

Discovery of YAP-TEAD Protein-Protein interaction (PPI) inhibitors for the treatment of cancer



Abstract # A129

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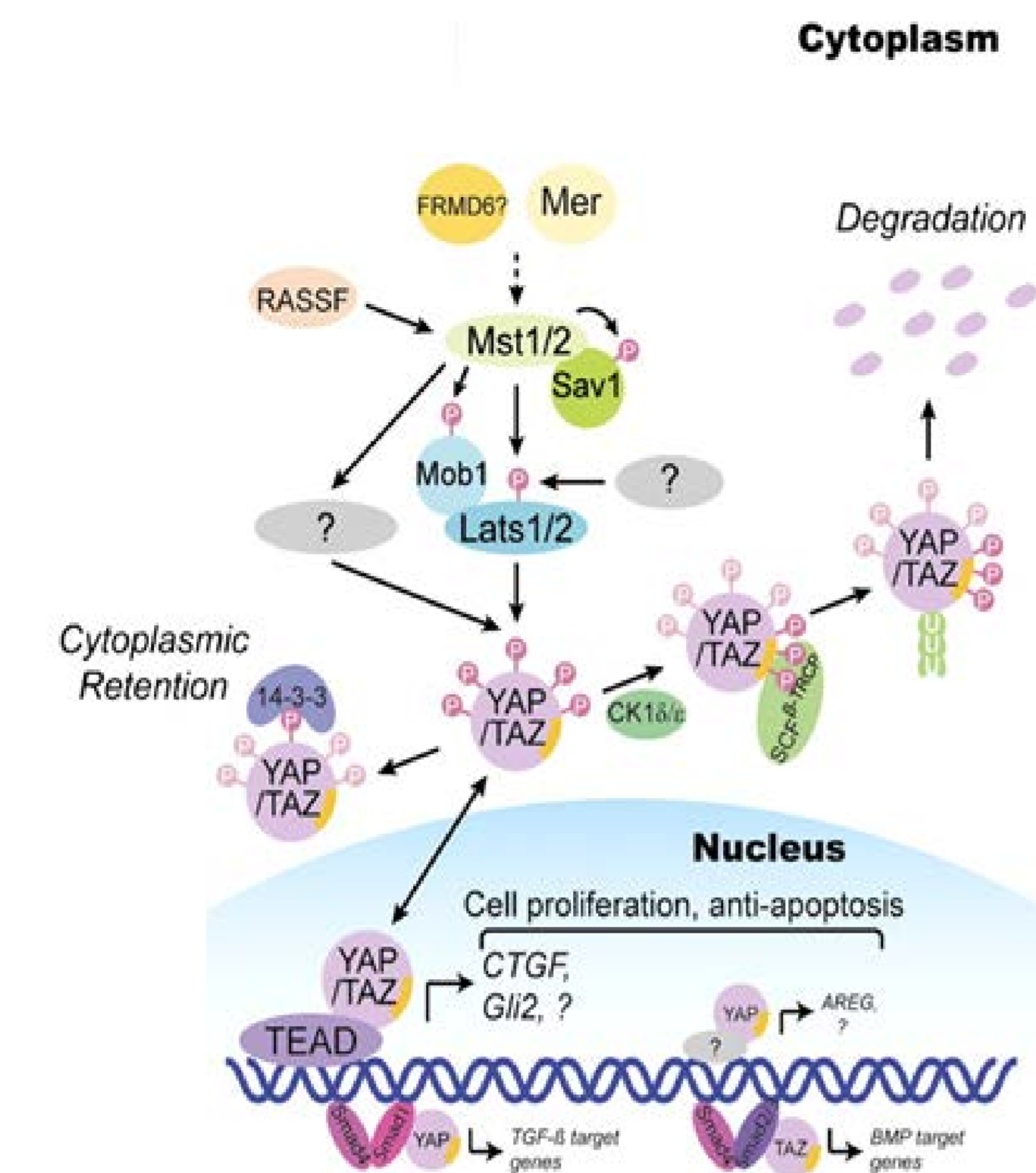
BACKGROUND

The Hippo Pathway

- 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 factor

Rationale in cancer

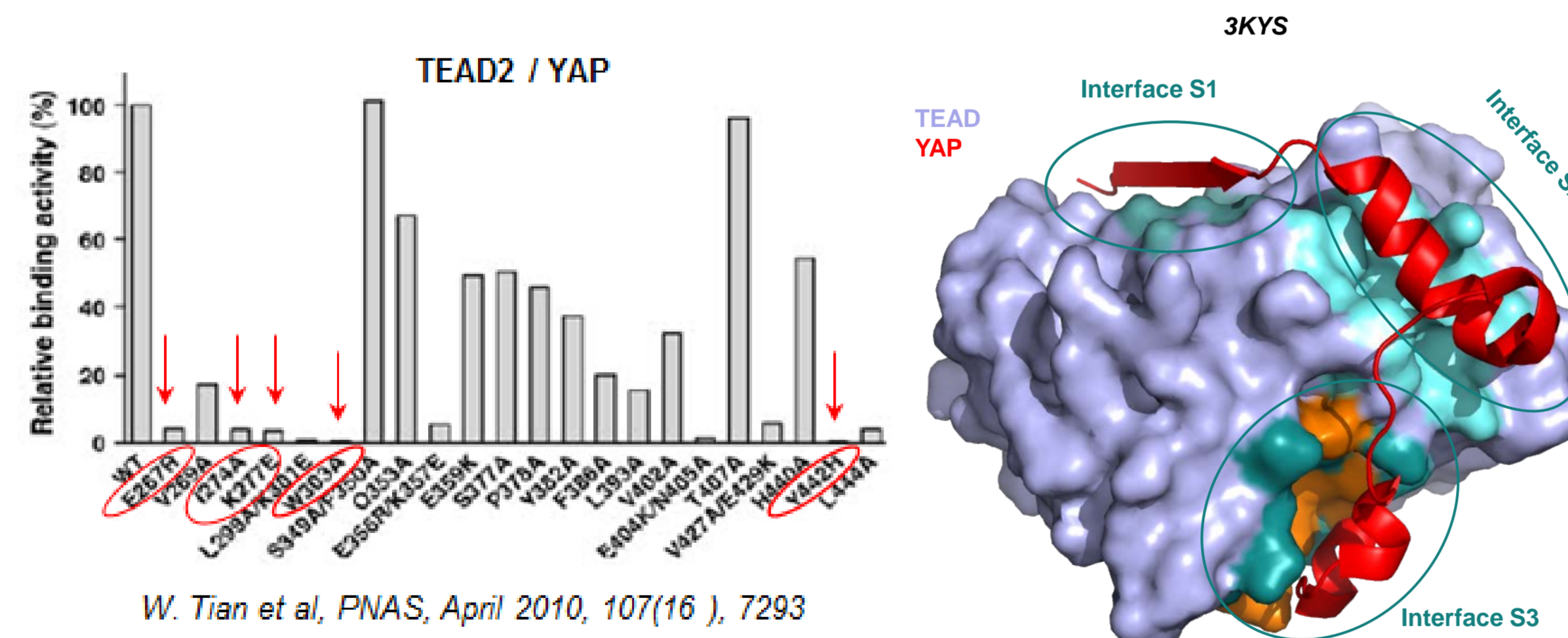
- High frequency of YAP nuclear localization in cancer biopsies
- NF2 is known to be mutationally inactivated in cancer (70% of Malignant Mesothelioma)
- YAP described as a critical oncogenic KRAS effector
- STK11 mutation in cancer results in Yap nuclear localization
- Blocking the hippo pathway can enhance the efficacy of RAF and MEK inhibitors in patients with a broad range of BRAF- and RAS-mutant tumors



Our strategy: Block YAP-TEAD interaction with a small molecule

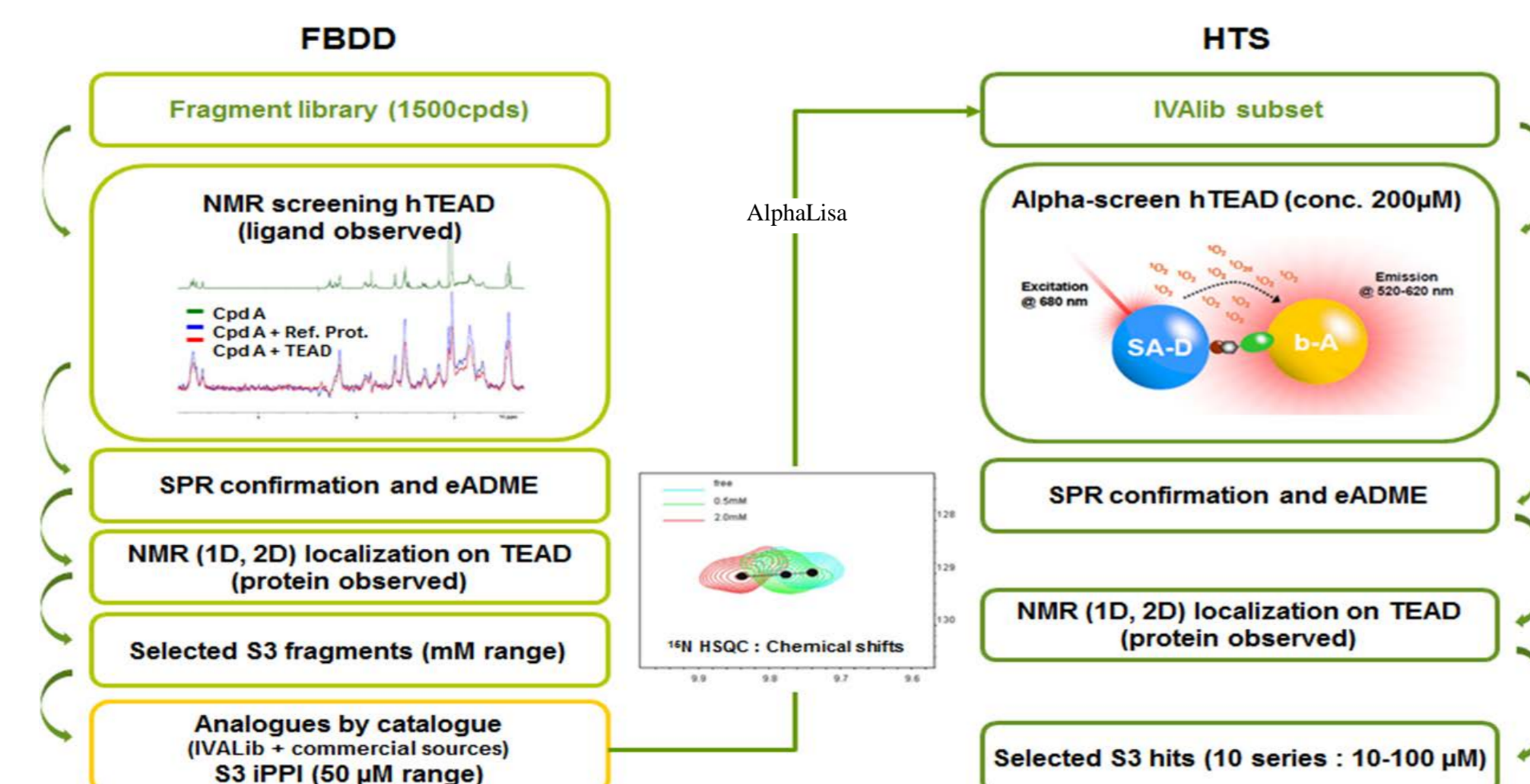
STRATEGY TO IDENTIFY YAP-TEAD INHIBITORS

- YAP-TEAD PPI has 3 interfaces
- YAP: IDP (Intrinsically Disordered Protein)
 - at least by sequence composition
 - YAP is stabilized by PPI with TEAD
- TEAD: globular protein
 - Hot Spot analysis by TEAD mutagenesis
 - 83% of YAP-TEAD interaction energy in S3



W. Tian et al, PNAS, April 2010, 107(16), 7293

- Hit finding : two approaches
 - FBS by NMR
 - HTS by AlphaLisa
- Identification of multiple YAP-TEAD iPPI series
 - TEAD binding confirmed by SPR
 - S3 localization confirmed by NMR



Hit-to-lead ongoing on Several TEAD S3 binder drug-like chemical series

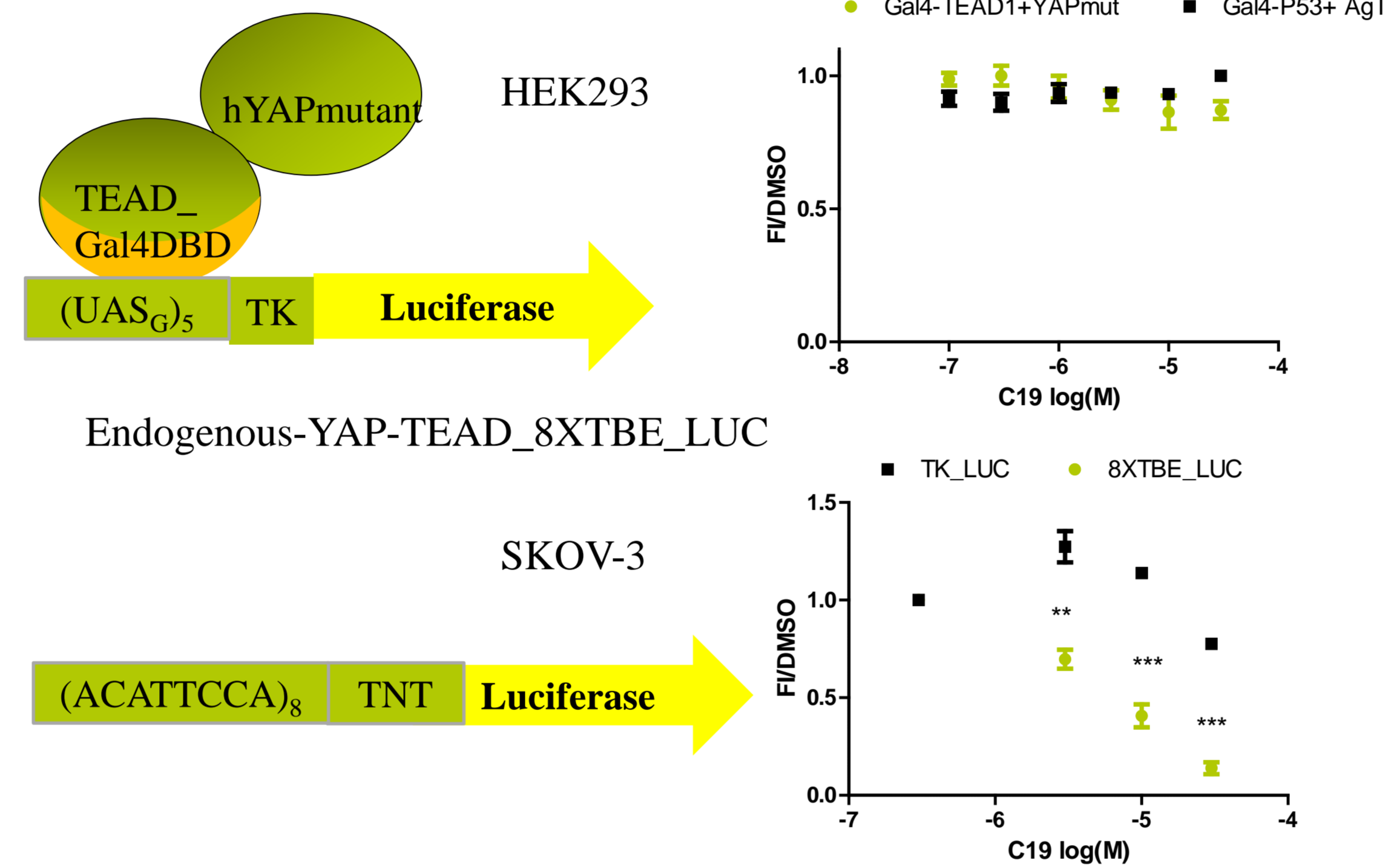
RESULTS

Functional assay set up for in vitro POC establishment

Transactivation assay

TEAD-Gal4DBD/YAPS127A_S397A/GAL4RE_LUC

Technological counter-screen : P53 -AgT transactivation assay

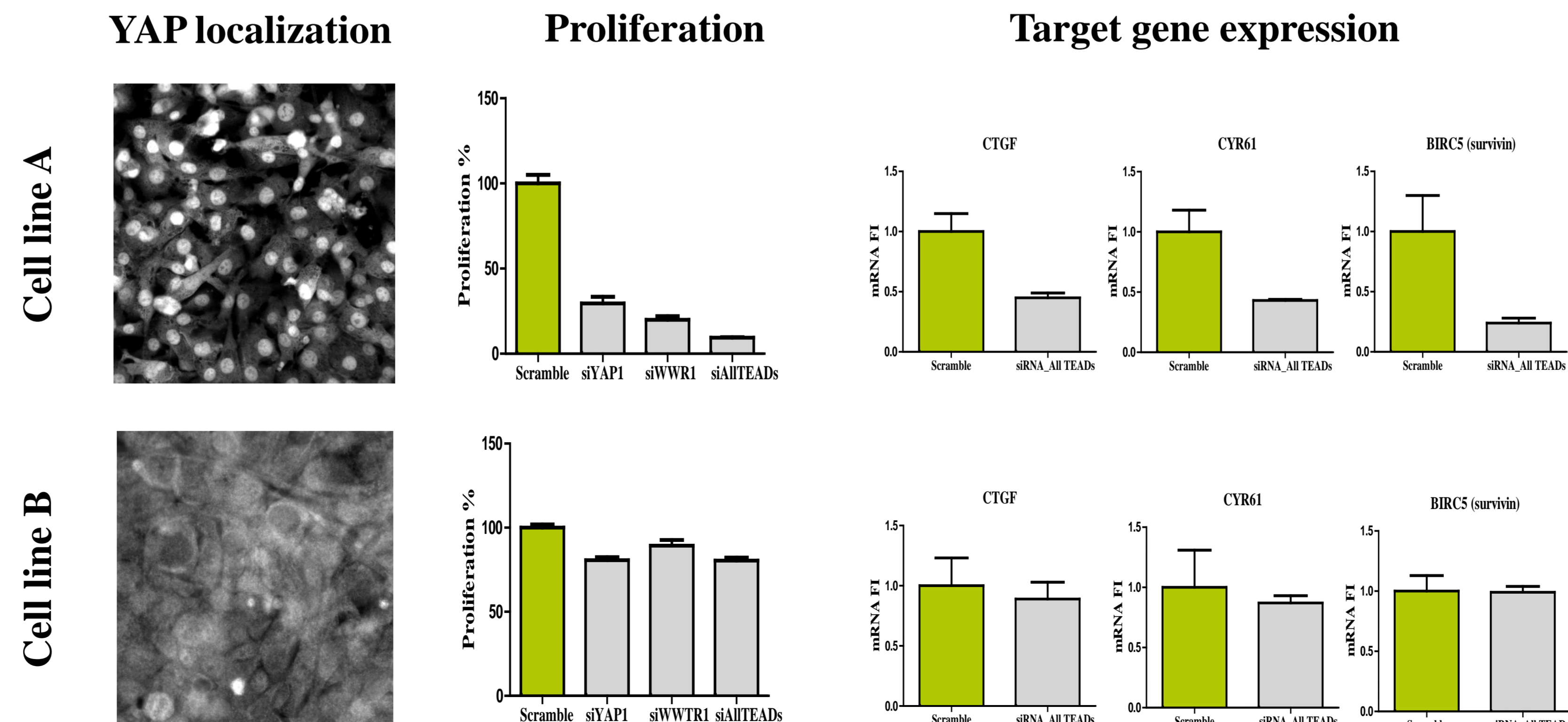


C19 compound, which induces activation of the kinases Mst/Lats (Basu *et al*, 2014) inhibits YAP-TEAD transactivation in a Hippo constitutive system (SKOV3 cell model)

but not in cell-based TEAD-GAL4 transactivation assay (HEK293)

Our assay allows us to screen compounds that block the direct interaction of YAP and TEAD

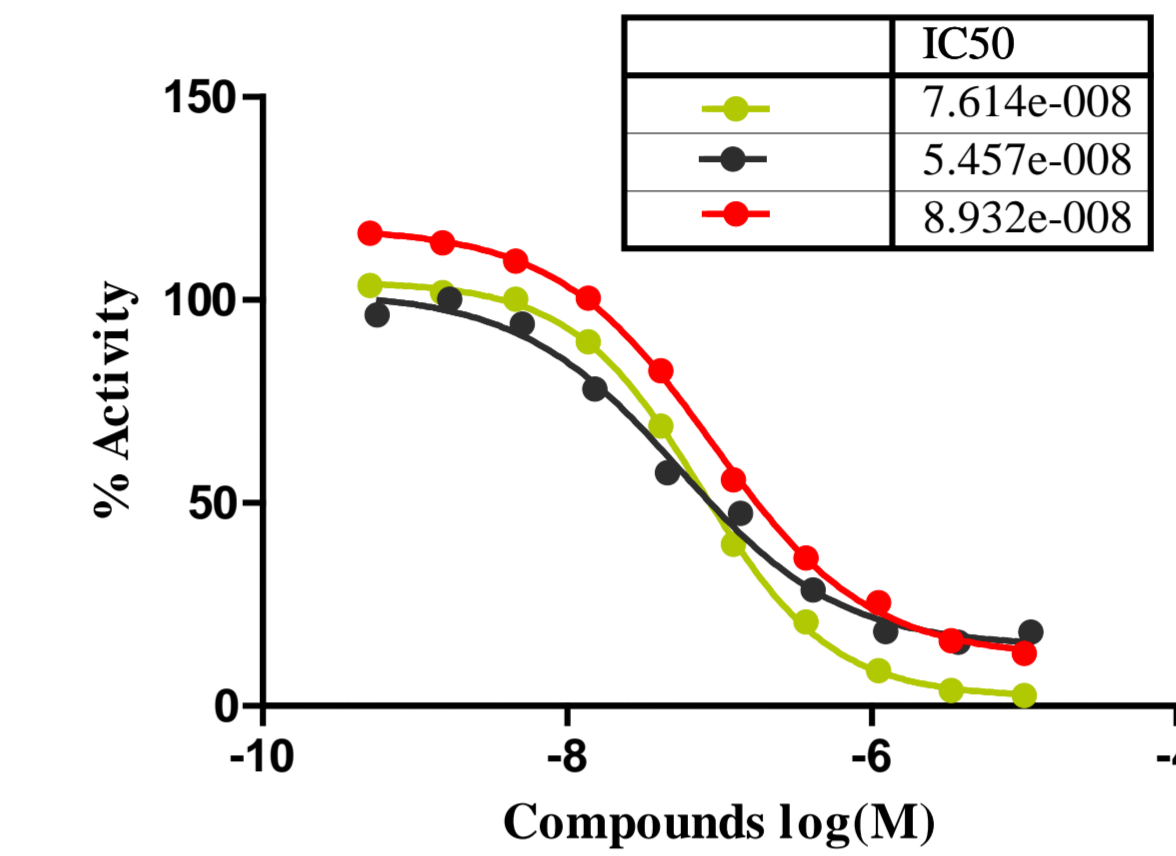
Selection of YAP-dependent and independent cell lines for drug screening



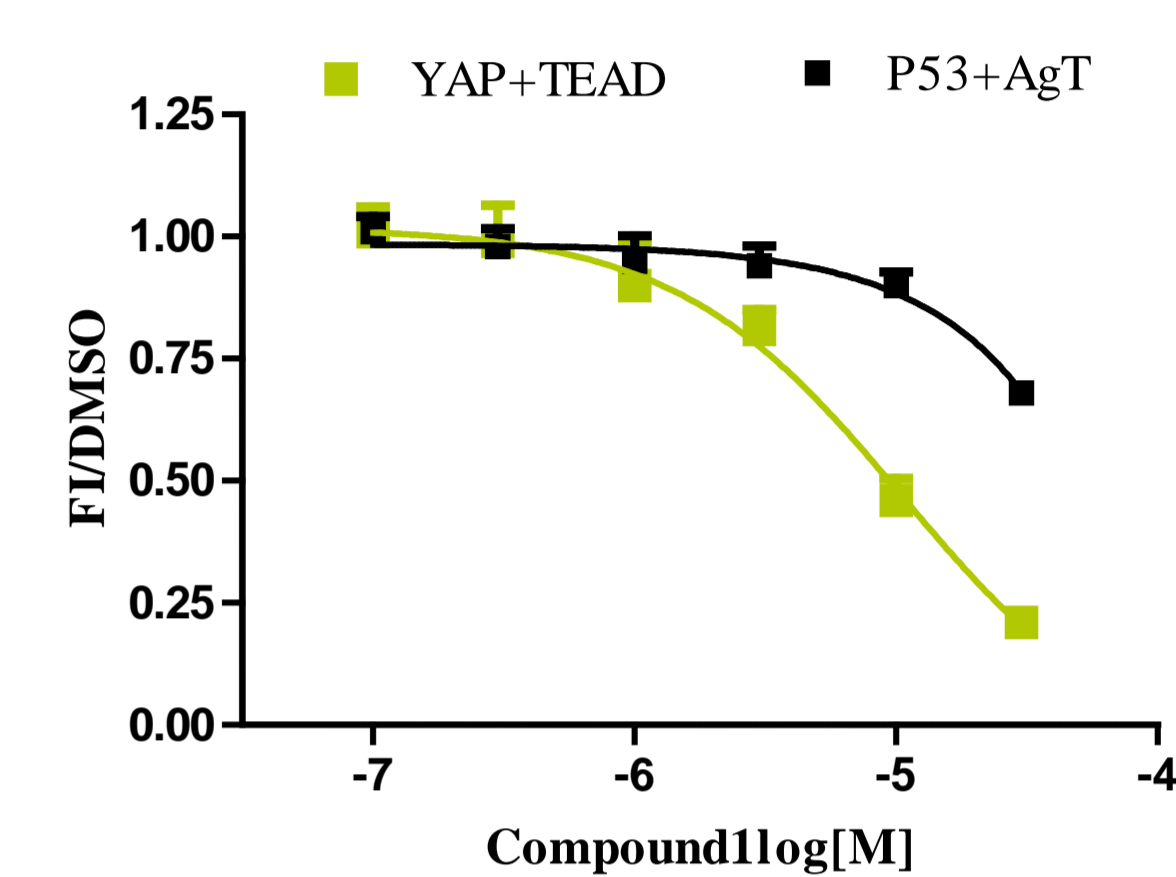
We have developed several cellular assays highly relevant for screening compounds aimed at inhibiting the YAP-TEAD interaction

Compound Profiling

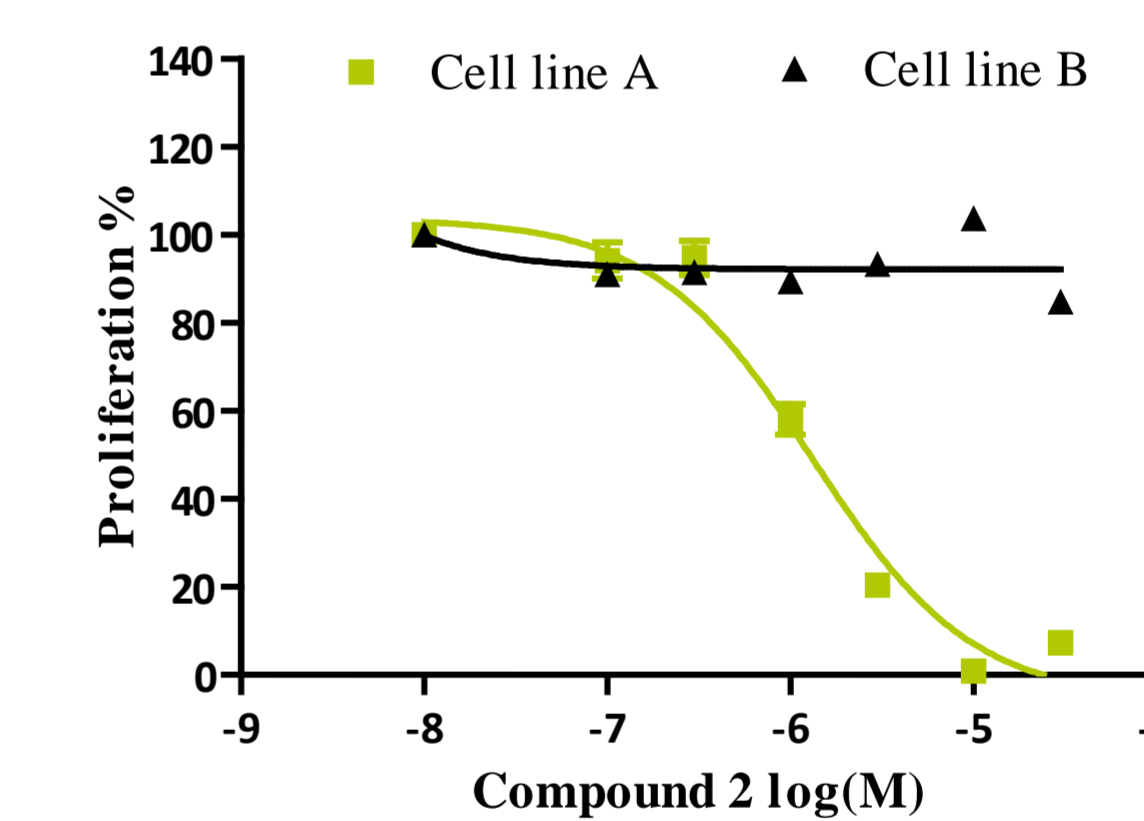
AlphaLisa



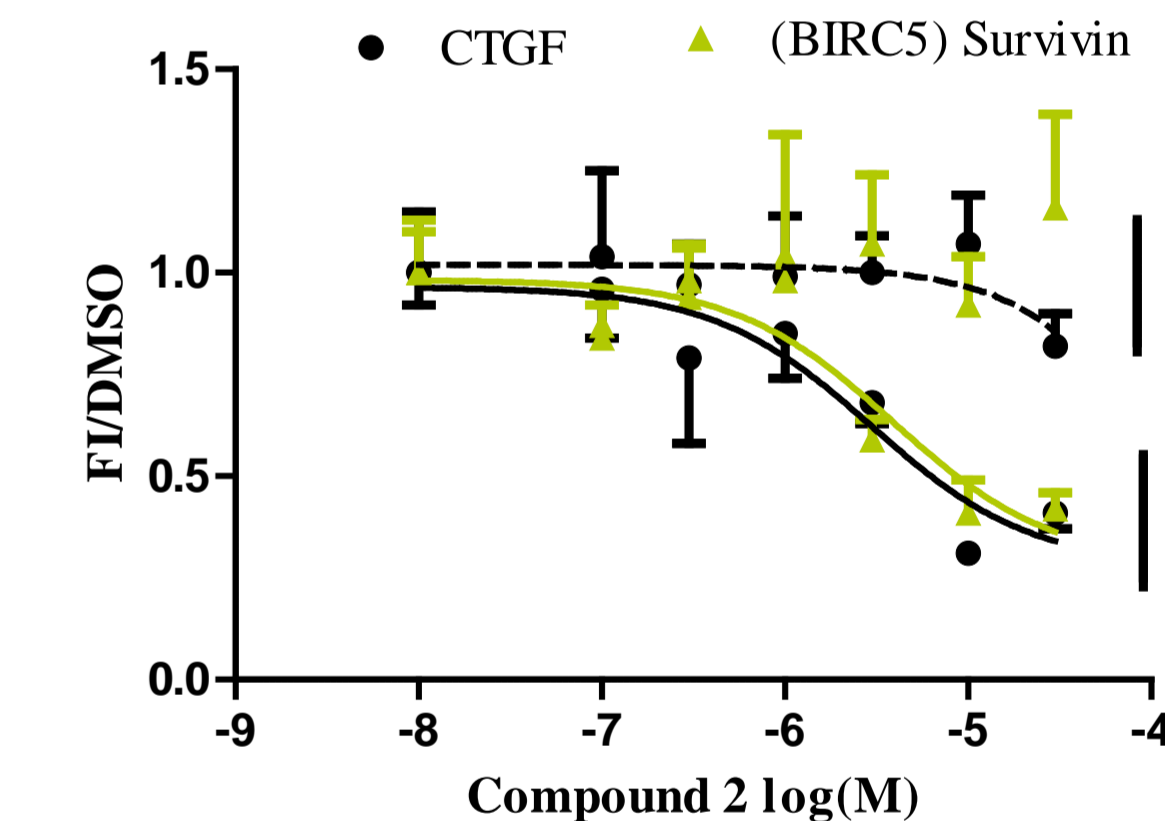
Transactivation assay



Proliferation



Target gene expression



CONCLUSIONS

- We have developed highly selective cell-based assays to screen YAP-TEAD inhibitors
- We have identified proprietary and druggable YAP-TEAD iPPI series:
 - Binding S3 (NMR)
 - Showing a marked inhibition in YAP-TEAD cell-based transactivation assays
 - Inhibiting tumor cell growth and modulating target genes in YAP "dependent" cancer cells
- We are progressing hit to lead phase