

A Soude, M. Barth, JM Luccarini, S. Delaporte, F. Chirade, G. Cheret, A. Boulay, C. Valaire, M. Dorchie, C. Estivalet, P. Tuya-Boustugue, C. Montalbetti, R. Tranchant*, D. Jean*, L. Quetel*, JB. Assié*, I. Konstantinova, JL. Junien & P. Broqua. Inventiva, Daix, France, *INSERM URMS 1138, Paris-Descartes, France

BACKGROUND

The Hippo Pathway, YAP/TAZ and cancer

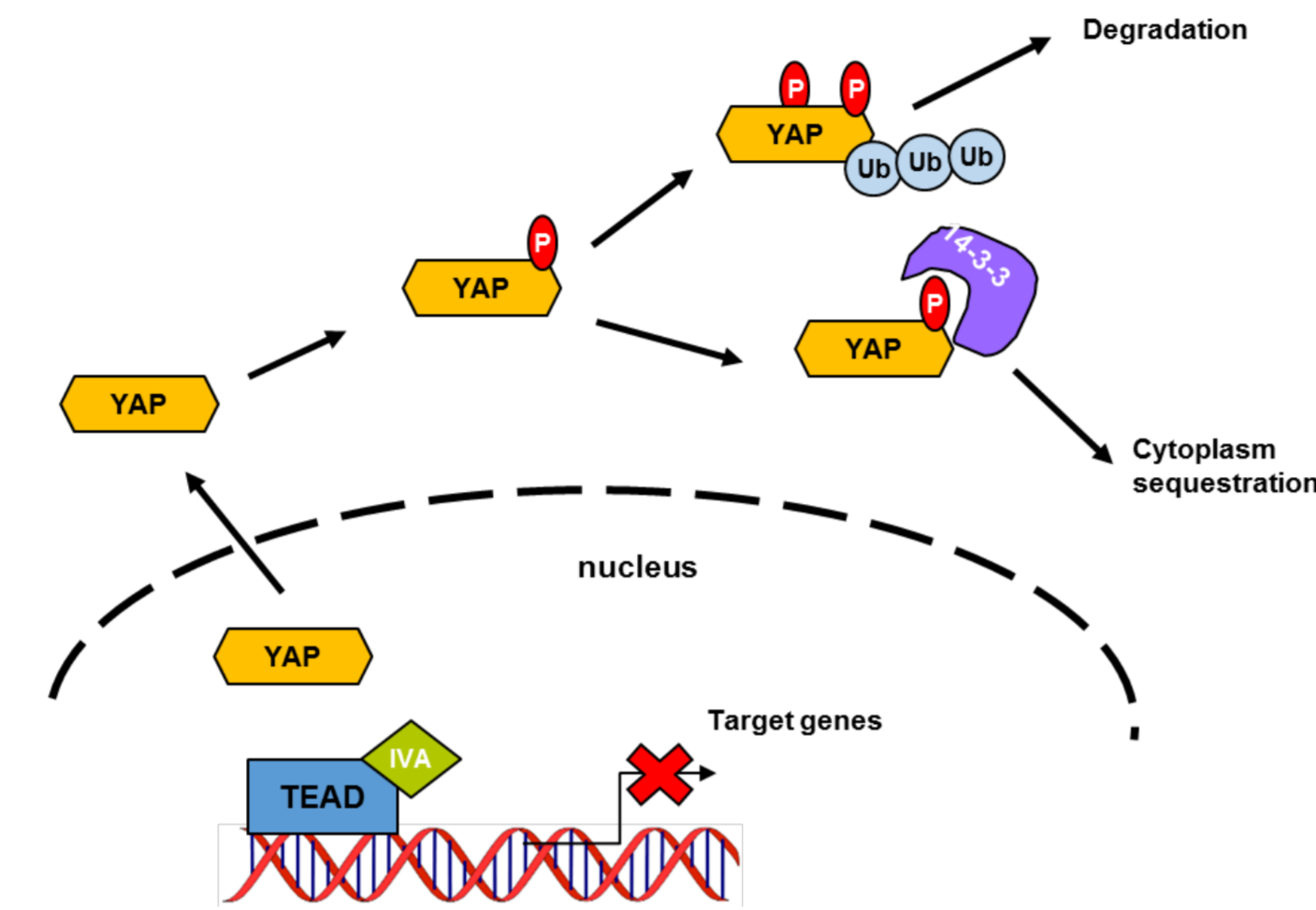
- Controls cell proliferation and organ size
- YAP and TAZ are drivers of tumorigenesis
- They are highly expressed in many cancer types
- YAP and TAZ bind to TEAD transcription factors

Rationale in Malignant Pleural Mesothelioma

- MPM is notoriously resistant to conventional cytotoxic chemotherapy
- All MPM subtypes display a high frequency mutation in the hippo pathway
- 70% of Malignant Pleural Mesothelioma, MPM have NF2 mutation driving YAP and TAZ activation
- High YAP nuclear expression is found in most of Mesothelioma samples

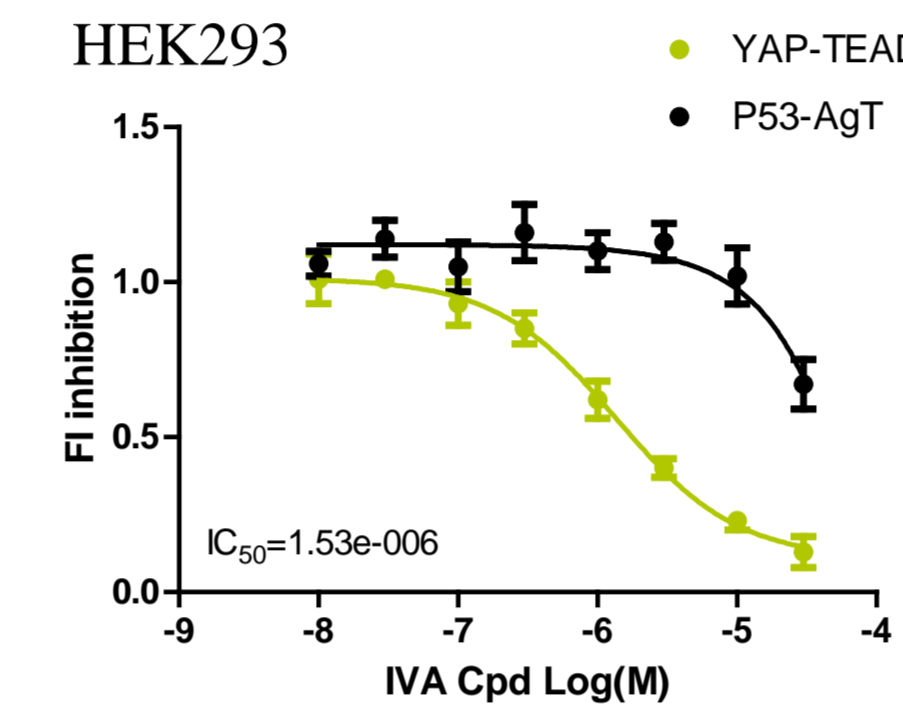
IVA compounds MoA

Small molecules disrupting YAP-TEAD interaction

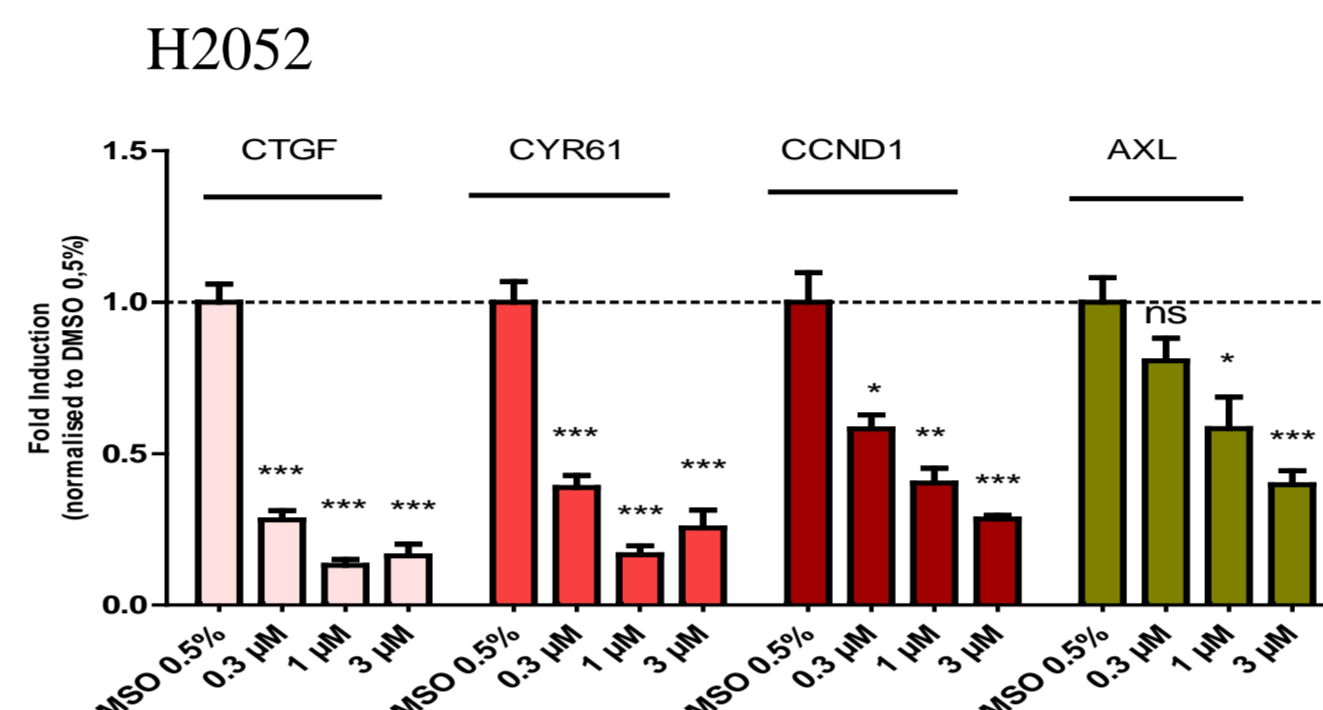


IVA LEAD CANDIDATE DECREASES YAP-TEAD INTERACTION AND INHIBITS YAP-TEAD TRANSCRIPTIONAL ACTIVITY

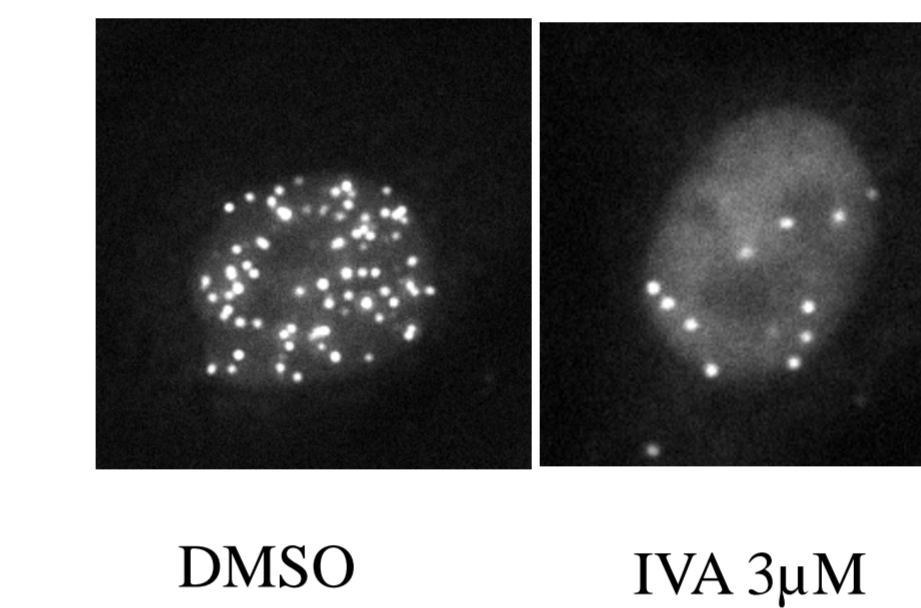
Transactivation assay



YAP target genes expression

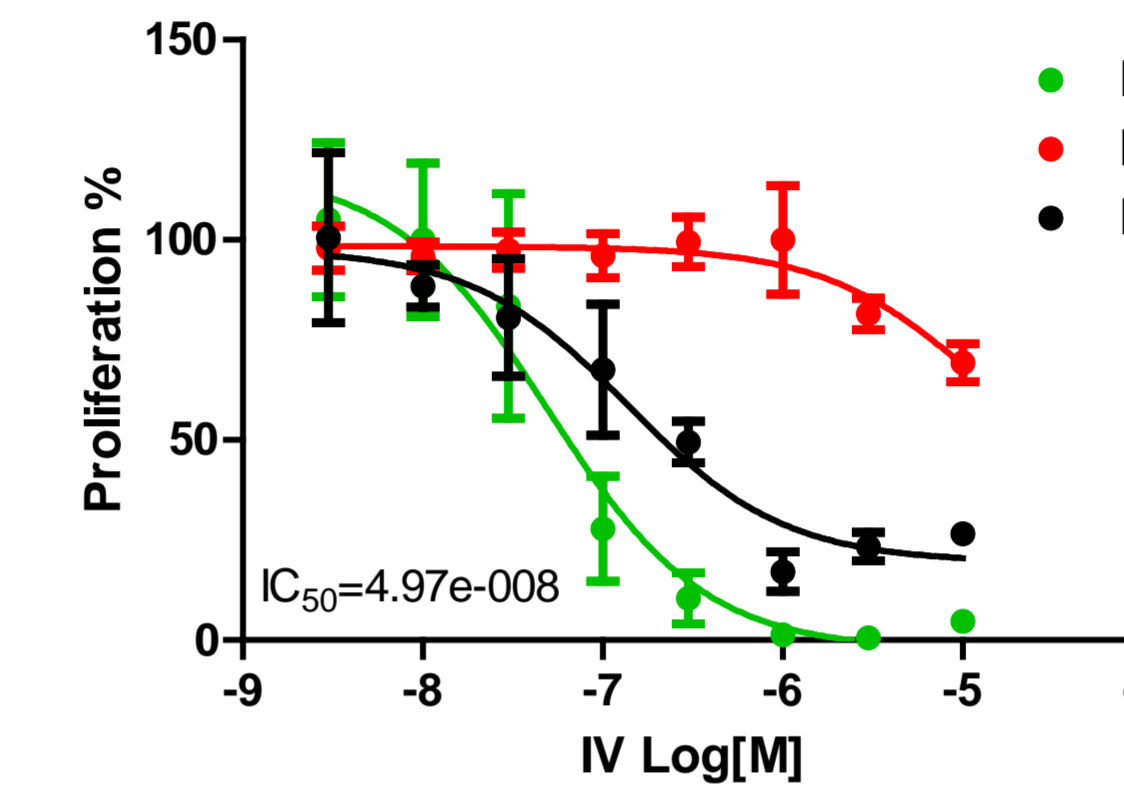


YAP-TEAD interaction (PLA)

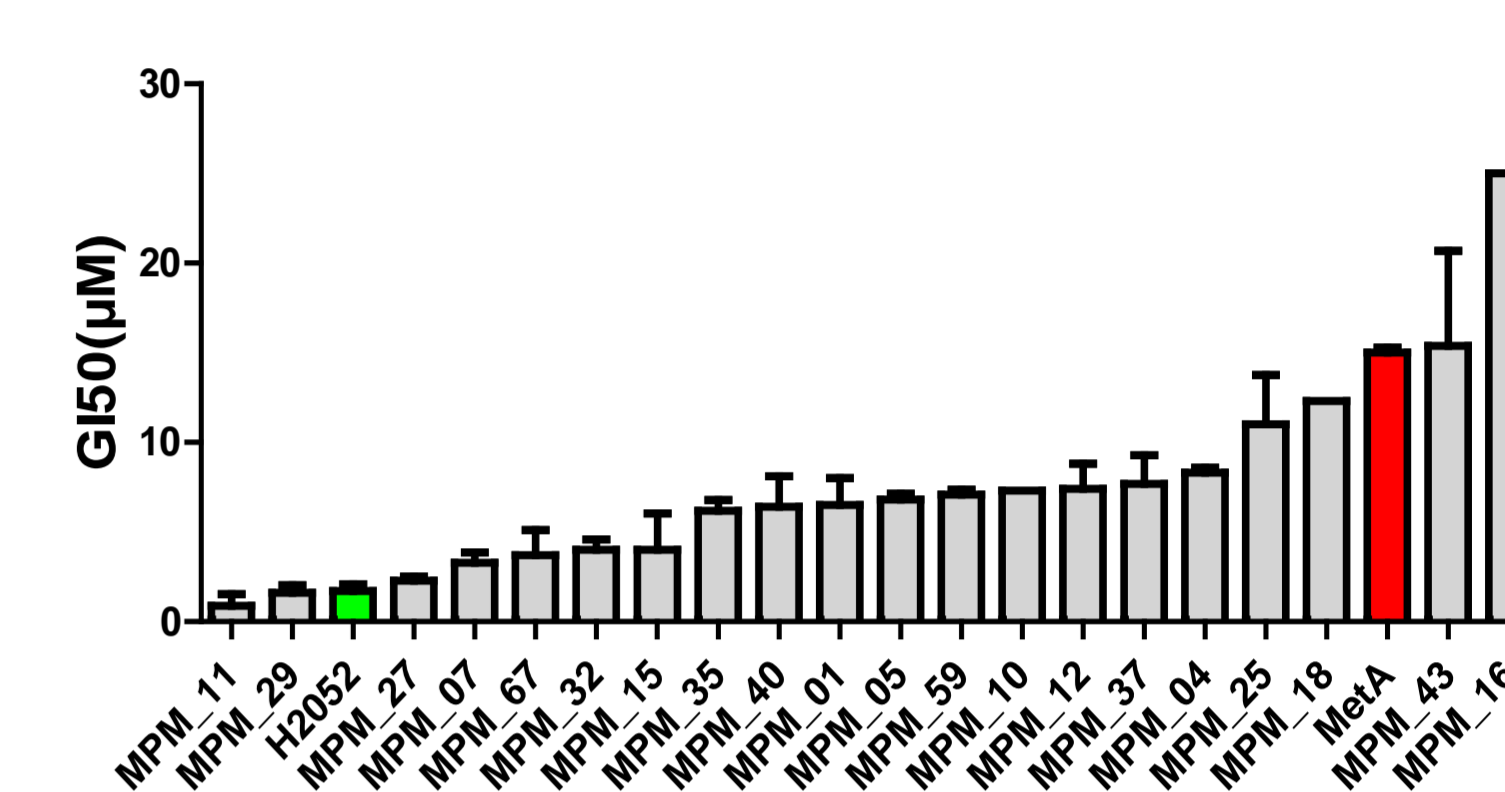


IVA LEAD CANDIDATE INHIBITS MESOTHELIOMA CELL PROLIFERATION WITHOUT AFFECTING PROLIFERATION OF NORMAL CELLS

Mesothelioma cell lines



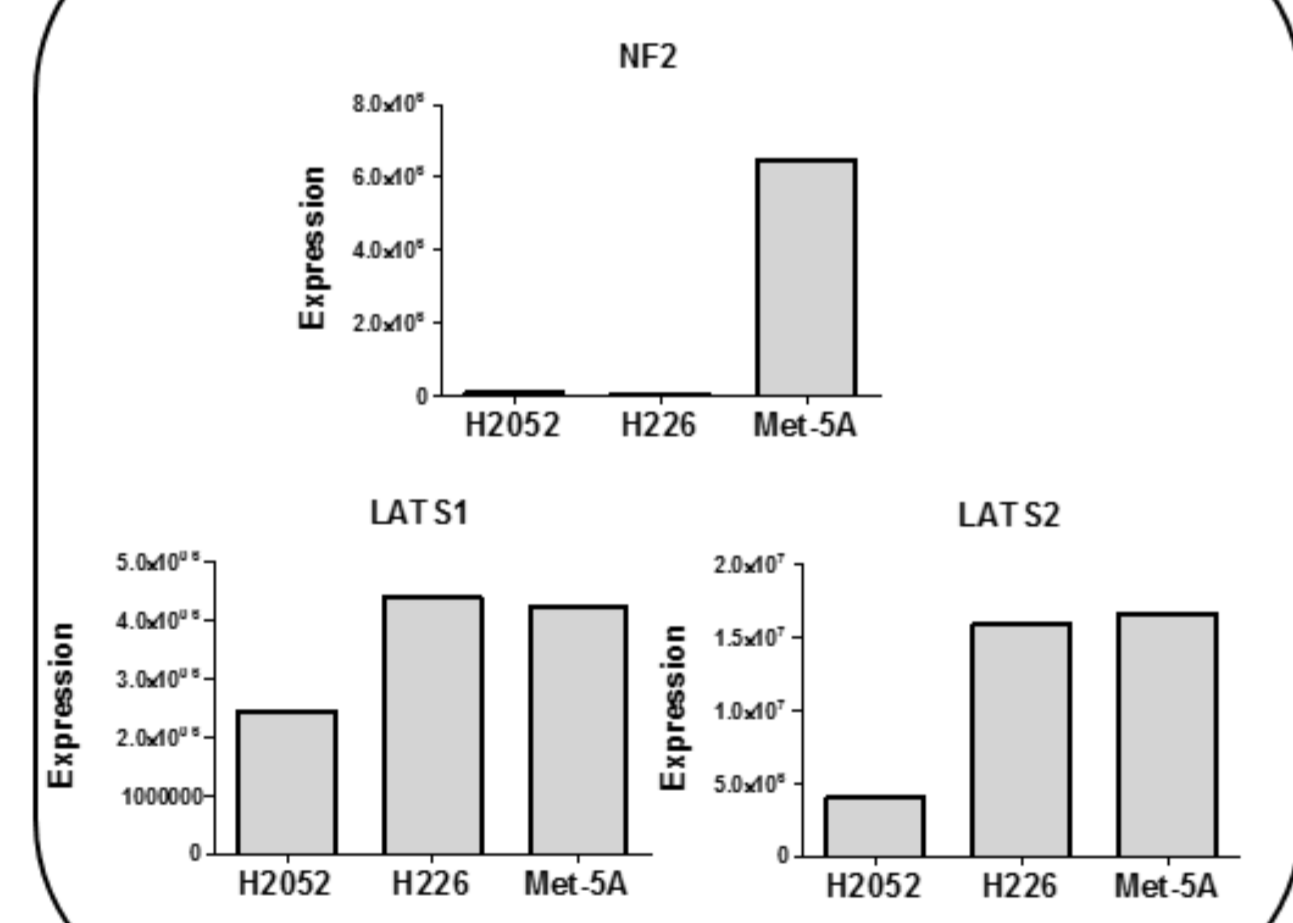
Mesothelioma primary cells



2D proliferation assay

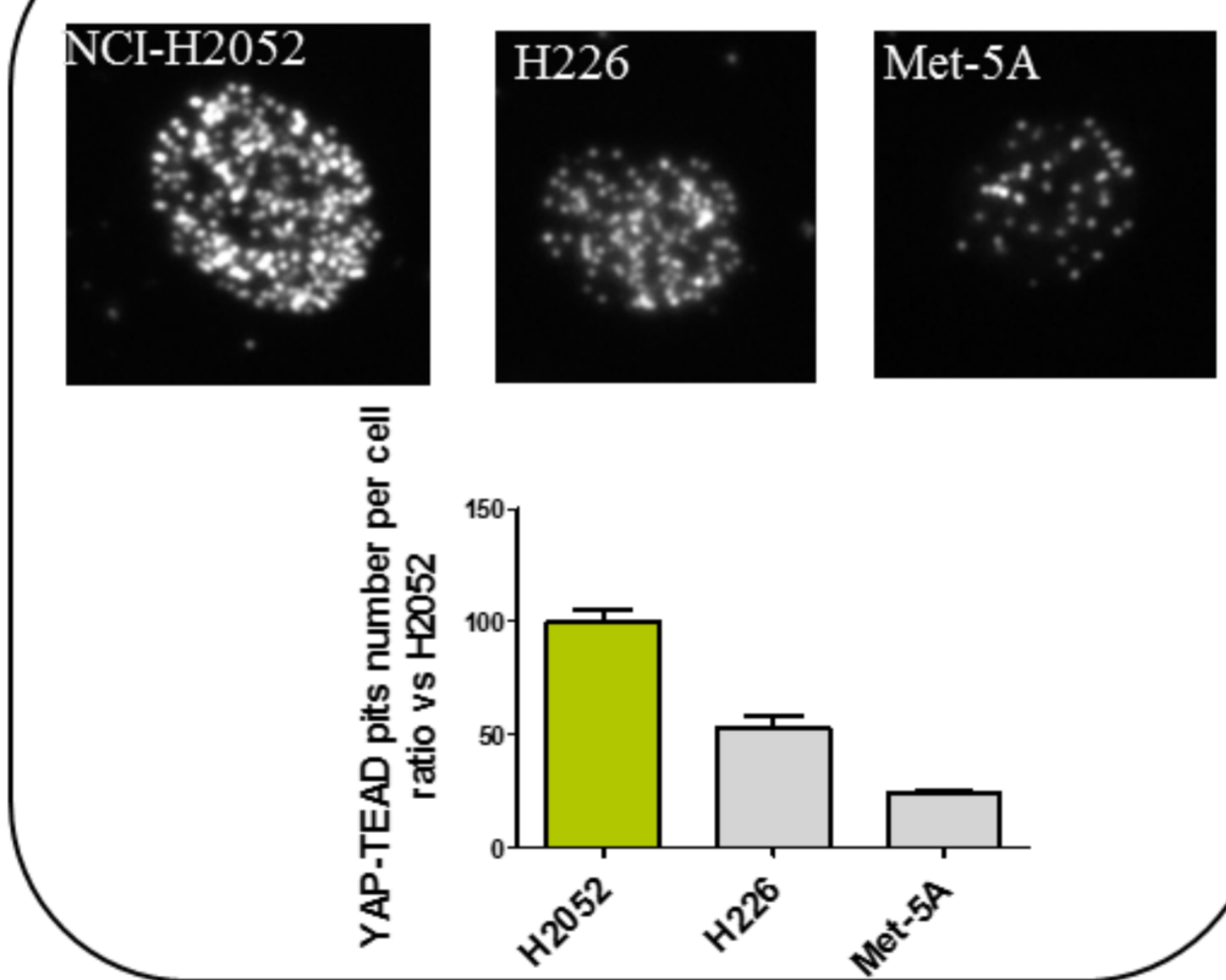
YAP DEPENDENCY IN MESOTHELIOMA CELL LINES

Hippo key proteins expression

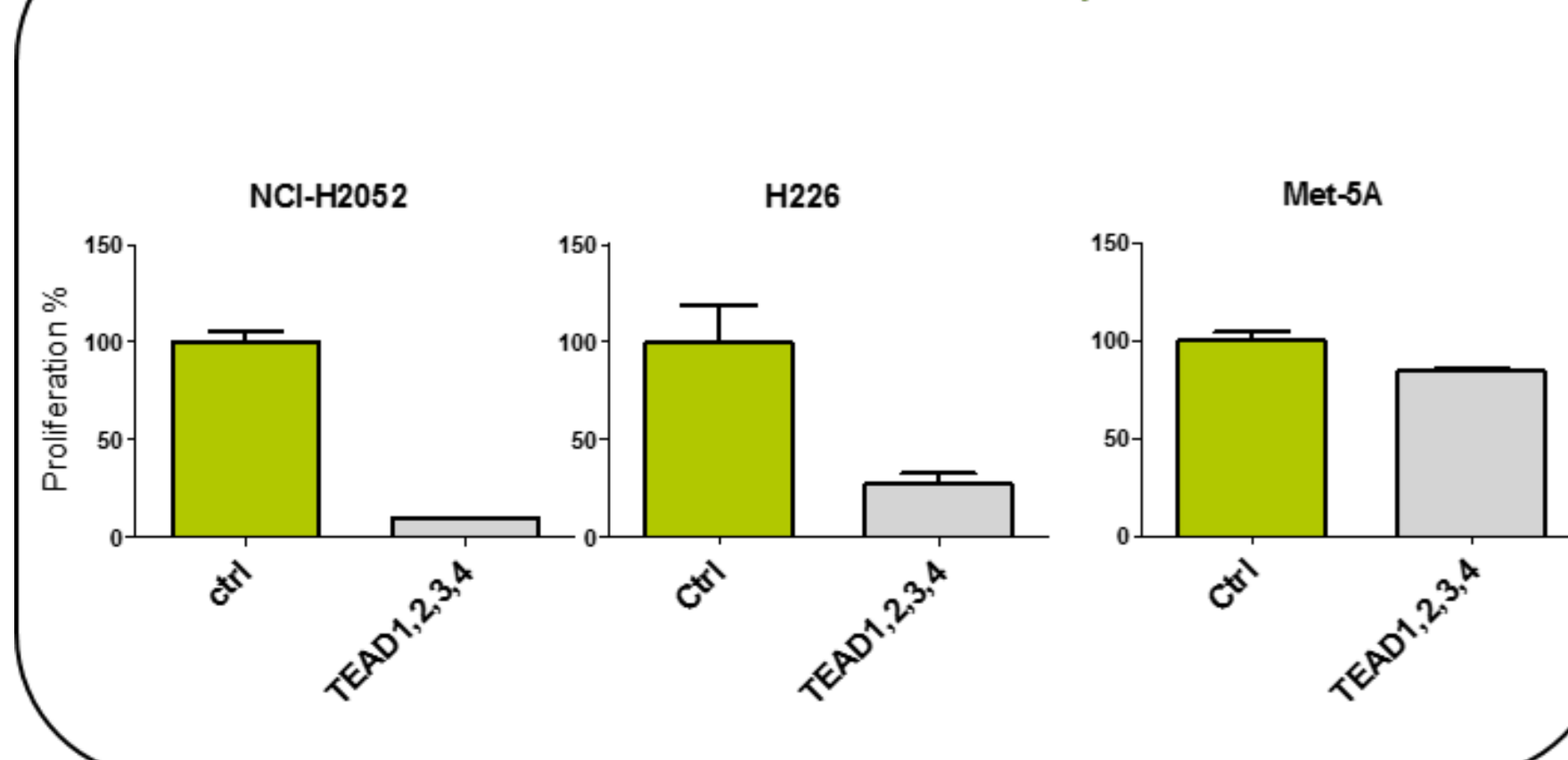


← YAP-TEAD relevant cell lines →

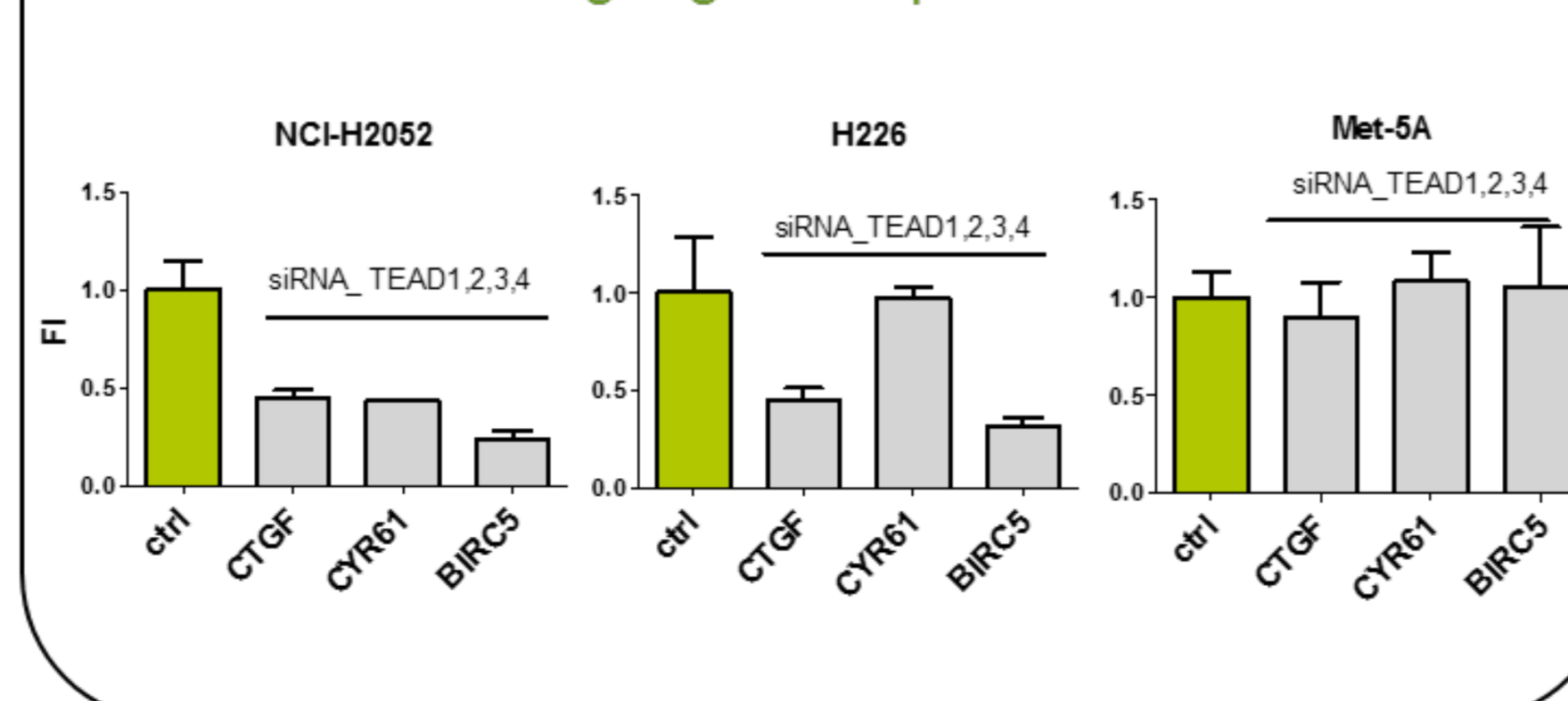
YAP-TEAD interaction



TEAD1,2,3,4 siRNA effect on proliferation

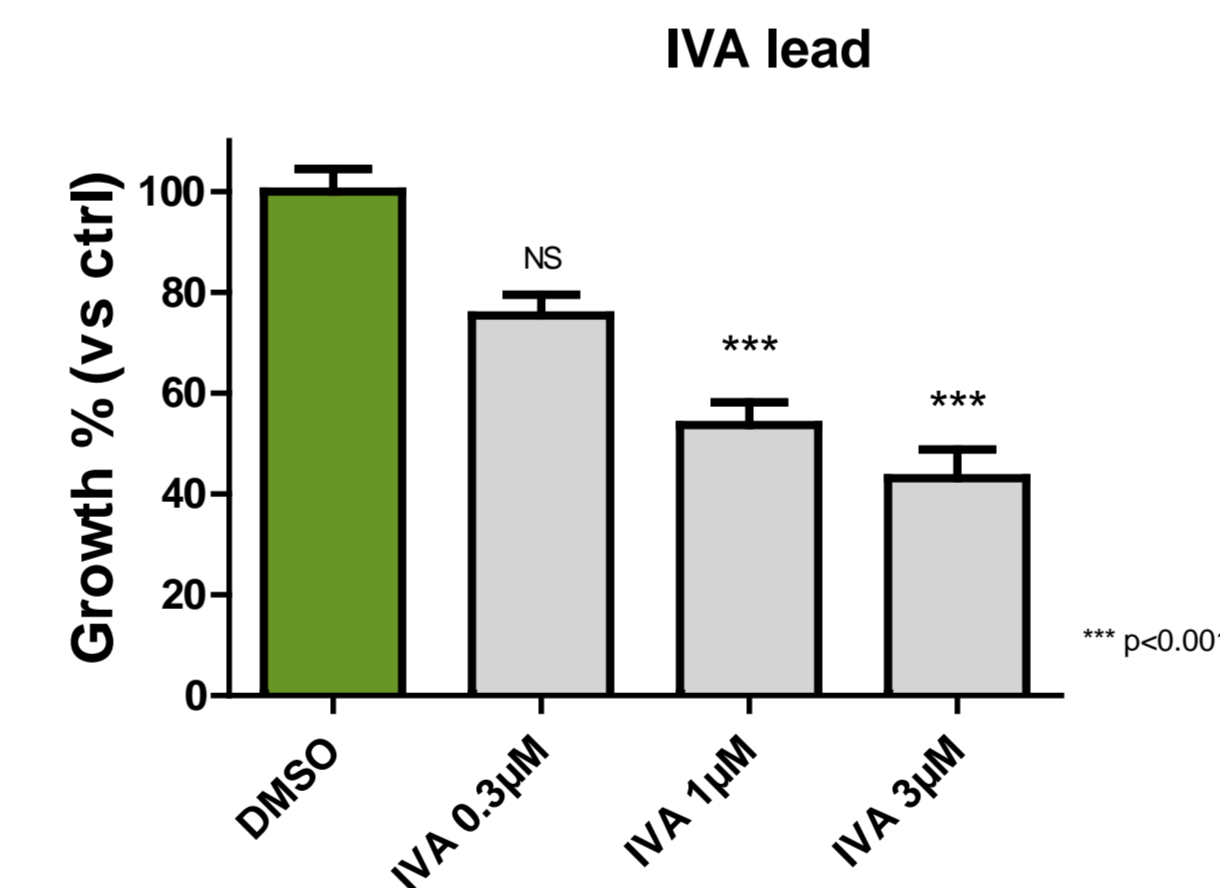


TEAD1,2,3,4 siRNA effect on target gene expression

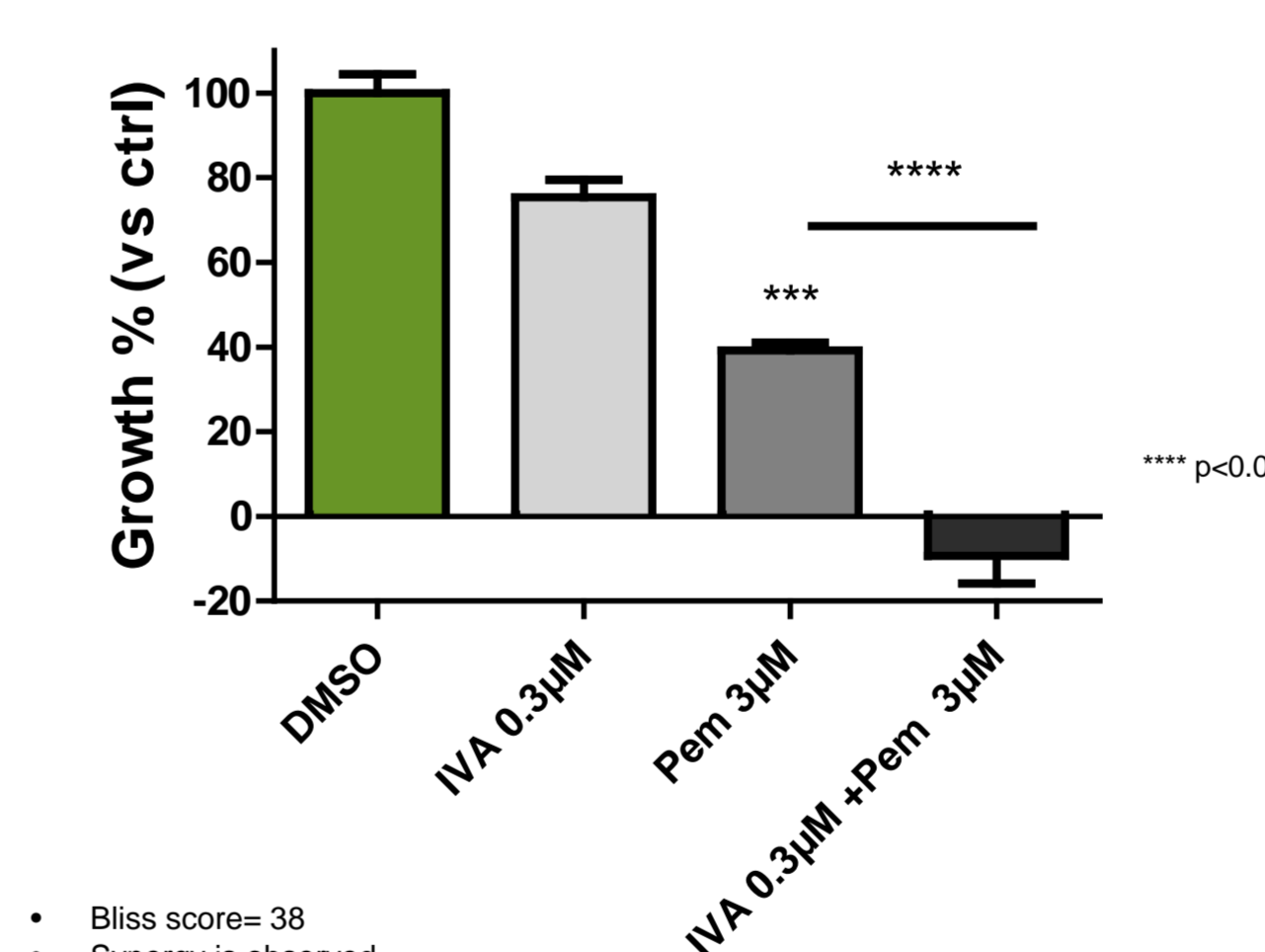


IVA LEAD CANDIDATE ABOLISHES MPM TUMOR SPHEROID GROWTH ALONE AND IN COMBINATION WITH PEMETREXED

H2052_3D assay

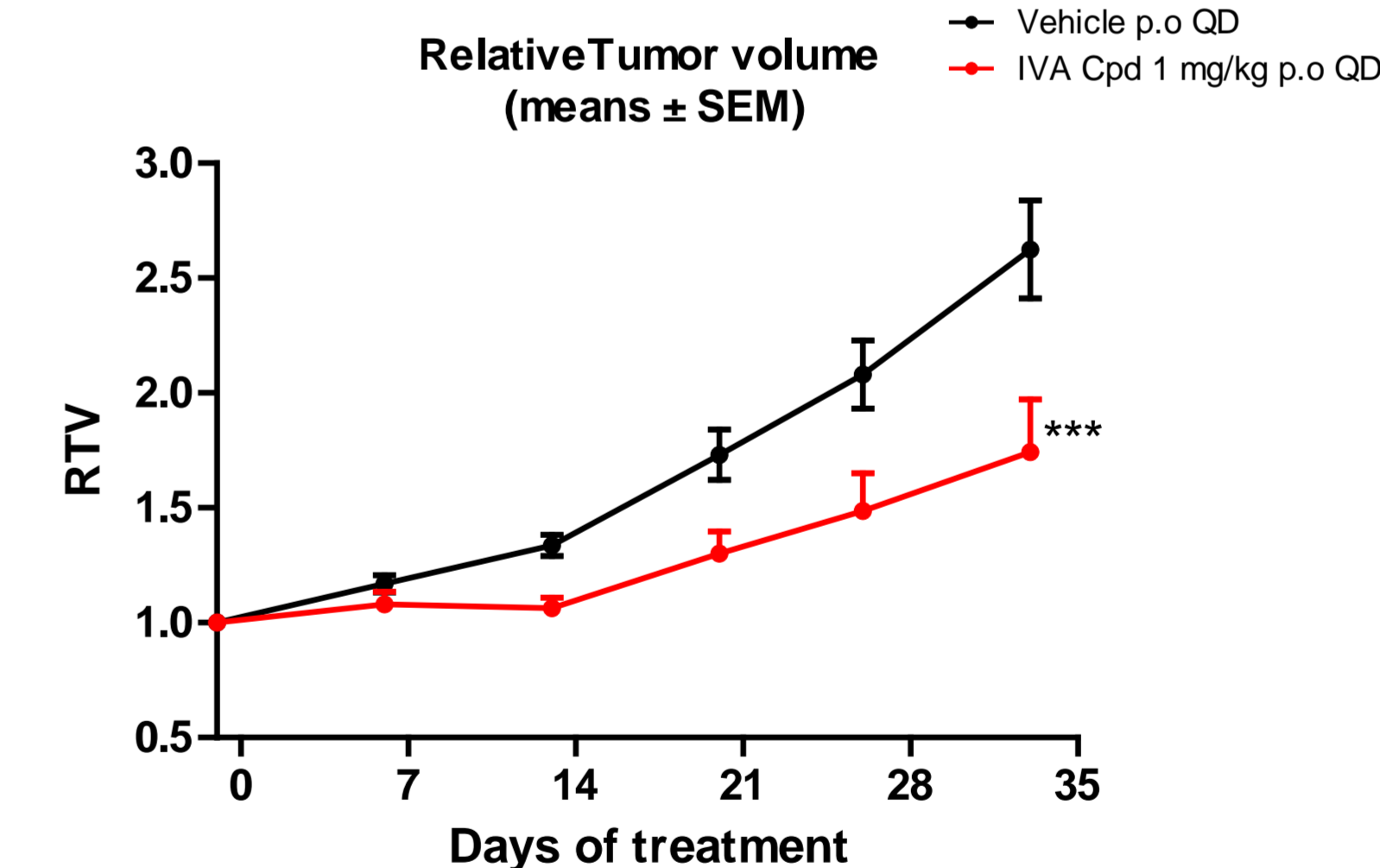


IVA lead + Pemetrexed

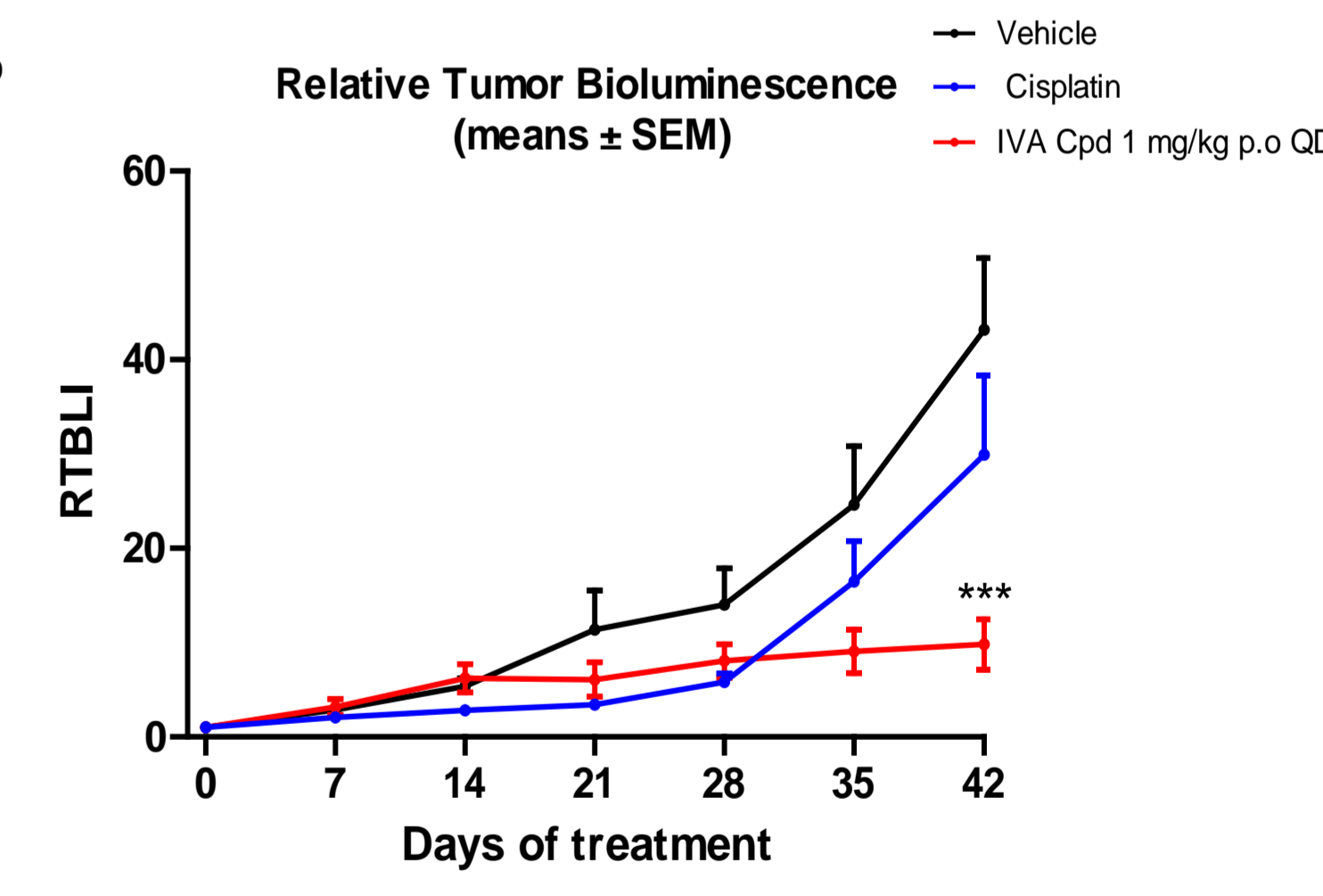


• Bliss score = -38
• Synergy is observed

H2052 subcutaneous xenograft



MPM_Luc orthotopic model



CONCLUSIONS

- We have discovered small molecules able to inhibit YAP-TEAD and TAZ-TEAD protein-protein interaction
- We have shown evidence of YAP-TEAD disruption
 - Inhibition of YAP-TEAD dependent transactivation assay
 - Decrease of YAP-TEAD interaction level

- In MPM cancer cells, IVA lead candidate:
 - decreases levels of YAP-TEAD interaction
 - decreases expression of YAP-TEAD target genes
 - inhibits mesothelioma cancer cell lines proliferation
- IVA lead candidate has a synergistic effect with pemetrexed and offers the potential to overcome drug resistance for the treatment of Malignant Pleural Mesothelioma
- IVA lead candidate shows strong inhibition of tumor growth after oral administration in vivo in sc xenograft as well as in orthotopic model