

Mechanisms and therapeutic developments in liver fibrosis

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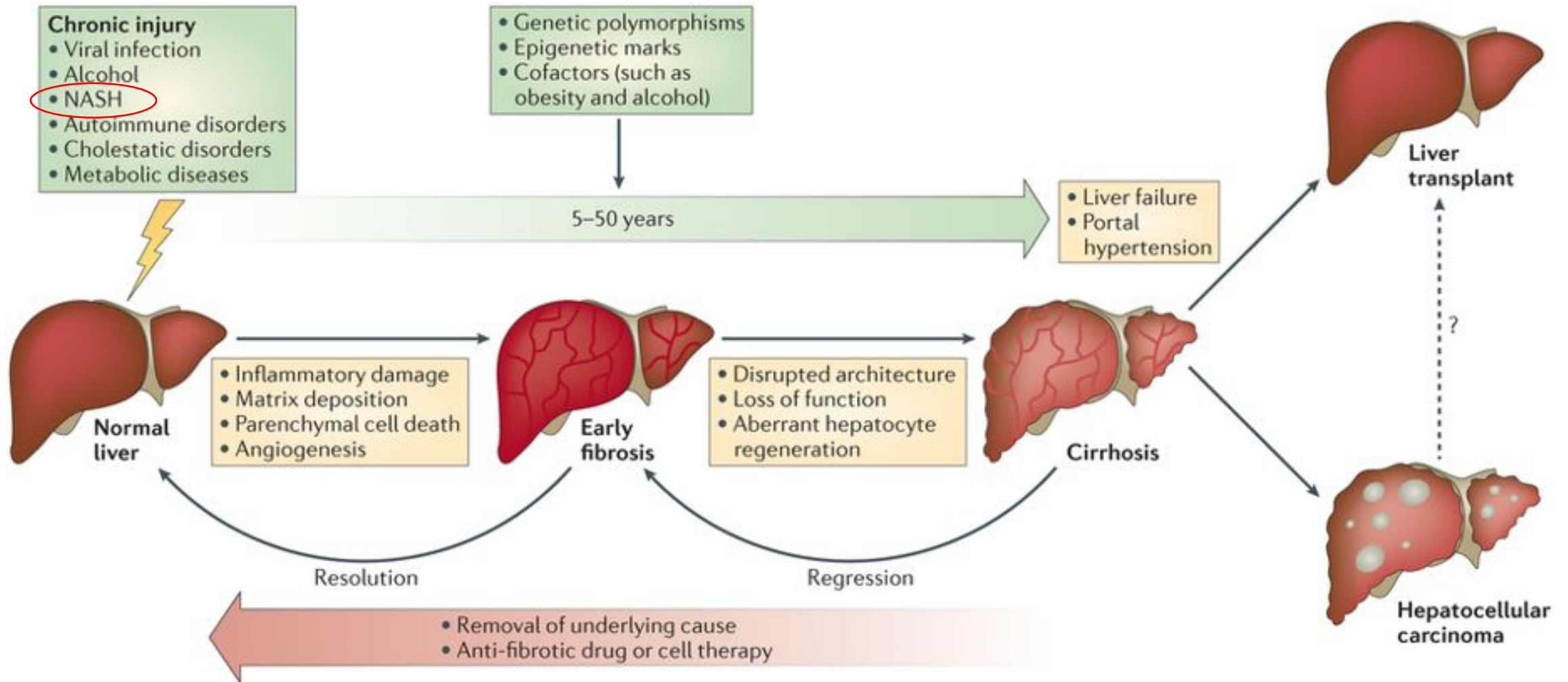
DISCLOSURES

I am a Founder, Director, CSO and major shareholder of the pre-clinical CRO FibroFind Ltd

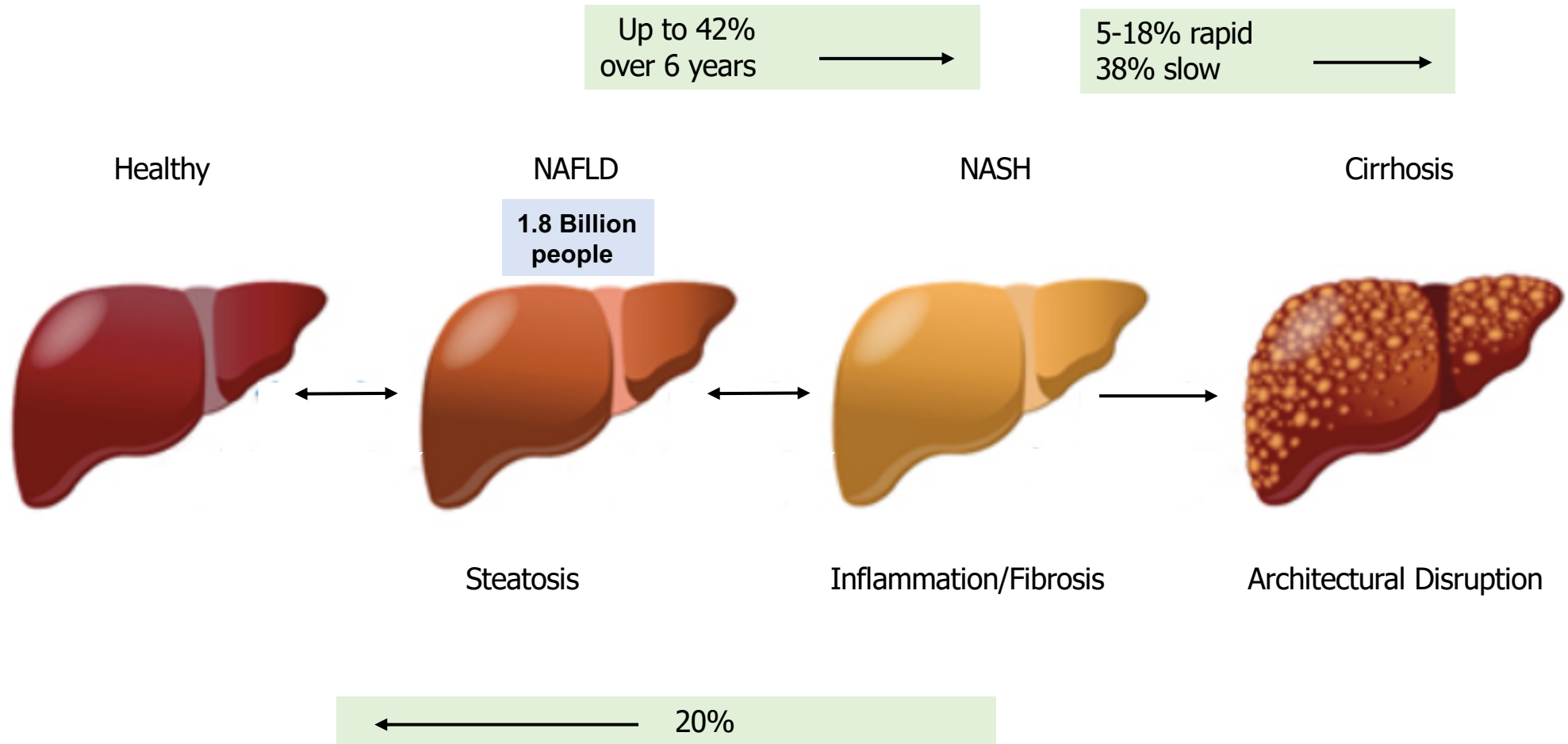
I am a member of the scientific advisory board of Galectin Therapeutics

I am in receipt of research grant funding from GSK

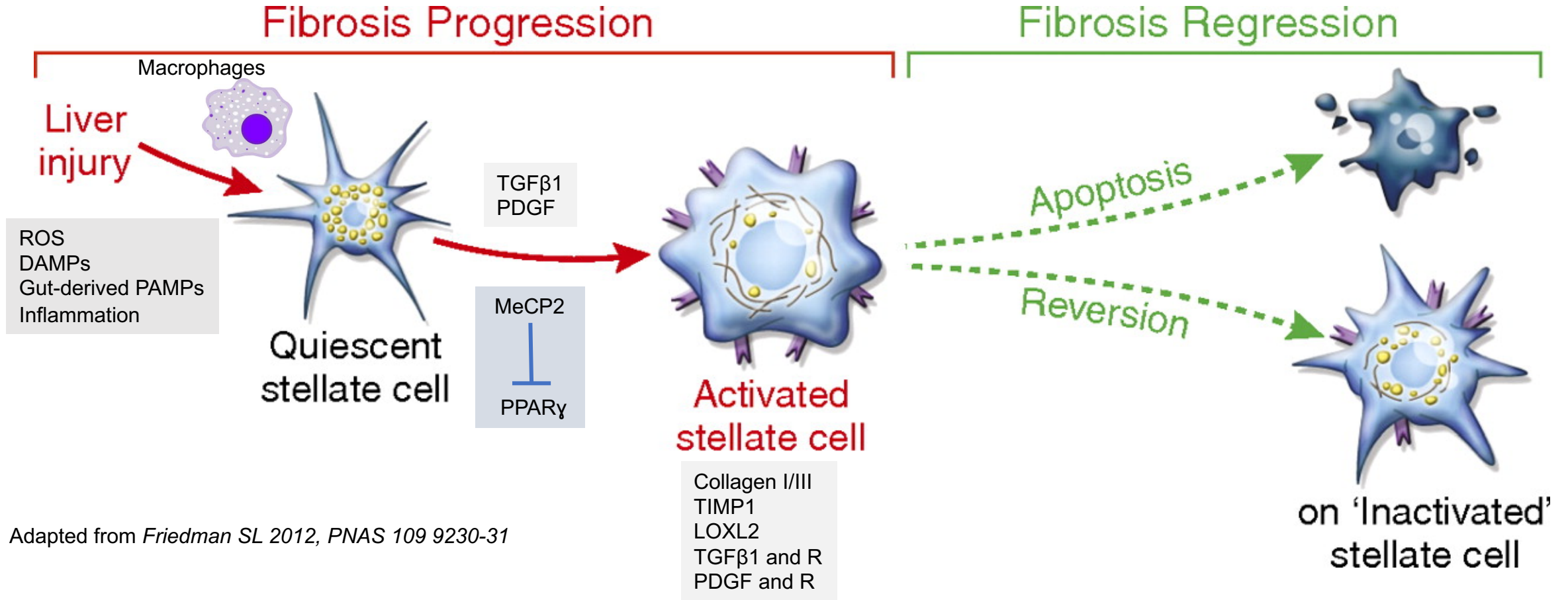
Natural history of chronic liver disease



Variable Progression of Non-Alcoholic Fatty Liver Disease



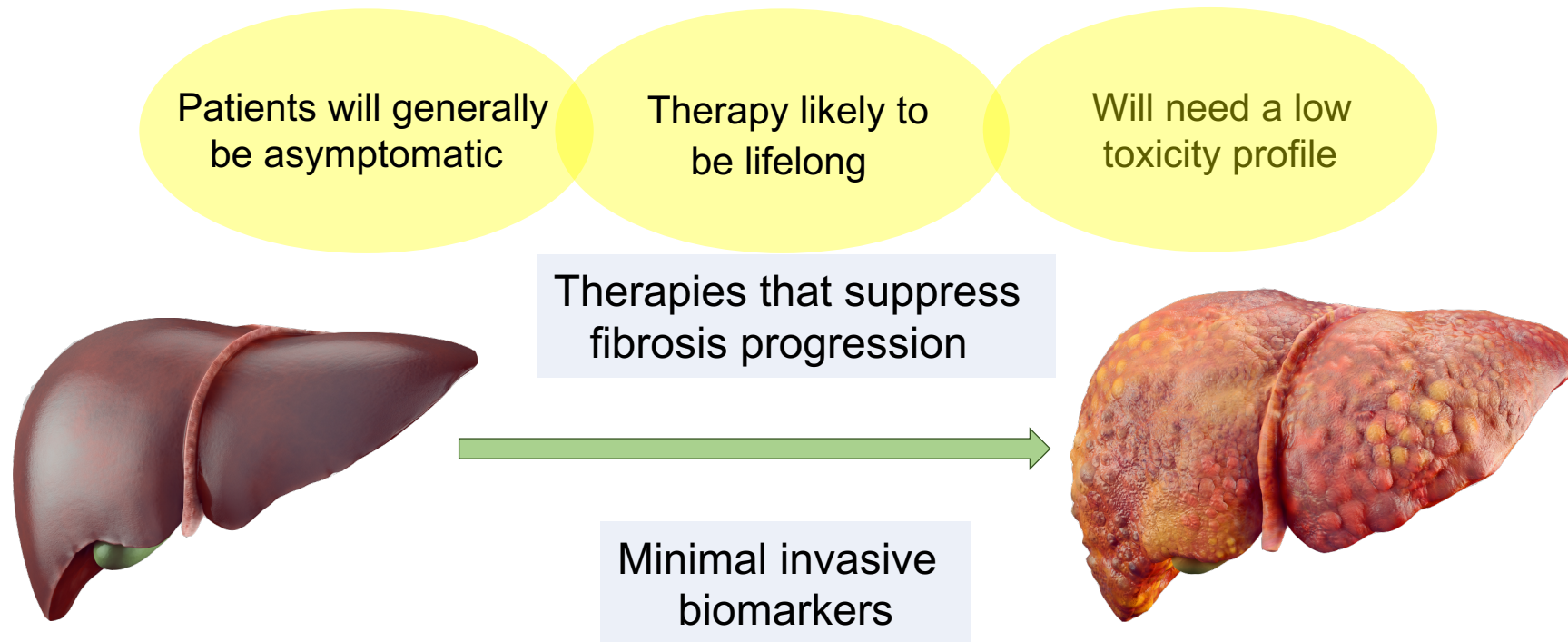
Hepatic stellate cells are the major source of collagen



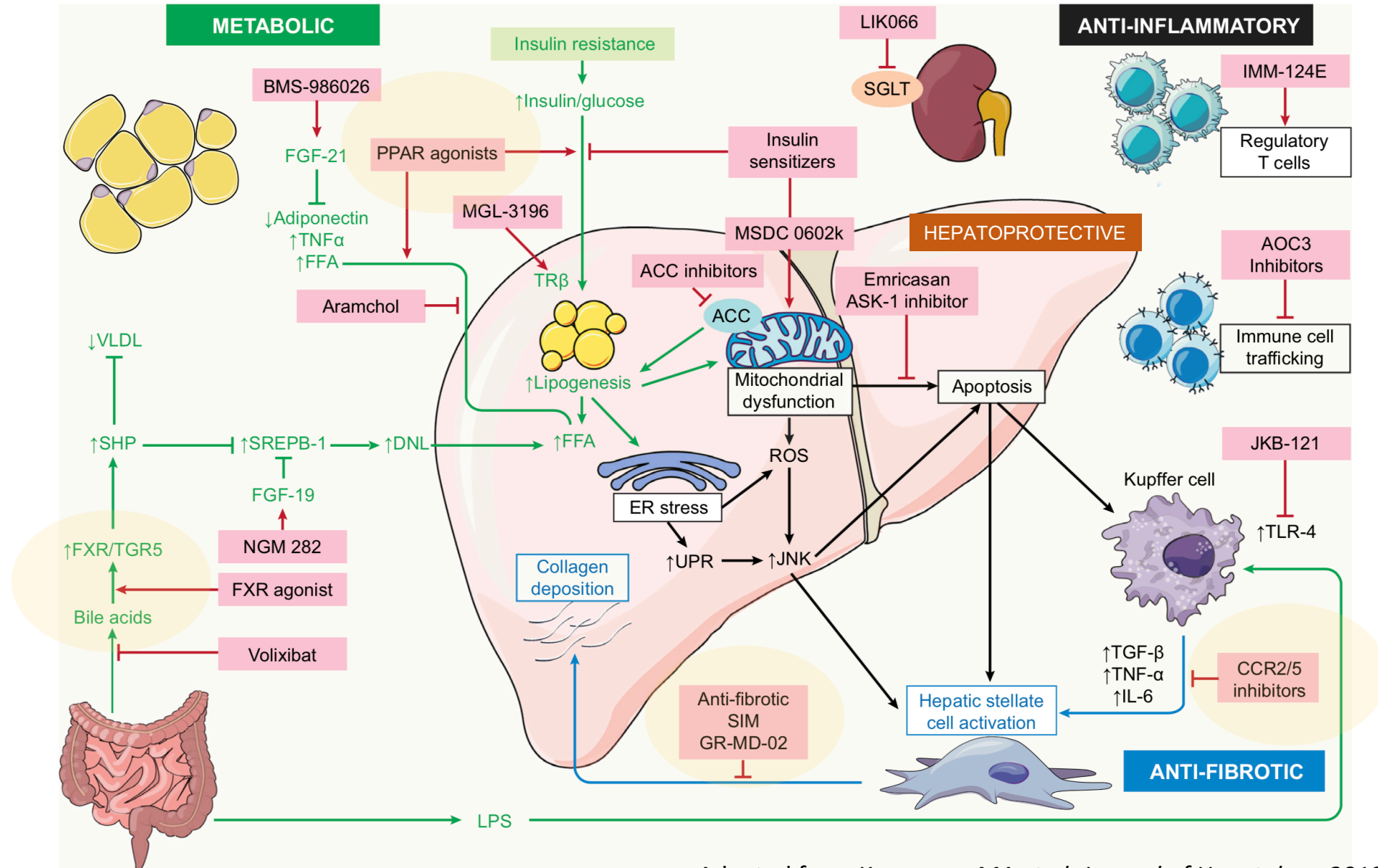
Adapted from Friedman SL 2012, PNAS 109 9230-31

Fibrogenesis in the liver is highly dynamic and even in advanced disease waxes and wanes

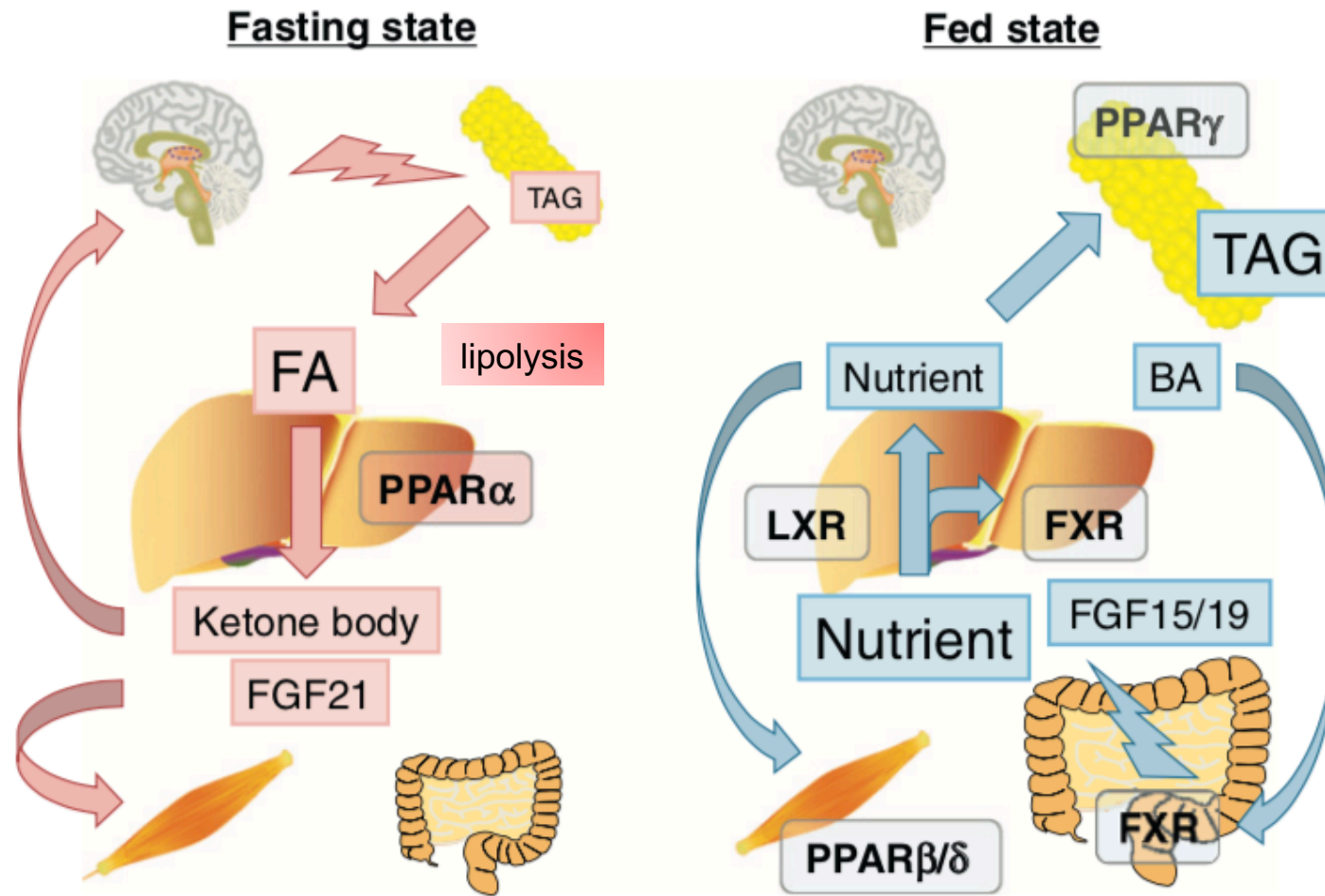
The clinical imperatives



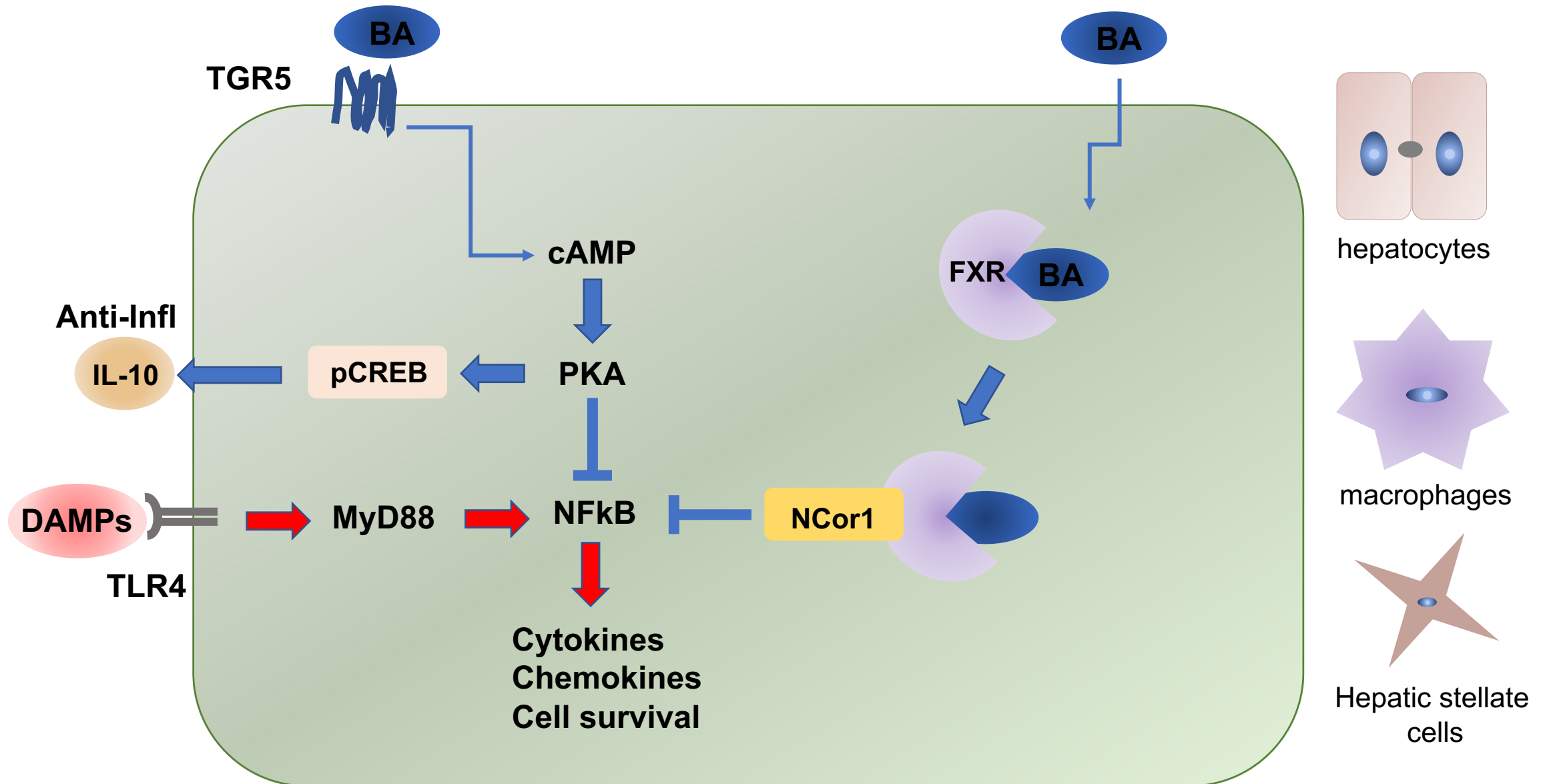
Current Landscape of Clinical Trials in NAFLD



Nuclear Receptors as “energy vectors” in the liver

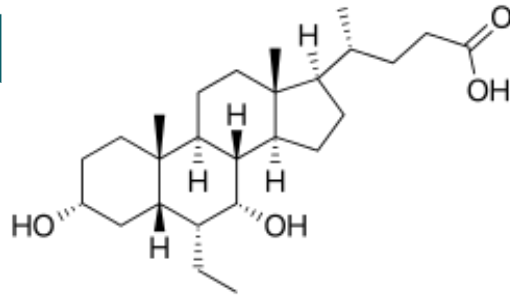


Bile acid agonists of receptors TGR5 and FXR



FXR Agonist obeticholic acid (OCA) – a promising anti-fibrotic

Intercept



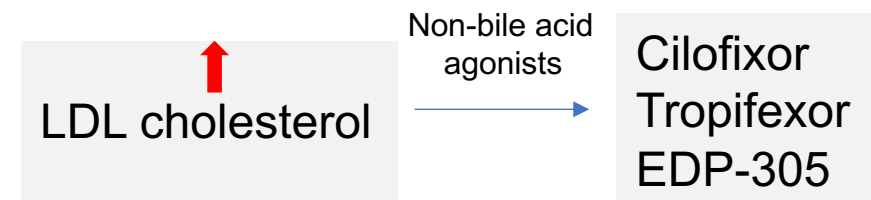
Semi-synthetic bile acid analog
Used in treatment of primary biliary cholangitis (PBC)

REGENERATE – Phase 3 study in NASH with stage 2 or 3 liver fibrosis

Primary Efficacy Analysis (ITT population: NASH with stage 2 and 3 liver fibrosis)	Placebo n=311	OCA 10 mg n=312	OCA 25 mg n=308
Fibrosis improvement (≥ 1 stage) with no worsening of NASH*	11.9%	17.6% p=0.0446	23.1% p=0.0002**
Mild to moderate puritis	19%.	28%.	51%

18 months

Repeat biopsy for histological end-point

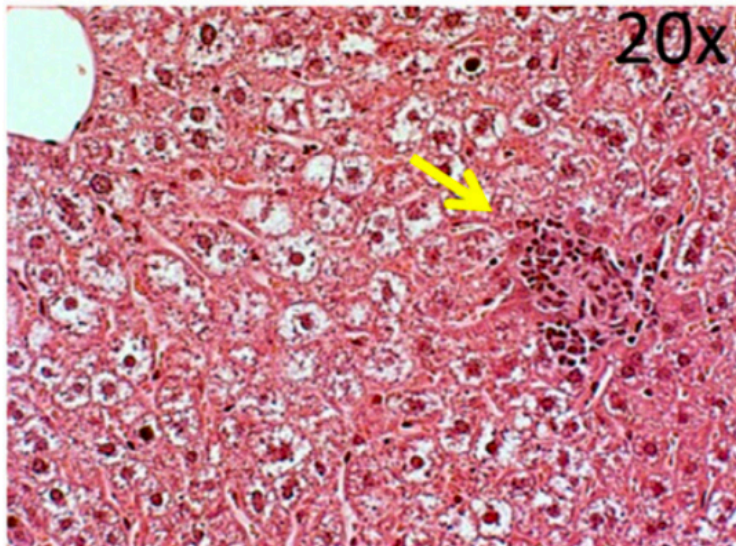


Awaiting FDA approval

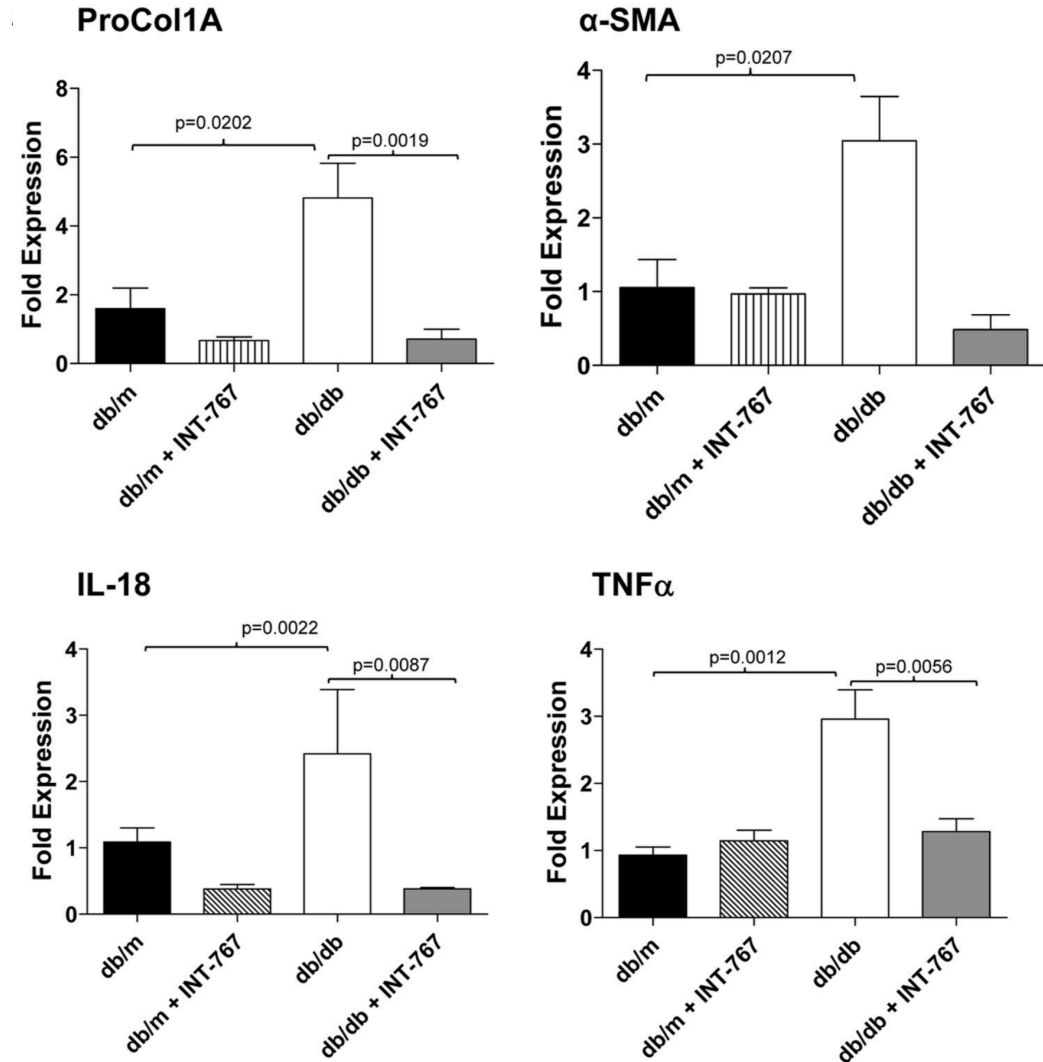
INT-767 a dual FXR/TGR5 agonist ameliorates NASH and fibrosis



db/db leptin-receptor deficient obese mouse

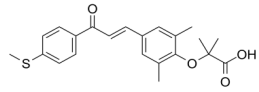


Phase 1 clinical trial completed



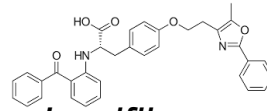
Anti-inflamm

Multicellular functions of the PPARs



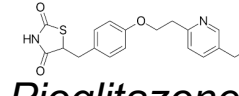
Elafibrinor

PPAR α/β agonist



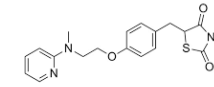
Lanifibranor

PPAR $\alpha/\delta/\gamma$ agonist



Pioglitazone

PPAR γ agonist

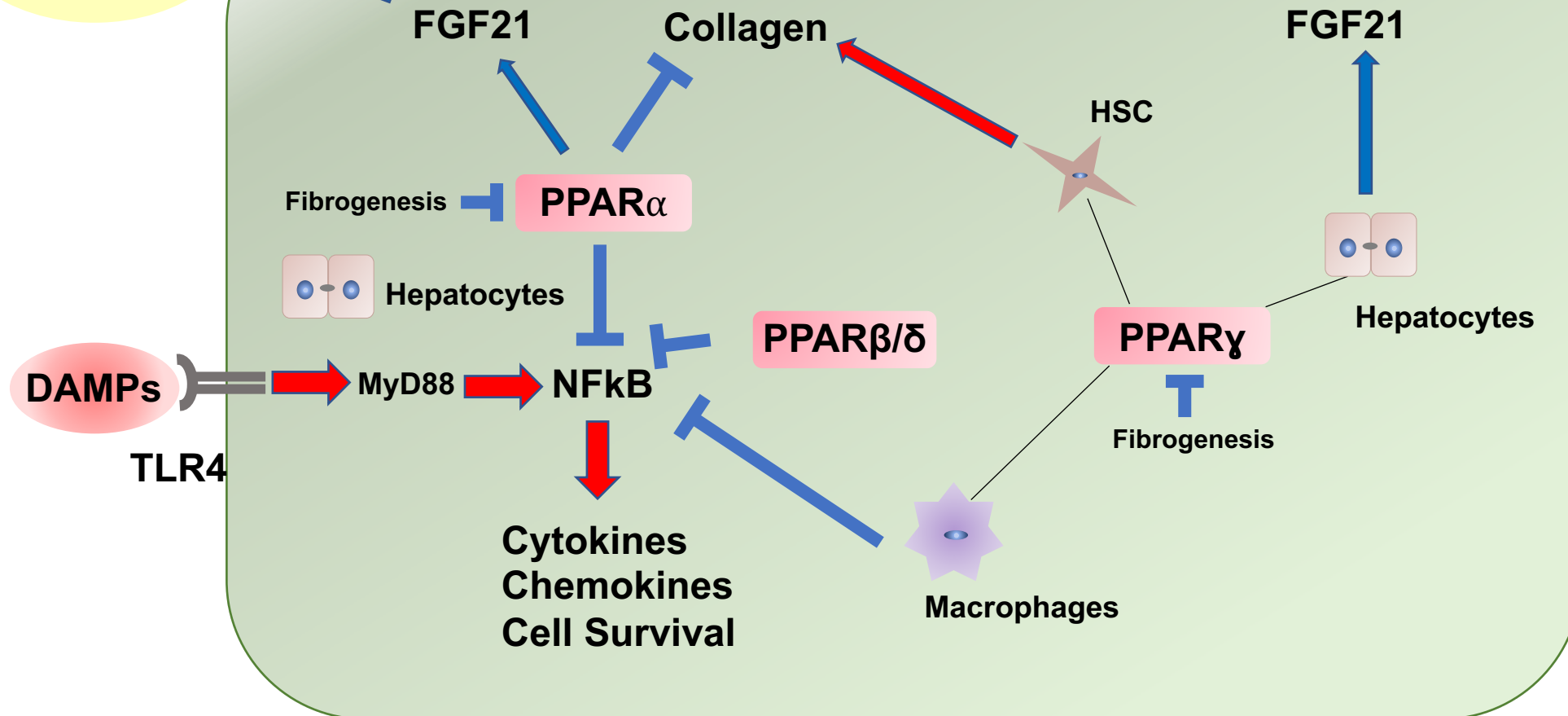


Rosiglitazone

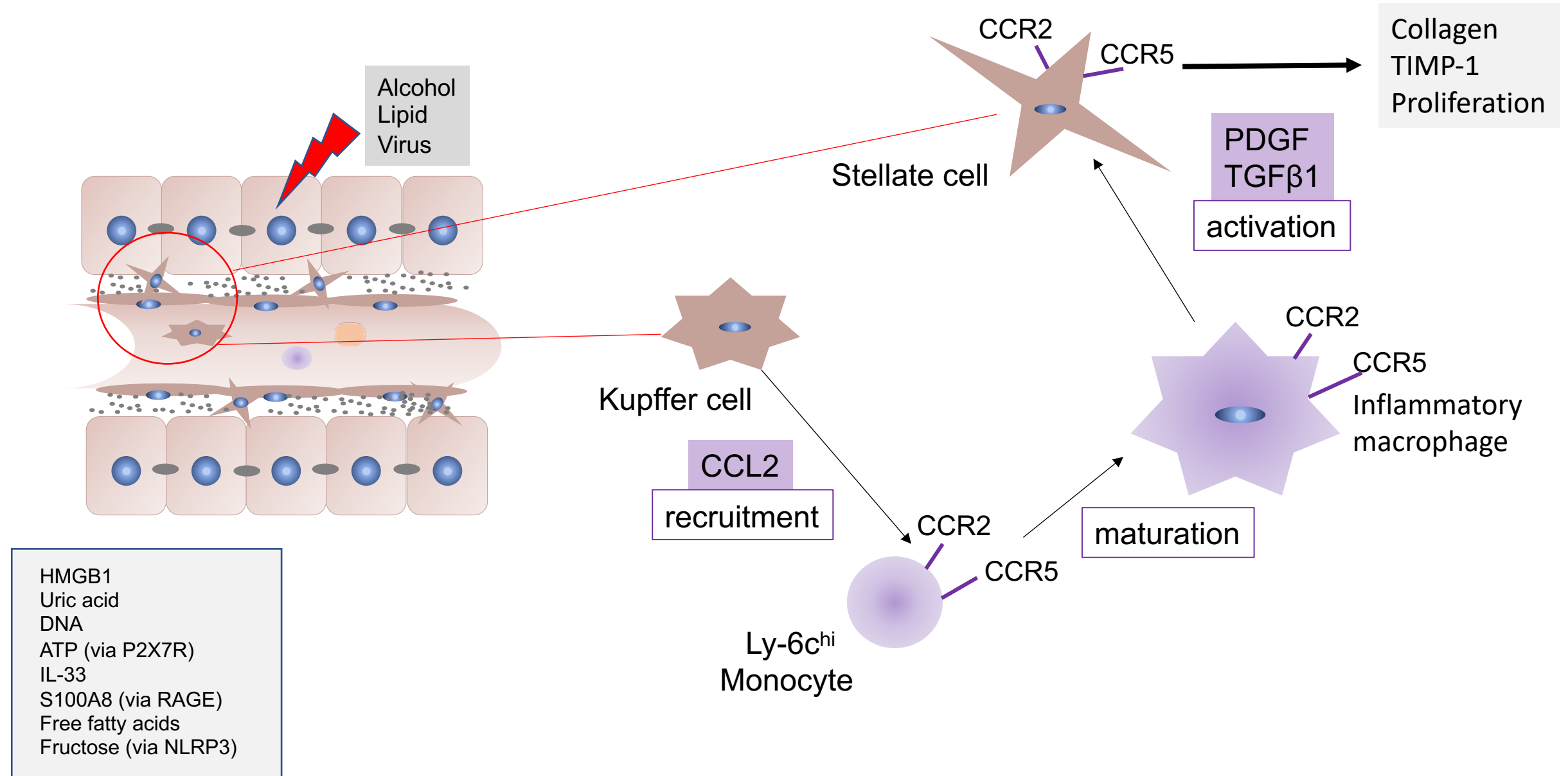
PPAR γ agonist

Hepatoprotective
Insulin sensitivity
Anti-oxidant

Hepatoprotective
Insulin sensitivity
Anti-oxidant



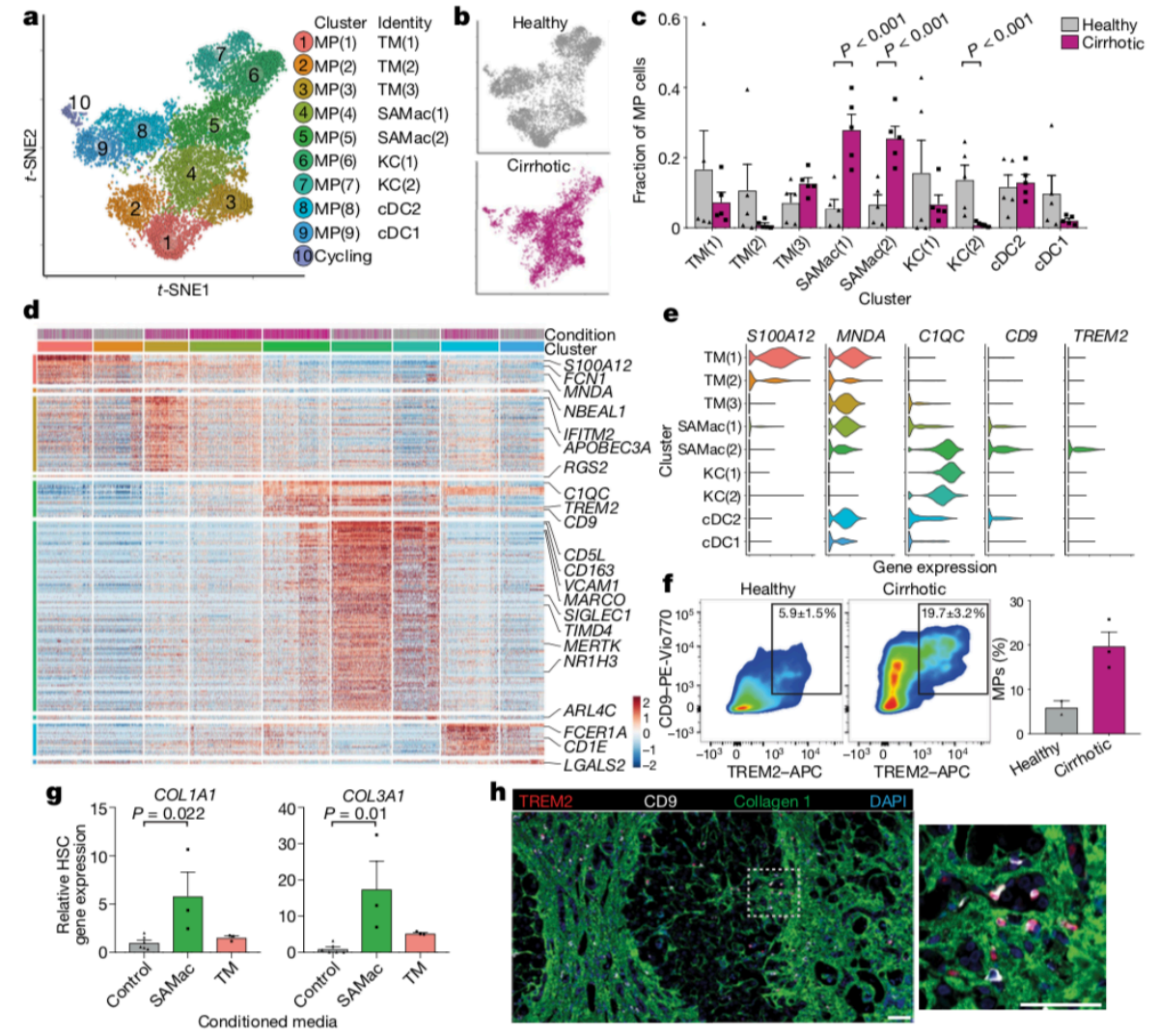
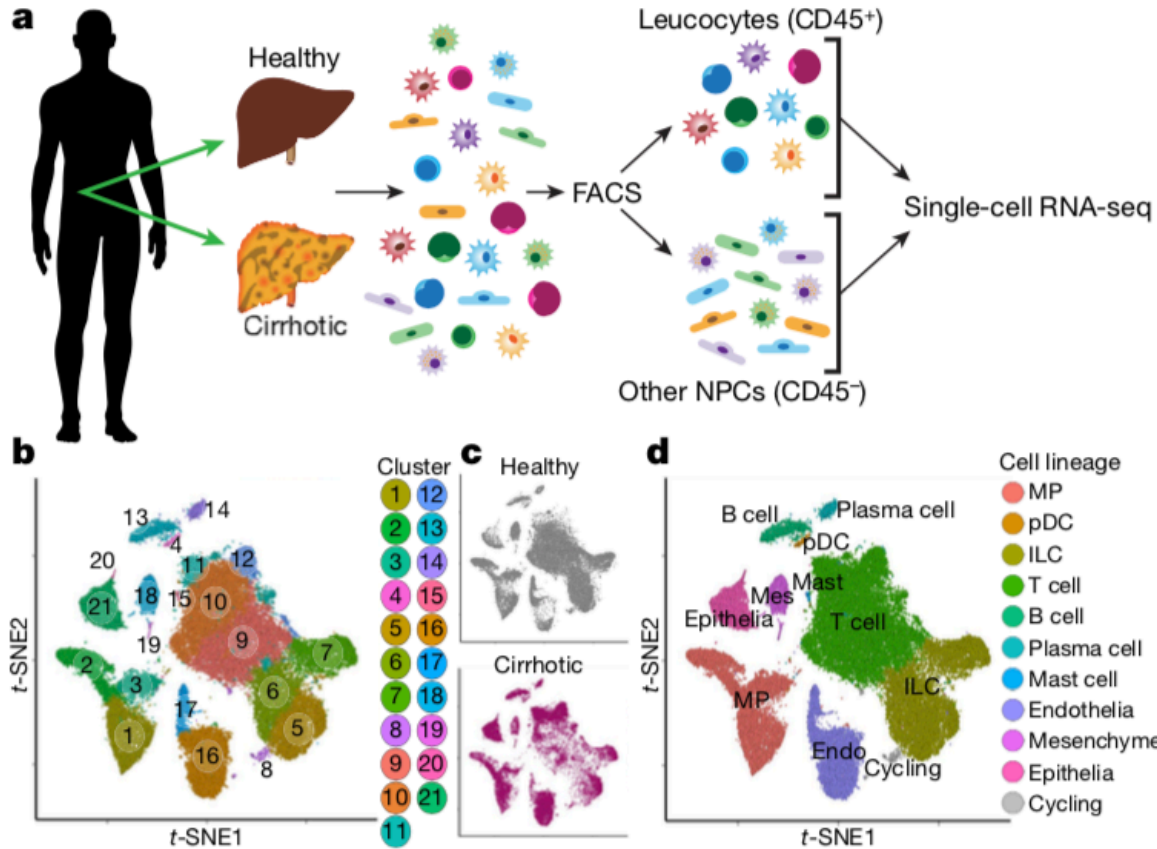
Myeloid inflammatory cross-talk in liver fibrosis





Distinct macrophage phenotypes in the fibrotic niche

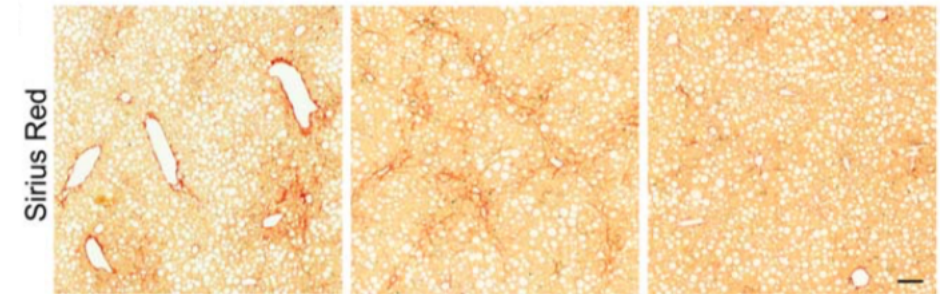
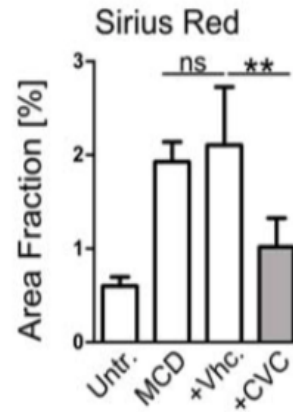
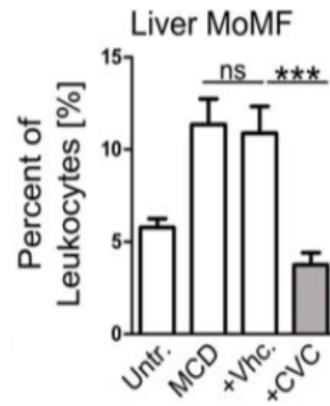
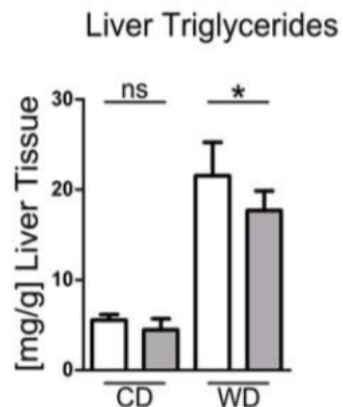
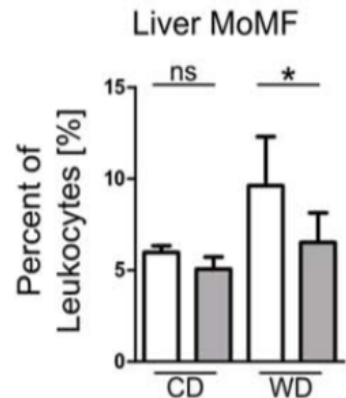
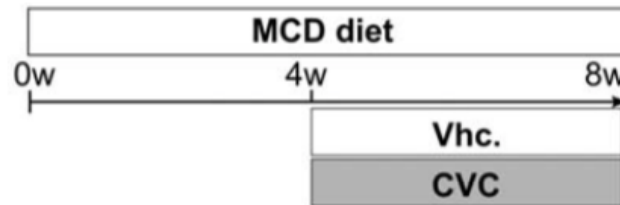
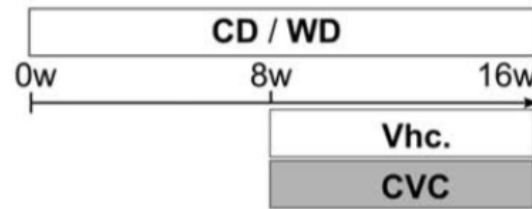
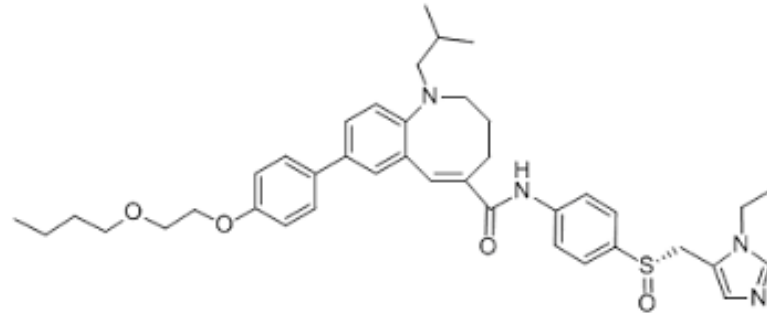
Neil Henderson



SAMac = Monocyte-derived *TREM2*⁺, *IL1B*⁺, *SPP1*⁺, *LGALS3*⁺, *CCR2*⁺, *TNFSF12*⁺

Ramachandran P et al, Nature Oct 2019

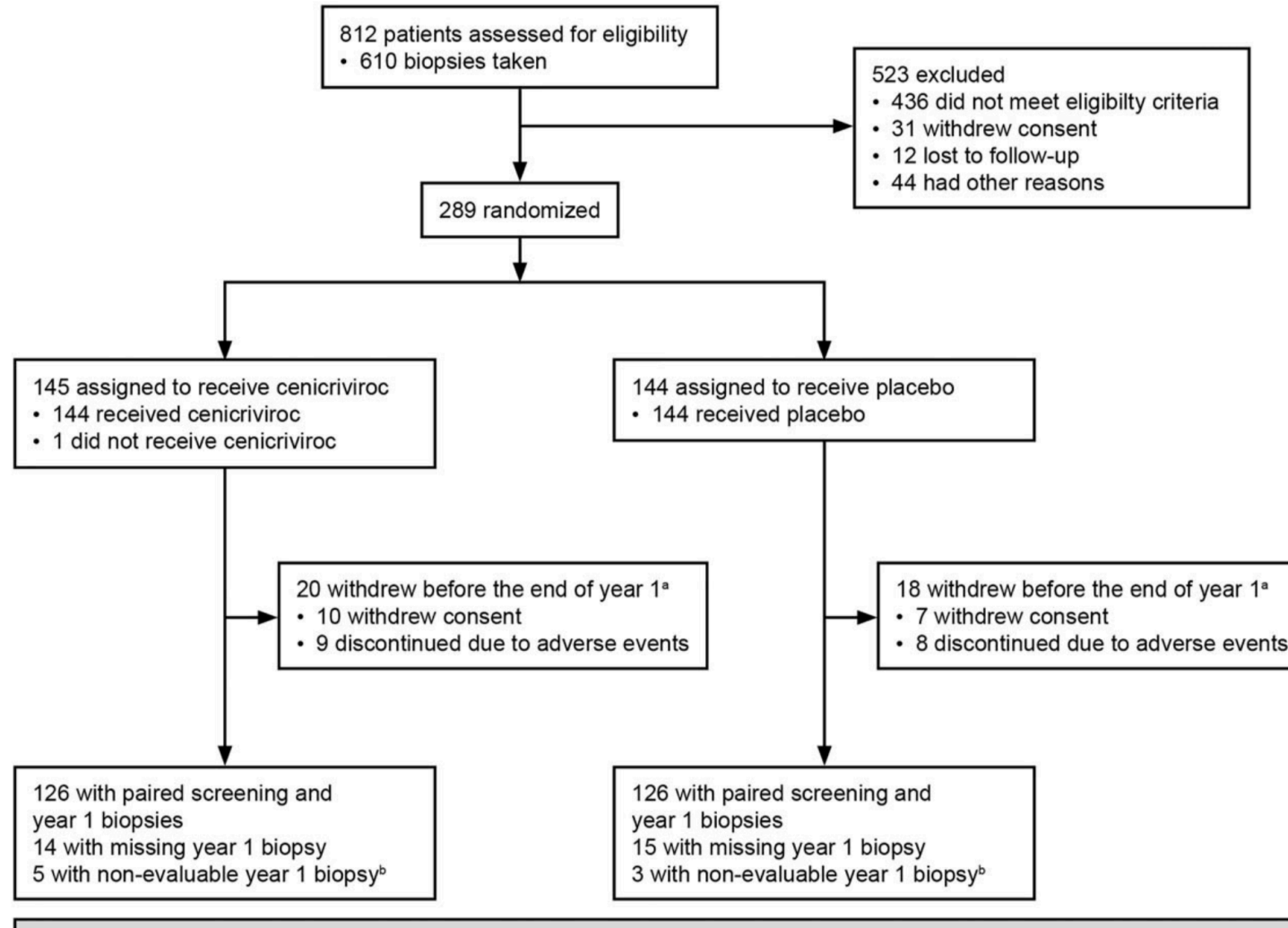
Ceniciviroc (CVC): an oral CCR2/CCR5 inhibitor



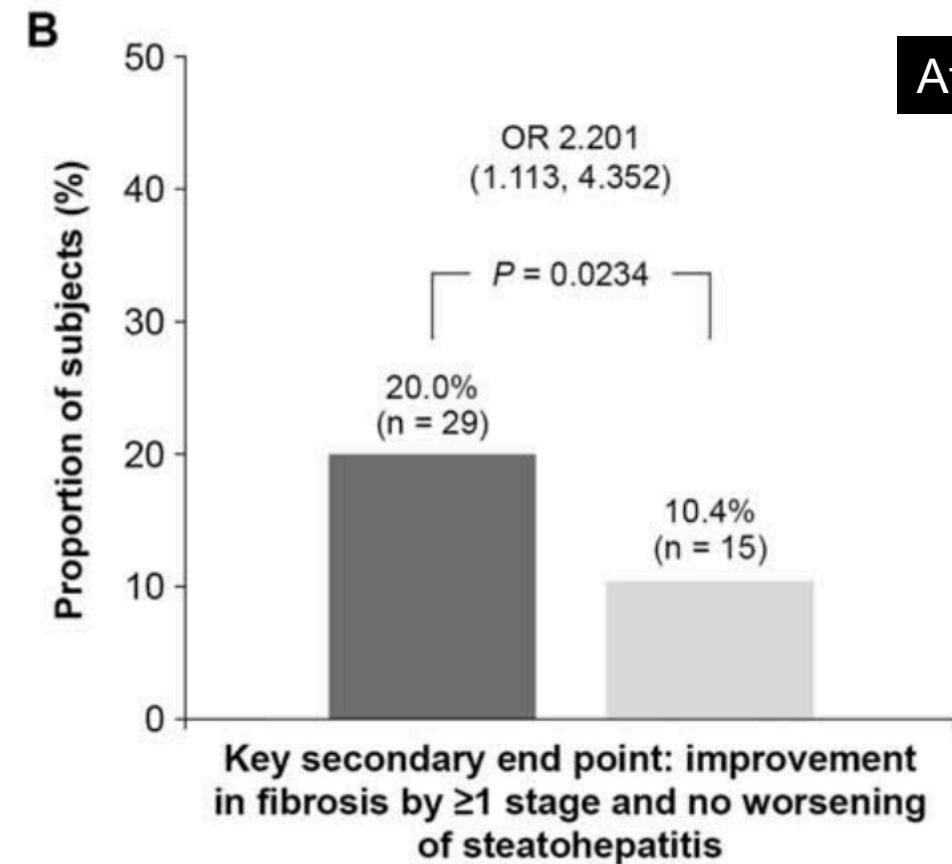
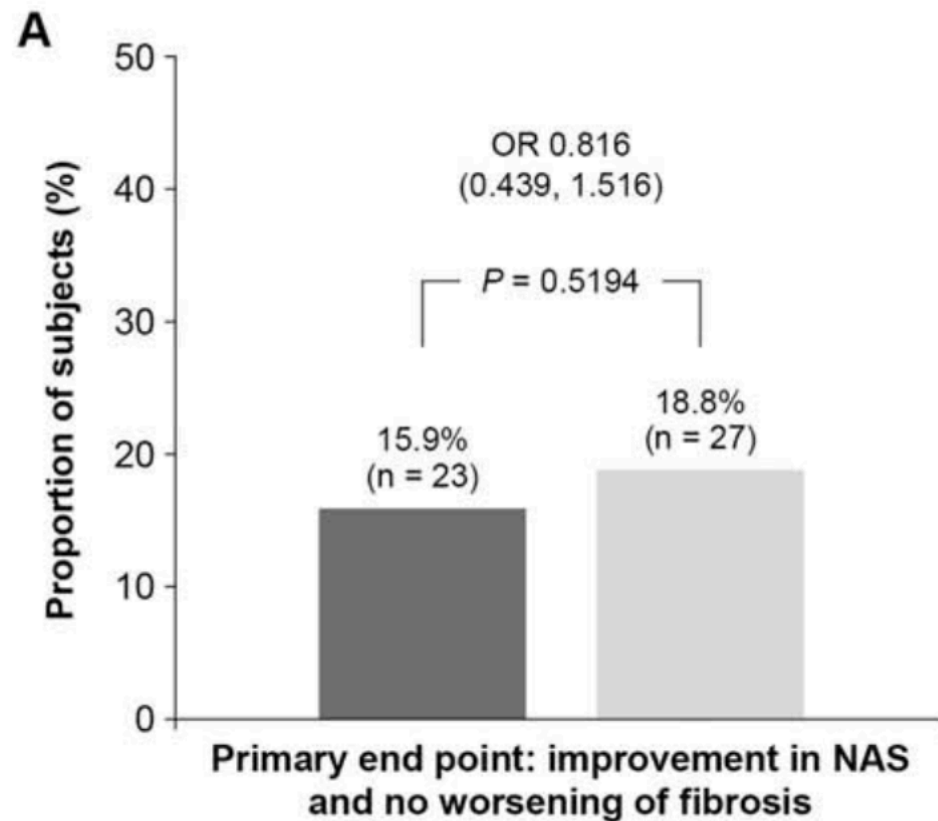


Scott Friedman

CENTAUR: phase 2 testing efficacy of CVC in NASH



CVC achieves significant anti-fibrotic benefit compared with placebo



At 1 year

Frequency of adverse events (fatigue, headache, diarrhea) similar between treatment and placebo

10 patients on CVC and 5 on placebo achieved full resolution of fibrosis

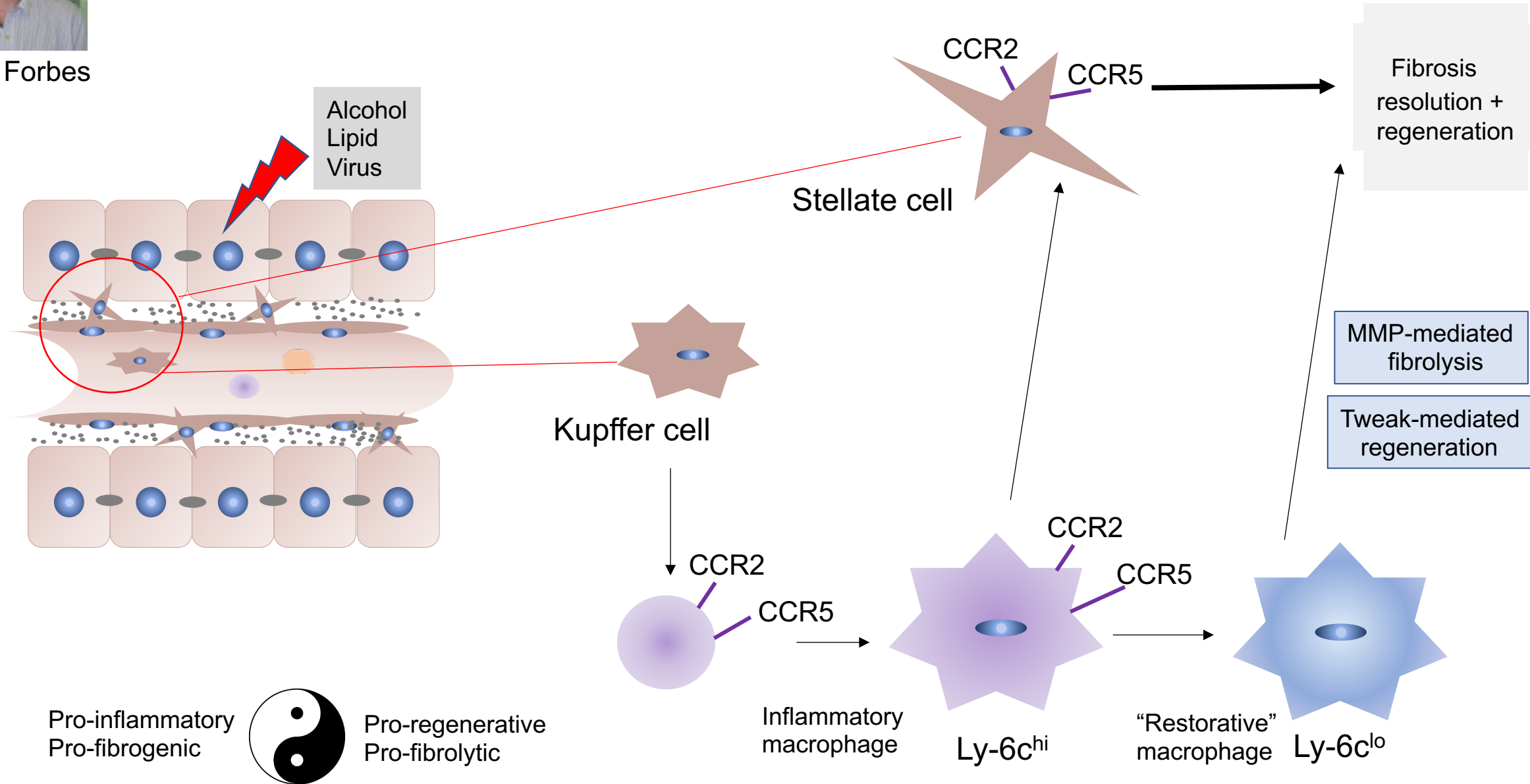
Now awaiting AURORA Phase 3 data (n=2000)



Stuart Forbes

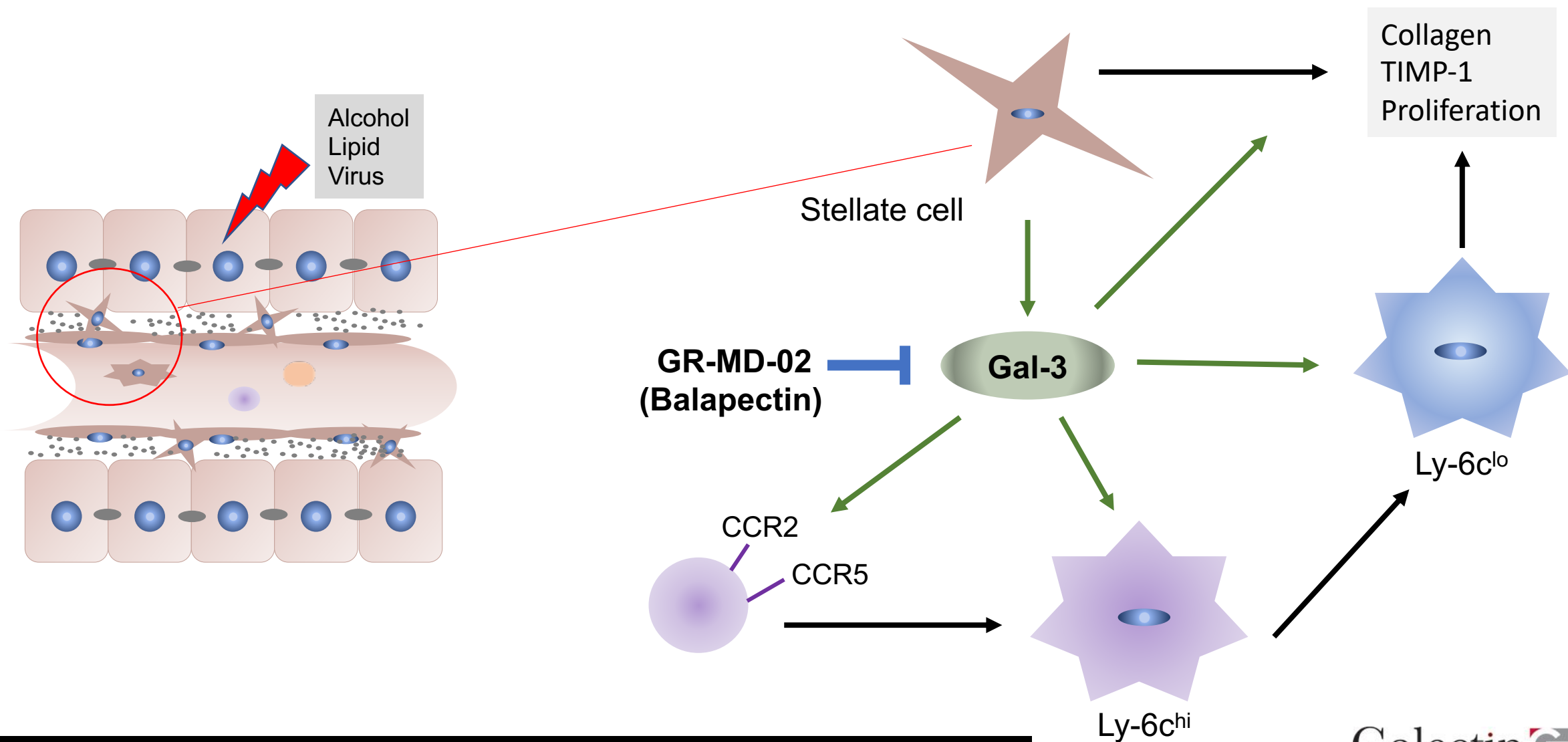
Anti-Fibrotic

Pro-resolving macrophages



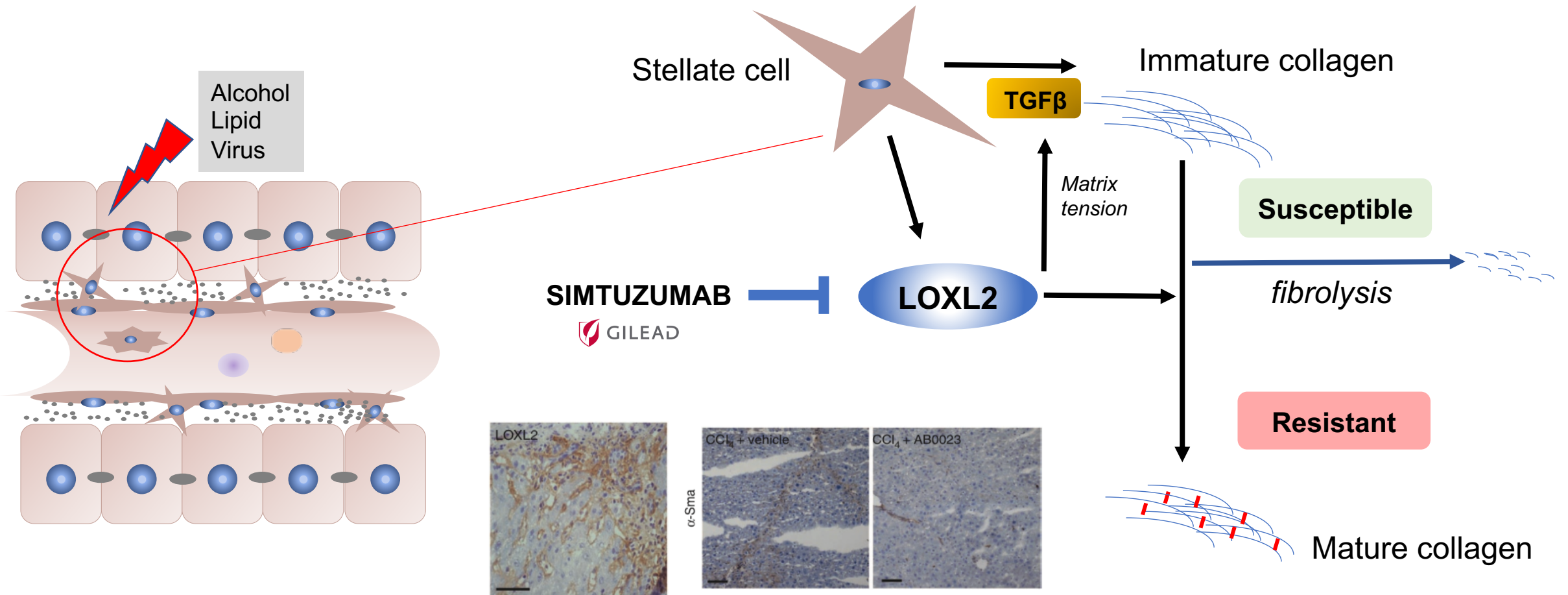
Anti-Fibrotic

Galectin-3



Phase-2b in NASH were negative but clinical benefits in some patients

LOXL2 (Cu-dependent amine oxidase)



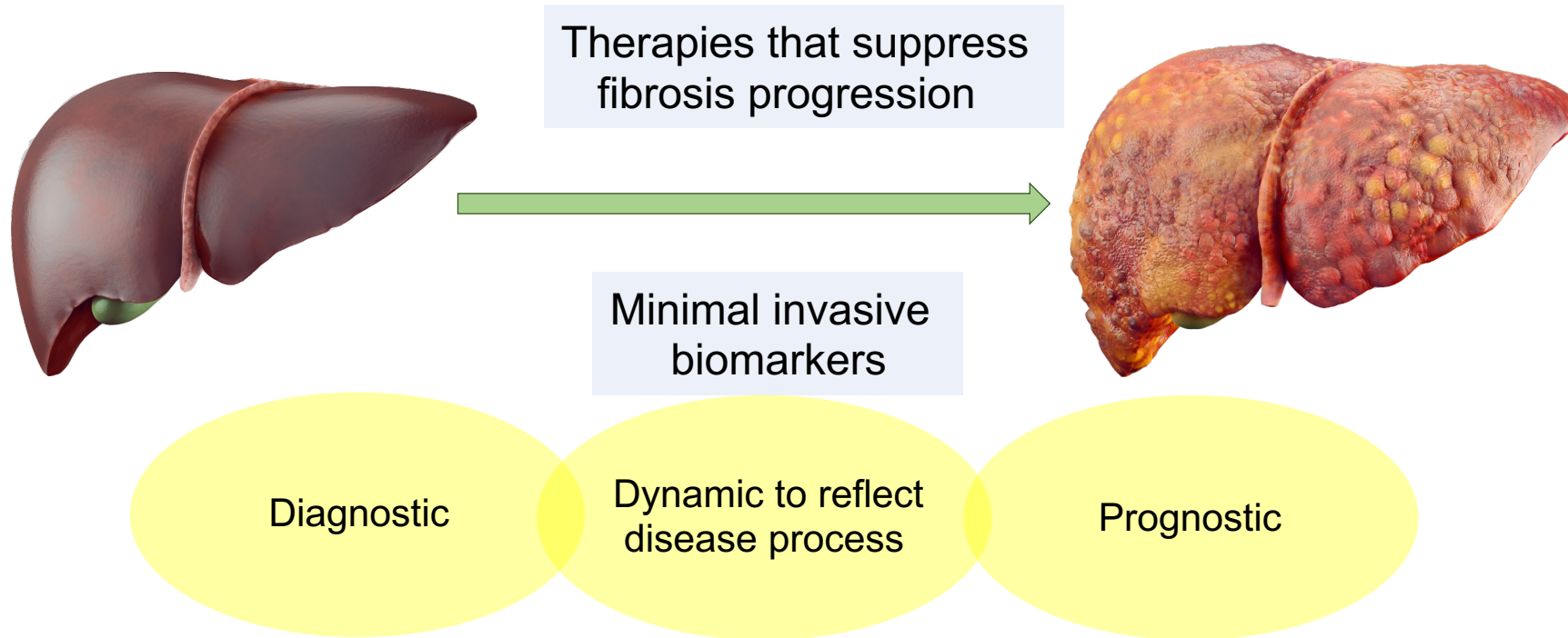
Barry-Hamilton V et al 2010, Nat Med 16; 1009

Three trials in liver disease failed to demonstrate improvement in fibrosis (+ adverse events)

Summary/Conclusions so far.....

- Despite promising pre-clinical data we are yet to translate mechanistic biology to an effective anti-fibrotic
 - Manipulating the recruitment and/or phenotype of monocyte-derived macrophages is promising.
-
- Variability of disease progression (and regression) is a major challenge for NAFLD clinical trails
 - Ideally we should be treating patients who are rapid progressors.....
 - Our pre-clinical models are imperfect
 - Ideally we need complex human models of fat-driven liver fibrogenesis.....

The clinical imperatives

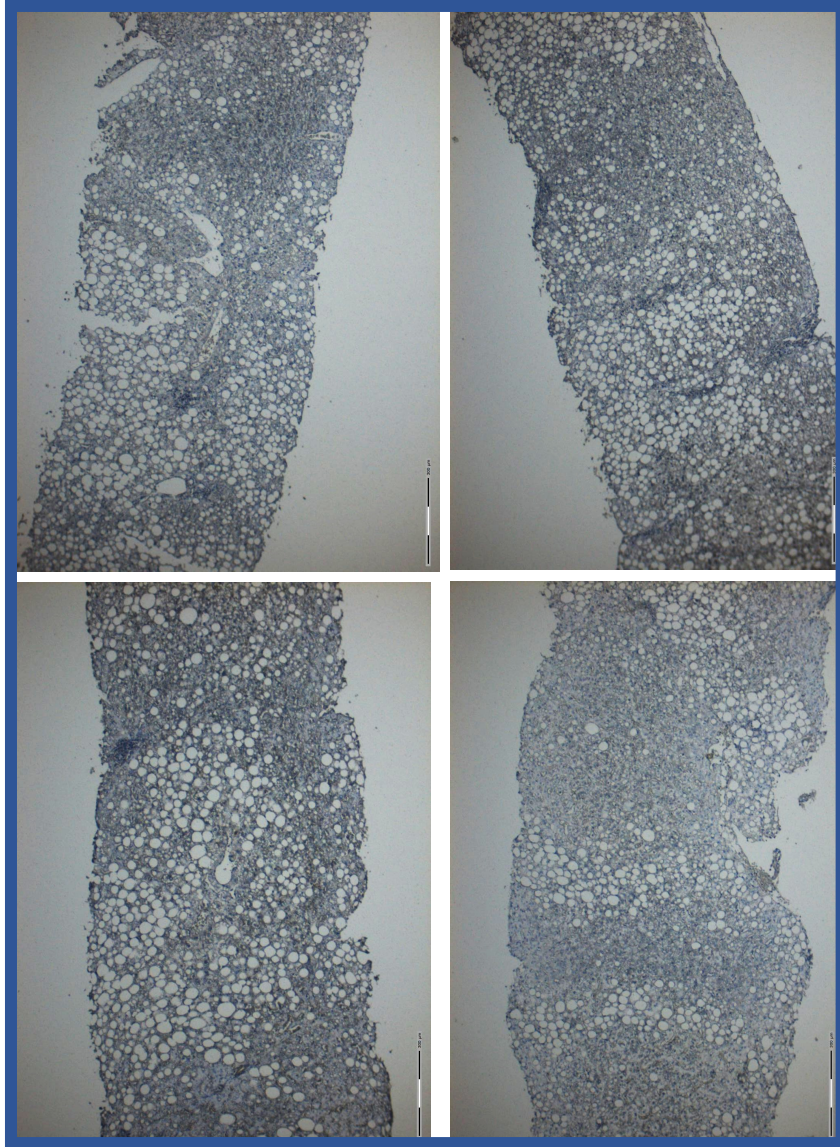


Genetic (e.g. PNLPA3), metabolic (e.g. Leptin), inflammatory (e.g. IL-6, CCL2), fibrogenic (e.g. Pro-C3, TIMP1)

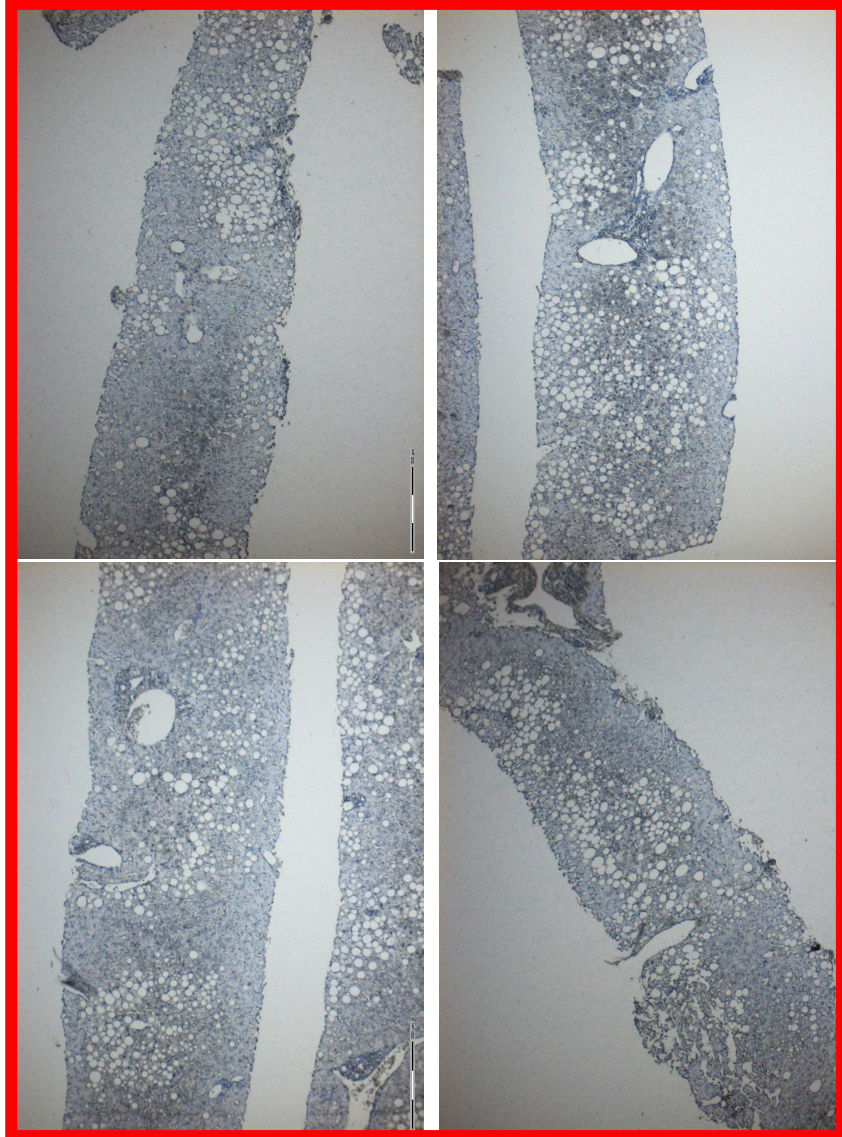
Can the DNA methylome progression of steatosis to cirrhosis?

NAFLD diagnostic liver biopsy (F0)

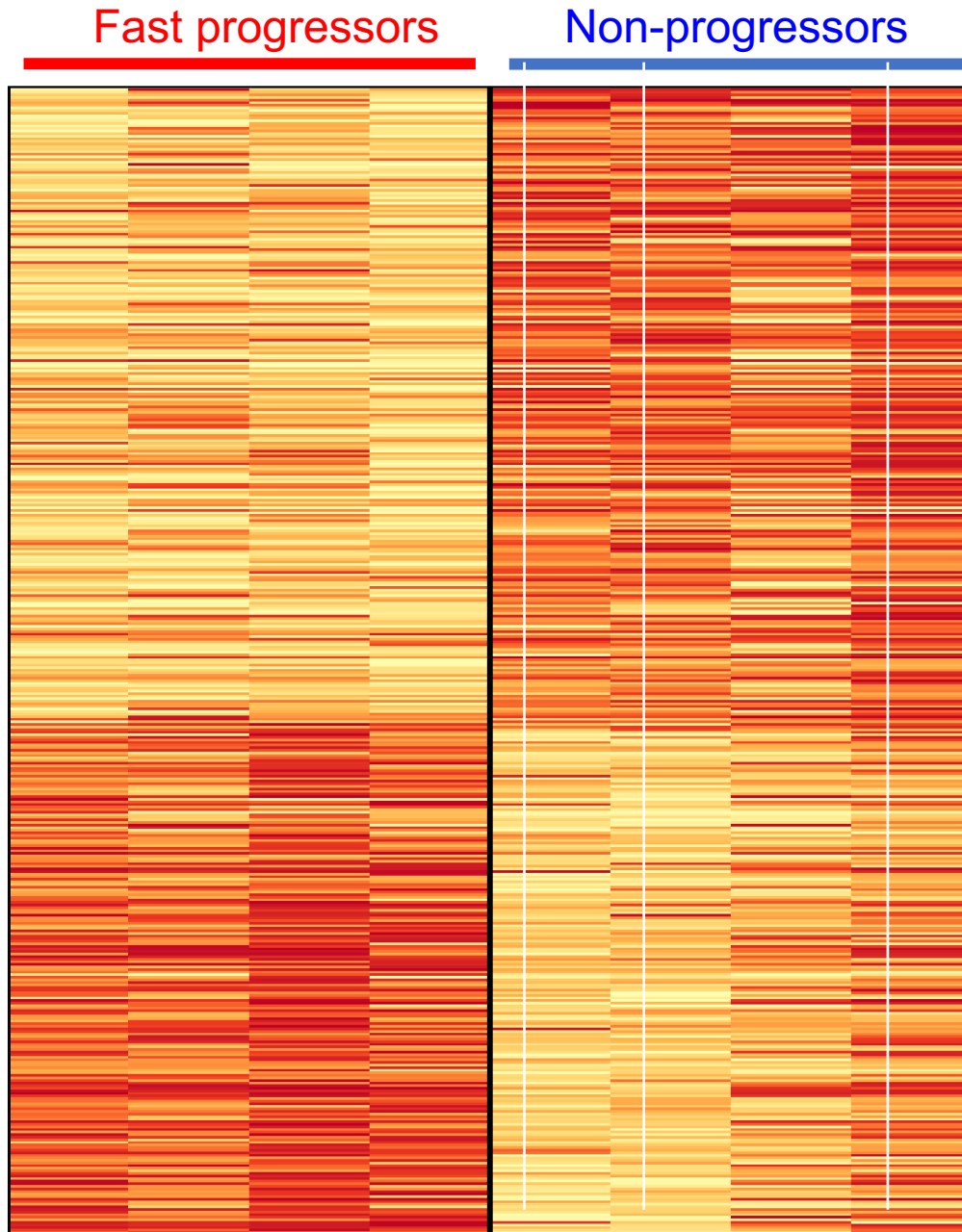
Non-
progressors



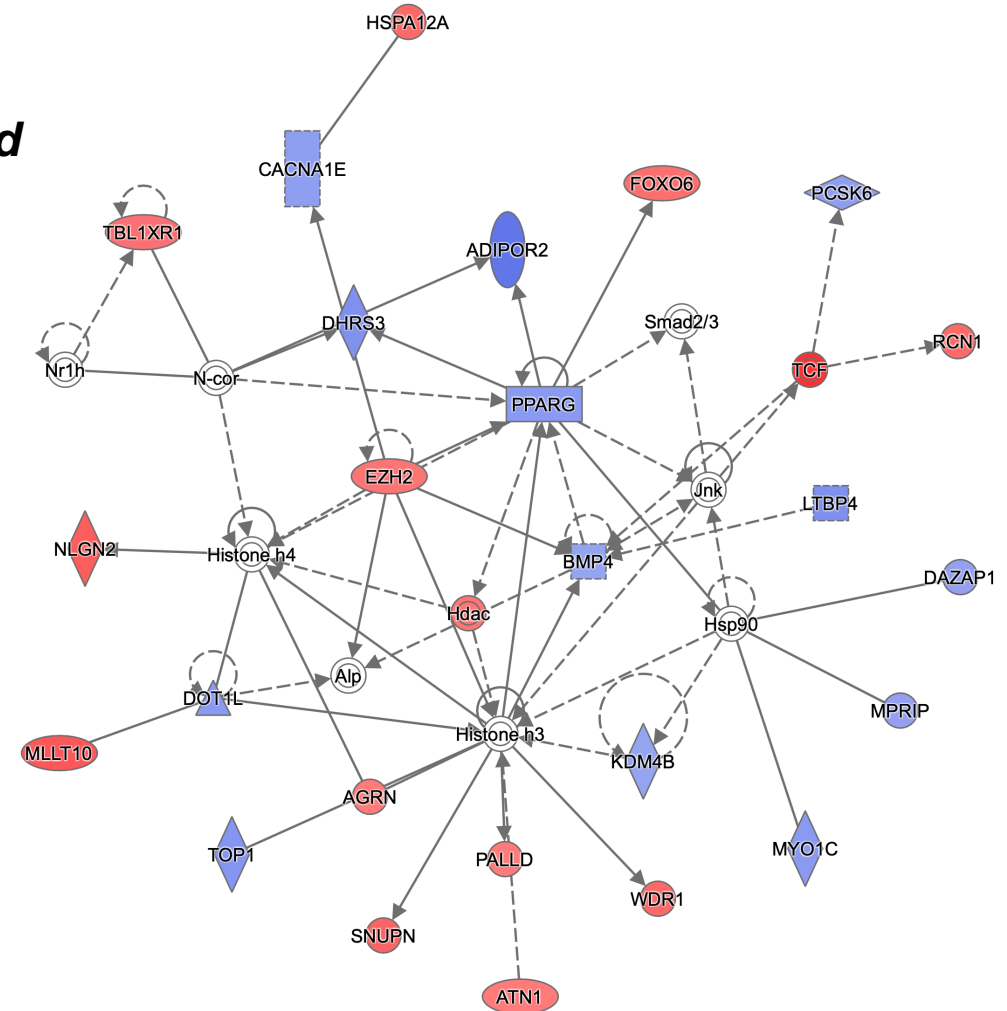
Fast
Progressors



A Fibrosis methylome landscape



Unpublished



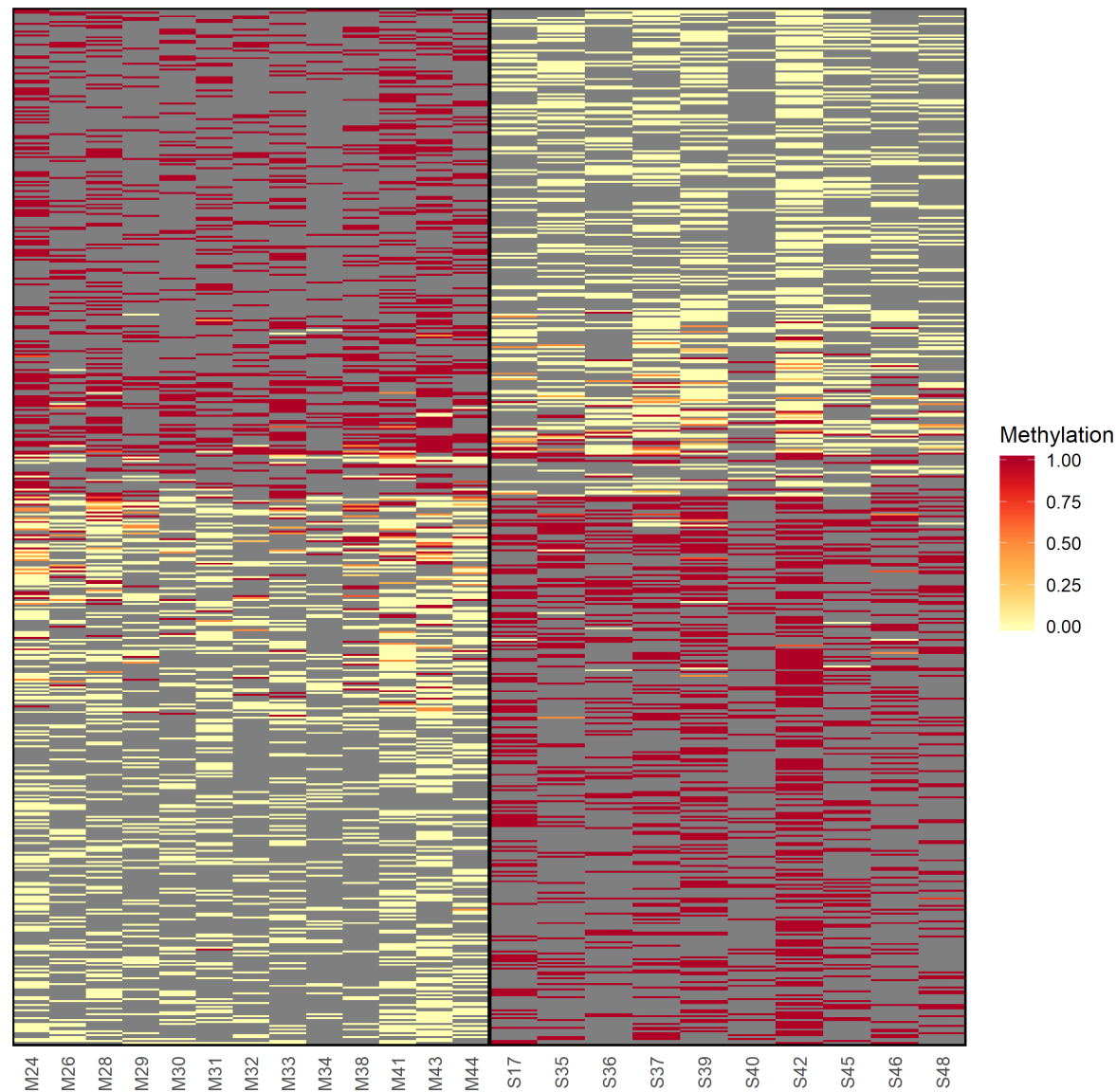
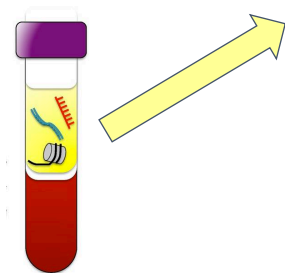
Red = hypermethylated in np
Blue = hypermethylated in fp

Whole Genome Bisulfite Sequencing on cc-fDNA

12 Mild/stable vs 12 Advanced NAFLD

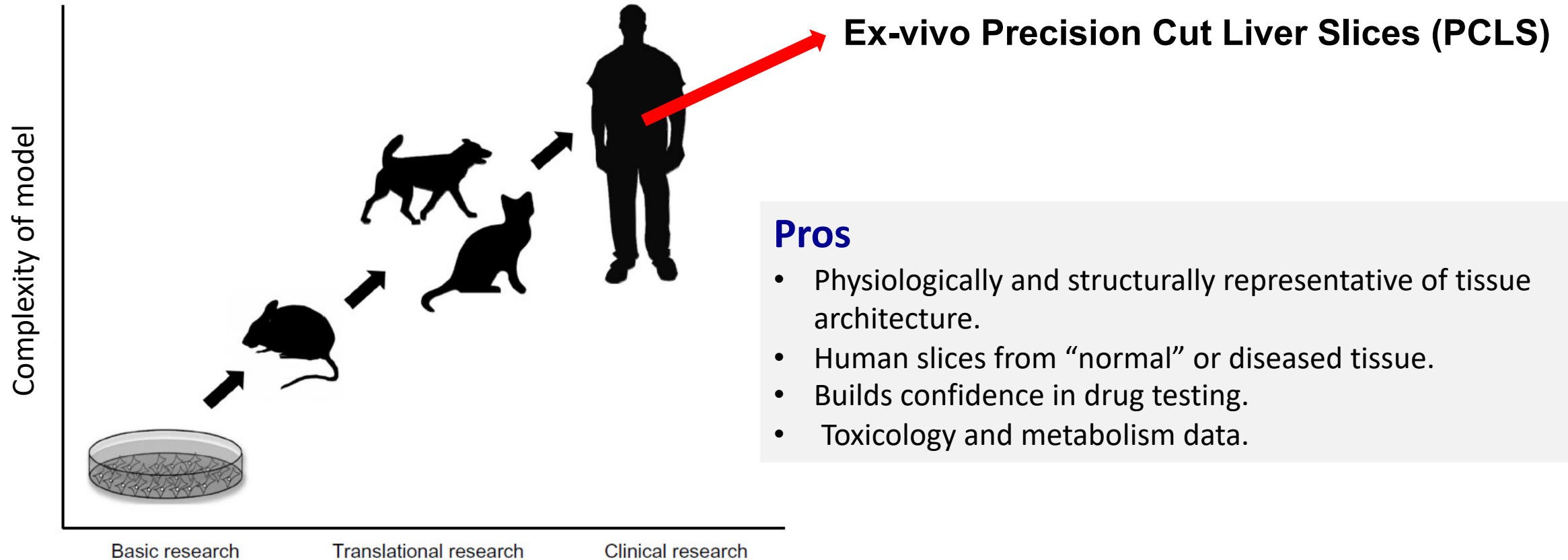
Grade 0-2 NAFLD

Grade 3-4 NAFLD

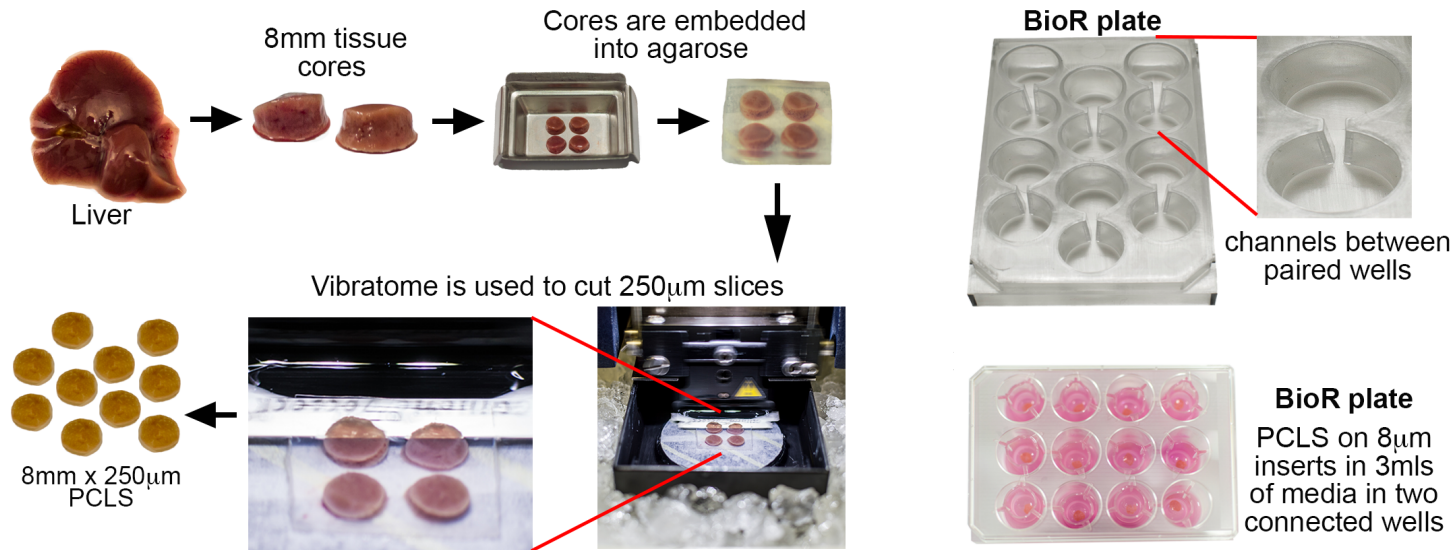


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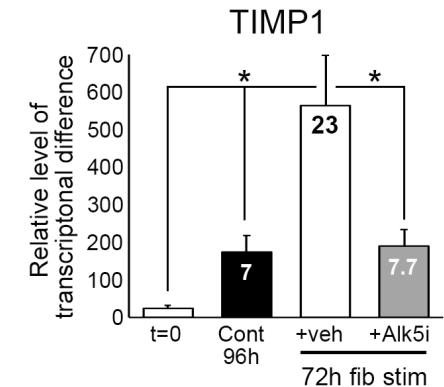
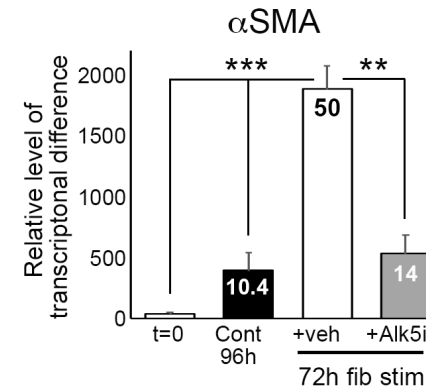
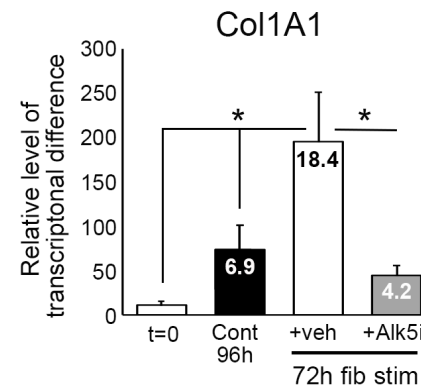
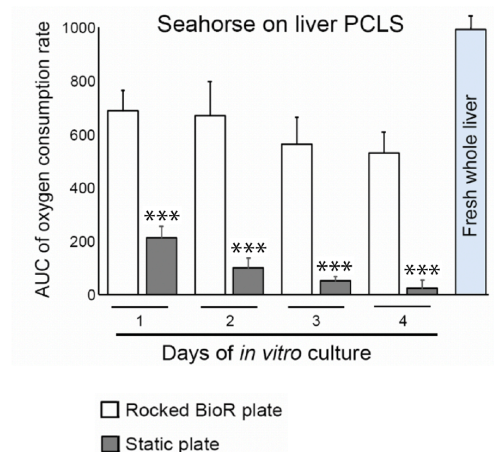
Improved (human-based) pre-clinical drug development platforms



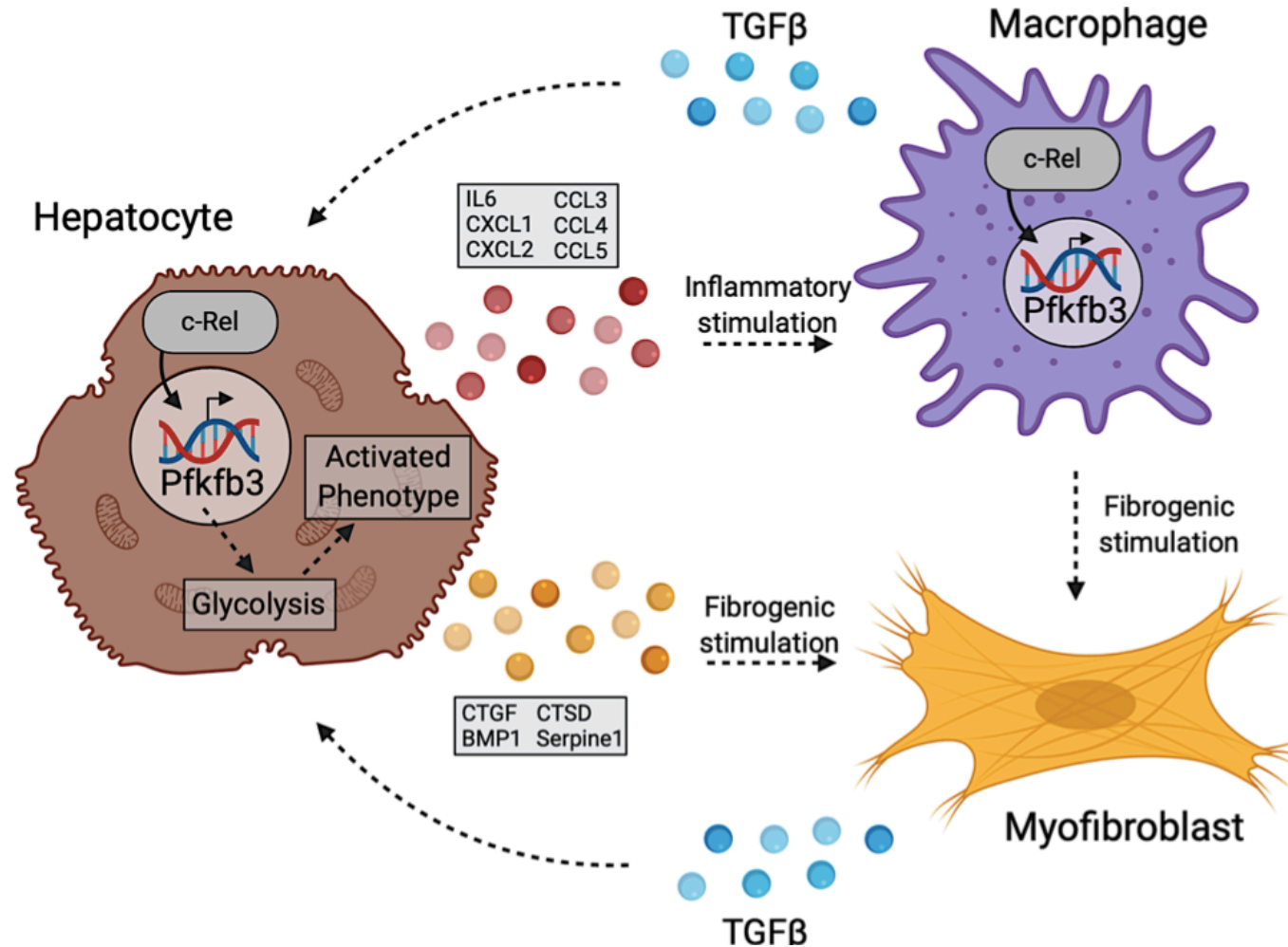
Modelling fibrogenesis in human PCLS



Paish HL et al 2019, Hepatology 70: 1377-91



c-Rel orchestrates energy-dependent epithelial and macrophage reprogramming in fibrosis

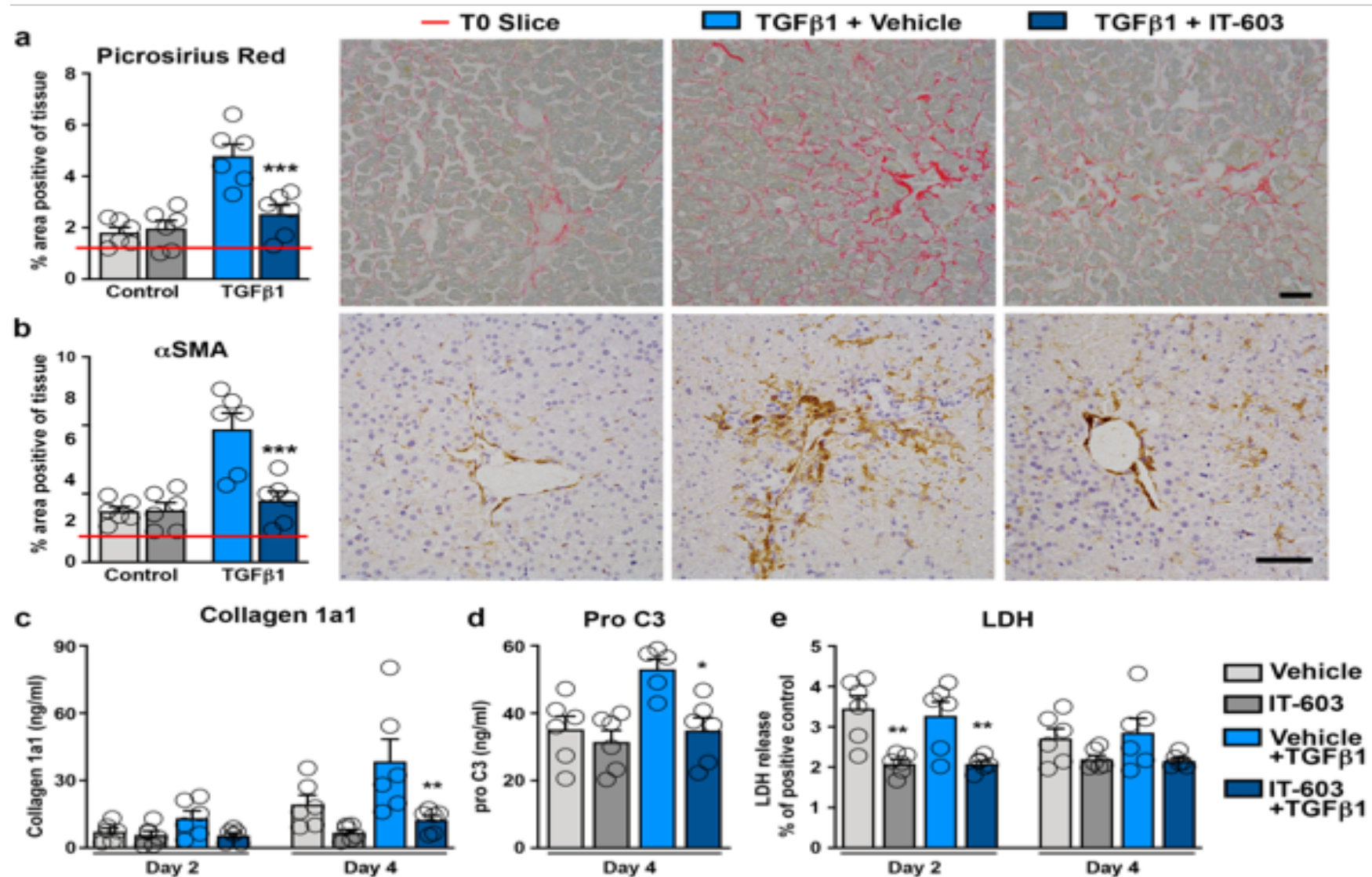


Dr Jack Leslie

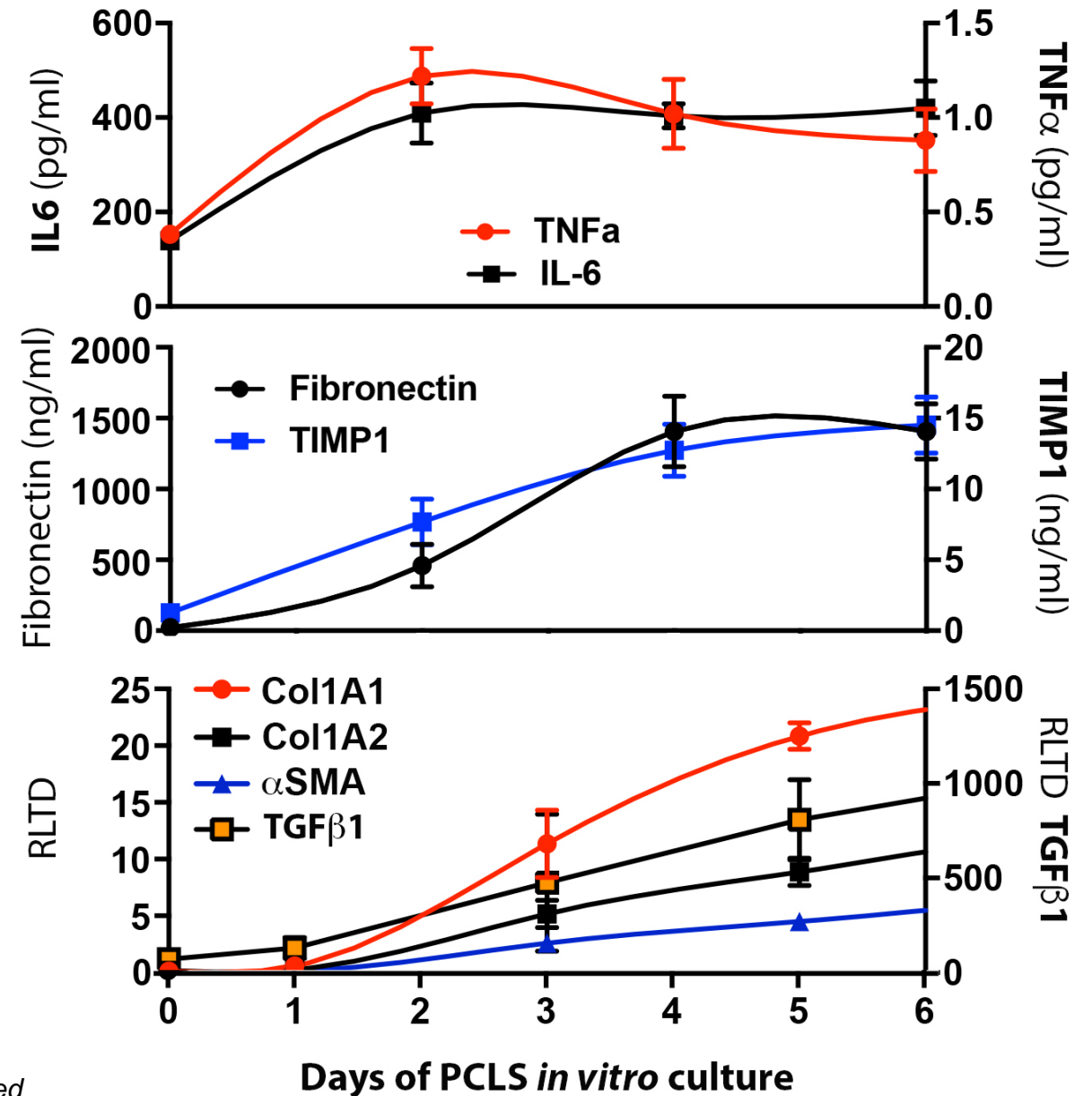
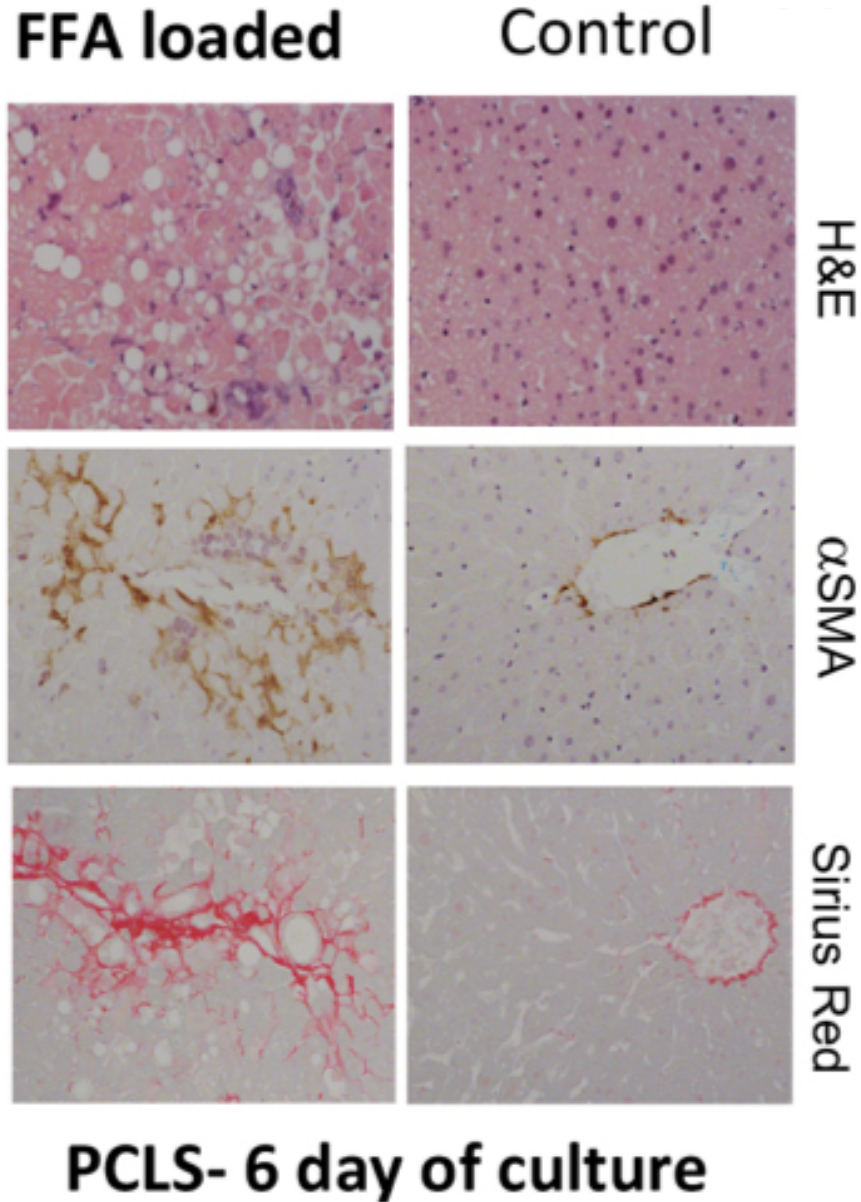


Prof Fiona Oakley

C-Rel inhibitor IT-603 blocks fibrosis in human liver slices

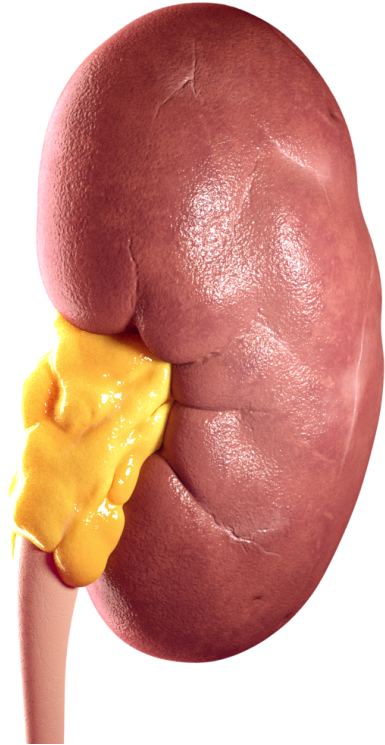


Modelling NAFLD in human PCLS

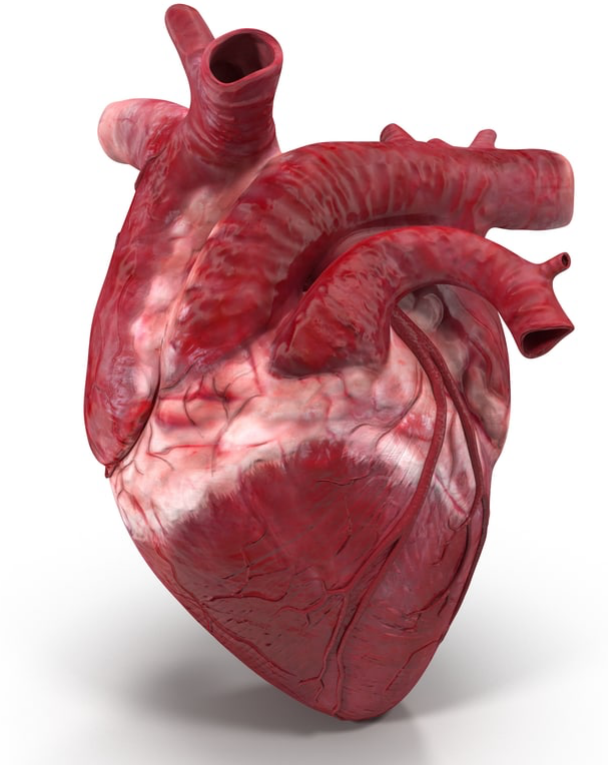


Unpublished

Modelling fibrosis in other organs



PCKS



PCHS



Newcastle Fibrosis Research Group

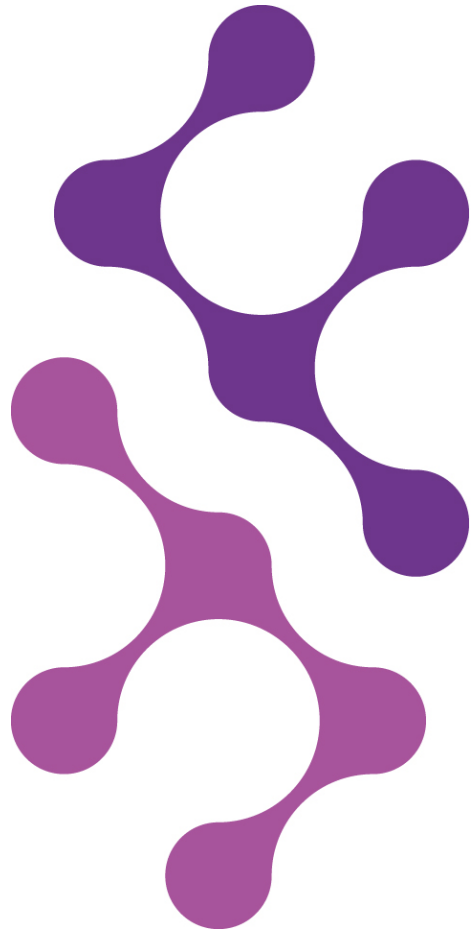
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Lee Reed
Agata Page
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