumor models with dysregulated Hippo pathway

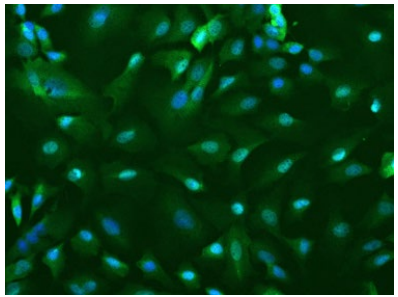
IK-930 Overcomes EGFRi/MEKi Resistance In Vitro

Enhancing YAP1 nuclear accumulation then apoptosis in therapy-resistant cancer cells in vitro in combination with IK-930

DMSO

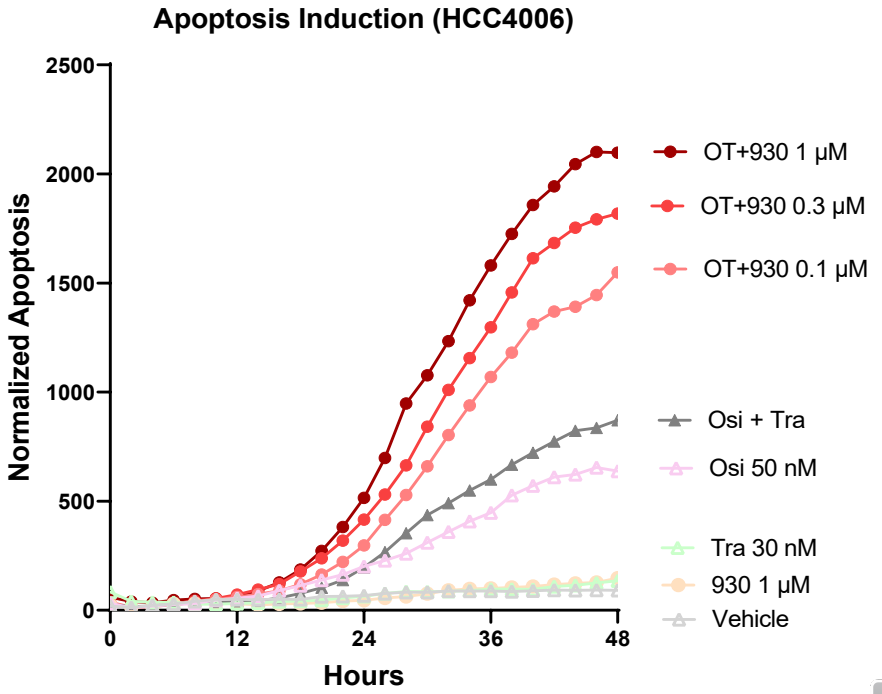


Osi + Tram



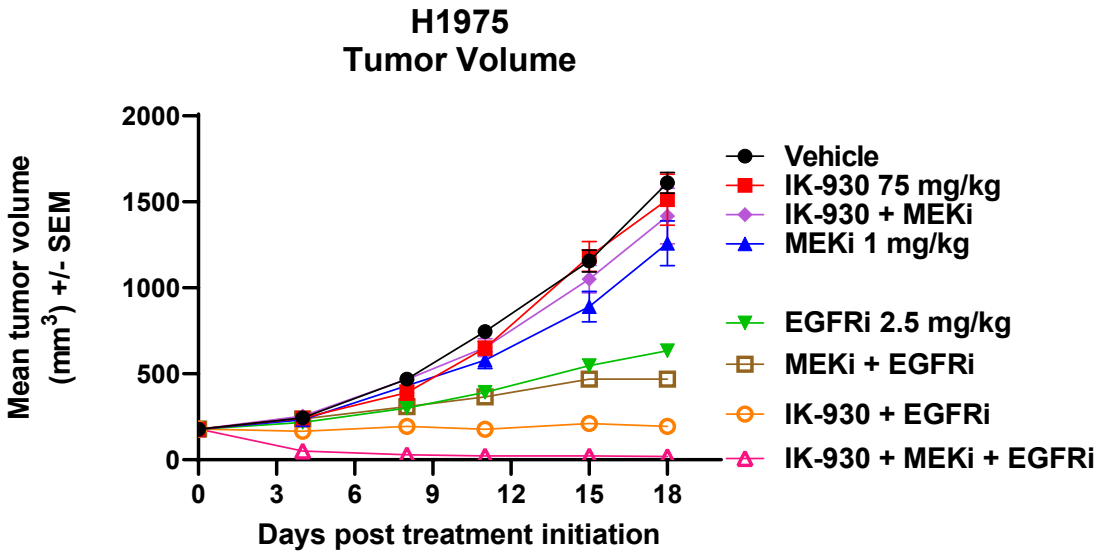
IF: α-YAP1 + DAPI

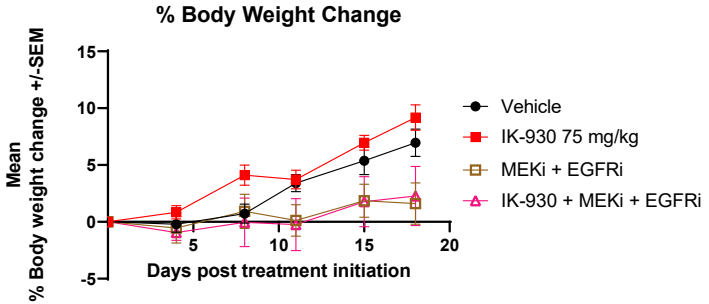
NCI-H1975 (EGFR L858R/T790M)

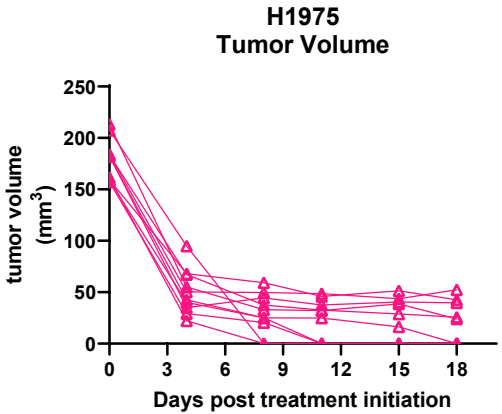


IK-930 Overcomes EGFRi/MEKi Resistance In Vitro and In Vivo

Driving regression and CR in vivo

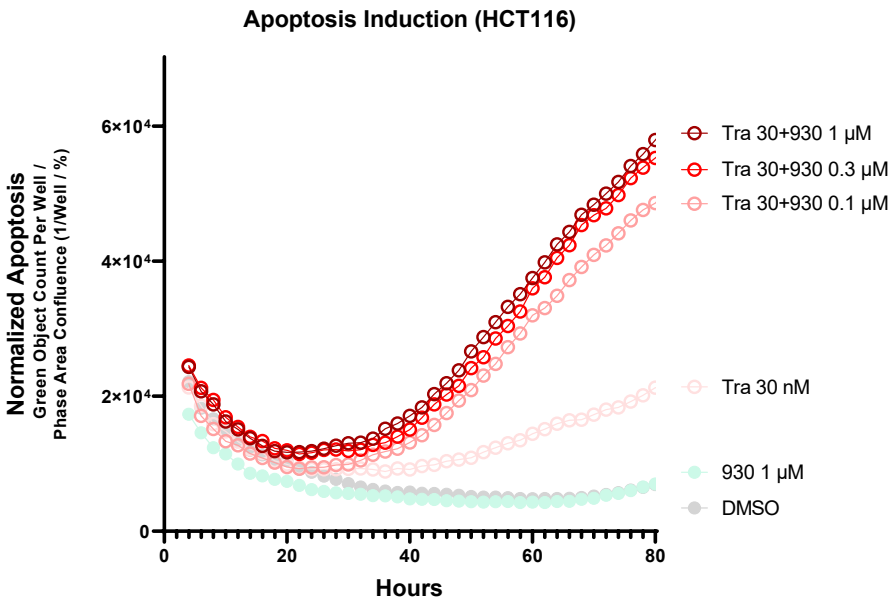


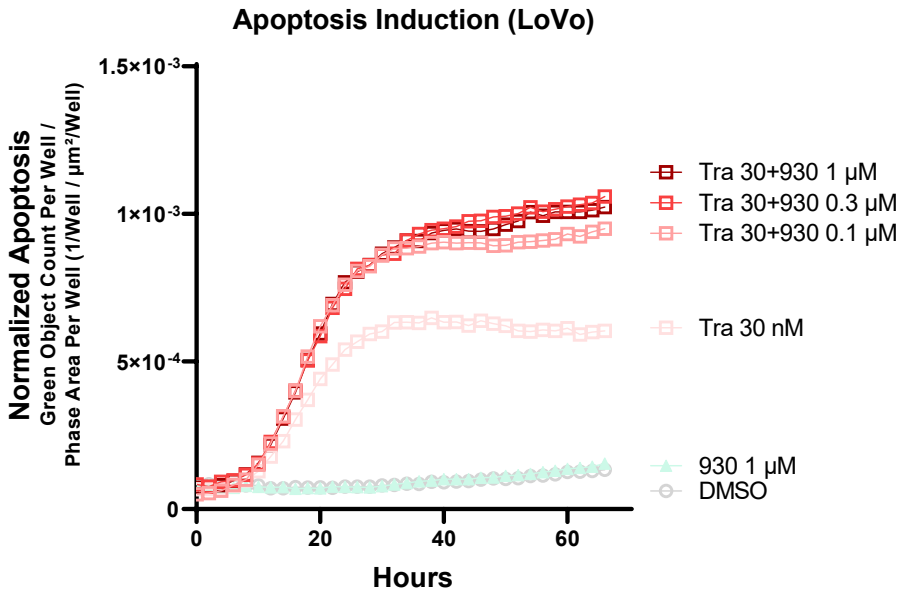




IK-930 Overcomes mutant KRAS MEKi Resistance In Vitro

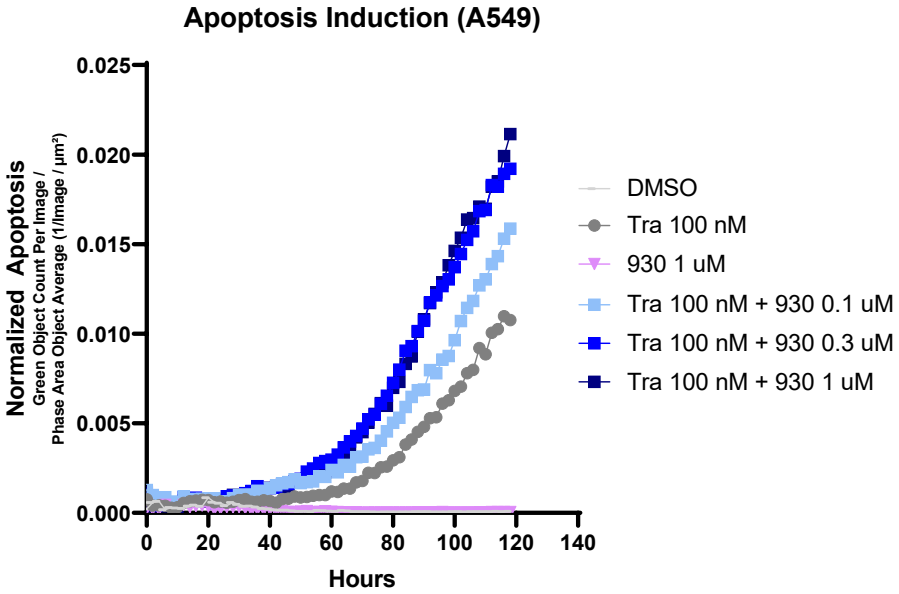
Enhancing apoptosis and killing therapy-resistant colon cancer cells in vitro

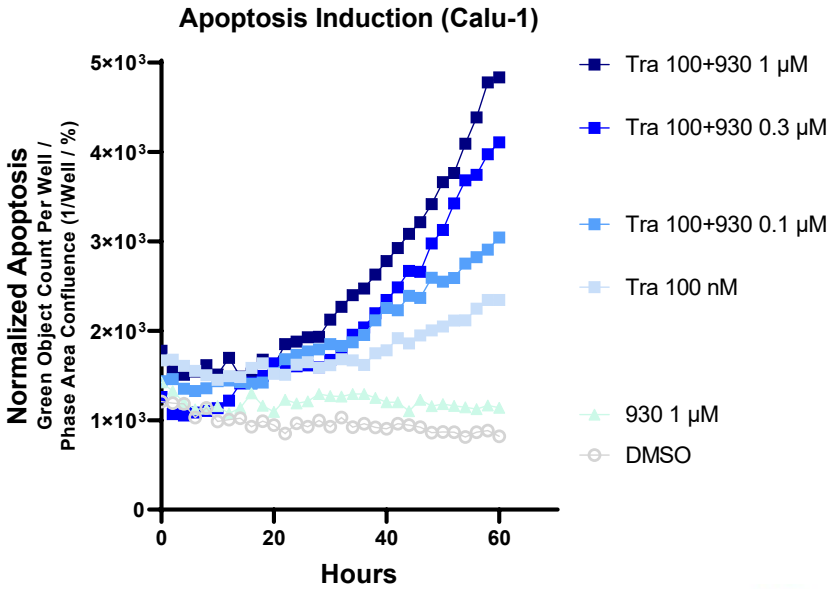




IK-930 Overcomes mutant KRAS MEKi Resistance In Vitro and In Vivo

Enhancing apoptosis and killing therapy-resistant cancer cells in vitro





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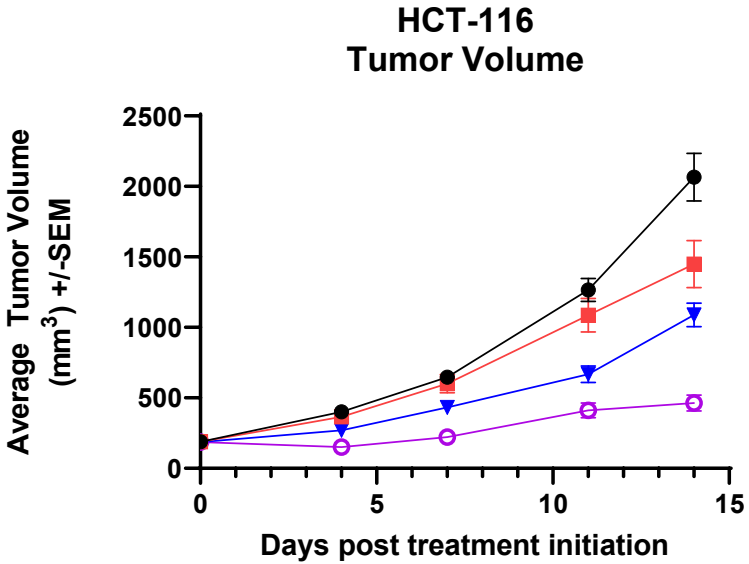

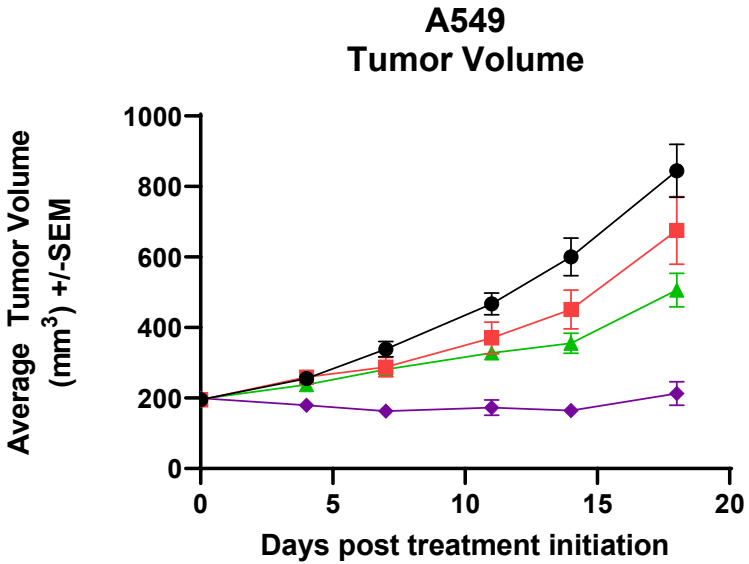

Conclusions

- IK-930 is a potent and selective TEAD inhibitor
- IK-930 has single agent activity in vitro and in vivo in Hippo dysregulated mesothelioma
- IK-930 can be combined with EGFR and MEK inhibitors to enhance apoptosis and enhance anti-tumor activity in EGFR-mutant NSLC
- IK-930 can be combined with MEK inhibition to enhance apoptosis and enhance anti-tumor activity in KRAS mutant cancers from a variety of indications

Acknowledgements

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