Past, Present and Future of Therapeutics for Liver Fibrosis

Paris NASH Symposium
July 2017

Scott Friedman, M.D.
Fishberg Professor of Medicine
Dean for Therapeutic Discovery
Chief, Division of Liver Diseases
Icahn School of Medicine at Mount Sinai

Mount Sinai

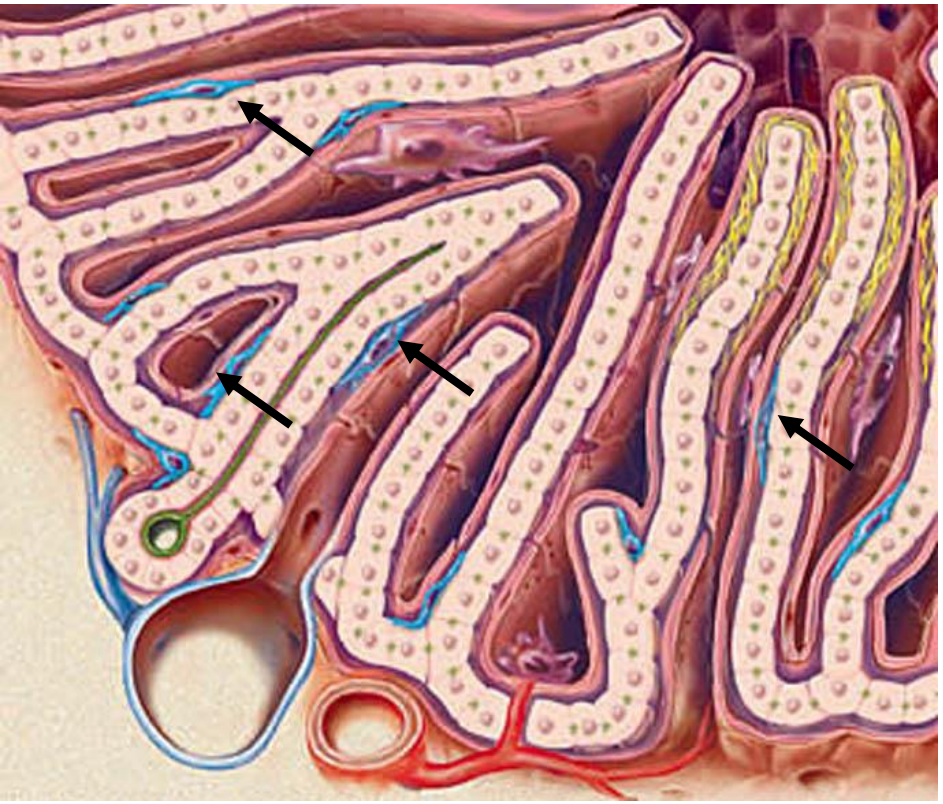
The Past: *Origins of the Fibrosis Field*

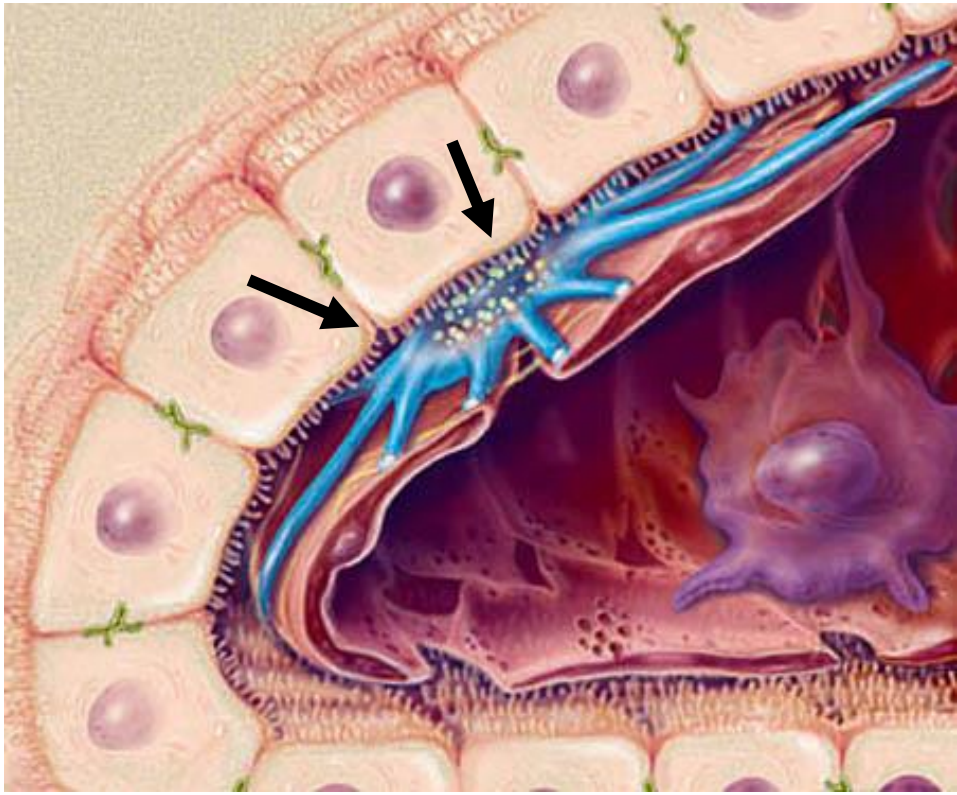
“ Of greatest interest is fiber accumulation within the parenchyma….

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

H. Popper and F. Schaffner. Progress in Liver Disease 1:86-106, 1961

Hepatic Stellate cells - Perisinusoidal cells of Normal Liver





Friedman and Arthur, *Science & Medicine, 2002*

Proc. Natl. Acad. Sci. USA
Vol. 82, pp. 8681–8685, December 1985
Medical Sciences

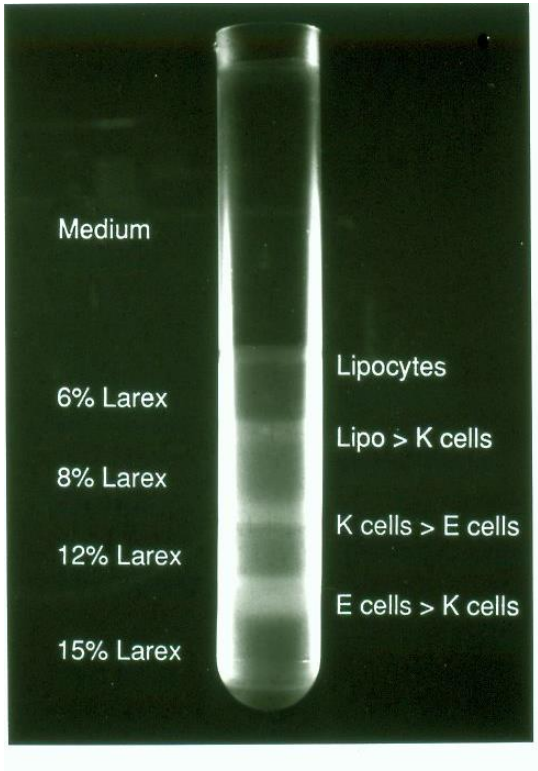
Hepatic lipocytes: The principal collagen-producing cells of normal rat liver

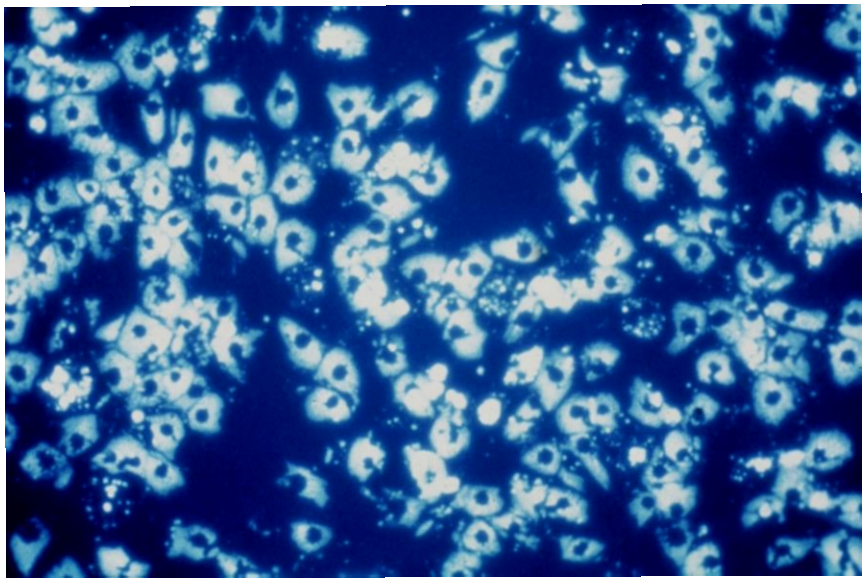
(hepatocytes/sinusoidal endothelium/vitamin A/liver cell culture)

SCOTT L. FRIEDMAN*†, F. JOSEPH ROLL*, JANET BOYLES‡, AND D. MONTGOMERY BISSELL*

*Liver Center, San Francisco General Hospital, and Department of Medicine, University of California, San Francisco, CA 94110; and ‡Gladstone Foundation Laboratories for Cardiovascular Disease, Department of Pathology and Cardiovascular Research Institute, University of California, San Francisco, CA 94143

Communicated by Rudi Schmid, August 6, 1985





Also, de Leeuw et al, ***Hepatology*** 1984

The Past:

1828 THE NEW ENGLAND JOURNAL OF MEDICINE June 24, 1993

SEMINARS IN MEDICINE
OF THE
BETH ISRAEL HOSPITAL, BOSTON

JEFFREY S. FLIER, M.D., *Editor*
LISA H. UNDERHILL, *Assistant Editor*

THE CELLULAR BASIS OF HEPATIC FIBROSIS

Mechanisms and Treatment Strategies

SCOTT L. FRIEDMAN, M.D.

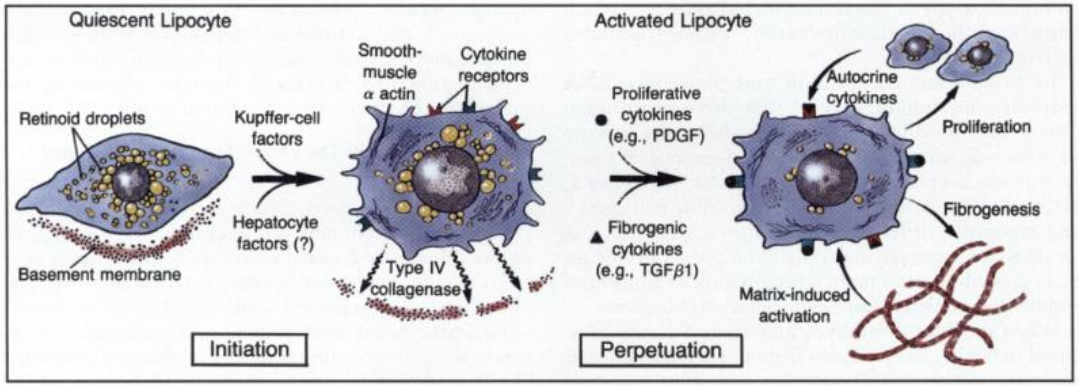


Table 1. Treatment Strategies for Hepatic Fibrosis.

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

*TGFβ1 denotes transforming growth factor β1.

The Present

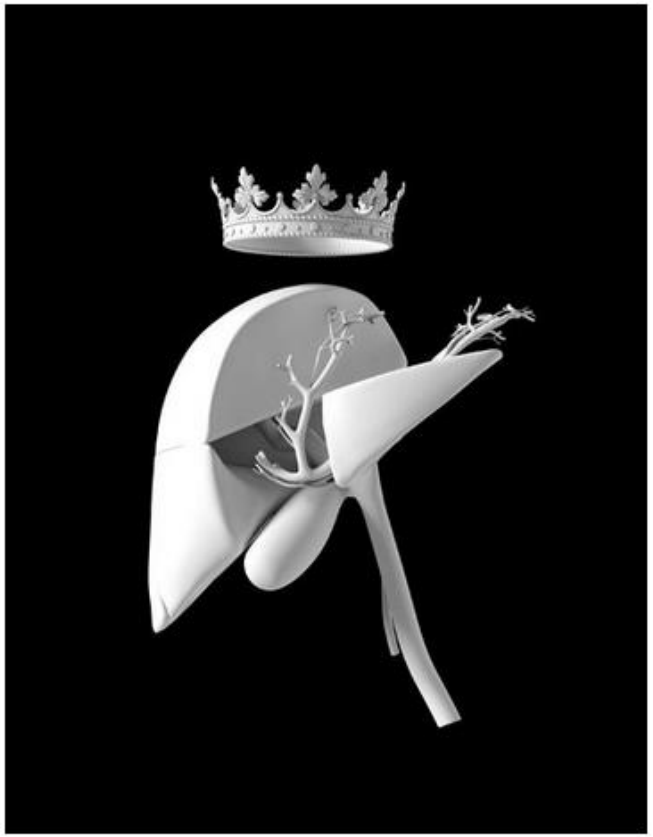
The New York Times | HEALTH

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.

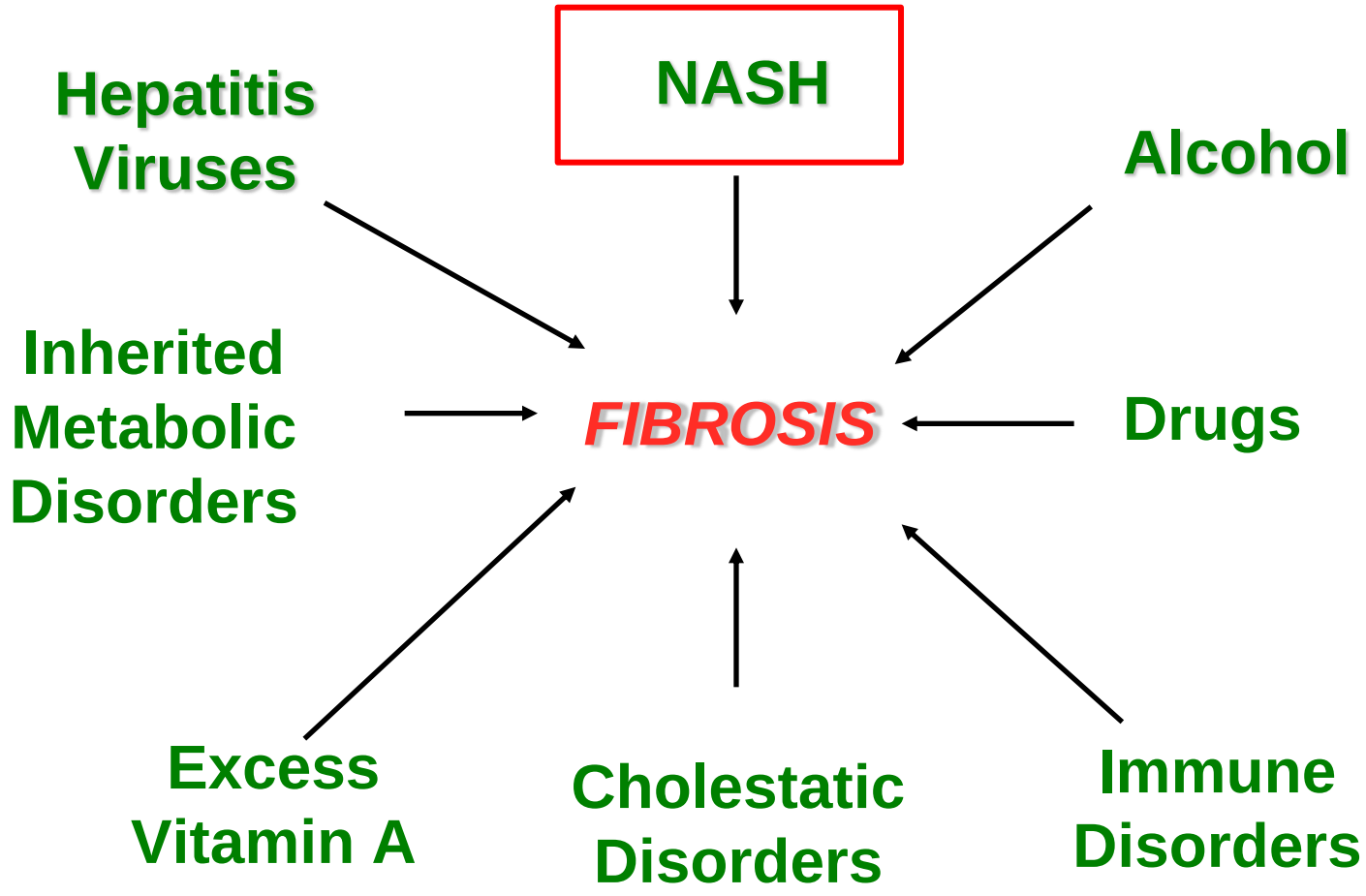
Basics

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



Regulatory Challenges In Developing Novel Drugs for Inflammation and Fibrosis

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

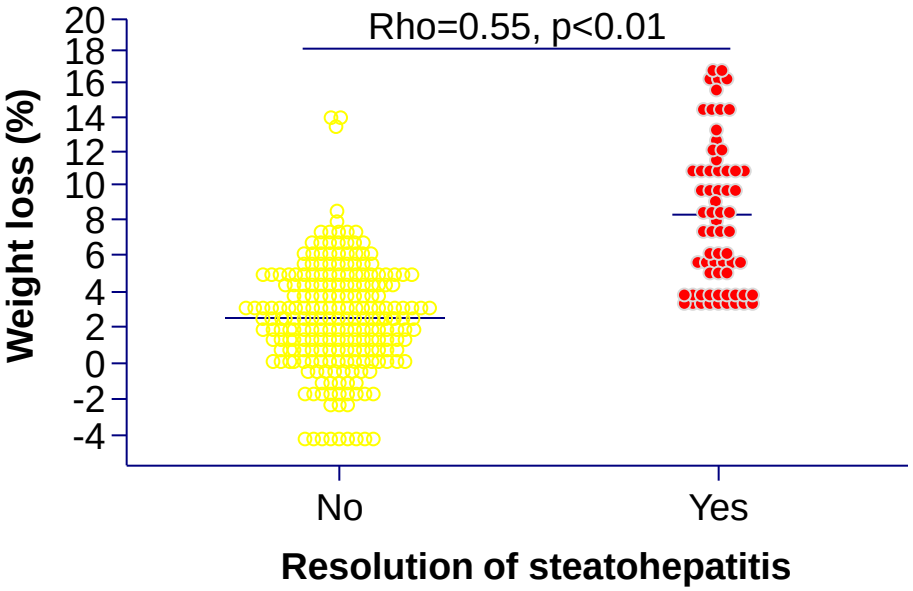
2. Surrogate markers that correlate with clinical outcomes are sorely needed. These may include:
   - *Functional tests* (incl. HVPG, breath tests, cholate clearance)
   - *Novel imaging tests* that quantify collagen or fibrolytic enzymes
   - *Tests to measure fat content* (MR proton density, CAP)

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

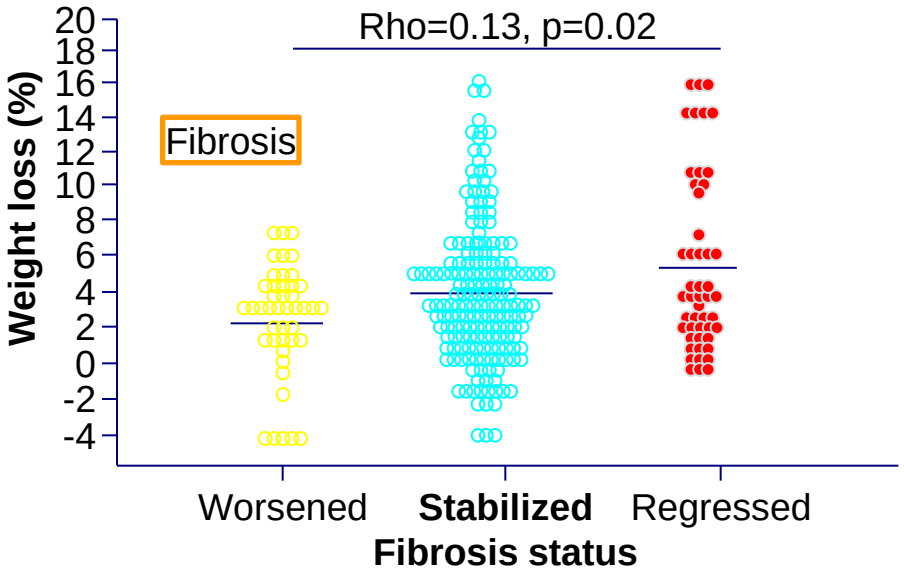
4. Cooperation among stakeholders is a key element of success – *The Liver Forum.*

Weight loss Improves NASH Histology after 52 weeks of Lifestyle Modification

Correlations* between WL and steatohepatitis resolution



Correlations between WL and fibrosis status at the end of intervention



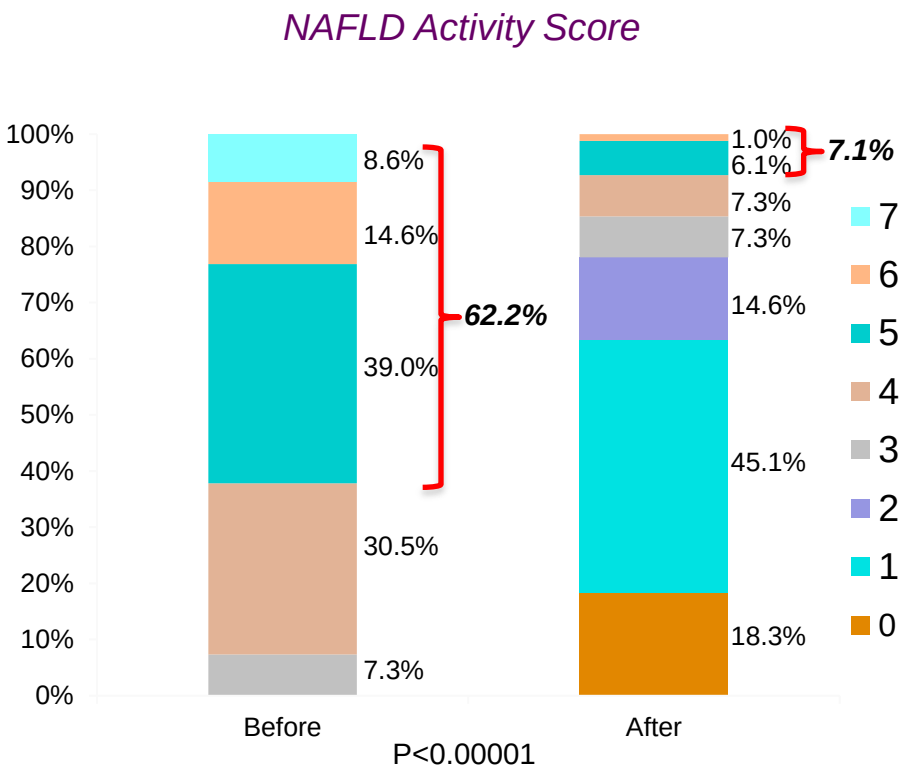
No significant correlation was found with changes in the physical activity score at the end of the intervention

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

Vilar-Gomez E, et al. Gastroenterology 2015

Effect of Bariatric Surgery on NASH

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



Lassailly, et al. ***Gastroenterology***, 2015

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

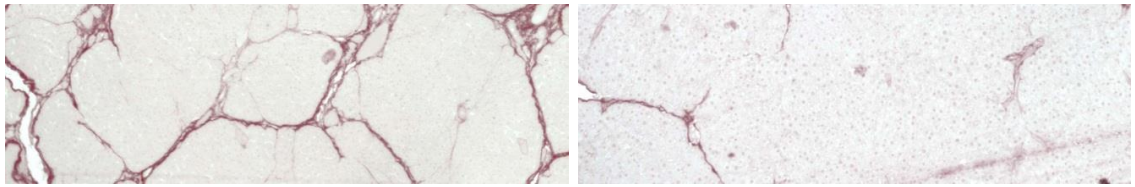
- Establish and apply validated biomarkers that provide early and reliable readouts of drug efficacy

FXR ligand (OCA) is Antifibrotic in TAA-Induced Liver Disease in Rats

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

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

Len Verbeke,[1] Ricard Farre,[2,3] Jonel Trebicka,[4] Mina Komuta,[5] Tania Roskams,[5] Sabine Klein,[4] Ingrid Vander Elst,[1] Petra Windmolders,[1] Tim Vanuytsel,[2] Frederik Nevens,[1] and Wim Laleman[1]

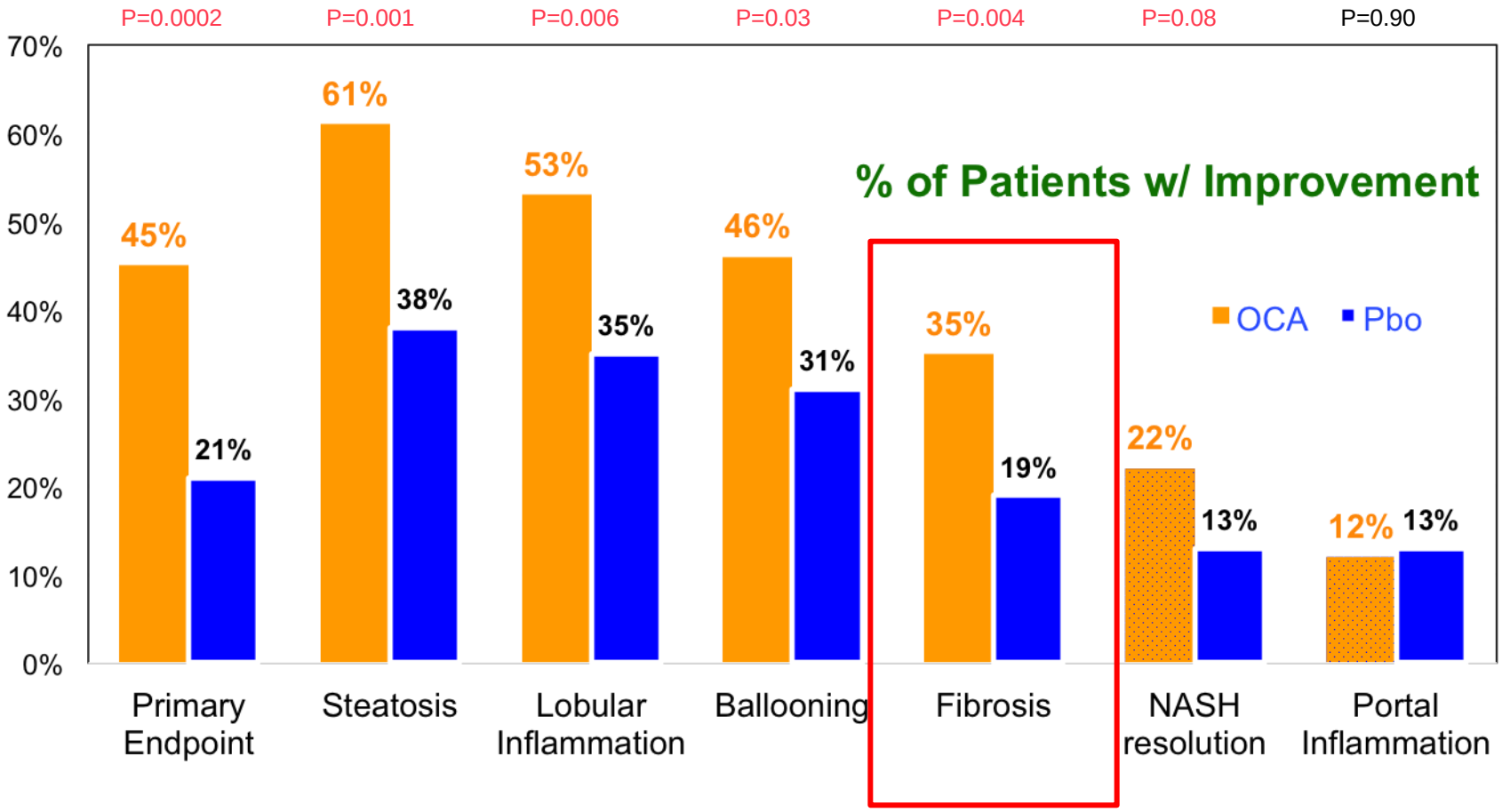


OCA also lowered portal pressure

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.

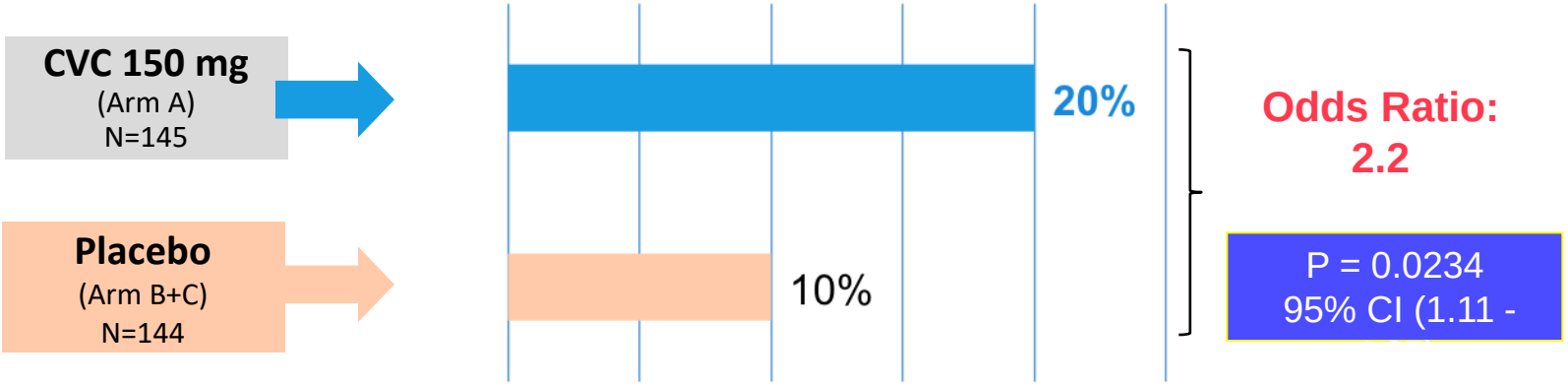
Tetri et al, ***The Lancet,*** publ. online Nov 7, 2014

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

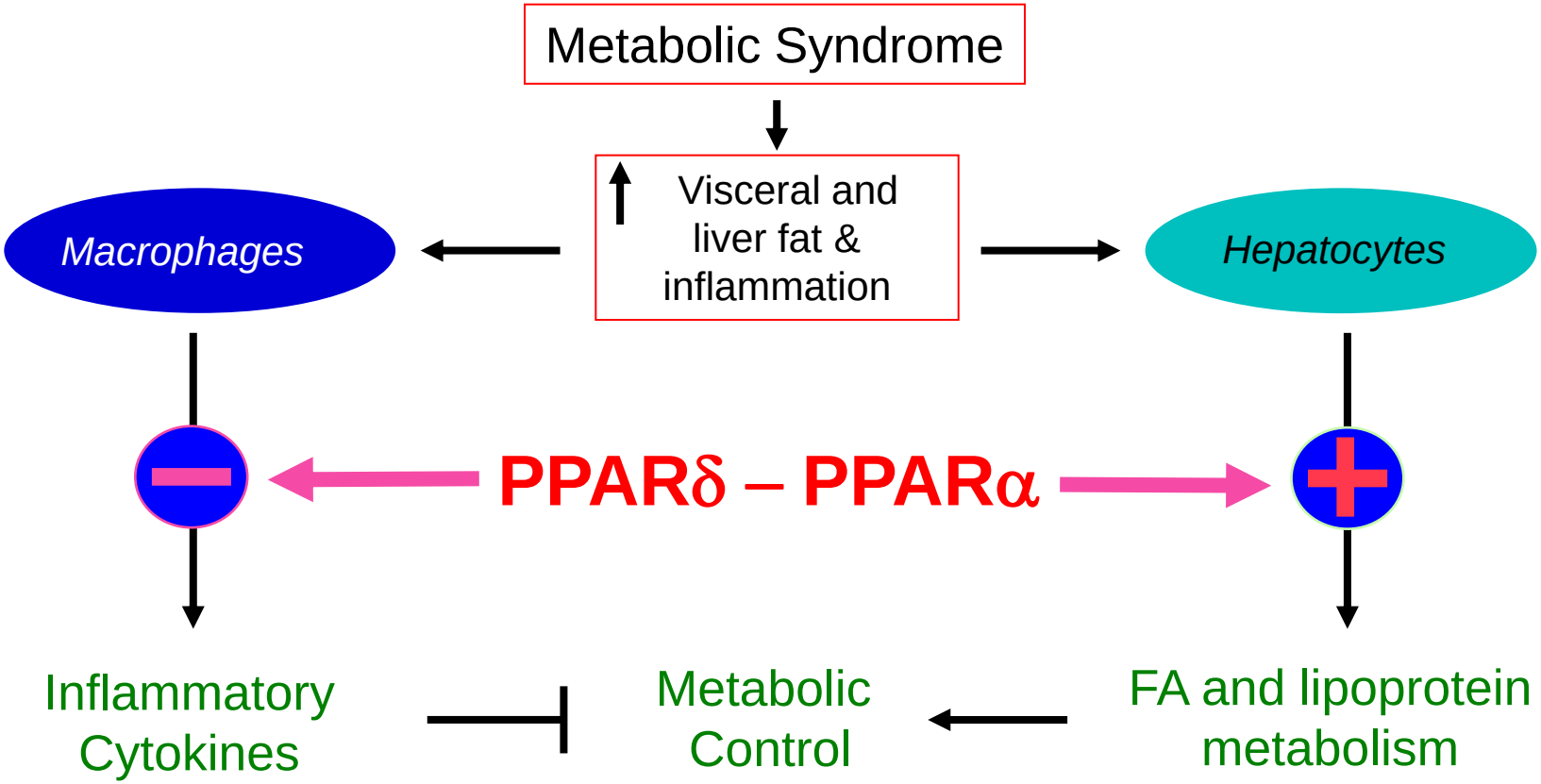


Other NAFLD related endpoints

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

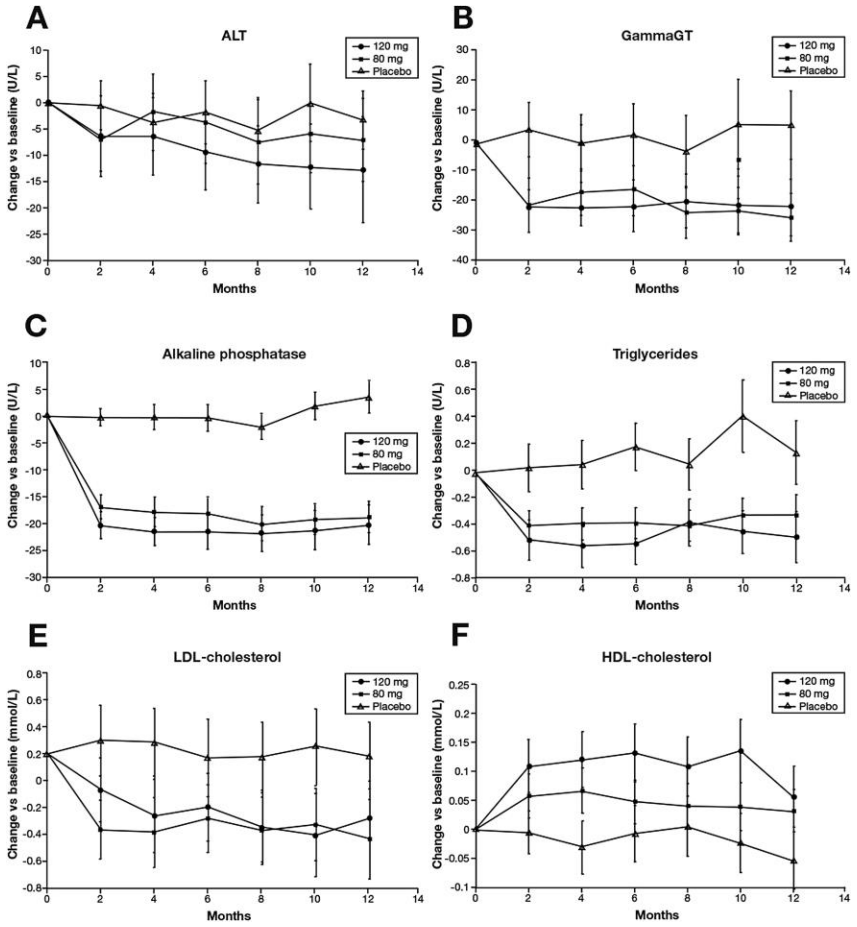
AASLD 2016, **Late Breaker** Monday afternoon to follow

Potential Mechanisms of PPARα/δ Benefit in NASH



Tailleux, Wouters & Staels BBA 2012 ;1821:809-18

GOLDEN Trial Results – Elafibrinor (PPAR α,δ agonist)



Primary Endpoint Was Not Met:

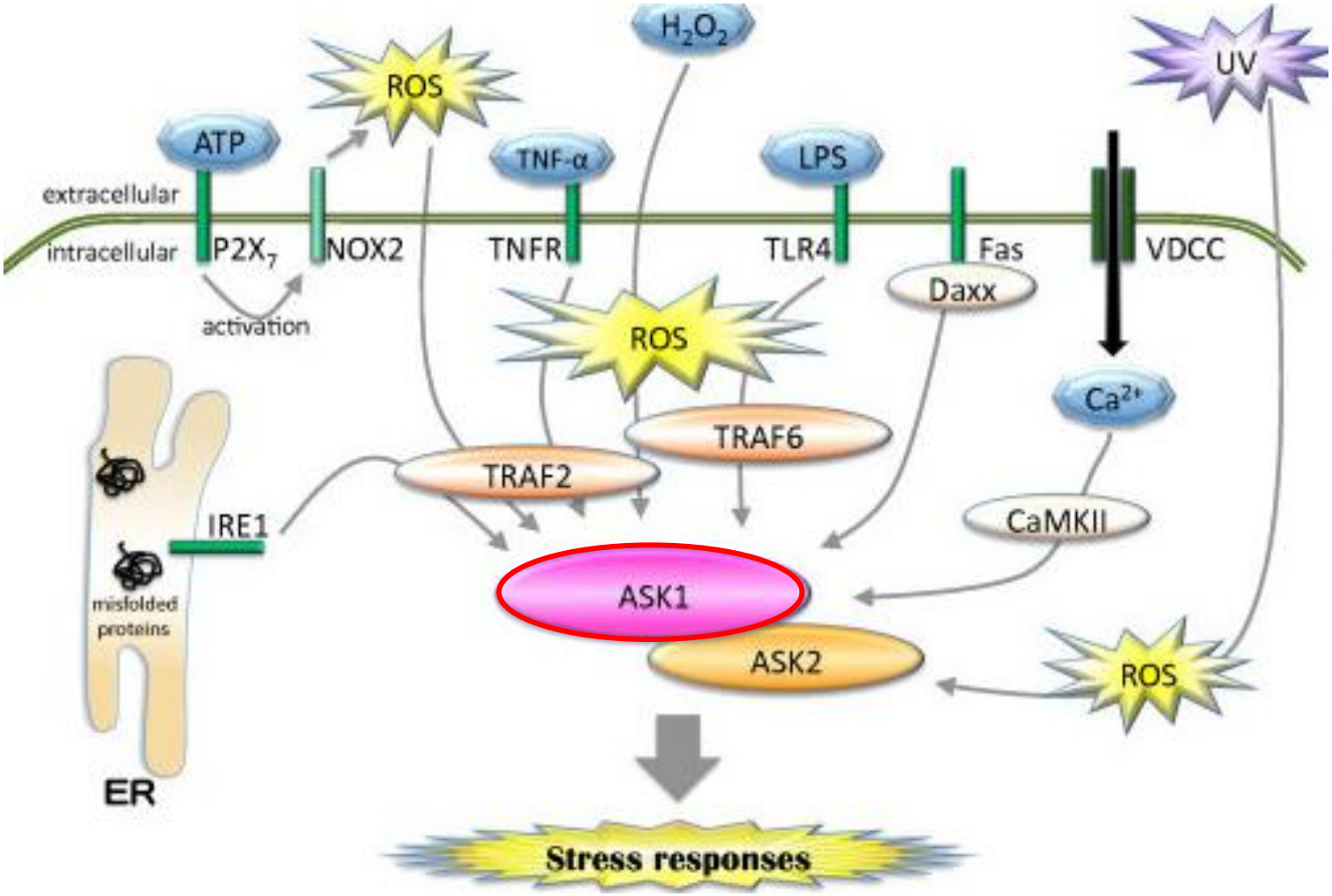
Reversal of NASH without worsening of fibrosis

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.

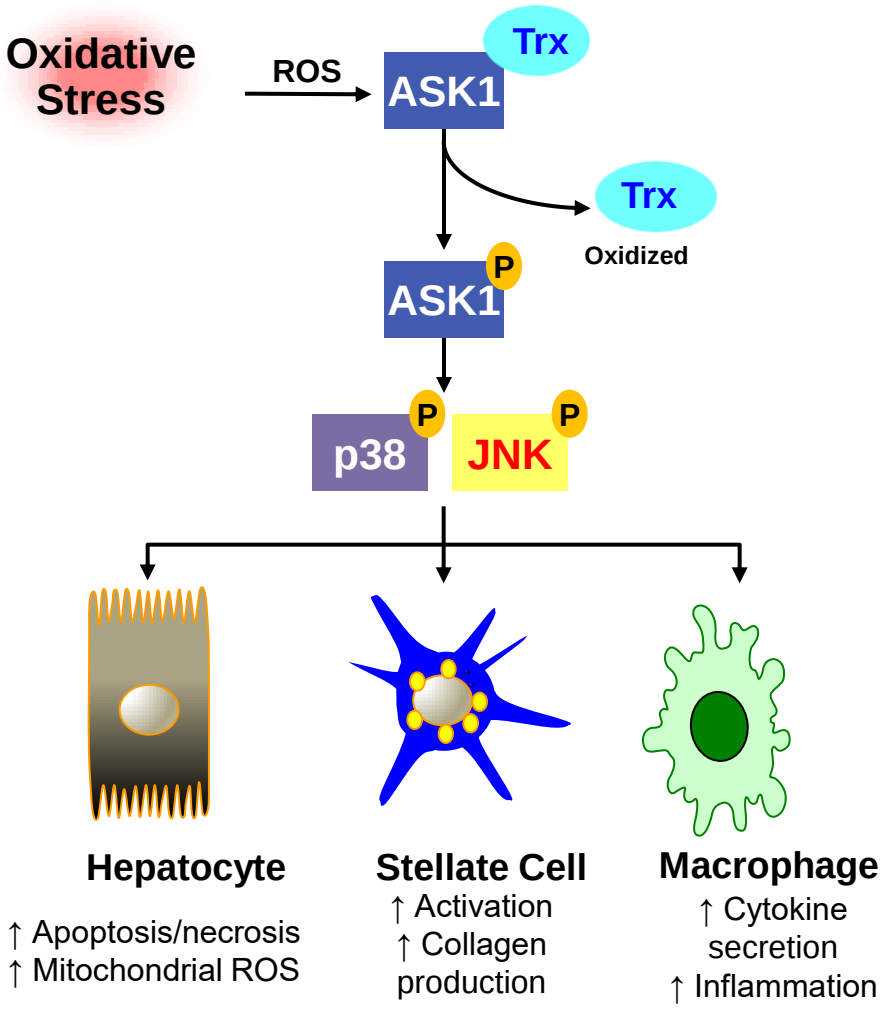
Ratziu et al, **Gastroenterology** 2016

Apoptosis Signal-Regulating Kinase 1 (ASK1) is at the Nexus of Convergent Stress Signals



Hattori K. **Cell Commun. Signal** (2009)

Apoptosis Signal-Regulating Kinase 1 (ASK1)

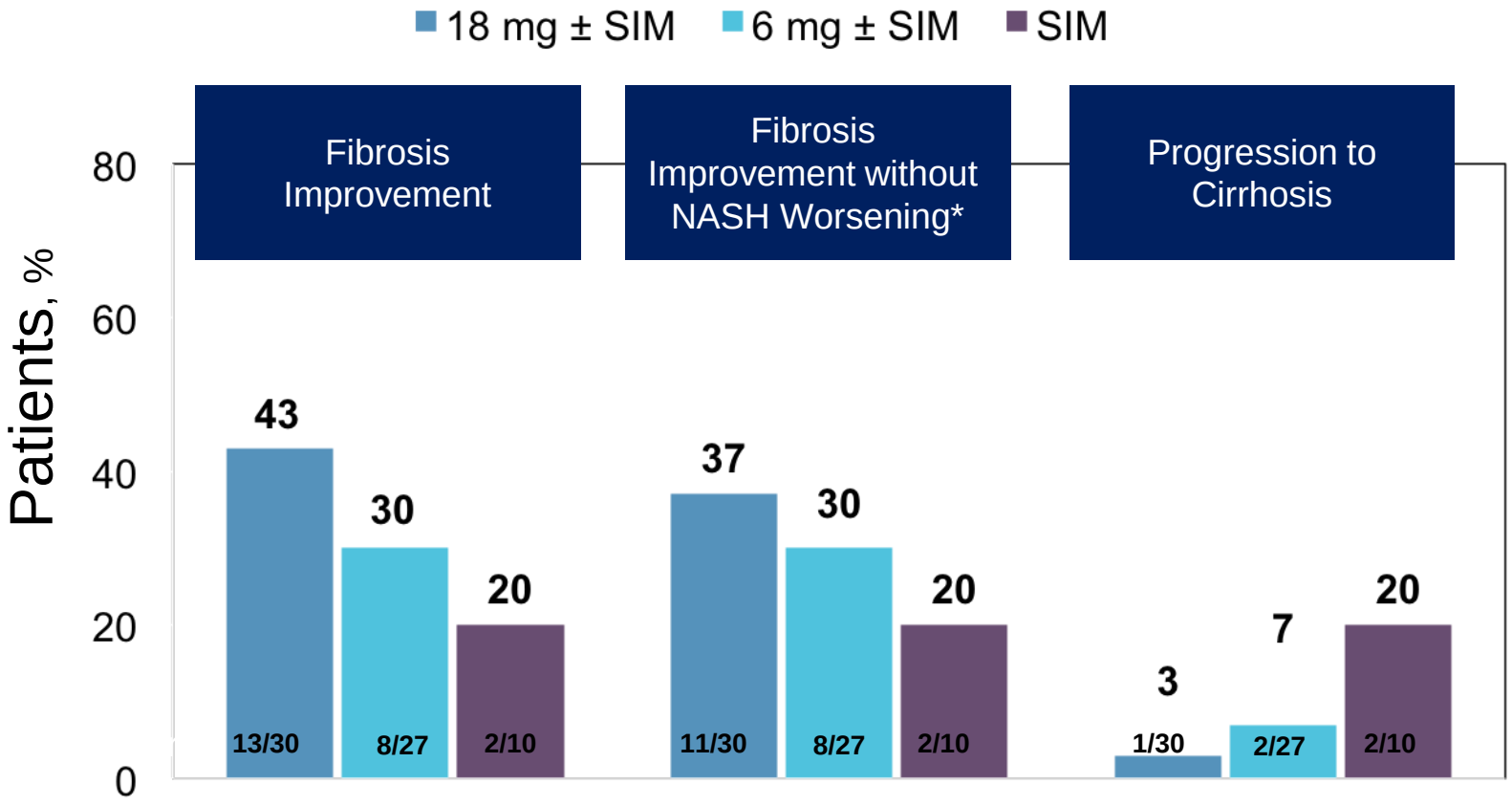


- Promotes cell death, fibrosis and inflammation via JNK and p38 MAPK
- ASK1$^{-/-}$ mice are normal, protected in models of liver injury and fibrosis
- ASK1 pathway activated in NASH: Correlates with fibrosis stage

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).

Courtesy of Rohit Loomba

The Future - *Combination Therapies for NASH Fibrosis*

Single Agent	***Drug Combinations***
• Biology is more straightforward	• Broader target coverage can ‘hedge bets’ in the absence of clarity about ‘driver’ pathogenic events

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.