Establishing the foundation for a novel, first-in-class, fatty acid synthase inhibitor, TVB-2640, for NASH treatment

G. DUKE[1], A. WAGMAN[1], D. BUCKLEY[1], W. MCCULLOCH[1] and G. KEMBLE[1]
[1]3-V Biosciences, Inc., Menlo Park, United States

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INTRODUCTION

Increased hepatic *de novo* lipogenesis (DNL) drives liver fat deposits and inflammation in non-alcoholic fatty liver disease and plays a role in developing non-alcoholic steatohepatitis (NASH). Targeting fatty acid synthase (FASN), a key enzyme of DNL, could treat liver diseases. We have reported that FASN inhibition prevents diet induced liver steatosis in mice and blunts inflammatory responses. A clinical trial of TVB-2640, an oral, selective FASN inhibitor, in >130 cancer patients showed this drug was generally well tolerated, absorbed efficiently through the gut and inhibited DNL in the skin.

CONCLUSIONS & NEXT STEPS

FASN inhibition reduces diet induced liver damage in mice & inhibits lipogenesis in humans

Preclinical – diet induced obese mice show FASN inhibition:
- Reversed steatosis
- Reduced inflammatory cytokines and the adipokine leptin
- Reduced fibrosis
- Decreased liver triglycerides & cholesterol
- Decreased plasma ALT & AST levels
- Effective at very low doses

Clinical – TVB-2640, a once-daily oral FASN inhibitor
- Inhibited lipogenesis in solid tumor patients
- Exhibited excellent absorption and PK

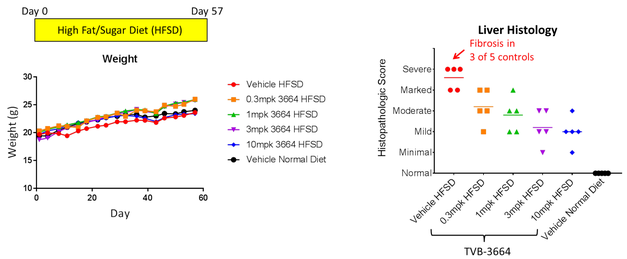
TVB-2640: potential backbone NASH therapy
- Treatment inhibits multiple pathogenic drivers of NASH
- Currently evaluating inhibition of hepatic lipogenesis in humans to identify doses for NASH clinical development

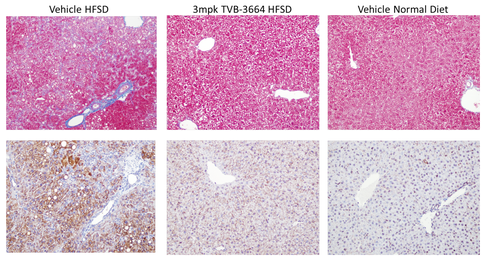
METHODS

- FASN inhibitor (TVB-3664) was dosed daily by oral gavage in mice.
- TVB-3664: close analog of TVB-2640 with better murine PK & potency
- Results left panel - Male C57BL/6J mice were fed high fat/sugar diet (Research Diets #D09100301) (CARE LLC, Fort Collins, CO)
- Results top middle panel - Male C57BL/6J mice were fed high fat/sugar diet (Research Diets # D14120701) (Gubra , Denmark)).
- Results lower middle panel - Male C57BL/6NTac mice were fed high fat/sugar diet (Research Diets #D12492) (CARE LLC, CO)
- Quantitative sebum fatty acid analysis was performed on Sebutape® Patches collected for biomarker analysis during the TVB-2640 Phase 1 trial, CLIN-002. Analysis was performed at Metabolon, Inc. using GC-FID after lipid hydrolysis and esterification.

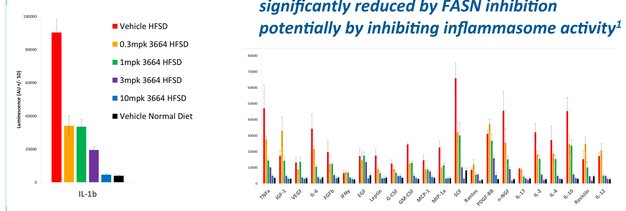
RESULTS

FASN inhibition prevents development of steatosis, inflammation & fibrosis in mice on a high fat/sugar diet



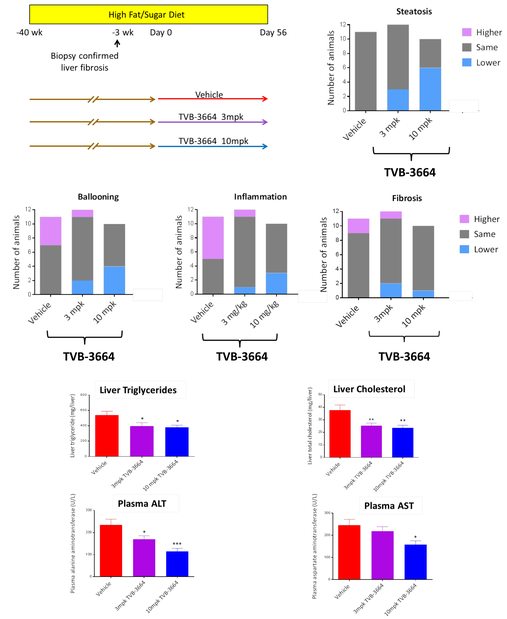


Inflammation (cytokines)



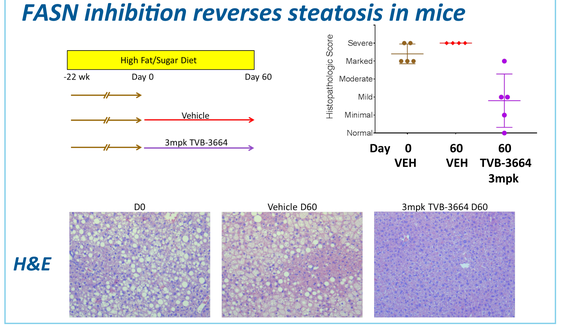
IL-1β and other cytokines including leptin significantly reduced by FASN inhibition potentially by inhibiting inflammasome activity[1]

FASN inhibition treats liver damage in mice with established steatohepatitis and fibrosis

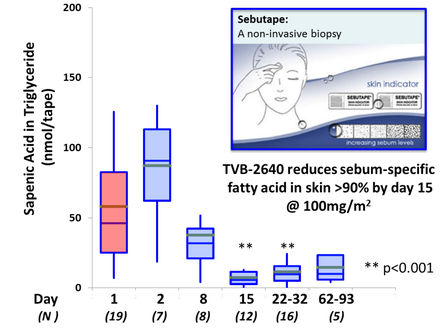


Data expressed as mean ± SEM (NASH groups n=10-12).
*p<0.05, **p<0.01, ***p<0.001 vs. Vehicle; One-Way ANOVA with Dunnet's multiple comparison test.

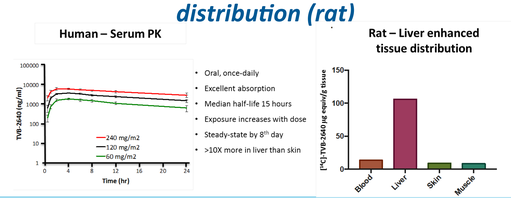
FASN inhibition reverses steatosis in mice



TVB-2640 inhibits lipogenesis in humans: non-invasive skin assay in solid tumor patients



TVB-2640 clinical pharmacokinetics (human) and drug distribution (rat)



TVB-2640 impacts the foundation of NASH - steatosis, inflammation, fibrosis -

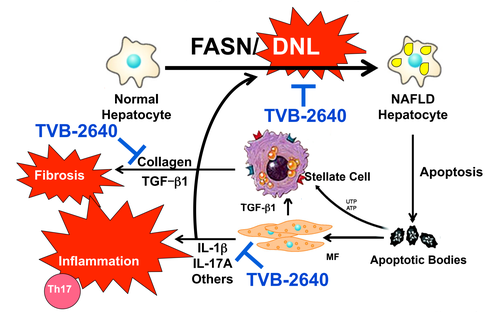


Figure adapted from Mahli[2]

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[2] Malhi, H. M.E. Guicciardi, and G.J Gores (2010). *Hepatocyte Death: A Clear and Present Danger*. Physiol Rev 90: 1165-1194

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George.Kemble@3VBIO.com
Dennis.Hom@3VBIO.com