A rational approach for discovery of inhibitors of 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: inhibit the YAP-TEAD PPI
- YAP/TAZ and TEAD are major downstream effectors enabling the targeting of 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

RESULTS
A Dual FBDD and HTS Screening Approach
- Target drugability assessment:
  - FBS by NMR: Identification of S3 binding fragments (mM range)
  - Compound by Catalogue (IVAliDb 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 (NMR and SPR)

Multiple series undergoing H2L program
- Rapid First Round of Optimization µM to sub µM IC_{50}

CONCLUSIONS
- We have been able to demonstrate TEAD S3 druggability
- We have identified multiple YAP-TEAD iPPI series confirmed to bind at S3 (NMR and SPR)
- Three series have been selected for hit to lead phase, and optimization µM to sub µM IC_{50}