

Preclinical studies characterize tumor type sensitivity to FASN inhibition and the mechanism and efficacy of novel drug combinations with TVB-2640

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### Introduction

**3-V Biosciences’ lead, oral FASN inhibitor is in Phase I clinical development for the treatment of solid tumors**

- Fatty acid synthesis (FASN) catalyzes the synthesis of palmitate from acetyl-CoA,malonyl-CoA, and NADPH
- Tumor cells have an increased dependence on FASN-synthesized palmitate compared to non-tumor cells
- FASN inhibition decreases cellular levels of palmitate and saturated fatty acids and induces tumor cell apoptosis
- In vitro and in vivo studies have identified multiple mechanisms of action for FASN inhibition: (1) Membrane and lipid raft architecture remodeling; (2) Tumor cell gene expression reprogramming; (3) Signal transduction pathway inhibition
- Studies to understand the mechanisms of action and biological consequences of FASN inhibition are guiding the discovery of tumors highly dependent on FASN and biomarkers for assessment of pharmacodynamic activity and patient selection

### Results

**Classification of Tumor Lipogenicity and Epithelial Gene Expression Aligns with FASN-Inhibitor Sensitivity In Vitro**

Published literature reports gene expression signatures of lipogenic, glycolytic, epithelial, and mesenchymal phenotypes
- Lipogenic and epithelial phenotypes co-segregate
- Glycolytic and mesenchymal phenotypes co-segregate
- Application to 3-V in vitro data shows association with FASN inhibitor sensitivity
- Application to TCGA tumor data (8588 samples) to identify candidate tumor types and biomarkers of FASN inhibitor response
- Stratification and analysis of molecular genetic features of tumors

**KRAS-Mutant NSCLC Tumors are More Lipogenic**

- Multiple biological functions of gene pathways involved in FASN inhibition with TVB-3166.
- Decreased expression of lipid synthesis genes and increased expression of fatty acid oxidation genes.
- Increased expression of lipid metabolic genes, and decreased expression of sugars and glycolytic genes.
- TVB-3166 inhibited tumor growth in all KRAS mutant cell lines.

**RAS Mutation Associated with FASN Sensitivity in NSCLC Cell Lines**

- Combined FASN and PD1 immunotherapy enhances xenograft efficacy.
- TVB-2640 biomarker in CLIN-002 tumor summary

**Conclusion**

- Lipogenic gene expression signatures classify FASN sensitivity
- Lipogenic gene expression is increased in KRAS-mutant NSCLC tumors
- KRAS-Mutant NSCLC cell lines have increased FASN sensitivity
- Palmitoylation of Ras-associated signaling proteins is increased in KRAS-mutant NSCLC cell lines
- FASN inhibition combines with PD1 immunotherapy or VEGF inhibition (bevacizumab) to significantly increase in vivo tumor xenograft efficacy
- TVB-2640 CLIN-002 tumor inhibits EGFR, k-Ras, and VEGFR and Ras pathway dysregulation in response to, not unresponsive, patients