A rational approach for the discovery of inhibitors of the YAP-TEAD interaction

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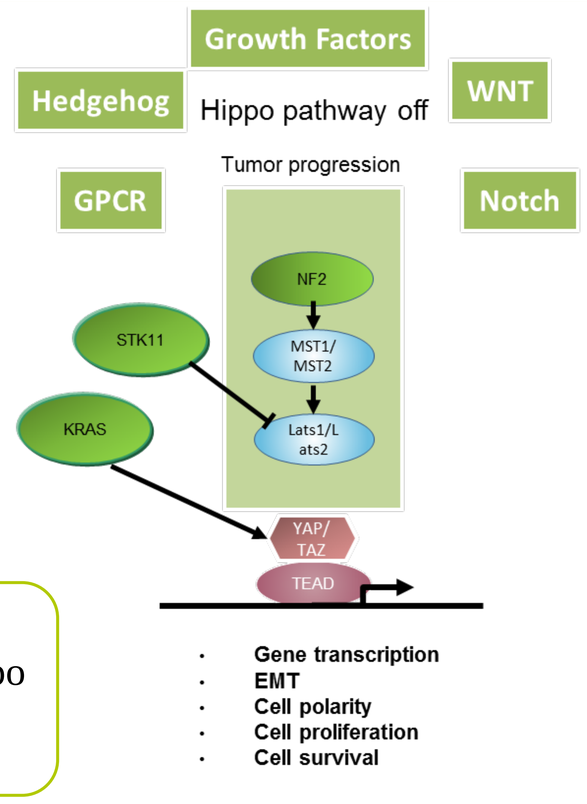
BACKGROUND

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
- 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

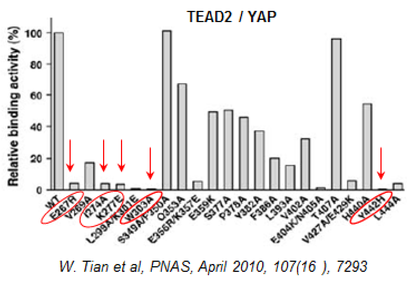


Inventiva's strategy: To inhibit the YAP-TEAD PPI

- YAP/TAZ and TEAD are major downstream effectors enabling to target all the major Hippo signaling pathway at once
- Offers potential to overcome drug resistance and escape mechanism

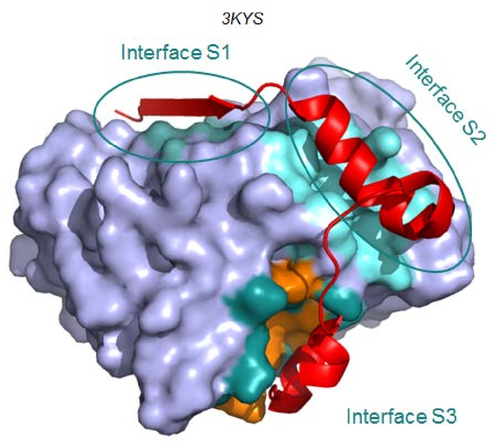
YAP-TEAD A DRUGGABLE INTERACTION

- 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 Ala-scan



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

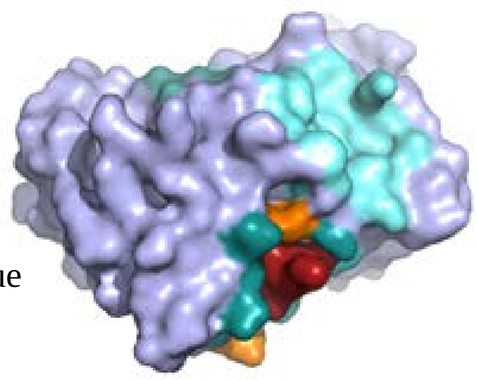
All critical residues for YAP-TEAD interaction belong to interface 3



NMR Guided Docking

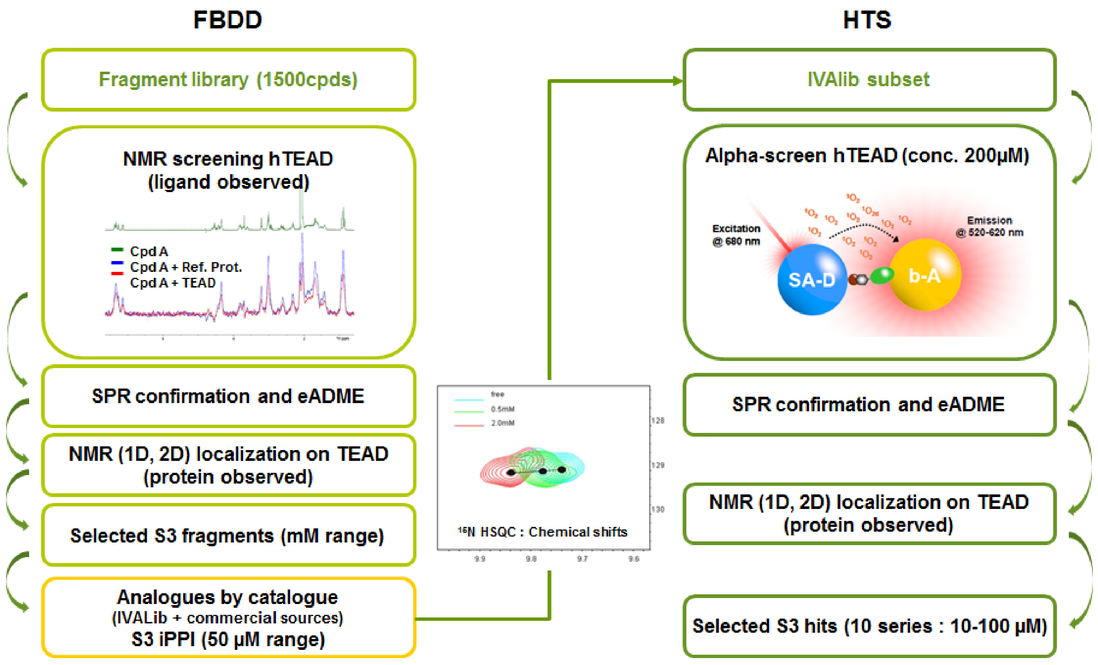
FBS

Compound by catalogue



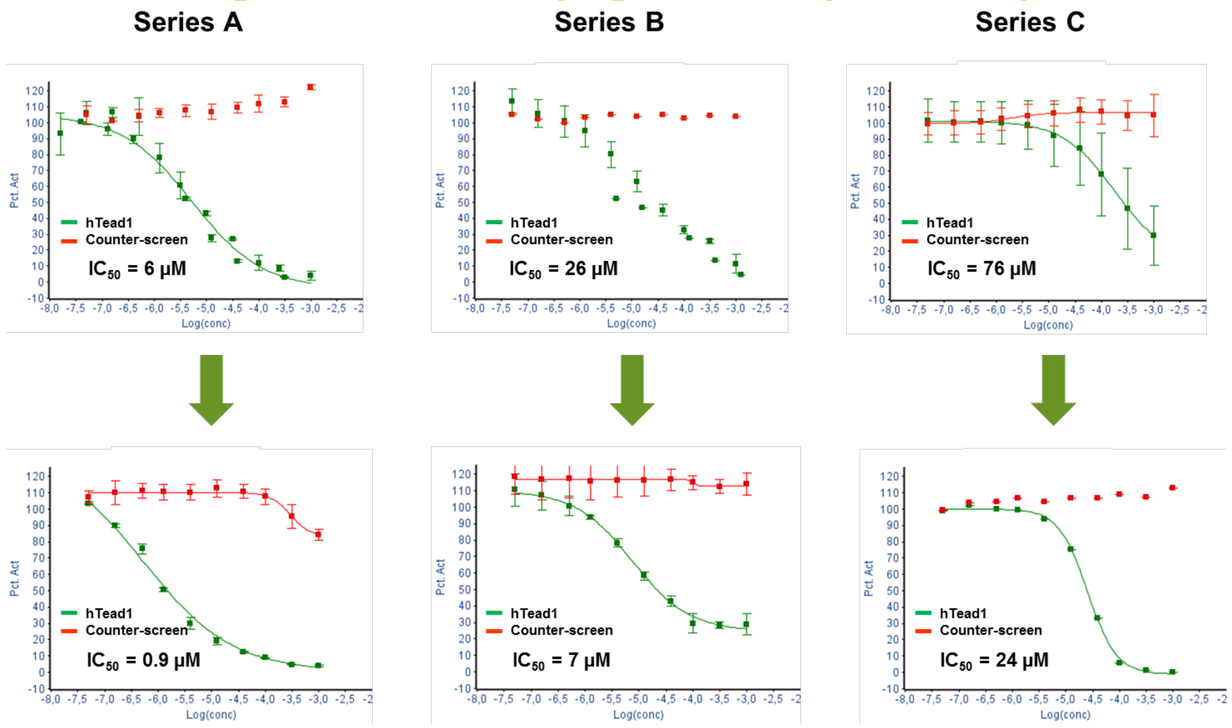
RESULTS

A Dual FBDD and HTS Screening Approach



- Target druggability assessment:
  - FBS by NMR: Identification of S3 binding fragments (mM range)
  - Compound by Catalogue (IVALib and commercial sources): Identification of S3 binders that were confirmed as PPI inhibitors (µM range)
  - HTS: Identified multiple YAP-TEAD iPPI series confirmed to bind at S3 (RMN and SPR)

Rapid First Round of Optimization µM to sub µM IC50



Multiple series undergoing H2L program

TEAD ligands	✓	• SPR, KD : 60µM - 3mM • LE : 0.17 – 0.27
YAP – TEAD inhibitors	✓	• Alpha-screen : IC50 : 0.9µM - 10µM with max > 80%
TEAD S3 binders	✓	• NMR HSQC localization studies
Lipinski rules	✓	• Mw : 213 – 500 • HA : 0 – 7 • HD : 0 – 2 • LogP : 0.6 – 4 • PSA : 15 -150
Early ADME	✓	• Solubility > 100µM • Metabolic stability < 21µl/min/mg protein • Permeability moderate to high on Caco2
SAR	✓	• Emerging trends

CONCLUSIONS

- We have been able to demonstrate TEAD S3 druggability
- We have identified multiple YAP-TEAD iPPI series confirmed to bind at S3 (RMN and SPR)
- Three series have been selected for hit to lead phase optimization