Past, Present and Future of Therapeutics for Liver Fibrosis

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Dean for Therapeutic Discovery
Chief, Division of Liver Diseases
Icahn School of Medicine at Mount Sinai
“Of greatest interest is fiber accumulation within the parenchyma....

An increase in fibers is noted with increased activity and accumulation of neighboring mesenchymal cells”.

Hepatic Stellate cells - Perisinusoidal cells of Normal Liver

Friedman and Arthur, Science & Medicine, 2002
Hepatic lipocytes: The principal collagen-producing cells of normal rat liver

(hepatocytes/sinusoidal endothelium/vitamin A/liver cell culture)

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Communicated by Rudi Schmid, August 6, 1985
The Past:

Table 1. Treatment Strategies for Hepatic Fibrosis.

<table>
<thead>
<tr>
<th>Approach</th>
<th>Mechanism*</th>
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<tbody>
<tr>
<td>Current therapies</td>
<td>Discontinue alcohol, hepatoxins</td>
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<td>Remove the inciting stimulus</td>
<td>Antihelmintic therapy (for schistosomiasis)</td>
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<td>Biliary decompression</td>
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<td>Phlebotomy, chelation (for metal overload)</td>
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<td>Antiviral therapy?</td>
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<td>Corticosteroids</td>
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<td>Prostaglandins?</td>
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<td>Colchicine?</td>
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<td>Antiinflammatory agents</td>
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<tr>
<td>Future therapies</td>
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<td>Control lipocyte activation</td>
<td>Gamma interferon</td>
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<td>Retinoids</td>
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<tr>
<td>Neutralize proliferative and fibrogenic mediators</td>
<td>Neutralizing antibodies to platelet-derived growth factor, TGFβ1</td>
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<td></td>
<td>Recombinant cytokine-binding proteins (e.g., decorin)</td>
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<td>Cytokine-receptor antagonists</td>
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<tr>
<td>Inhibit matrix synthesis or assembly</td>
<td>Prolyl 4-hydroxylase inhibitors</td>
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<tr>
<td>Enhance matrix degradation</td>
<td>Exogenous proteases or stimulation of endogenous proteases</td>
</tr>
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</table>

*TGFβ1 denotes transforming growth factor β1.
The Liver: A ‘Blob’ That Runs the Body

The underrated, unloved liver performs more than 300 vital functions. No wonder the ancients believed it to be the home of the human soul.

Basics
By NATALIE ANGIER  JUNE 12, 2017
The Present: The Worldwide Community of Stellate cell Investigators
Fibrosis is a Common Pathway Among Different Etiologies of Liver Disease

- Hepatitis Viruses
- Inherited Metabolic Disorders
- Excess Vitamin A
- Cholestatic Disorders
- Immune Disorders
- Drugs
- Alcohol
- NASH

FIBROSIS
1. Liver biopsy is the standard, but needs to be replaced or complemented by non-invasive markers.

2. Surrogate markers that correlate with clinical outcomes are sorely needed. These may include:
   • *Functional tests* (incl. HVPG, breath tests, cholate clearance)
   • *Novel imaging tests* that quantify collagen or fibrolytic enzymes
   • *Tests to measure fat content* (MR proton density, CAP)

3. Trials in non-cirrhotic patients cannot be powered for clinical outcomes as they will take too long.

4. Cooperation among stakeholders is a key element of success – *The Liver Forum*. 
Weight loss Improves NASH Histology after 52 weeks of Lifestyle Modification

5% weight loss improved steatosis
7% weight loss improved hepatocellular ballooning
10% weight loss needed for fibrosis improvement

No significant correlation was found with changes in the physical activity score at the end of the intervention.

Effect of Bariatric Surgery on NASH

Impact on histology at 1 year after bariatric surgery (82 pts):


NAFLD Activity Score

Before

- 8.6%
- 14.6%
- 39.0%
- 30.5%
- 7.3%

After

- 1.0%
- 7.3%
- 14.6%
- 45.1%
- 18.3%

P < 0.00001

Fibrosis Stage (Metavir)

Before

- 0%
- 10%
- 20%
- 30%
- 40%
- 50%
- 60%
- 70%
- 80%
- 90%
- 100%

After

- 7.5%
- 21.2%
- 40.0%
- 27.5%

What are the Features of an Ideal Antifibrotic Trial?

- Optimize selection of a treatment population
  - Use genetic markers to stratify based on risk of progression
  - Establish other markers of progression risk

- Attack molecular targets that are critical to disease pathogenesis
  - Strong validation in human liver
  - Relevant animal models that recapitulate features of human disease

- Establish and apply validated biomarkers that provide early and reliable readouts of drug efficacy
FXR ligand (OCA) is Antifibrotic in TAA-Induced Liver Disease in Rats

Obeticholic Acid, a Farnesoid X Receptor Agonist, Improves Portal Hypertension by Two Distinct Pathways in Cirrhotic Rats

Len Verbeke, Ricard Farre, Jonel Trebicka, Mina Komuta, Tania Roskams, Sabine Klein, Ingrid Vander Elst, Petra Windmolders, Tim Vanuytsel, Frederik Nevens, and Wim Laleman

OCA also lowered portal pressure

Source: Friedman et al. AASLD 2005.
also Verbeke et al, *Sci Reports*, 2016
FLINT: Primary and Secondary Histological Endpoints


* All p-values compared to placebo.
CENTAUR Topline Results – Efficacy

Significant improvement in potentially registrational endpoint after 1 yr of treatment with CCR2/CCR5 antagonist

**Improvement in Fibrosis by at Least One Stage** **AND** **No Worsening of Steatohepatitis** *

ITT Population; n=289

- **CVC 150 mg** (Arm A) N=145
- **Placebo** (Arm B+C) N=144

**Odds Ratio:** 2.2

P = 0.0234
95% CI (1.11 - 4.35)

**Other NAFLD related endpoints**

- 2 point change in NAS with no worsening of fibrosis: comparable to placebo
- Resolution of NASH with no worsening of fibrosis: comparable to placebo

AASLD 2016, Late Breaker Monday afternoon to follow
Potential Mechanisms of PPAR\(\alpha/\delta\) Benefit in NASH

Metabolic Syndrome

Visceral and liver fat & inflammation

Macrophages

PPAR\(\delta\) – PPAR\(\alpha\)

Hepatocytes

Inflammatory Cytokines

Metabolic Control

FA and lipoprotein metabolism

Tailleux, Wouters & Staels BBA 2012; 1821:809-18
GOLDEN Trial Results – Elafibrinor (PPAR α,δ agonist)

Primary Endpoint Was Not Met: 
Reversal of NASH without worsening of fibrosis

Post-hoc analysis: 
Elafibranor (120 mg/d for 1 year) resolved NASH without fibrosis worsening, based on a modified definition, in the intention-to-treat analysis and in patients with moderate or severe NASH.

Ratziu et al, Gastroenterology 2016
Apoptosis Signal-Regulating Kinase 1 (ASK1) is at the Nexus of Convergent Stress Signals

Apoptosis Signal-Regulating Kinase 1 (ASK1)

- Promotes cell death, fibrosis and inflammation via JNK and p38 MAPK
- ASK1−/− mice are normal, protected in models of liver injury and fibrosis
- ASK1 pathway activated in NASH: Correlates with fibrosis stage

Selonsertib (SEL) is a selective, potent competitive ASK1 inhibitor

Courtesy of Rohit Loomba
ASK1 Inhibitor: Fibrosis Responses
24 weeks

- Data for patients with liver biopsies evaluable for fibrosis at baseline and week 24 (N=67).
- * Defined as any increase in NAS (NAS increased from 5 to 6 in 2 patients).

<table>
<thead>
<tr>
<th>Patients, %</th>
<th>Fibrosis Improvement</th>
<th>Fibrosis Improvement without NASH Worsening*</th>
<th>Progression to Cirrhosis</th>
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<tbody>
<tr>
<td></td>
<td>18 mg ± SIM</td>
<td>6 mg ± SIM</td>
<td>SIM</td>
</tr>
<tr>
<td>13/30</td>
<td>43</td>
<td>37</td>
<td>3</td>
</tr>
<tr>
<td>8/27</td>
<td>30</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>2/10</td>
<td>20</td>
<td>20</td>
<td>2/10</td>
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Courtesy of Rohit Loomba
# The Future - Combination Therapies for NASH Fibrosis

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<th>Single Agent</th>
<th>Drug Combinations</th>
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<td>- Biology is more straightforward</td>
<td>- Broader target coverage can ‘hedge bets’ in the absence of clarity about ‘driver’ pathogenic events</td>
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Antifibrotic Therapies – Past, Present and Future

Summary

1. The arc of past success in hepatic fibrosis has reached clinical trials – we now know the cellular sources of fibrosis and many key mediators.

2. The framework of stellate cell activation provides many, but not all targets for anti-fibrotic therapies - macrophages are increasingly important.

3. Fibrosis regression may be possible in NASH, even with direct anti-fibrotic/antiinflammatory approaches.

4. The present holds great promise with evidence that fibrosis is responsive to well tolerated therapies.

5. The future is likely to see combination therapies that translate into improved outcomes (ie., delayed progression to cirrhosis, reduced complications or HCC), leveraging novel genetic and noninvasive markers for patient selection and early readouts of efficacy.