Biomarker Analyses from Dose Escalation and Expansion Phases of FASN Inhibitor TVB-2640 Phase 1 Study Shows Target Engagement in Solid Tumor Patients

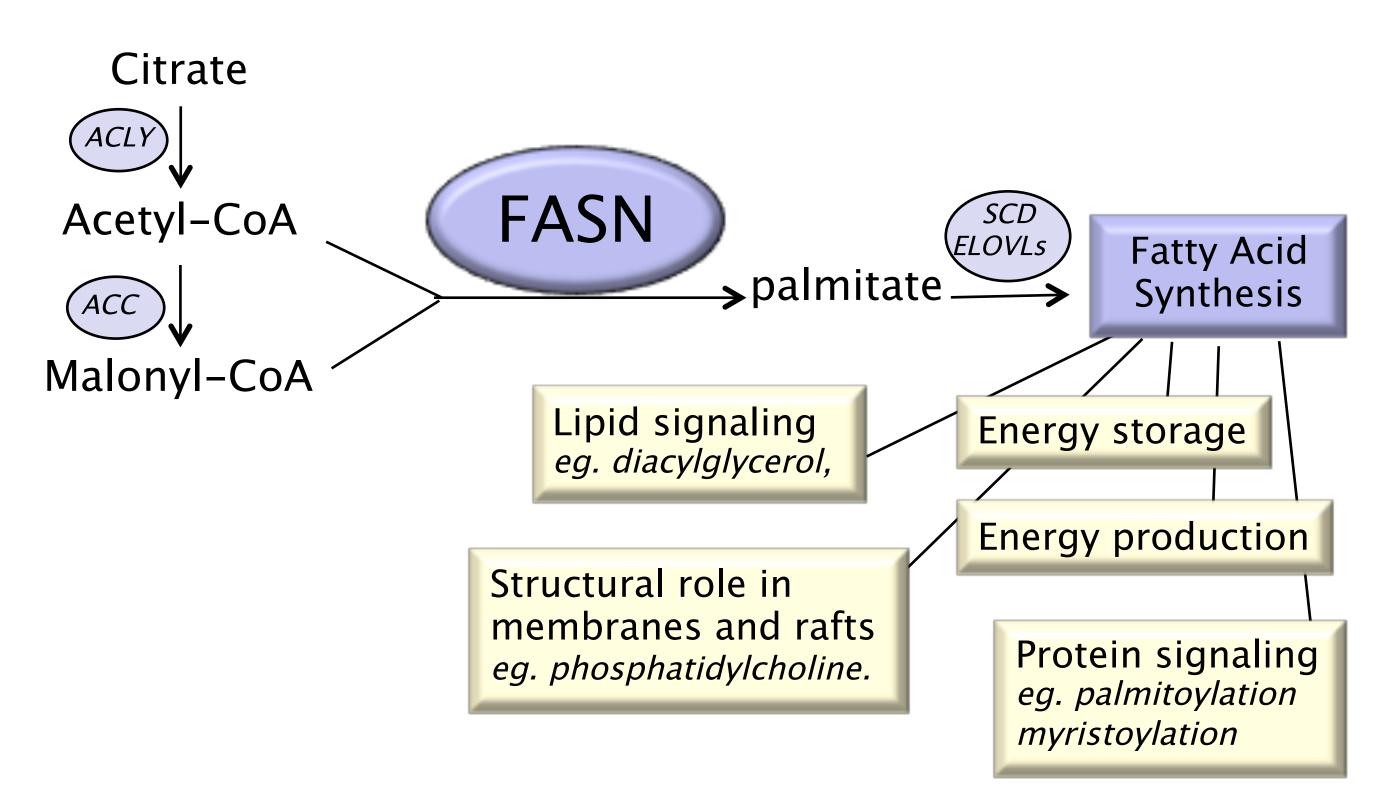
M. O'Farrell, R. Crowley, T. Heuer, M. Fridlib, D. Buckley, W. McCulloch, G. Kemble 3-V Biosciences, Menlo Park, USA.





Fatty Acid Synthase (FASN)

- Central mediator of neoplastic lipogenesis
- Generates palmitate, the building block of long chain fatty acids, providing a mechanism to convert glucose and other carbon sources into lipids to support cancer cell signaling
- Upregulated in tumor vs normal tissue, and correlates with poor prognosis in certain tumor types



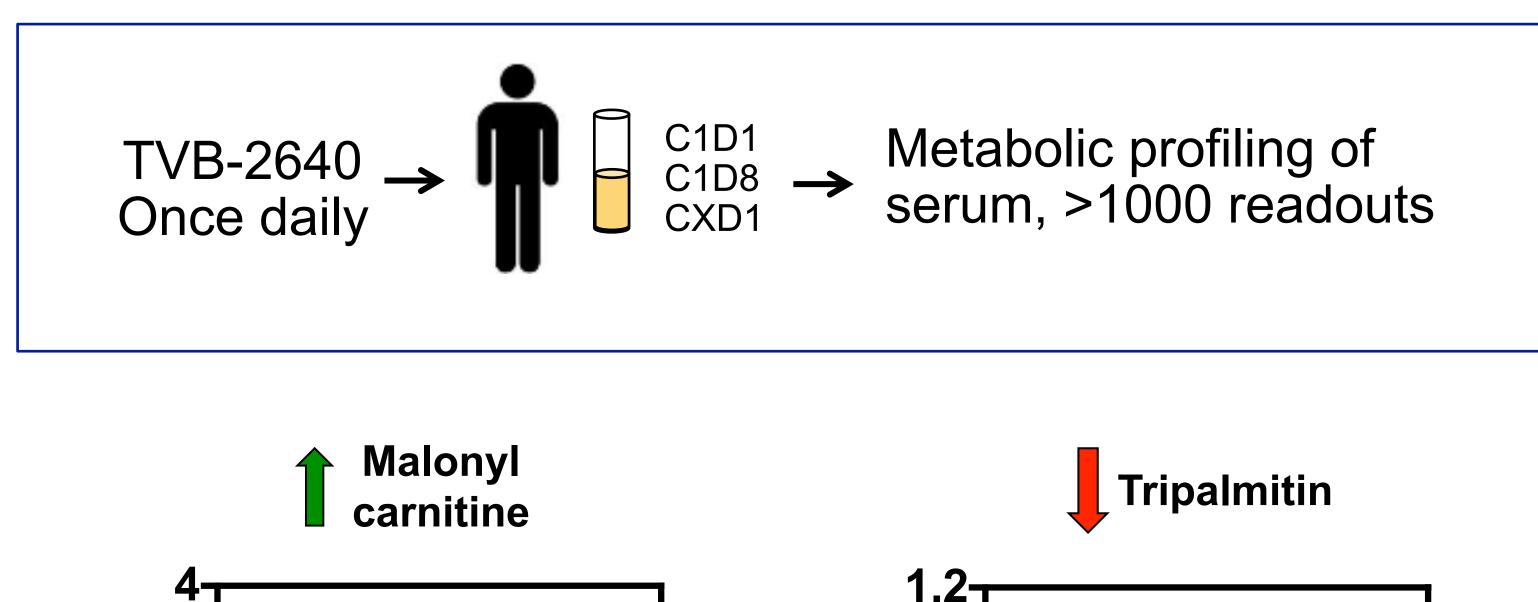
TVB-2640; FASN inhibitor in Phase 1 in Solid Tumors (Study 3V2640-CLIN-002)

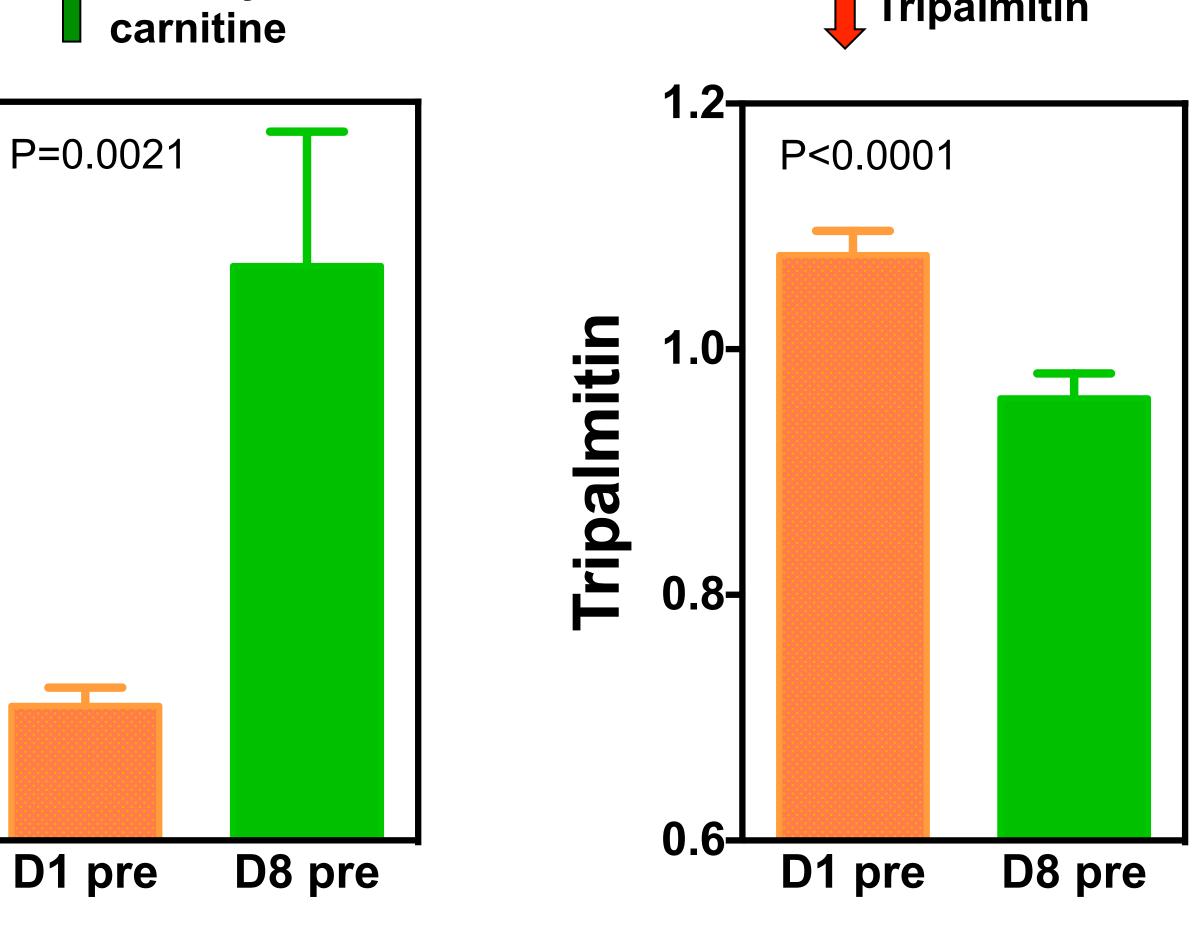
- Oral, first-in-class, small-molecule reversible inhibitor of FASN
- $IC_{50} < 0.05 \mu M$.
- Multicenter, open label, ongoing phase 1 study (1)
- Oral, once daily with 21/28 day continuous cycles
- Currently in expansion phase at RP2D of 100 mg/m²
 TVB-2640 as monotherapy or in combination with paclitaxel
- Approximately 90 patients enrolled to date

Comprehensive Biomarker Sampling in CLIN-002 for First-In-Class FASNi

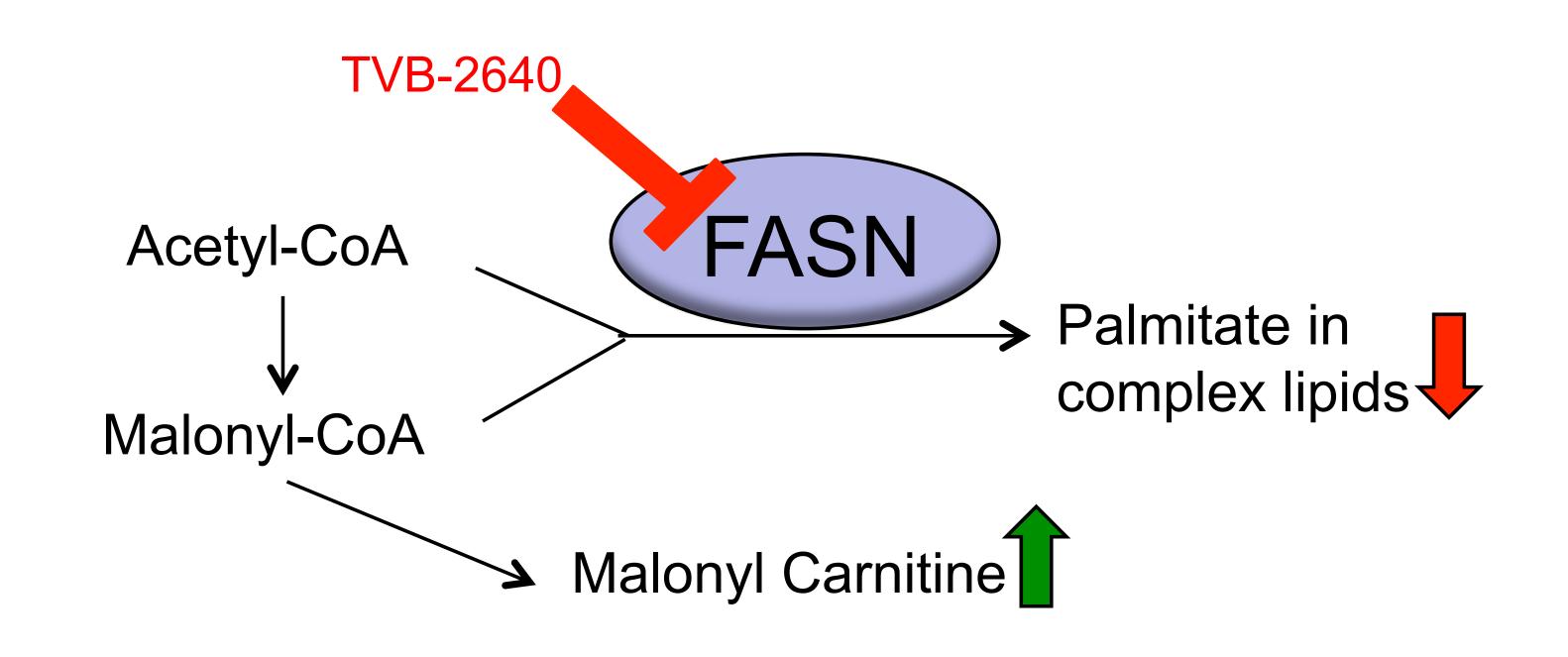
| Tissue | Assay | Purpose |
|-----------------|---|---|
| Serum | Metabolomics Proteomics | Global metabolite profiling, mechanism studies. PD (pharmacodynamic) biomarkers including secreted FASN, cytokines, disease markers |
| Sebum | Lipidomics | PD lipid biomarkers in surrogate tissue |
| Tumor | Genotype Gene expression IHC | Characterize population, direct PD biomarkers, potential patient enrichment biomarkers. |
| Tumor real-time | ¹¹ C-acetate PET imaging in prostate cancer patients | Direct real-time PD biomarker. Preclinical models show decreased acetate uptake with FASNi. |
| Blood cells | Gene expression | Assess blood cells as a surrogate tissue. |

Malonyl Carnitine and Tripalmitin Show Inhibition of FASN in Patients





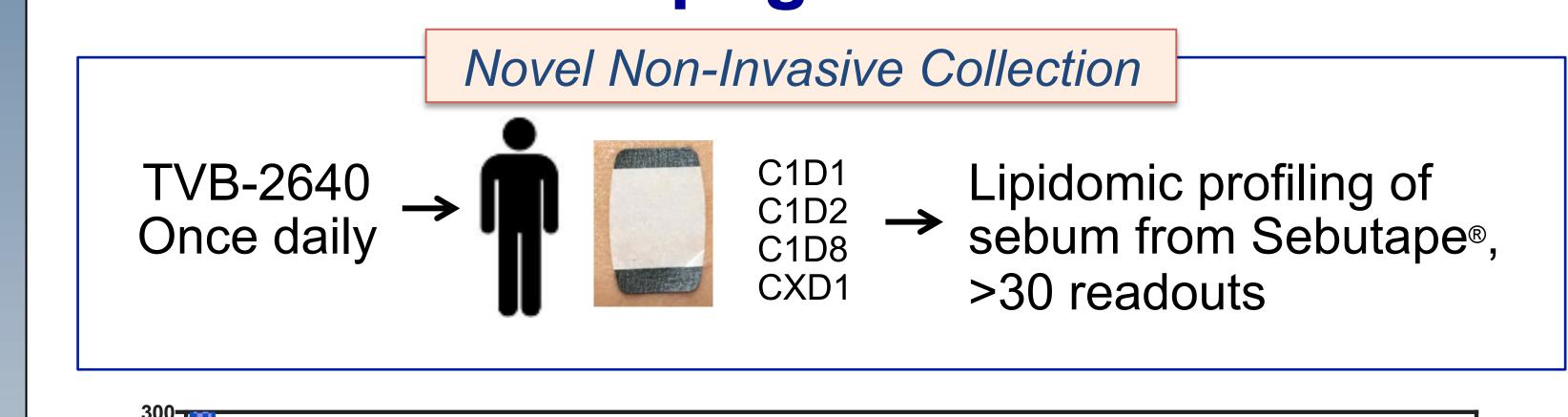
Serum used for global metabolite profiling by UPLC-MS/MS at Metabolon. Mean +/- SEM, N=19 at 60,100,120 or 240 mg/m², various tumor types

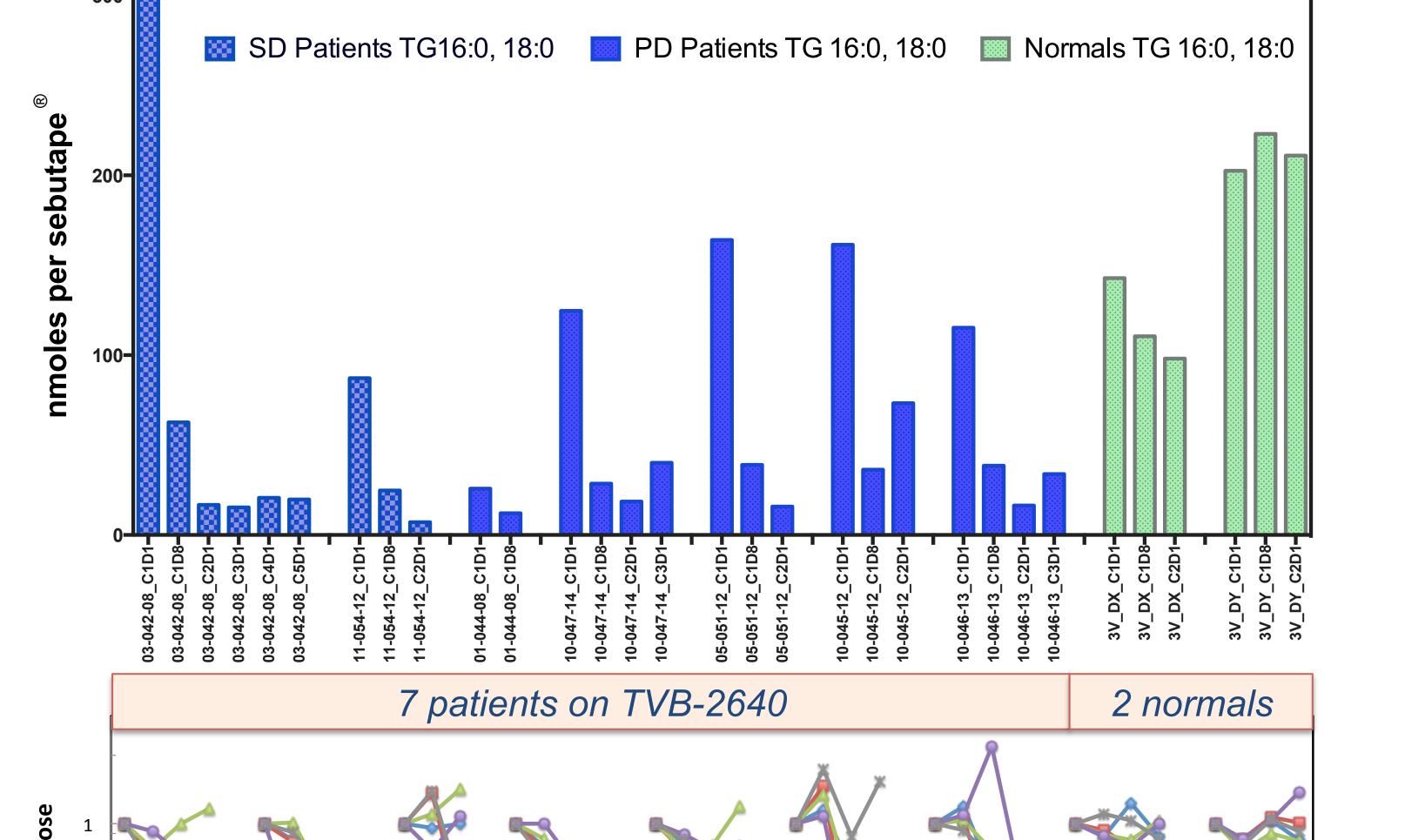


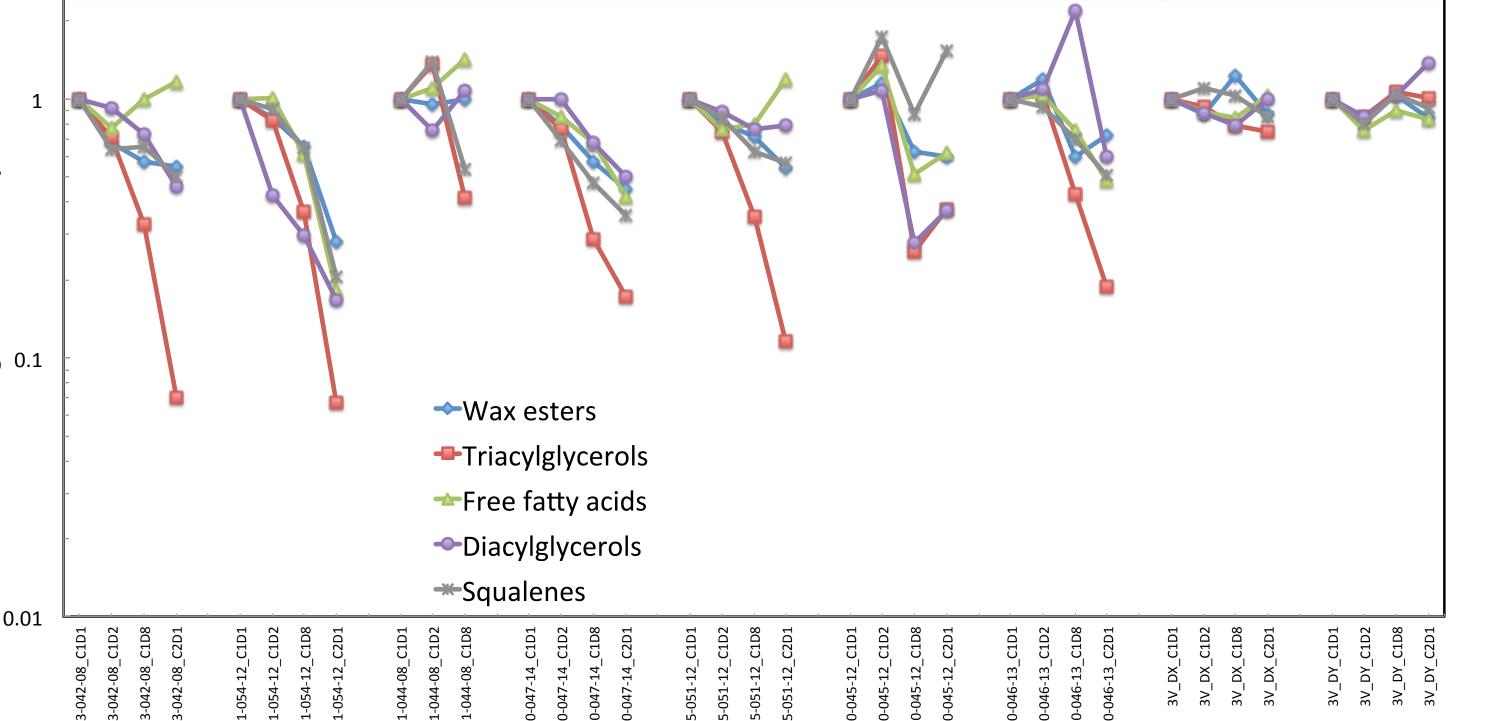
- 90% patients increased malonyl carnitine, mean of 2.9-fold, up to 7-fold
- 90% patients decreased TG16:0 palmitate and other palmitate derivatives also decreased (not shown)
- Similar effects in in both serum and tumor compartments in rat Colo-205 xenograft model (2).

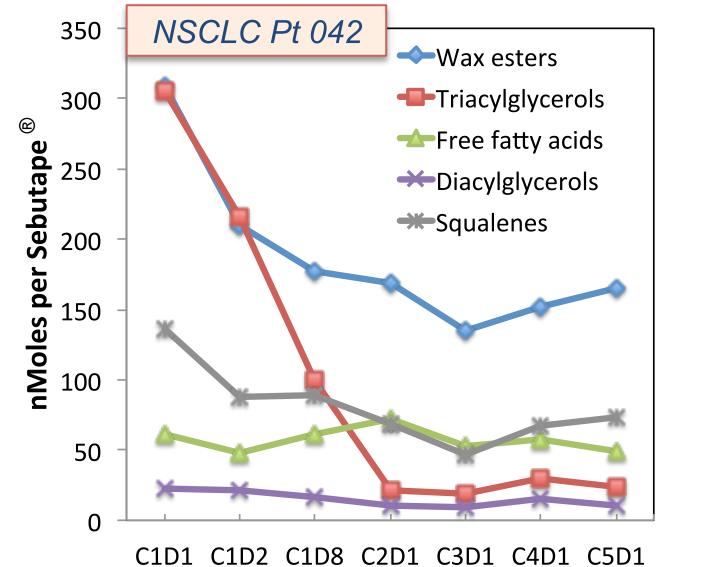
(1) Brenner et al., AACR-NCI-EORTC 2015, Abstract A54, 2015.
(2) Heuer et al., AACR-NCI-EORTC 2015, Abstract C175, 2015.
(3) Buckley et al., AACR Special Conference: Metabolism and Cancer. Abstract 75, 2015.

Decreases in Sebum Composition Show Inhibition of Lipogenesis in Patients









Sebum was collected using sebutape patches on the forehead for 30 minutes, and profiled by GC-MS and MS-flame ionization detection for lipid content at Metablon. N=7 patients in CLIN-002, plus 2 normal donors not receiving TVB-2640. Various tumor types, both monotherapy and combination patients

- Known requirement for FASN pathway to generate sebum lipids
- Consistent decreases in several classes in 7/7 patients
- No restriction on dietary intake, which indicates dependence on de novo lipogenesis
- Similar hypothesis for lipogenesis-addicted tumors

Exploratory Assessment of Tumor Biopsies from CLIN-002 Patients

TVB-2640
Once daily

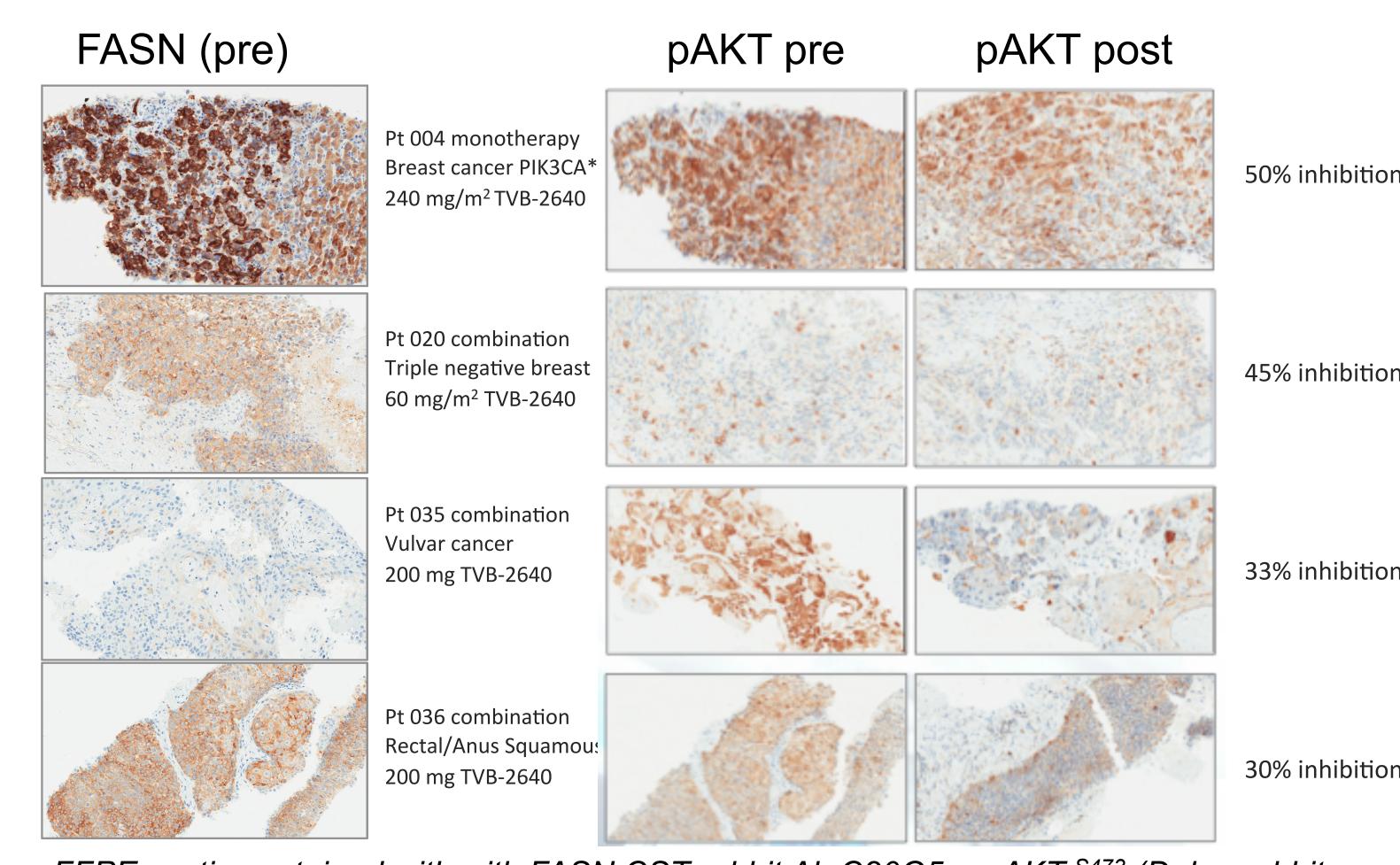
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C1D1
C2D1

C2D1

C1D1
Gene expression
Genotyping (baseline)

- Matched pre and post dose tumor IHC for 9 patients to date
- pAKT S473 decreased after 1 cycle in 5/9 patients, including 2/2 breast cancer patients. No change in total AKT.
- FASN expressed at moderate to high levels (H score >100) in most biopsies to date
- RNA-Seq showed significant gene expression changes compared to adjacent normal tissue in 2 breast cancer patients (3). Additional testing ongoing with emphasis on gene expression signatures and genotype analyses



FFPE sections stained with with FASN CST rabbit Ab C20G5or pAKT S473 (Dako, rabbit clone 14-5) (CST rabbit Ab C20G5) using a validated IHC method. H-score in tumor quantitated by standard pathology review (staining intensity graded 0-3+ and % cells positive). 20x. Performed by Mosaic Laboratories.

Summary

- TVB-2640 is a first-in-class FASN inhibitor
- Excellent QD oral PK profile, previously published
- FASN inhibition consistently shown across patients using novel biomarker approaches in two surrogate tissues, serum and sebum, including dose level used in expansion cohorts
- Exploratory tumor analysis shows inhibition of pAKTS473 and gene expression changes after TVB-2640 treatment consistent with decreased de novo lipogenesis
- Poised to understand the clinical impact of FASN inhibition

Thanks to the patients and their families. Also to Metabolon, Mosaic, Personalis and BioAgilityx for sample analysis in this study. Poster available at www.3vbio.com