Targeting VAP-1 Inhibition in NASH

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NASH-TAG
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Introduction

- NAFLD/NASH prevalence is increasing and is associated with life-threatening complications including cirrhosis and hepatocellular carcinoma\(^1\)
- New treatments for NASH are urgently needed, including treatments targeting inflammatory and fibrotic mechanisms in the liver that contribute to disease
- Vascular adhesion protein-1 (VAP-1, SSAO, AOC3) is a cellular adhesion protein with amine oxidase activity that may play a role in hepatic inflammation and fibrosis that has been identified as a potential target for the treatment of NASH\(^2\)

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\(^1\) Liu et al. *Lancet Gastroenterol Hepatol* 2019
\(^2\) Weston et al. *Journal of Clinical Investigation* 2015
Role of VAP-1 in NASH

- VAP-1 may contribute to hepatic inflammation and fibrosis in NASH by:
  - Converting amines to aldehyde and hydrogen peroxide in the liver, leading to local oxidative stress
  - Recruitment of inflammatory leukocytes to the liver
VAP-1 Expression is Increased in NASH Patients with Liver Fibrosis

- VAP-1 is significantly and broadly over-expressed starting in moderate-severe fibrotic livers

Scale bars: 50 μm. Adapted from Weston et al, JCI, 2015
Soluble VAP-1 is Elevated in NASH Patients

- Plasma VAP-1 concentration increased in NAFLD and NASH patients
- Increasing fibrosis stage correlates with increasing plasma VAP-1 concentrations

Adapted from Weston et al, JCI, 2015
Potential role of VAP-1 in Steatosis

- Genetic deletion of VAP-1 (AOC3−/−) protects against high fat diet induced steatosis in mice\(^1\)
- Anti-VAP-1 antibody can reduce steatosis in methionine choline deficient mice\(^1\)
- Methylamine (endogenous VAP-1 substrate) increases BMI and abdominal fat in transgenic mice overexpressing VAP-1\(^2\)
- VAP-1 activity reduces triglyceride secretion and increases steatosis in human liver tissue\(^3\)
- VAP-1 activity in human liver tissue upregulates lipid transporter molecule gene expression including fatty acid binding proteins (FABP 2 and 4)\(^3\)

\(^{1}\)Weston et al. 2015 J Clin Invest
\(^{2}\)Stolen et al. 2004 FASEB J
\(^{3}\)Shepherd et al. 2020 World J Hepatol
VAP-1 Inhibition Reduces ALT and CK-18 in NASH Patients

ALT and CK-18 decrease with VAP-1 inhibitors in NASH patients indicating potential for decreased inflammation and liver injury.

Source: (LEFT) VAP-1 data from BI 1467335 (10mg) Phase 2a, 12-week NASH study from clinicaltrials.gov (NCT03166735); (RIGHT) CK-18: cytokeratin 18; M30 measures apoptosis and M65 measures apoptosis and necrosis. VAP-1 data from BI 1467335 (10mg) Phase 2a, 12-week NASH study from clinicaltrials.gov (NCT03166735); ASK1 data from selonsertib (18mg) Phase 2, 24-weeks NASH study from Hepatology. 2018; 67(2): 549–559; CCR2/5 data from cenicriviroc (150mg) Phase 2, 52-week NASH study from Hepatology. 2018; 67(5): 1754-1767
TERN-201: Highly selective VAP-1 inhibitor in development for the treatment of NASH

- TERN-201 is a novel, potent VAP-1 inhibitor with high liver distribution in Phase 1 development for the treatment of NASH
- TERN-201 is a highly selective inhibitor of VAP-1 with minimal potential to inhibit other human amine oxidases

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>VAP-1</th>
<th>MAO-A</th>
<th>MAO-B</th>
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<tr>
<td>TERN-201</td>
<td>0.0065</td>
<td>&gt;50</td>
<td>&gt;50</td>
</tr>
<tr>
<td>BI 1467335</td>
<td>0.005</td>
<td>&gt;100</td>
<td>2.7</td>
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Biochemical activity (IC$_{50}$, μM)

IC$_{50}$: 50% inhibitory concentration; MAO: monoamine oxidase
TERN-201 Improved Inflammation and Fibrosis in a Rat CDAA/HFD NASH Model

- **Induction:** CDAA/HFD
- **In vivo treatment:** CDAA/HFD, 3x weekly IP NaNO₂

**Liver histology**

- **Steatosis Score**
- **Inflammation Score**
- **Fibrosis Score**

**Treatment schedule:**
- **Week -4** (baseline)
- **Week 0:** Treatment start
- **Week 8:** Treatment end

**Analysis:**
- 1. Histology
- 2. Liver mRNA
- 3. RNAseq

**Groups:**
- Vehicle
- TERN-201 (7.5MPK)
- TERN-201 (25MPK)
TERN-201 Rat CDAA/HFD NASH Model
Reduced expression of fibrosis and inflammation markers
TERN-201 Rat CDAA/HFD NASH Model

Reduced expression of hepatic stellate cell activation markers

Markers of hepatic stellate cell (HSC) activation

log2 fold-change

-3 -2 -1 0 1

Ecm1 Il1r1 Adgrl1 Reln Masp1 Timp2 Pdgfrb Bgn Sema3c Ramp1 Efemp2 Ackr3 Adamts2 Col6a2 Timp1 Fstl1 Col4a1 Adamts1 Lamb1 Col3a1 Ccl2 Sparc Igfbp7 Ednra Sfrp1 Itga8 Gpx3 Fbln1 Nbl1 Aebp1 Cpxm1 Loxl1 Ogn Eln Ddr2 Cpe Igfbp5 Adamts5 Col1a1 Htra3 Lum Clec3b
TERN-201 Single Ascending Dose Phase 1 Study

Generally well tolerated; sustained, near complete VAP-1 inhibition with once daily dosing

Plasma VAP-1/SSAO-specific activity (% pre-dose)

All TERN-201 dose levels were generally well tolerated
TERN-201 Multiple Ascending Dose Phase 1 Study
Sustained suppression of plasma VAP-1-specific activity

Inhibition of plasma amine oxidase activity

Sustained suppression after last dose

Jones et al, AASLD 2020
TERN-201 Development Status

Preclinical NASH Model
- Improved liver inflammation and fibrosis
- Reduced gene expression and biomarkers of liver inflammation, fibrosis and stellate cell activation

Phase 1 in Healthy Subjects
- Generally well-tolerated
- Inhibited plasma VAP-1 activity

Next step: 12-week Phase 1b study in NASH patients to assess
- TERN-201 safety and tolerability
- Biomarkers of liver inflammation, fibrosis and steatosis

Data expected in 1H 2022 to inform TERN-201 subsequent development, potentially in combination with metabolically active NASH treatment.
**TERN-201 and Terns’ NASH Pipeline**

**Combination opportunities**

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<th>Single Agents</th>
<th>Combinations</th>
<th>PRE-CLINICAL</th>
<th>PHASE 1</th>
<th>PHASE 2a</th>
<th>PHASE 2b</th>
<th>PHASE 3</th>
<th>NEXT MILESTONE</th>
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<tbody>
<tr>
<td><strong>TERN-101</strong> (FXR Agonist)</td>
<td><strong>TERN-101 + TERN-501</strong> (FXR + THR-β)</td>
<td><strong>LIFT</strong></td>
<td>NASH Phase 2a Data (3Q 2021)</td>
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<td><strong>TERN-201</strong> (VAP-1 Inhibitor)</td>
<td><strong>TERN-201 Combo</strong> (VAP-1 + Metabolic)</td>
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<td>NASH Phase 1b Trial start (1H 2021)</td>
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<tr>
<td><strong>TERN-501</strong> (THR-β Agonist)</td>
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<td>Phase 1a  Trial start (1H 2021)</td>
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<td>GLP-1R Agonist</td>
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<td>Nominate candidate (2H 2021)</td>
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**Single Agents**

- TERN-101 (FXR Agonist)
- TERN-201 (VAP-1 Inhibitor)
- TERN-501 (THR-β Agonist)
- GLP-1R Agonist

**Combinations**

- TERN-101 + TERN-501 (FXR + THR-β)
- TERN-201 Combo (VAP-1 + Metabolic)
Summary

• VAP-1 is a cellular adhesion protein with ectoenzyme amine oxidase activity
• NASH patients have hepatic VAP-1 overexpression which may contribute to hepatic inflammation and fibrosis
• VAP-1 may also potentiate hepatic steatosis in NAFLD/NASH
• VAP-1 inhibition resulted in reduced plasma VAP-1 activity, transaminase levels and biomarkers of liver inflammation in a 12-week clinical trial in NASH patients

• TERN-201 is a VAP-1 inhibitor in clinical development
  – high liver penetration
  – high selectivity for VAP-1 inhibition and minimal potential for off-target monoamine oxidase inhibition
• TERN-201 was generally well-tolerated in Phase 1 clinical trials and exhibited near complete and sustained inhibition of plasma VAP-1 specific activity
• Further studies of TERN-201 as a potential treatment for NASH are warranted
  – 12-week Phase 1b study in NASH patients to initiate in 1H2021
  – Data expected in 1H2022