Sebum Analysis from Dose Escalation and Expansion Phases of the FASN Inhibitor TVB-2640 Phase 1 Trial, A Non-Invasive Biomarker of Target Engagement

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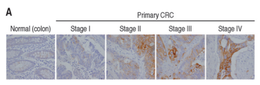
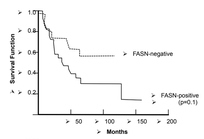
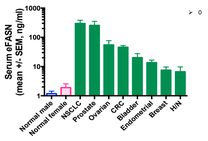
Introduction

FASN: A Well-Credentialed Target in Oncology



- FASN Expression Correlates with
- Poorer Survival in NSCLC Patients



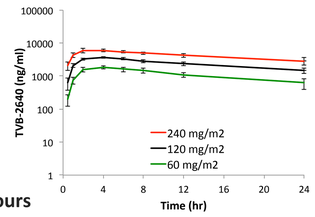


Zaytseva et al. CR. 2012
Visca, et al, Anticancer Res, 2004
Weiss, et al, Biol. Chem 367:905 (1986)
De Schryver, et al. Cancer Res 63:3799 (2003)
Menendez & Lupu, Nature Rev Cancer 7:763 (2007)

- Fatty acid synthase (FASN) levels increased in tumors, especially in later stage disease
- High FASN levels predict mortality in several cancers including NSCLC
- High blood FASN levels found in broad array of cancer types
- Normal cell survival not generally dependent on de-novo palmitate synthesis
- Tumor cells become addicted to palmitate, FASN inhibition causes apoptosis
- Chemical and genetic FASN inhibitors have antitumor effects in multiple xenograft models
- FASN-derived palmitate integrates into critical oncogenic signaling pathways

TVB-2640 – A Novel FASN Inhibitor with Excellent Human Exposure

- TVB-2640 FASN inhibitor
  - First in class
  - Potent
  - Highly selective
  - Reversible
- Pharmacokinetics in human
  - Plasma levels increase with dose
  - Mean half-life approximately 15 hours
  - Steady state reached by day 8
  - Exceeds threshold for preclinical efficacy at all doses

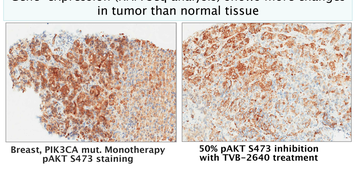


CLIN-002 – A Phase 1 Study of TVB-2640 in Human Subjects with Advanced Solid Tumors

- **Design**
  - Oral, once daily; DLT period 21 days (monotherapy) or 28 days (with paclitaxel); continuous cycles
  - Adult patients (ECOG 0-1), with pathologically confirmed metastatic or advanced-stage solid tumors, who met accepted ph-1 In/ Exclusion criteria
  - Clinically significant ophthalmologic finding, including history of dry eye excluded
- **Primary Objective**
  - Safety, MTD, recommended Phase-2 dose (monotherapy and in combination with paclitaxel)
- **MTD identified, currently in expansion cohorts**
  - All comers solid tumors dose escalation cohorts completed
  - MTD declared at 100mg/m^2 for monotherapy and in combination with paclitaxel

TVB-2640 PD Activity in Patient Tumor and Serum Previously Demonstrated

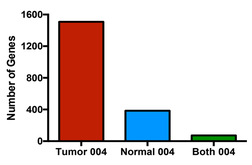
Tumor
Gene expression (RNA Seq analysis) shows more changes in tumor than normal tissue



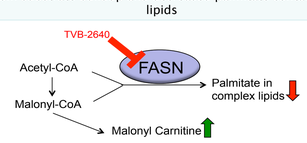
Breast, PIK3CA mut. Monotherapy pAKT S473 staining

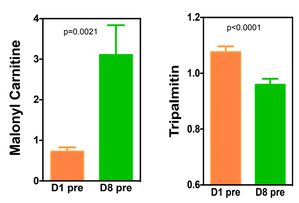
50% pAKT S473 inhibition with TVB-2640 treatment

5-fold Change Post TVB-2640



Serum
Metabolomic analysis shows increased malonyl carnitine from substrate buildup and decreased palmitate containing lipids



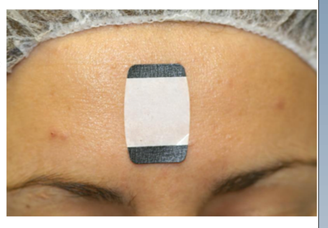


Methods

Sampling Forehead Sebum with Sebutape®

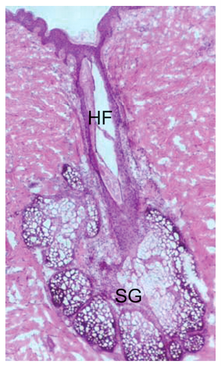
Why study sebum?

- Lipid composition suggests high FASN activity
- Easily accessed, high patient compliance
- Completely non-invasive sampling
- Potential for a rapid quantitative assay of TVB-2640 activity in human subjects



Sebaceous Gland Secretion

- Sebum secretion by holocrine production – release of entire cellular contents by lysis of the sebocyte
- Transit time for holocrine secretion in man ~1 week
- Both dietary fatty acids and newly synthesized lipids are incorporated into sebum



K. R. Smith, and D. M. Thiboutot J. Lipid Res. 2008;49:271-281

Table 1 **Components of skin surface lipids**

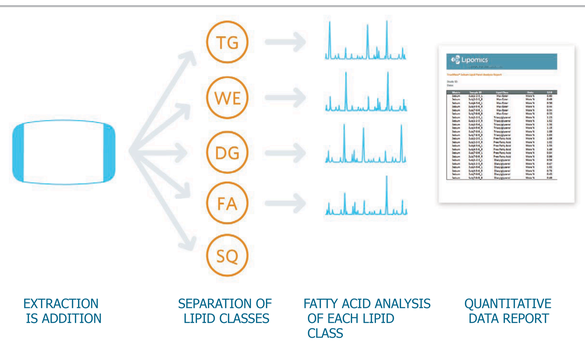
	Sebum Composition
Glycerides	30–50
Free Fatty Acids	15–30
Wax Esters	26–30
Squalenes	12–20
Cholesterol Esters	3.0–6.0
Cholesterols	1.5–2.5

M Picardo , M Ottaviani, E Camera, A Mastrofrancesco
Dermatoendocrinol. 2009 1(2):68-71

Sebutape® Analysis Method

TRUEMASS® SEBUM LIPID PANEL

COMPLETE ANALYSIS OF LIPID CLASS CONCENTRATION AND COMPOSITION



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Acknowledgments

The authors gratefully acknowledge the contributions of:

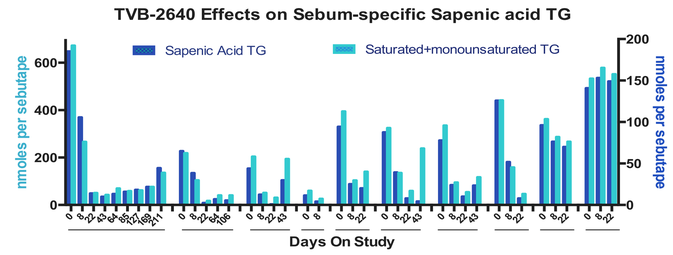
- The patients, families and investigatiors who have participated in the CLIN-002 Trial
- The Lipidomics Group at Metabolon® for performing the sebum lipid analysis
- The team at 3V Biosciences, Inc.

Poster #1022
Poster will be available after the meeting at:
http://www.3vbio.com

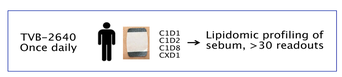
Results

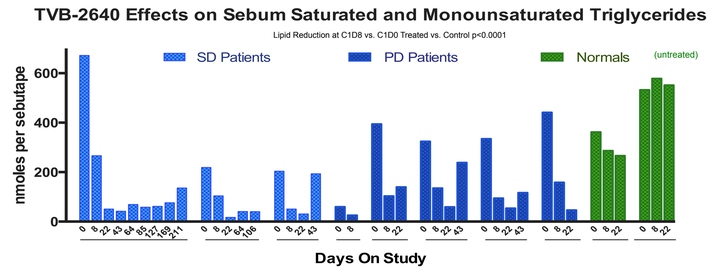
Sebum-specific Lipid Sapenic Acid in TG

Sapenic Acid is an immediate downstream derivative of palmitate (FASN)

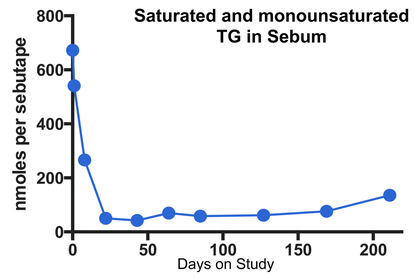


TVB-2640 Monotherapy – Sebum Triglycerides

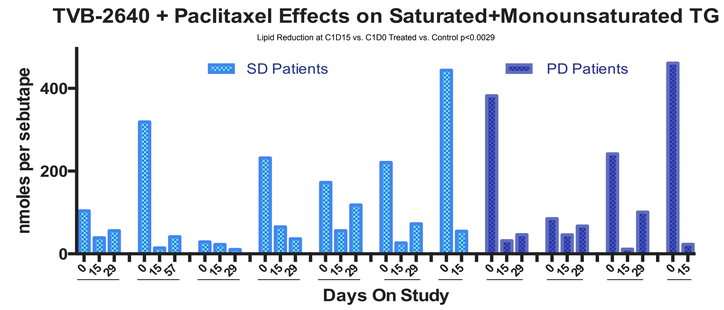




TVB-2640 - Persistent Inhibition of Lipogenesis >30 Weeks in a NSCLC Patient - KRAS^{mut}



TVB-2640/Paclitaxel Combo – Effects on Sebum Triglycerides



Conclusions

- Sebum analysis provides a completely non-invasive means of assessing TVB-2640 PD activity in patients
- Daily administration of TVB-2640 as monotherapy or in combination with paclitaxel causes significant inhibition of de novo lipogenesis by sebocytes
- Sebum lipid production was significantly reduced after 7 days exposure to TVB-2640
- Patients with stable disease do not show different sebum lipid responses to TVB-2640 when compared to patients with progressive disease
- Dietary lipids do not substitute for de novo synthesized lipids in sebum production