

# MÁSTER EN HEPATOLOGÍA



Asignatura: CIRROSIS I

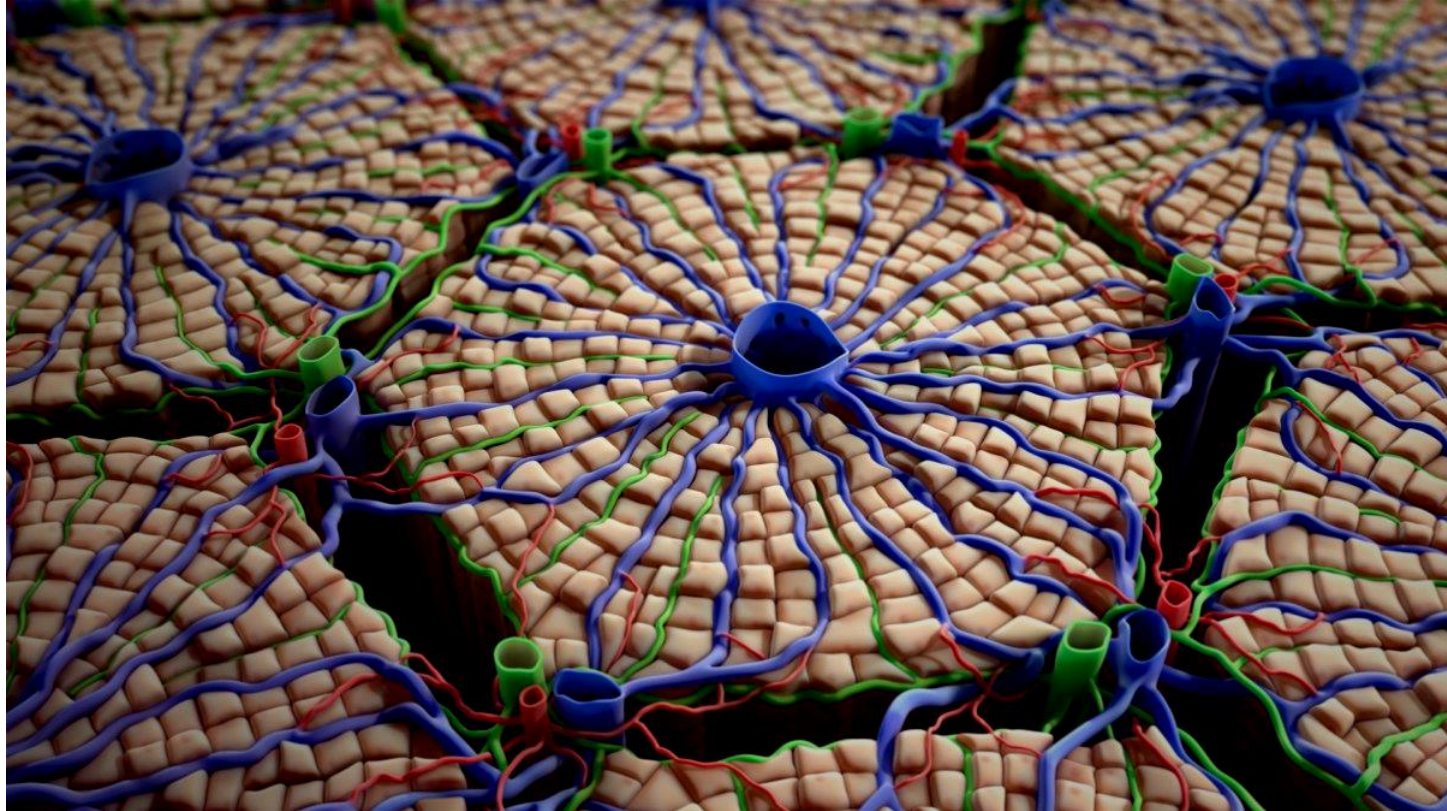
**“El sinusoides hepático: biología en la cirrosis y en la enfermedad hepática crónica”**

Jordi Gracia - Sancho

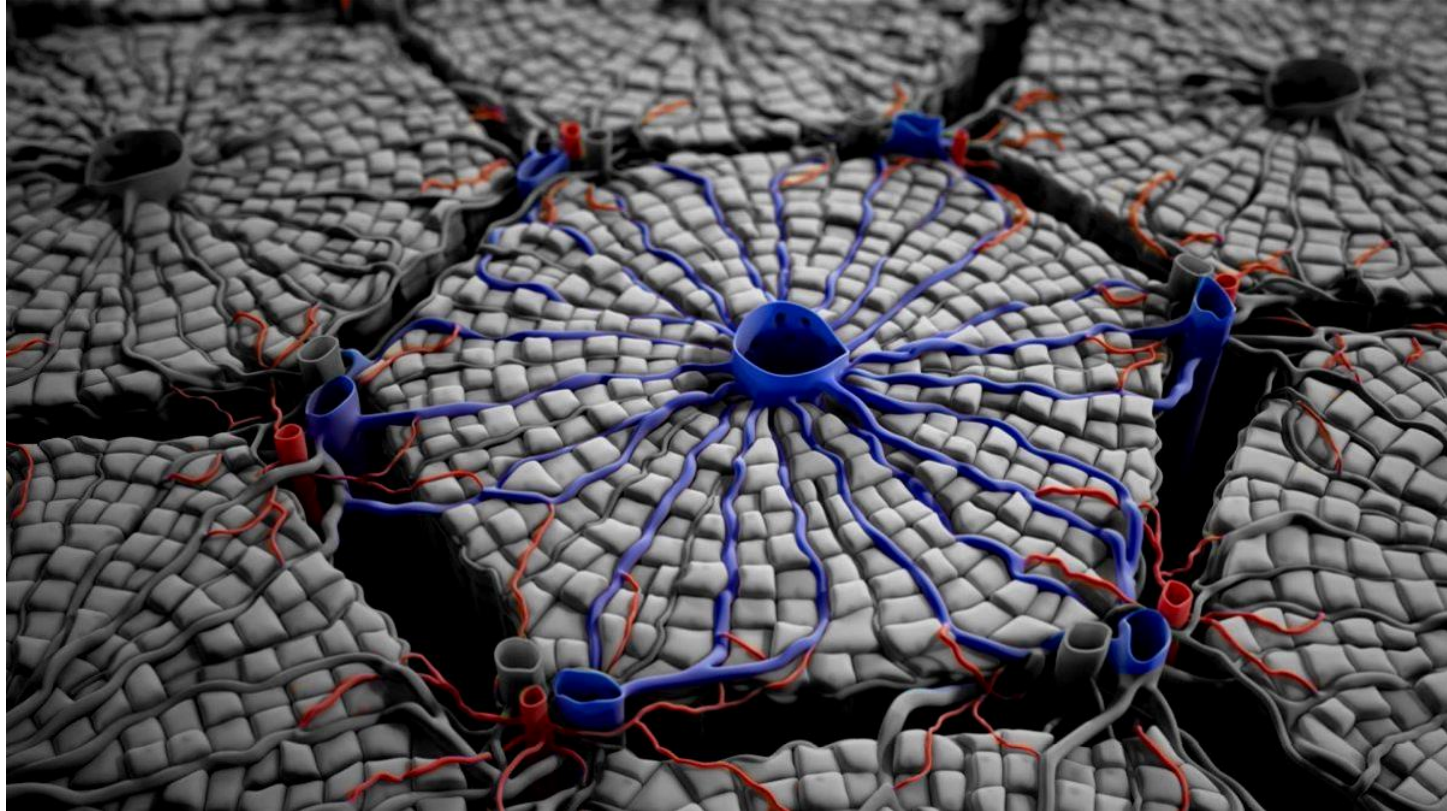
Liver Vascular Biology Research Group. IDIBAPS, Barcelona

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

# Liver microcirculation



# Liver microcirculation

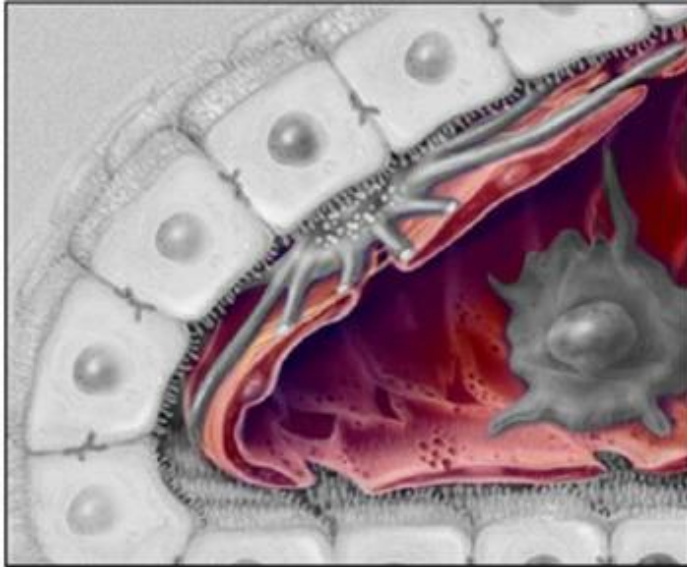


# The liver sinusoid



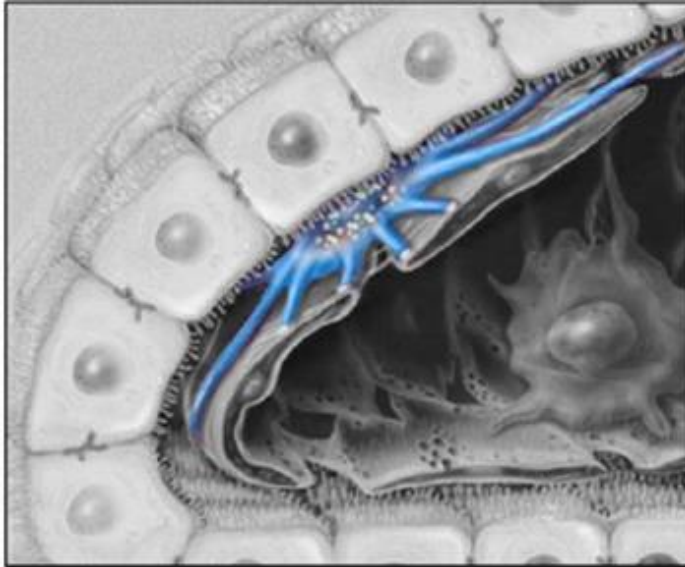
Friedman SL. *Nat Clin Pract Gastroenterol Hepatol* 2004

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.

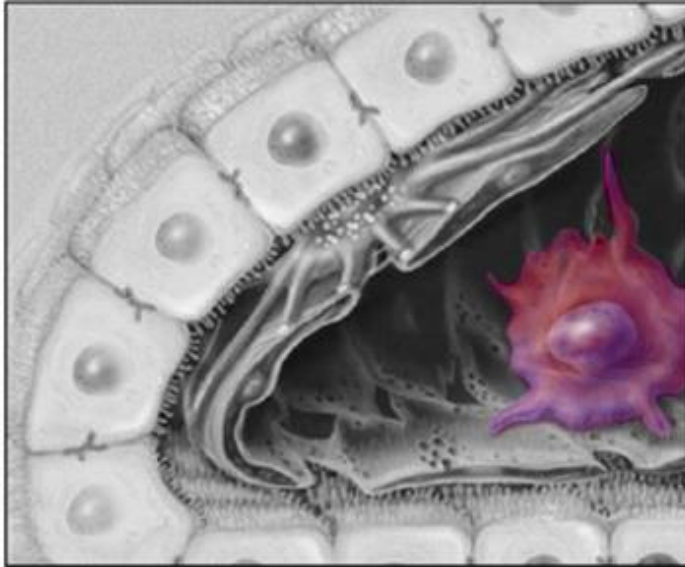


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## Hepatic Stellate Cells (HSC)

- Contractile properties.
- Vitamin A storage



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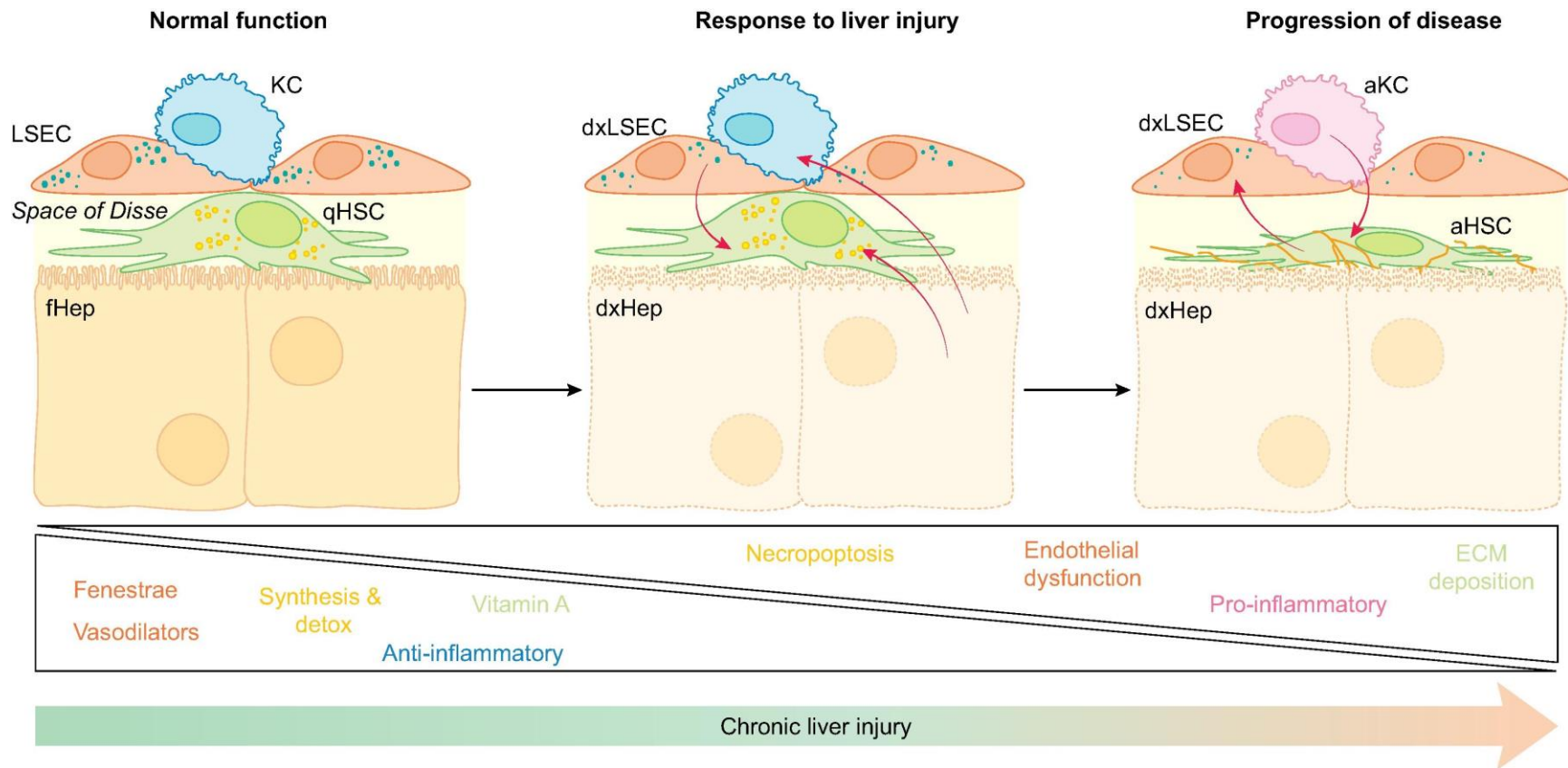
- Contractile properties.
- Vitamin A storage

## Kupffer Cells (KC)

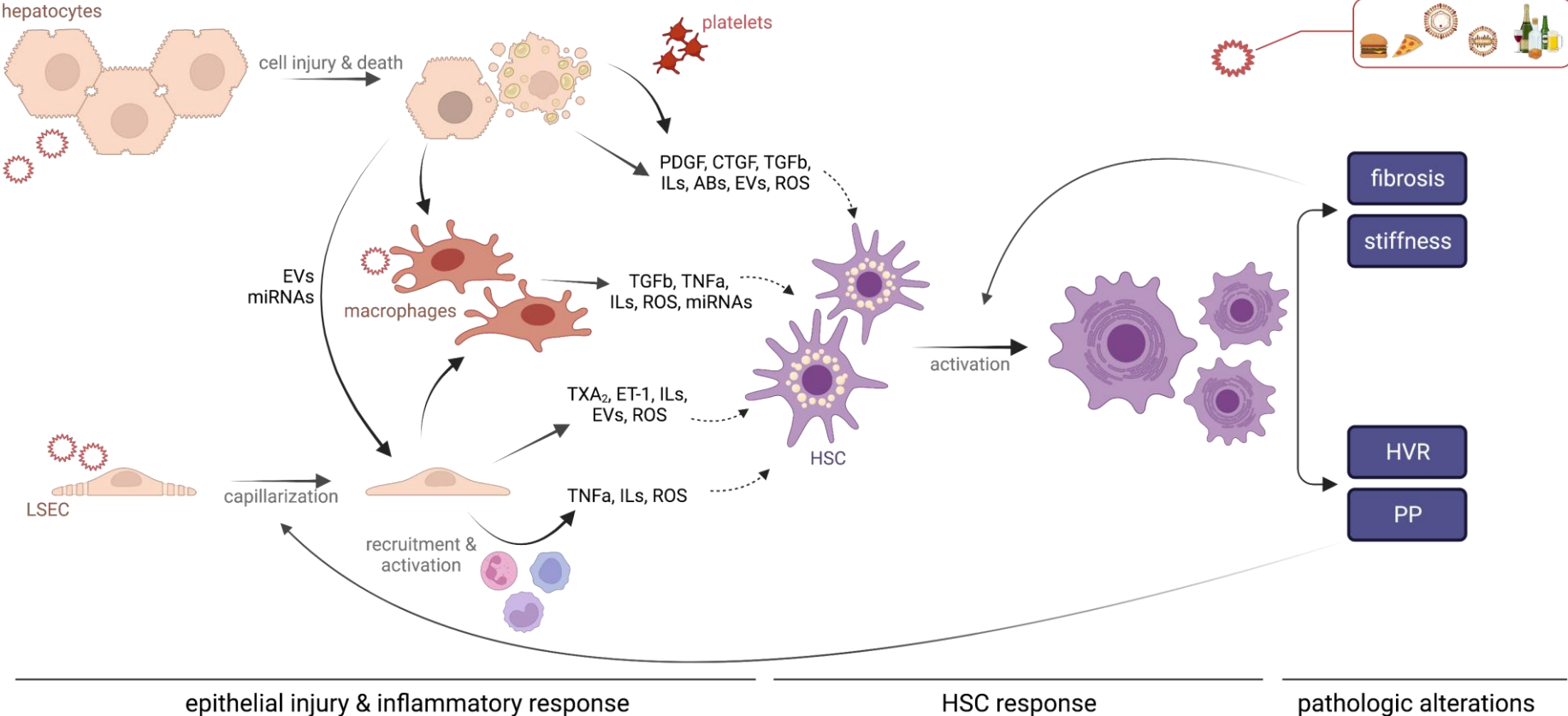
- Resident macrophages: defense, inflammation, tissue remodelling.



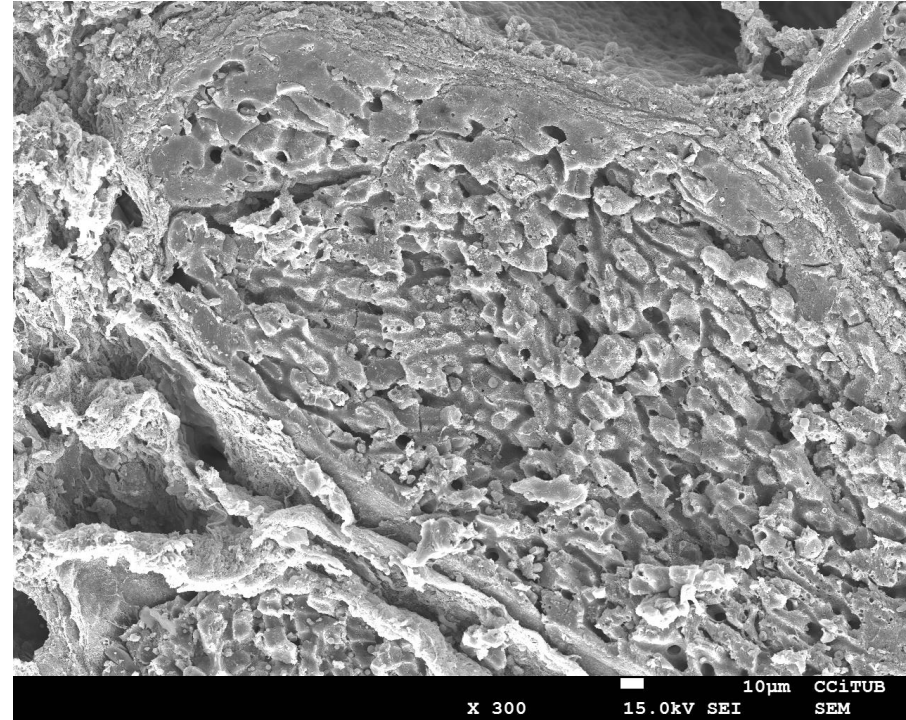
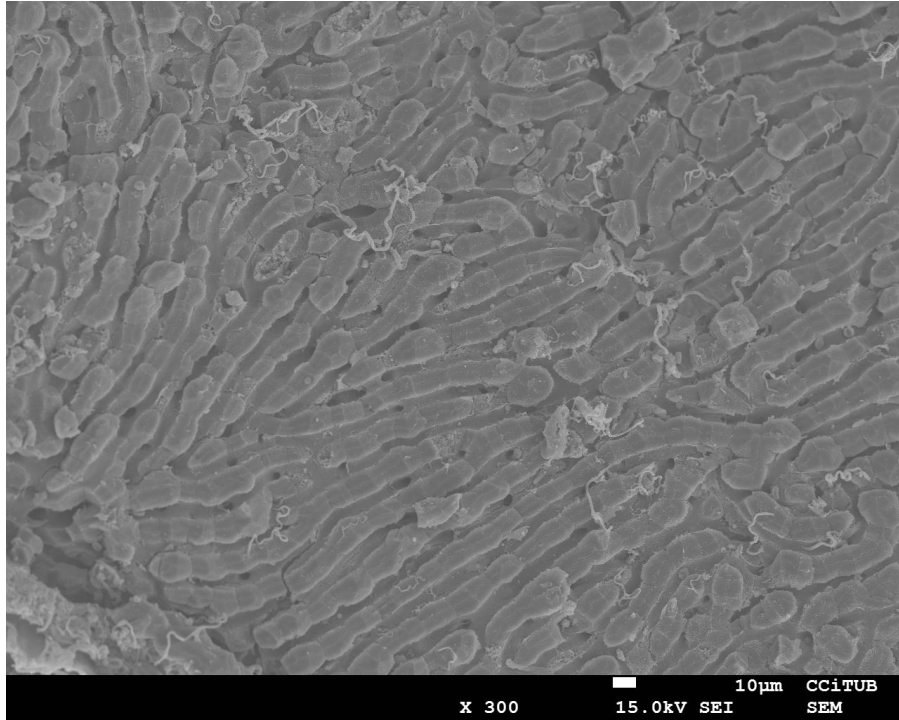
# The liver sinusoid in the progression of CLD



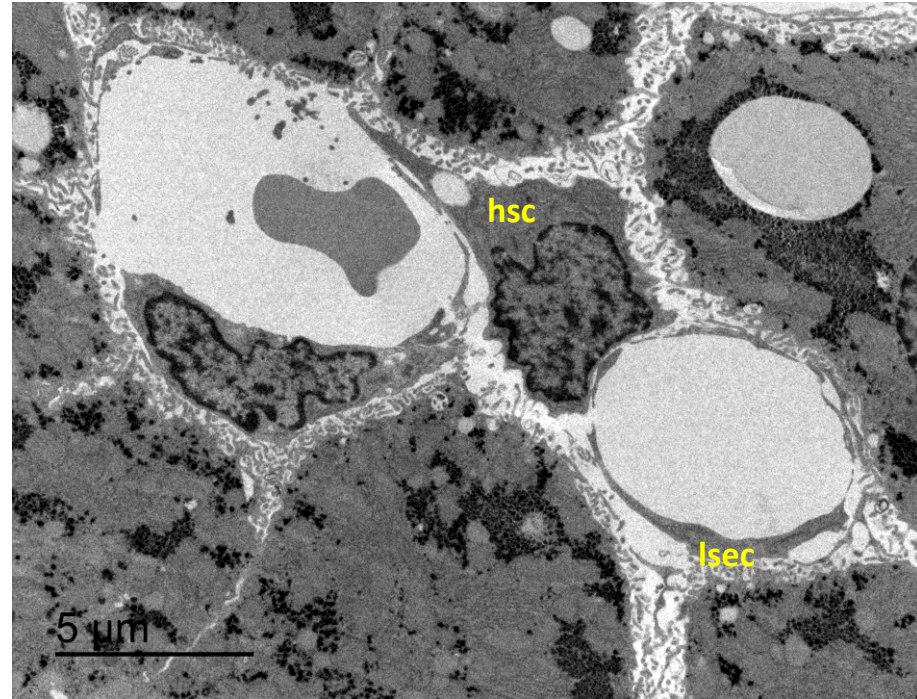
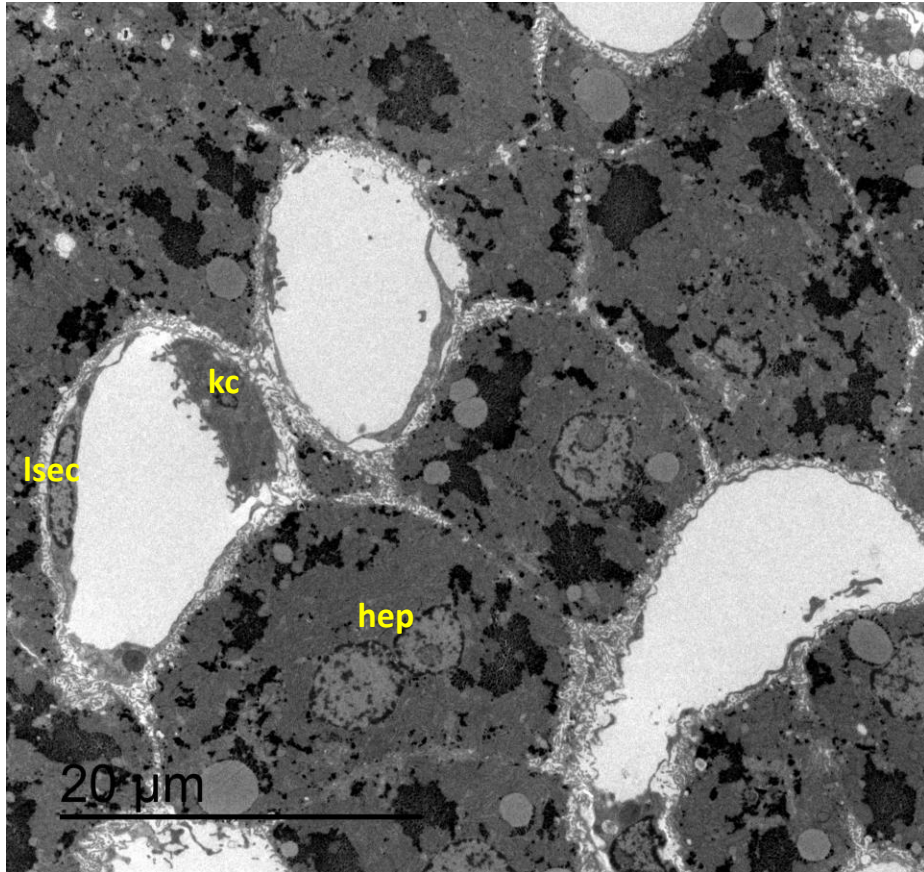
# Overview of CLD progression



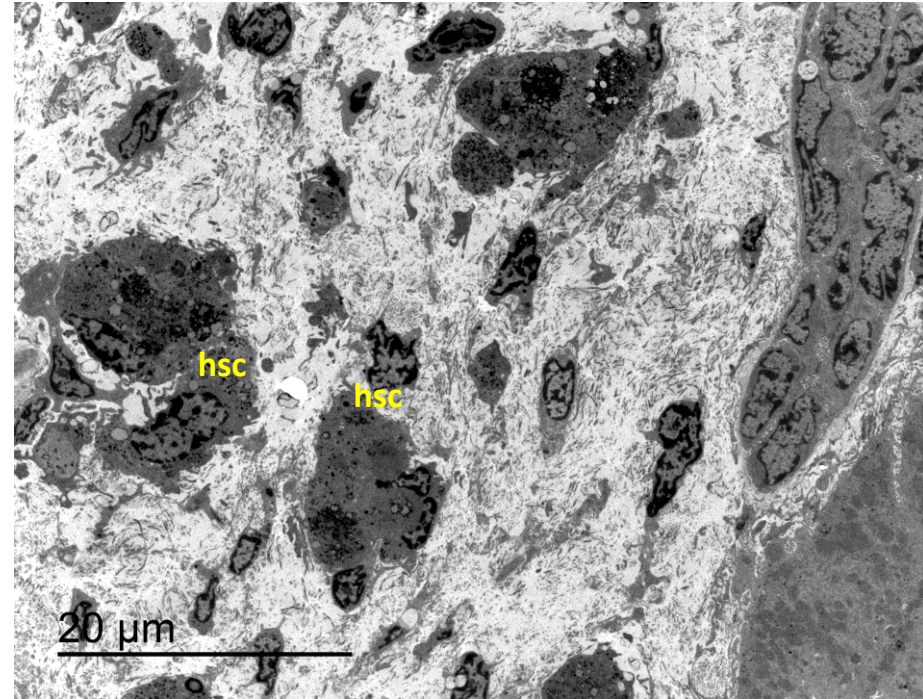
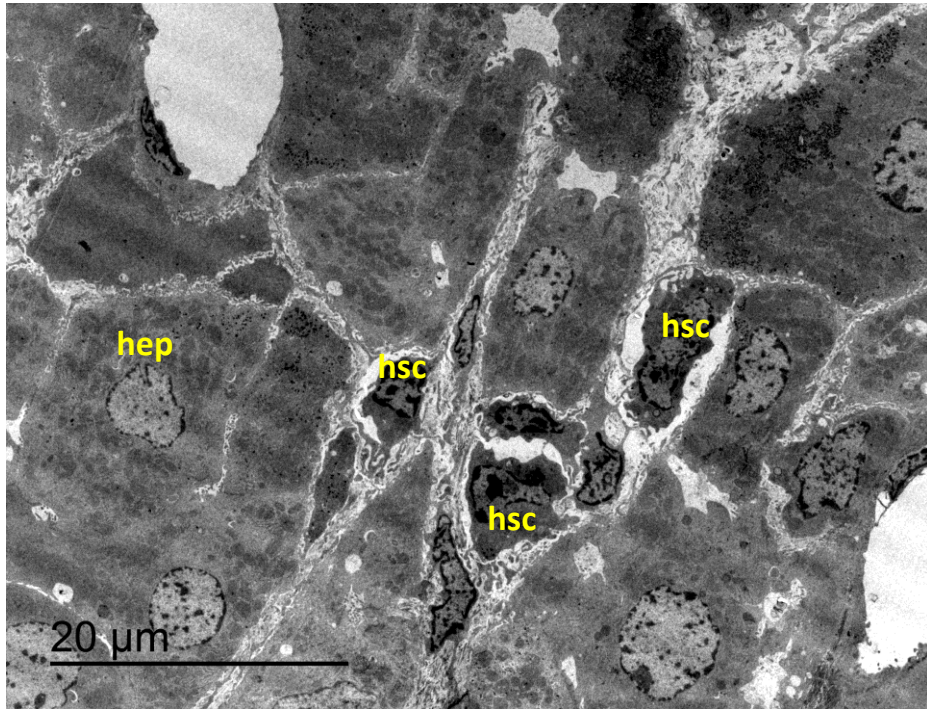
# The liver sinusoid



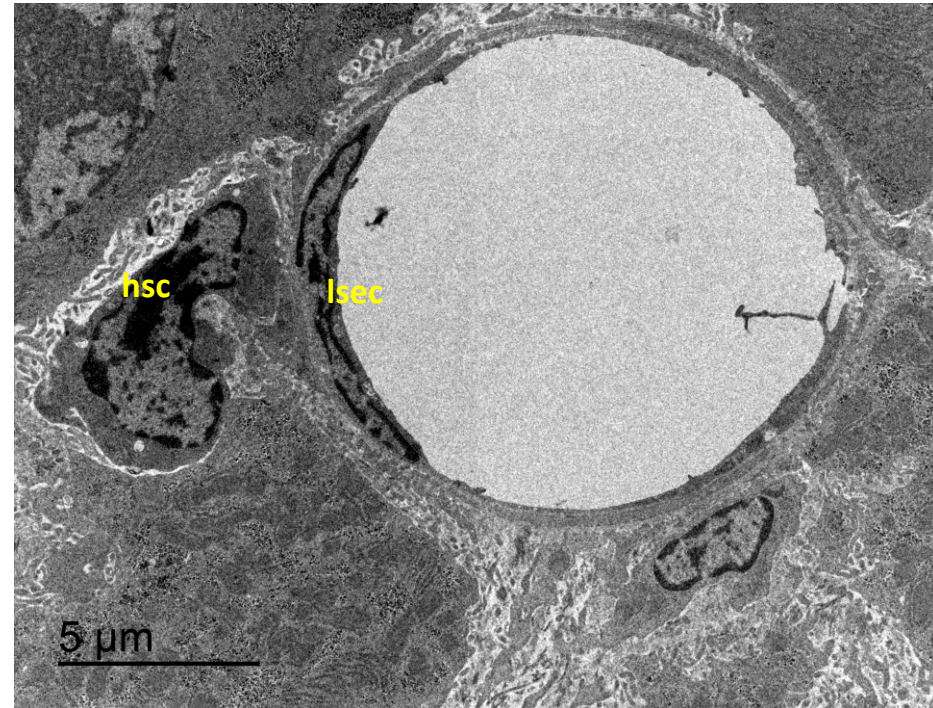
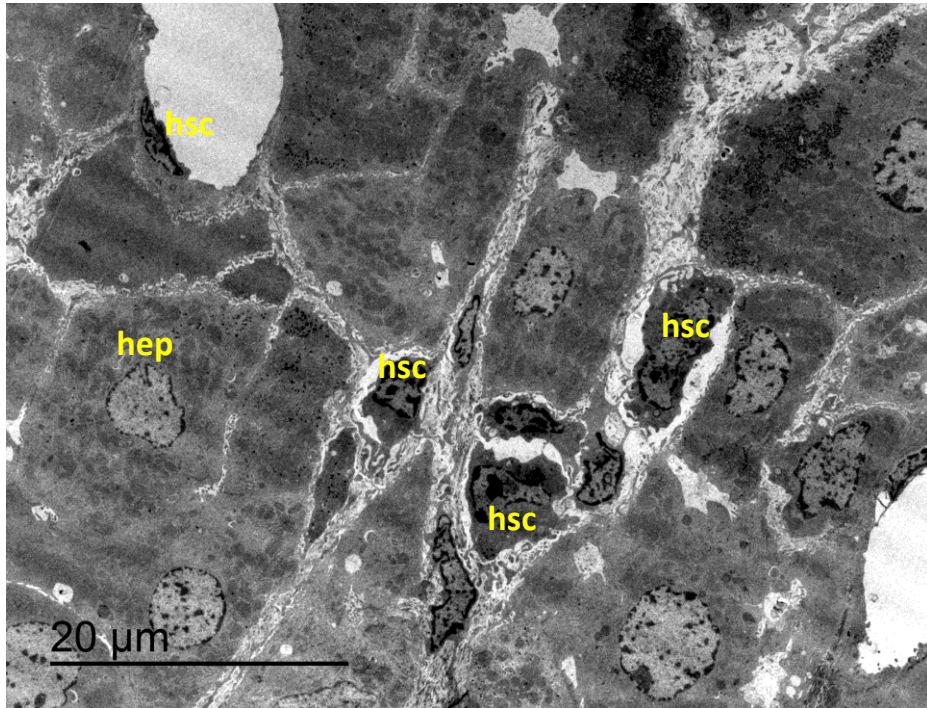
# The liver sinusoid



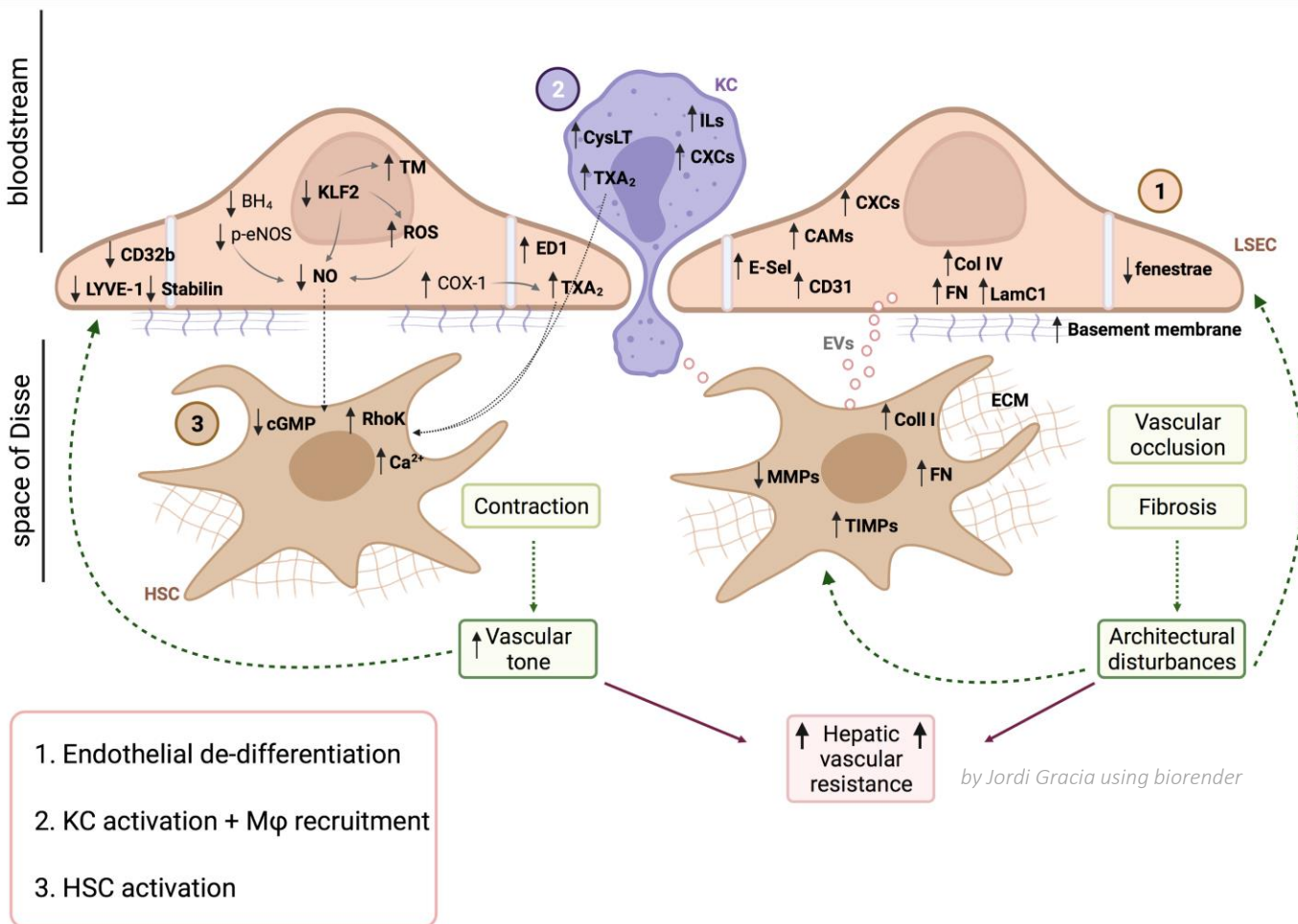
# The liver sinusoid in cirrhosis



# The liver sinusoid in cirrhosis



# Hepatic microcirculatory dysfunction



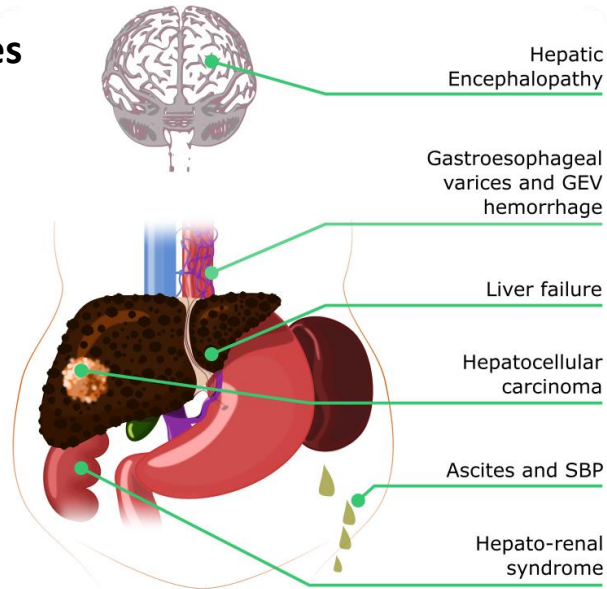
1. Endothelial de-differentiation
2. KC activation + Mφ recruitment
3. HSC activation

↑ Hepatic vascular resistance

*by Jordi Gracia using biorender*

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

**Consequences**



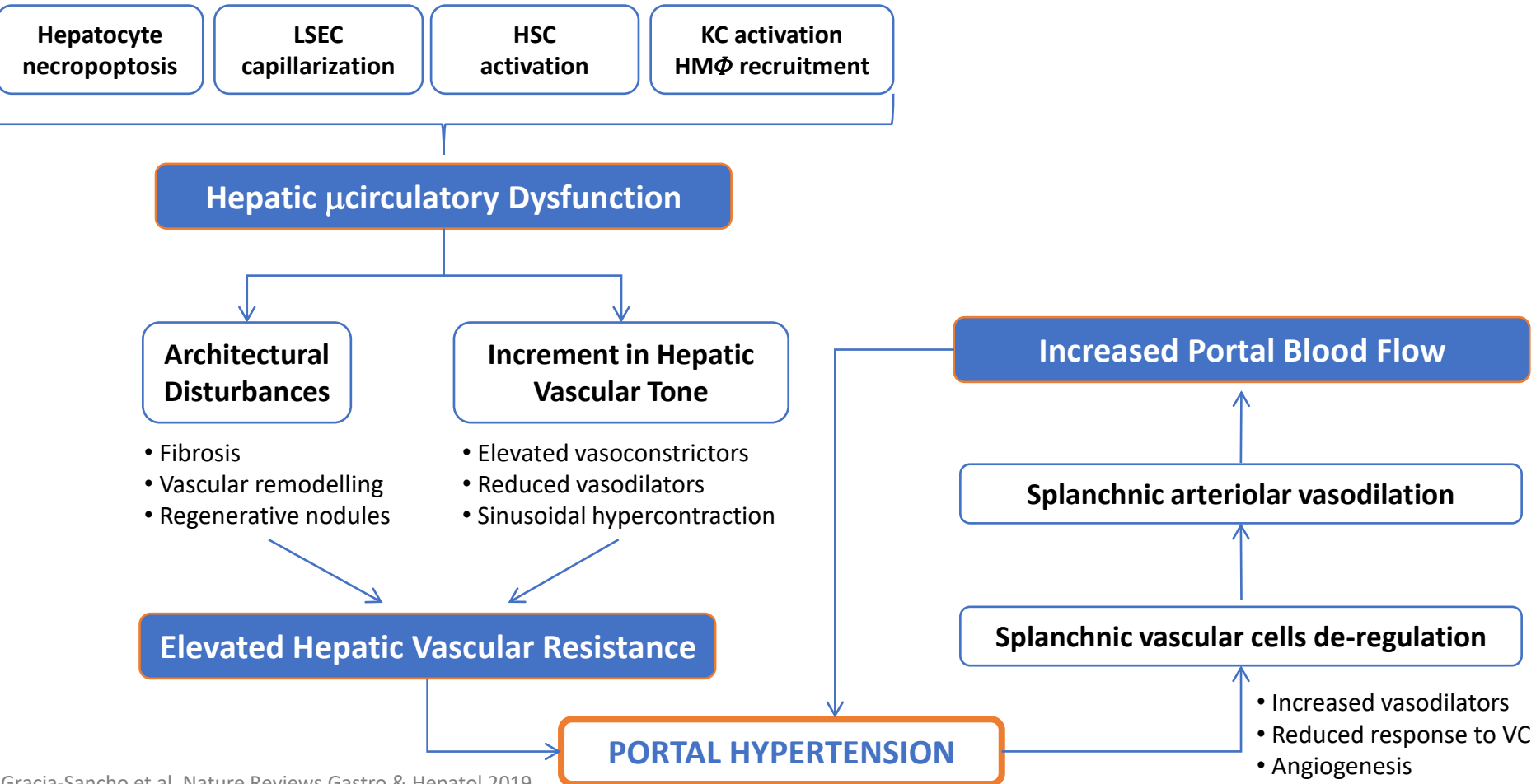
**Reversible by decreasing portal pressure**

**170.000 deaths/year in the EU**

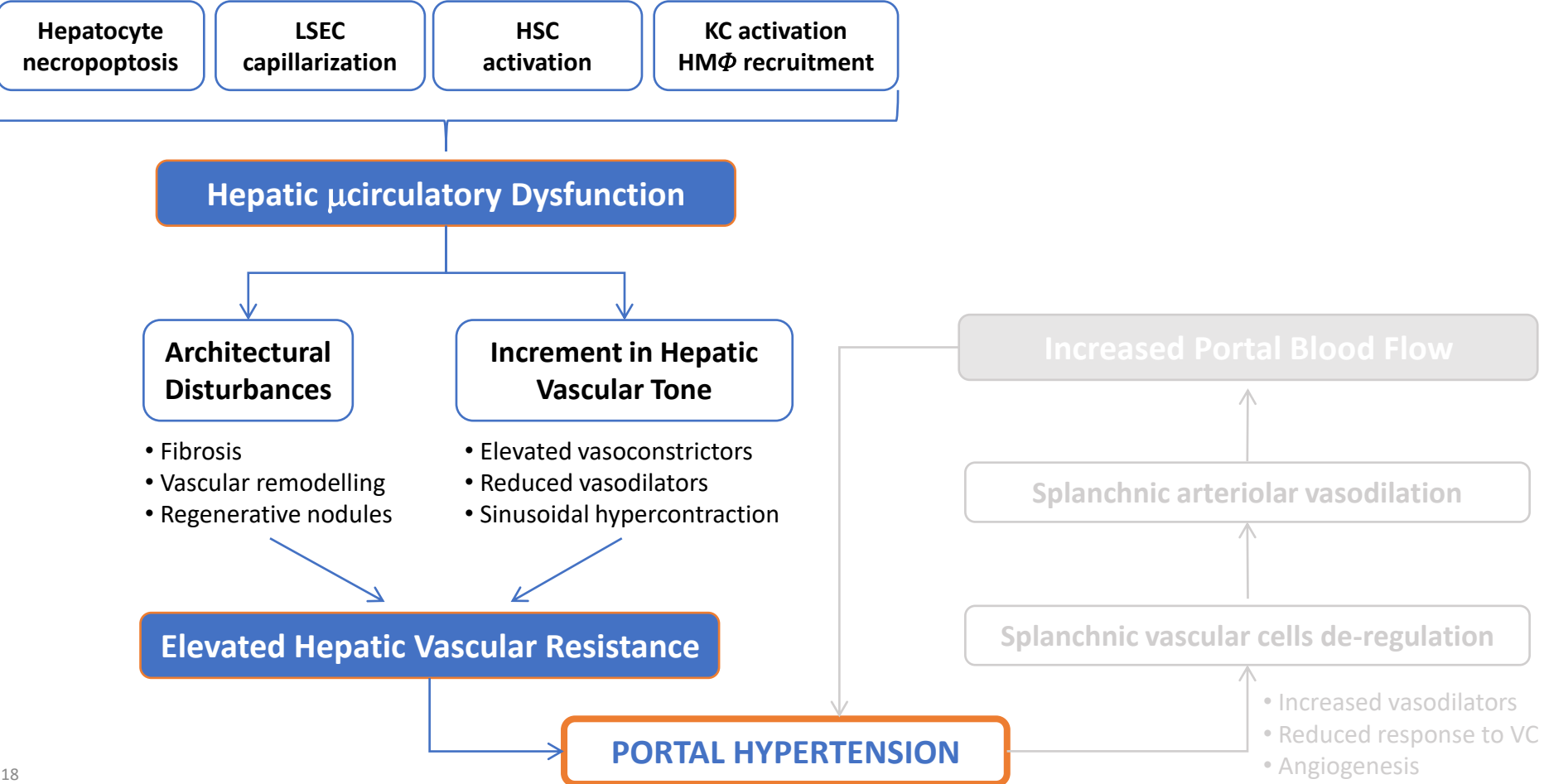
**1.300.000 deaths/year worldwide**



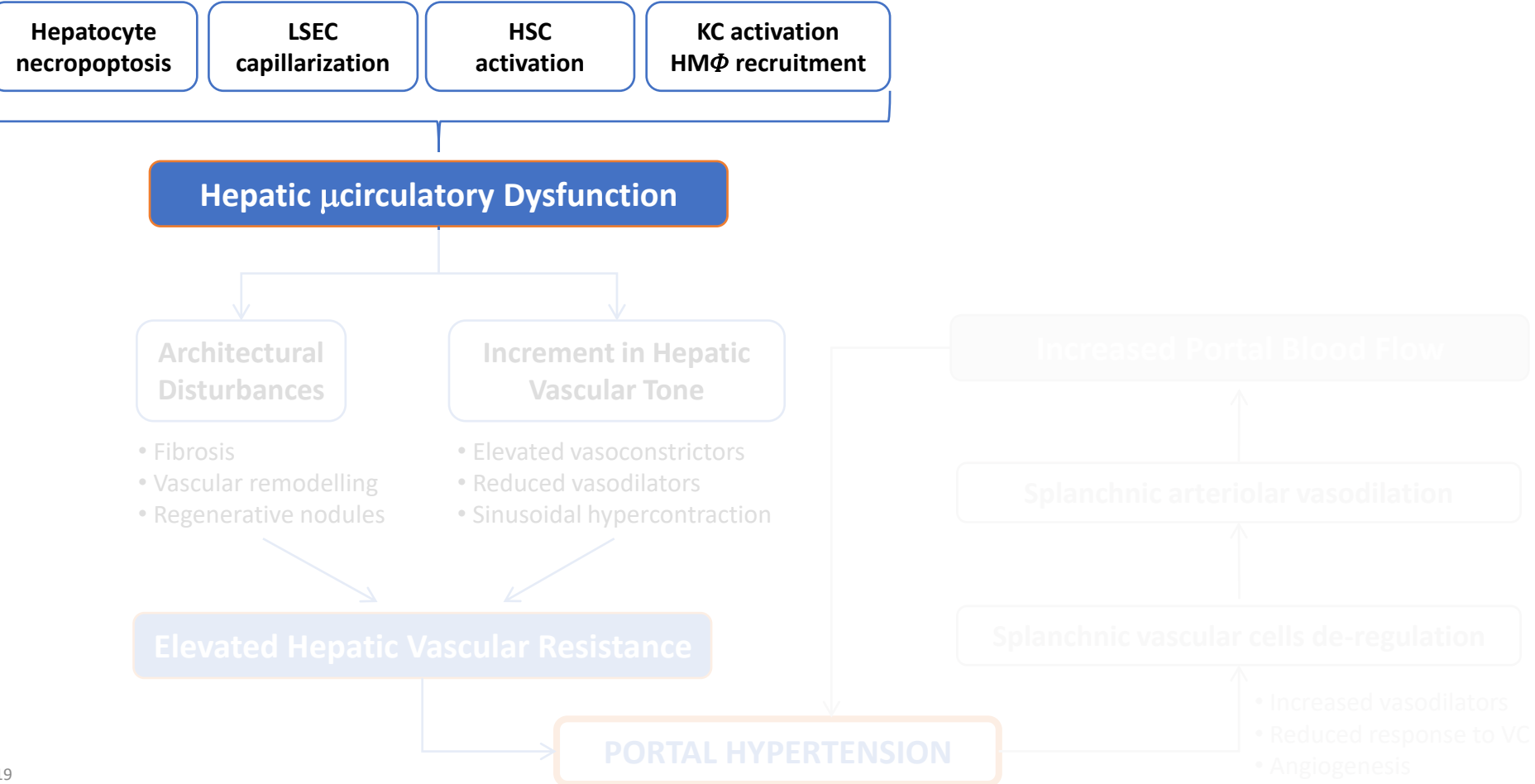
# Portal Hypertension Pathophysiology – The Global Picture



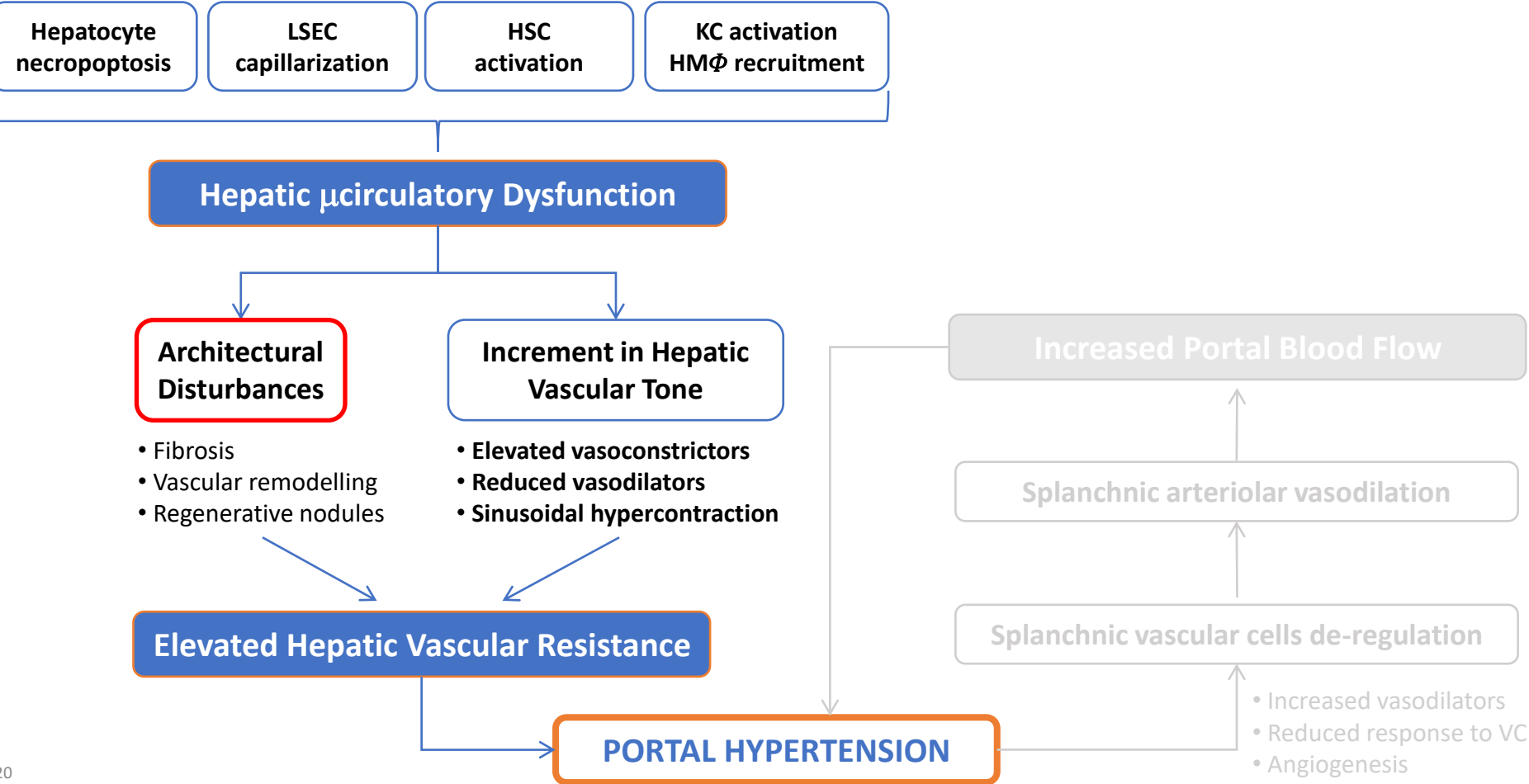
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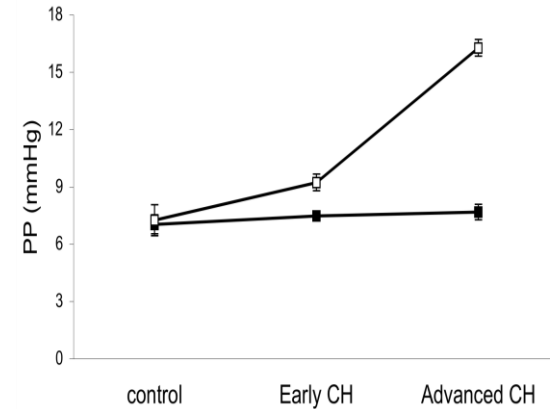
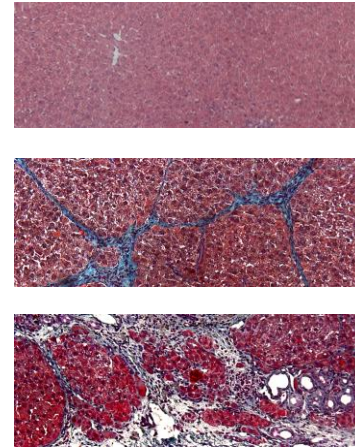
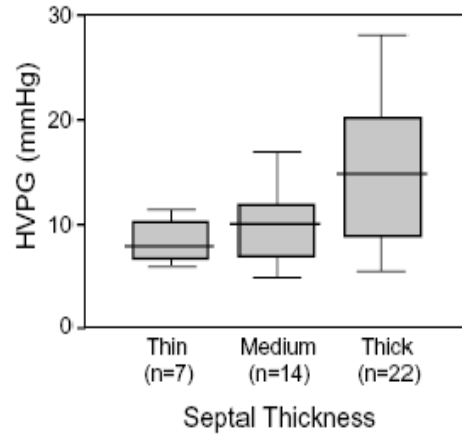
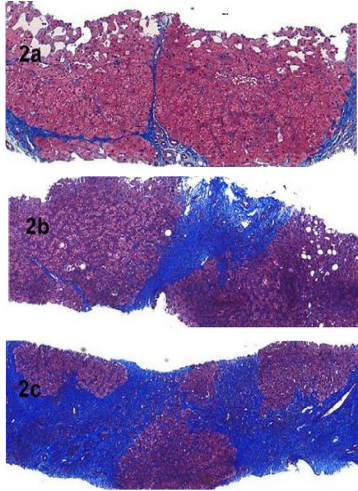
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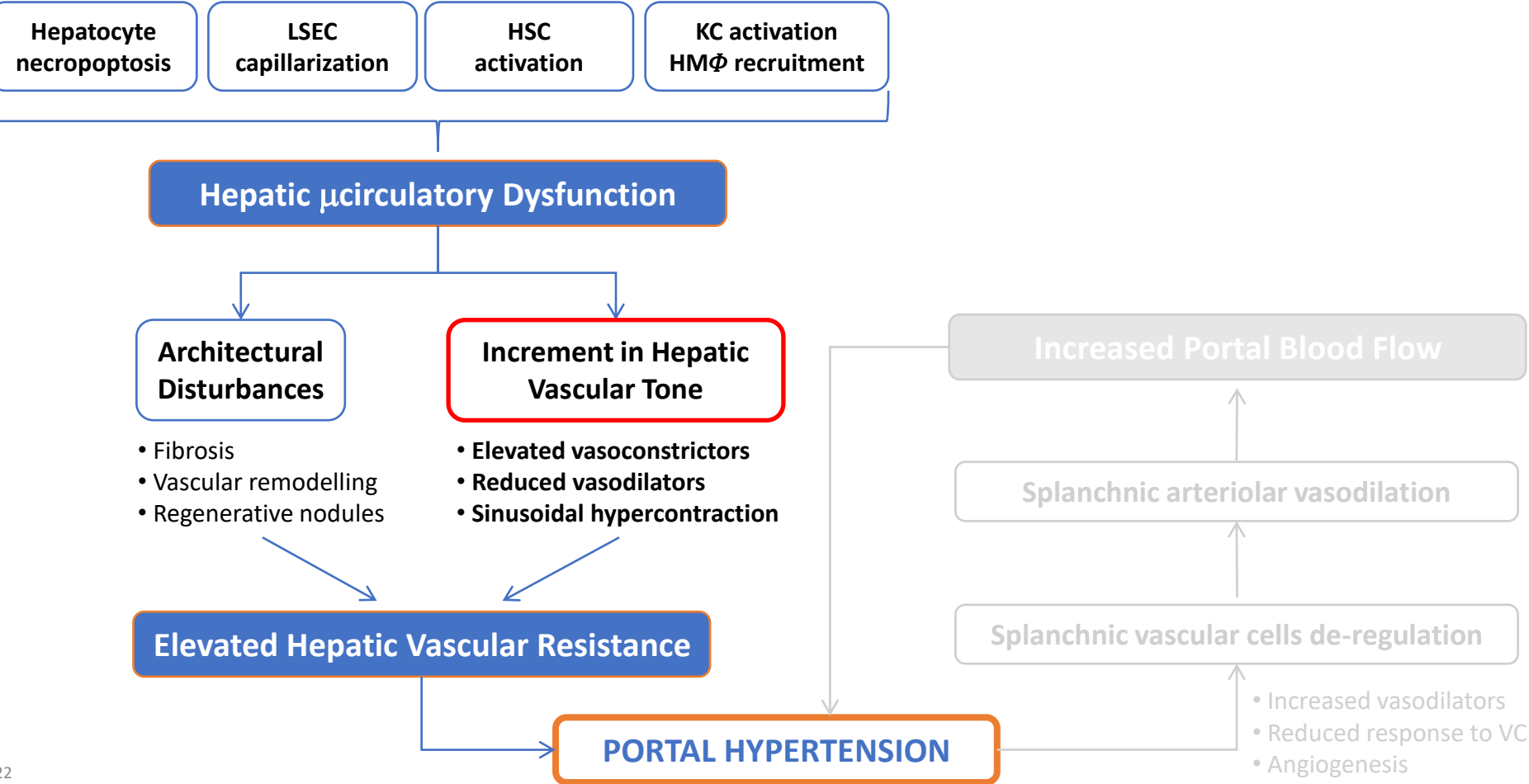
# Portal Hypertension Pathophysiology – Architectural disturbances



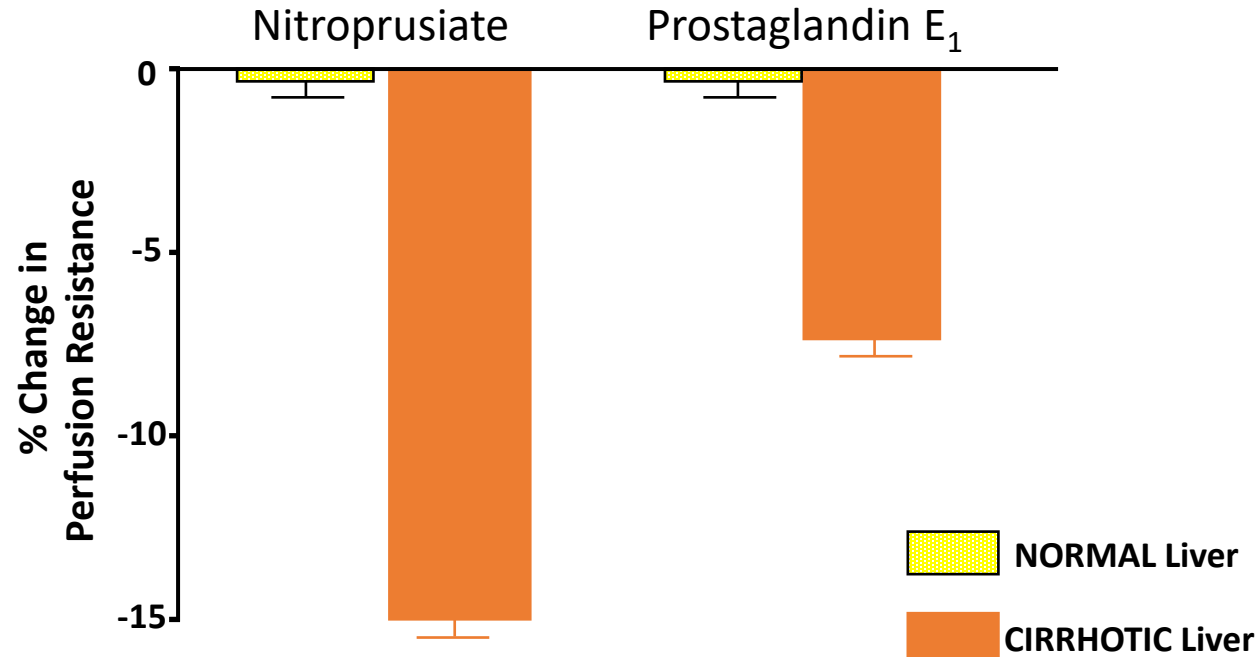
Nagula et al. J Hepatol 2006

Gracia-Sancho et al. Gut 2011

# Portal Hypertension Pathophysiology – The Global Picture

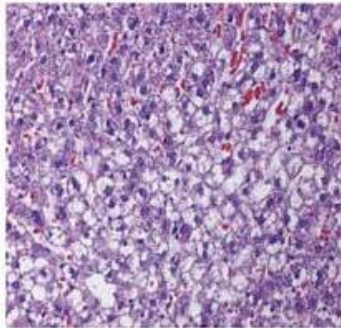
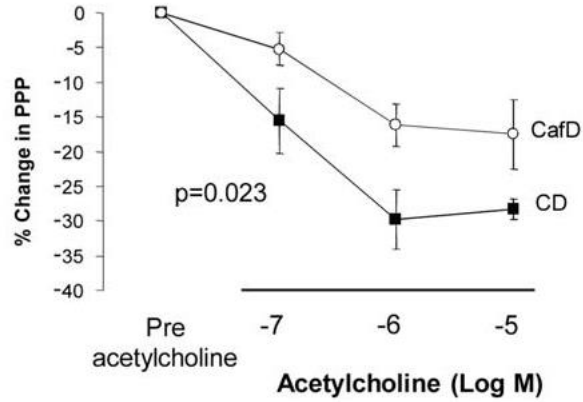


# Portal Hypertension Pathophysiology – Vascular disturbances

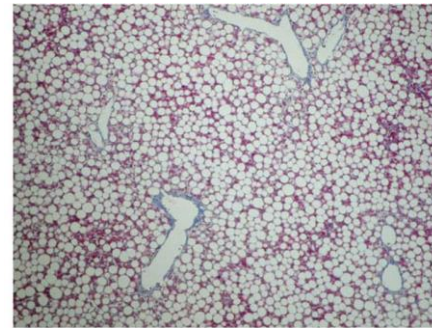
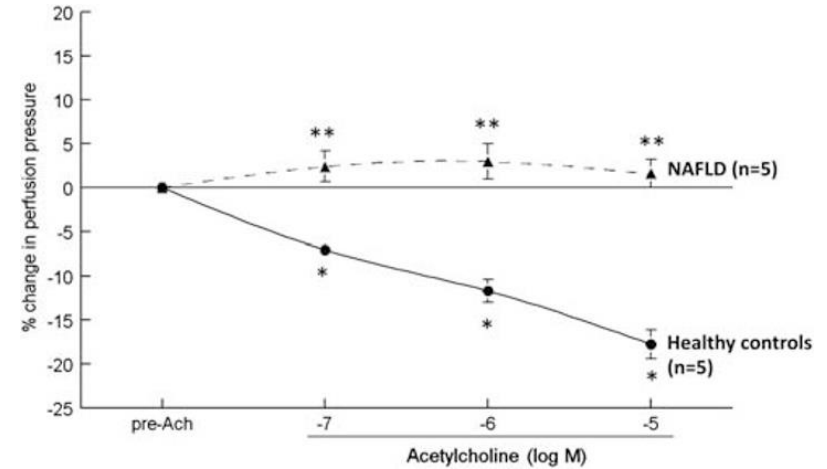


# Portal Hypertension Pathophysiology – Vascular dysfunction development

4w CafD



4w MCD



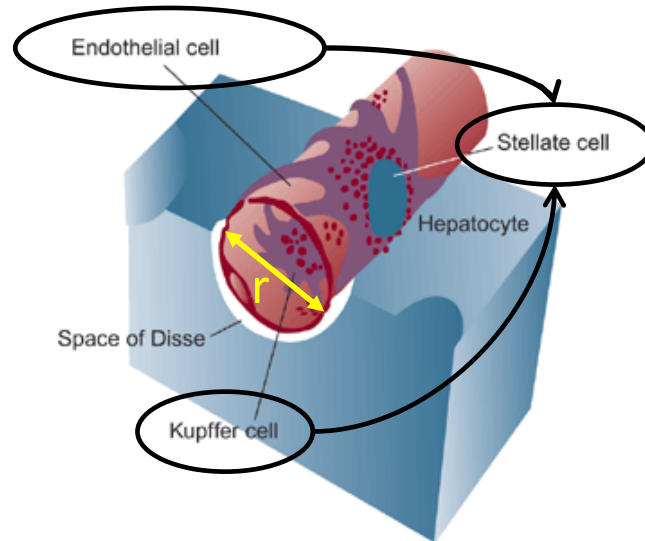


# Portal Hypertension Pathophysiology – Dynamic component of the HVR

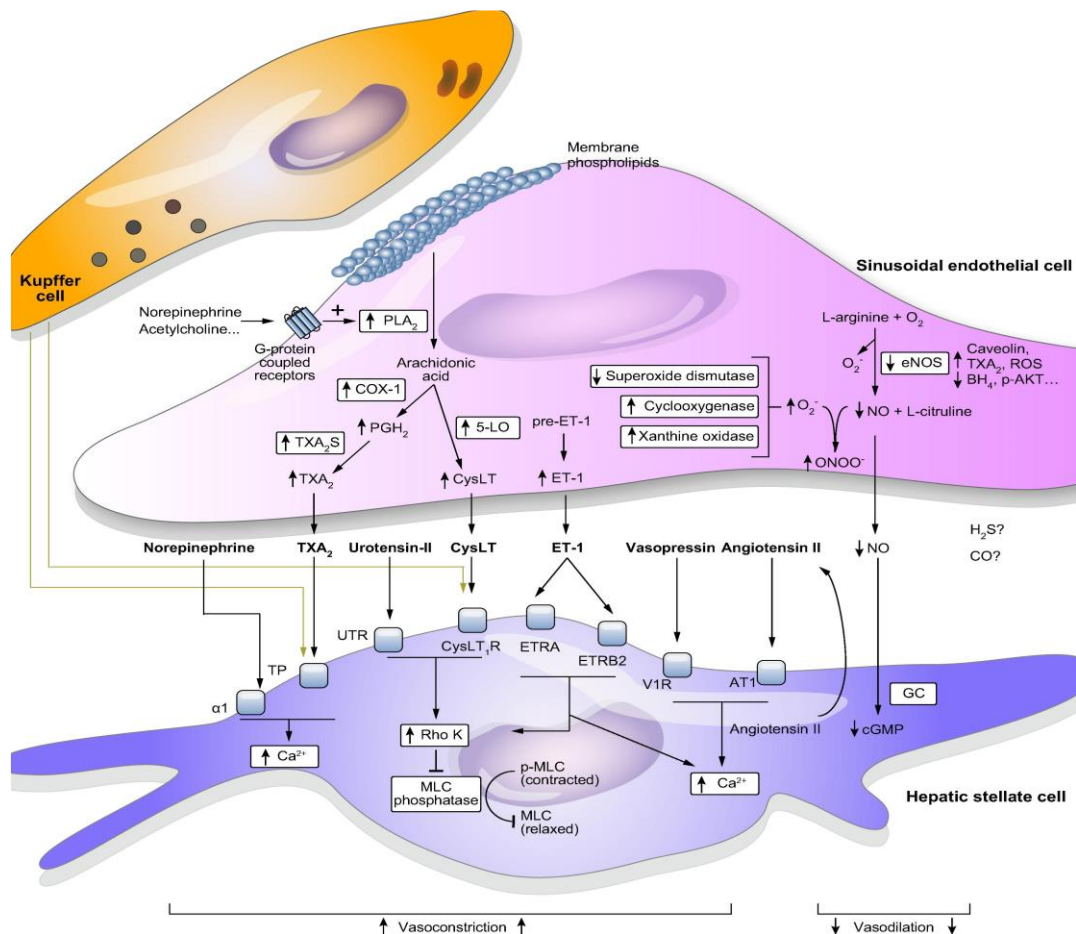
$$R = 8\eta L / r^4$$

Intrahepatic contractile elements

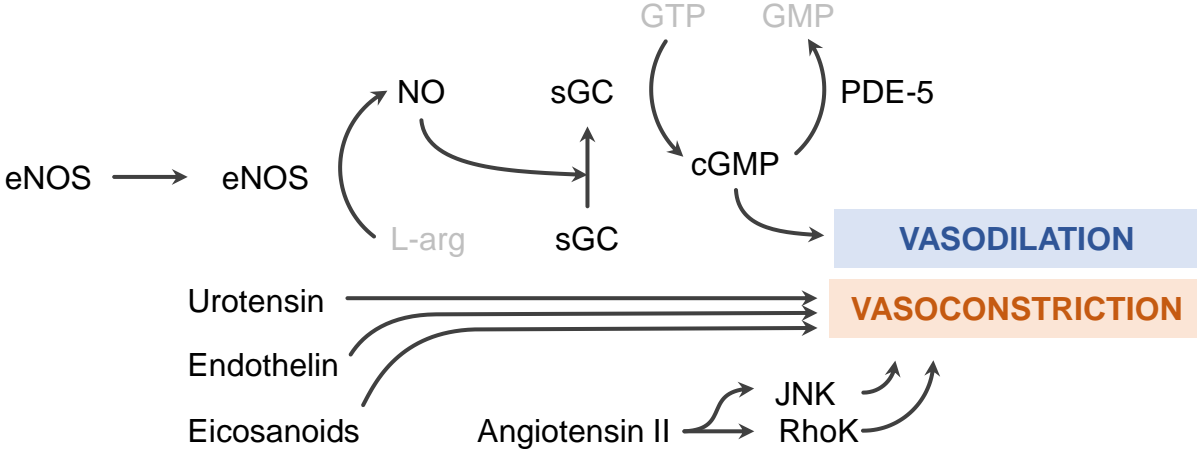
Regulation of contraction



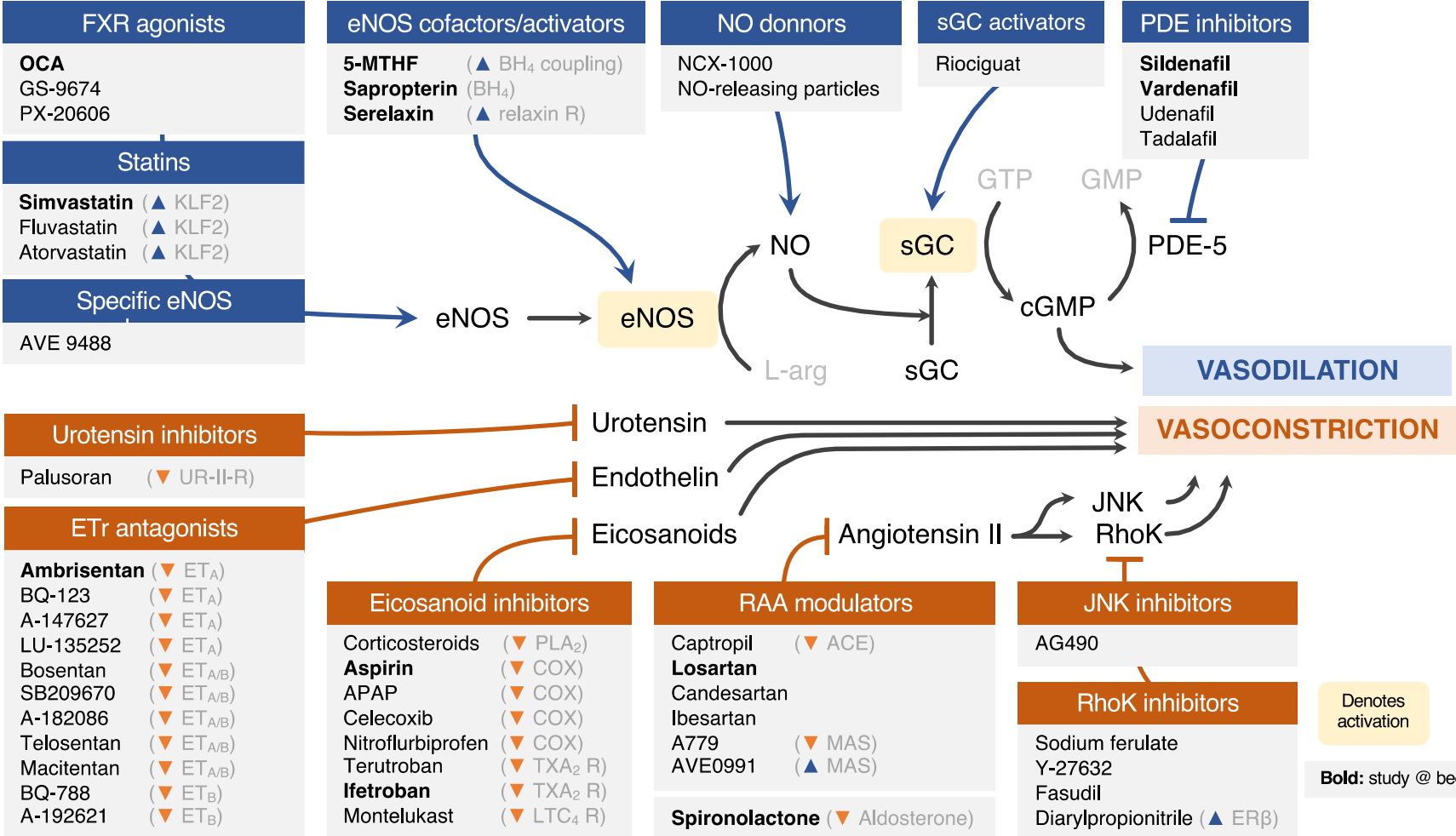
# Portal Hypertension Pathophysiology – Dynamic component of the HVR



# Promoting CLD regression: Targeting the sinusoid



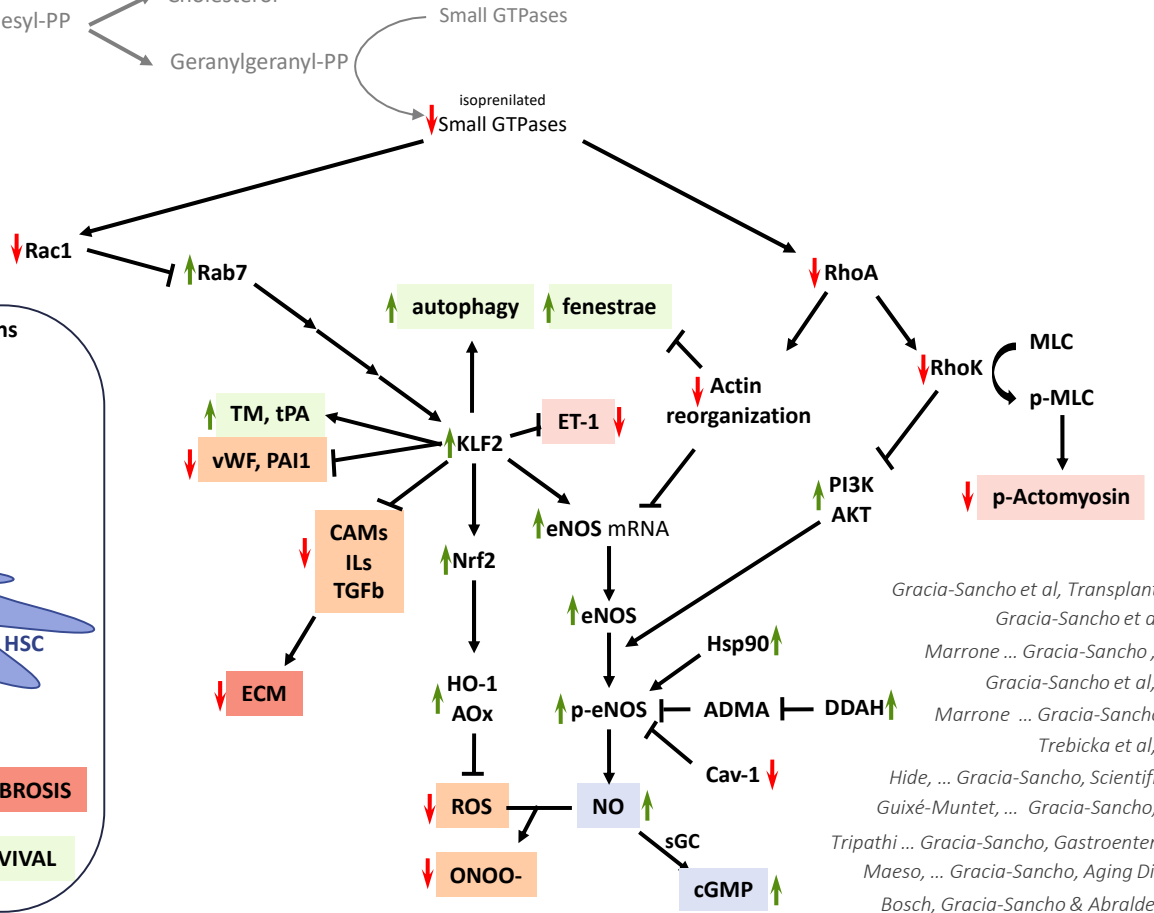
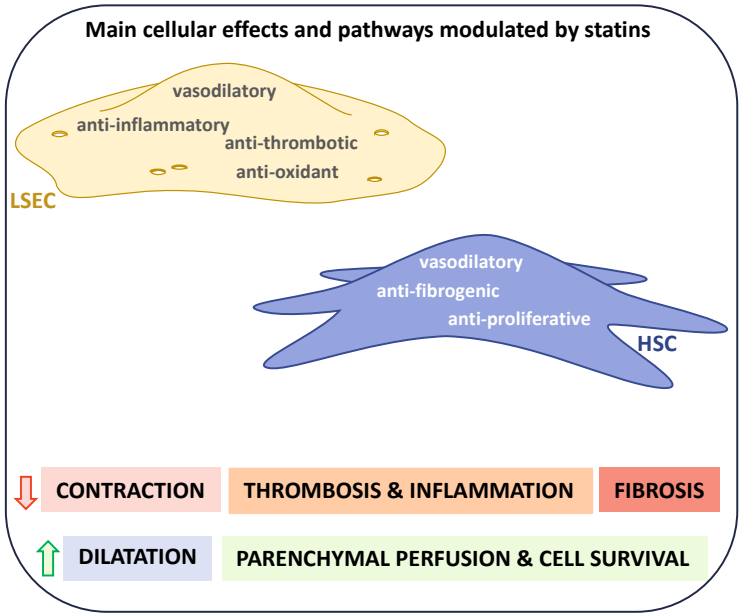
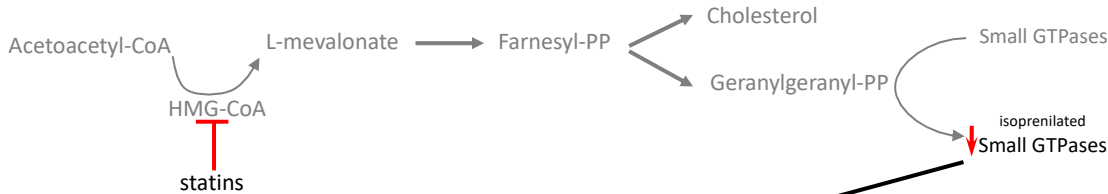
# Promoting CLD regression: Targeting the sinusoid



# Promoting CLD regression: therapeutics - statins

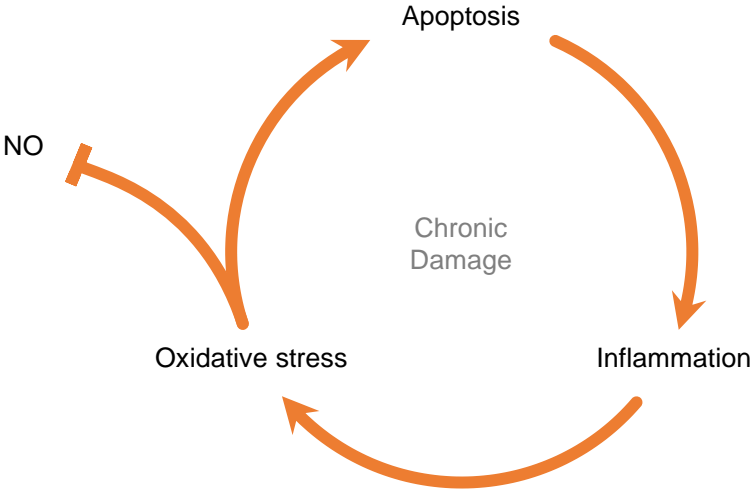
		Acute liver injury		Chronic liver disease		Acute on chronic liver failure	
		ischaemia/reperfusion	infection			cirrhosis + infection	
		24h - 3days	24h - 3days	24h - 3days	7-14days	24h - 3days	
LIVER PATHOBIOLOGY	Molecular pathways	KLF2-eNOS-NO KLF2-Nrf2-Aox KLF2-Autophagy	KLF2-eNOS-NO KLF2-CAMs	KLF2-eNOS-NO 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	
	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 <sub>4</sub> chronic TAA BDL - simvastatin - - atorvastatin -	chronic CCl <sub>4</sub> aged animals BDL - simvastatin -	chronic CCl <sub>4</sub> + LPS chronic TAA + LPS compensated & decompensated cirrhosis BDL + LPS - simvastatin -	
Clinical evidence	Observational studies - diverse statins -		Observational studies - diverse statins - Proof-of-concept RCTs - simvastatin - RCT with clinical end points - simvastatin -		Ongoing phase III RCT - simvastatin -		

# Promoting CLD regression: therapeutics - statins

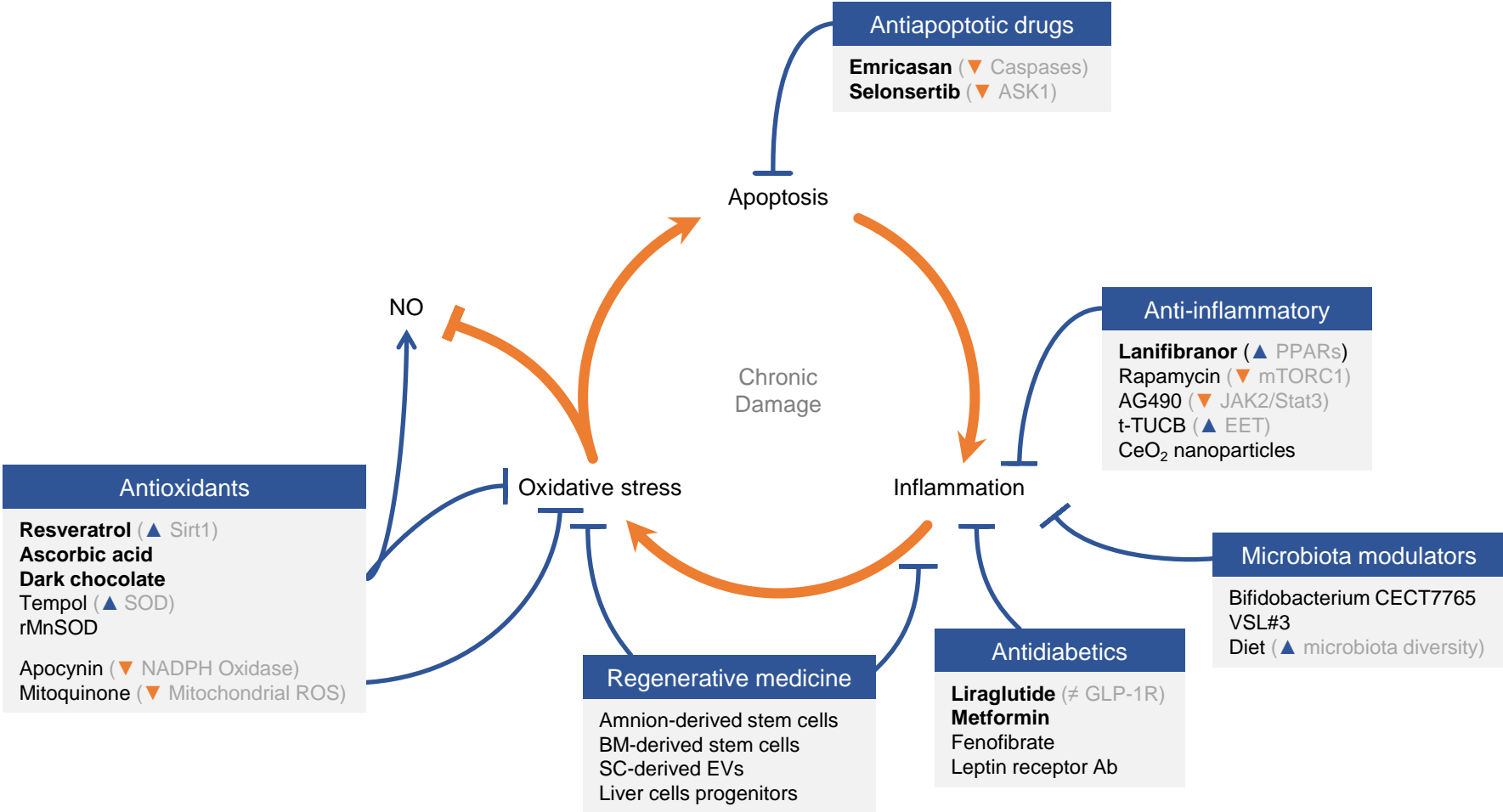


Gracia-Sancho et al, Transplantation 2010  
 Gracia-Sancho et al, Gut 2011  
 Marrone ... Gracia-Sancho, JHep 2013  
 Gracia-Sancho et al, JHep 2013  
 Marrone ... Gracia-Sancho, Gut 2015  
 Trebicka et al, JHep 2010  
 Hide, ... Gracia-Sancho, Scientific Rep 2016  
 Guixé-Muntet, ... Gracia-Sancho, JHep 2017  
 Tripathi ... Gracia-Sancho, Gastroenterology 2018  
 Maeso, ... Gracia-Sancho, Aging Disease 2019  
 Bosch, Gracia-Sancho & Abraldes, Gut 2020  
 Hide, ... Gracia-Sancho, J Gerontol 2021

# Promoting CLD regression: targeting the sinusoid

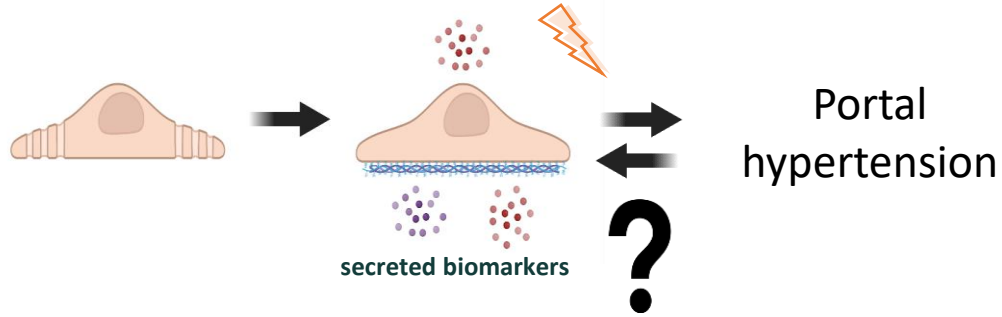


# Promoting CLD regression: targeting the sinusoid

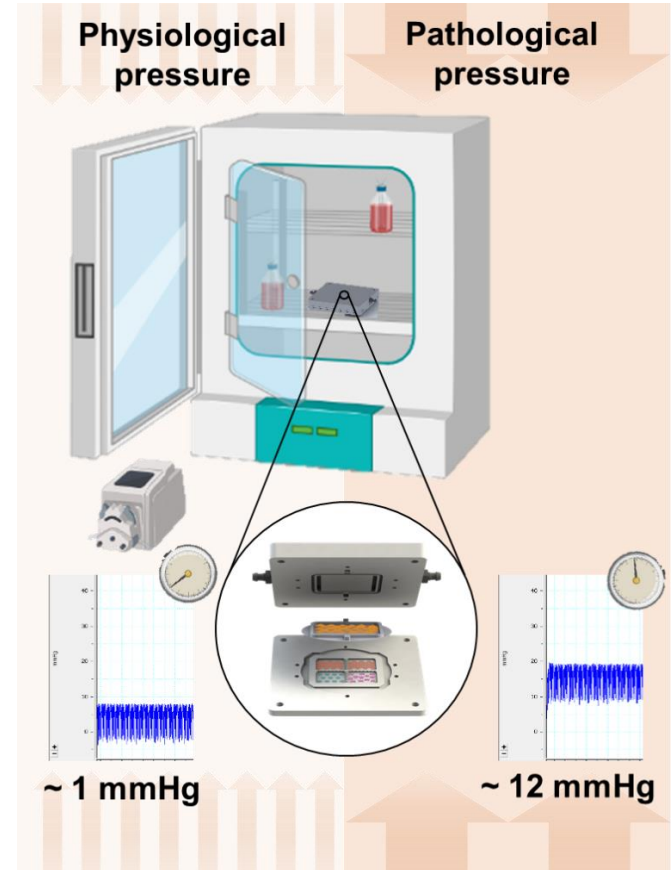




# Biomarkers of hepatic microvascular dysfunction

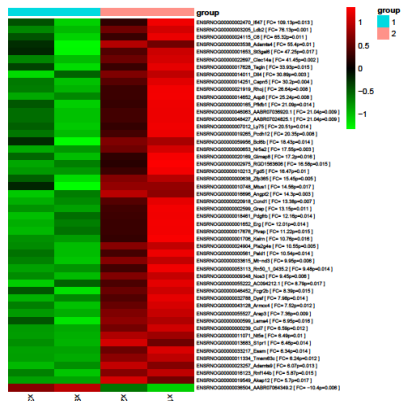


- Understand the effects of PH on LSEC (RNAseq)
- Define novel transcriptional regulators of LSEC dysf
- Identify new biomarkers of PH

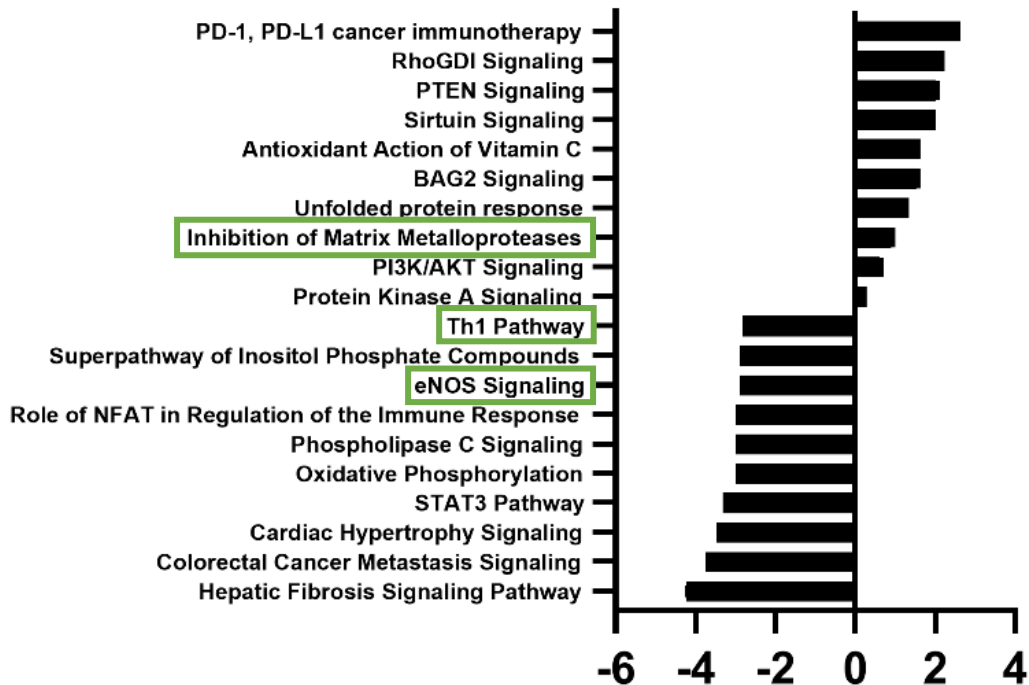


# Biomarkers of hepatic microvascular dysfunction

## Canonical Pathways

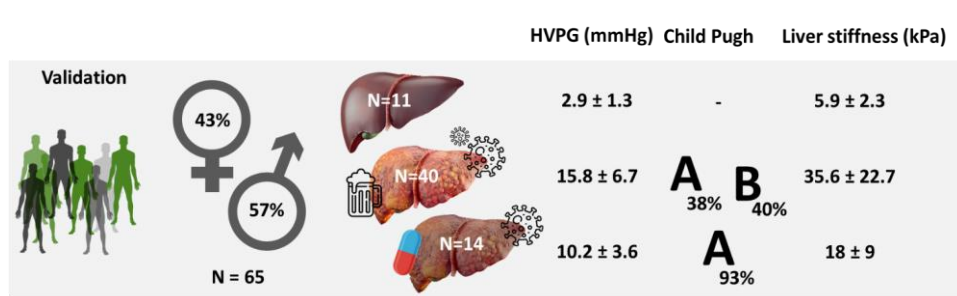


↓  
CBX7

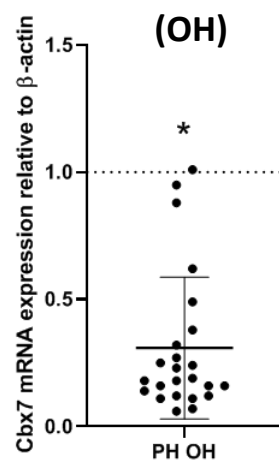


z-score

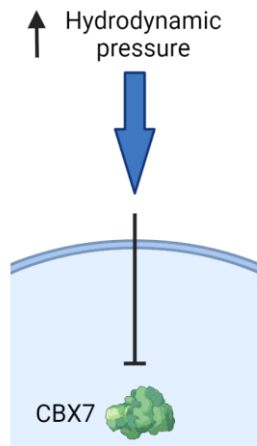
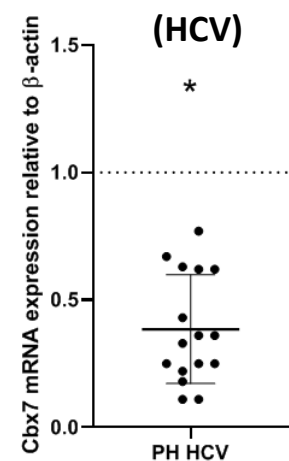
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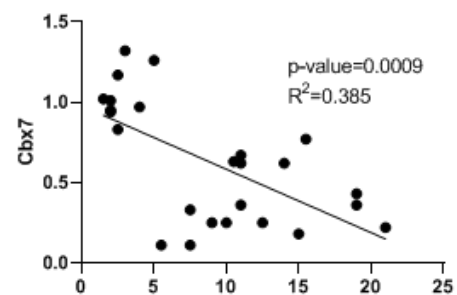
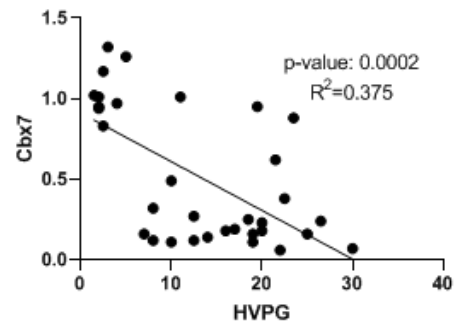
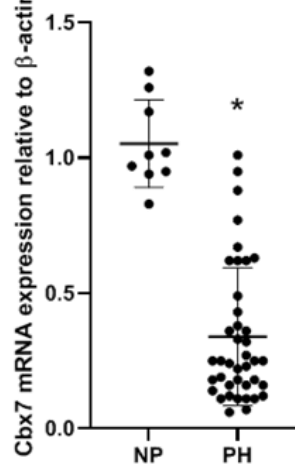
## Validation cohort



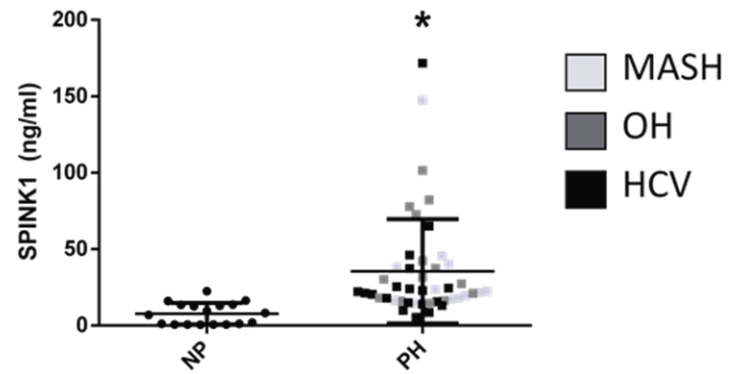
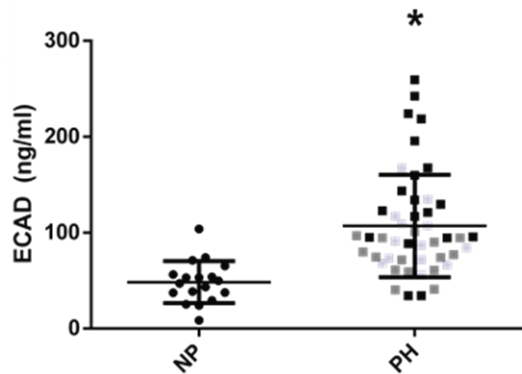
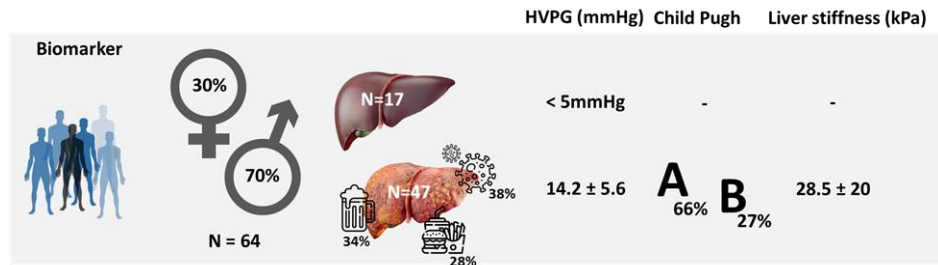
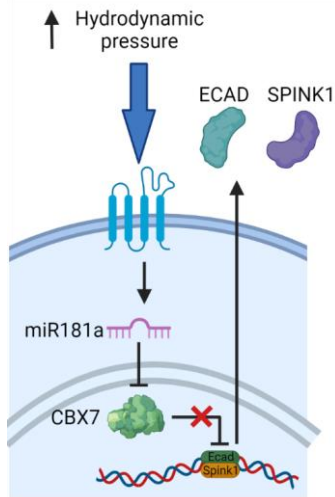
## Validation cohort



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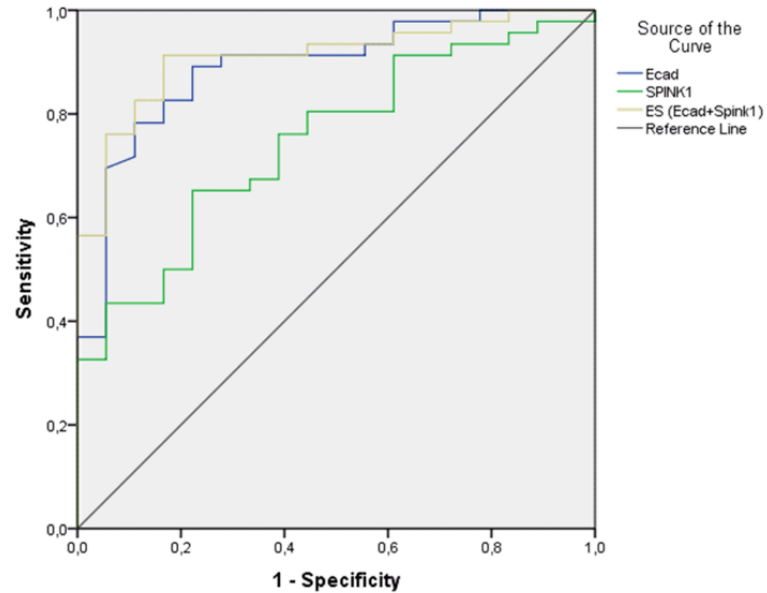


# Biomarkers of hepatic microvascular dysfunction



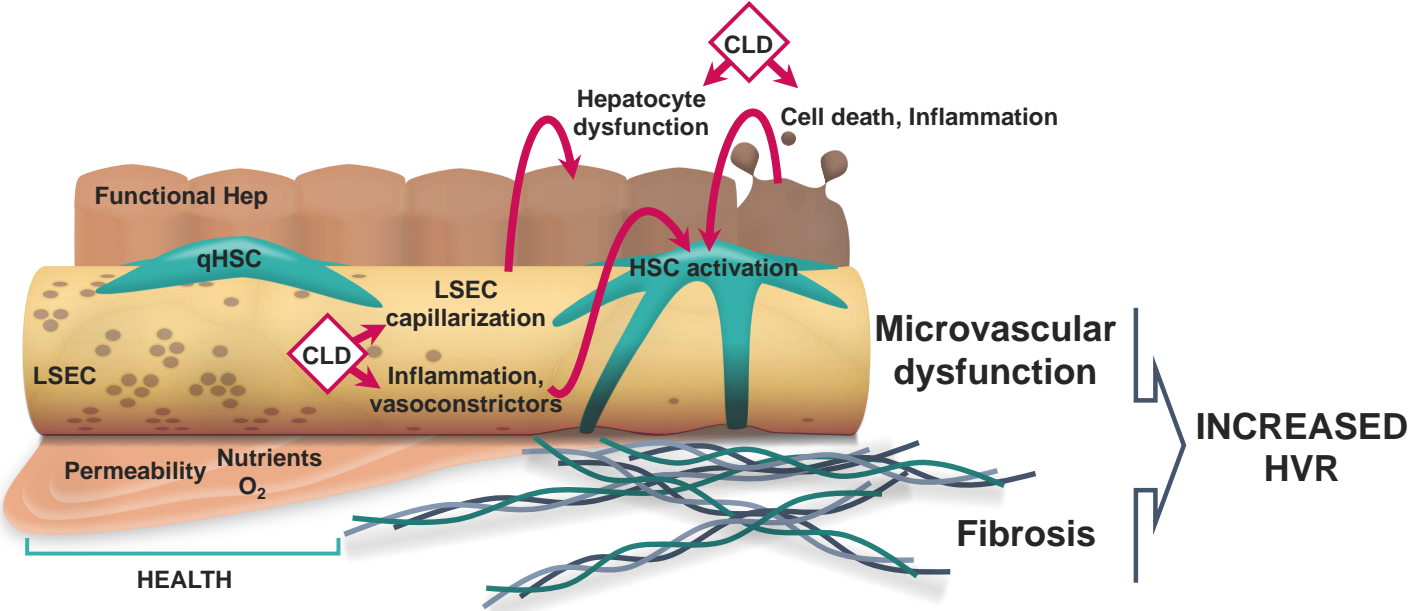
\*p<0.05

# Biomarkers of hepatic microvascular dysfunction

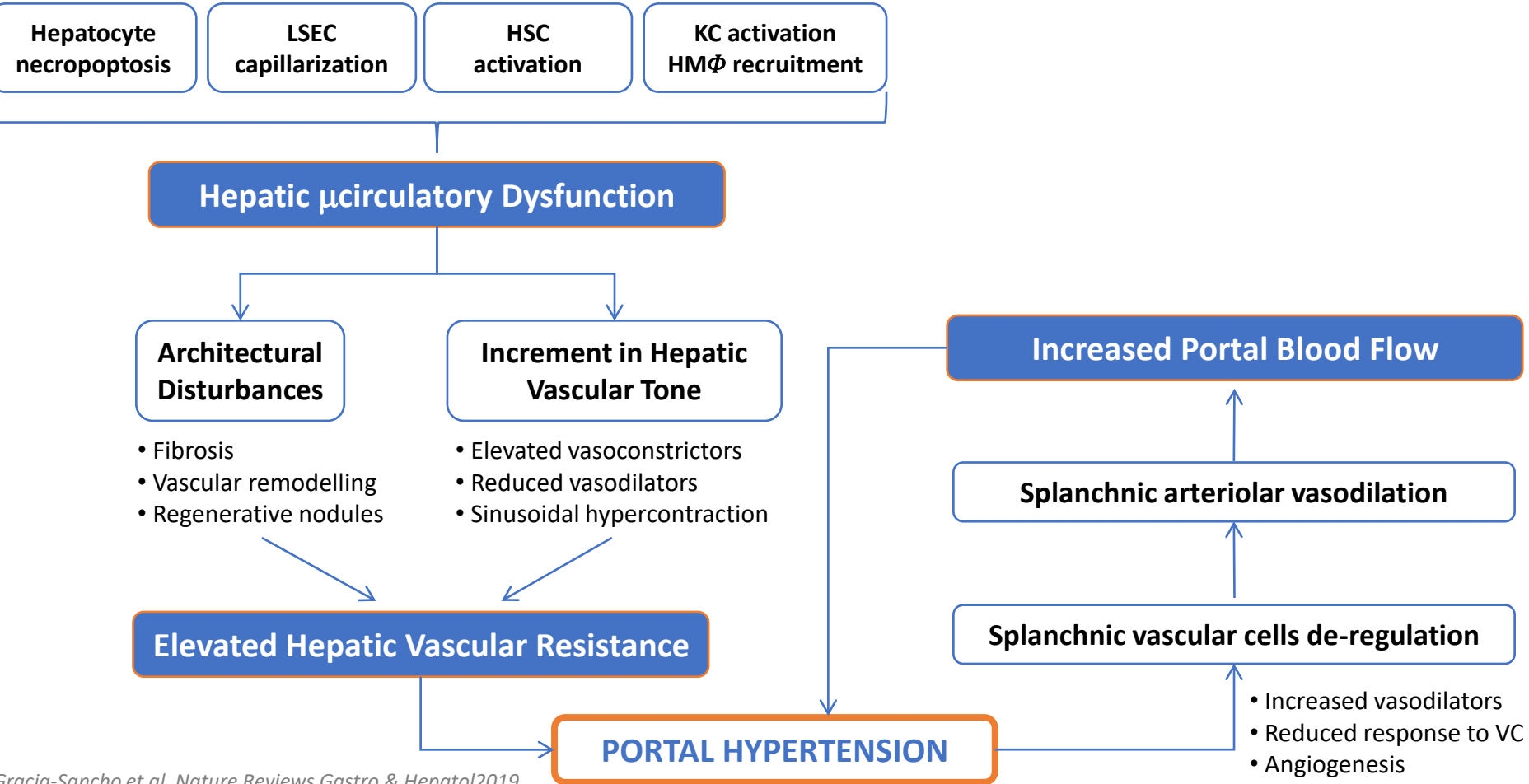


Marker	n (</> 5mmHg)	AUROC (95% CI)	Cut-off	Sens (%)	Spec (%)	PPV (%)	NPV (%)
ECAD	18/46	0.889 (0.802 to 0.977)	57.673	89.1	77.8	91.12	73.64
SPINK1	18/45	0.747 (0.622 to 0.871)	16.040	80.0	55.6	81.83	52.65
ECAD + SPINK1	18/46	0.911 (0.838 to 0.983)	0.579	91.3	83.3	93.32	78.93

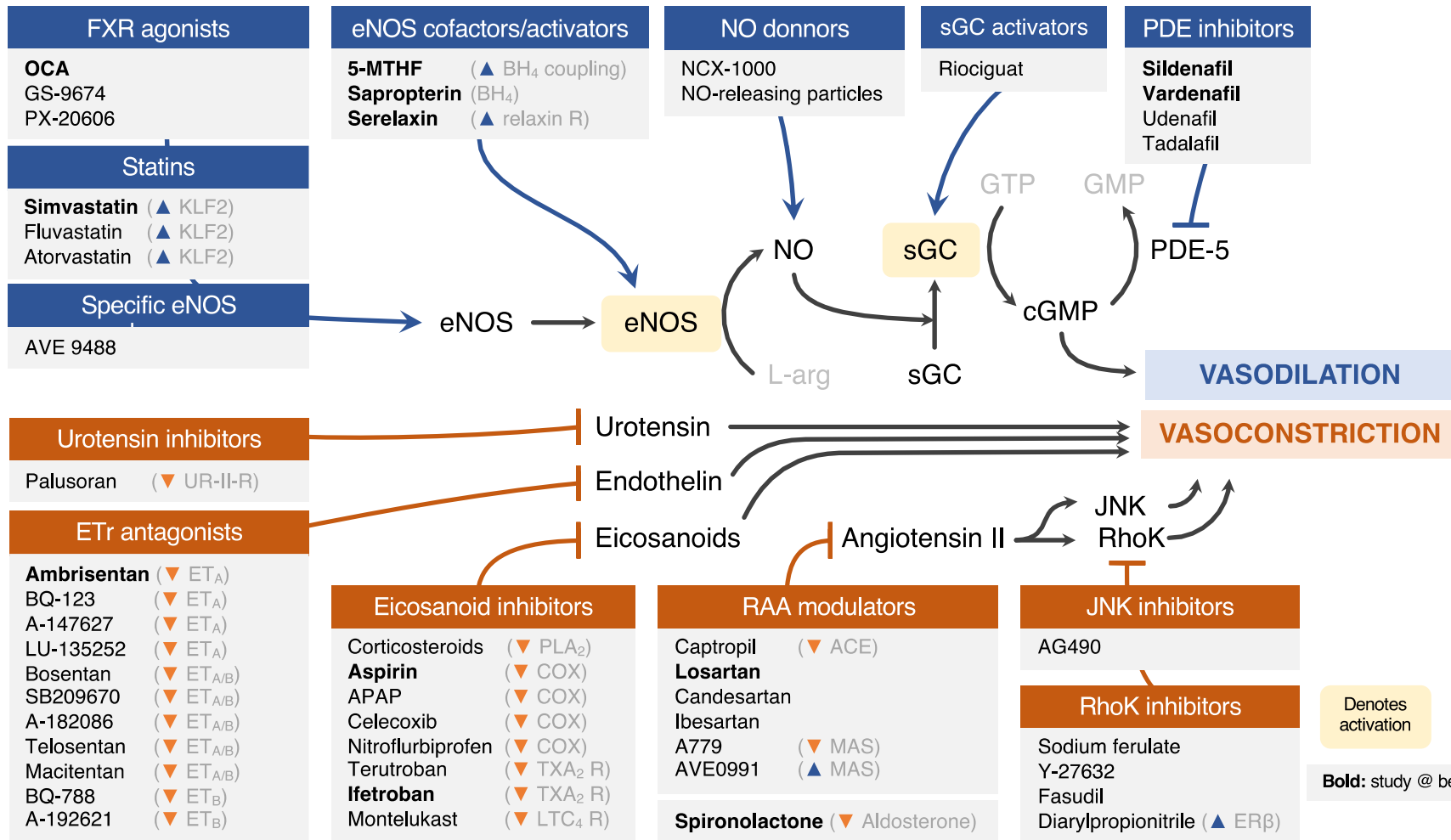
# Wrap-up 1: Progression of CLD and PH



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

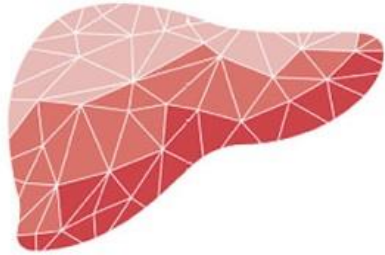


# Wrap-up 3: therapeutics for PH targeting the sinusoid





# MÁSTER EN HEPATOLOGÍA



**UAM**

Universidad Autónoma  
de Madrid



Universidad  
de Alcalá