MÁSTER EN HEPATOLOGÍA

UAM Universidad Autónoma de Madrid

Universidad de Alcalá

El sinusoide hepático: biología en la cirrosis y en la enfermedad hepática crónica

Jordi Gracia-Sancho, PhD

Liver Vascular Biology Research Group
IDIBAPS, Barcelona
Inselspital, Bern

jordi.gracia@idibaps.org

@jsgracia

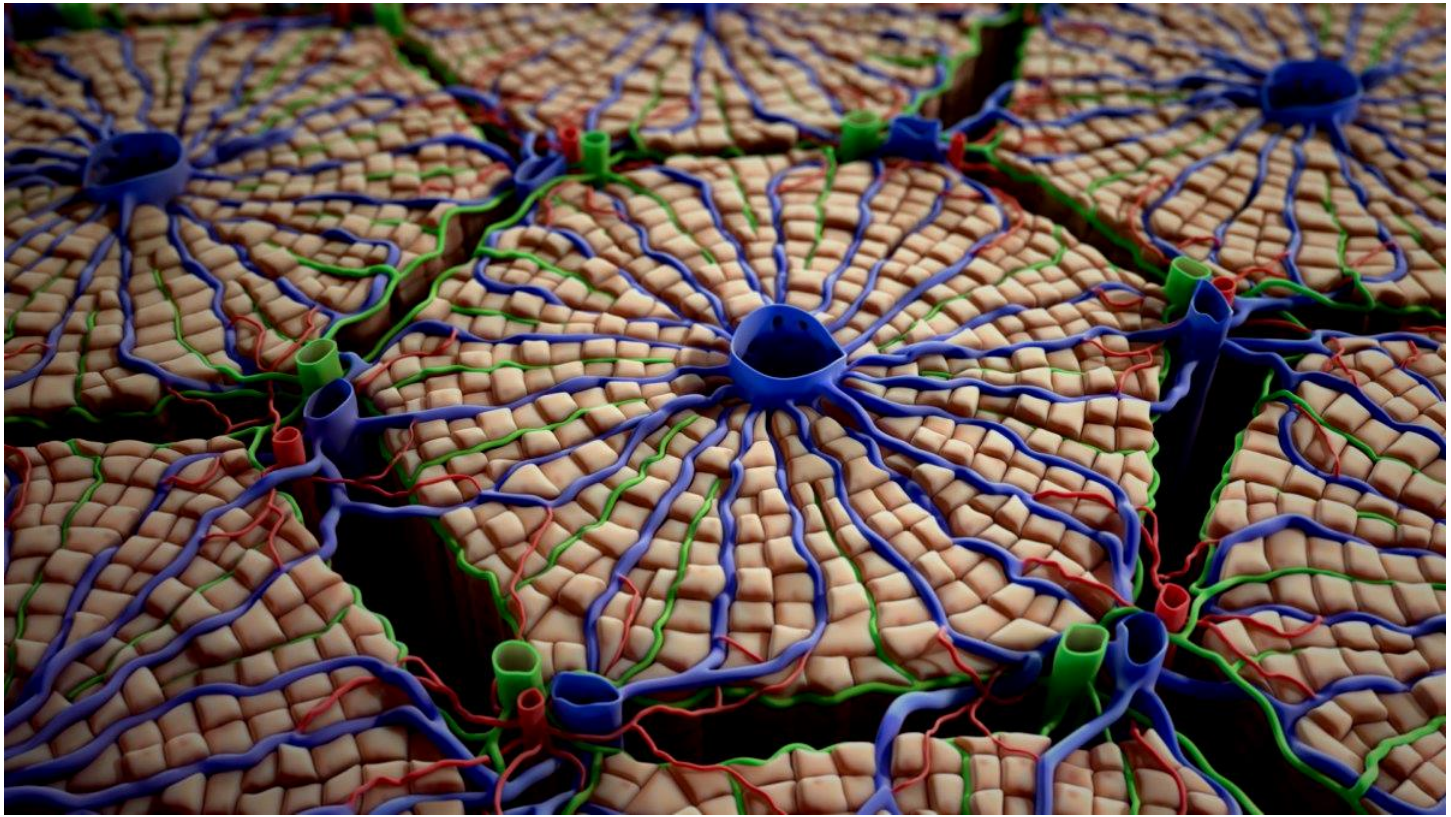
Agenda

- Liver microcirculation & the hepatic sinusoid

- Modulation of liver microcirculation – impact on PH

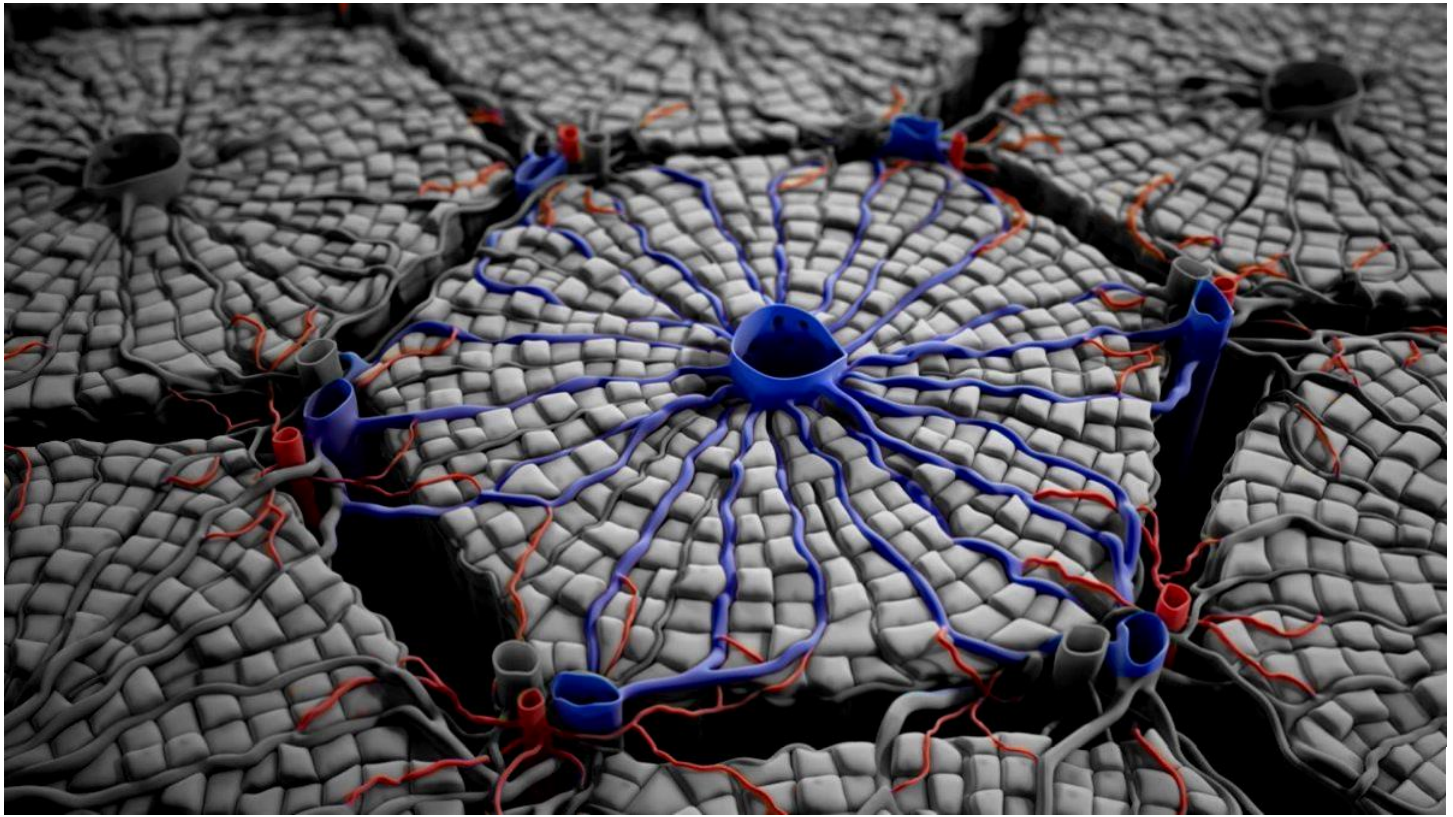
- Novel therapeutics to improve the hepatic sinusoid

Liver microcirculation

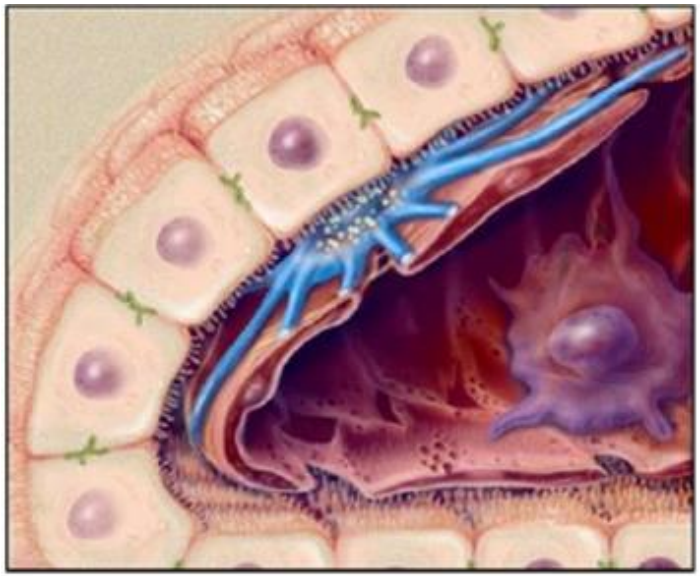


Aird WC. *Circ Res*. 2007

Liver microcirculation



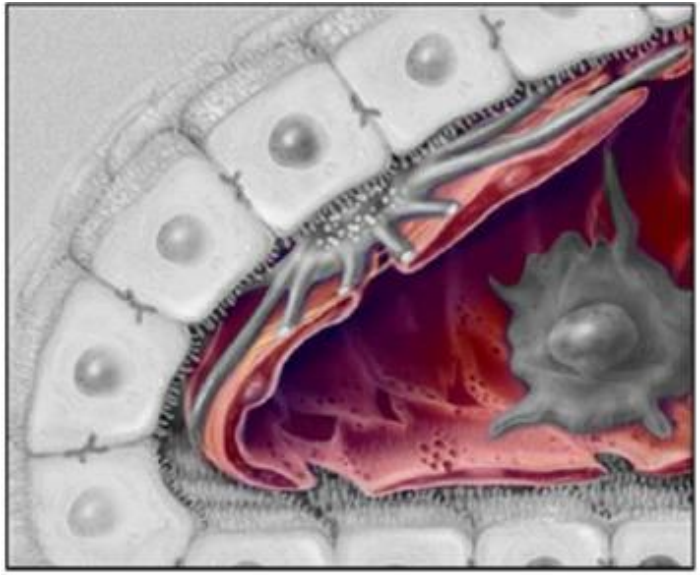
The liver sinusoid



Friedman SL. *Nat Clin Pract Gastroenterol Hepatol* 2004

Gracia-Sancho J et al, *Nature Reviews Gastro & Hepatol* 2021
Tsuchida T, Friedman SL, *Nature Reviews Gastro & Hepatol* 2017
Tacke F. *Journal of Hepatology* 2017

The liver sinusoid - LSEC

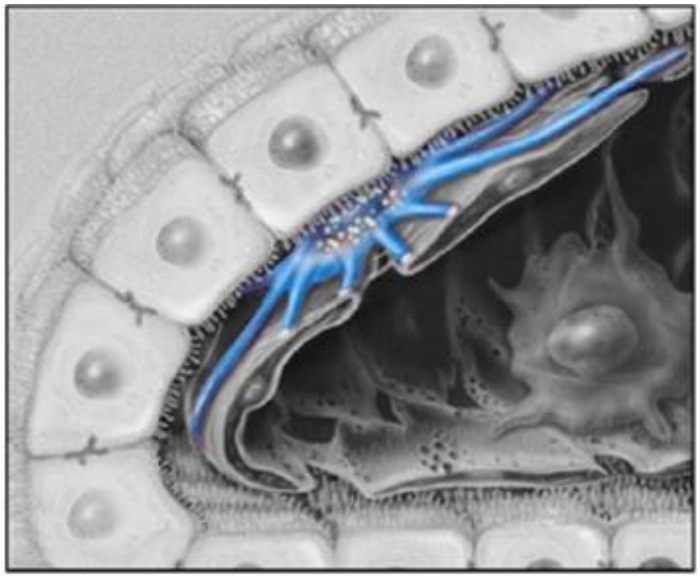


Liver Sinusoidal Endothelial Cells (LSEC)

- Discontinuous (fenestrae, lack of basal membrane).
- Haemostasis, inflammation, toxicants clearance and regulation of vascular tone.

Gracia-Sancho J et al, *Nature Reviews Gastro & Hepatol* 2021
Tsuchida T, Friedman SL, *Nature Reviews Gastro & Hepatol* 2017
Tacke F. *Journal of Hepatology* 2017

The liver sinusoid - HSC



Liver Sinusoidal Endothelial Cells (LSEC)

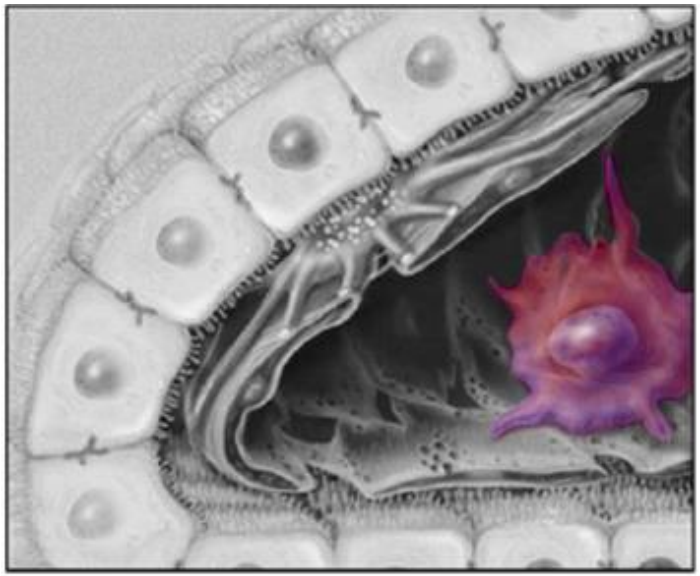
- Discontinuous (fenestrae, lack of basal membrane).
- Haemostasis, inflammation, toxicants clearance and regulation of vascular tone.

Hepatic Stellate Cells (HSC)

- Contractile properties.
- Vitamin A storage

Gracia-Sancho J et al, *Nature Reviews Gastro & Hepatol* 2021
Tsuchida T, Friedman SL, *Nature Reviews Gastro & Hepatol* 2017
Tacke F. *Journal of Hepatology* 2017

The liver sinusoid - KC



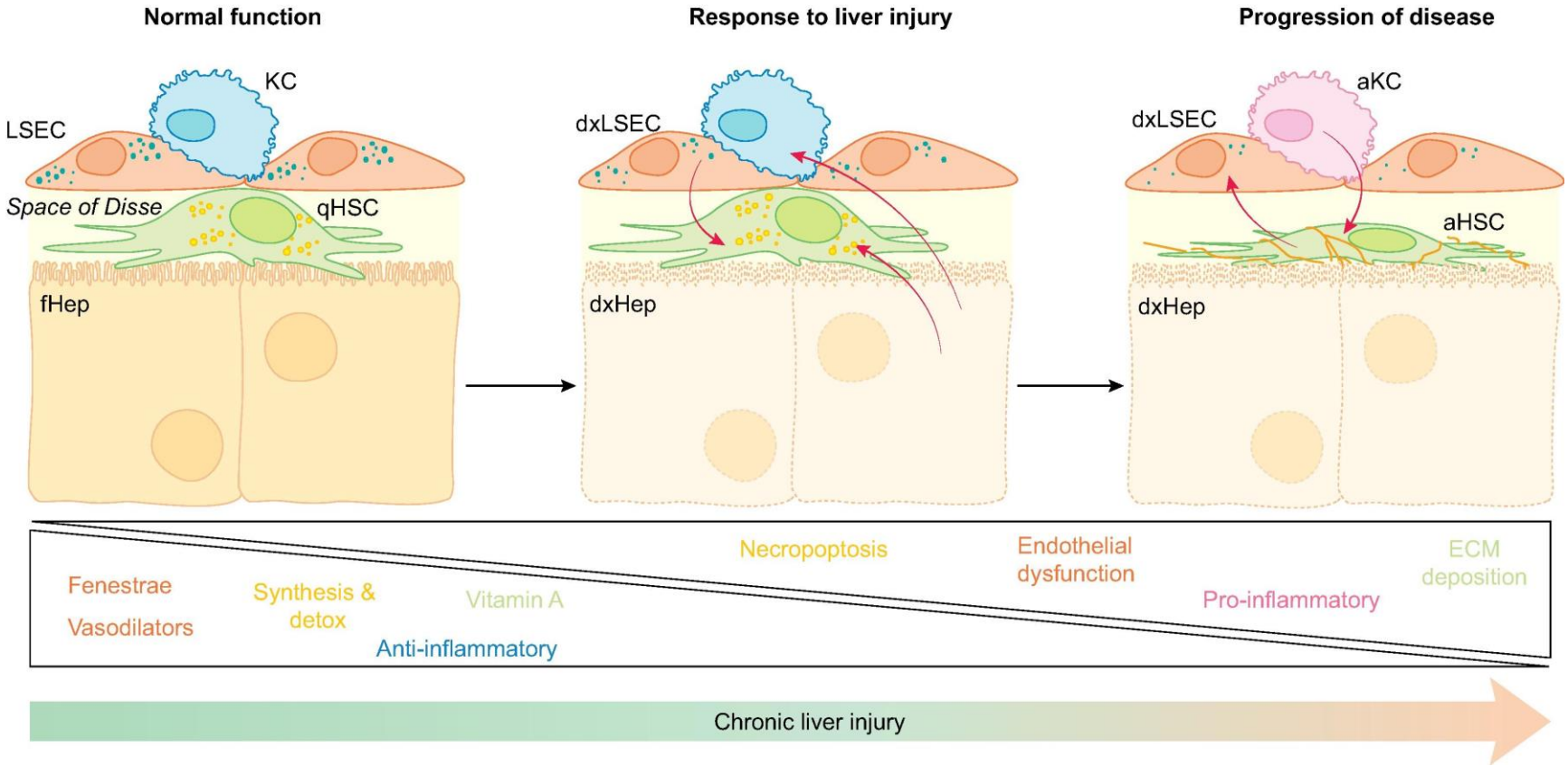
Liver Sinusoidal Endothelial Cells (LSEC)
- Discontinuous (fenestrae, lack of basal membrane).
- Haemostasis, inflammation, toxicants clearance and regulation of vascular tone.

Hepatic Stellate Cells (HSC)
- Contractile properties.
- Vitamin A storage

Kupffer Cells (KC)
- Resident macrophages: defense, inflammation, tissue remodelling.

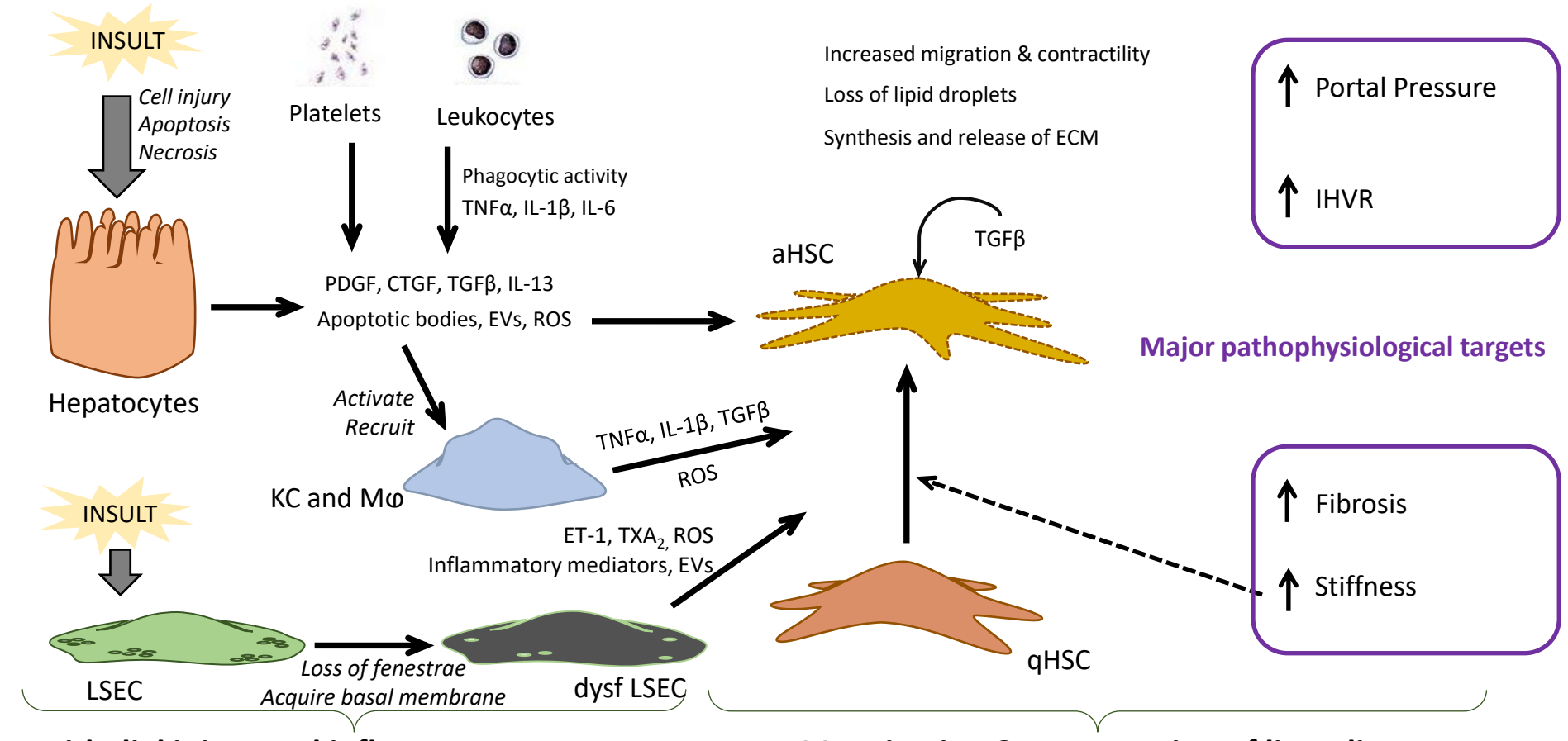
Gracia-Sancho J et al, *Nature Reviews Gastro & Hepatol* 2021
Tsuchida T, Friedman SL, *Nature Reviews Gastro & Hepatol* 2017
Tacke F. *Journal of Hepatology* 2017

The liver sinusoid in the progression of CLD

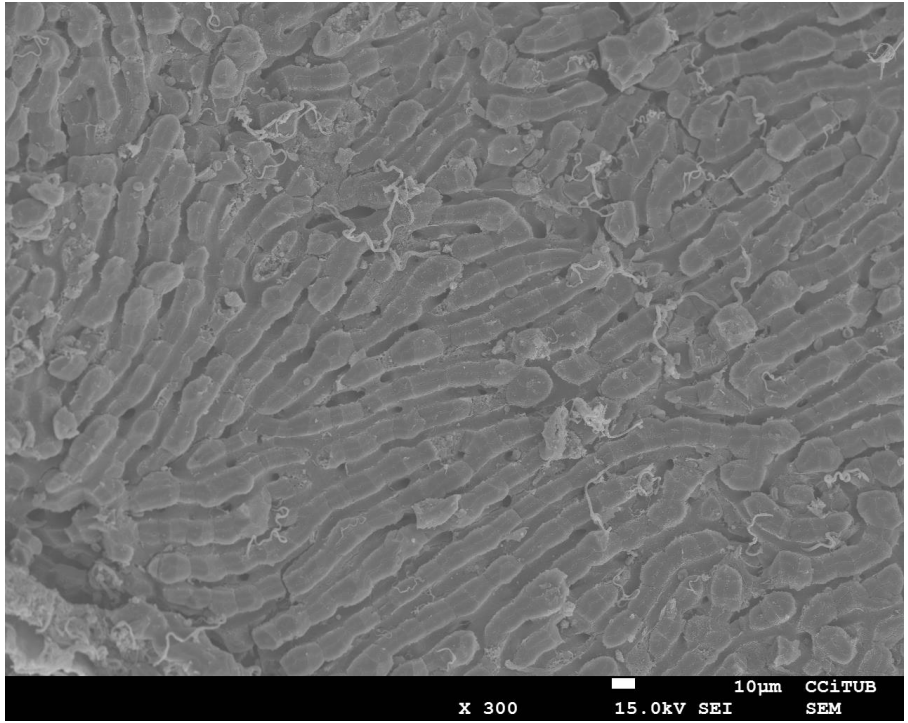


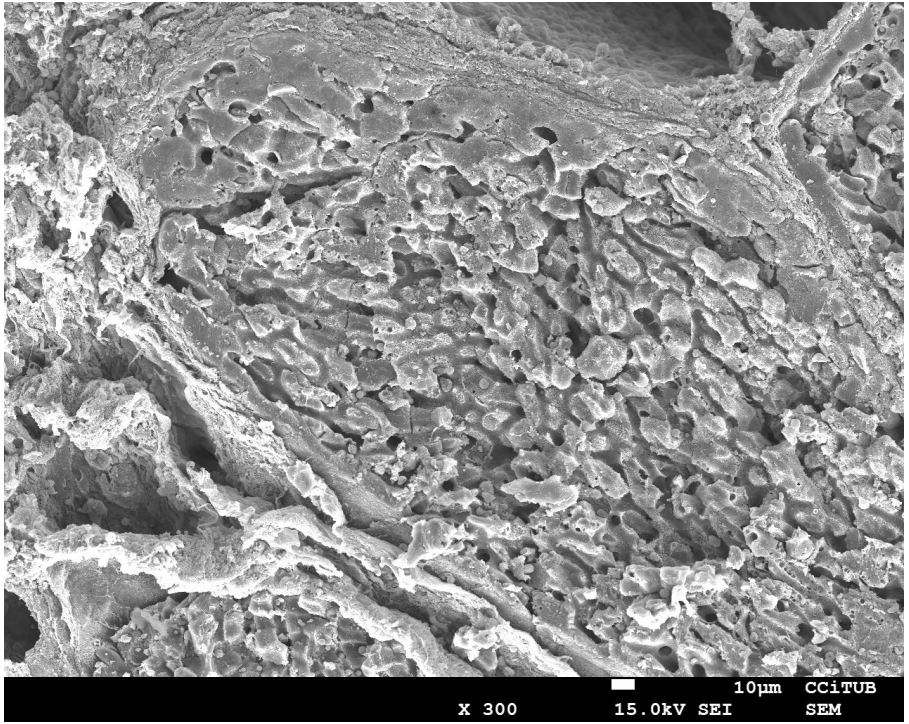
Marrone, Shah & Gracia-Sancho, Journal of Hepatology 2016

Overview of CLD progression

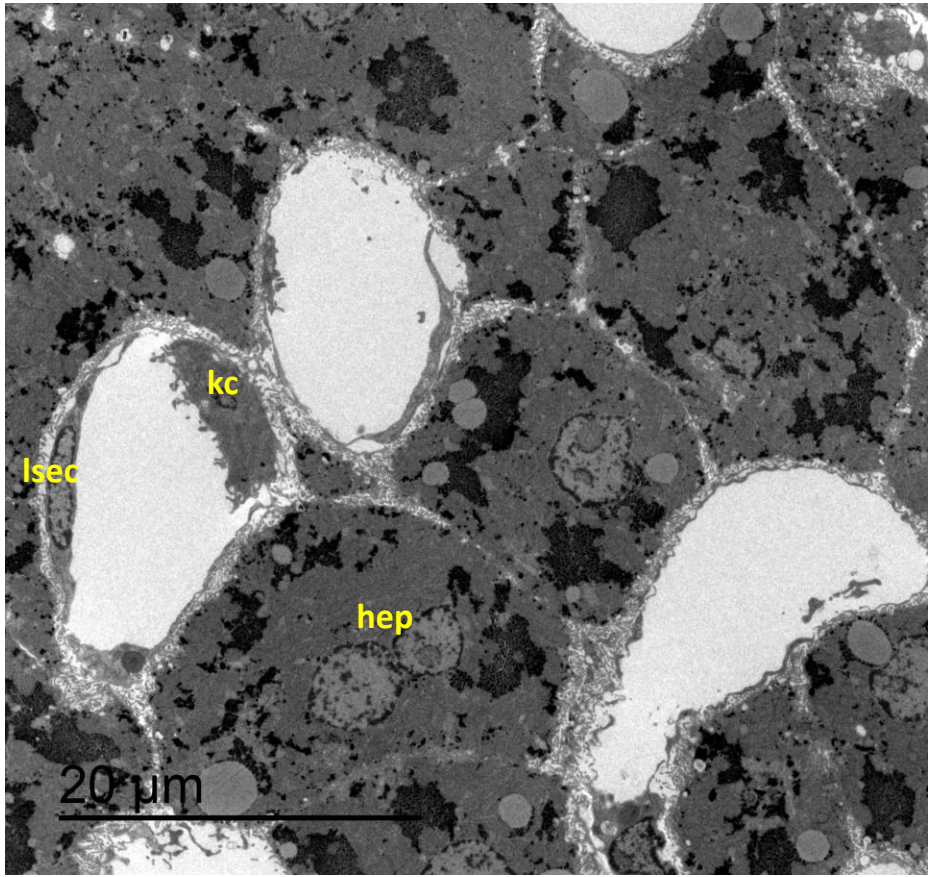


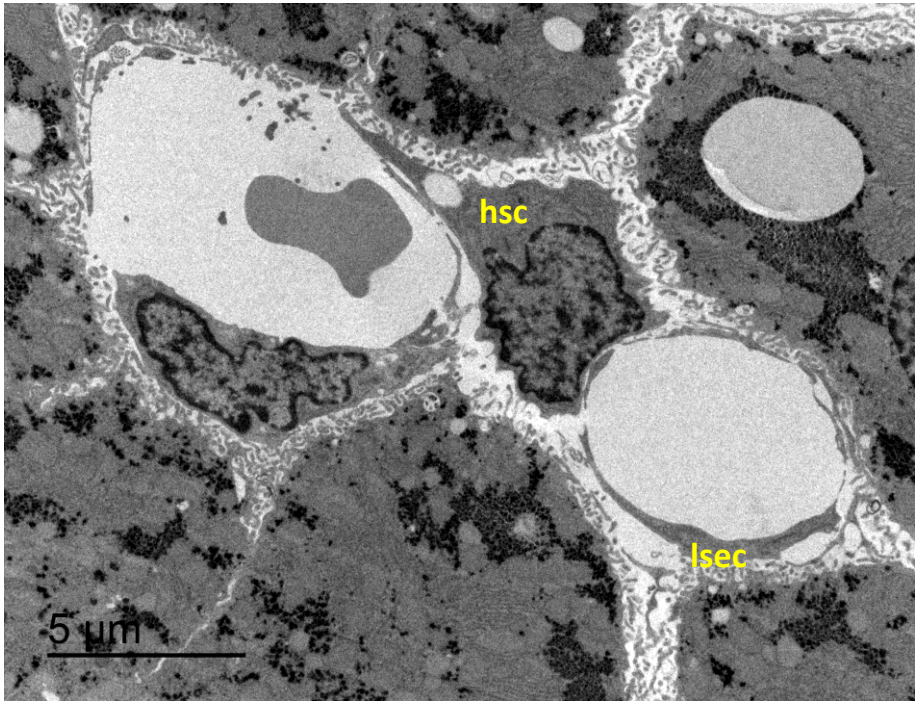
The liver sinusoid



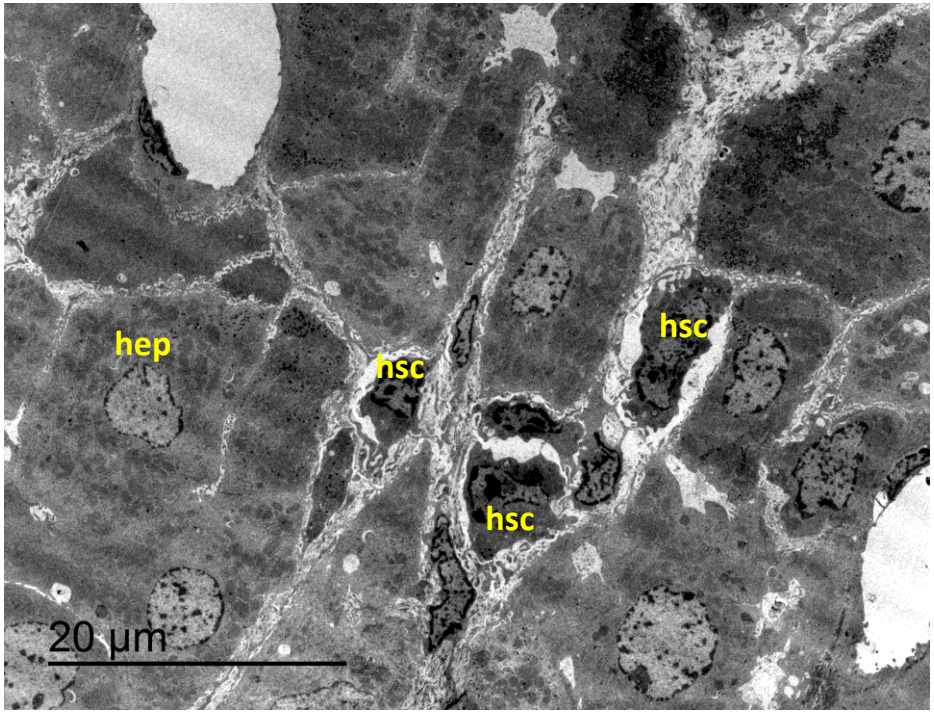


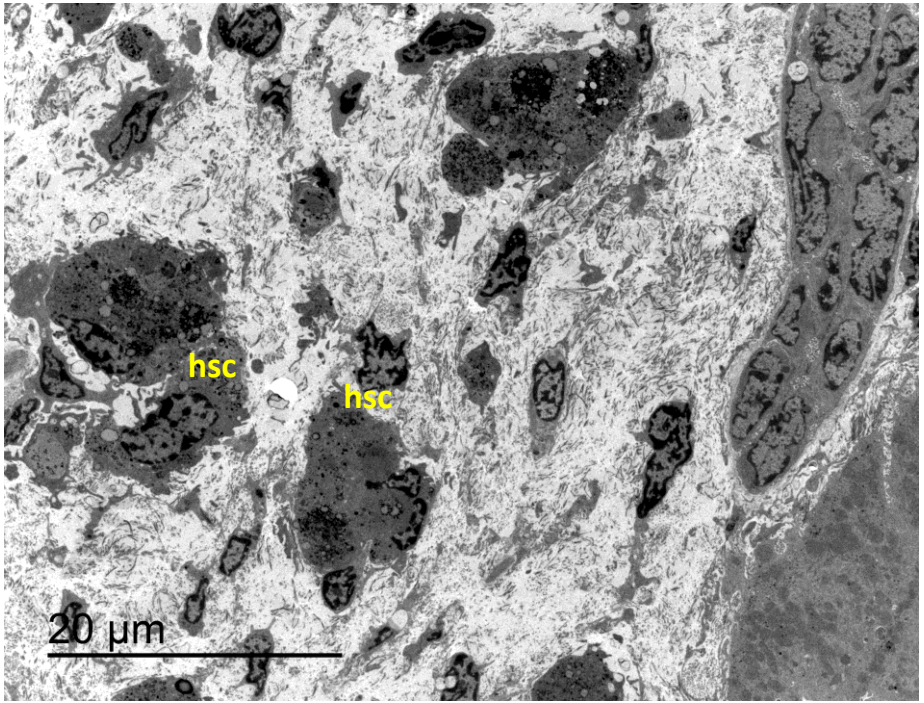
The liver sinusoid



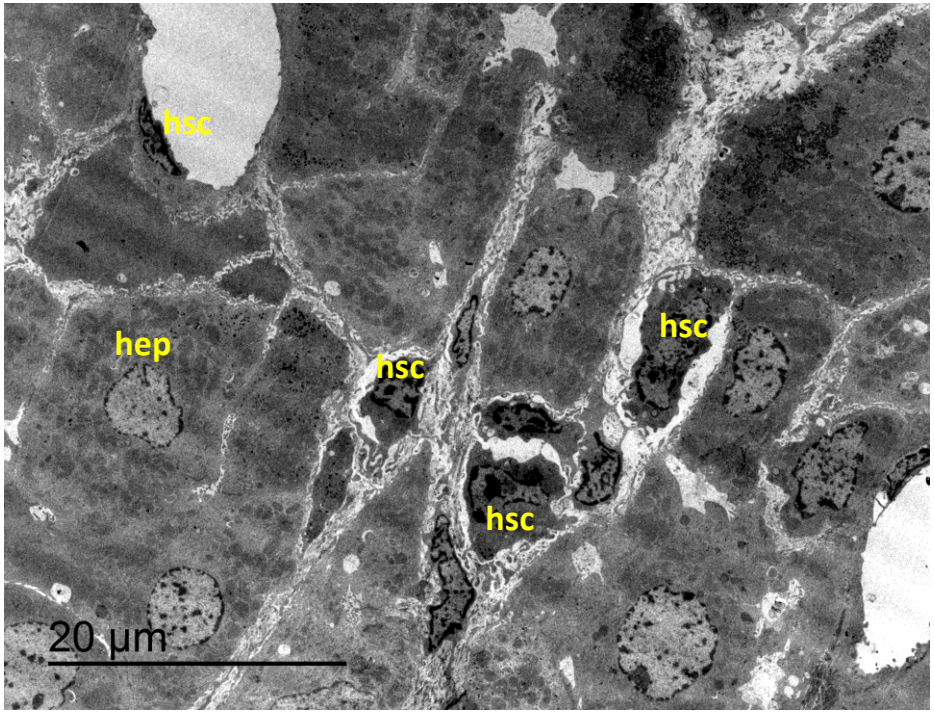


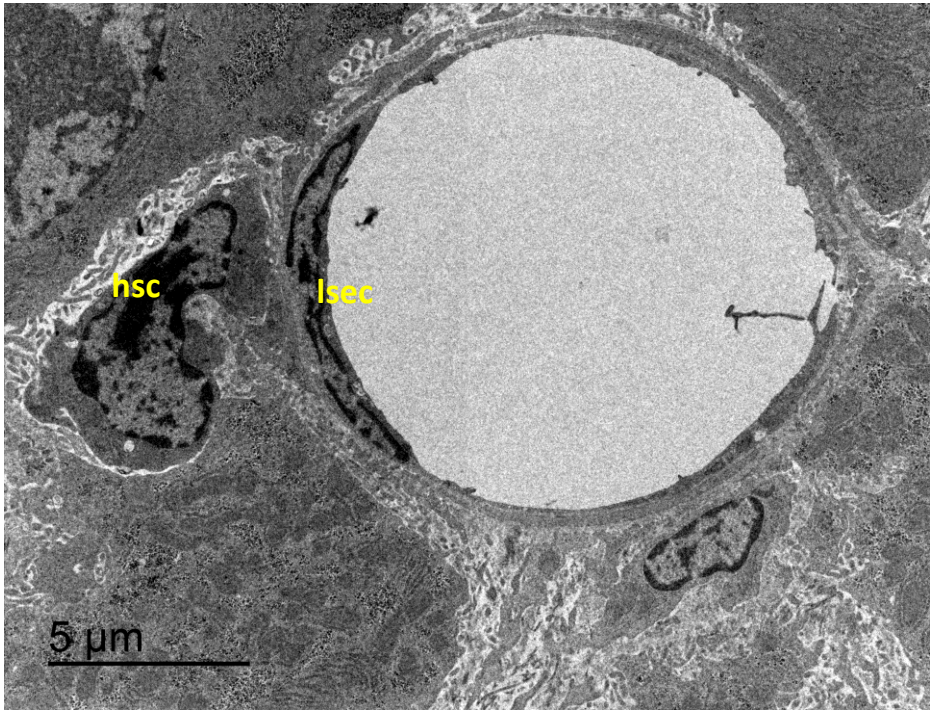
The liver sinusoid in cirrhosis



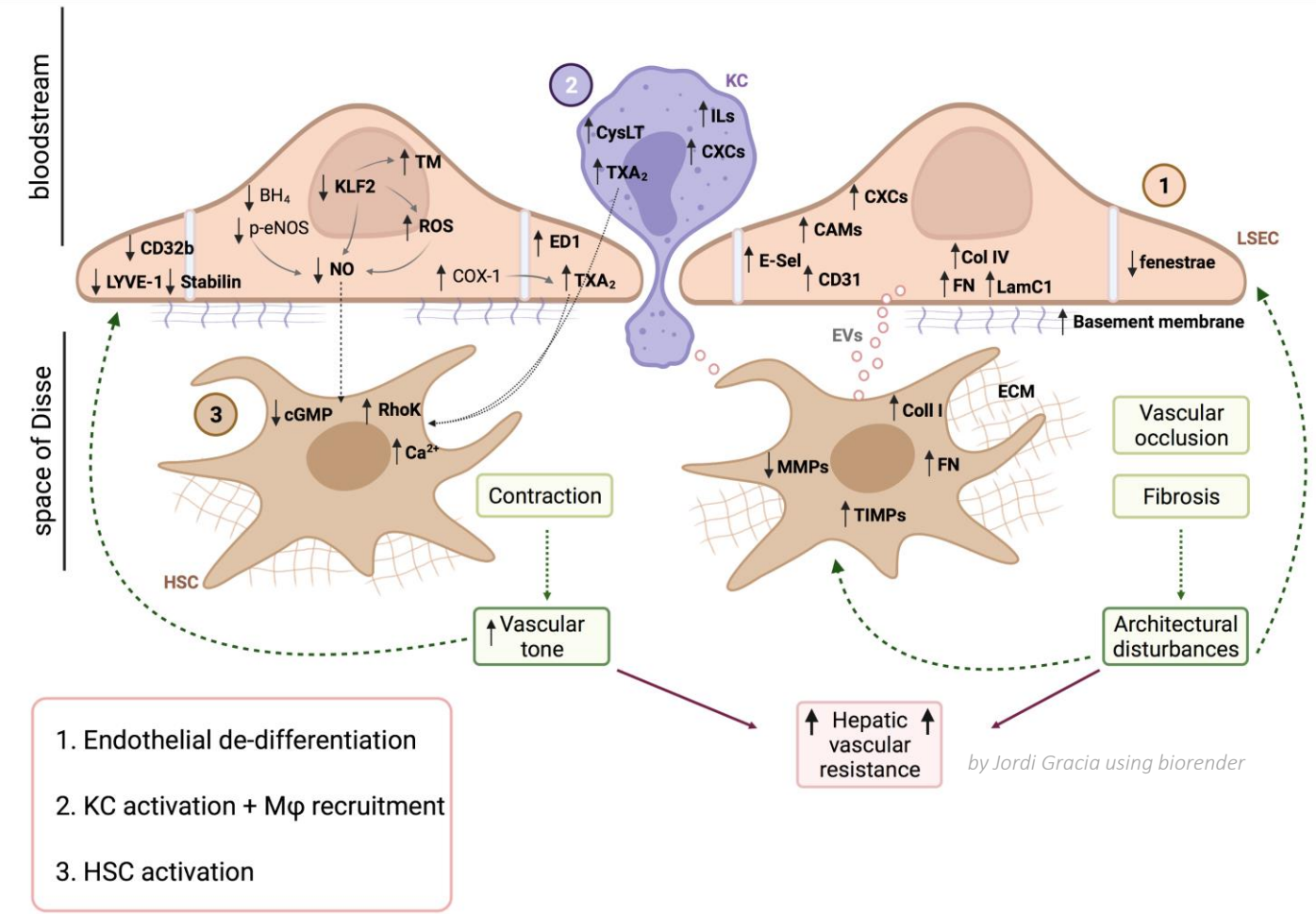


The liver sinusoid in cirrhosis



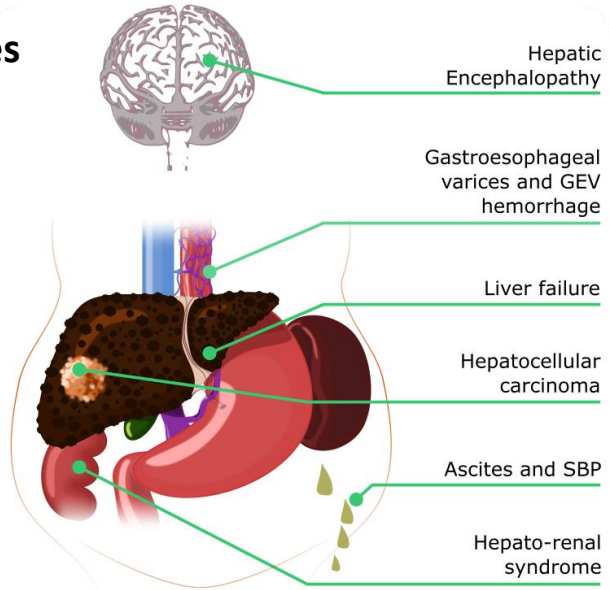


Hepatic microcirculatory dysfunction



Clinical syndrome very frequent in cirrhosis characterized by a pathological increase in the portal pressure gradient or HVPG (>5 mmHg)

Consequences

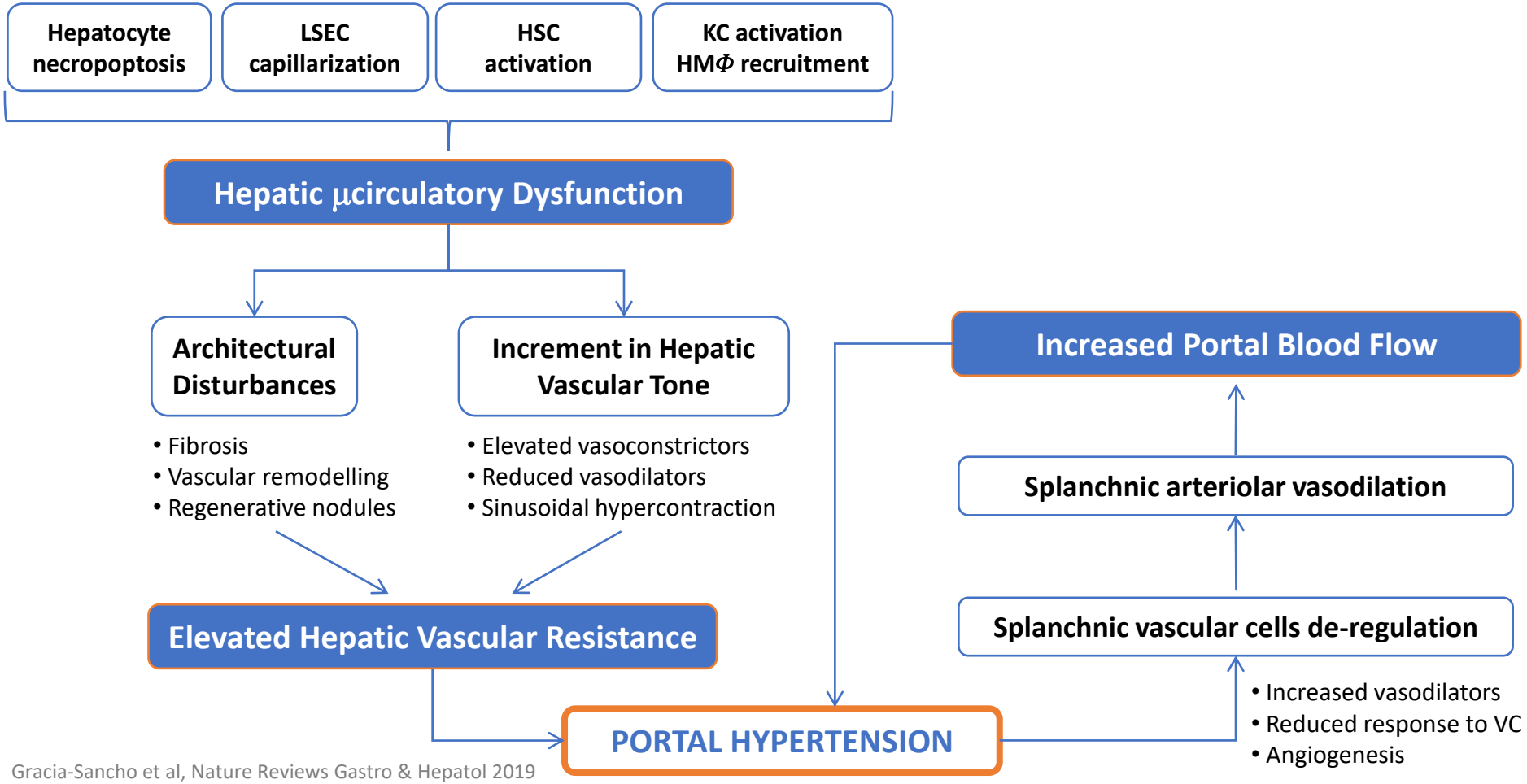


Reversible by decreasing portal pressure

170.000 deaths/year in the EU

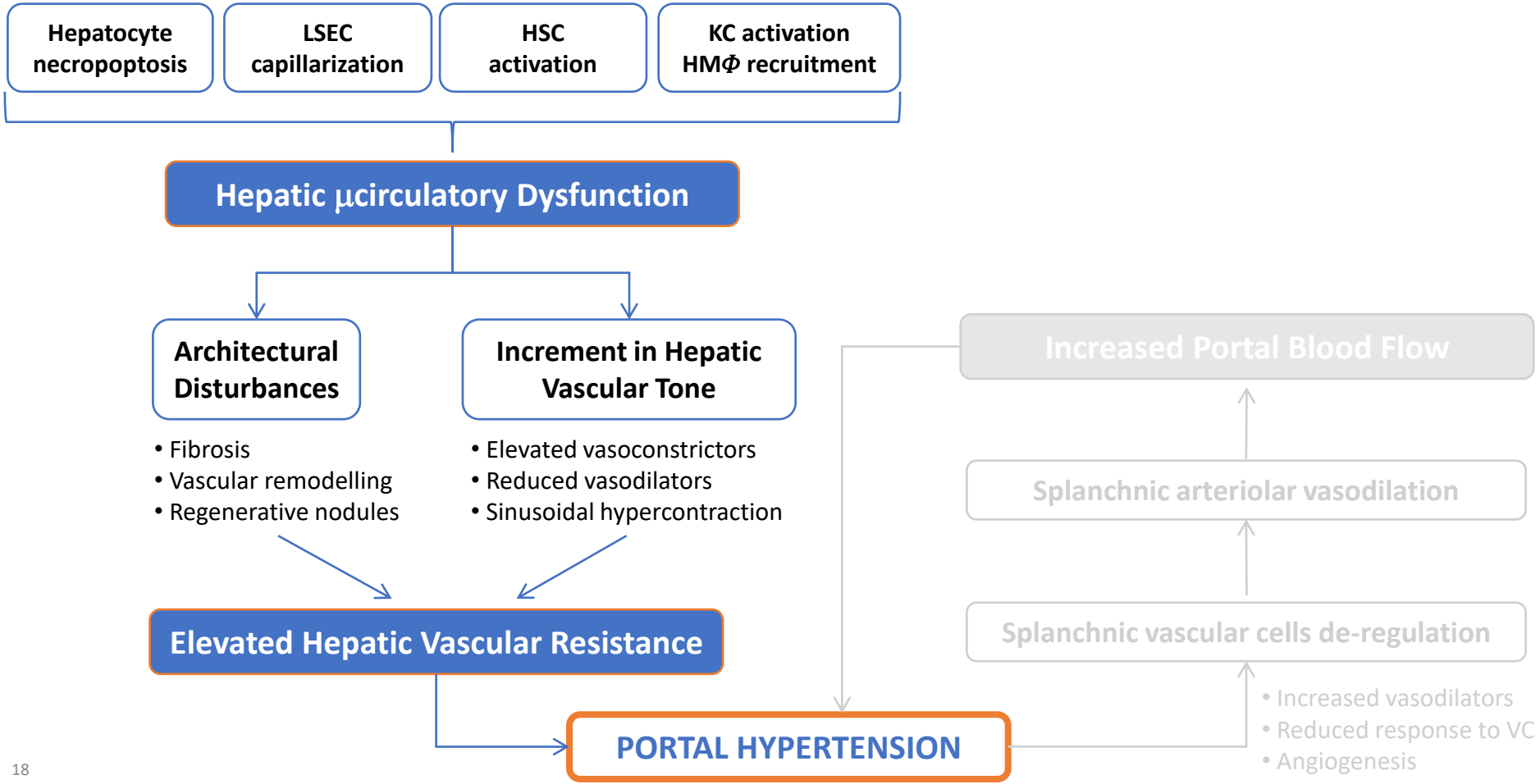
1.300.000 deaths/year worldwide

Portal Hypertension Pathophysiology – The Global Picture

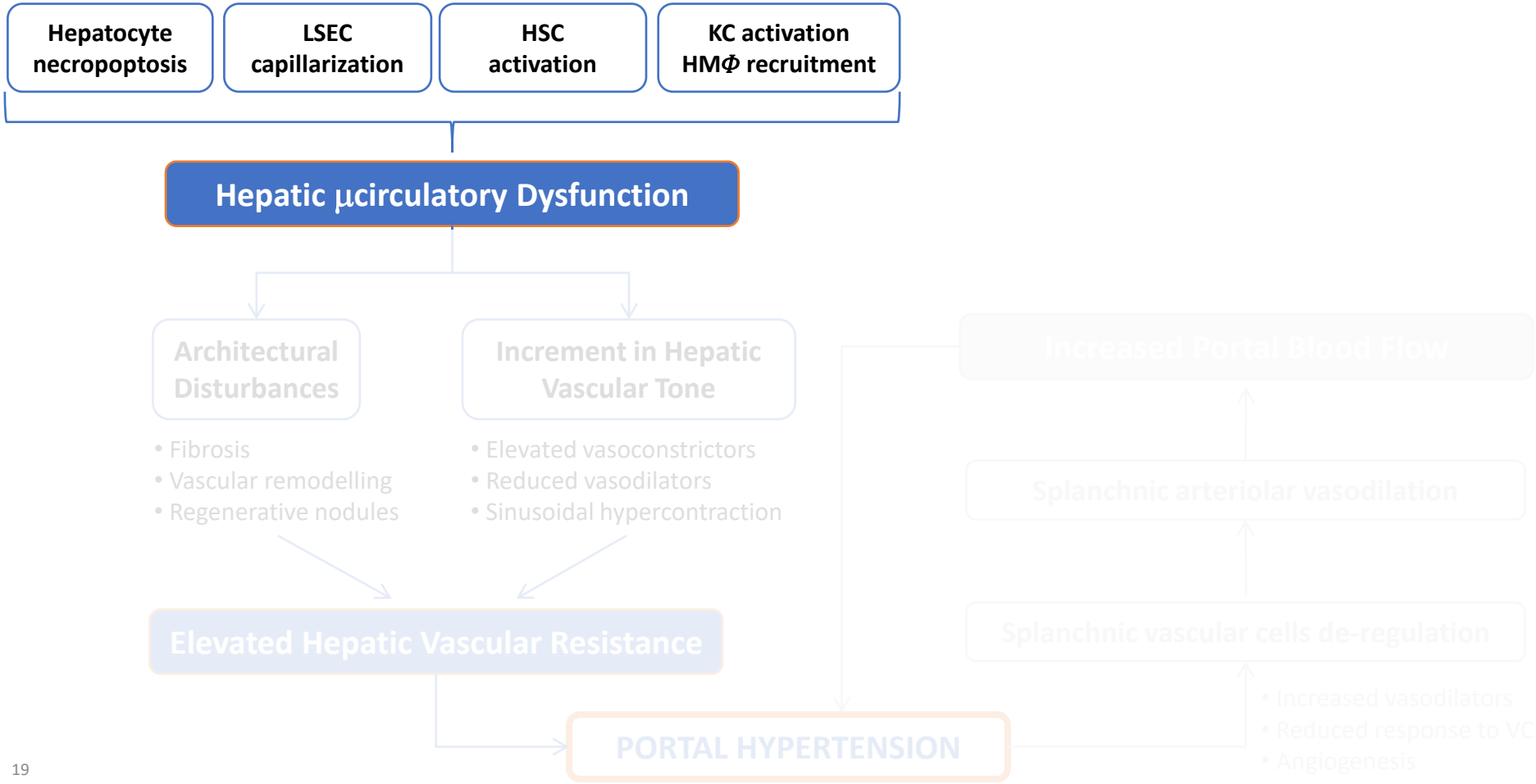


Gracia-Sancho et al, Nature Reviews Gastro & Hepatol 2019

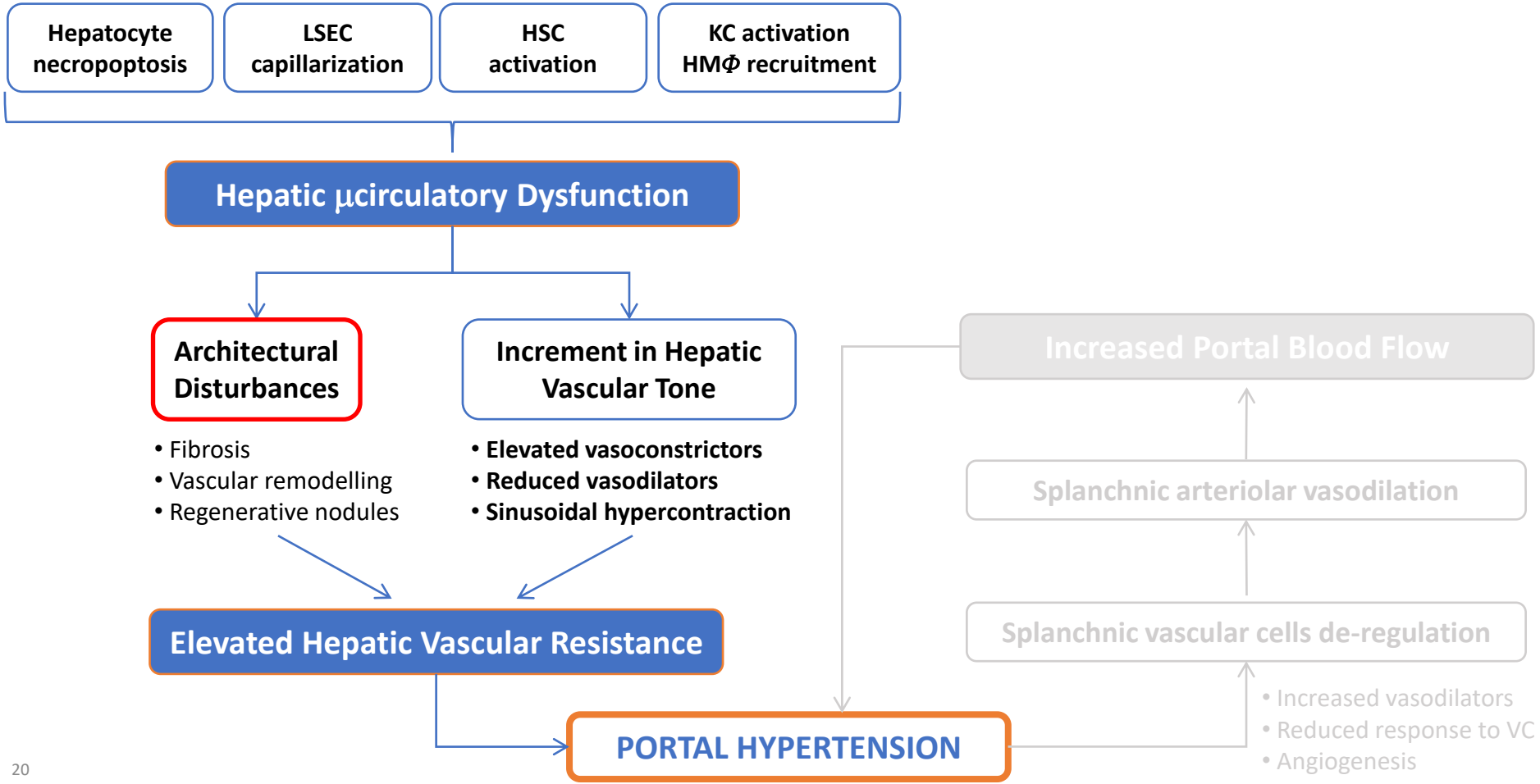
Portal Hypertension Pathophysiology – The Global Picture



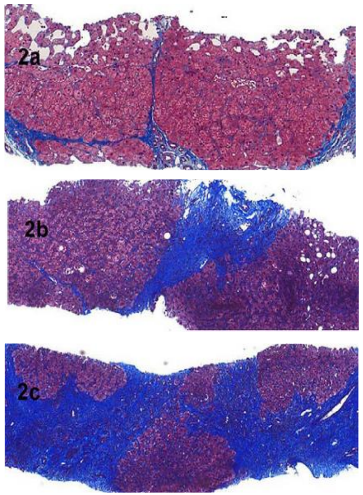
Portal Hypertension Pathophysiology – The Global Picture

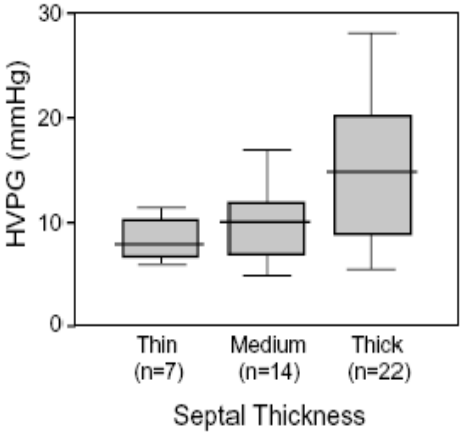


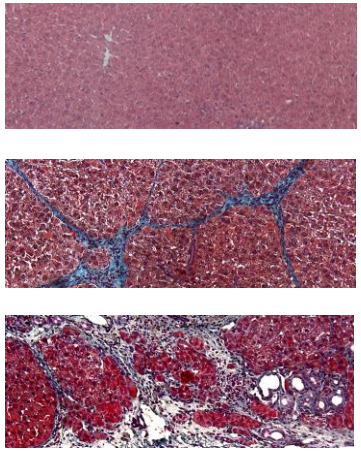
Portal Hypertension Pathophysiology – The Global Picture

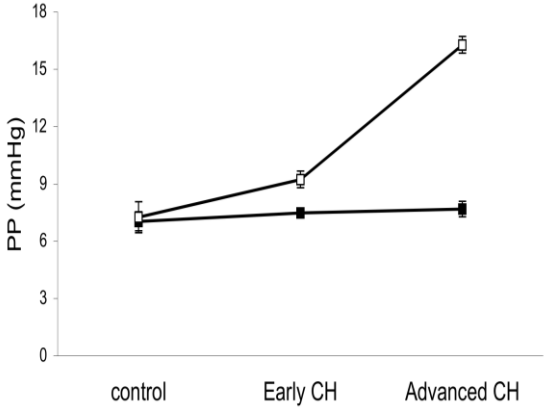


Portal Hypertension Pathophysiology – Architectural disturbances





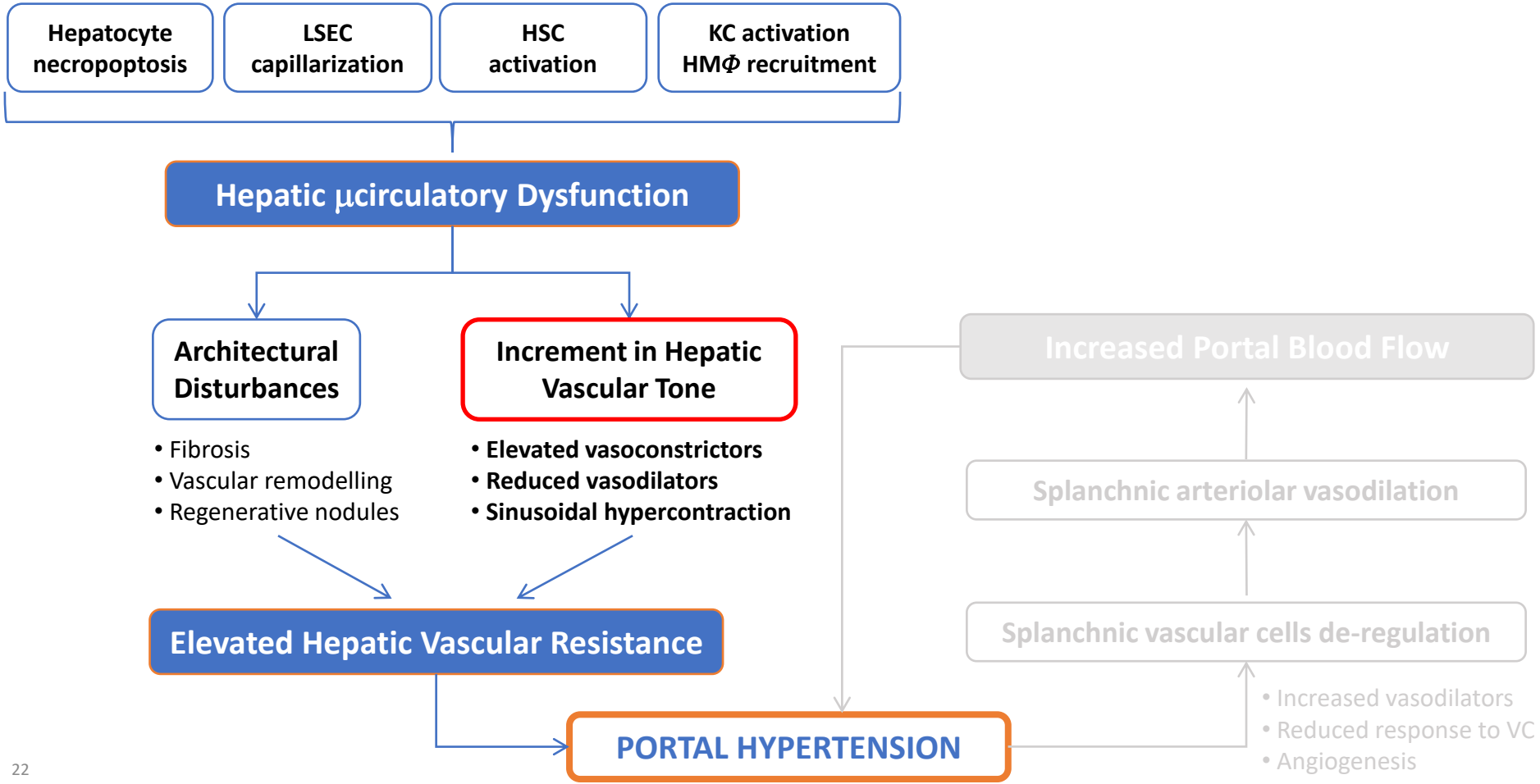




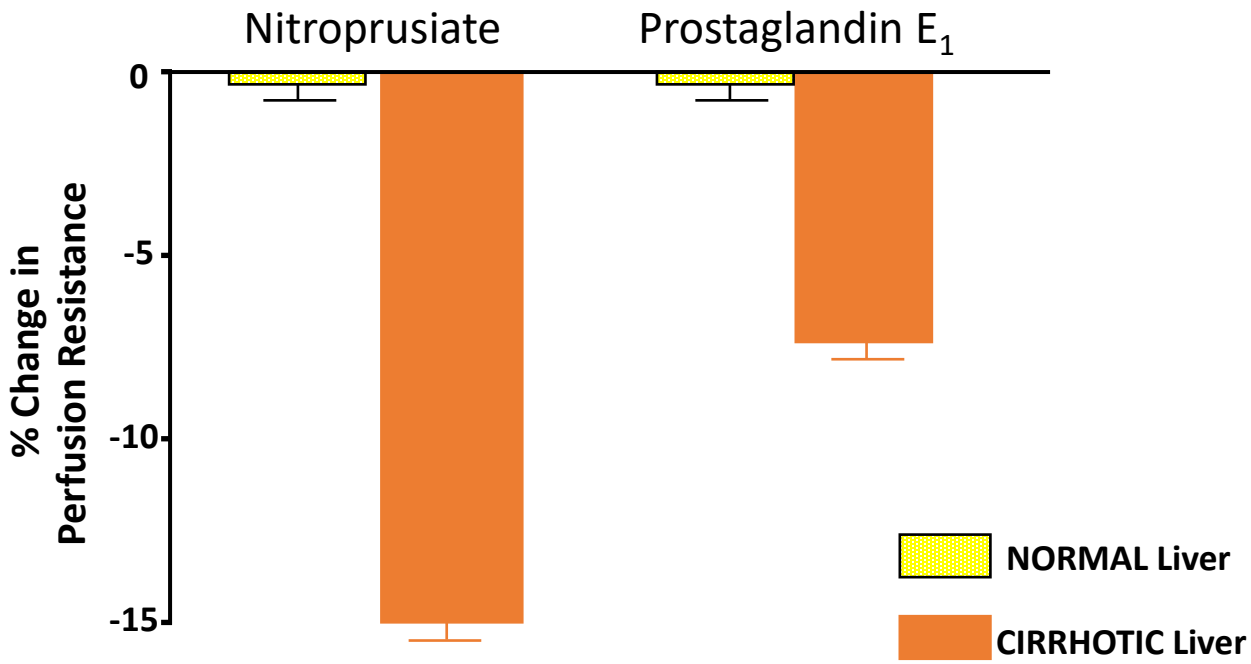
Nagula et al. J Hepatol 2006

Gracia-Sancho et al. Gut 2011

Portal Hypertension Pathophysiology – The Global Picture



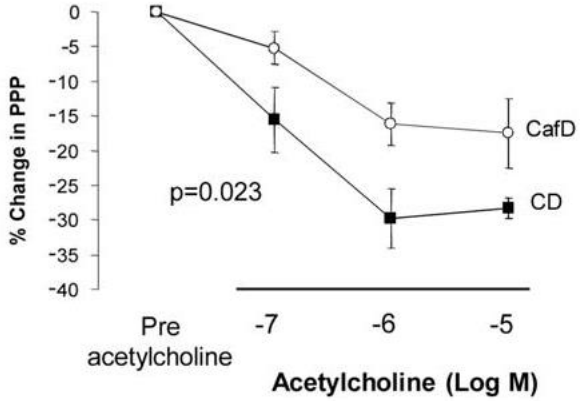
Portal Hypertension Pathophysiology – Vascular disturbances

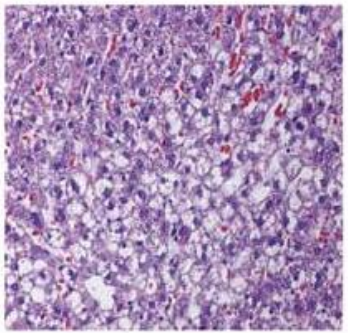


Bhathal and Grossman. J Hepatol 1985

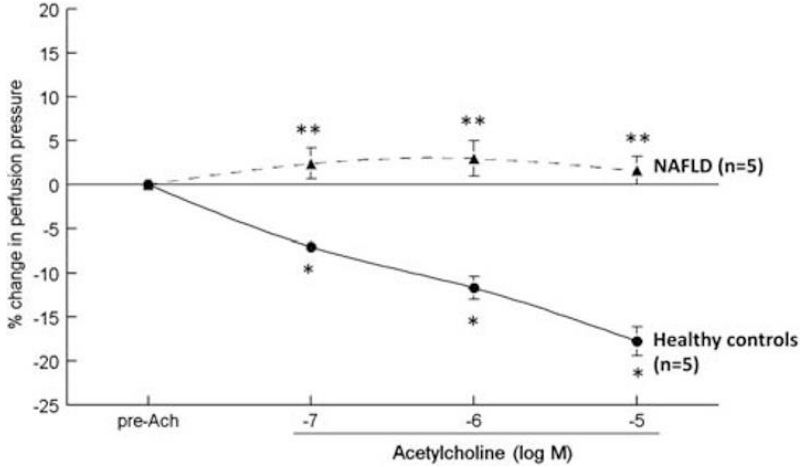
Portal Hypertension Pathophysiology – Vascular dysfunction development

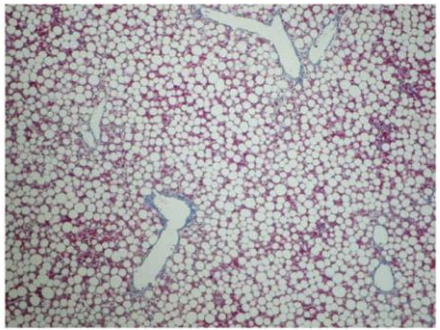
4w CafD





4w MCD





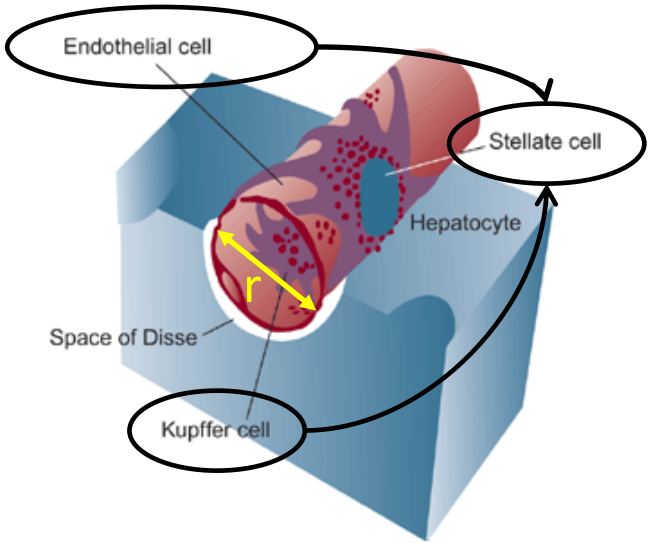
Pasarín et al. Plos One 2012

Franque et al. Lab Invest 2012

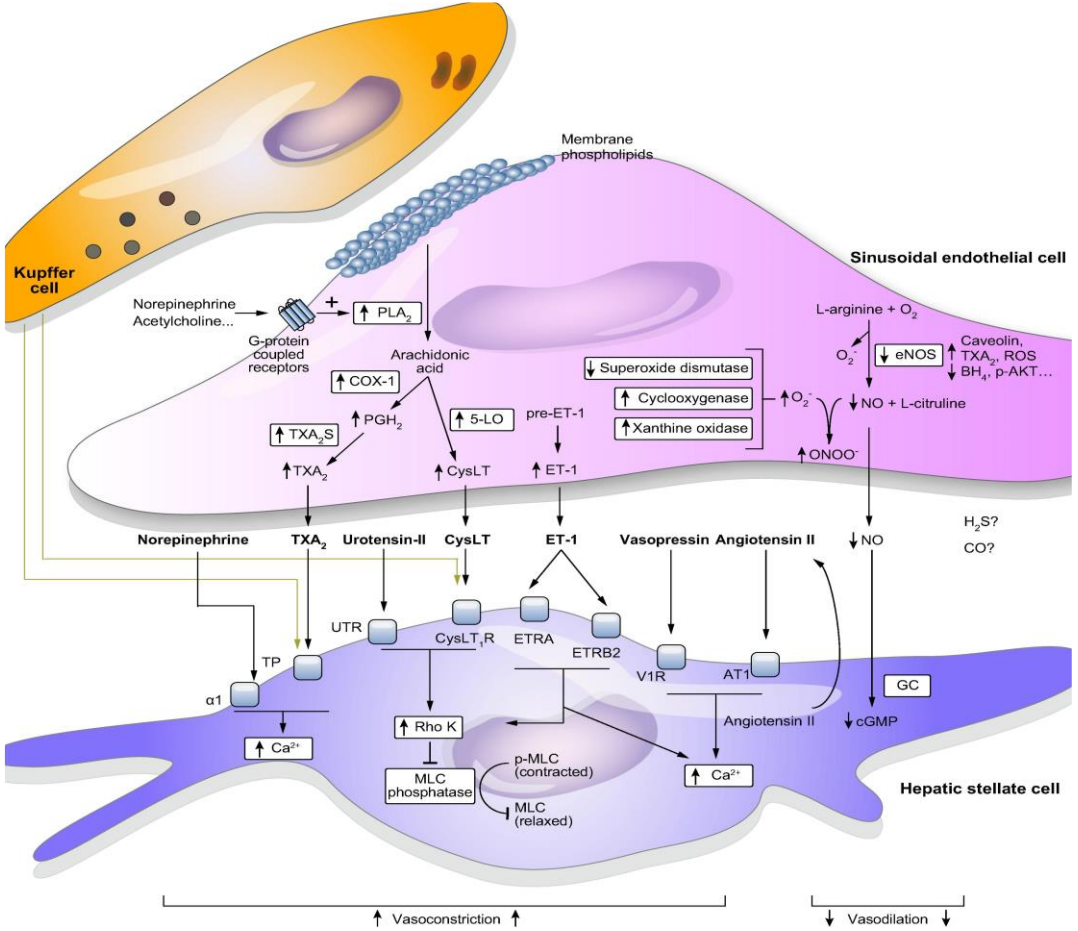
Portal Hypertension Pathophysiology – Dynamic component of the HVR

$$R = 8\eta L / r^4$$

Intrahepatic contractile elements	Regulation of contraction

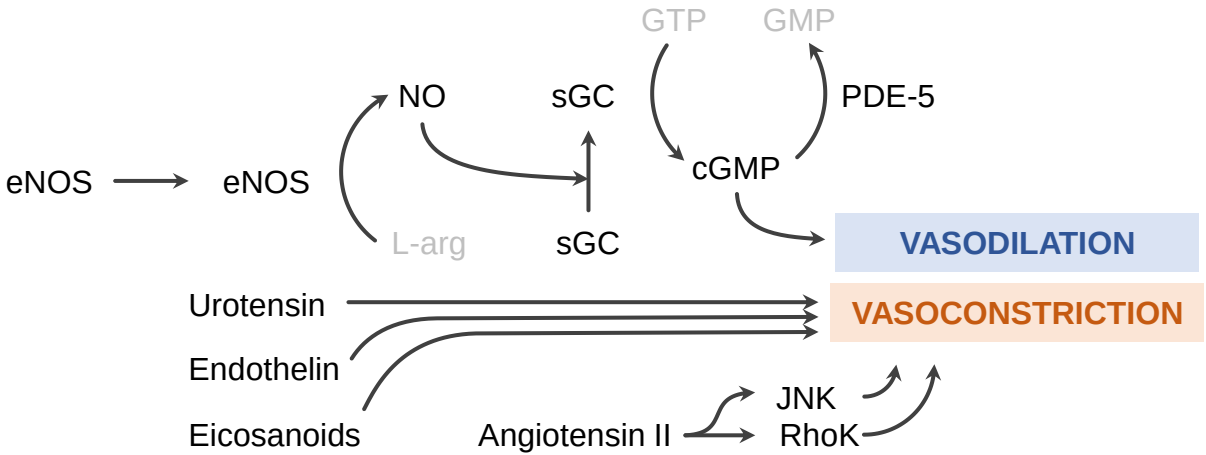


Portal Hypertension Pathophysiology – Dynamic component of the HVR



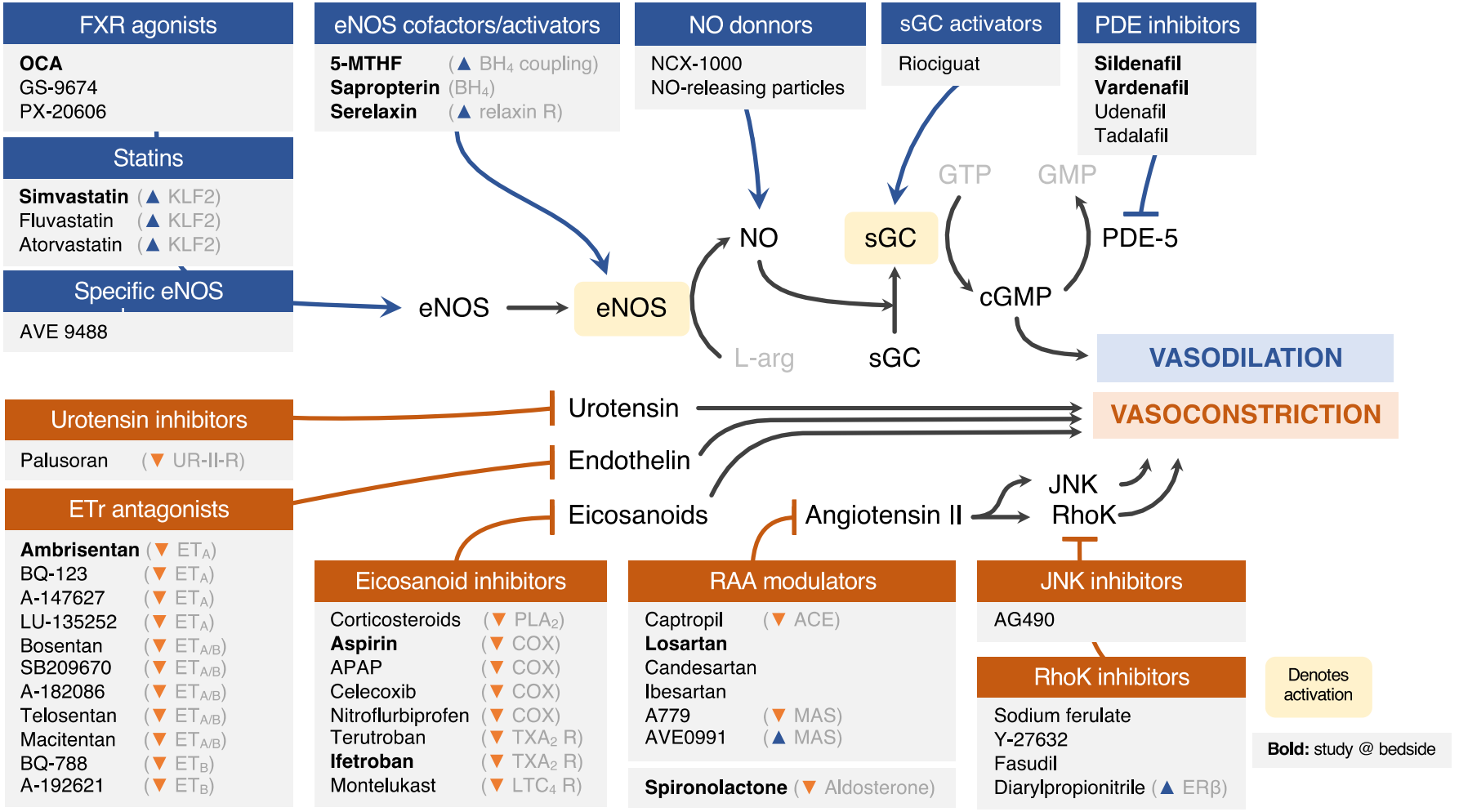
García-Pagán, Gracia-Sancho, Bosch. JHEP 2012

Promoting CLD regression: Targeting the sinusoid

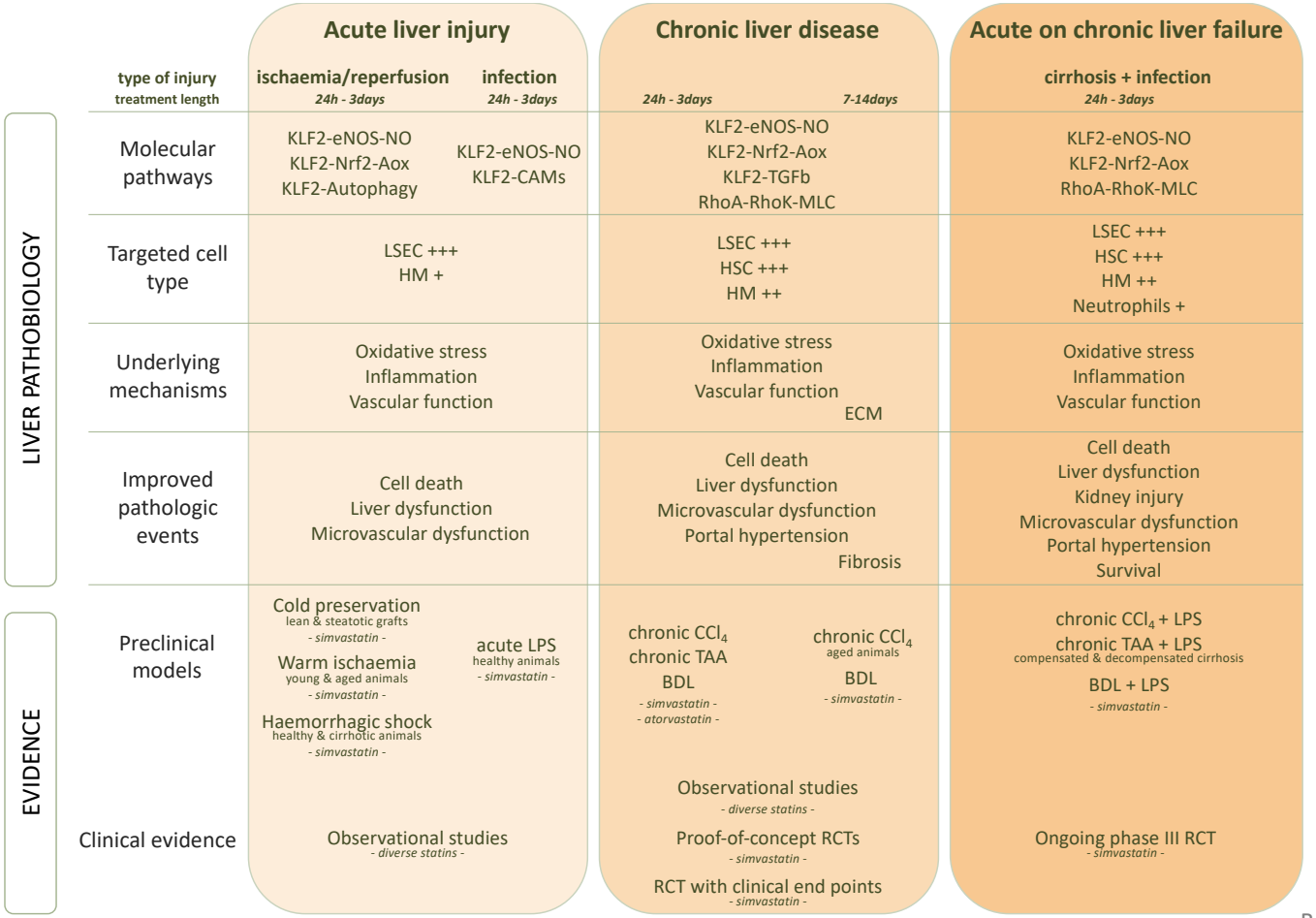


Promoting CLD regression: Targeting the sinusoid

Vilaseca, Guixé…Gracia-Sancho. Ther Adv Gastro 2018

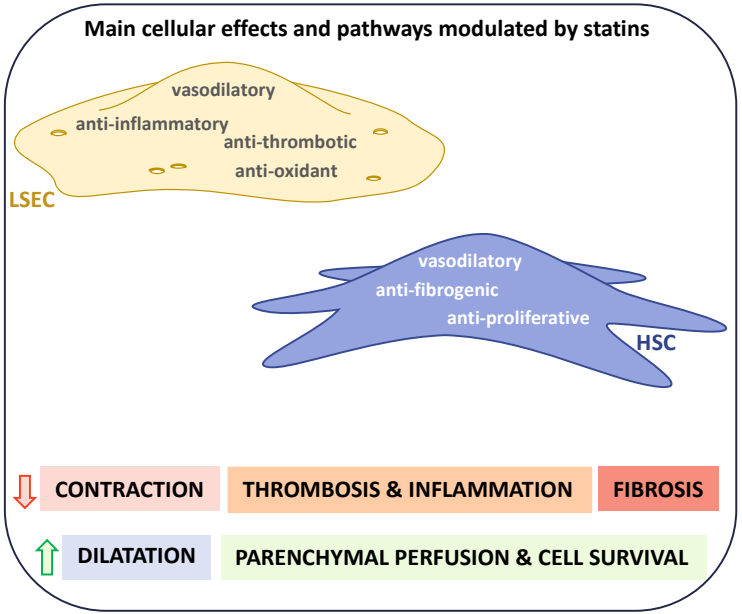


Promoting CLD regression: therapeutics - statins



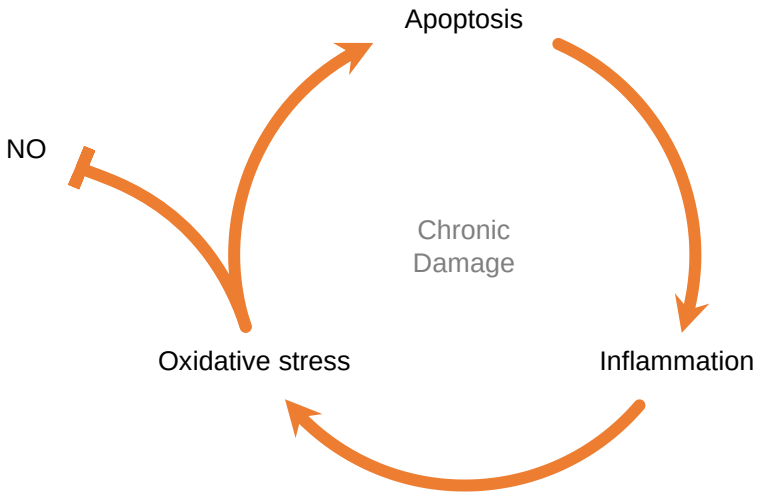
Bosch, Gracia-Sancho & Abraldes, Gut 2020

Promoting CLD regression: therapeutics - statins



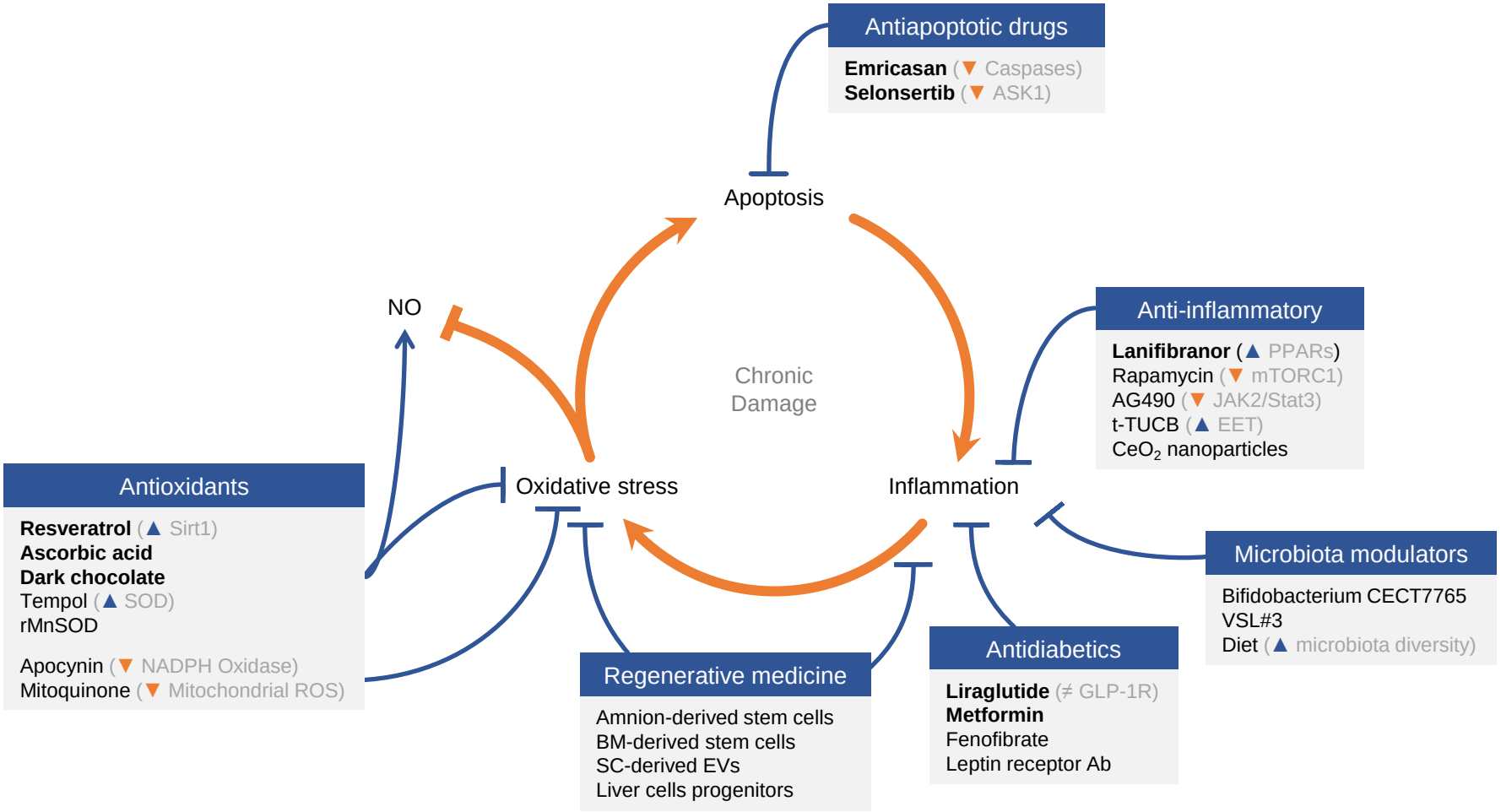
Gracia-Sancho et al, Gut 2011
Marrone … Gracia-Sancho , JHep 2013
Gracia-Sancho et al, JHep 2013
Marrone … Gracia-Sancho, Gut 2015
Trebicka et al, JHep 2010
Hide, … Gracia-Sancho, Scientific Rep 2016
Guixé-Muntet, … Gracia-Sancho, JHep 2017
Tripathi, Vilaseca … Gracia-Sancho, Gastro 2018
Maeso, … Gracia-Sancho, Aging Disease 2019
Bosch, Gracia-Sancho & Abraldes, Gut 2020

Promoting CLD regression: targeting the sinusoid

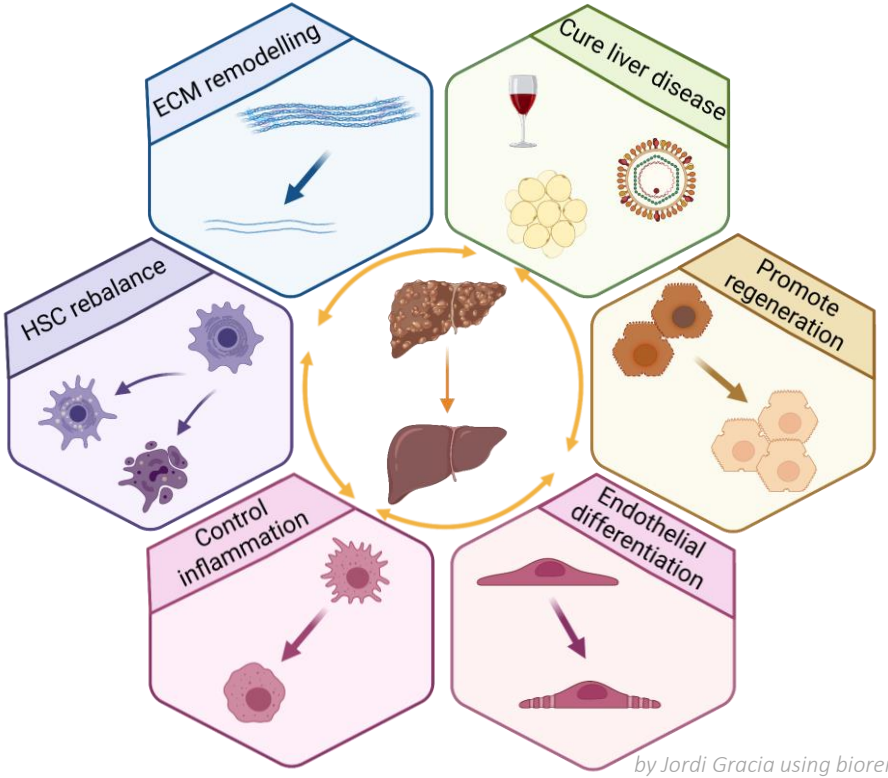


Promoting CLD regression: targeting the sinusoid

Vilaseca, Guixé…Gracia-Sancho. Ther Adv Gastro 2018

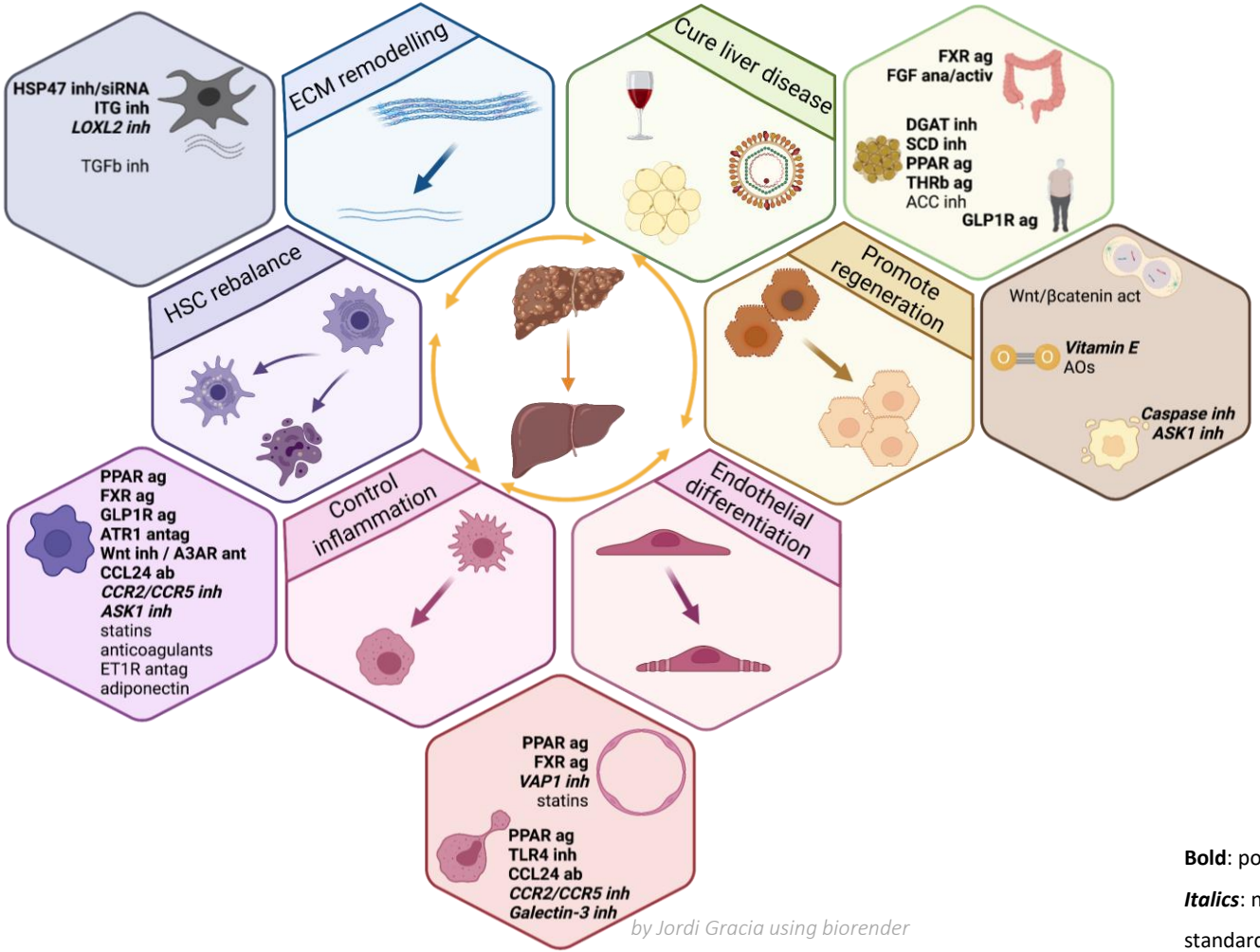


Promoting fibrosis regression: targeting the sinusoid



by Jordi Gracia using biorender

Promoting fibrosis regression: targeting the sinusoid



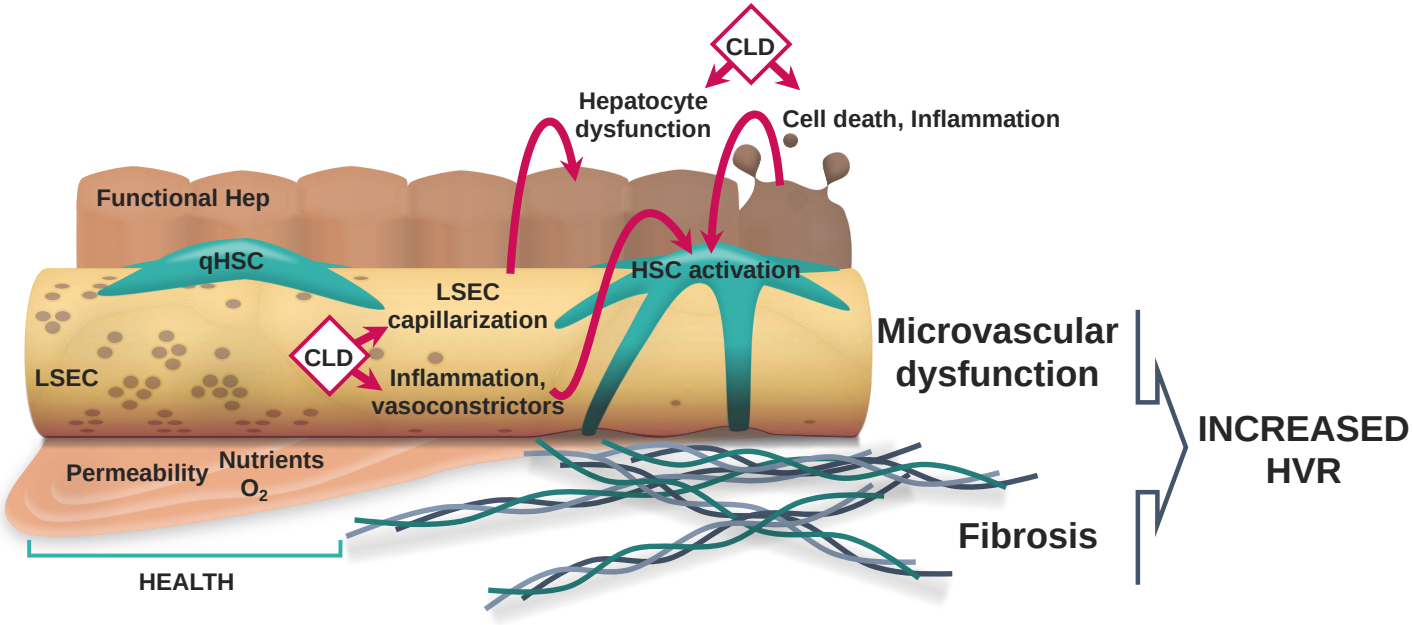
by Jordi Gracia using biorender

Bold: positive or ongoing CT

Italics: negative CT

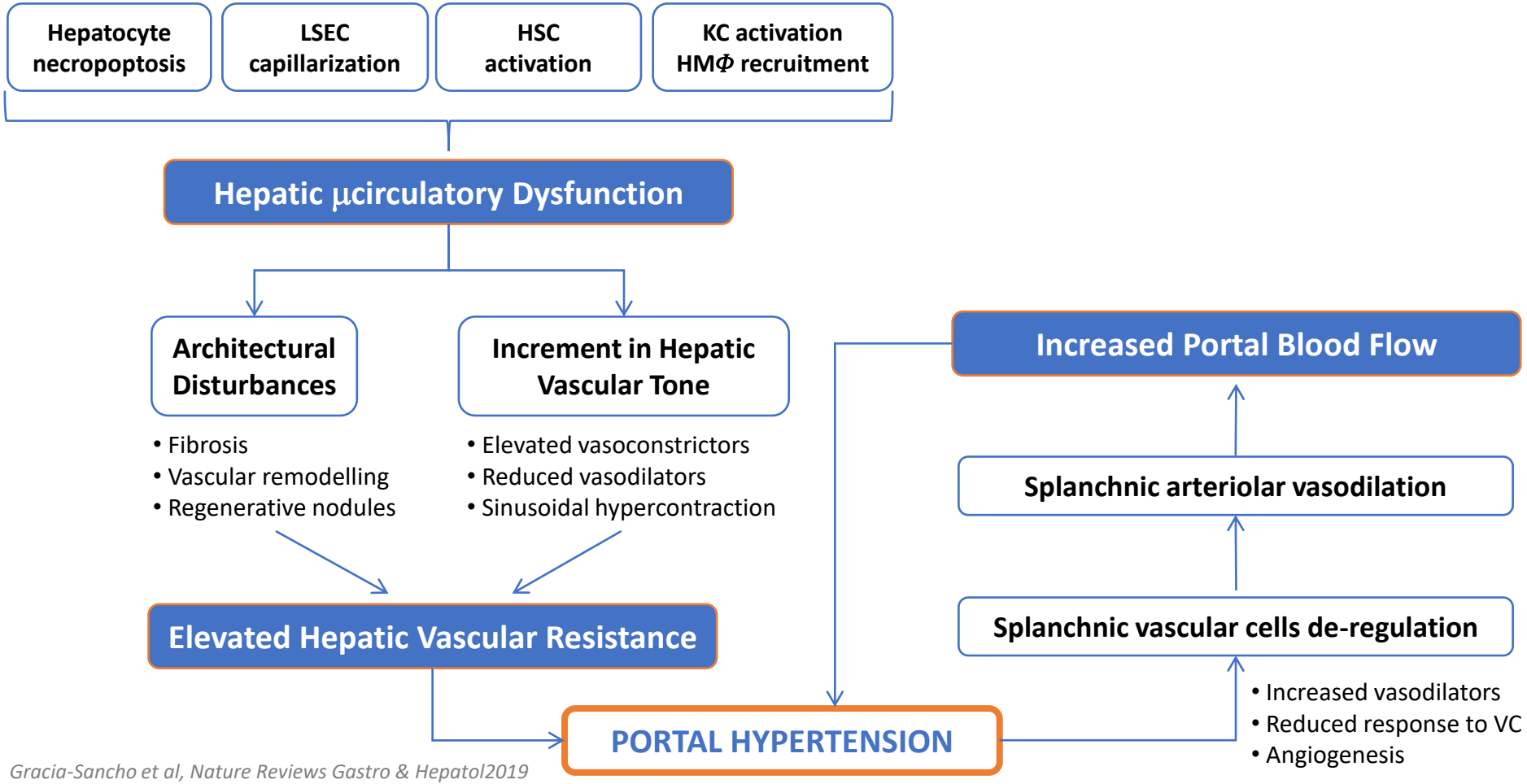
standard: pre-clinical research

Wrap-up 1: Progression of CLD and PH



Guixé … Gracia-Sancho, Pharmacol & Therapeutics 2020

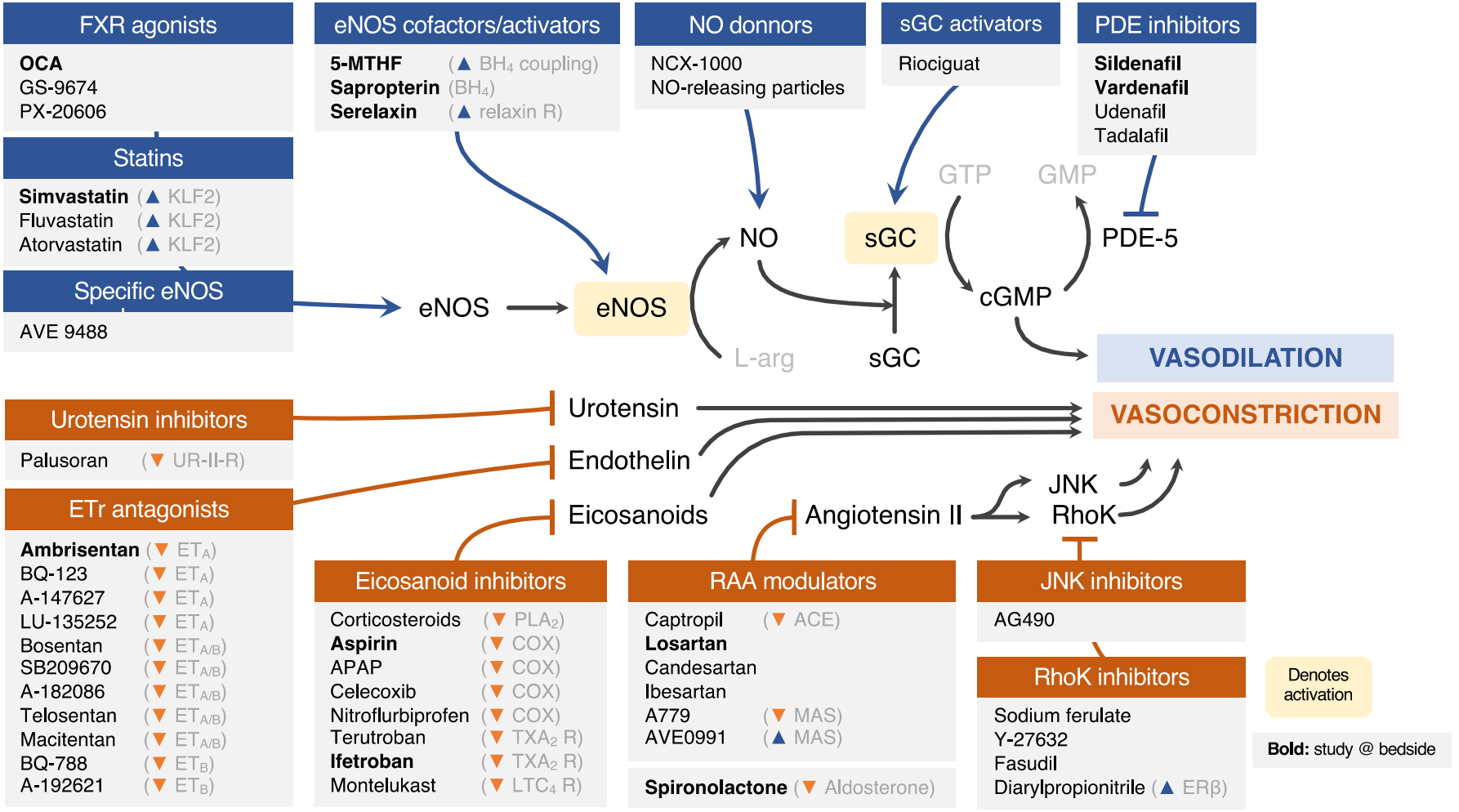
Wrap-up 2: Role of the hepatic sinusoid in the pathophysiology of PH



Gracia-Sancho et al, Nature Reviews Gastro & Hepatol2019

Wrap-up 3: therapeutics for PH targeting the sinusoid

Vilaseca, Guixé…Gracia-Sancho. Ther Adv Gastro 2018



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