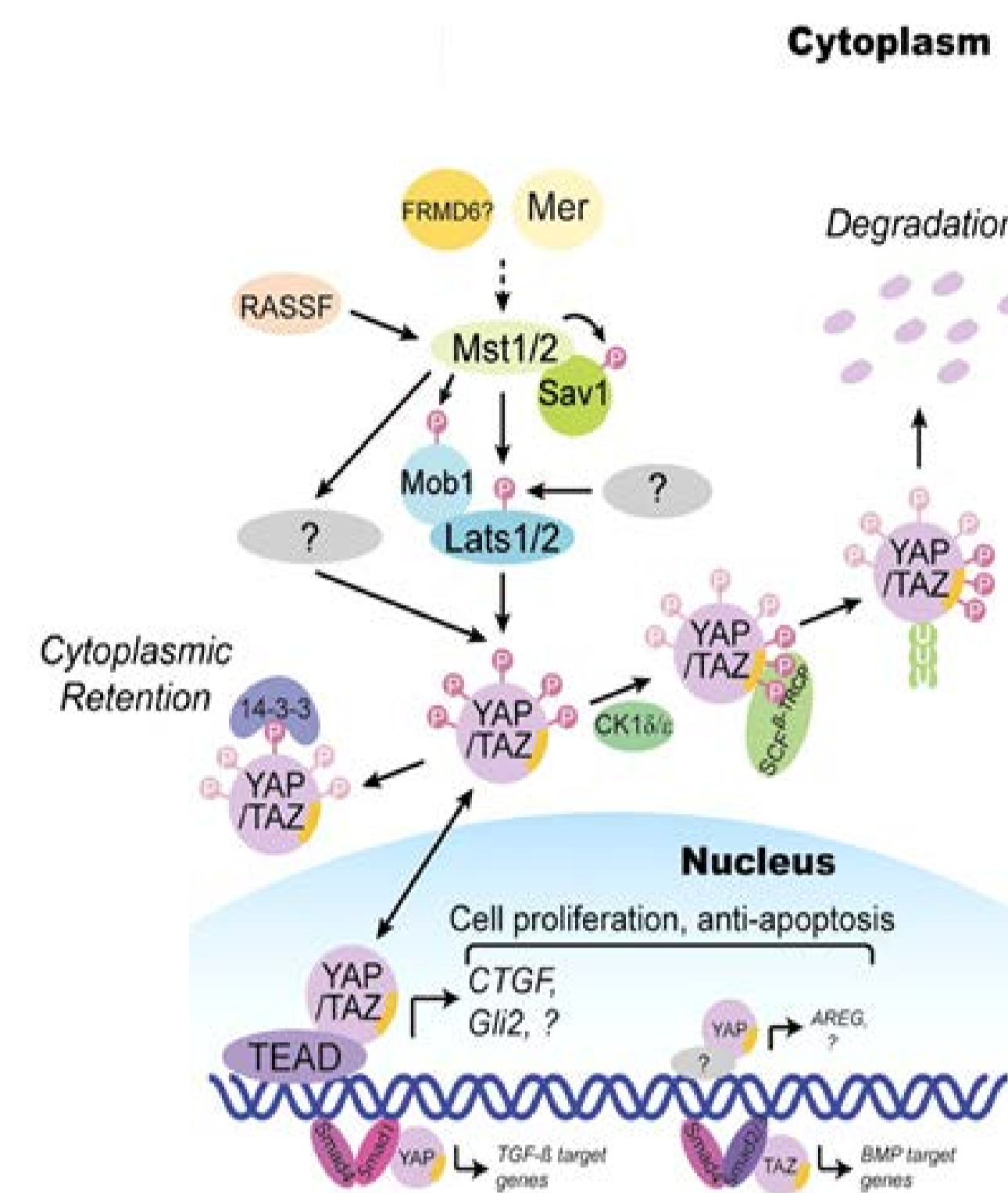


BACKGROUND

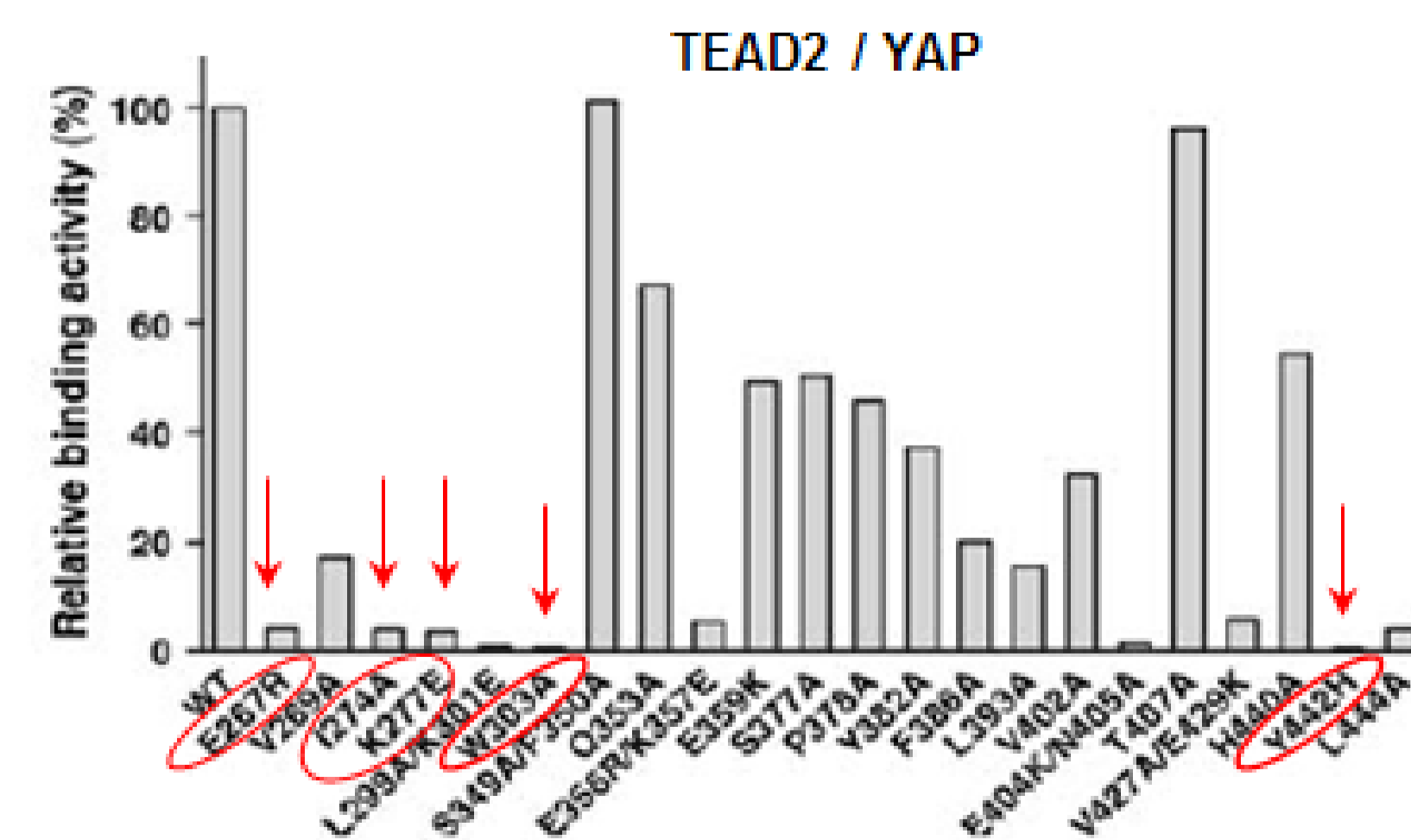
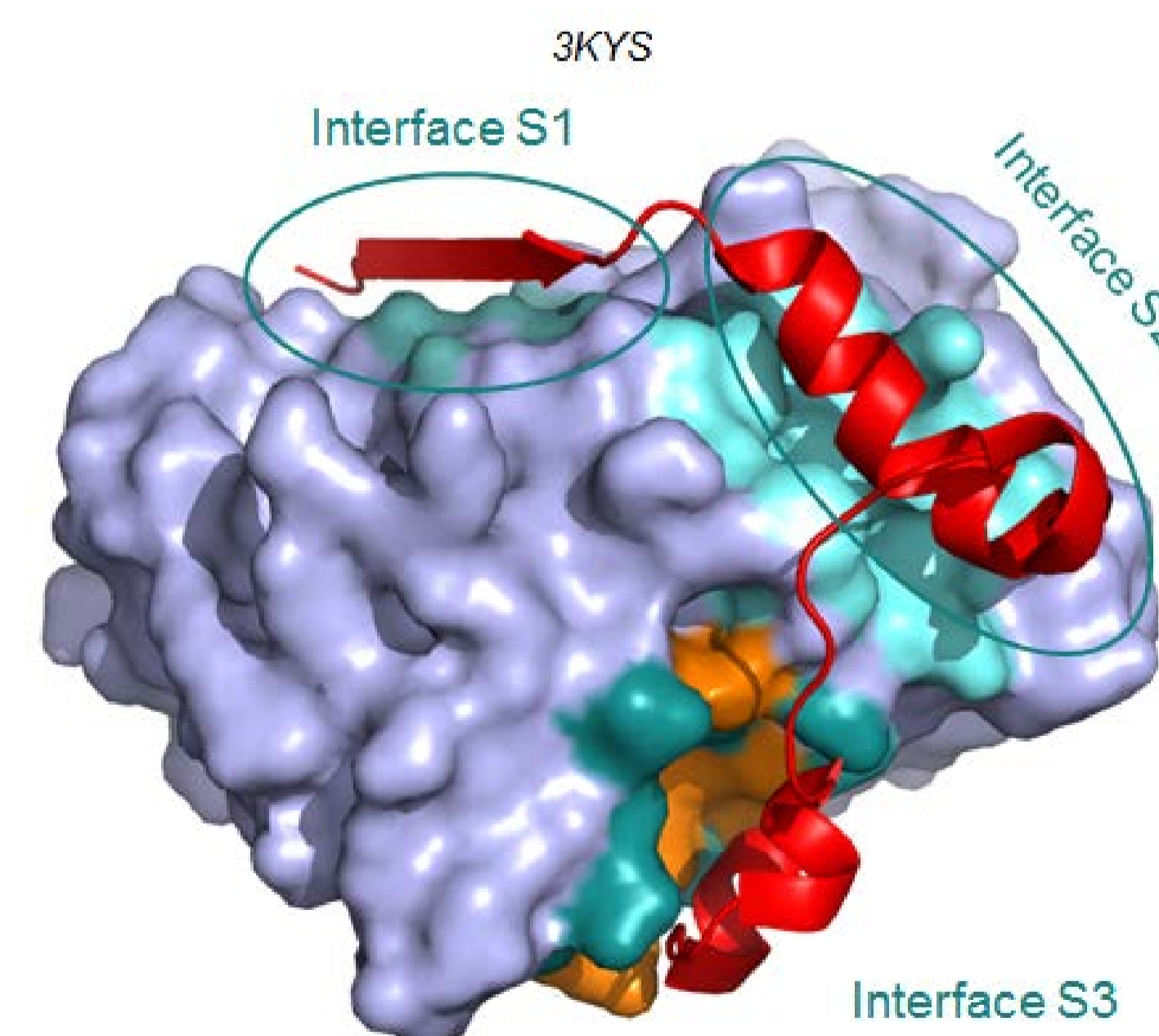
- The Hippo pathway plays a major role in organ growth regulation and tumorigenesis
- By sensing contact inhibition, the central kinase network of the hippo pathway controls YAP nuclear translocation
- YAP interacts with the TEAD family of transcription factors and drives expression of gene involved in cell survival and proliferation
- YAP, TAZ and TEADs over-expressed in cancer:
 - Colon
 - Lung
 - Gastric
 - Ovarian
- Knockdown of YAP inhibits proliferation and metastasis of gastric cancer cells
- A dominant-negative TEAD molecule suppresses YAP-induced liver tumorigenesis



Our strategy: To block the YAP-TEAD interaction with a small molecule

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

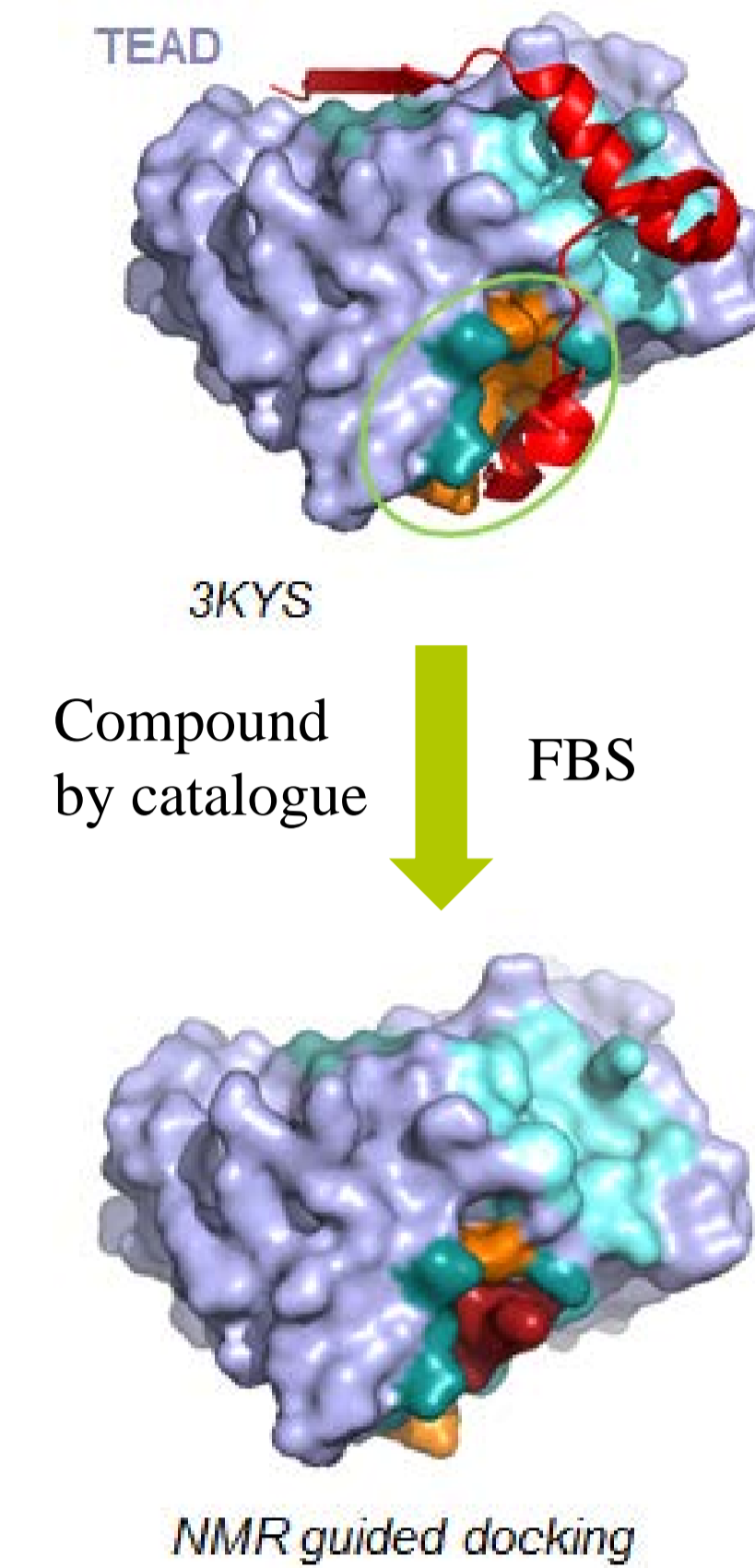
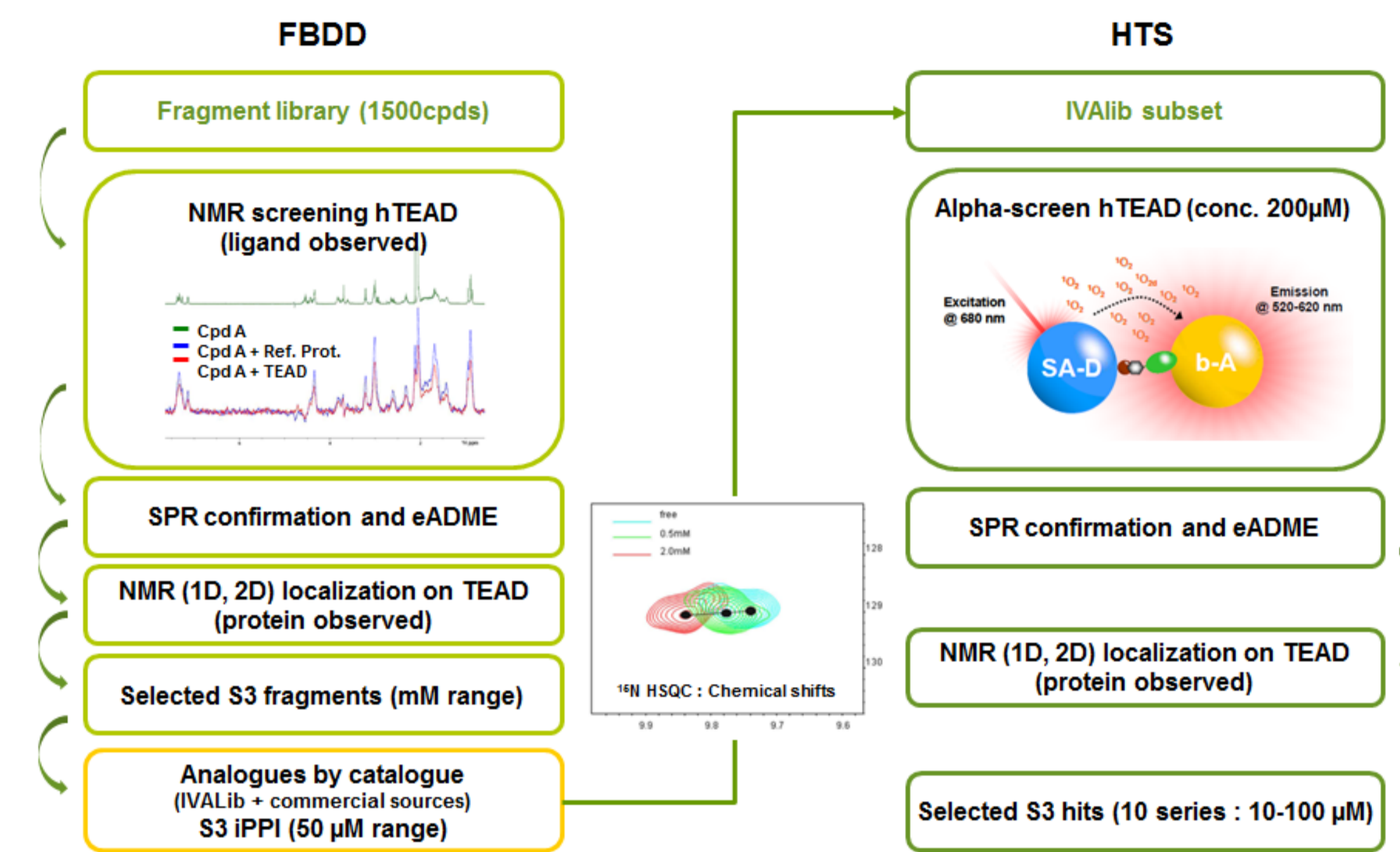
Discover interface S3-TEAD binders to inhibit YAP-TEAD interaction

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

RESULTS

HIT identification

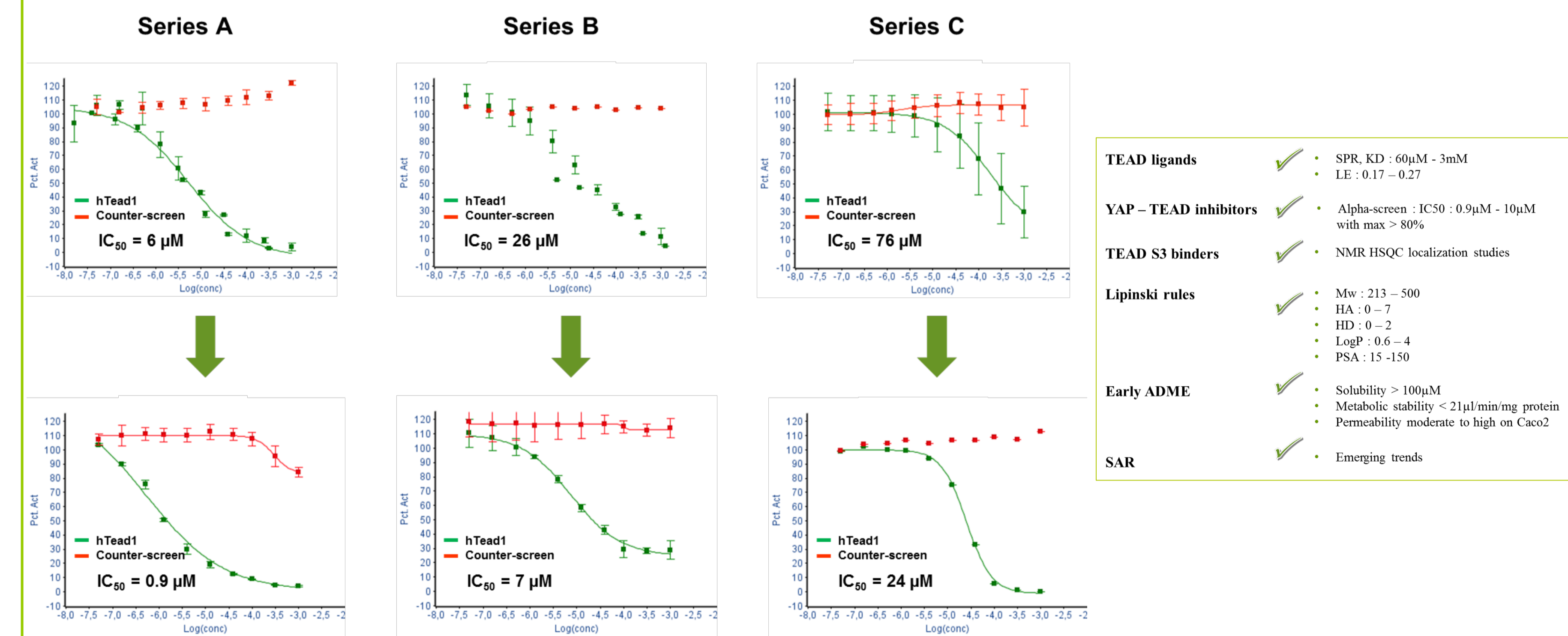
A Dual FBDD and HTS Screening Approach



- Drugability 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 by Apha-Screen: Identified multiple YAP-TEAD iPPI series confirmed to bind at S3 (RMN 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 drugability
- 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, and optimization μM to sub μM IC_{50}