Pharmacological inhibition of FASN prevents high fat diet induced liver damage in mice and significantly reduces *de novo* lipogenesis in humans

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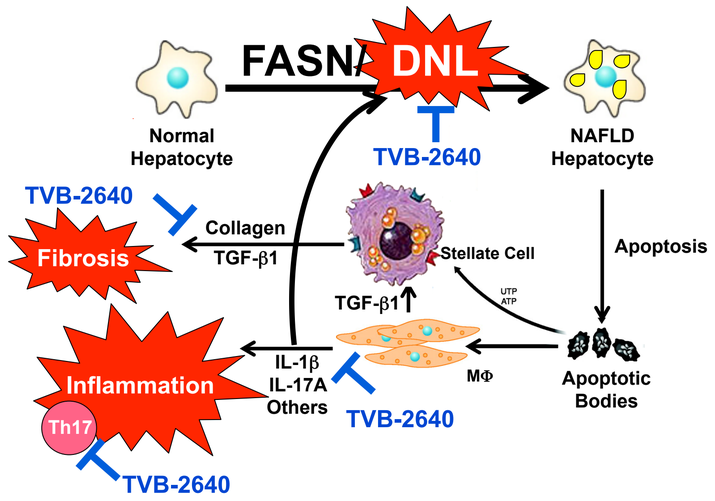
FASN (fatty acid synthase) Critical lipogenesis & inflammatory target in NASH



Conclusions

3-V's FASN Inhibitors:

- Reduce high fat diet liver damage in mice
  - 38% reduction in liver steatosis
  - Inhibited IL-1β production in serum
  - Treated established disease with short therapy
- Ex vivo stimulated human PBMC
  - Inhibited IL-1β production
  - Inhibited differentiation to Th17 – replaced with Treg

TVB-2640: oral, potent, first-in-class FASN inhibitor

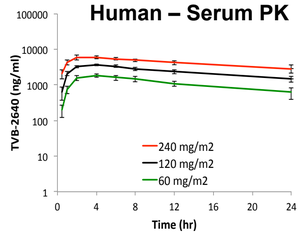
- Demonstrated inhibition of FASN & lipogenesis in humans
- Excellent PK – liver enhanced distribution
- Potential to significantly reduce dose for NAFLD/NASH

Next step: Phase 1b – Identify dose for hepatic DNL in metabolic syndrome

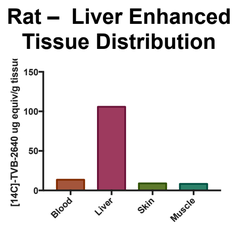
- Evaluate low doses of TVB-2640 to inhibit hepatic lipogenesis (collaboration with E. Parks at University of Missouri)

TVB-2640 – clinical experience Oral, potent, FASN inhibitor

Excellent pharmacokinetics



- Plasma levels increase with dose
- Mean half-life ~15 hours
- Steady state by day 8
- Exceeds preclinical efficacy
- >10X liver distribution vs skin



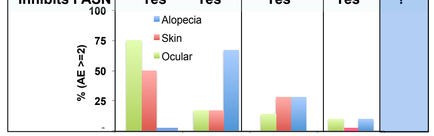
Phase 1 – Cancer patients treated with TVB-2640 (n>62) PK, PD and AE profiles point to promising opportunity for NASH

Standard design for Oncology – Accelerated titration - rapidly identify MTD

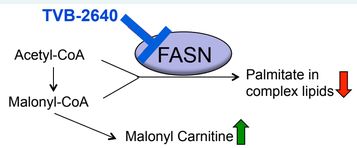
- Identified target-related AE's (alopecia, hand foot syndrome, ocular)
- Manageable and reversible AEs
- Decreased AEs at lower doses (reduced severity & frequency)
- Evidence of anti-tumor activity

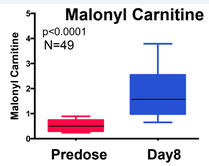
#Ph1b Study – DNL Metabolic syndrome

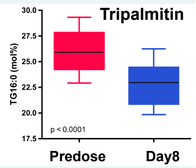
TVB-2640 (Daily, oral)	Above MTD		Oncology (MTD)	NASH ➡	
Dose (mg/m²)	240	120	100	60-80	<60
N	4	6	42	10	TBD#
Inhibits FASN	Yes	Yes	Yes	Yes	?



TVB-2640 – Serum metabolomics – inhibition of FASN in humans

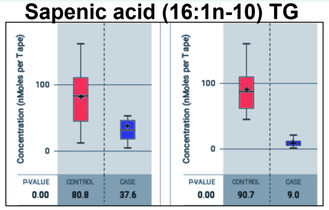






TVB-2640 inhibits lipogenesis in human skin (sebum)

Sebutape: A non-invasive biopsy



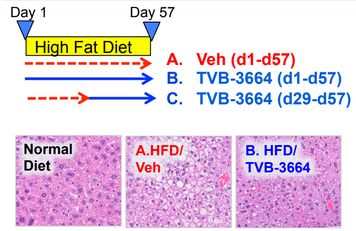
Predose vs Day8: 2.15 Fold Change N=7

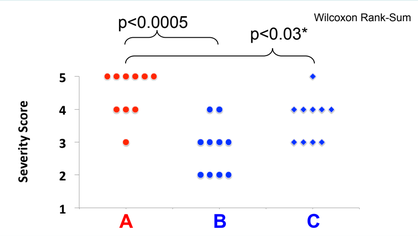
Predose vs ~Day30: 10.1 Fold Change N=8

- TVB-2640 dose for cancer patients inhibits lipogenesis in skin by >90%
- Expecting much lower doses needed to inhibit liver fat synthesis in NASH patients based on tissue distribution of TVB-2640

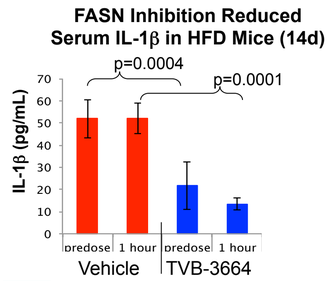
3-V FASN inhibitors – preclinical studies Prevent diet induced steatosis & inflammation

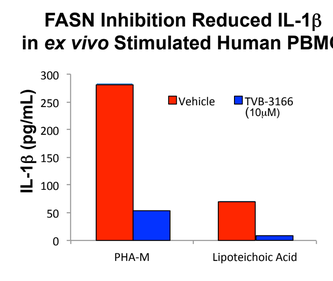
TVB-3664* prevents steatosis in mice fed a high fat (Western) diet



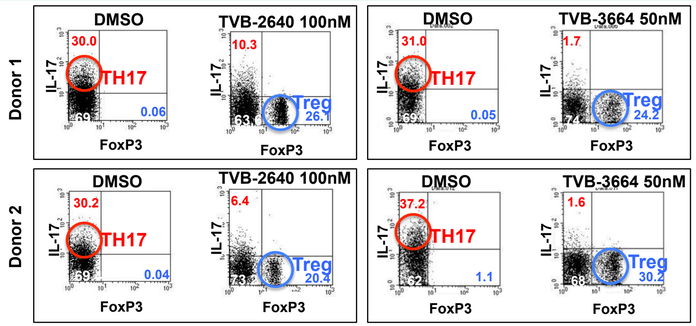


IL-1β response inhibited by 3-V FASN inhibitors





TVB-3664* and TVB-2640 direct human T-cell differentiation away from pro-inflammatory TH17 and toward anti-inflammatory Treg



Human CD4+ Naïve T cells under 4 days of Th17 differentiation conditions

*TVB-3664 is a TVB-2640 analog with better murine PK and potency

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