

Discovery of promising anti-cancer drug combination using YAP-TEAD inhibitors with standard of care treatment in mesothelioma and NSCLC cells



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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
- In NSCLC, YAP overexpression is associated with disease development, progression and poor prognosis
- NF2 is mutationally inactivated in cancer (70% of Malignant Pleural Mesothelioma, MPM) driving YAP and TAZ activation

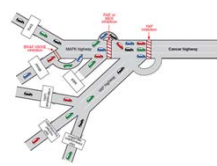
Rationale drug resistance and drug combination

- YAP has been identified as a key factor in cancer resistance to various chemotherapeutic drugs
- MPM is notoriously resistant to conventional cytotoxic chemotherapy
- YAP expression positively correlates with chemotherapeutic drug resistance
- Spheroids represent a promising model to investigate drug response and develop novel strategy to overcome chemoresistance

HYPOTHESIS

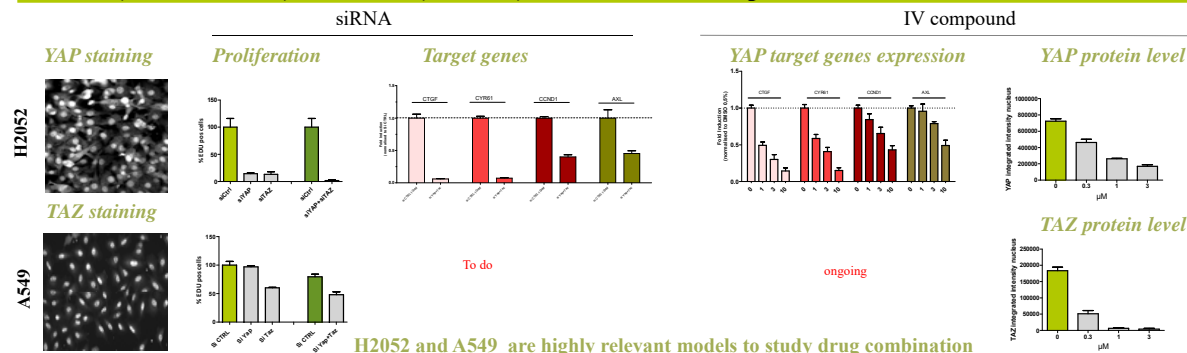
Small molecules could disrupt YAP-TEAD interaction

In relevant cellular model a combination of YAP-TEAD inhibitor and SOC could synergize to induce tumor growth inhibition



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H2052 (mesothelioma) and A549 (NSCLC) are YAP-TEAD dependent cell lines

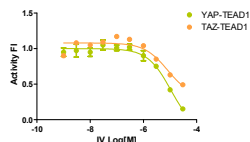
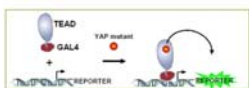


H2052 and A549 are highly relevant models to study drug combination

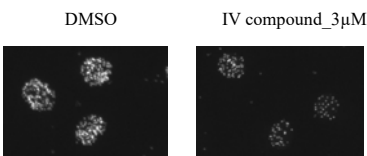
Discovery of YAP/TAZ-TEAD inhibitors and MoA highlights

Transactivation assay

- Assays established in HEK293 cell lines
- TEAD Gal4DBD/hYAP mutant construct (S127/S397)
- Counter-screen p53-AgT transactivation assay
- Specific of YAP-TEAD heterodimer

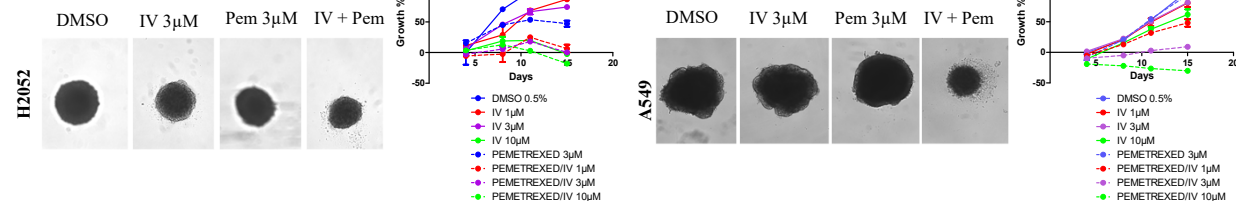


YAP-TEAD interaction (Proximity ligation assay, PLA)



YAP-TEAD inhibitors sensitize H2052 and A549 cells to SOC Pemetrexed

Spheroid model: area measurement



CONCLUSIONS

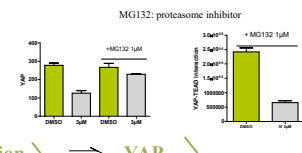
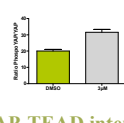
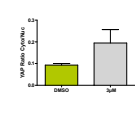
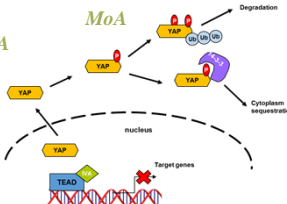
- We have discovered small molecules able to inhibit YAP-TEAD and TAZ-TEAD protein-protein interaction
- We have shown evidence of YAP-TEAD disruption
 - Inhibition of YAP-TEAD dependent transactivation assay
 - Decrease of YAP-TEAD interaction level
 - YAP-TEAD disruption leads to a degradation of YAP
- IV compounds decrease expression of YAP-TEAD target genes
- IV compounds lead to YAP protein degradation via YAP-TEAD interaction inhibition
- IV compound inhibit H2052 proliferation
- We have demonstrated that combination of YAP/TAZ-TEAD inhibitors with pemetrexed offers the potential to overcome drug resistance for the treatment of Malignant Pleural Mesothelioma as well as NSCLC

Ratio YAP cyto/nuc

YAP phosphorylation (Ser127)

YAP degradation

YAP-TEAD interaction, PLA



YAP-TEAD interaction \Rightarrow YAP