Abstract # 340

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
- 70% of Malignant Pleural Mesothelioma, MPM have NF2 mutation driving YAP and TAZ activation

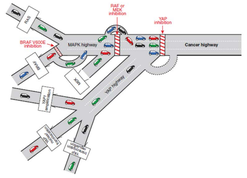
Rationale for drug combination in drug resistance

- 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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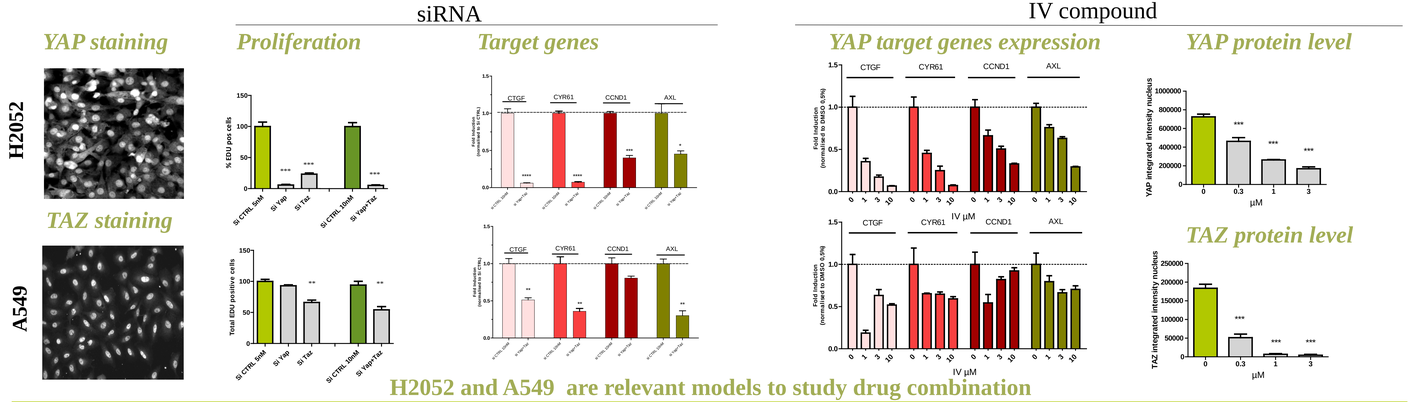
H2052 (mesothelioma) are more sensitive to YAP/ TAZ-TEAD inhibitors than A549 (NSCLC)

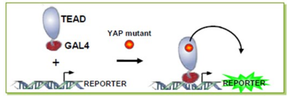


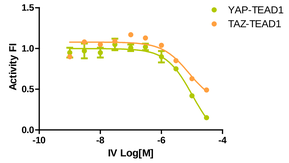
H2052 and A549 are relevant models to study drug combination

Discovery of YAP/TAZ-TEAD inhibitors and MoA highlights

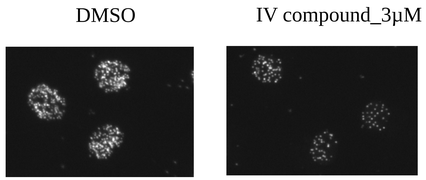
Transactivation assay

- Assays established in HEK293 cell lines
- hTEAD_Gal4DBD/hYAP mutant construct (S127/S397)
- Counter-screen p53-AgT transactivation assay
- Specific of YAP-TEAD heterodimer

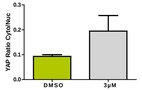




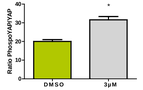
YAP-TEAD interaction (Proximity ligation assay, PLA)



Ratio YAP cyto/nuc

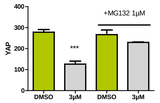


YAP phosphorylation (Ser127)

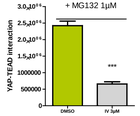


YAP degradation

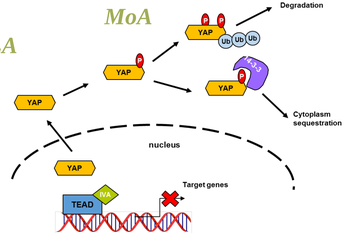
MG132: proteasome inhibitor



YAP-TEAD interaction, PLA



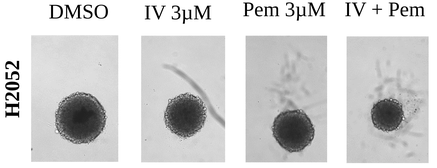
MoA

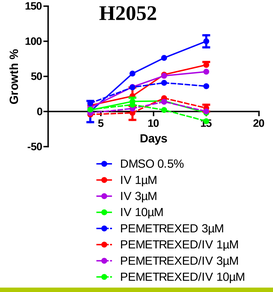


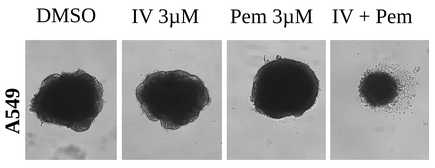
YAP-TEAD interaction ⇒ *YAP*

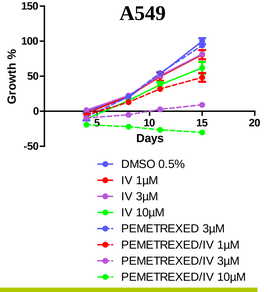
YAP-TEAD inhibitors sensitize H2052 and A549 cells to SOC Pemetrexed

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**