Liver fibrosis in NASH: A Roadmap for Drug Discovery and Pharmacotherapy

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Beth Israel Deaconess Medical Center

HARVARD MEDICAL SCHOOL

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Institute for Translational Immunology

EPoS
Elucidating Pathways of Steatohepatitis

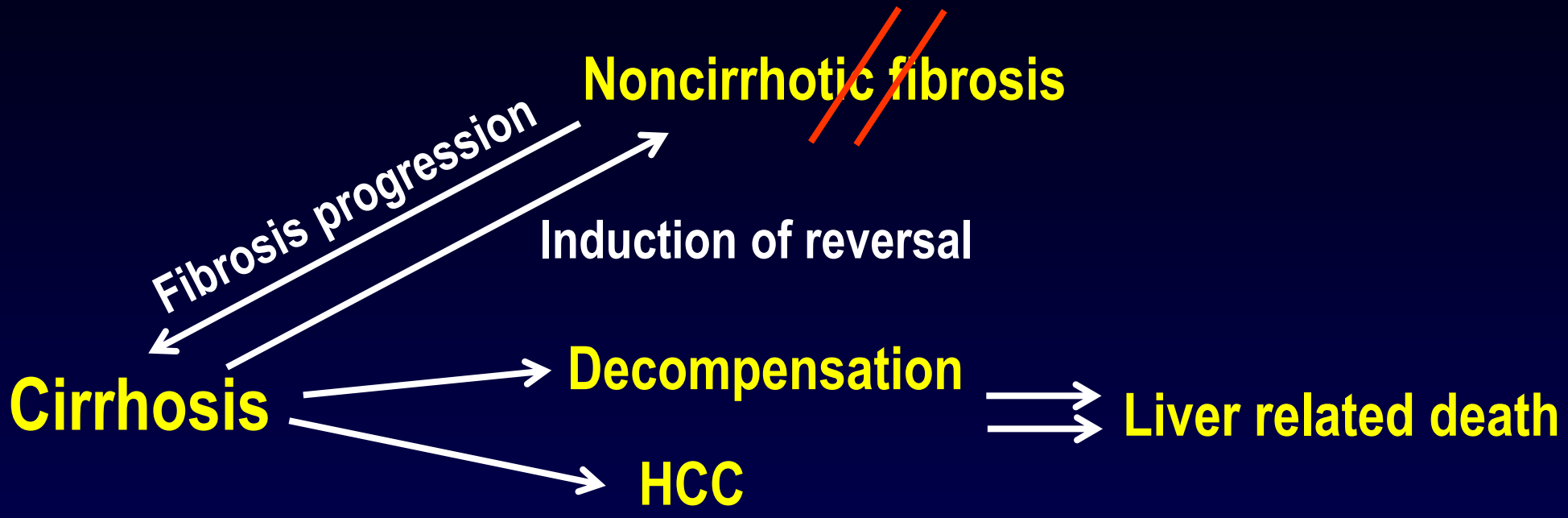
LITMUS

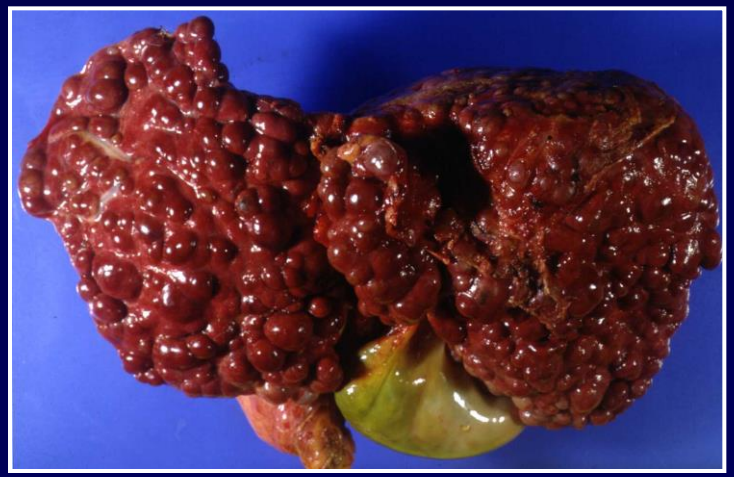
imi innovative medicines initiative

FZI Research Center for Immune Therapy

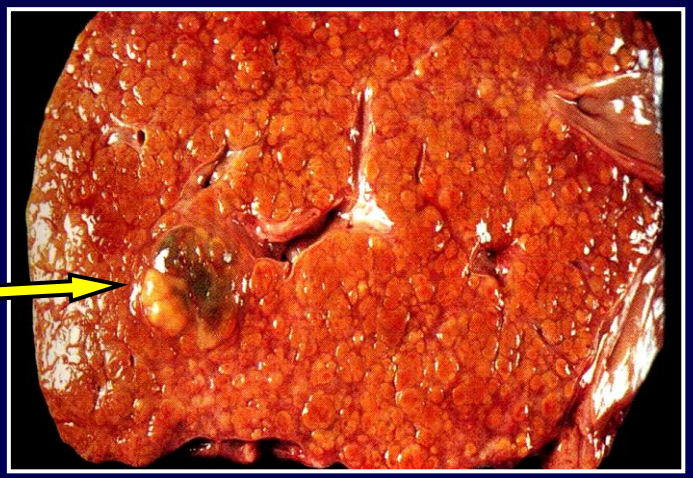
I have no conflicct of interest to declare

Relevance of advanced liver fibrosis/cirrhosis as endpoint

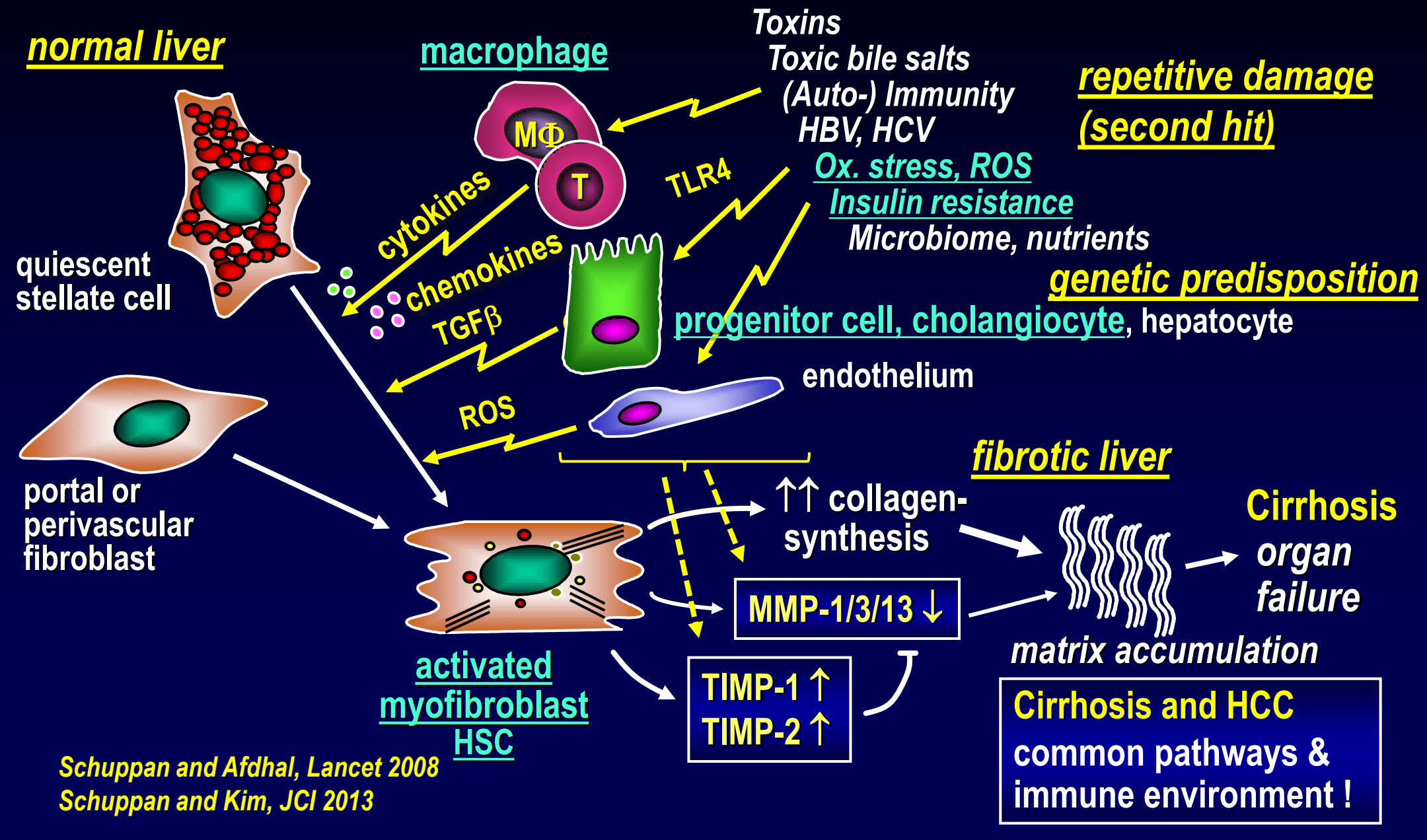




HCC



Fibrogenesis is a Multicellular Process



Schuppan and Afdhal, Lancet 2008
Schuppan and Kim, JCI 2013

Reversibility of advanced fibrosis after removal/suppression of the primary causal hit

Cirrhosis Regression with Longterm Tenofovir Treatment

1-5 yr extension of 48 week tenofovir trial ***(Marcellin P et al, NEJM 2008)***

489/615 pts (76%) included **5 yr biopsy: 348/489 (71%)**

Baseline: no cirrhosis

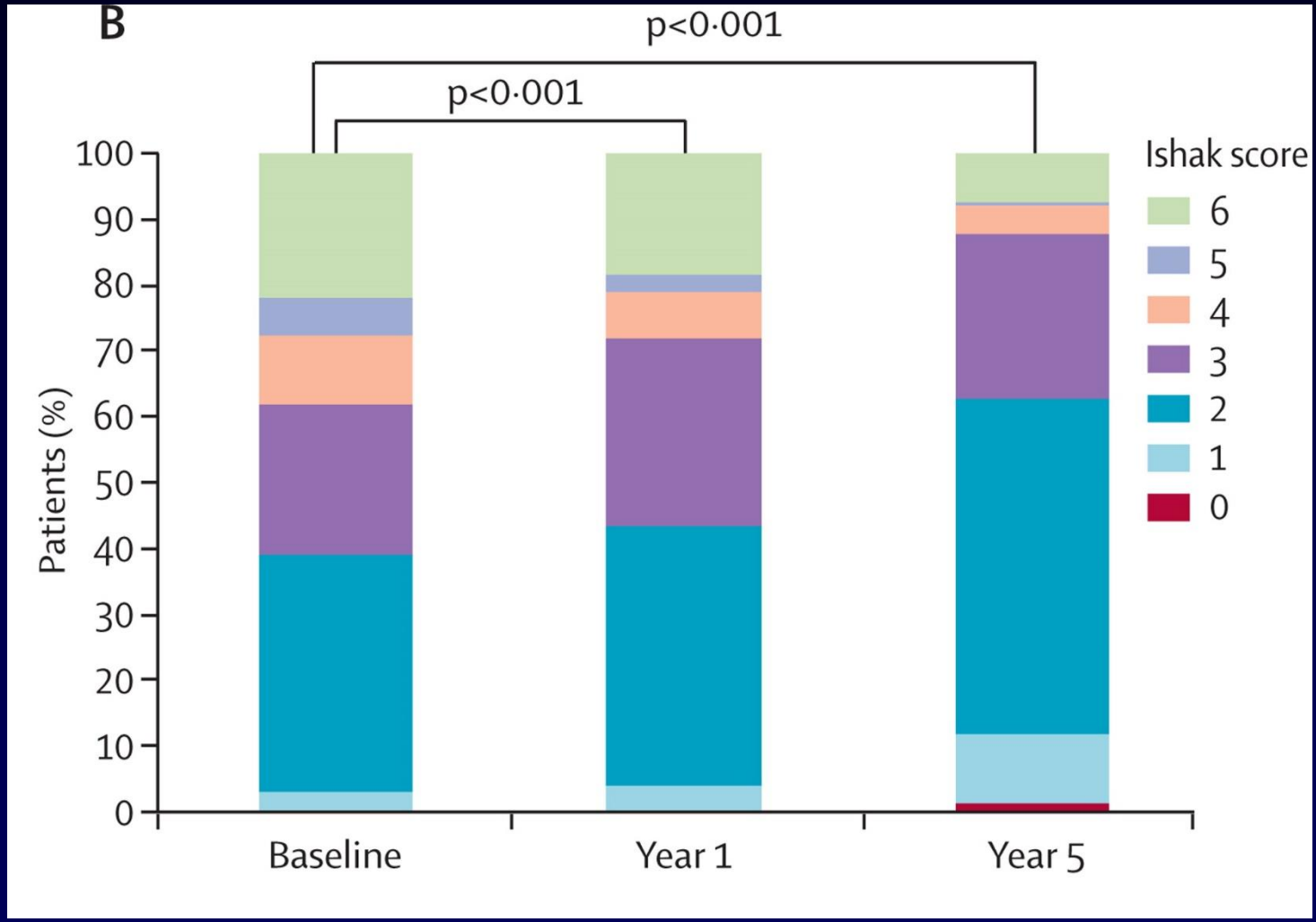
Better 105/252

Worse 12/252

Baseline: cirrhosis

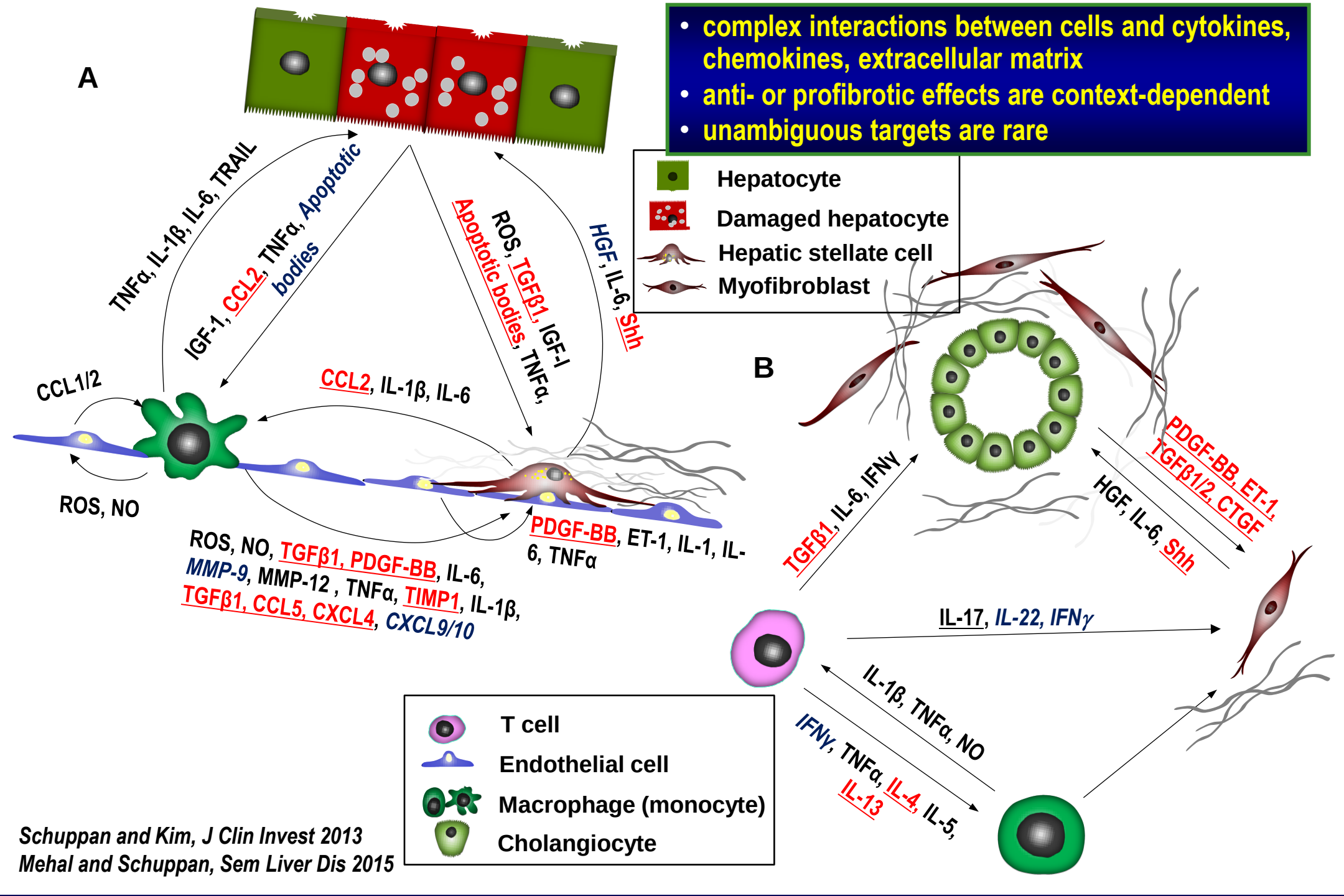
Better 71/96

(≥2 stages: 70/71)



Marcellin P et al, Lancet 2013

Antifibrotic approaches



Schuppan and Kim, J Clin Invest 2013
Mehal and Schuppan, Sem Liver Dis 2015

Role of activated cholangiocytes in fibrosis progression

Progenitors ("activated cholangiocytes") as driving force of fibrogenesis

Proliferation stimulus *inflammation*

2nd hit

e.g. oxidative stress in NAFL

Hepatocyte growth arrest / lipoapoptosis

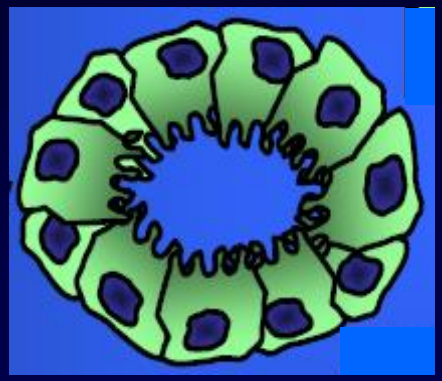
Rise of fibrogenic progenitor cells *ductular reaction*

Tweak ↑

Fn14

Kuramitsu K et al, Hepatology 2013

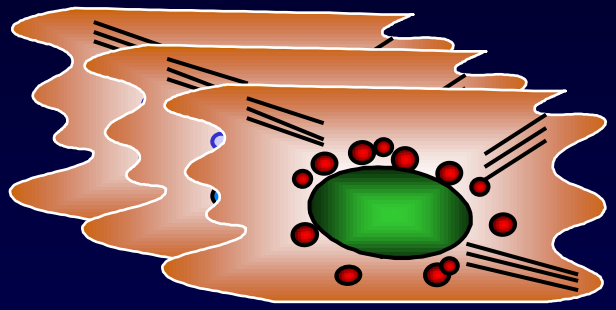
EMT-like changes



activated progenitor cells/ cholangiocytes

PDGF-BB, ET-1
TGFβ1, TGFβ2
CTGF, MCP-1

HGF, bFGF, IL-6, Shh



activated myofibroblasts

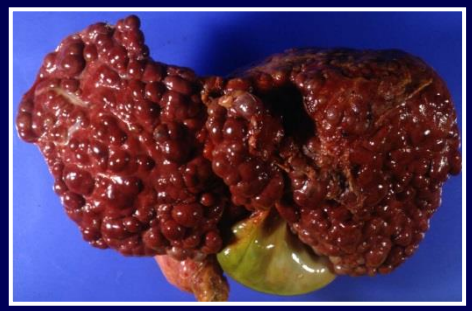
Integrin αvβ6 ↑↑

αvβ6 inhibitors

Wang et al, Hepatology 2007; Popov Y et al, J Hepatology 2008; Patsenker E et al, Gastroenterology 2008

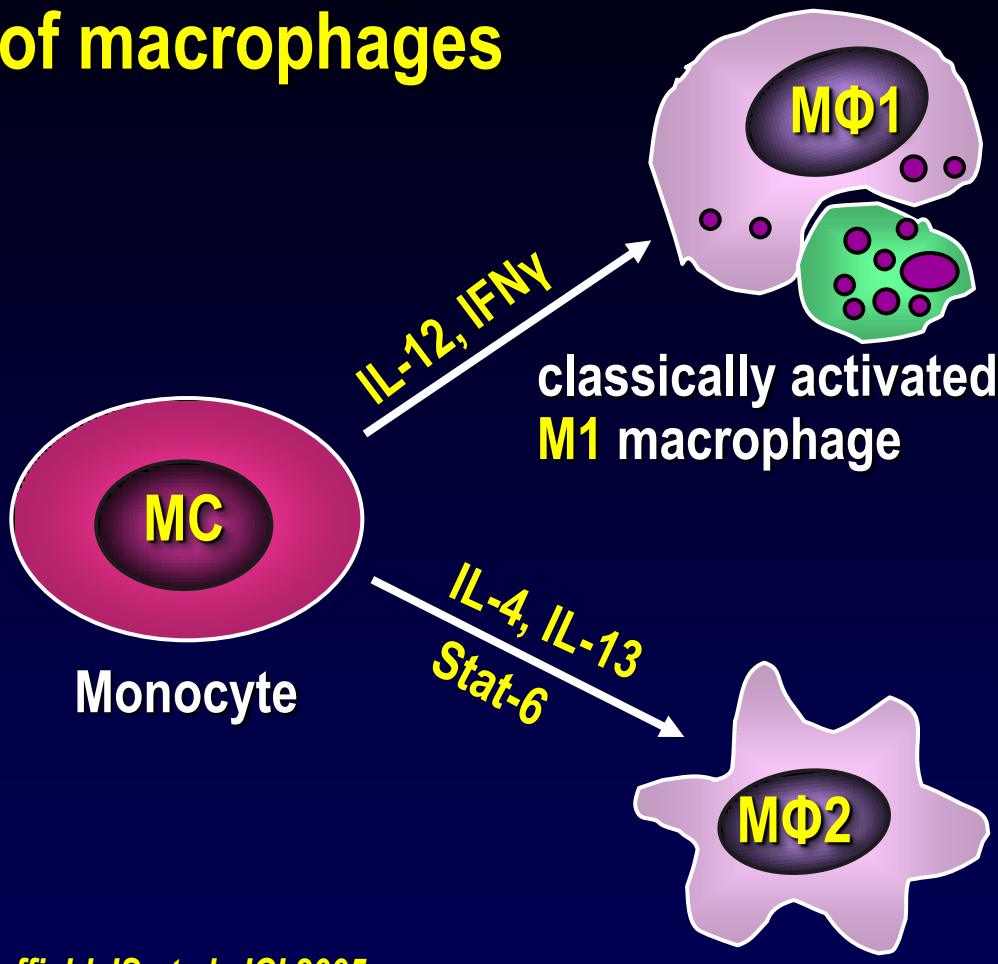
General *mechanism in fibrosis ≥ F2*

FCH: Davies SE et al, Hepatology 1991
ALH: Ray MB et al, Liver 1993
Various CLD: Lowes KN, Am J Pathol 1999
HCV: Clouston A et al, Hepatology 2005
NASH: Richardson MM et al, Gastroenterology 2007



Cirrhosis/HCC

Pharmacological repolarization of macrophages



Phagocytosis of debris and apoptotic cells
Generation of pro-inflammatory cytokines
"Resolution of fibrosis"
Immune-activating & cancer-suppressive

Pro-resolution macrophage
CD11b+ F4/80+ Ly6C^{low}

Targeted modulation

Promotion of angiogenesis
Generation of anti-inflammatory cytokines
"Promotion of fibrosis"
Immune-suppressive & cancer promoting

Duffield JS et al, JCI 2005
Fallowfield JA, J Immunol 2007
Duffield JS et al, JCI 2007
Popov Y et al, Am J Physiol 2010
Ramachandran S et al, PNAS 2012
Schuppan and Kim, JCI 2013
Mehal and Schuppan, Sem Liver Dis 2015
Ramachandran P et al, Sem Liver Dis 2015

Macrophages of „wounds that do not heal"
= fibrosis- and tumor-associated macrophages

Mechanism based antifibrotic therapies in clinical development

Drugs in phase I-II clinical trials to address fibrosis (1)

ECM, EMT, Progenitor activation (inflammation, hepatocyte apoptosis)

- Gilead: GS6624 (Simtuzumab): α-Loxl2 Mab *(>700 patients with ≥ stage 2 NASH or PSC)*
- Gilead: GS9654 (Selonisertib): Ask1 (apoptosis signaling kinase 1) inhibitor *(70 patients with ≥ stage 2 NASH)*
- Biogen-Stromedix: STX-100: α-Integrin αVβ6 Mab
- Biogen-Idec: anti-Tweak
- Sanofi-Genzyme: Fresolimumab: α-TGFβ Mab
- Pfizer-Fibrogen: FG3019: α-CTGF Mab
- Novartis: Seculizumab, α-IL-17 Mab
- Conatus: Emricasan: Caspase inhibitor *(>250 pts with NASH)*
- Boehringer-Ingelheim: VAP-1 antagonist *(>200 pts with NASH)*

Schuppan and Kim, J Clin Invest 2013;
Mehal and Schuppan, Sem Liver Dis 2015
Torok et al, Hepatology 2015
Trautwein et al, J Hepatol 2015

Drugs in phase I-II clinical trials to address fibrosis (2)

(M2) Macrophages, hepatic stellate cells

- Janssen: Carlumab: α-MCP-1/CCL2 Mab
- Pfizer: Selzentry: CCR5 antagonist
- Tobira/Allergan: Cenicriviroc: CCR2/CCR5 antagonist *(289 patients with NASH)*
- BMS: Peg-FGF21
- Novartis: QUAX576: α-IL-13 Mab
- Sanofi: SAR156597: α-IL-4/IL-13 Mab
- Isis and own group: IL4Rα1, IL13Rα1……. antisense-DNA
- Promedior: RM-151: rec. Pentraxin-2 (SAP)
- Novo Nordisc: GLP-1 agonist/Semaglutide) *(300 pts with NASH)*

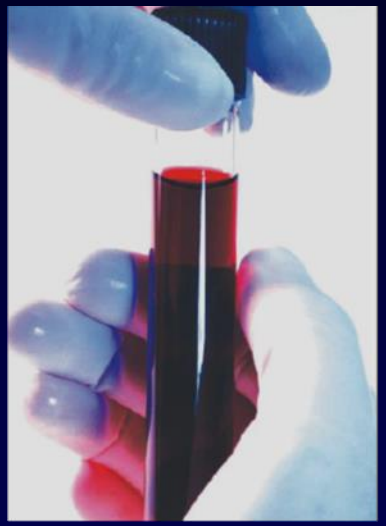
Schuppan and Kim, J Clin Invest 2013;
Mehal and Schuppan, Sem Liver Dis 2015
Torok N et al, Hepatology 2015
Trautwein et al, J Hepatol 2015

An anti-inflammatory agents are not necessarily antifibrotic, examples:

- anti-TGFβ1: blocks fibrosis, enhances inflammation
- anti-CCR2, CCR5… : blocks inflammatory and restorative macrophage infiltration/activation, HSC activation

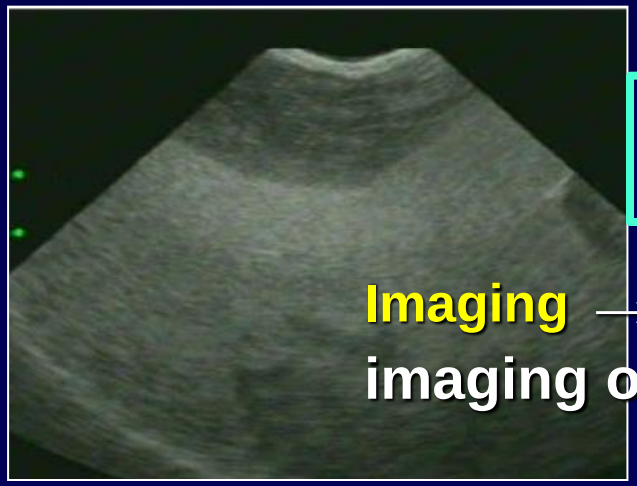
Current and evolving options for fibrosis assessment

Liver Biopsy – crude assessment, not dynamic



Fibrosis serum markers

→ validated markers of fibrogenesis and fibrolysis



Imaging → targeted and quantitative imaging of fibrogenesis

Elastography – crude assessment, not dynamic

Sampling variability in staging & grading

HCV, laparoscopic biopsy of right and left liver, n=124, Metavir-score

Difference	n	%
≥ 1 stage	41/124	33.1
≥ 2 stages	3/124	2.4
≥ 1 grade	30/124	24.2
≥ 2 grade	2/124	1.6
cirrhosis vs. stage 3	18/124	14.5

liver biopsy samples only 1/ 50.000 of the whole liver

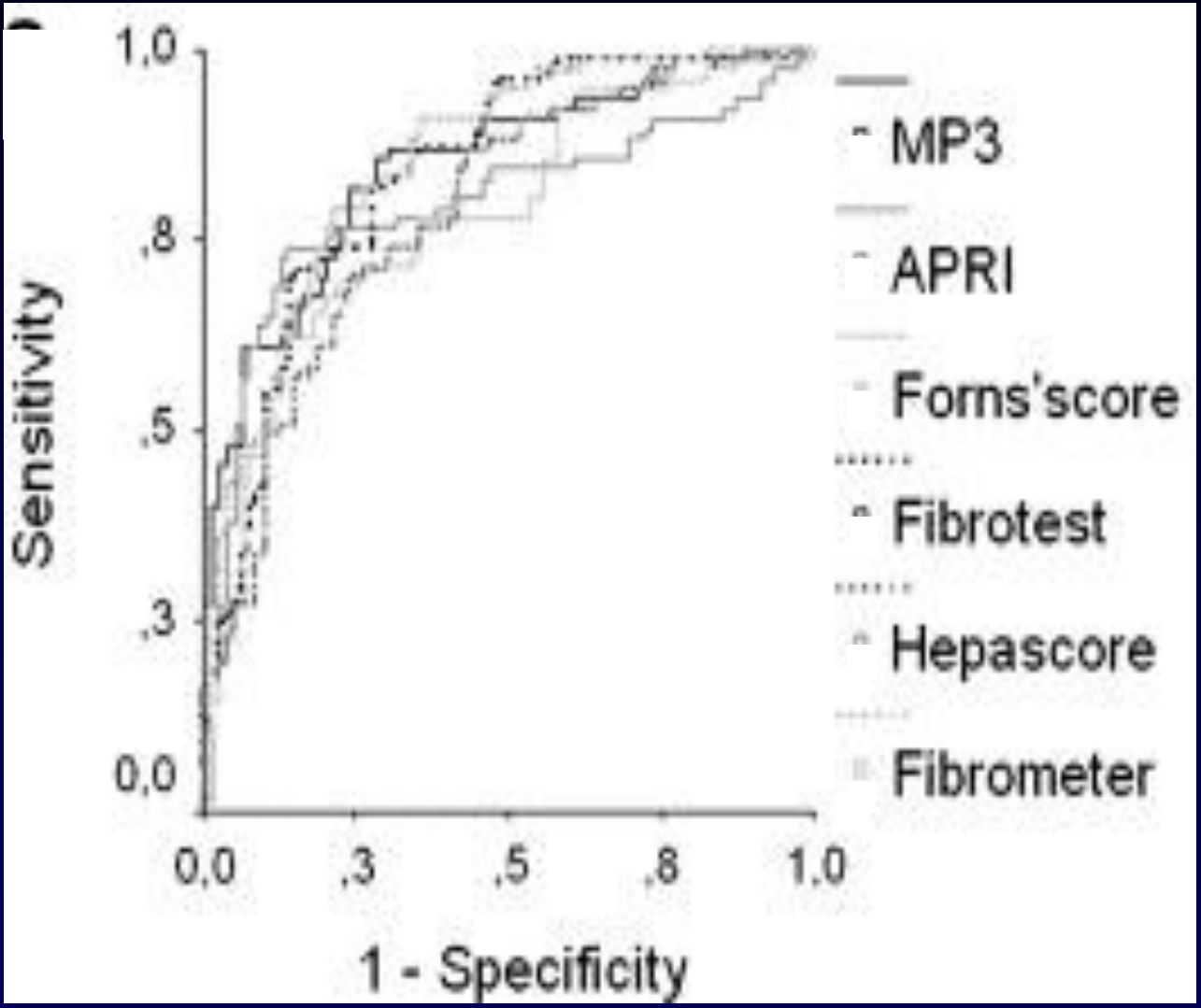
Regev et al., Am. J. Gastroenterol. 97, 2614, 2002

≥ 1 stage discordance

NASH > 40% *Ratziu V, Gastroenterology 2005; Merriman RB et al, Hepatology 2006*

PBC/PSC > 60% *Olsson R et al & Garrido MC et al, J Clin Pathol 1995 & 1996*

Comparison of 6 biomarker scores in 180 pts with CHC (F0-1 vs. F2-4)



MP3: PIIINP, MMP-1

APRI: AST / platelets

Forns: γGT, cholesterol, platelets, age

Fibrotest: age, Bili, γGT, γ-globulin, haptoglobin, α2M

Hepascore: age, gender, α2M, HA, Bili

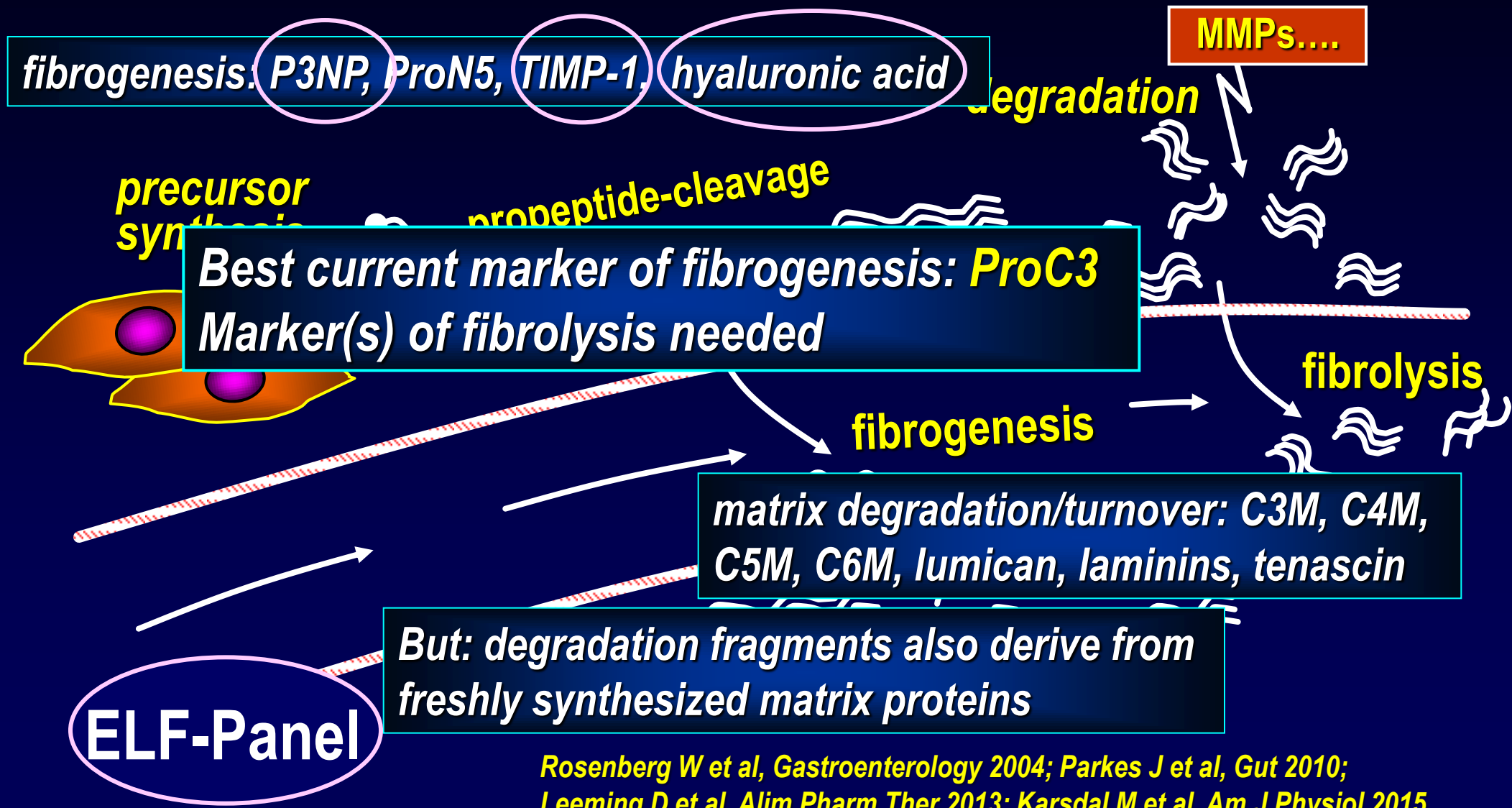
Fibrometer: age, INR, platelets, AST, urea, α2M, HA

All with AUROCs 0.80-0.85 = only modest tests to distinguish no/mild vs. significant fibrosis

Leroy V et al, J Hepatol 2007

Biological plausibility:

Direct markers of fibrosis dynamics



Rosenberg W et al, Gastroenterology 2004; Parkes J et al, Gut 2010; Leeming D et al, Alim Pharm Ther 2013; Karsdal M et al, Am J Physiol 2015

NB biomarkers - established assays –validation for liver:

C5M (MMP-mediated type V collagen degradation)

C6M (MMP-mediated type VI collagen degradation)

ProC3 (type III collagen formation) - fibrogenesis

ProN4 (type IV collagen formation)

ProC5 (type V collagen formation)

ProC6 (type VI collagen formation, adipokine) – fibrogenesis, adipose tissue fibrosis (NASH)

UMCM biomarkers of progression or reversal derived from serum iTRAQ and Somascan proteomics:

WDR85, WDR90, Ephrin B3, A9*, IB3*, PR8*, MK3* - fibrogenesis

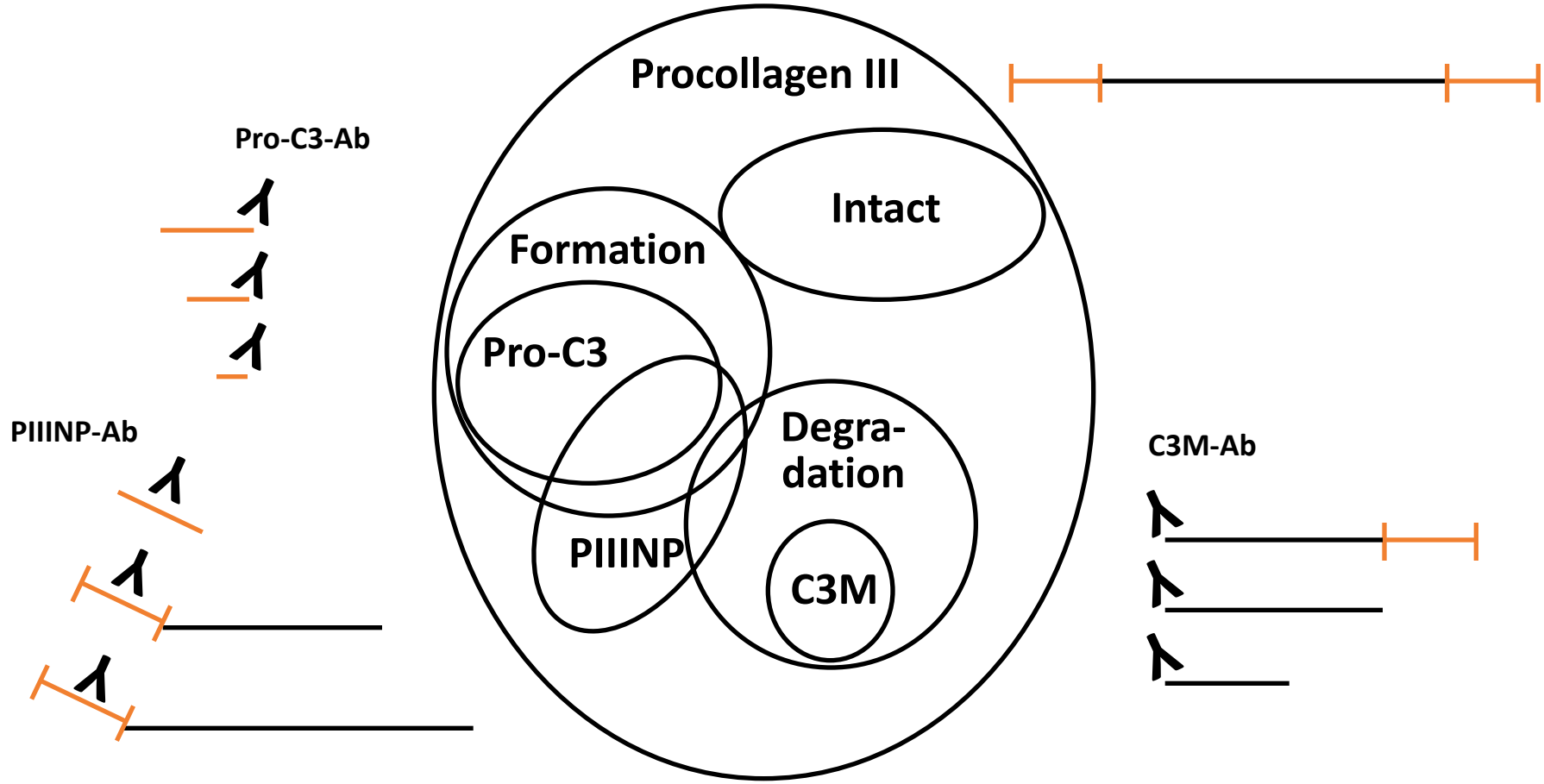
IB3*, PR8*, MK3*, A2*, A14*, CS17*, CS26*, TP2* - fibrolysis

* in validation, listed for patent protection

Nielsen M et al, Liver Int 2015
Karsdal MA et al, Am J Physiol 2016
Leeming D et al, submitted
Surabattula R et al, submitted

Procollagen type III processing

each variant of the same protein carries unique information



NORDIC BIOSCIENCE

GASTROENTEROLOGY 2010;138:1365–1373

Farglitazar Lacks Antifibrotic Activity in Patients With Chronic Hepatitis C Infection

JOHN McHUTCHISON,* ZACHARY GOODMAN,‡ KEYUR PATEL,* HALA MAKHLOUF,‡ MARIBEL RODRIGUEZ–TORRES,§ MITCHELL SHIFFMAN,‖ DON ROCKEY,¶ PETR HUSA,# WAN–LONG CHUANG,** ROBERT LEVINE,‡‡ MARK JONAS,§§ DICKENS THEODORE,‖‖ RICHARD BRIGANDI,‖‖ ALISON WEBSTER,¶¶ MARGARET SCHULTZ,‖‖ HELEN WATSON,¶¶ BRITT STANCIL,‖‖ and STEPHEN GARDNER‖‖ on behalf of the Farglitizar Study Investigators

*Duke Clinical Research Institute and Division of Gastroenterology, Duke University Medical Center, Durham, North Carolina; ‡Armed Forces Institute of Pathology, Washington, DC; §Fundación de Investigación de Diego, San Juan, Puerto Rico; ‖Virginia Commonwealth University, Richmond, Virginia; ¶UT Southwestern Medical Center, Dallas, Texas; #FN Brno, Bohunice, Czech Republic; **Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; ‡‡SUNY Upstate Medical University, Syracuse, New York; §§Consultants for Clinical Research, Inc, Cincinnati, Ohio; ‖‖GlaxoSmithKline, Research Triangle Park, North Carolina; and ¶¶GlaxoSmithKline, Greenford, Middlesex, United Kingdom

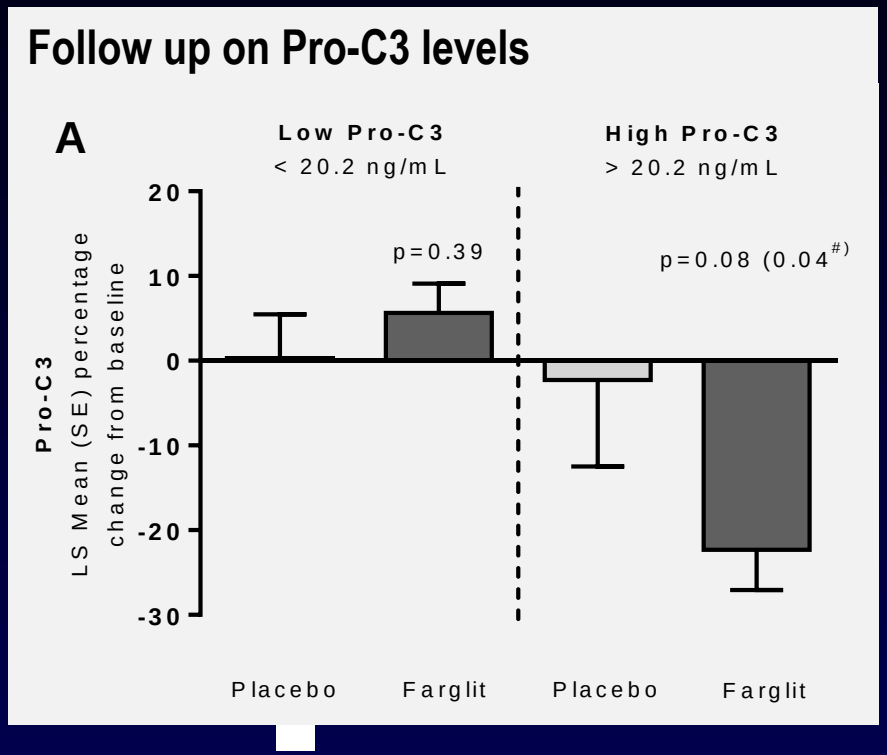
Nonresponders to HCV-antiviral therapy
Ishak fibrosis score 2-4
Treatment duration: 52 weeks with follow up biopsies (209/265=79%)
Placebo controls n=89
Farglitazar 0.5 mg/d: n=88
Farglitazar 1.0 mg/d: n=88
Histological quantification:
α-SMA, collagen (SR morphometry)

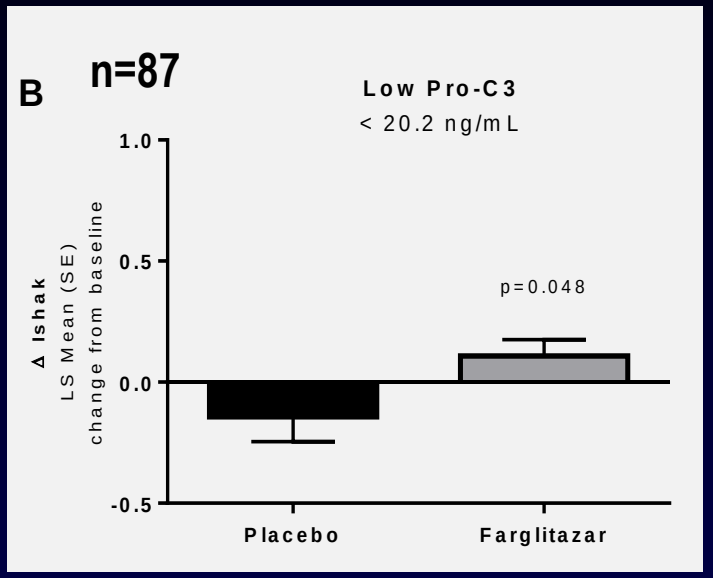
Non-TZDD PPAR-γ agonist with 100-1000fold higher activity than Pio-/Tro-/Rosi-glitazone

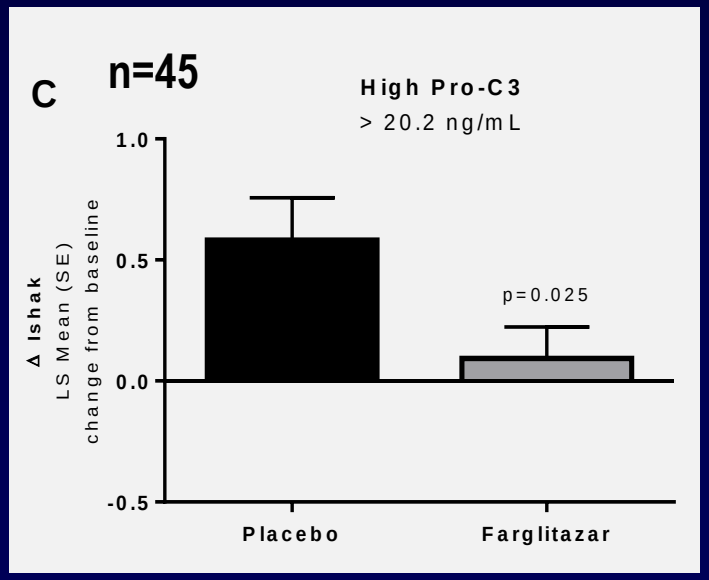
	collagen	α-SMA
Placebo controls	+49%	27%
Farglitazar 0.5 mg/d:	+58%	27%
Farglitazar 1.0 mg/d:	+52%	31%

no overall effect on fibrosis !

Pro-C3 identifies subjects who responded to antifibrotic therapy





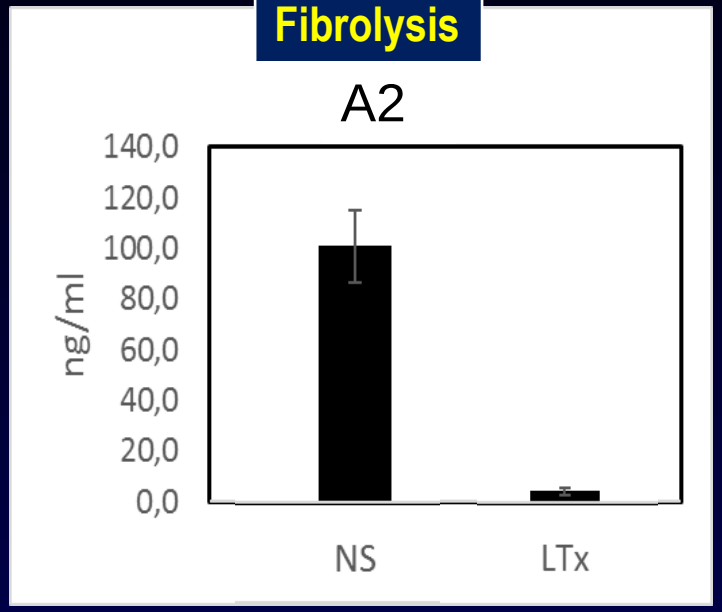


- > 20.2 ng/ml: selection criterion for responders
- a decline in serum levels indicates antifibrotic effect

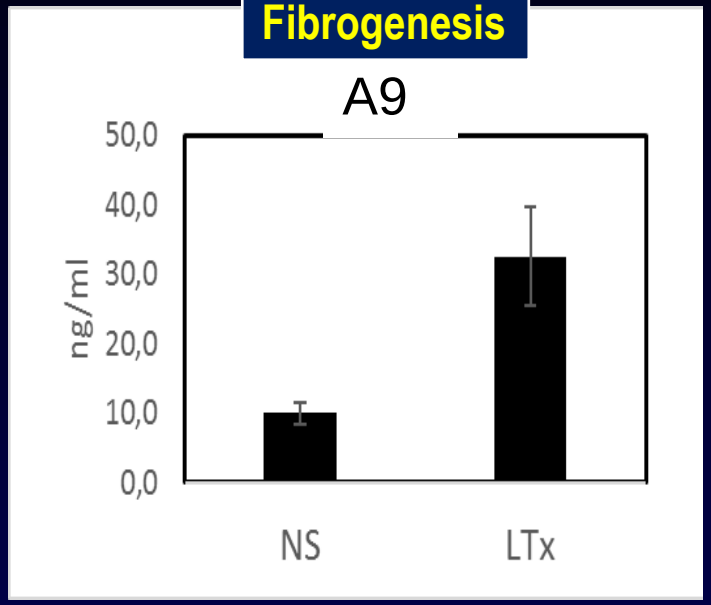
Karsdal MA et al, Am J Physiol 2016

Markers of fibrogenesis and fibrolysis:
A2, A9 and A14: cell membrane molecules involved in ECM remodeling

Fibrolysis

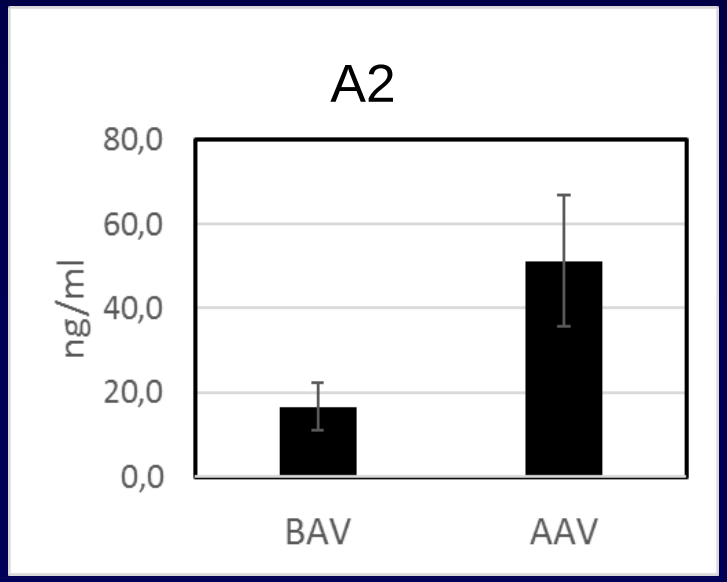


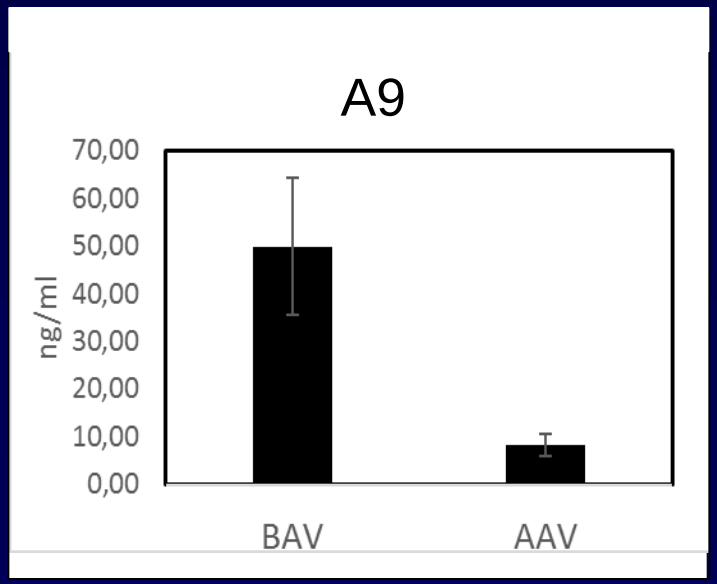
Fibrogenesis



NS, healthy ctr

LTX: post transplant with progression to cirrhosis within 5 yr





BAV: before antiviral Tx for HCV

AAV: 24 w after highly effective antiviral Tx for HCV

Surabattula R et al, unpublished

Summary (1)

- (early) **Cirrhosis is reversible** when the major fibrogenic (inflammatory) trigger is eliminated (HepB, HepC, ai-Hep)
- This may even be possible for (decompensated) cirrhosis
- Most NASH drugs target the **hepatocyte** and its metabolic derangement, possibly with secondary antifibrotic effects
- Some drugs target **inflammation**, but this does not necessarily correlate with antifibrotic activity
- Other drugs address **multiple cells** and net effects are difficult to predict

Summary (2)

- Major antifibrotic targets are related to fibrogenic cholangiocytes, macrophages and hepatic stellate cells
- Several (pharmacological) therapies that may inhibit progression and speed up reversal have entered the clinic
- Biologically plausible markers of fibrosis, fibrogenesis and fibrolysis to stratify patients and noninvasively monitor treatment response are being developed
- This should permit short and slim POC studies, testing of combinations and a personalized antifibrotic therapy