Fatty Acid Levels Align with Sensitivity to FASN Inhibition and Biomarker Candidates for Clinical Analysis

Introduction
- 3-V Biosciences' lead, oral FASN inhibitor is in Phase I clinical trials 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 expression increases with tumor progression in human tumors and associates with chemoresistance, metastasis, and diminished patient survival in many tumor types.
- Palmitate and palmitate-derived lipids comprise diverse cellular components and function in processes required for tumor cell proliferation and survival.
- 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 phosphomonoester activity and patient selection.
- Inhibition of the AKT and Wnt/-catenin pathways, including TCF-40 and B-catenin, is involved in tumor growth and pharmacodynamic analysis of COLO-205 tumors.

Results
FASN Inhibition of Tumor Cell Viability is an On-Target Effect
- Cell-based assays show alignment of IC50 values in NSCLC tumor cell lines with IC50 values in A549 NSCLC cell lines.
- TVB-2640 inhibits COLO-205 Rat Xenograft Tumor Growth in Association with g-Catenin, c-Myc and p-AKT Inhibition.

TVB-2640 Induces Gene Expression Changes in COLO-205 Rat Xenograft Tumors in Association with Treatment Efficacy
- Genes involved in the cell cycle, proliferation, and apoptosis are modulated by TVB-2640 treatment.

Additive and Synergistic Inhibition of Xenograft Tumor Growth by FASN Inhibition in Combination with Taxanes
- TVB-2640 demonstrates dose-dependent inhibition of tumor growth in the COLO-205 xenograft model.

Conclusions and Status
- TVB-2640 is a first-in-class oral FASN inhibitor, in Phase I clinical development for the treatment of solid tumors.
- TVB-2640 demonstrates dose-dependent single agent tumor growth inhibition in the COLO-205 xenograft tumor model.
- Tumor growth inhibition by TVB-2640 is associated with inhibition of g-catenin, c-Myc and AKT and modulation of tumor gene expression.
- FASN inhibition combined with paclitaxel or docetaxel shows synergistic tumor growth inhibition, including tumor regression in many different xenograft tumor models that include NSCLC, ovarian, and prostate tumor models.
- The mechanism of FASN-taxane synergy likely includes: (1) decreased expression of g-tubulin and disrupted microtubule organization as a result of FASN inhibition; (2) taxane-mediated sensitization of tumor cells to modulation of gene expression by FASN inhibition.

Mechanism of Taxane Synergy Insights: FASN Inhibition Affects Tubulin Expression and Microtubule Organization
- Combined FASN-Paclitaxel Inhibition Induces PDX mRNA Changes in Apoptosis, Metabolism, and Tubulin-Associated Genes.

TVB-2640 Inhibits COLO-205 Rat Xenograft Tumor Growth in Association with g-Catenin, c-Myc and p-AKT Inhibition

TVB-2640 Induces Gene Expression Changes in COLO-205 Rat Xenograft Tumors in Association with Treatment Efficacy

Additive and Synergistic Inhibition of Xenograft Tumor Growth by FASN Inhibition in Combination with Taxanes

Conclusions and Status
- TVB-2640 is a first-in-class oral FASN inhibitor, in Phase I clinical development for the treatment of solid tumors.
- TVB-2640 demonstrates dose-dependent single agent tumor growth inhibition in the COLO-205 xenograft tumor model.
- Tumor growth inhibition by TVB-2640 is associated with inhibition of g-catenin, c-Myc and AKT and modulation of tumor gene expression.
- FASN inhibition combined with paclitaxel or docetaxel shows synergistic tumor growth inhibition, including tumor regression in many different xenograft tumor models that include NSCLC, ovarian, and prostate tumor models.
- The mechanism of FASN-taxane synergy likely includes: (1) decreased expression of g-tubulin and disrupted microtubule organization as a result of FASN inhibition; (2) taxane-mediated sensitization of tumor cells to modulation of gene expression by FASN inhibition.

In-vitro and in-vivo evaluation of additional, potent drug combinations is ongoing.