



**PARIS
MASH
MEETING**

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Why Have Cirrhosis Trials Largely Failed? *Is Fibrosis the Wrong Target?*

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**Mount
Sinai**

Disclosures – Scott Friedman MD

Consulting: 89 Bio, Acceler Pharma, Agomab, Axcella Health, Boston Pharmaceuticals, Gordian Biotechnology, Glycotest, Hepgene, In vitro, Junevity, Korros Bio, Kriya, Merck Pharma, Laekna, Lerna, Overtone, Macomics, Morpnic Therapeutics, North Sea Therapeutics, Novartis, Ochre Bio, Pfizer Pharmaceuticals, Prosciento, Resolution Therapeutics, Takeda, Therasid Bio, Satellite Bio, Scholar Rock, Sunbird Bio, Surrozen




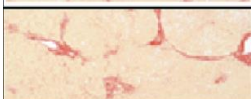


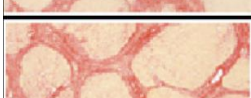
Stock options: Galmed, Hepgene, Junevity, Laekna, Lifemax, Metacrine, Morpnic Therapeutics, Nimbus, North Sea Therapeutics, Satellite Bio, Scholar Rock, Sunbird Bio, Surrozen. **Stock ownership:** HueDx (formerly Group K).

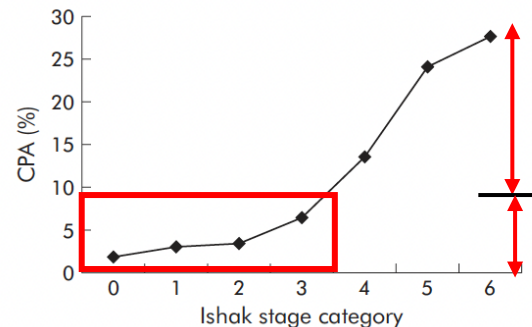
Research Activities with Commercial Entities: Novo Nordisk Abalone Bio (SBIR Grant)

Take Home Points

1. *Fibrosis regression in cirrhosis will take time.*
 - *Digital imaging is more sensitive to detect regression but not to subclassify cirrhosis*
2. *Cirrhosis is more than one stage*
 - *Collagen cross-linking makes regression harder*
 - *Portal hypertension likely marks irreversibility – for now...*
3. *Antifibrotic targets evolve during fibrosis progression*
 - *Increased autocrine signaling by hepatic stellate cells*
4. *Endpoints other than fibrosis content need evaluation*
 - *Functional tests may be more sensitive and informative*
5. *There are glimmers of antifibrotic success emerging*

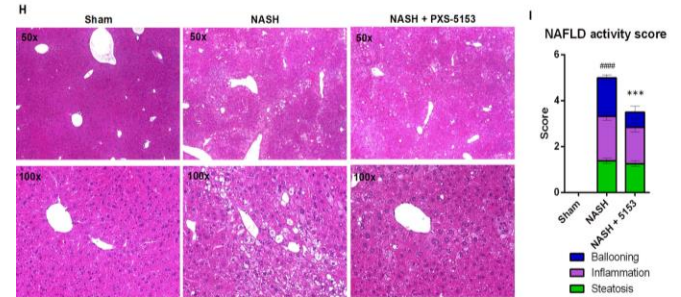
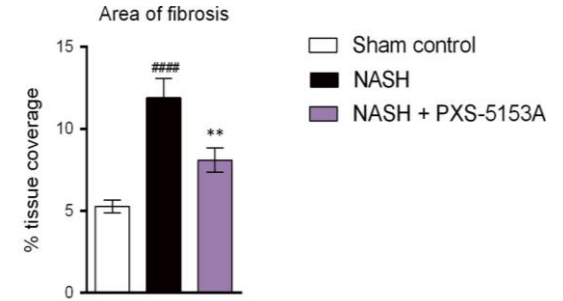
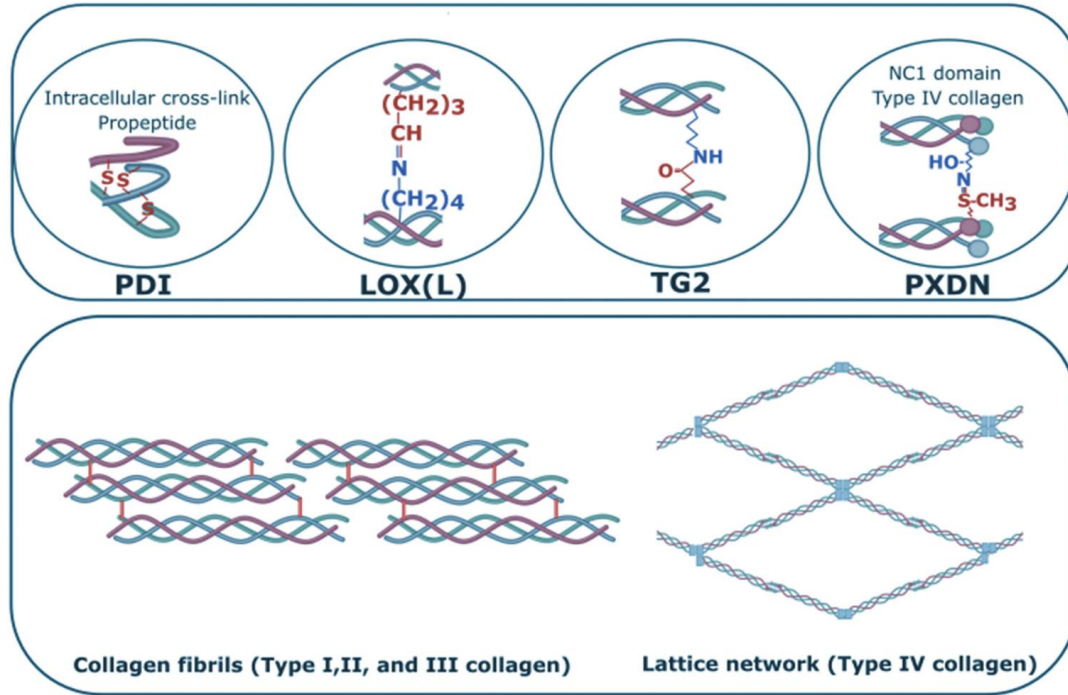
Increases in Collagen are Not Linear in Chronic Liver Dz – *Regression Will Take Time*

Appearance	Ishak stage: Categorical description	Ishak stage: Categorical assignment	Fibrosis measurement*
	No fibrosis (normal)	0	1.9%
	Fibrous expansion of some portal areas ± short fibrous septa	1	3.0%
	Fibrous expansion of most portal areas ± short fibrous septa	2	3.6%
	Fibrous expansion of most portal areas with occasional portal to portal (P-P) bridging	3	6.5%
	Fibrous expansion of portal areas with marked bridging (portal to portal (P-P) as well as portal to central (P-C))	4	13.7%
	Marked bridging (P-P and/or P-C), with occasional nodules (incomplete cirrhosis)	5	24.3%
	Cirrhosis, probable or definite	6	27.8%

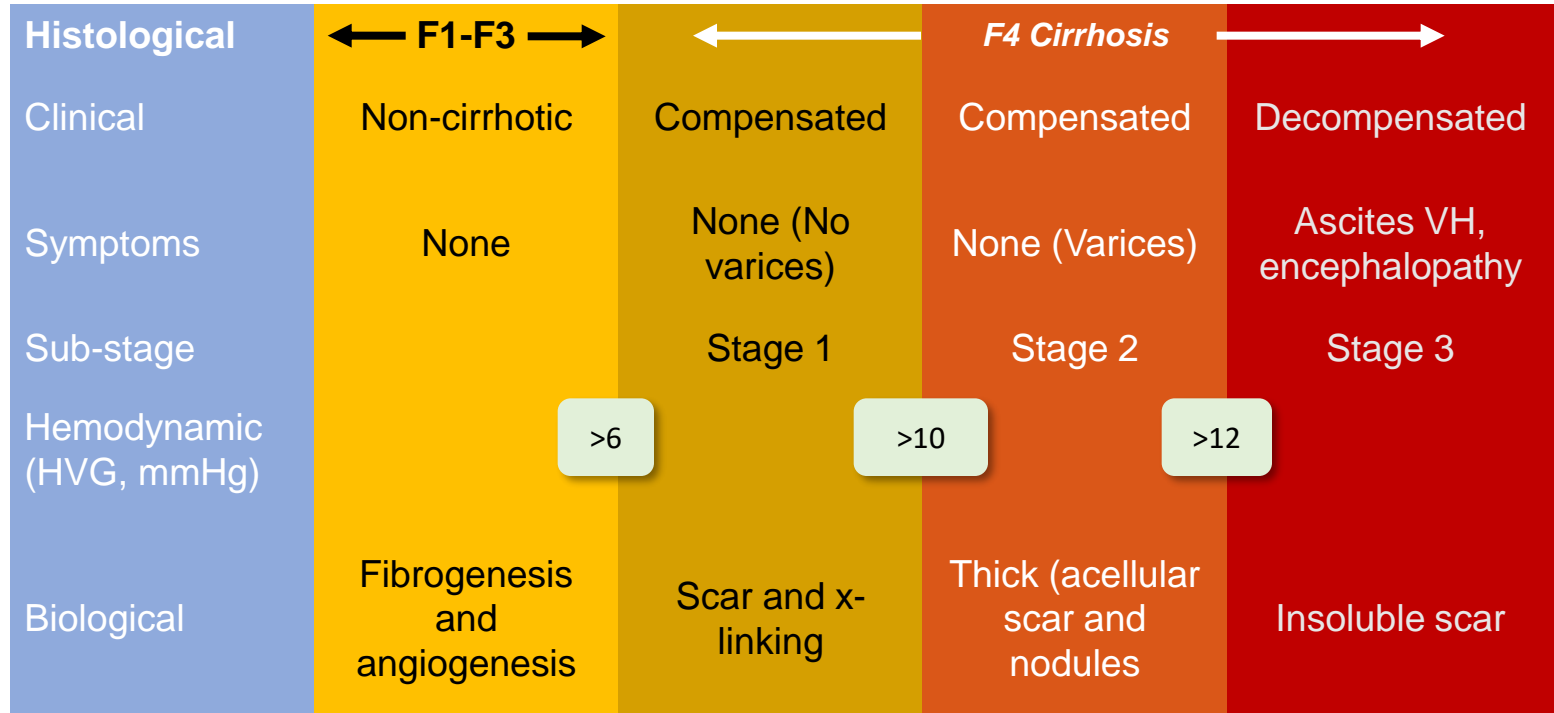


Standish et al, **Gut**, 2006

Progressive Collagen Cross-linking Impedes Degradation in Advanced Disease

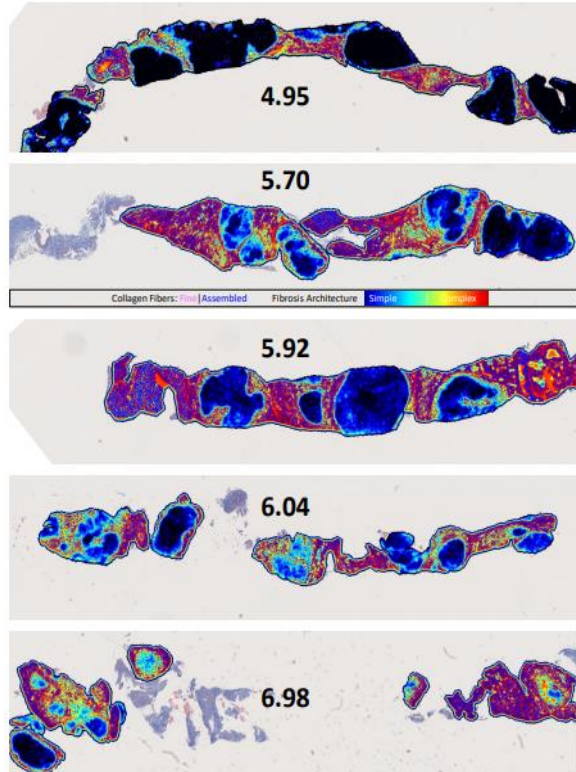


Cirrhosis Is More Than A Single Stage – *Therapeutic Targets Evolve During Disease Progression*

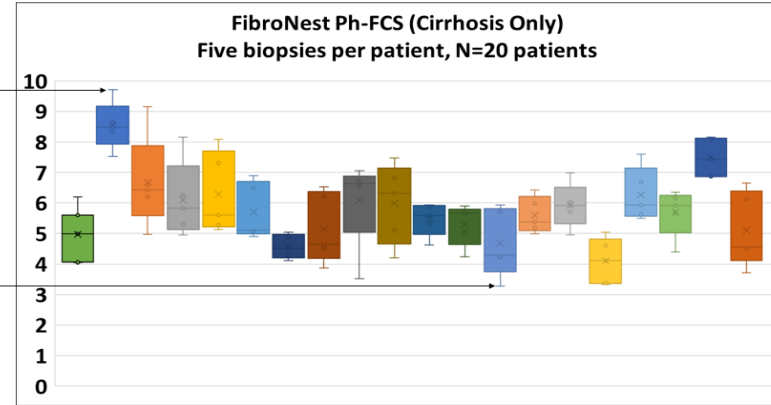
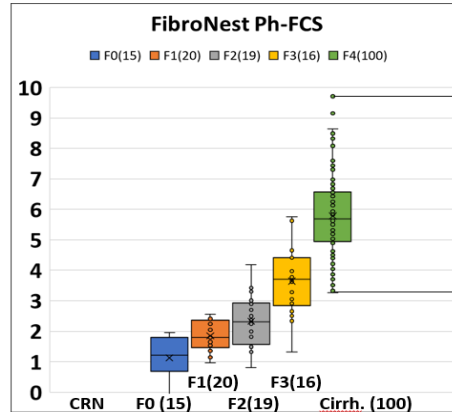


Liver Sampling Variability Makes it Impossible to Sub-classify Cirrhosis by Biopsy

N=20 HCV cirrhotic patients (post transplant livers with 5 biopsies, n=100 biopsies)



Same liver – 5 biopsies



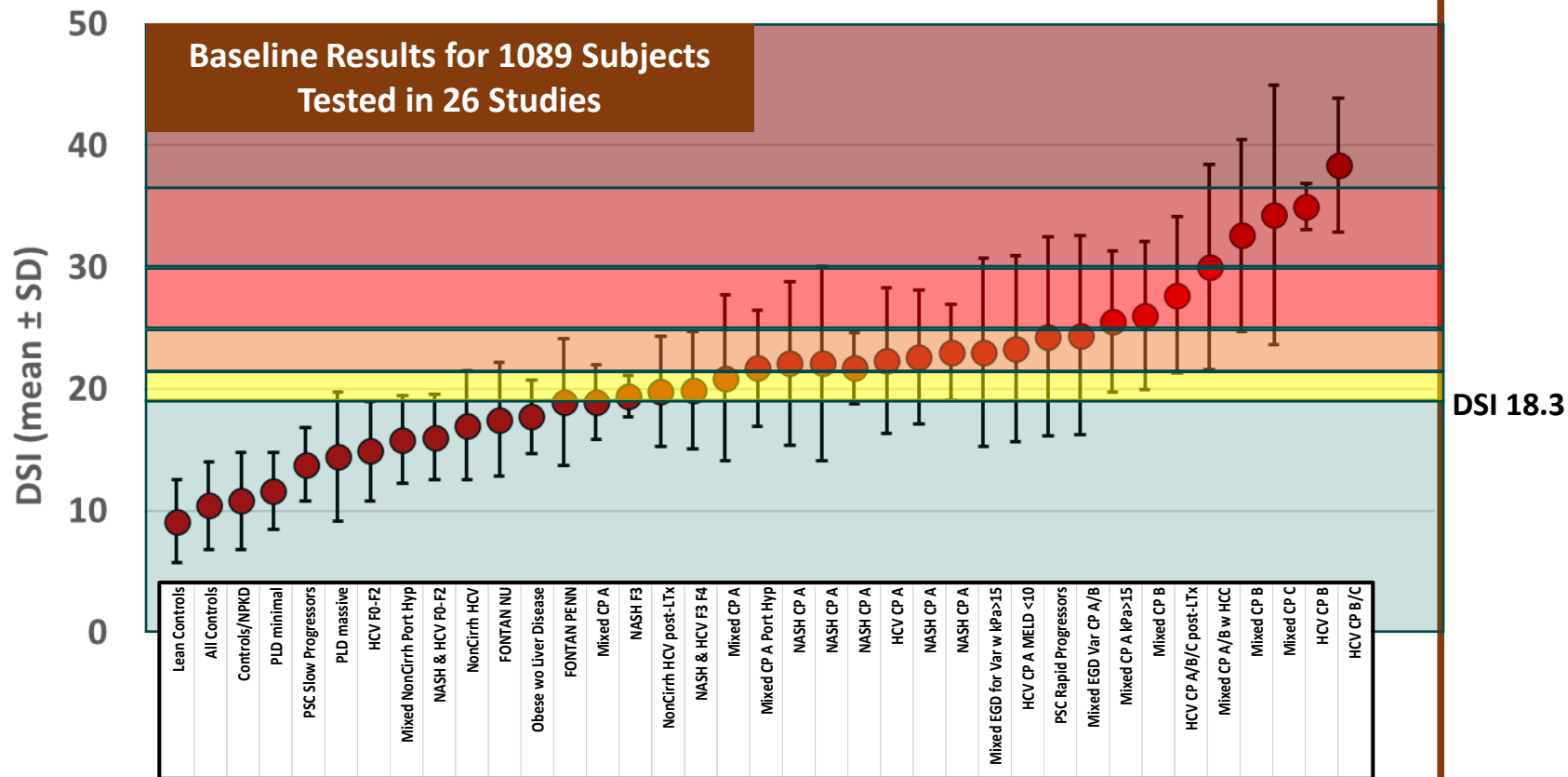
Coefficient of Variability

CPA% $47.3 \pm 4.5\%$ [Zhang, 2021]
Ph-FCS $16.7\% \pm 1.3\%$ [Petitjean, 2023]

CoV not related to cirrhosis severity

DSI Increases as the Severity of Liver Disease Worsens

Baseline Results for 1089 Subjects
Tested in 26 Studies

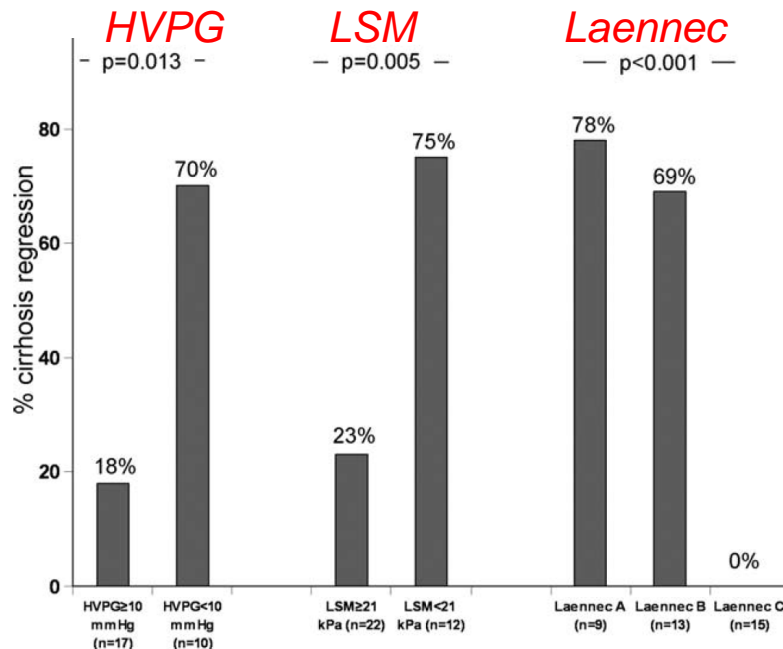


Each Bar / Whisker represents a set or subset of study subjects – spanning most common etiologies and stages of Chronic Liver Disease. (Data on File with HepQuant) – in every clinically-defined set or subset of subjects those with DSI above the mean would be at greater risk for complications or clinical outcome.

Predictors of Cirrhosis Regression post HCV-SVR

Recompensation in
~27% of HCV GT3 after
12 wk SVR (>6000 pts)
in separate cohort

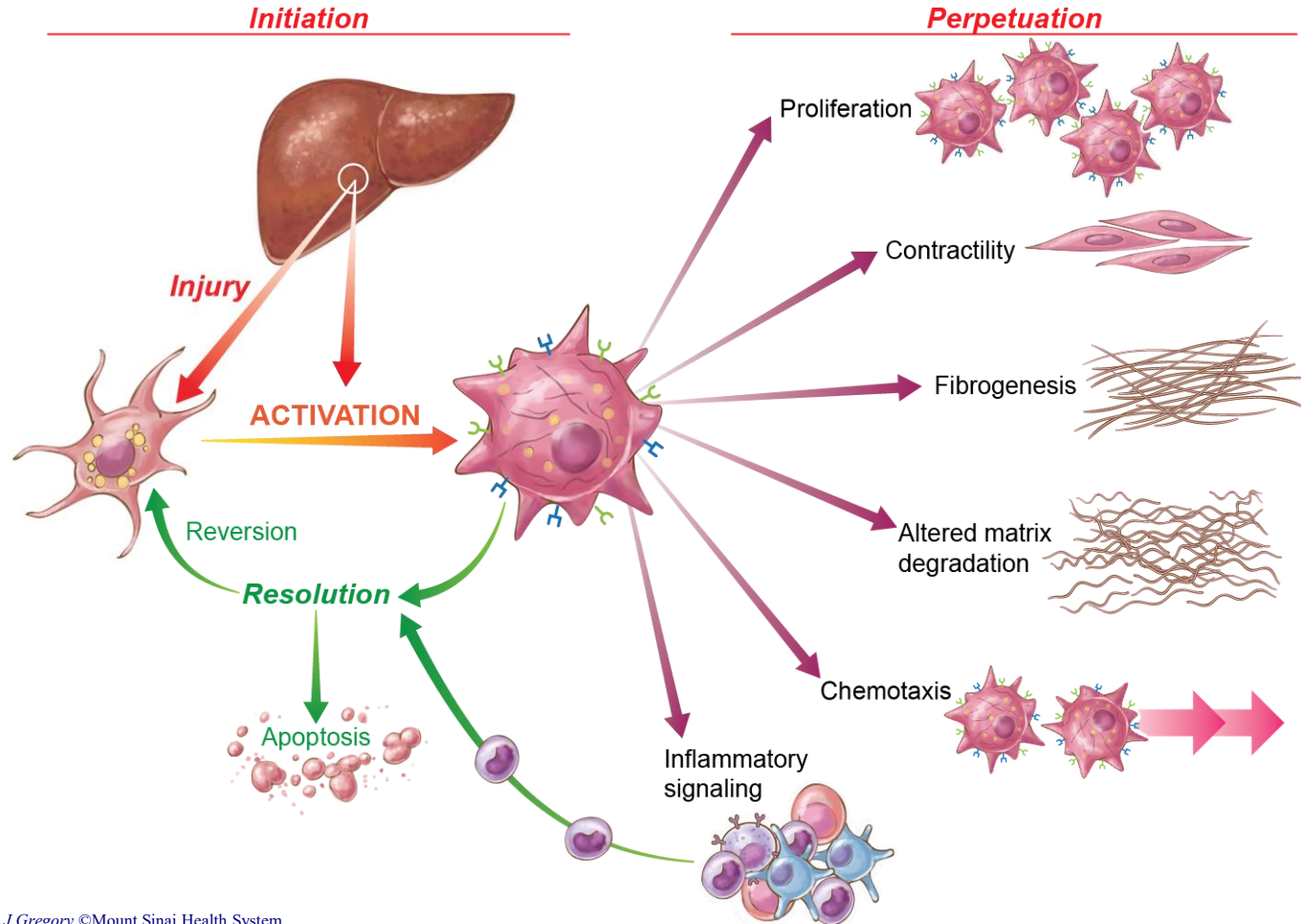
Premkumar, Gastro in press.



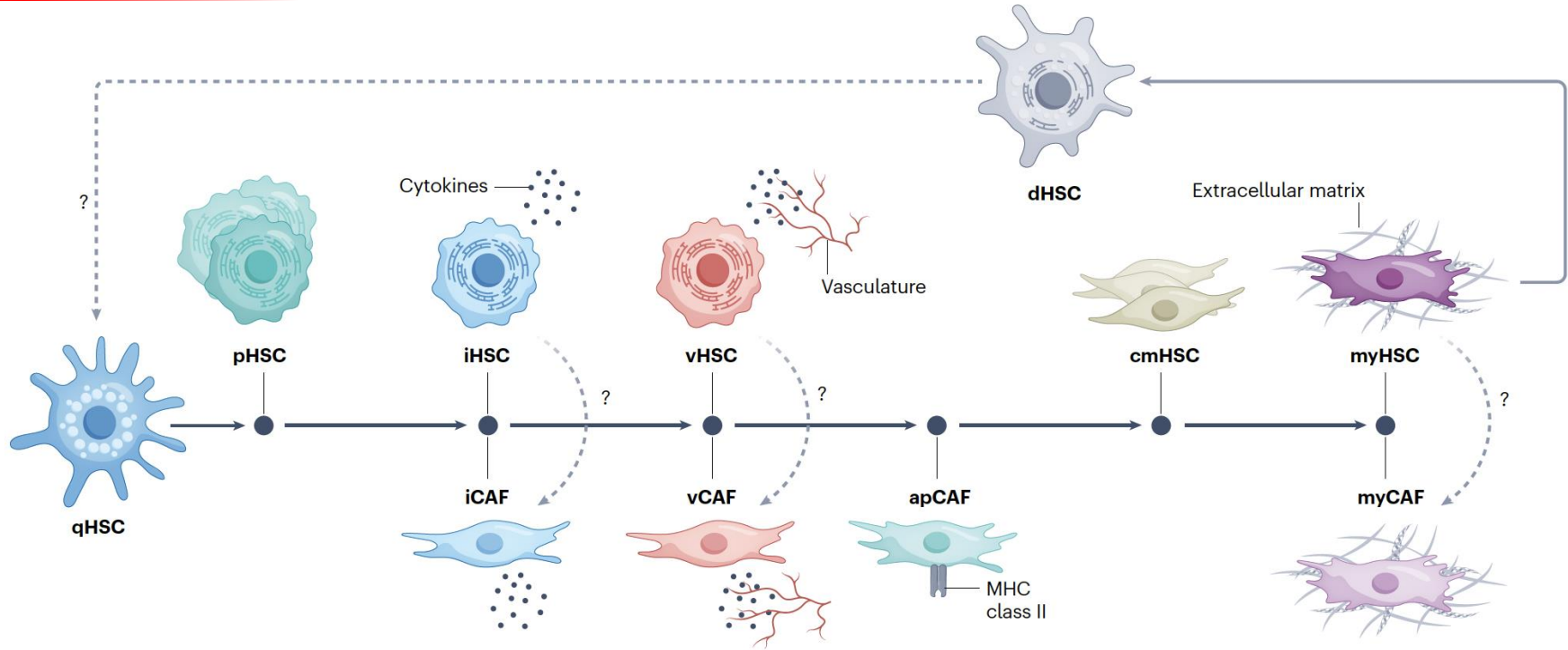
*Is a lack of
regression/recom-
pensation a failure
of regeneration,
loss of matrix
degradation, or
both?*

No patients with HVPG >14mmHg had evidence of regression

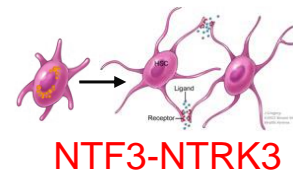
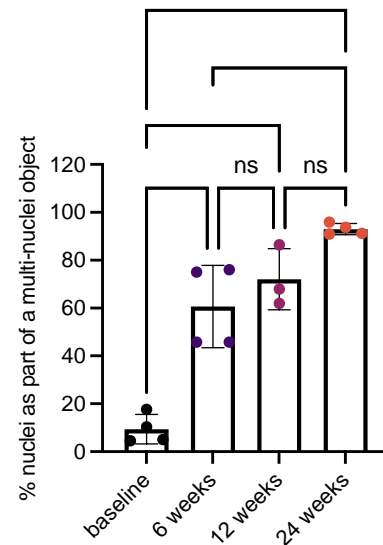
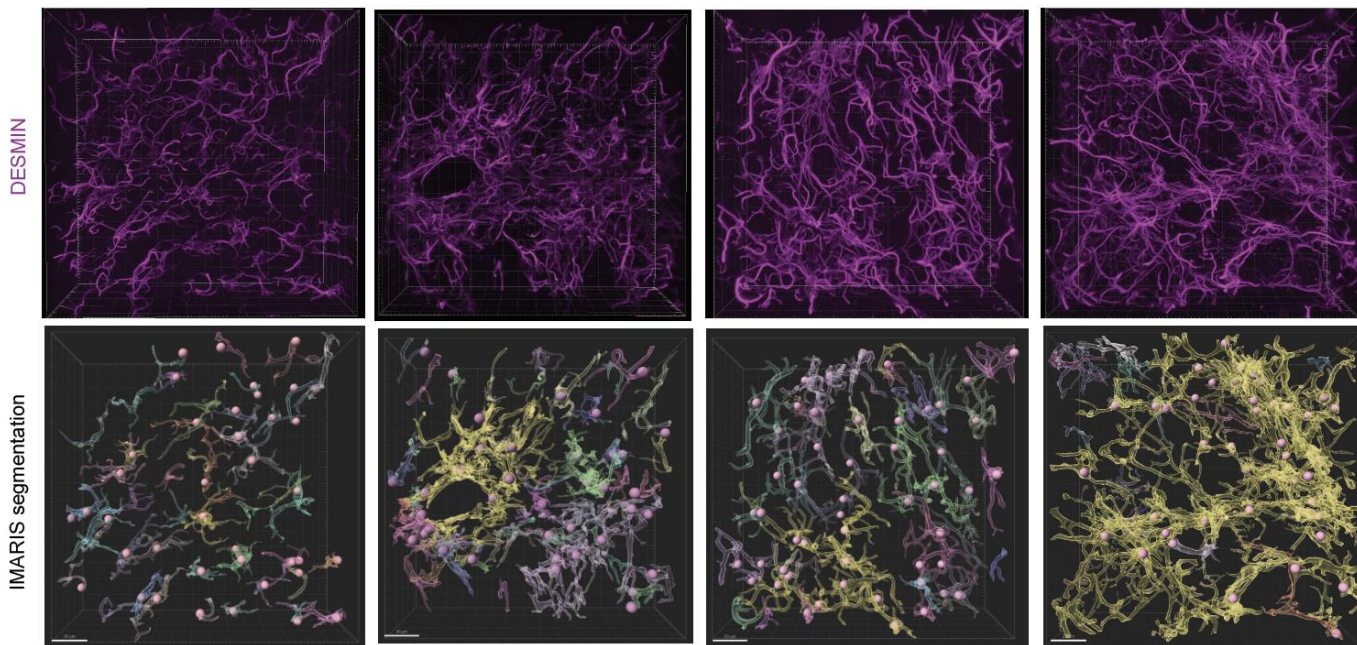
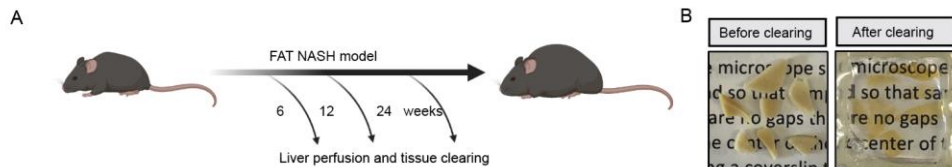
Hepatic Stellate cells in Fibrosis Progression and Regression – *the 2024 Version*



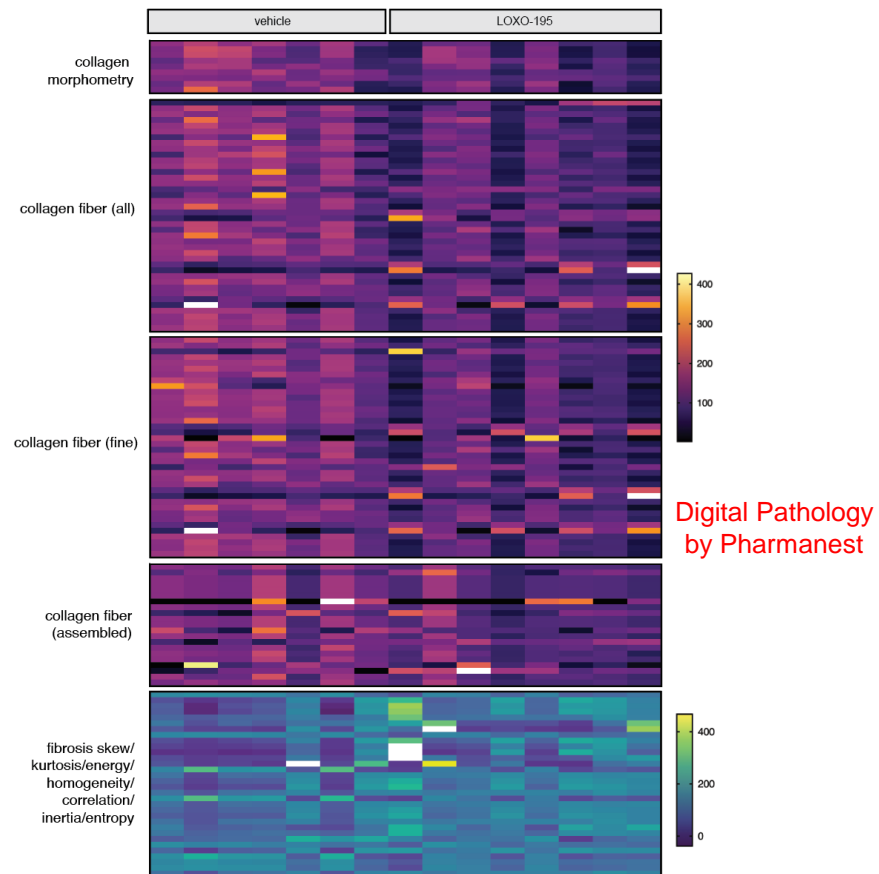
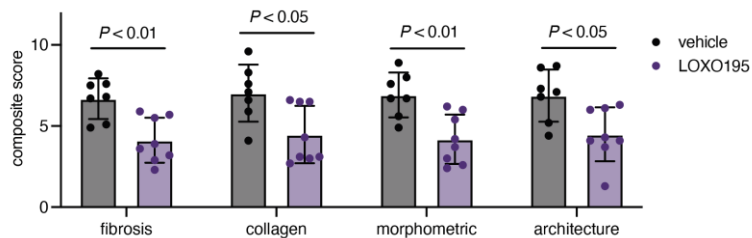
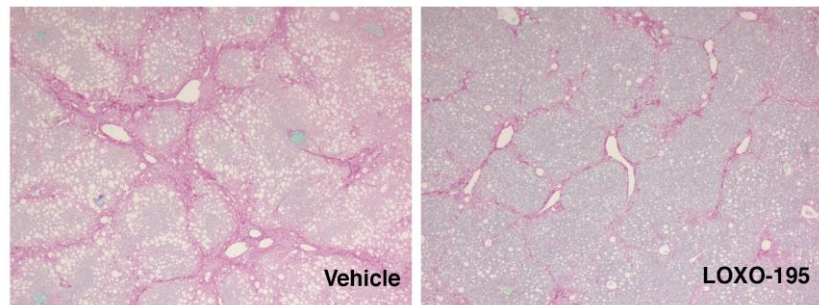
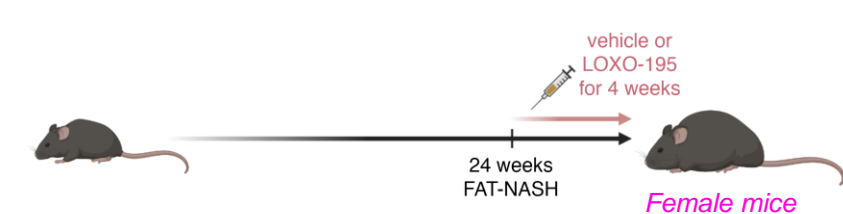
Hepatic Stellate Cell Plasticity; Opposing functions by different stellate cell subsets



Increased HSC cell-cell Contacts in MASH

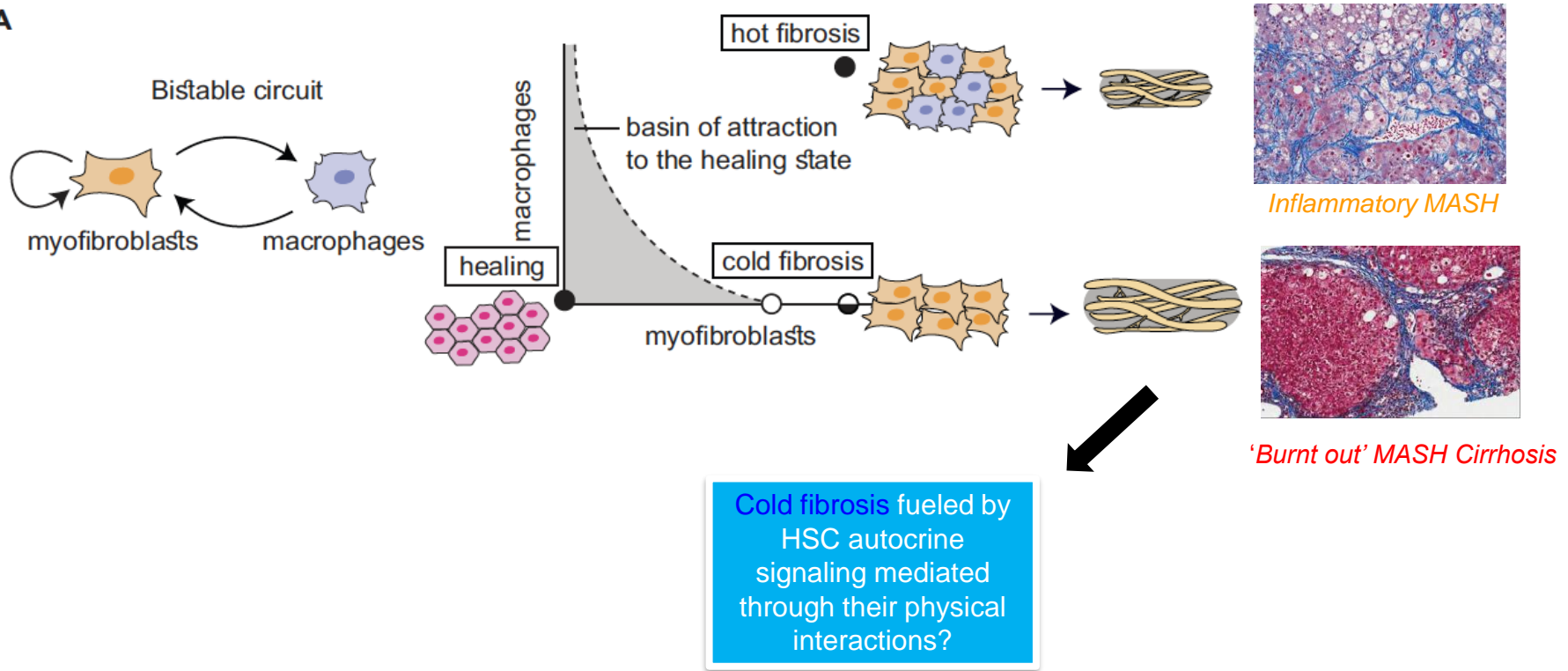


Antagonism of NTRK3, an Autocrine HSC Activation Driver, Reverses Advanced Fibrosis in FAT-NASH mice

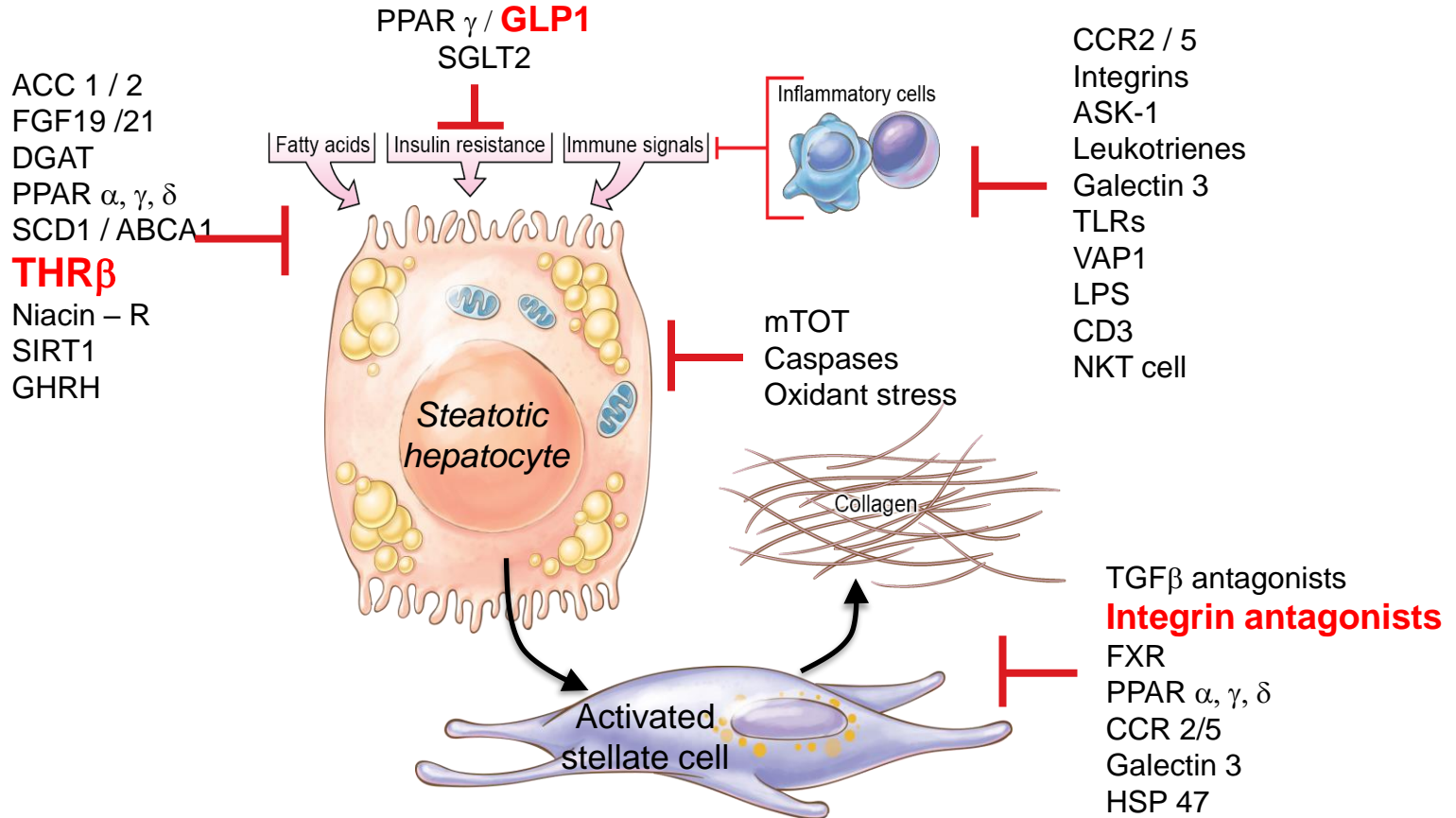


A Cell-circuit Framework for Autocrine Fibrogenic cell Interactions in MASH Fibrosis

A



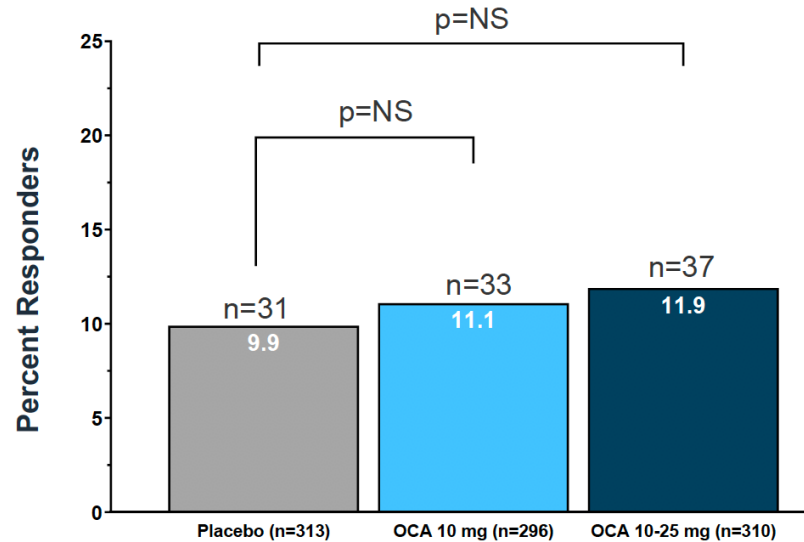
NASH Targets in Phase 2 or Phase 3 Trials



OCA Ineffective for NASH Cirrhosis

REVERSE: Results – Efficacy: Primary Endpoint

Improvement of Fibrosis by ≥ 1 Stage without Worsening of NASH at Month 12-18^{a,b}



NASH, nonalcoholic steatohepatitis; NS, not statistically significant; OCA, obeticholic acid

^aITT, intent to treat population (N=931)

^bNo worsening of NASH defined as no increase of hepatocellular ballooning, lobular inflammation, or steatosis

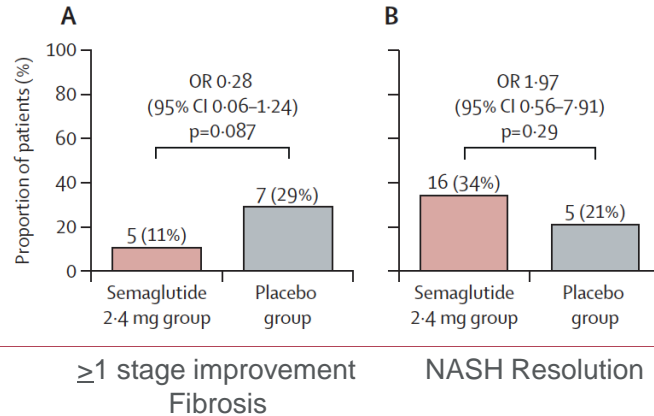
1. Intercept Pharmaceuticals [press release]. Sept 2022.

Semaglutide Ineffective for NASH Cirrhosis

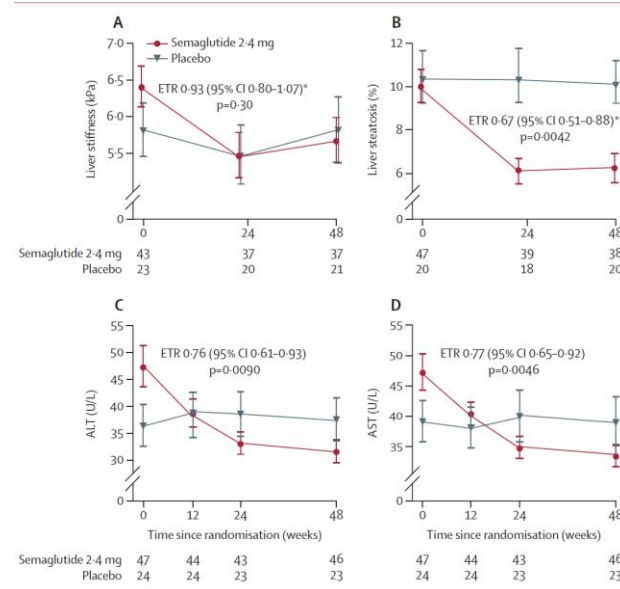
n=71

n=47 Semaglutide

n=24 Placebo



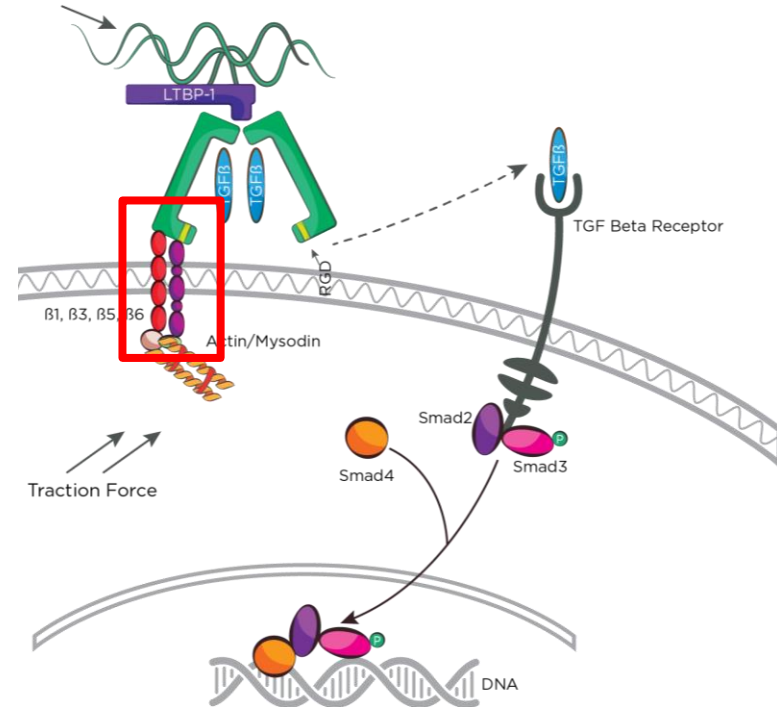
9% weight loss in Semaglutide group



Activation of TGF- β by Integrins Drives Fibrogenesis

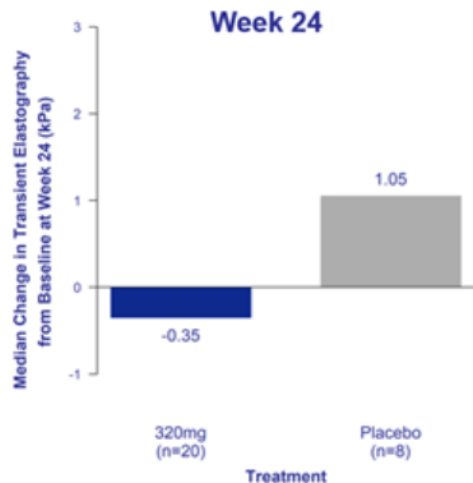
- TGF- β is a key driver of fibrogenesis
- α_V integrins convert latent TGF- β into its active form, resulting in profibrotic gene expression
 - Epithelial cells ($\alpha_V\beta_6$)
 - Fibroblasts ($\alpha_V\beta_1$)
- Dual inhibition of $\alpha_V\beta_6$ and $\alpha_V\beta_1$ are a targeted approach for blocking TGF- β activity

α_V Integrins promote fibrosis through activation of TGF- β

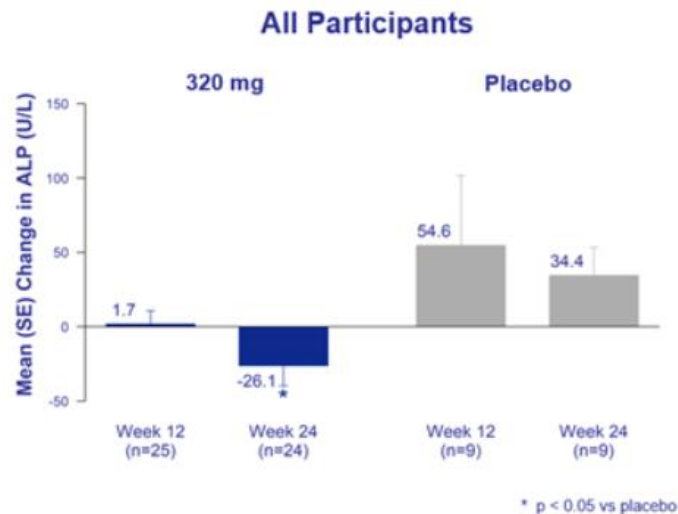


Moving Closer to a Pure Antifibrotic- *An Integrin Antagonist is Promising in Primary Sclerosing Cholangitis*

*Liver Stiffness –
Change from Baseline*



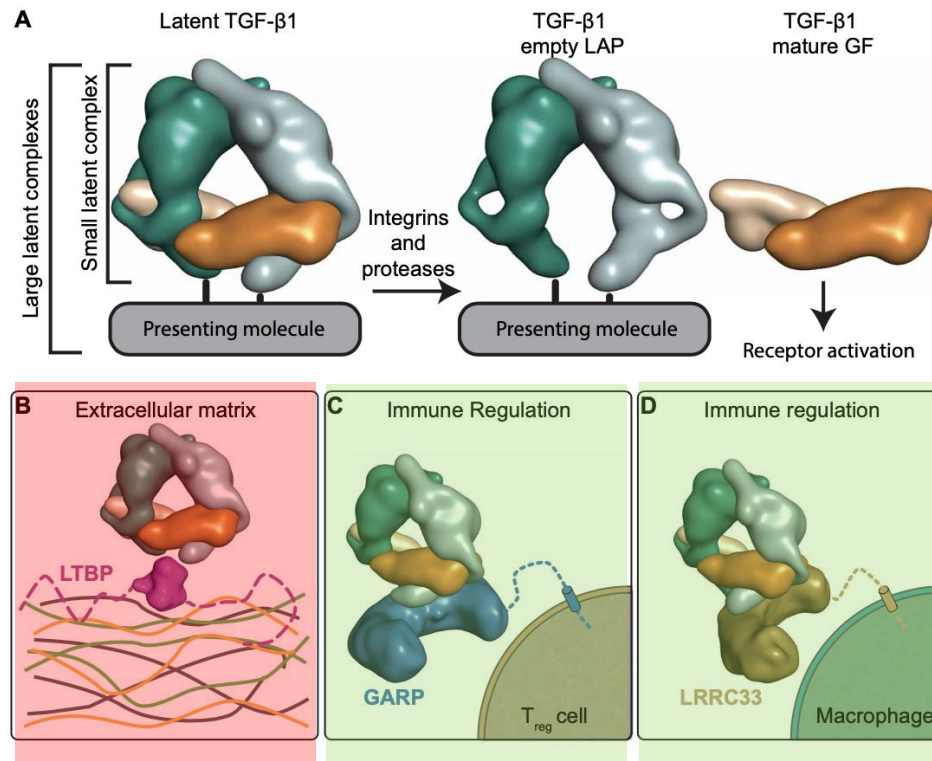
Alkaline Phosphatase



PLIANT
THERAPEUTICS

Press Release, July 15, 2024

Selective Inhibition of LTBP-Bound TGF β 1 is Anti-fibrotic but Avoids the Liabilities of Systemic TGF β 1 Inhibition



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