COMBINATION OF FATTY ACID SYNTHASE INHIBITOR WITH TYROSINE KINASE INHIBITORS SHOWS SYNERGISTIC EFFICACY IN HCC PRECLINICAL MODELS, A NOVEL POTENTIAL APPROACH FOR CLINICAL DEVELOPMENT

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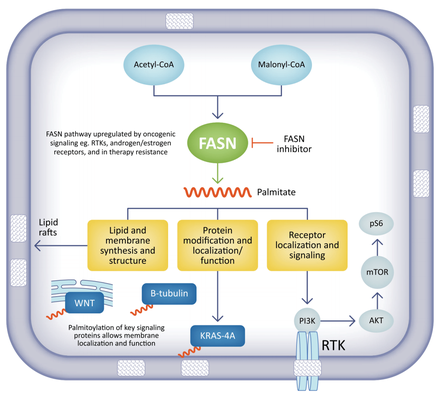
INTRODUCTION

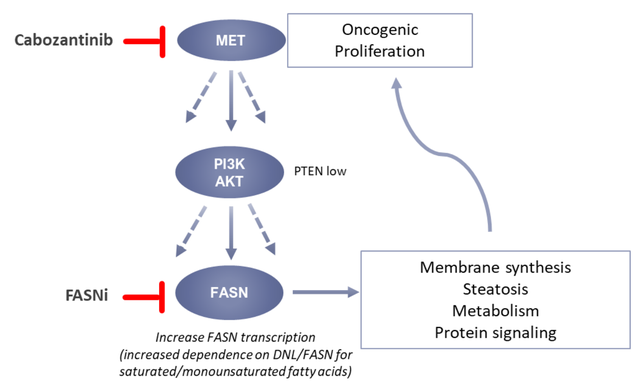
- **Fatty acid synthase (FASN) produces palmitate, which is further metabolized to make free fatty acids, lipotoxins and triglycerides including tripalmitin**
- **FASN is the last committed step in *de novo* lipogenesis (DNL) and is activated downstream of several driver oncogenes in cancer cells**
- **Specific cancer subtypes are <u>dependent on FASN</u>**
  - **increased membrane and lipid rafts**
  - **saturated lipids to avoid ROS induced death**
  - **palmitate for signaling; eg. KRAS4A palmitoylation**
  - **metabolic reprogramming as a resistance mechanism**
- **FASN inhibitors offer an opportunity for therapeutic drug development in HCC, particularly in the combination setting**
- **Denifanstat is a first in class FASN inhibitor, currently in Ph2b for NASH, and a Ph1 study in cancer patients has been completed (Falchook et al., 2021)**



FASN IN HCC

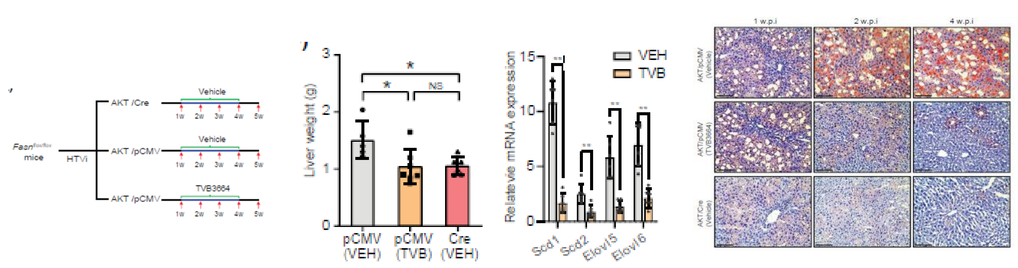
- **FASN is highly expressed in the liver and mediates de novo lipogenesis in hepatocytes and stellate cells, in addition to activating fibrosis in stellate cells**
- **Published results showed that FASN inhibition prevents development of HCC in a mouse NASH CCl4 model (O'Farrell et al., 2022)**
- **Prior studies have shown that FASN is required for AKT and MET mediated tumorigenesis in HCC models; oncogenes, such as loss of PTEN) and overexpression of c-MET. We therefore assessed the potential effect of combination of FASN inhibitors with approved kinase inhibitors in HCC preclinical models.**

Model for additive effect in FASN-dependent HCC

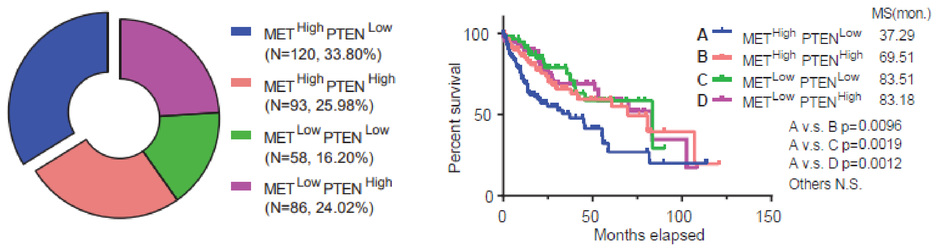


RESULTS - 1

- **FASN inhibitor prevents lipid accumulation driven by Akt in mouse liver**

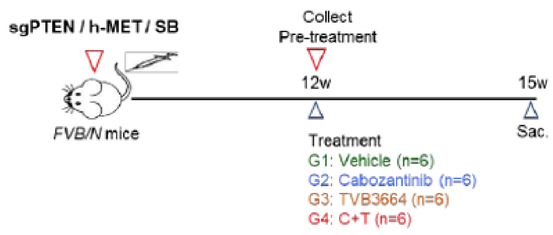


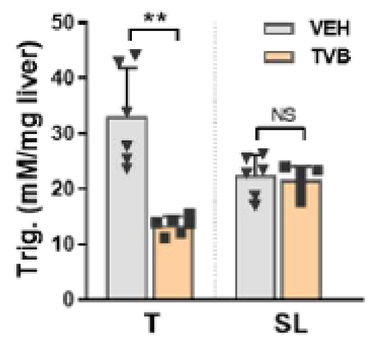
- **MET-hi/PTEN-lo constitutes 34% of human HCC based on TCGA analysis, and this population has poor overall survival**

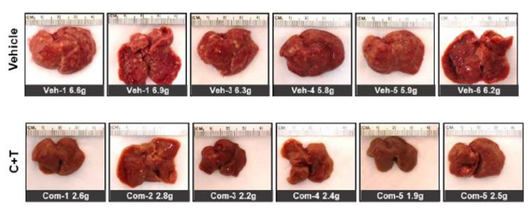


RESULTS - 2

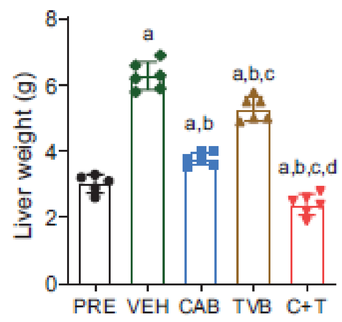
- **Combination of FASN inhibitor and cabozantinib decreased liver tumor burden significantly compared to single agents**

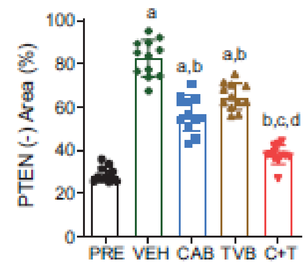


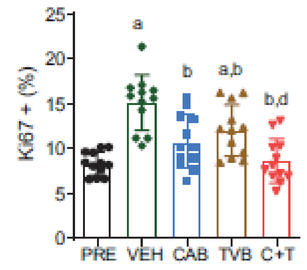




Combination agent	Target	sgPTEN/ high MET	high MYC	beta-catenin d90/high MET
		Additive or synergistic effect with FASNi		
Cabozantinib	MET, VEGFR	Yes	Yes	No
Sorafenib	RAF, VEGFR, PDGFR	-	Yes	-

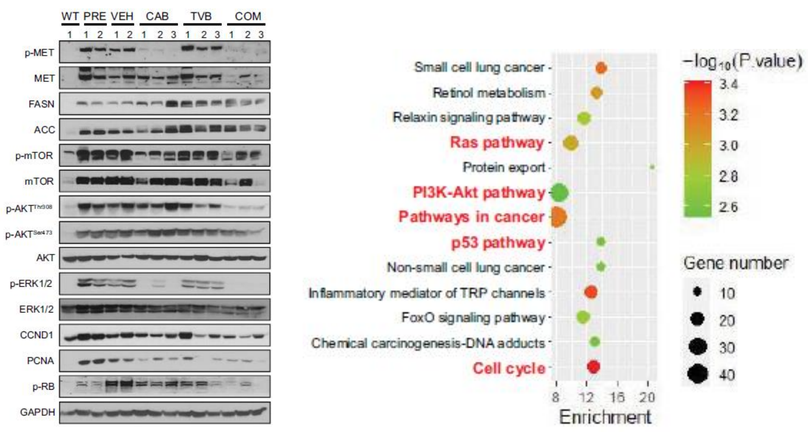






Mean ± SD; one-way ANOVA test. $p < 0.05$ (a) versus PRE; (b) versus VEH; (c) versus CAB; (d) versus TVB

- **Combination of FASN inhibitor and cabozantinib decreased cell cycle-related genes and proteins and pAKT T308**



SUMMARY

- **Combination therapy of a FASN inhibitor plus cabozantinib or sorafenib showed tumor regression in these models, and synergistic effects on cell cycle, pAKT and pERK were observed**
- **A Ph1 solid tumor study completed with denifanstat provides a foundation for additional clinical studies in cancer patients (Falchook et al., 2021)**
- **Next step: Analysis of human clinical databases for gene signatures corresponding to FASN sensitivity is the next step to translate these findings to patient selection for clinical trial design.**

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