Abstract #112: Combined inhibition of the MAPK and Hippo pathways drives efficacious tumor suppression in a faithful model of mutant *Kras* (KPC) PDAC

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Abstract

- Mutations in the KRAS oncogene hyperactivate the MAPK pathway, a key driver of oncogenesis in the majority of human malignancies. KRAS-driven tumors are aggressive and highly refractory to standard-of-care treatments, thus intense efforts have been devoted to developing inhibitors of its activity.
- Pioneering studies in engineered conditional *mKras* driven mouse models of pancreatic ductal adenocarcinoma (KPC) have demonstrated that while *mKras* is necessary for tumor maintenance, the anti-neoplastic effects of mKras extinction can be counteracted by activation of the Hippo pathway. These data strongly suggest that the full realization of MAPK pathway (including KRAS) inhibitors' clinical potential requires the concomitant suppression of the function of YAP/TEAD, the effectors of Hippo pathway.
- Sporos generated two families of next-generation TEAD palmitoylation site inhibitors with optimized TEAD isoform specificity maximizing anti-proliferative activity and minimizing toxicity
- Sporos BioDiscovery's next generation TEAD inhibitor (SPR1) - optimized to maximize anti-neoplastic activity and minimize toxicity through fine-tuning of TEAD paralog specificity, inhibits tumor growth and doubles life-span in a highly aggressive murine model of PDAC named KPC (*KrasG12D* mutant, *p53* null, PDAC) and mouse and human cell lines, demonstrating strong synergy between MAPK and Hippo pathways.

Strategies to target the HIPPO pathway in combination with MAPK pathway

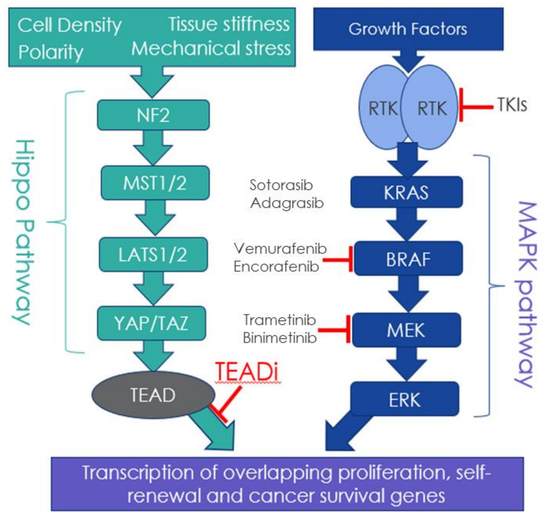


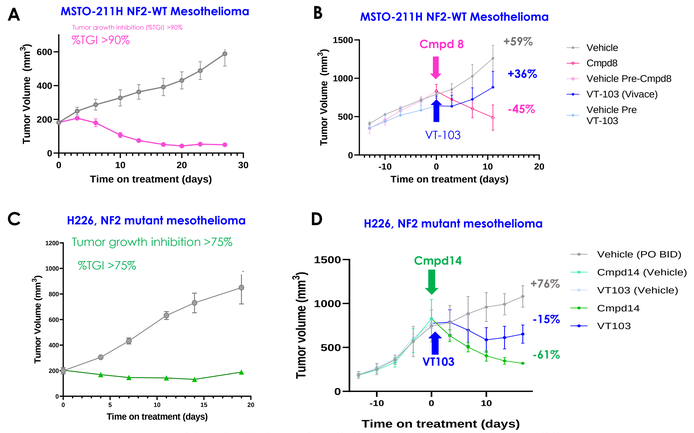
Figure 1. Sporos TEAD Inhibitors Synergize with Precision Oncology Drugs Targeting the MAPK pathway or its upstream inputs

Main Novel Findings

Sporos TEAD inhibitors drive regression even in very large tumors in monotherapy
Unique to Sporos with no comparable data from other TEAD inhibitors to date

Strong anti-neoplastic activity in a standard CDX protocol (<200 mm³)

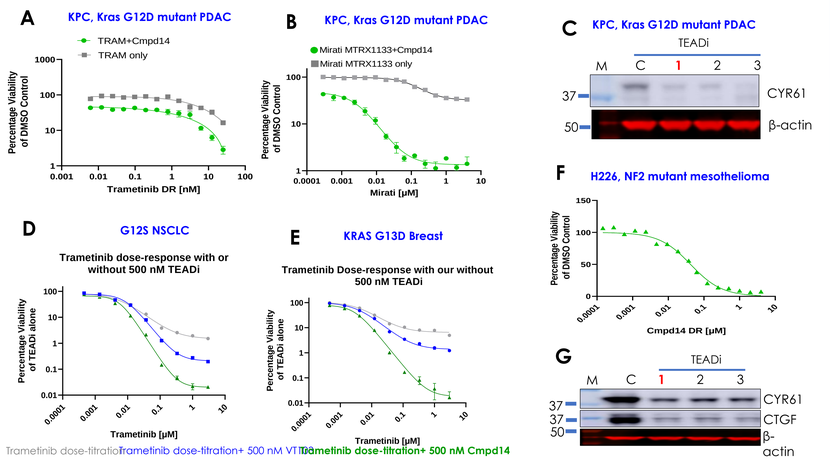
Sporos' TEAD inhibitor remains effective even against large tumors (>750 mm³), unlike leading competitor's



- **Low-nM potency, combined with broad activity in TEAD-dependent cell lines**
- **Minimal toxicity to non-transformed cells**

Figure 2. Demonstrated high efficiency in reducing tumor growth in standard small tumors (A,C) as well as unprecedented efficacy in reducing tumor burden when the tumors are large (800mm3) (B,D)

Sporos TEAD inhibitors synergize with precision oncology drugs targeting the MAPK pathway

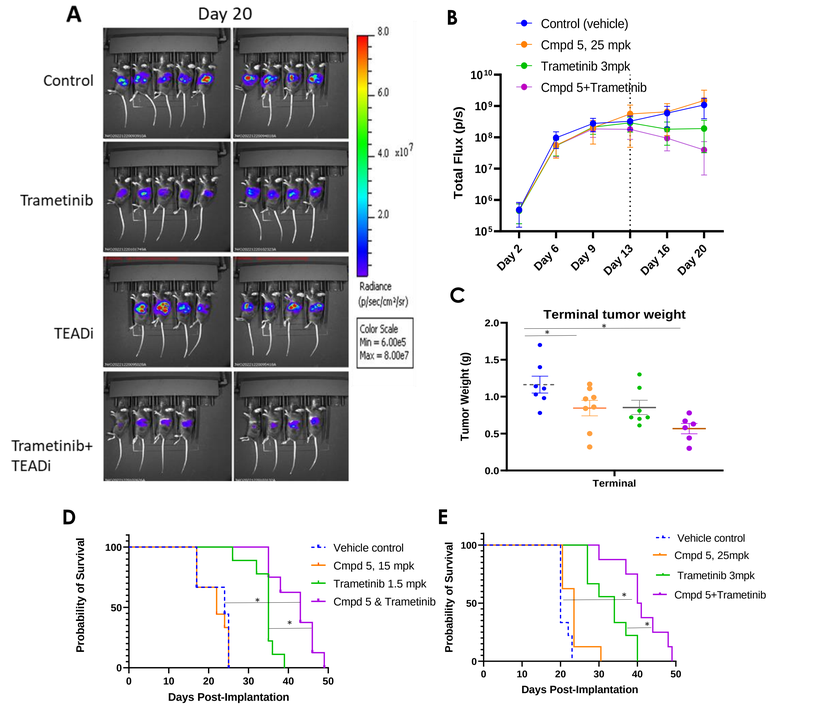


- **Cmpd14 outperforms competitor compound when combined with the MEK inhibitor Trametinib (Mekinist)**

Figure 3. Efficient synergy with drugs targeting the MAPK pathway (A-E) High efficiency as monotherapy agent in Hippo pathway mutant cell lines (F,G) through on target effect as evidenced by the downregulation of the downstream TEAD transcriptional targets in both and mouse and human cell lines (C,G)

Sporos TEAD inhibitors demonstrating *in vivo* efficacy in combination with MAPK pathway inhibitors

KPC, Kras G12D mutant PDAC



- **Sporos inhibitors hit additional isoforms other than TEAD1 without hitting the isoforms responsible for toxicity making it more efficacious in both *in vitro* and *in vivo***

Figure 4. (A) Luciferase imaging of mice at Day2 at randomization and at day 20 post-treatment with Trametinib (1.5 or 3mg/Kg) and TEADi (15 or 25mg/Kg) (B) BLI curves representing total flux over days of imaging. (C) Terminal tumor weights from euthanized mice (D and E) Increased survival of treated mice over time demonstrating efficacy of combination treatment and doubling of survival of the KPC mice.

Conclusion

- TEAD inhibitors show exceptional anti-tumor effects in pre-clinical models in vivo, with rapid regression in large tumors and extension of survival
- As molecular pathways predict, TEAD inhibitors strongly interact with direct inhibitors of Kras G12D or MAPK pathway inhibitors
- Sporos TEAD inhibitors show no toxicity even at high doses of 25mpk BID and does not induce weight loss in treated animals.

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