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

Jordi Gracia-Sancho, PhD

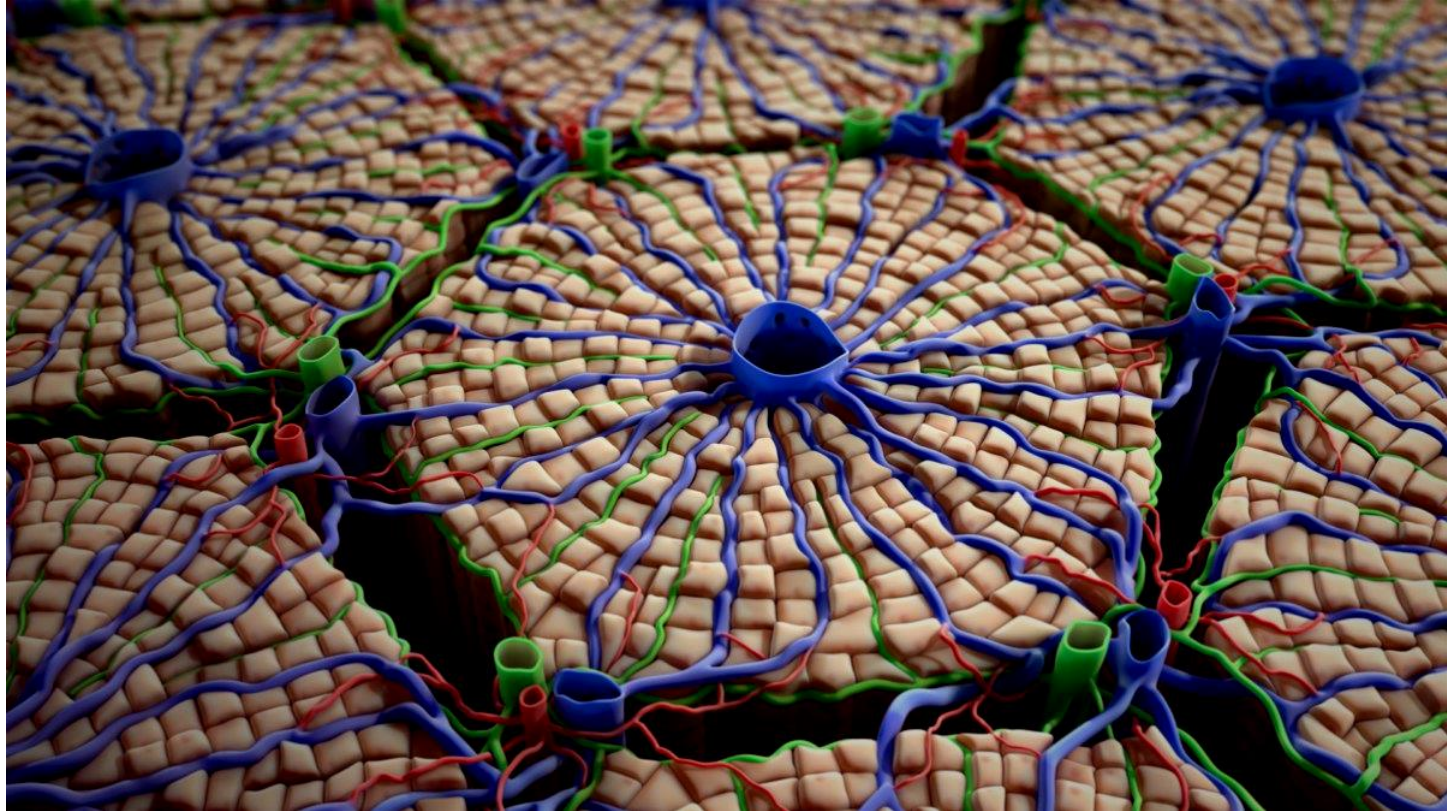
Liver Vascular Biology Research Group
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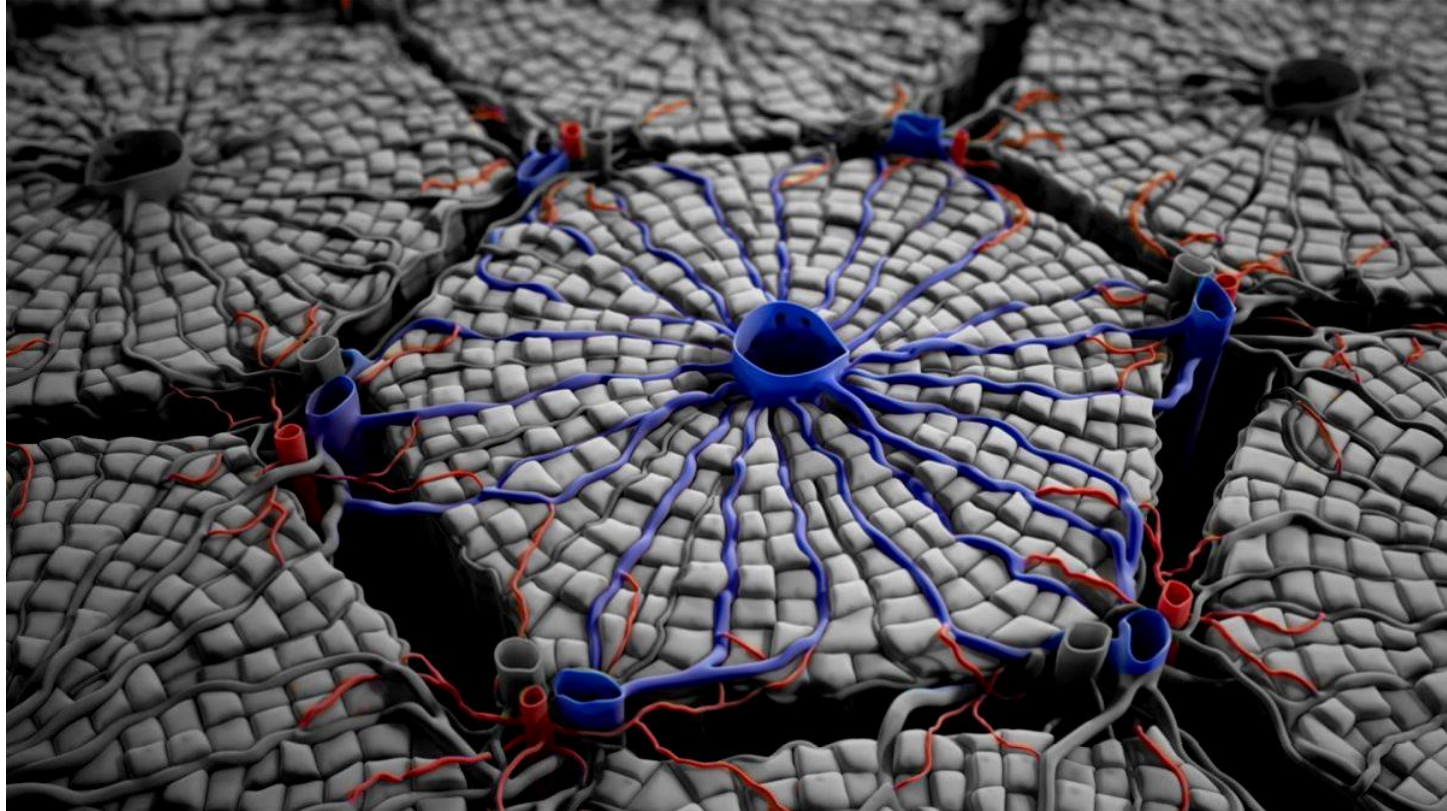
 @jsgracia

- Liver microcirculation & the hepatic sinusoid
- Modulation of liver microcirculation – impact on PH
- Novel therapeutics to improve the hepatic sinusoid

Liver microcirculation



Liver microcirculation

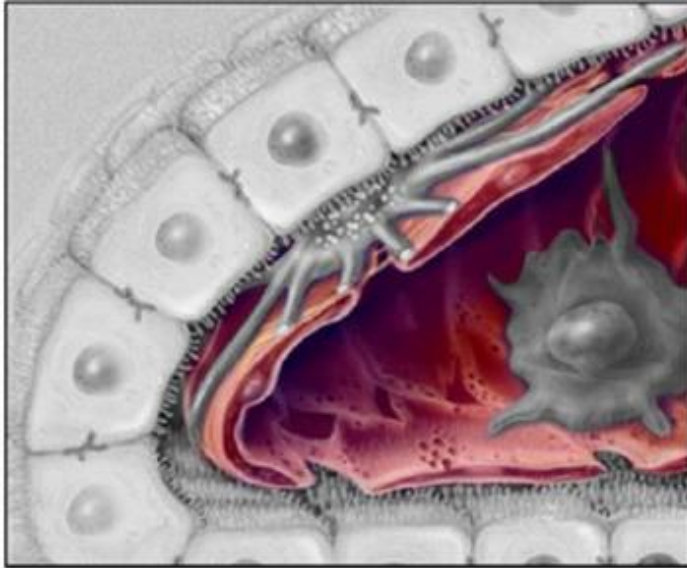


The liver sinusoid



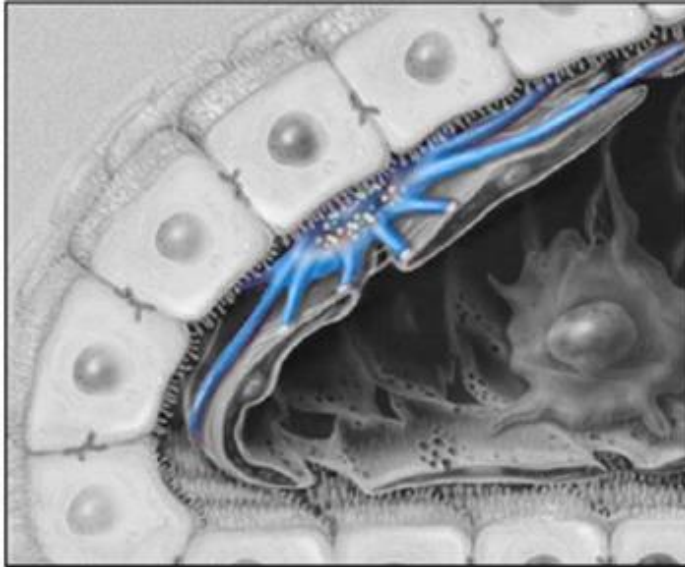
Friedman SL. *Nat Clin Pract Gastroenterol Hepatol* 2004

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



Liver Sinusoidal Endothelial Cells (LSEC)

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

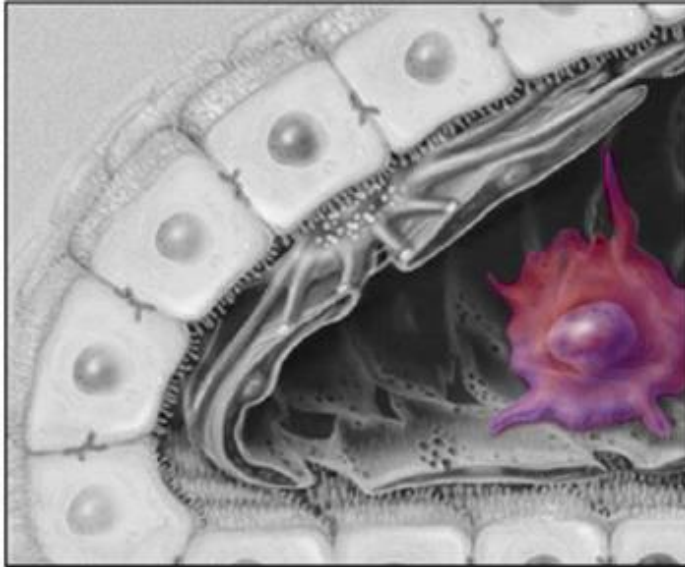


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Hepatic Stellate Cells (HSC)

- Contractile properties.
- Vitamin A storage



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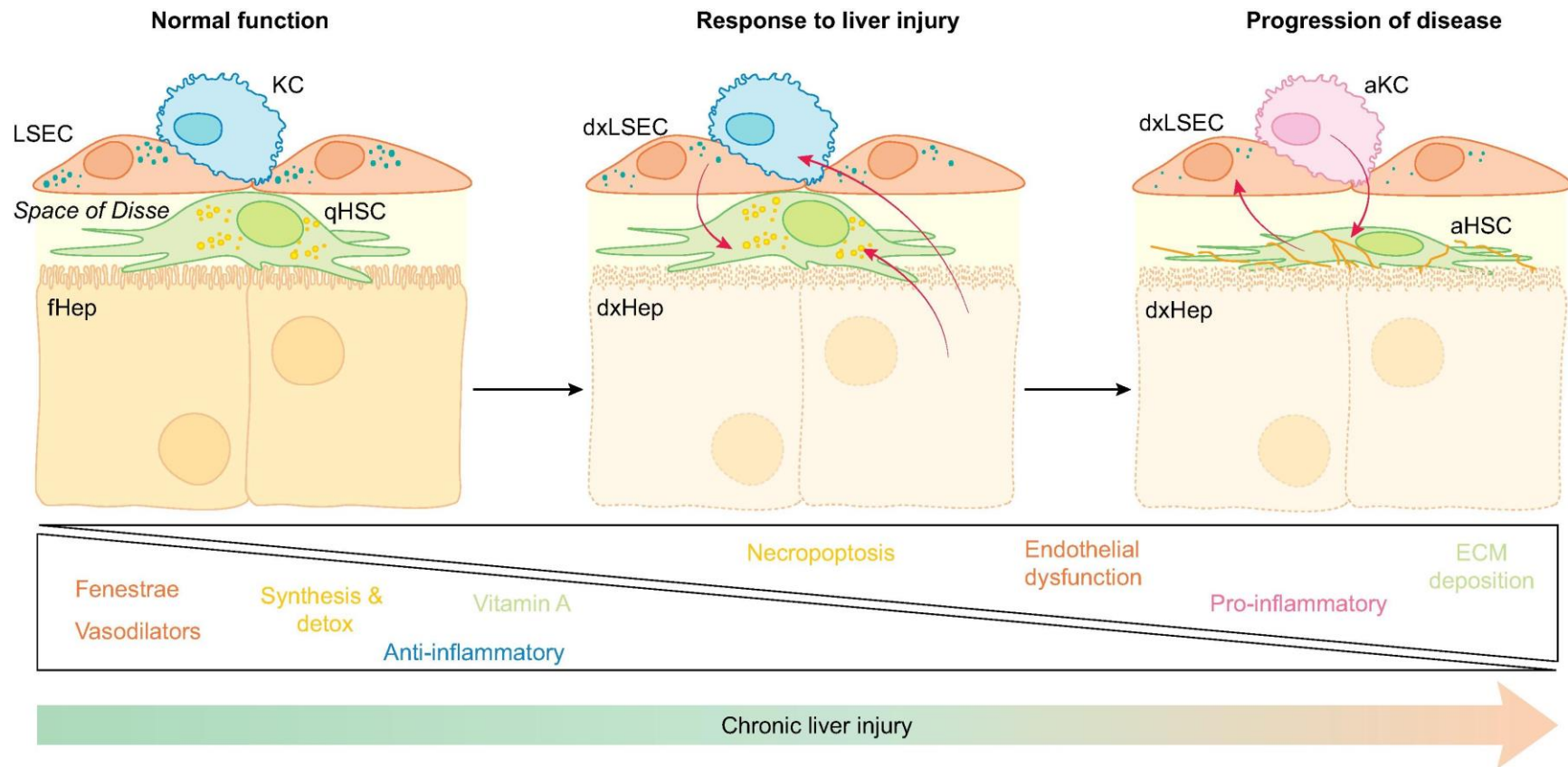
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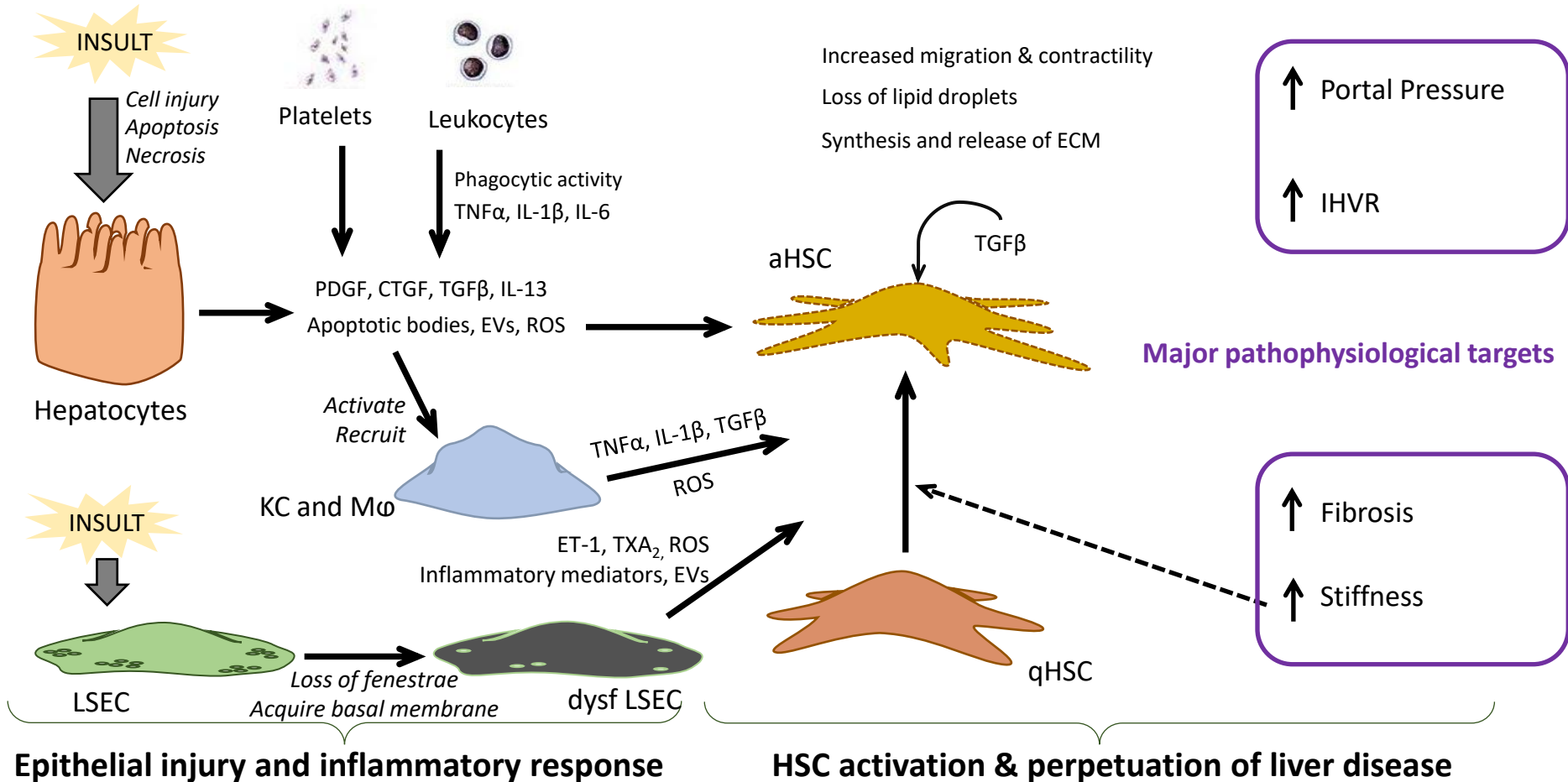
Kupffer Cells (KC)

- Resident macrophages: defense, inflammation, tissue remodelling.

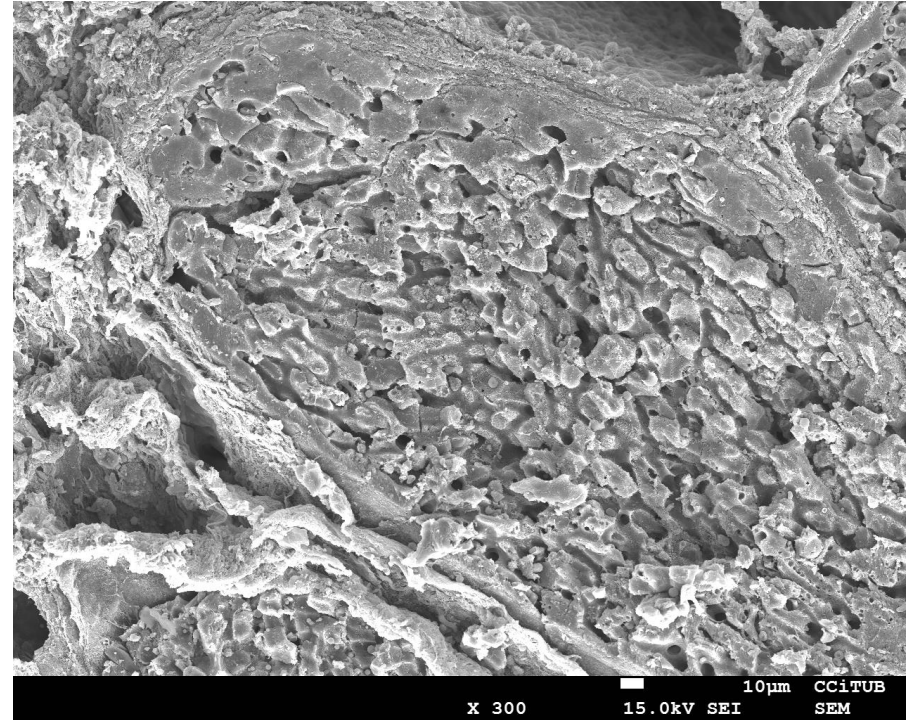
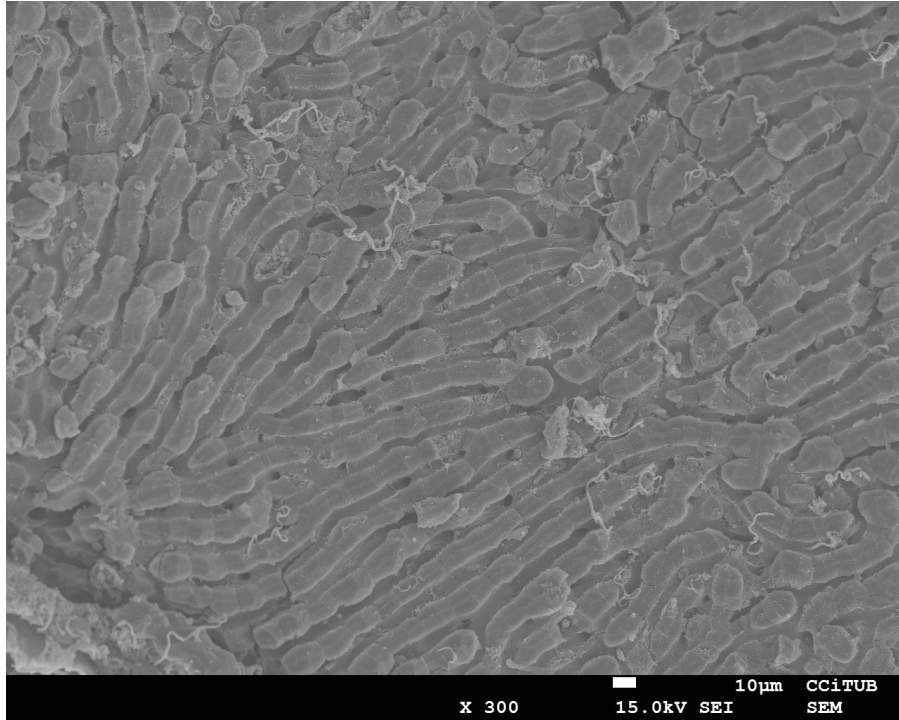
The liver sinusoid in the progression of CLD



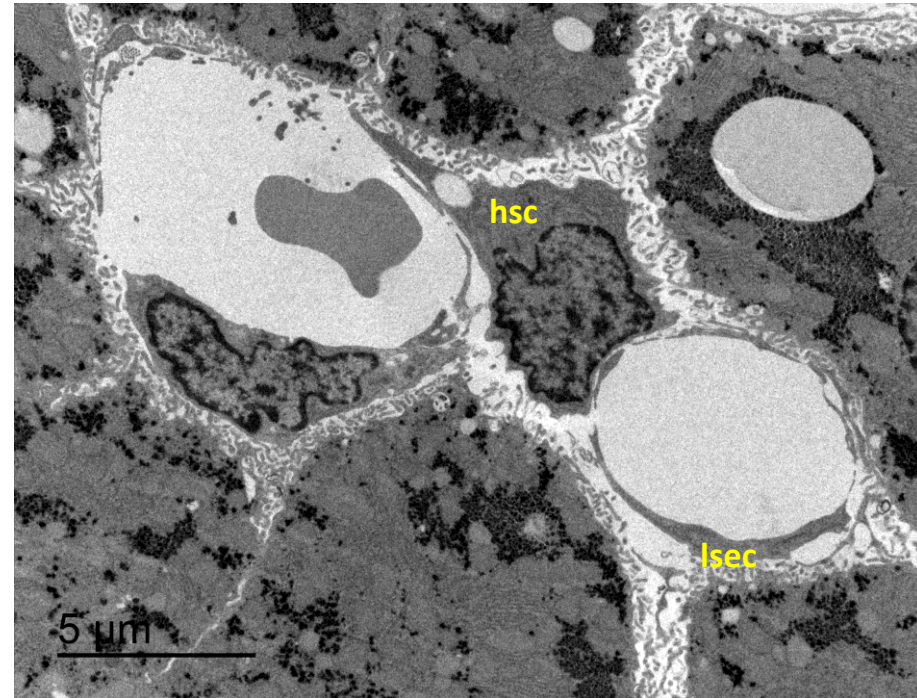
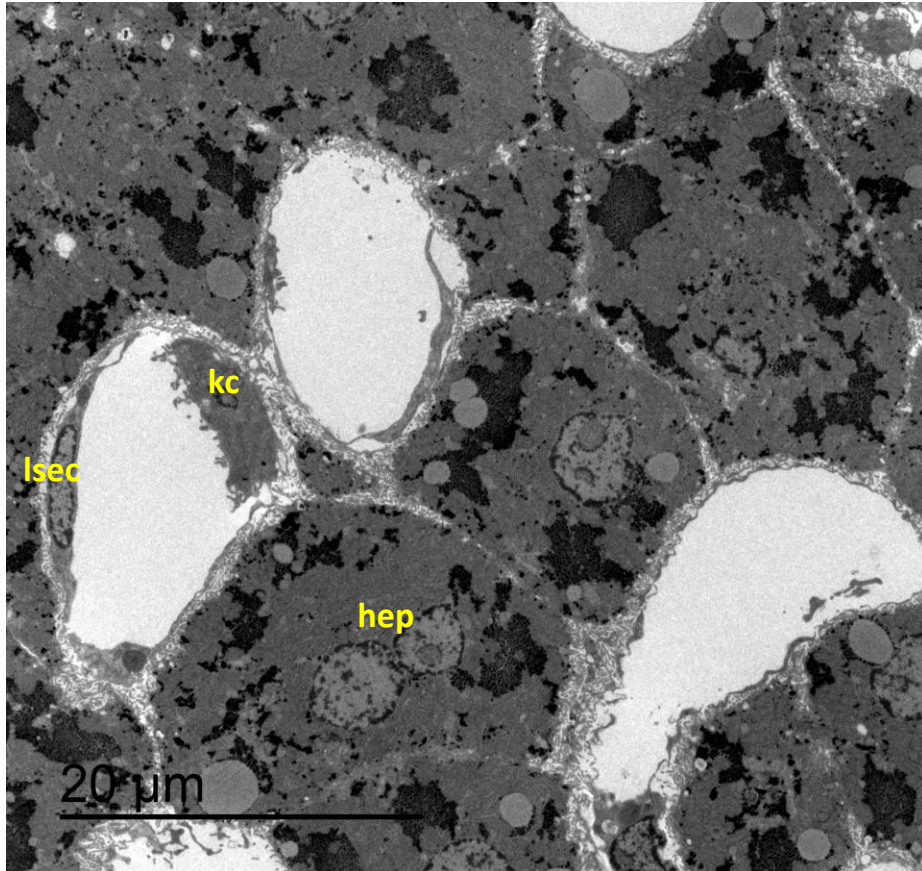
Overview of CLD progression



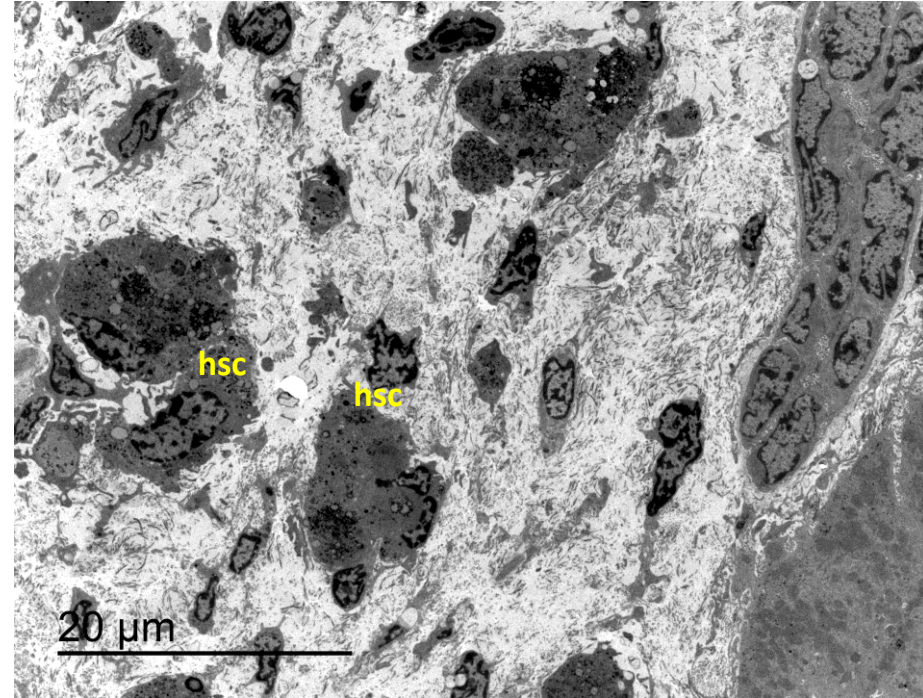
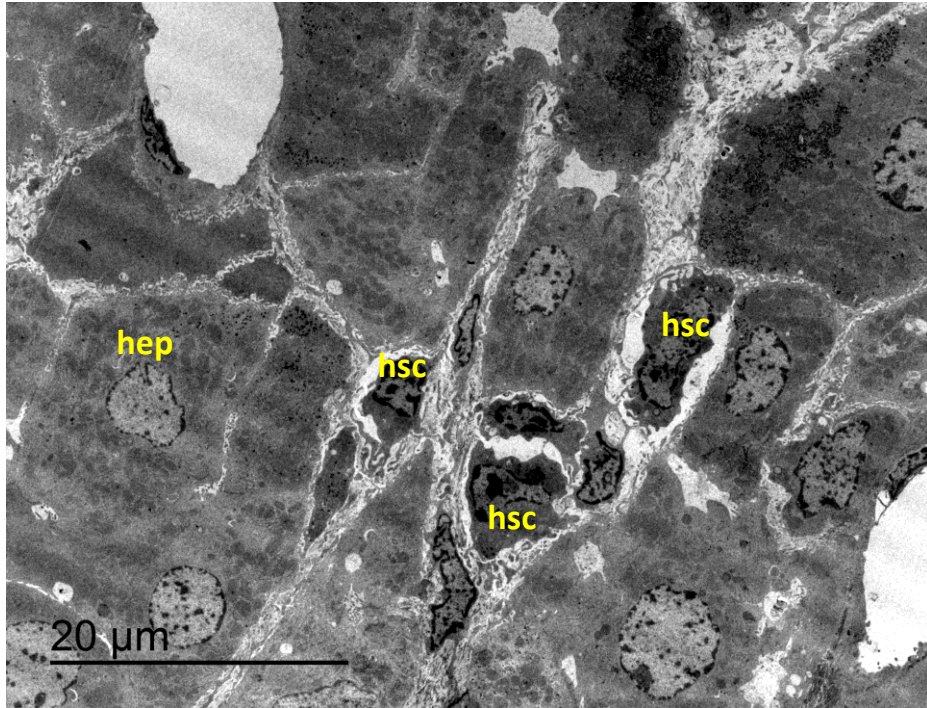
The liver sinusoid



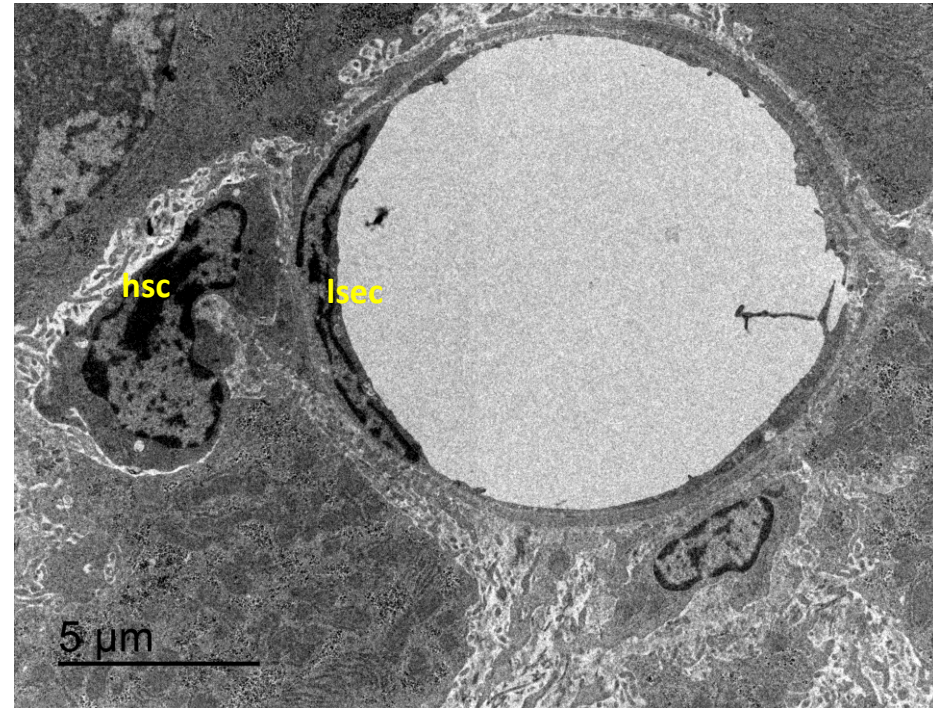
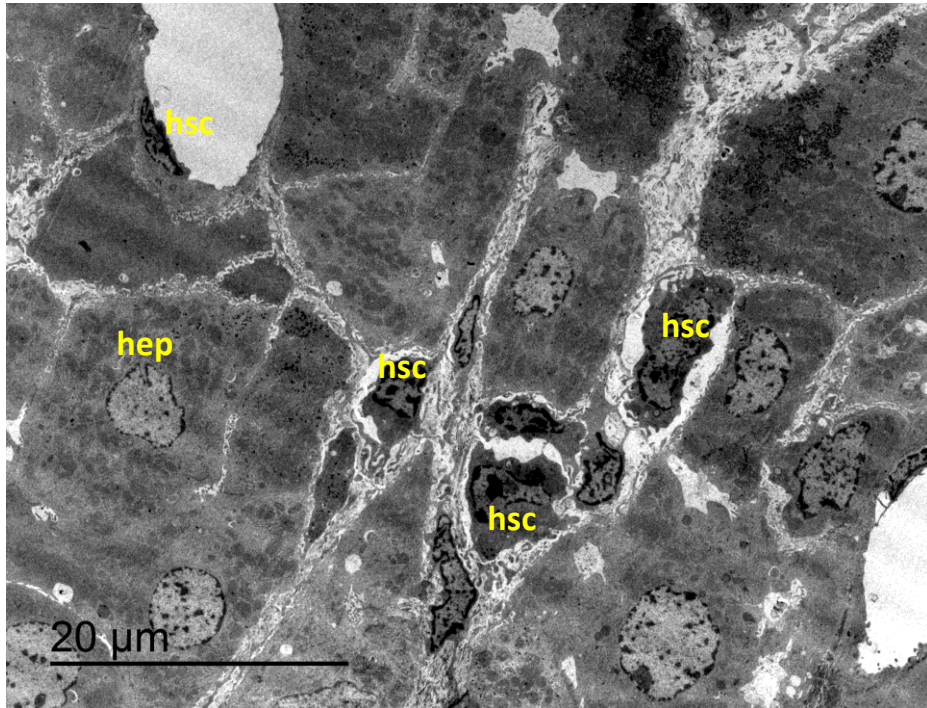
The liver sinusoid



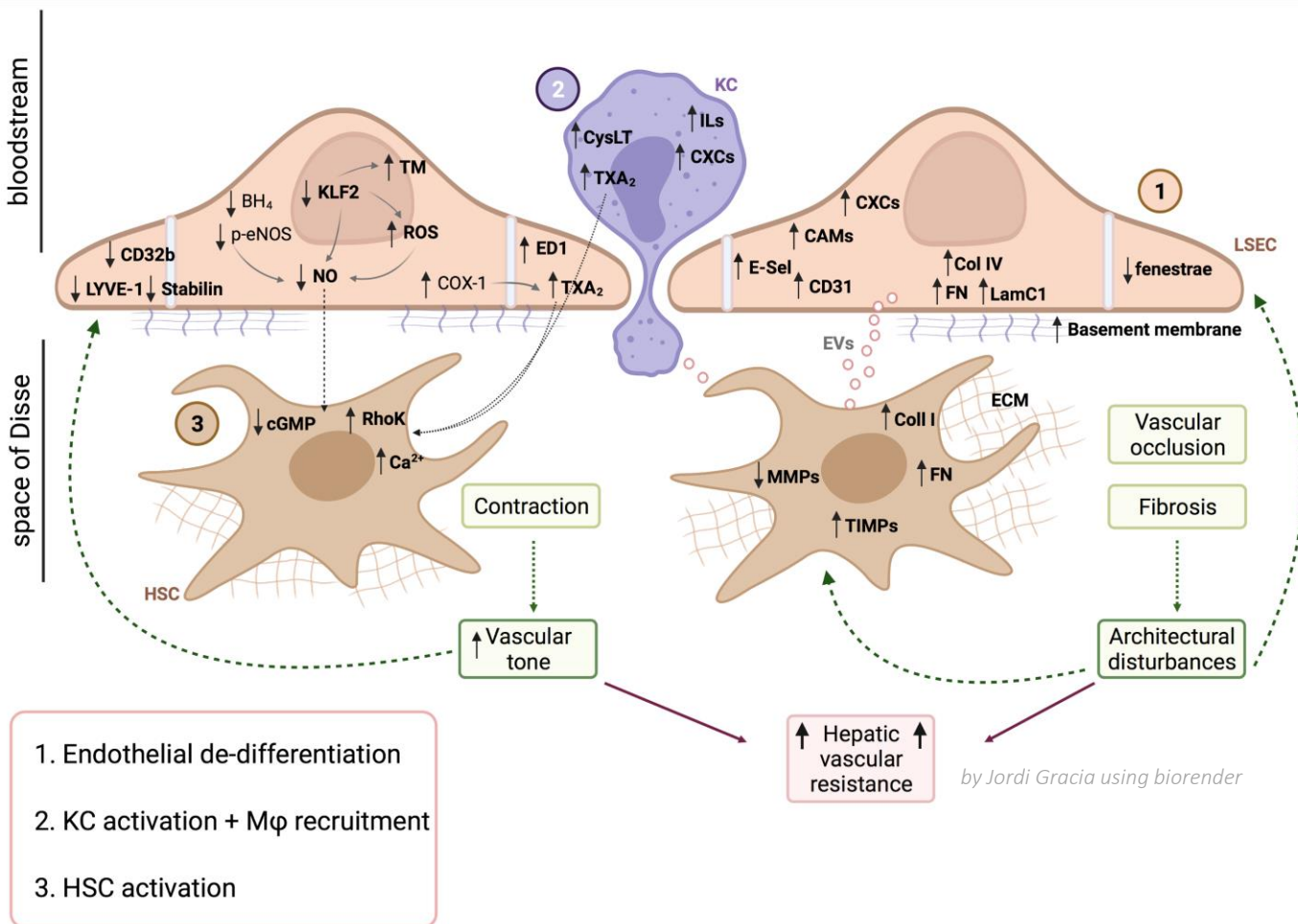
The liver sinusoid in cirrhosis



The liver sinusoid in cirrhosis

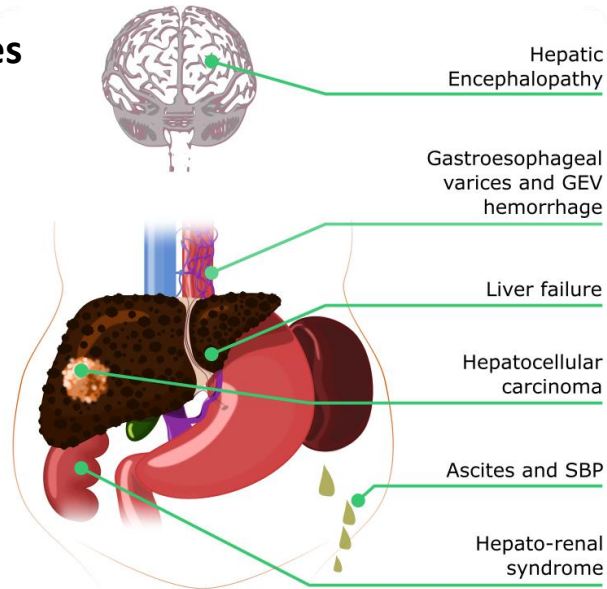


Hepatic microcirculatory dysfunction



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

Consequences

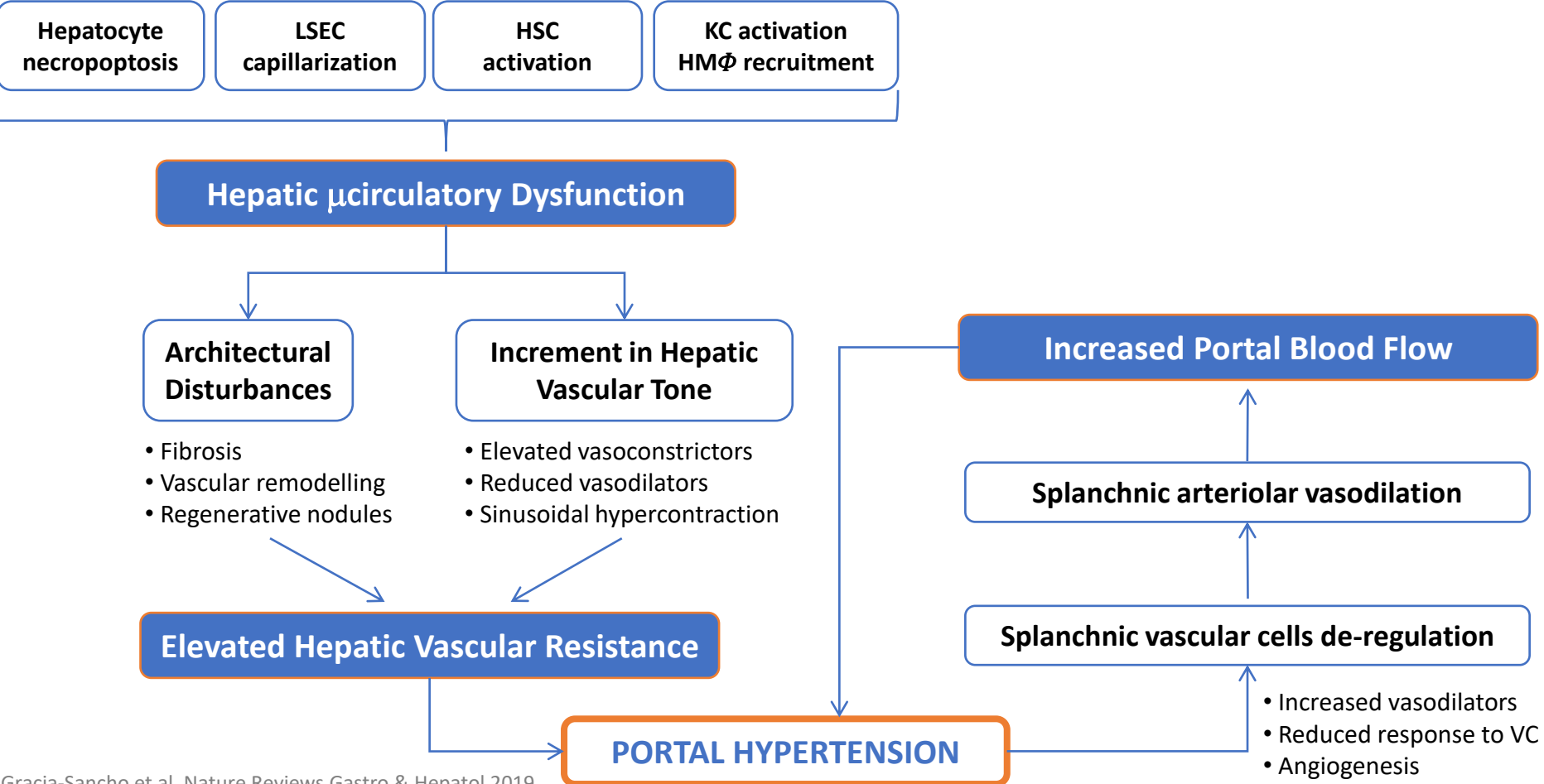


Reversible by decreasing portal pressure

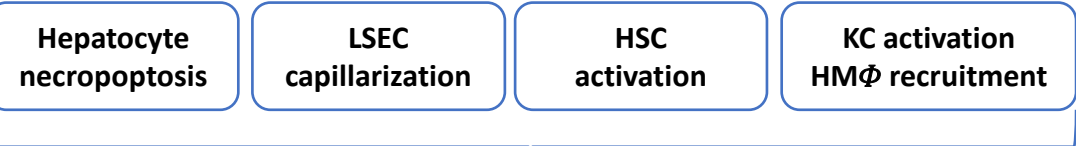
170.000 deaths/year in the EU

1.300.000 deaths/year worldwide

Portal Hypertension Pathophysiology – The Global Picture



Portal Hypertension Pathophysiology – The Global Picture



Hepatic μ irculatory Dysfunction

Architectural Disturbances

- Fibrosis
- Vascular remodelling
- Regenerative nodules

Increment in Hepatic Vascular Tone

- Elevated vasoconstrictors
- Reduced vasodilators
- Sinusoidal hypercontraction

Elevated Hepatic Vascular Resistance

PORTAL HYPERTENSION

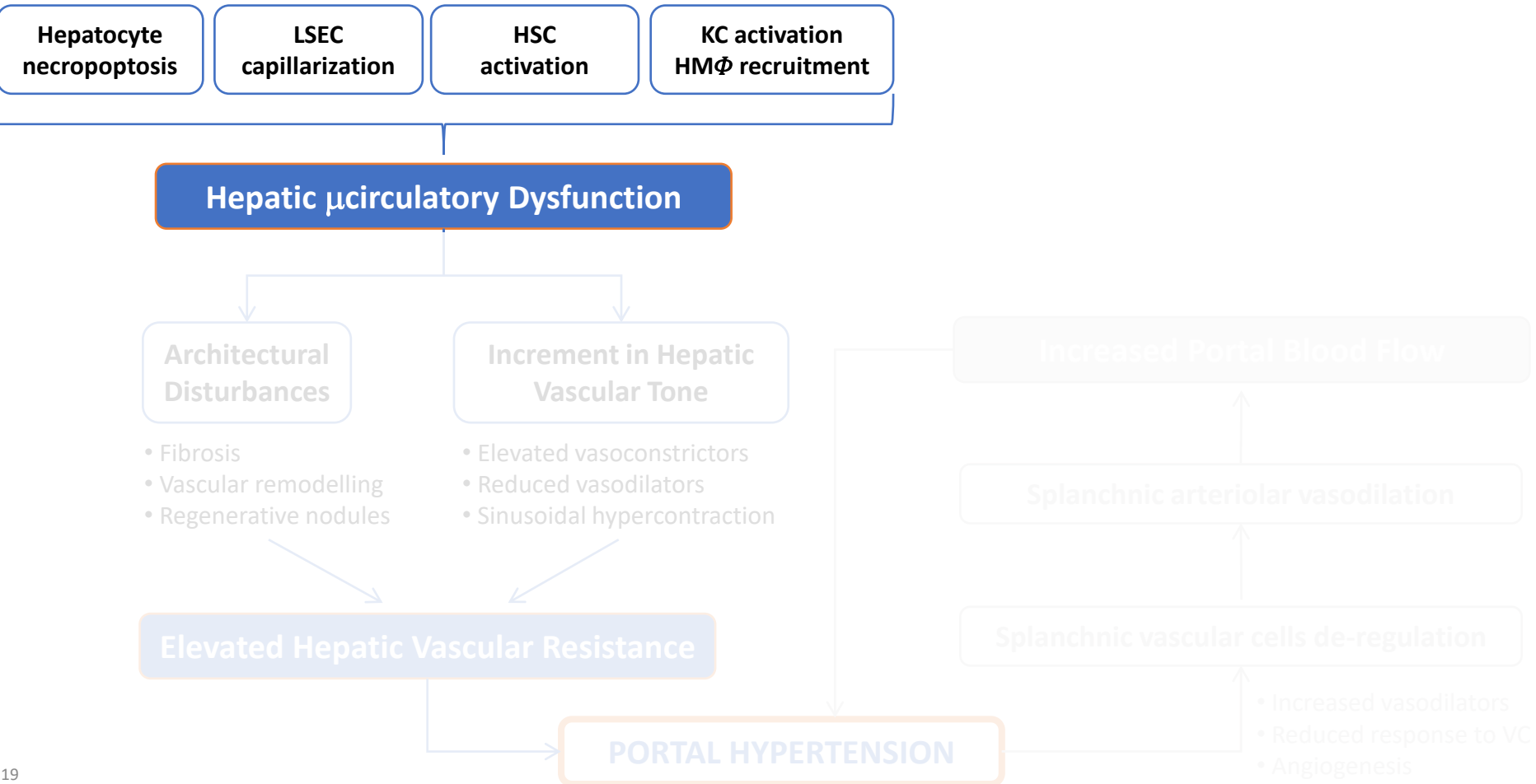
Increased Portal Blood Flow

Splanchnic arteriolar vasodilation

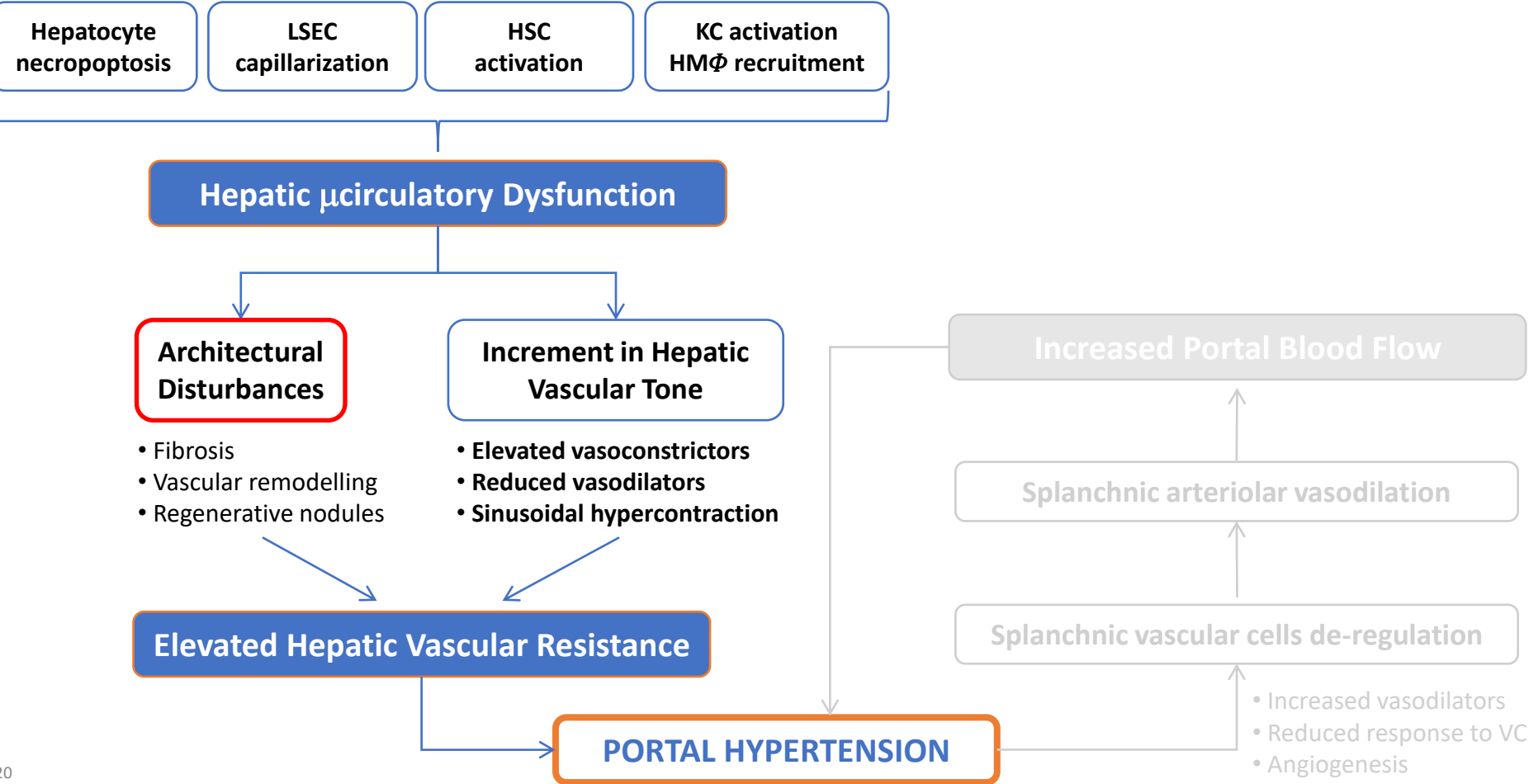
Splanchnic vascular cells de-regulation

- Increased vasodilators
- Reduced response to VC
- Angiogenesis

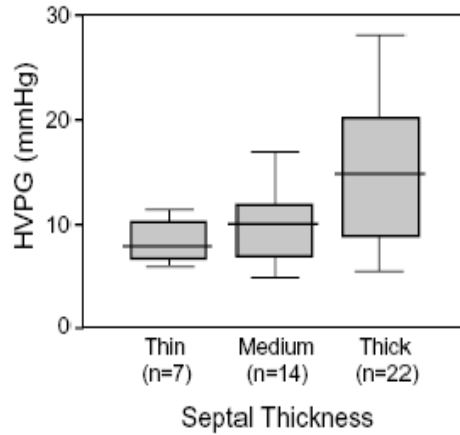
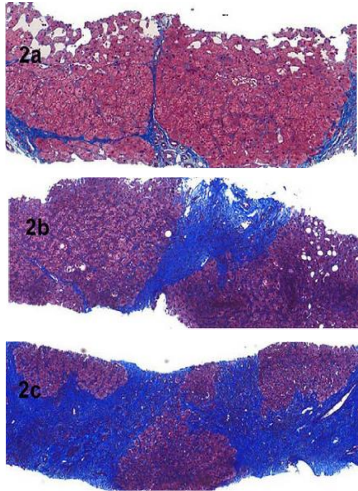
Portal Hypertension Pathophysiology – The Global Picture



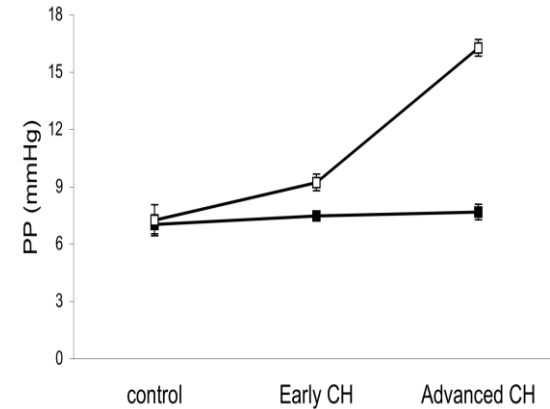
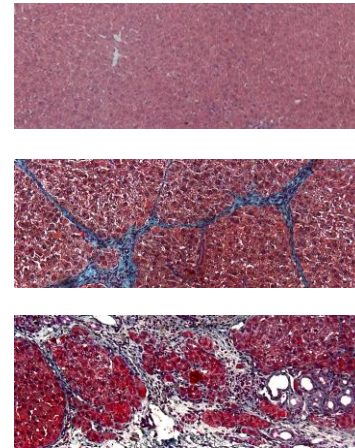
Portal Hypertension Pathophysiology – The Global Picture



Portal Hypertension Pathophysiology – Architectural disturbances

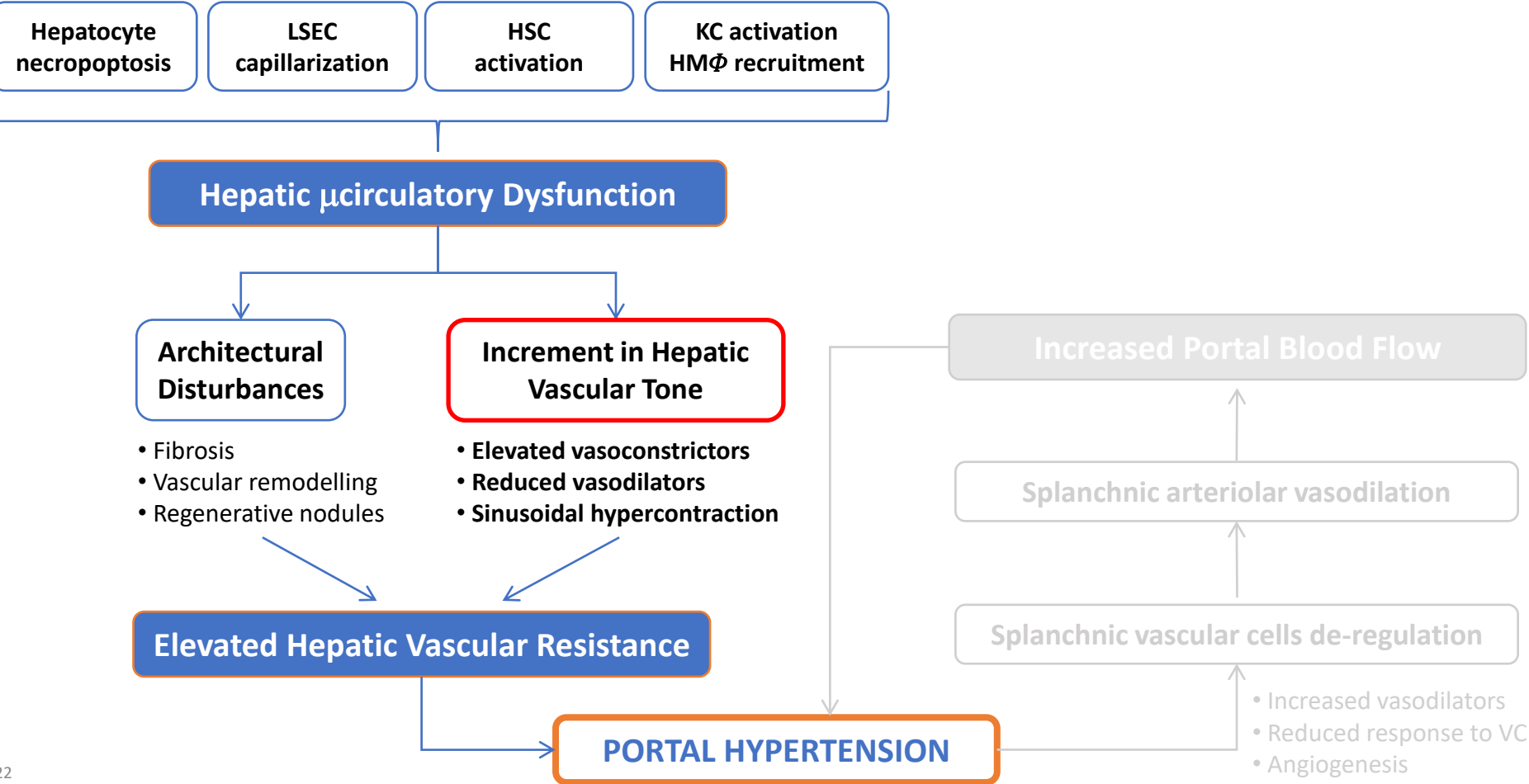


Nagula et al. J Hepatol 2006

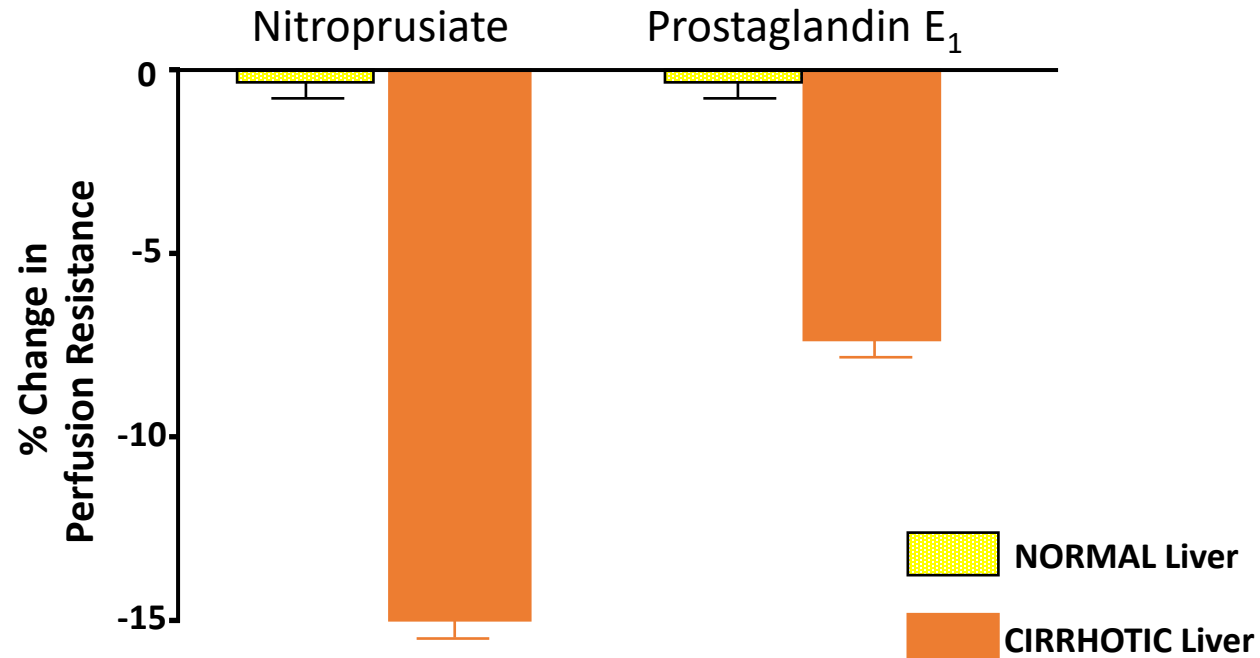


Gracia-Sancho et al. Gut 2011

Portal Hypertension Pathophysiology – The Global Picture

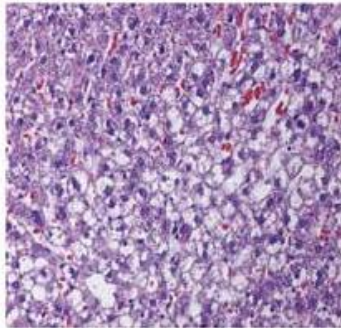
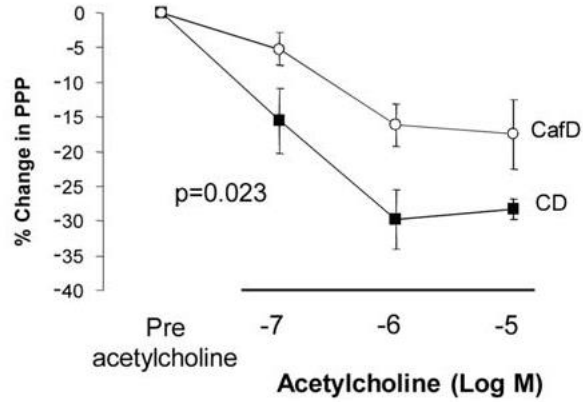


Portal Hypertension Pathophysiology – Vascular disturbances

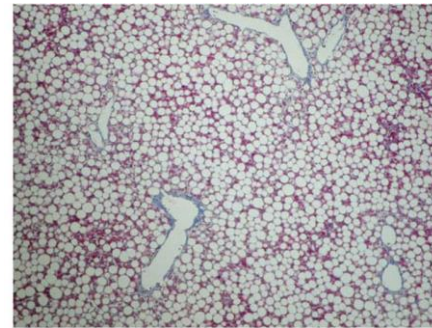
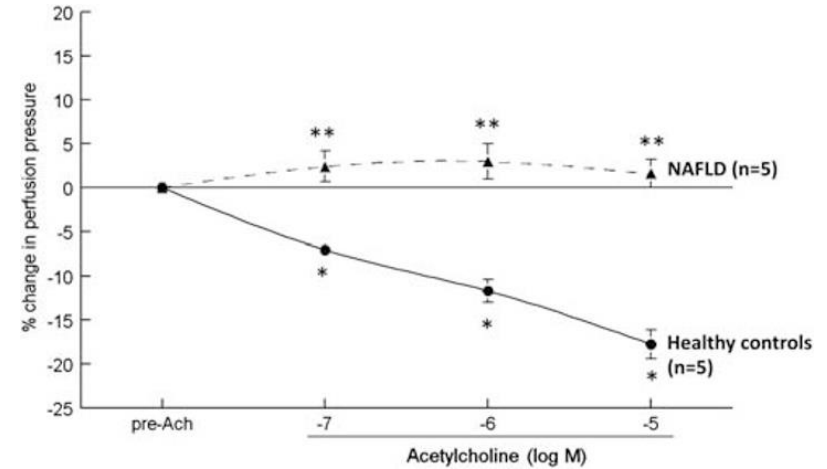


Portal Hypertension Pathophysiology – Vascular dysfunction development

4w CafD



4w MCD

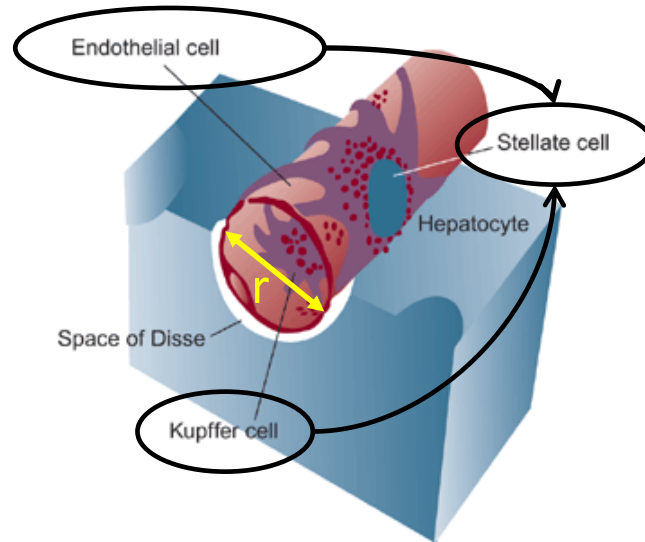


Portal Hypertension Pathophysiology – Dynamic component of the HVR

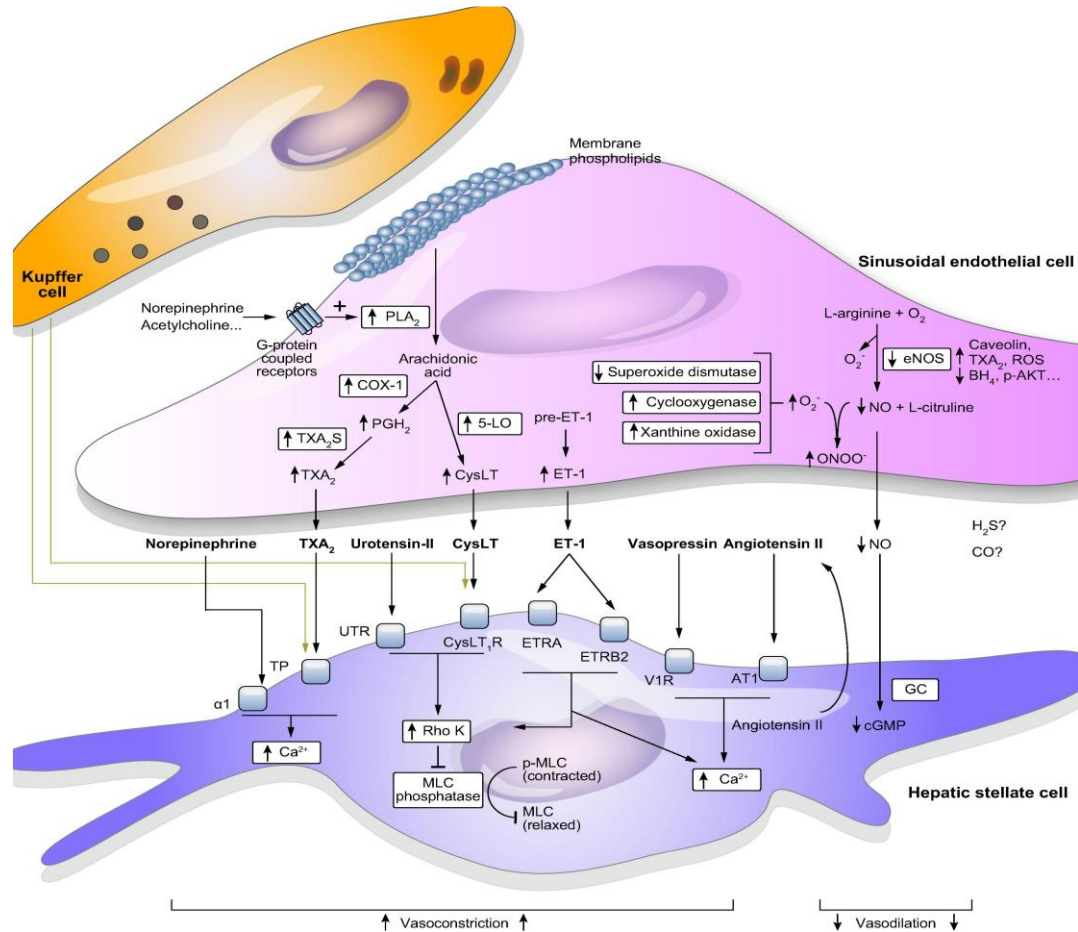
$$R = 8\eta L / r^4$$

Intrahepatic contractile elements

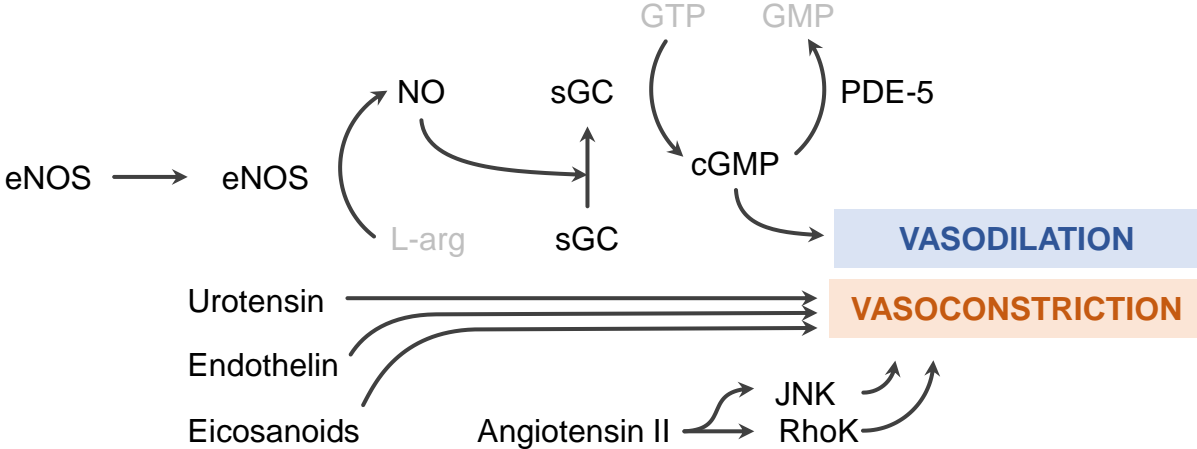
Regulation of contraction



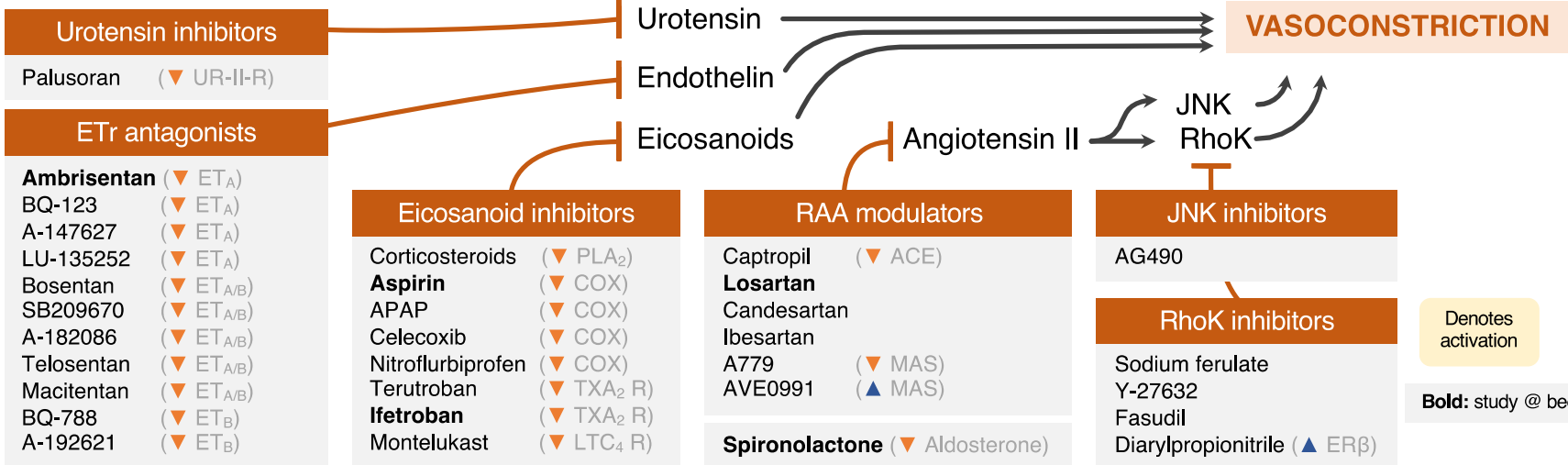
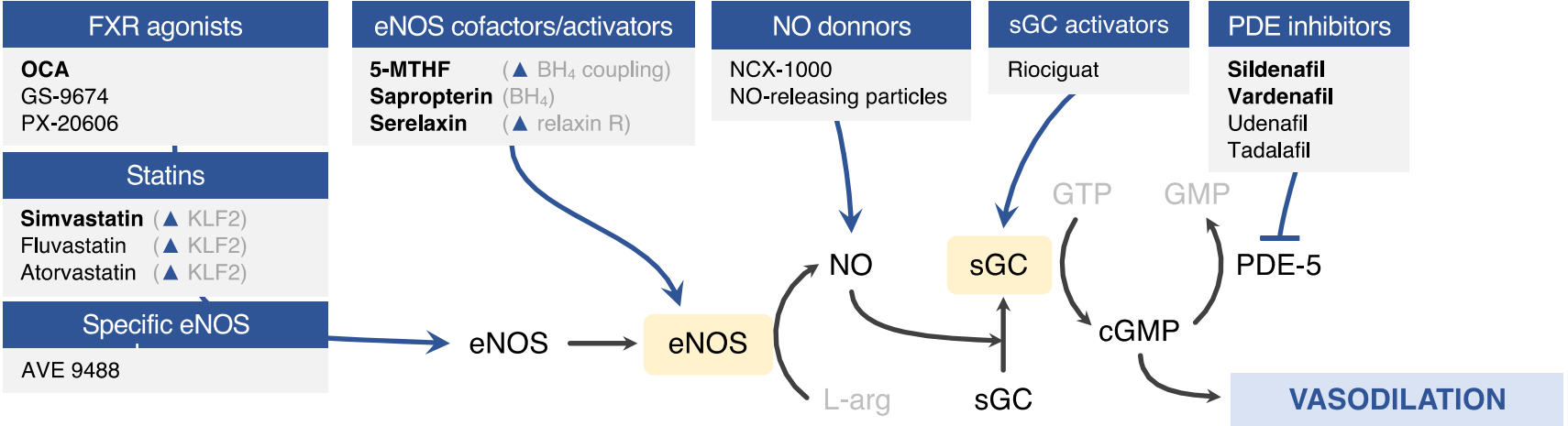
Portal Hypertension Pathophysiology – Dynamic component of the HVR



Promoting CLD regression: Targeting the sinusoid



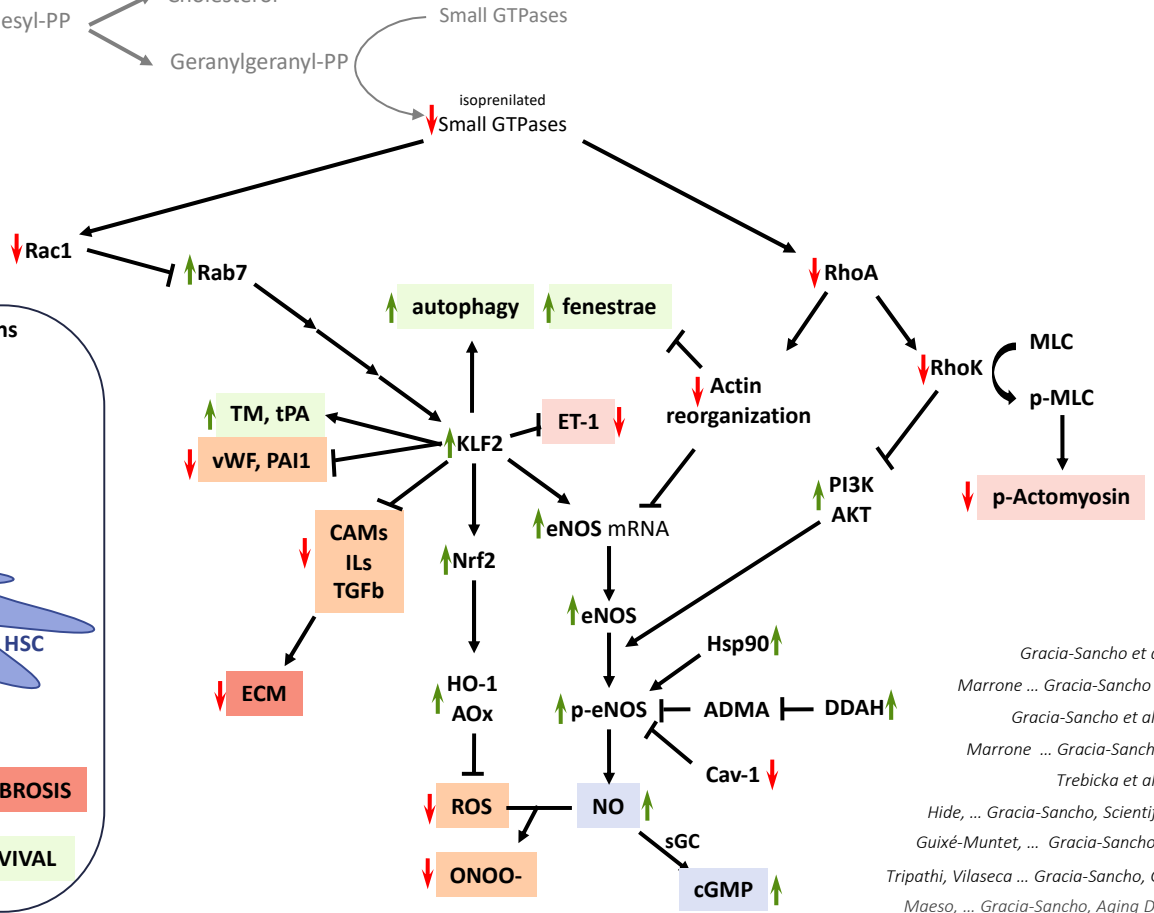
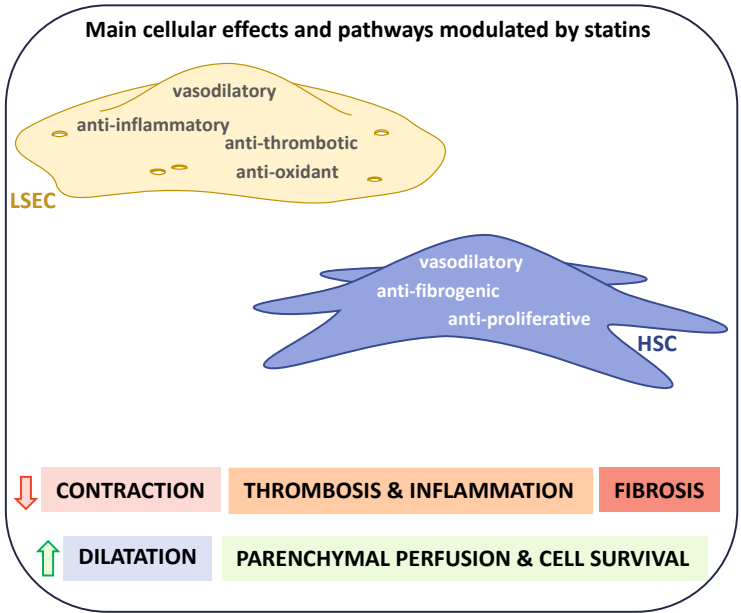
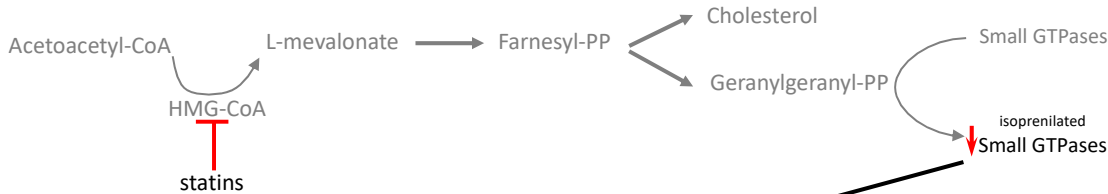
Promoting CLD regression: Targeting the sinusoid



Promoting CLD regression: therapeutics - statins

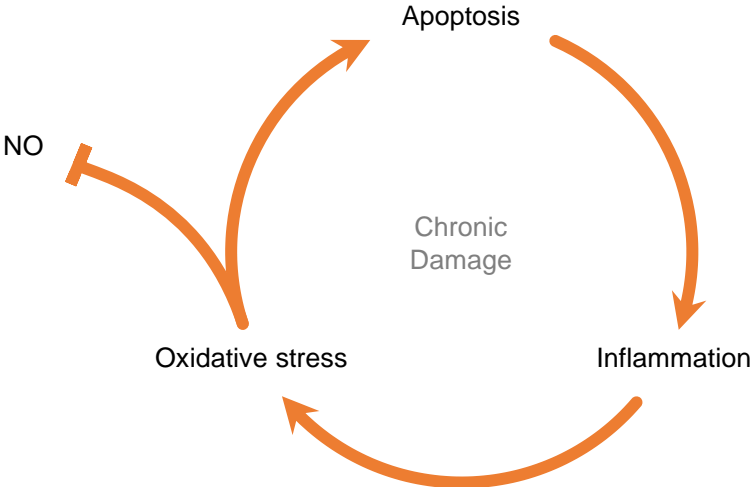
		Acute liver injury		Chronic liver disease		Acute on chronic liver failure	
		ischaemia/reperfusion	infection			cirrhosis + infection	
		24h - 3days	24h - 3days	24h - 3days	7-14days	24h - 3days	
LIVER PATHOBIOLOGY	Molecular pathways	KLF2-eNOS-NO KLF2-Nrf2-Aox KLF2-Autophagy	KLF2-eNOS-NO KLF2-CAMs	KLF2-eNOS-NO KLF2-Nrf2-Aox KLF2-TGFb RhoA-RhoK-MLC		KLF2-eNOS-NO KLF2-Nrf2-Aox RhoA-RhoK-MLC	
	Targeted cell type	LSEC +++ HM +		LSEC +++ HSC +++ HM ++		LSEC +++ HSC +++ HM ++ Neutrophils +	
	Underlying mechanisms	Oxidative stress Inflammation Vascular function		Oxidative stress Inflammation Vascular function ECM		Oxidative stress Inflammation Vascular function	
	Improved pathologic events	Cell death Liver dysfunction Microvascular dysfunction		Cell death Liver dysfunction Microvascular dysfunction Portal hypertension Fibrosis		Cell death Liver dysfunction Kidney injury Microvascular dysfunction Portal hypertension Survival	
	Clinical evidence	Observational studies - diverse statins -		Observational studies - diverse statins -		Proof-of-concept RCTs - simvastatin - RCT with clinical end points - simvastatin -	
EVIDENCE	Preclinical models	Cold preservation lean & steatotic grafts - simvastatin - Warm ischaemia young & aged animals - simvastatin - Haemorrhagic shock healthy & cirrhotic animals - simvastatin -	acute LPS healthy animals - simvastatin -	chronic CCl ₄ chronic TAA BDL - simvastatin - - atorvastatin -	chronic CCl ₄ aged animals BDL - simvastatin -	chronic CCl ₄ + LPS chronic TAA + LPS compensated & decompensated cirrhosis BDL + LPS - simvastatin -	

Promoting CLD regression: therapeutics - statins

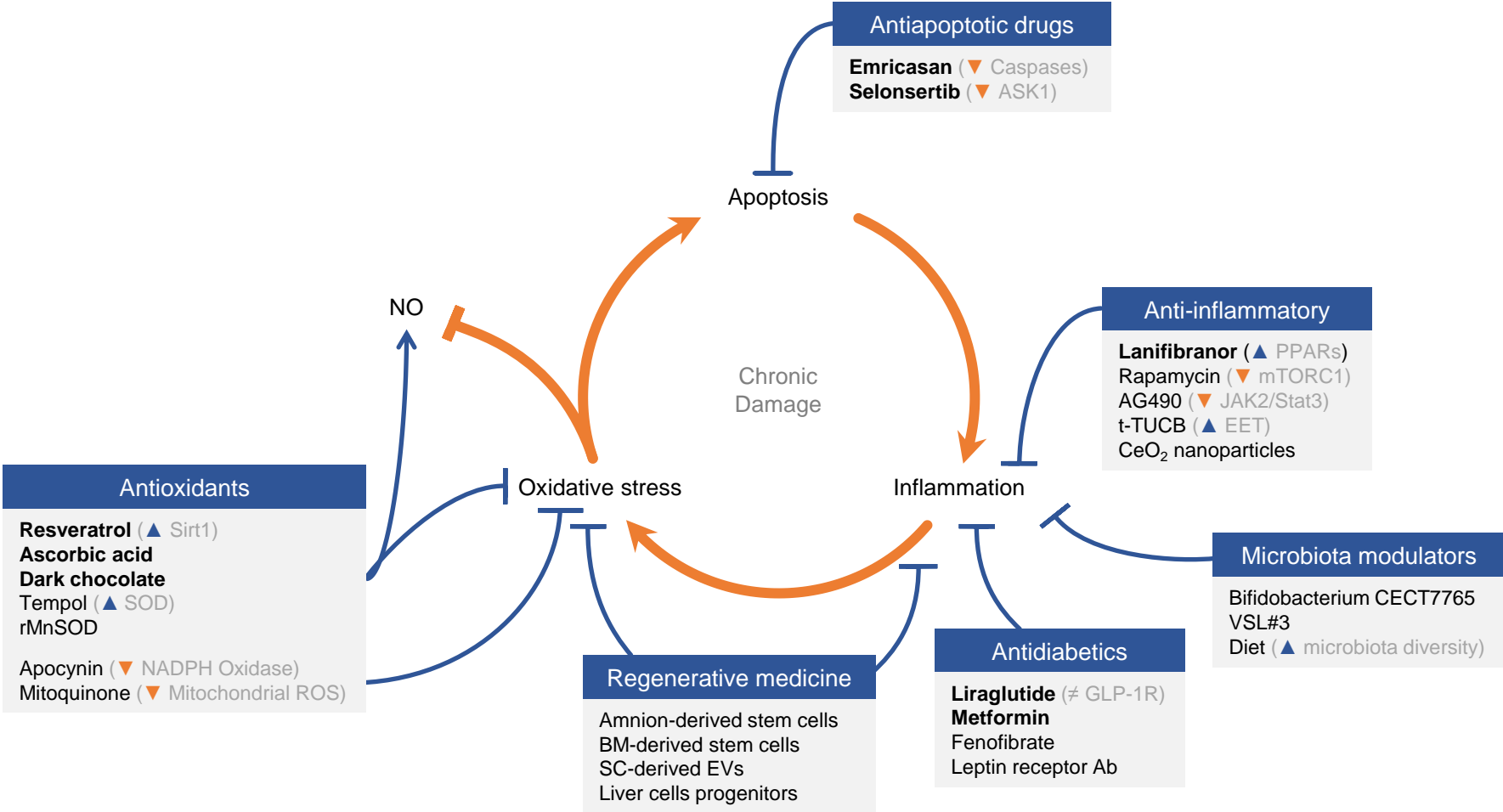


Gracia-Sancho et al, Gut 2011
 Marrone ... Gracia-Sancho, JHep 2013
 Gracia-Sancho et al, JHep 2013
 Marrone ... Gracia-Sancho, Gut 2015
 Trebicka et al, JHep 2010
 Hide, ... Gracia-Sancho, Scientific Rep 2016
 Guixé-Muntet, ... Gracia-Sancho, JHep 2017
 Tripathi, Vilaseca ... Gracia-Sancho, Gastro 2018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

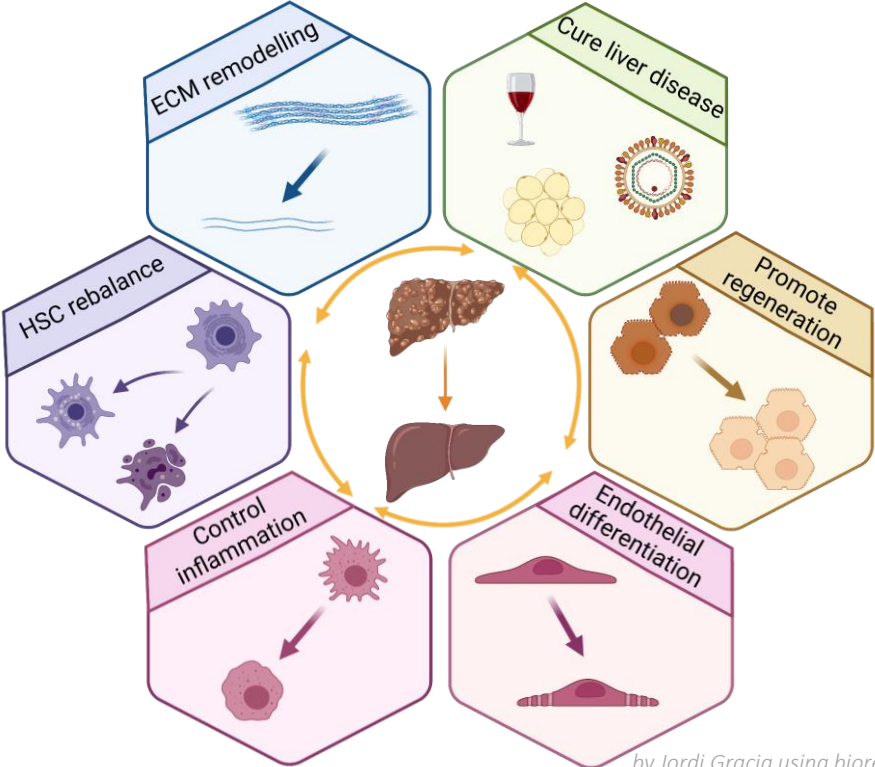
Promoting CLD regression: targeting the sinusoid



Promoting CLD regression: targeting the sinusoid

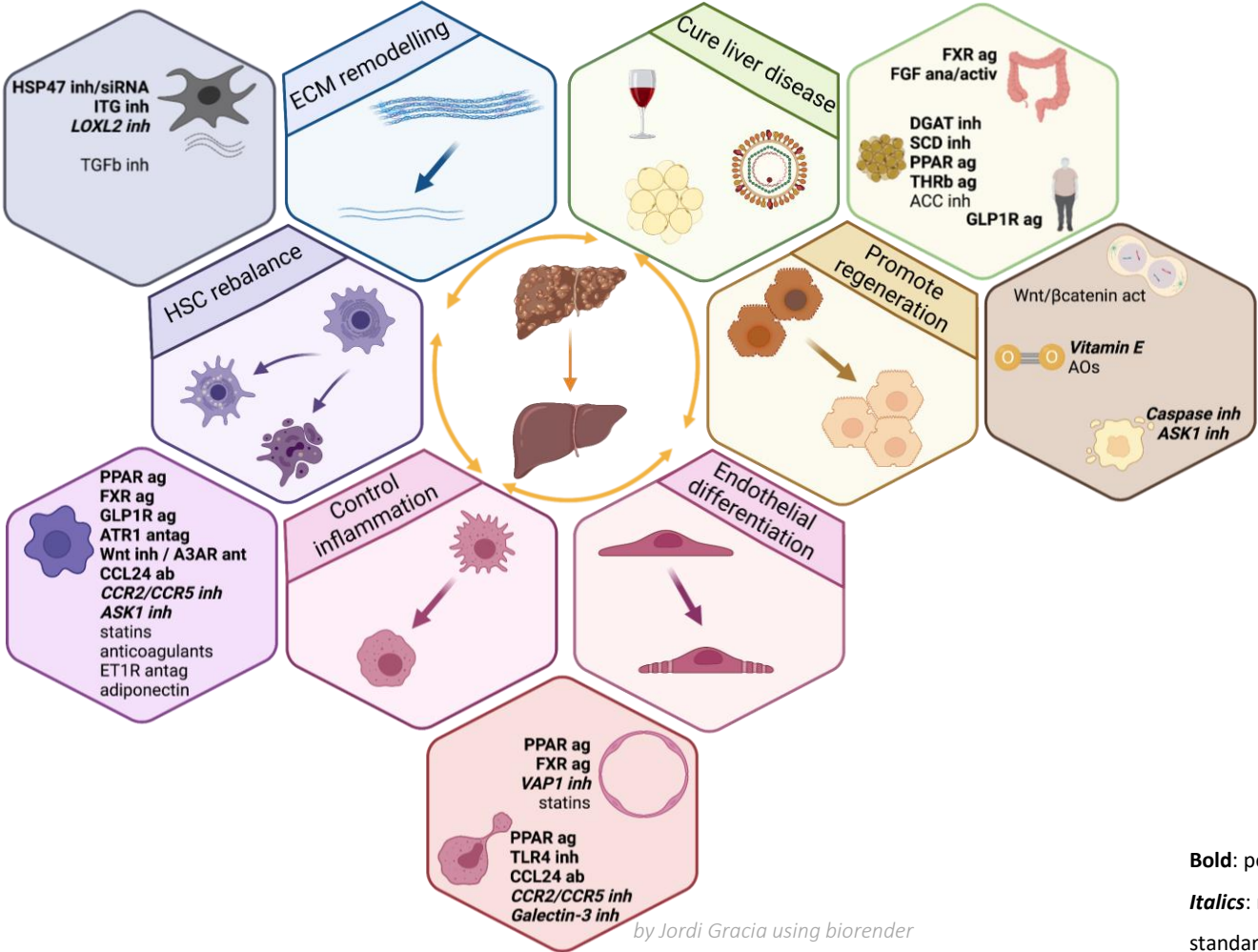


Promoting fibrosis regression: targeting the sinusoid



by Jordi Gracia using biorender

Promoting fibrosis regression: targeting the sinusoid



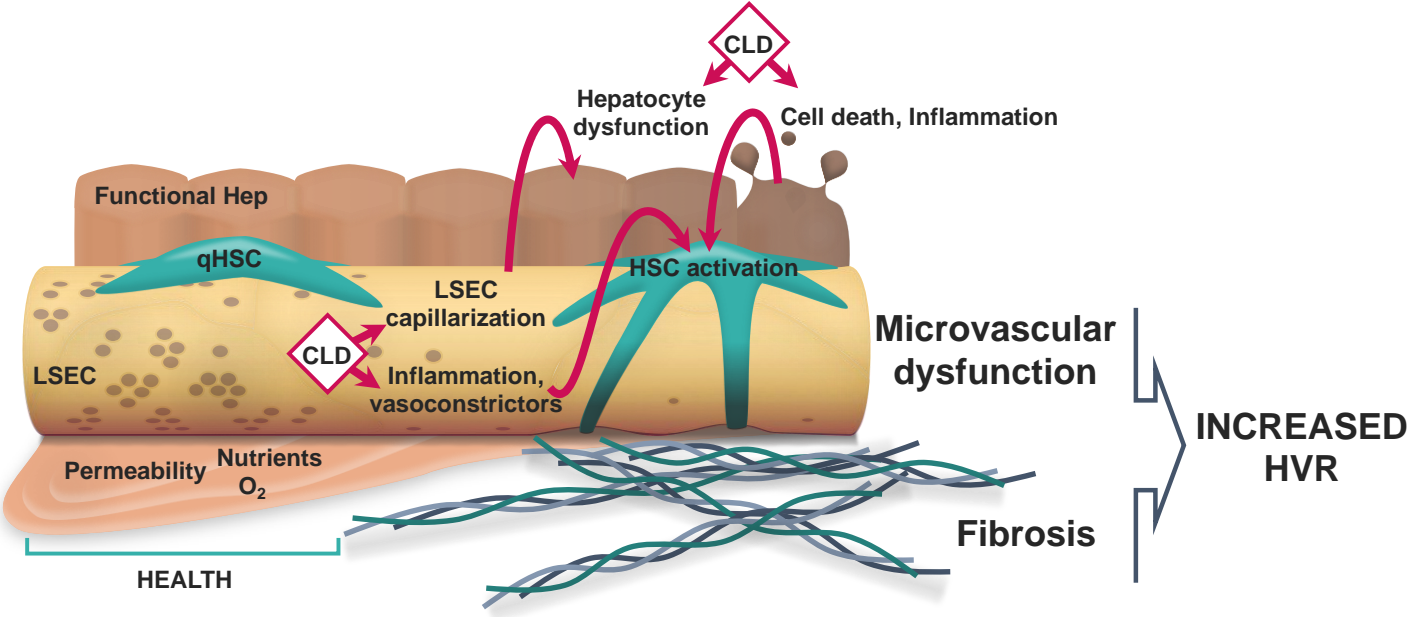
Bold: positive or ongoing CT

Italics: negative CT

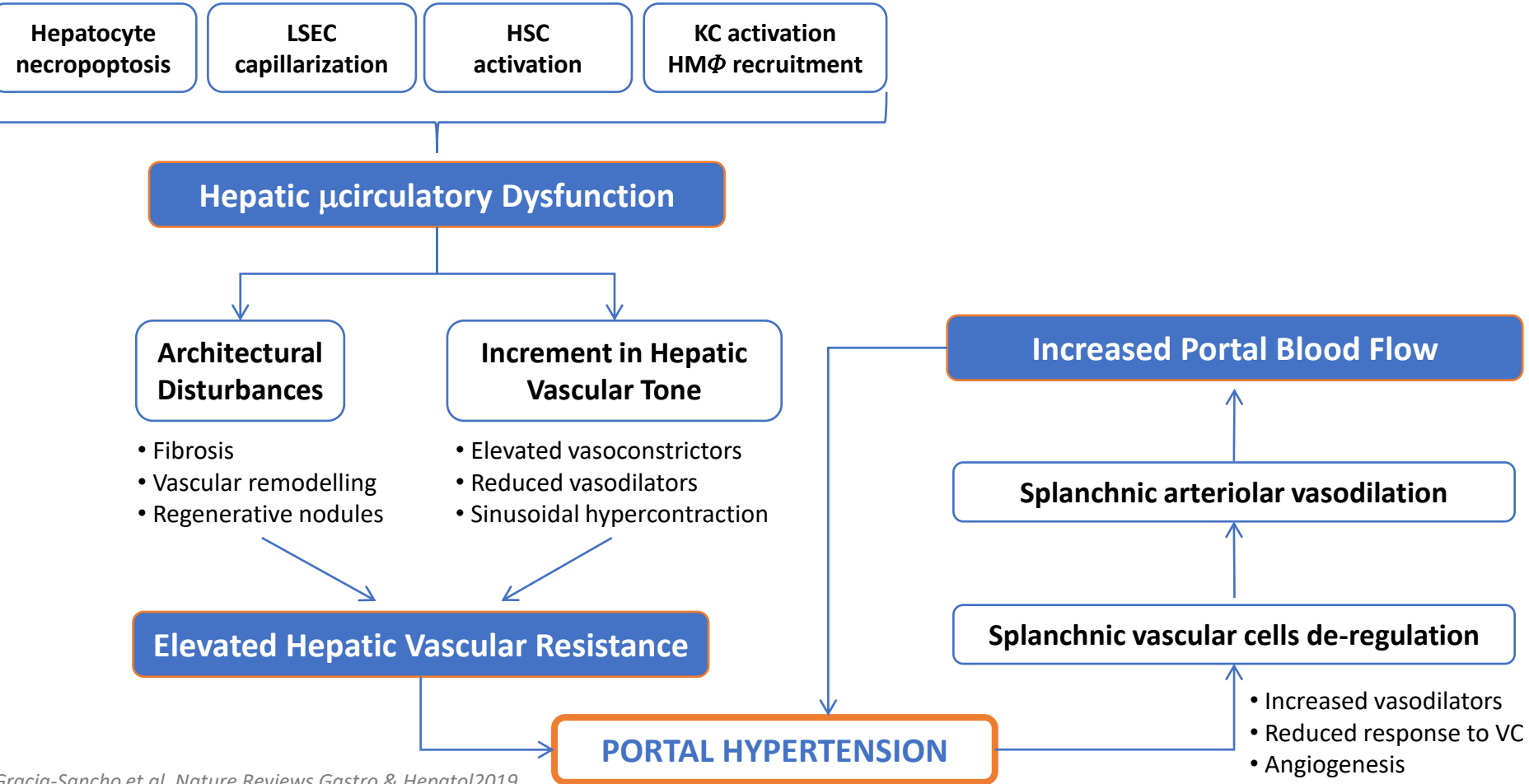
standard: pre-clinical research

by Jordi Gracia using biorender

Wrap-up 1: Progression of CLD and PH

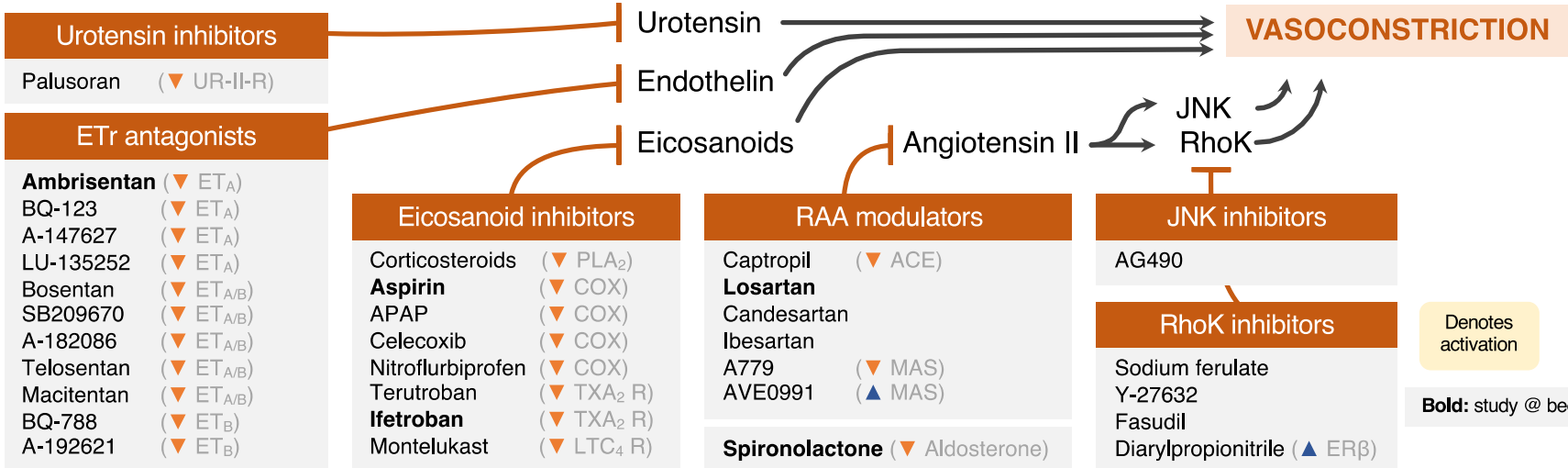
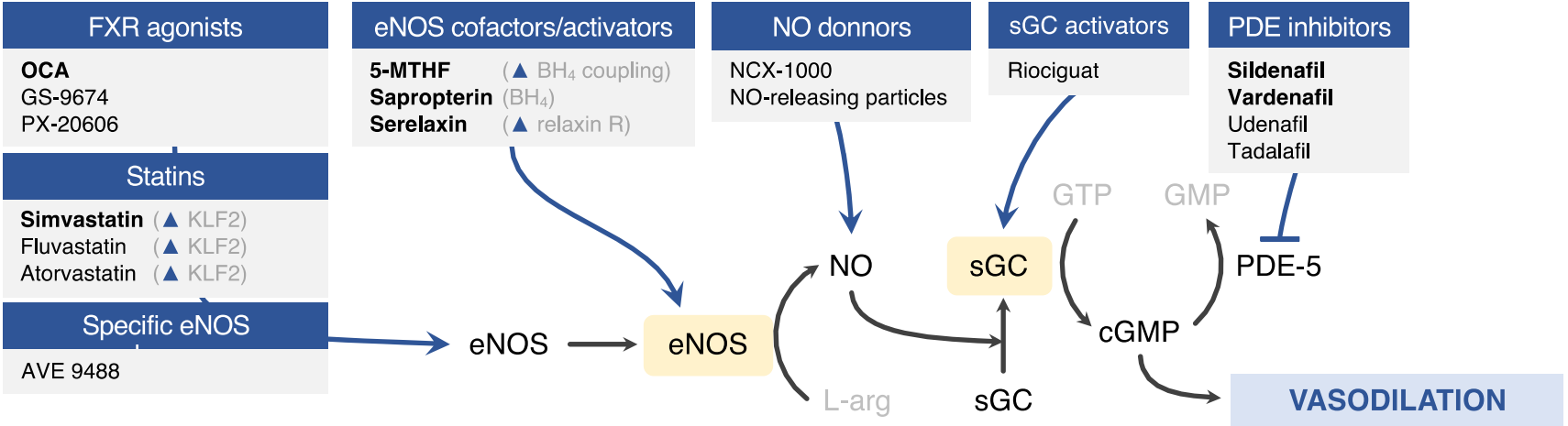


Wrap-up 2: Role of the hepatic sinusoid in the pathophysiology of PH



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

Wrap-up 3: therapeutics for PH targeting the sinusoid





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