



**APASL STC**  
**Cairo, July 30<sup>th</sup> 2022**

# Liver vascular dysfunction as trigger of fibrosis

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# COI



## **Dr Gracia-Sancho disclosures (last 3 years)**

I disclose COI with the following companies/organizations

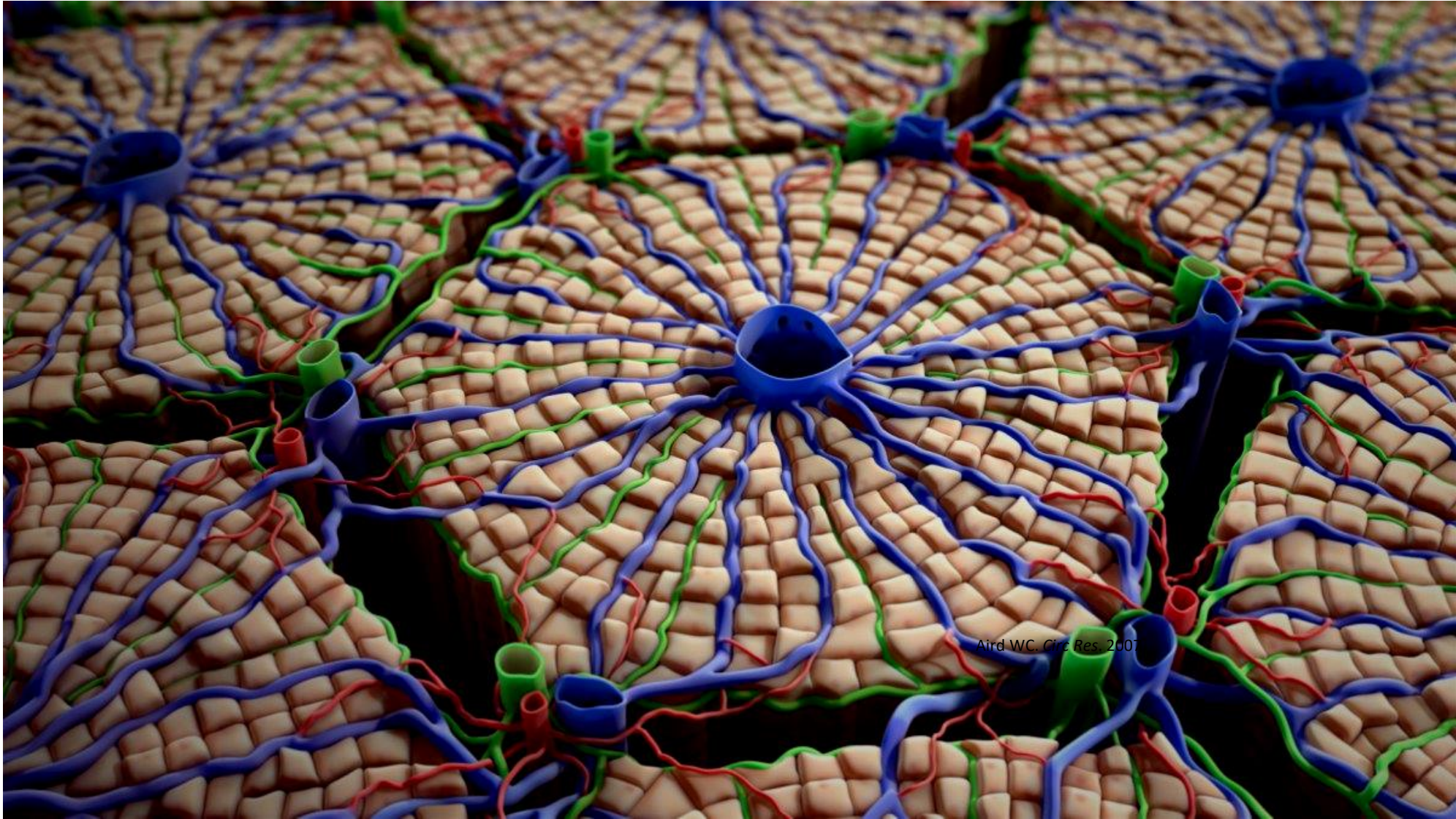
Ambys Medicines, Inventiva, Gilead Sciences, Conatus Pharmaceuticals, BrudyLab, GAT therapeutics, BLB Surrozen, Novo Nordisk

# Agenda



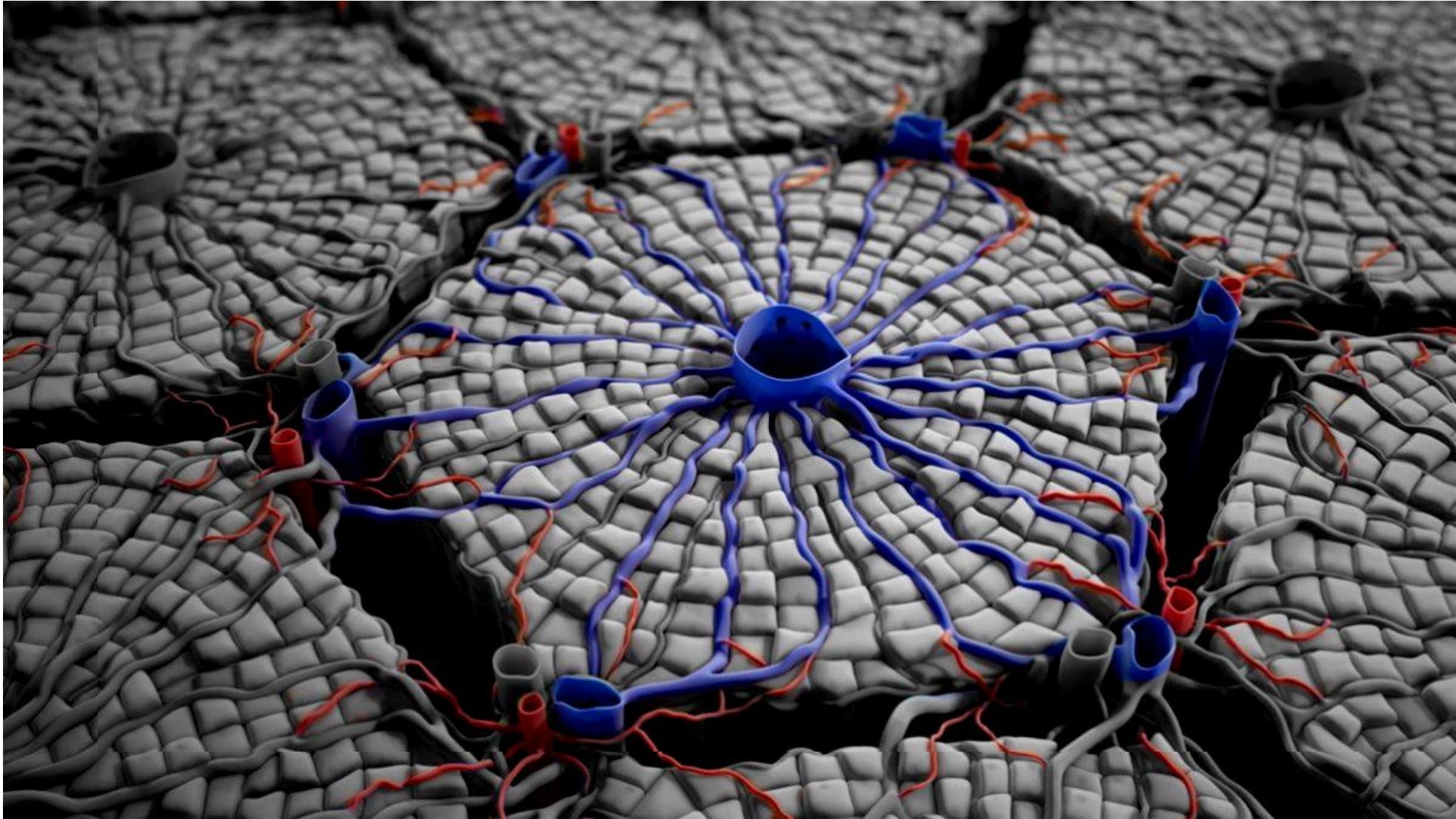
- Hepatic microcirculation in health and disease
- Liver microvascular dysfunction & fibrosis
- Therapeutics to improve fibrosis

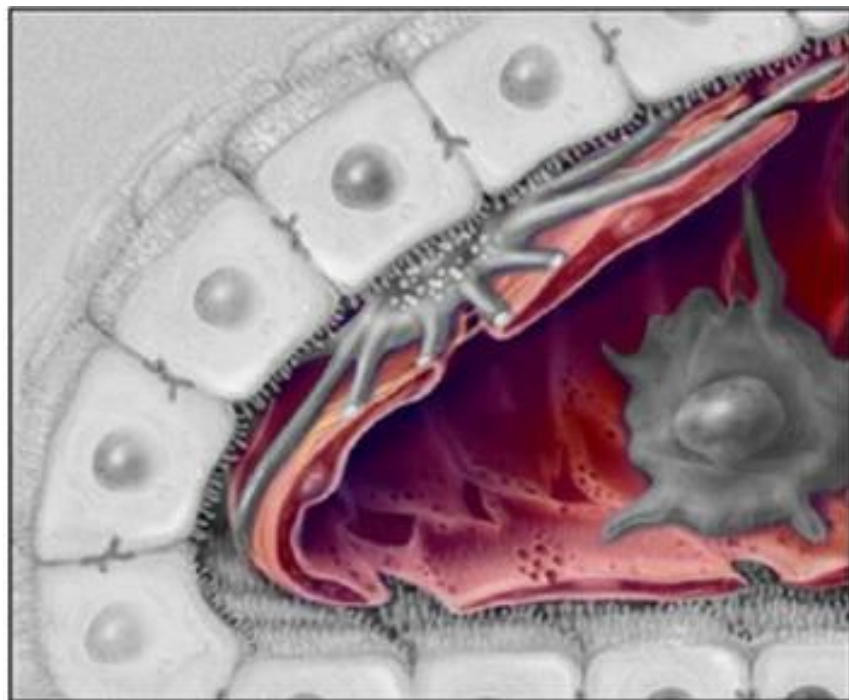
# The liver sinusoid



Aird WC. *Circ Res*. 2007

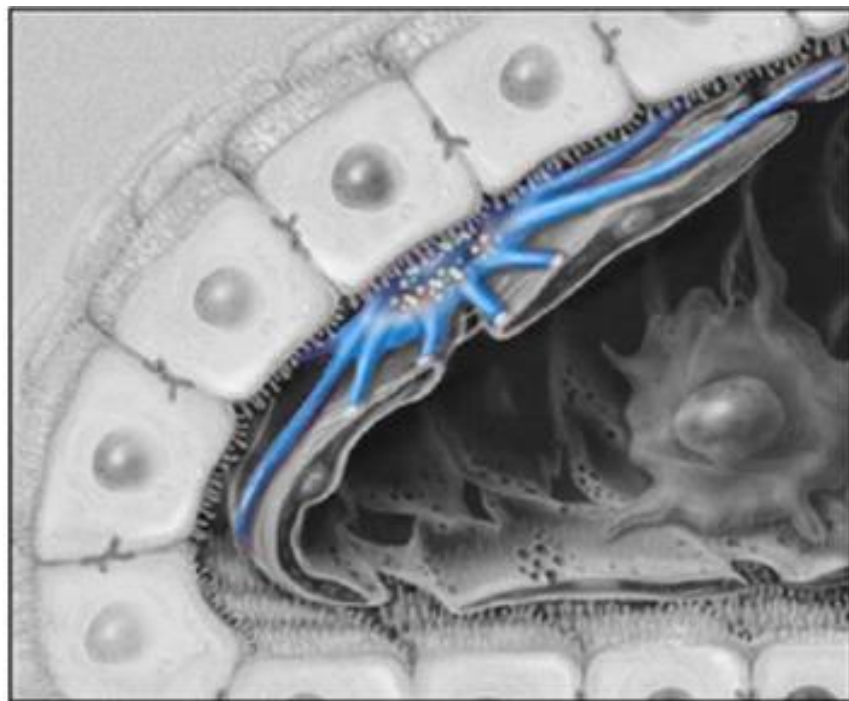
# The liver sinusoid





## Liver Sinusoidal Endothelial Cells (LSEC)

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

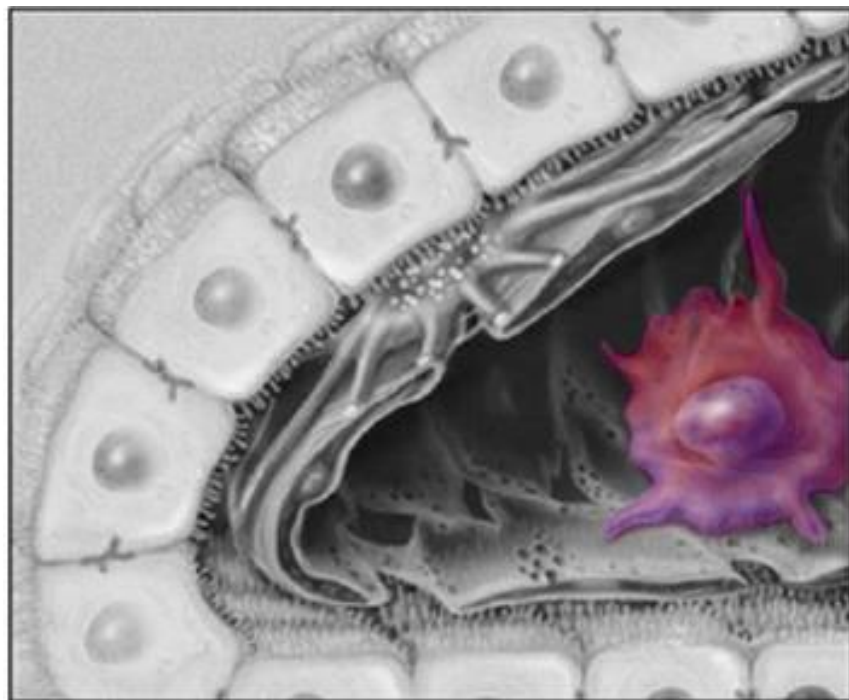


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## Hepatic Stellate Cells (HSC)

- Contractile properties.
- Vitamin A storage



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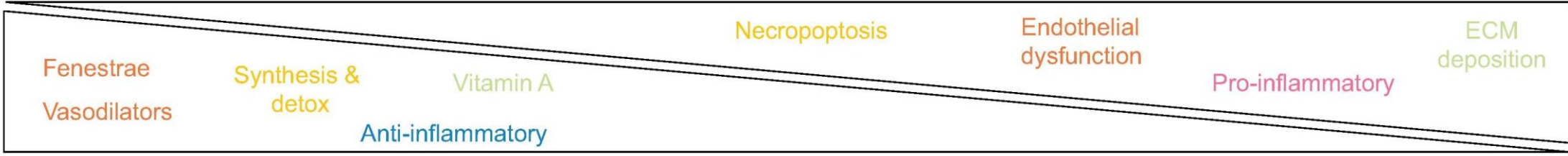
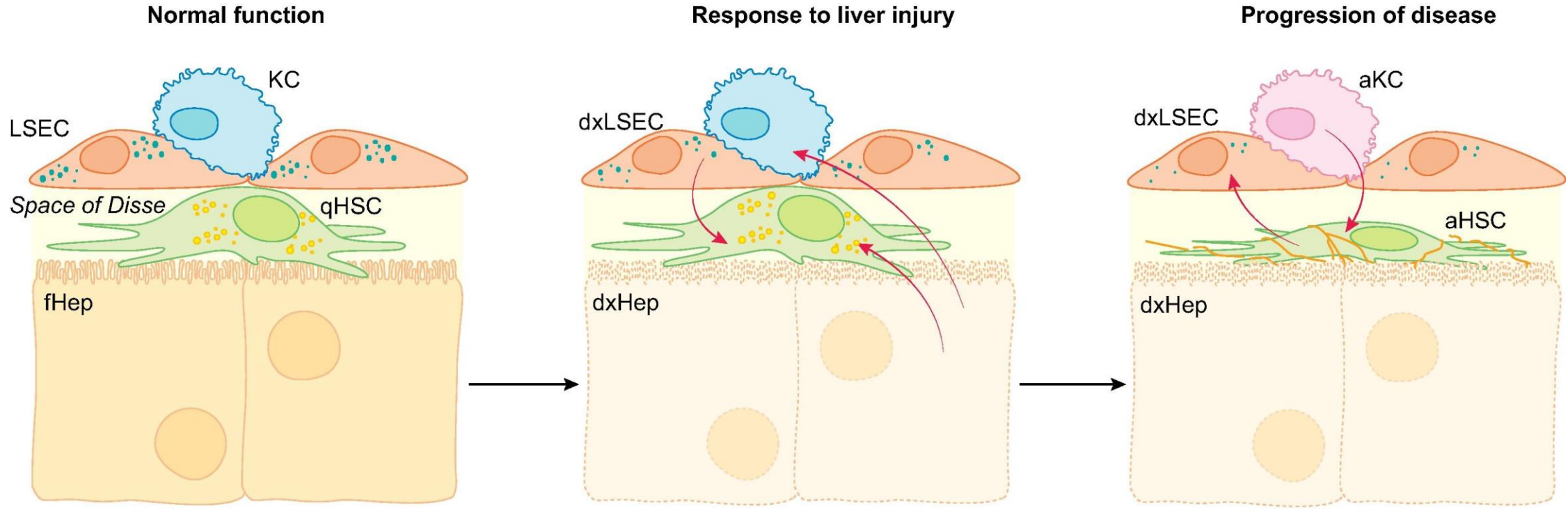
- Contractile properties.
- Vitamin A storage

## **Kupffer Cells (KC)**

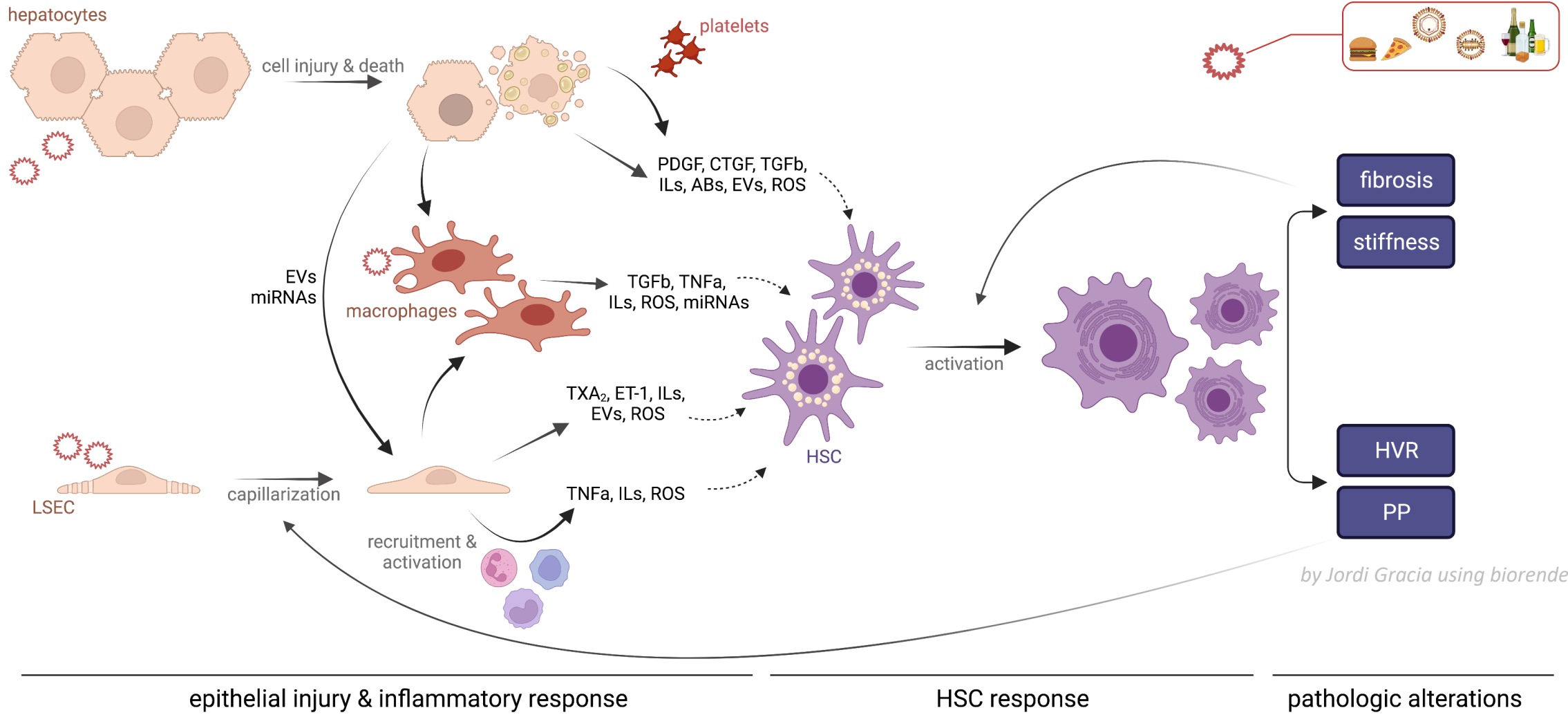
- Resident macrophages: defense, inflammation, tissue remodelling.



# The liver sinusoid during CLD progression

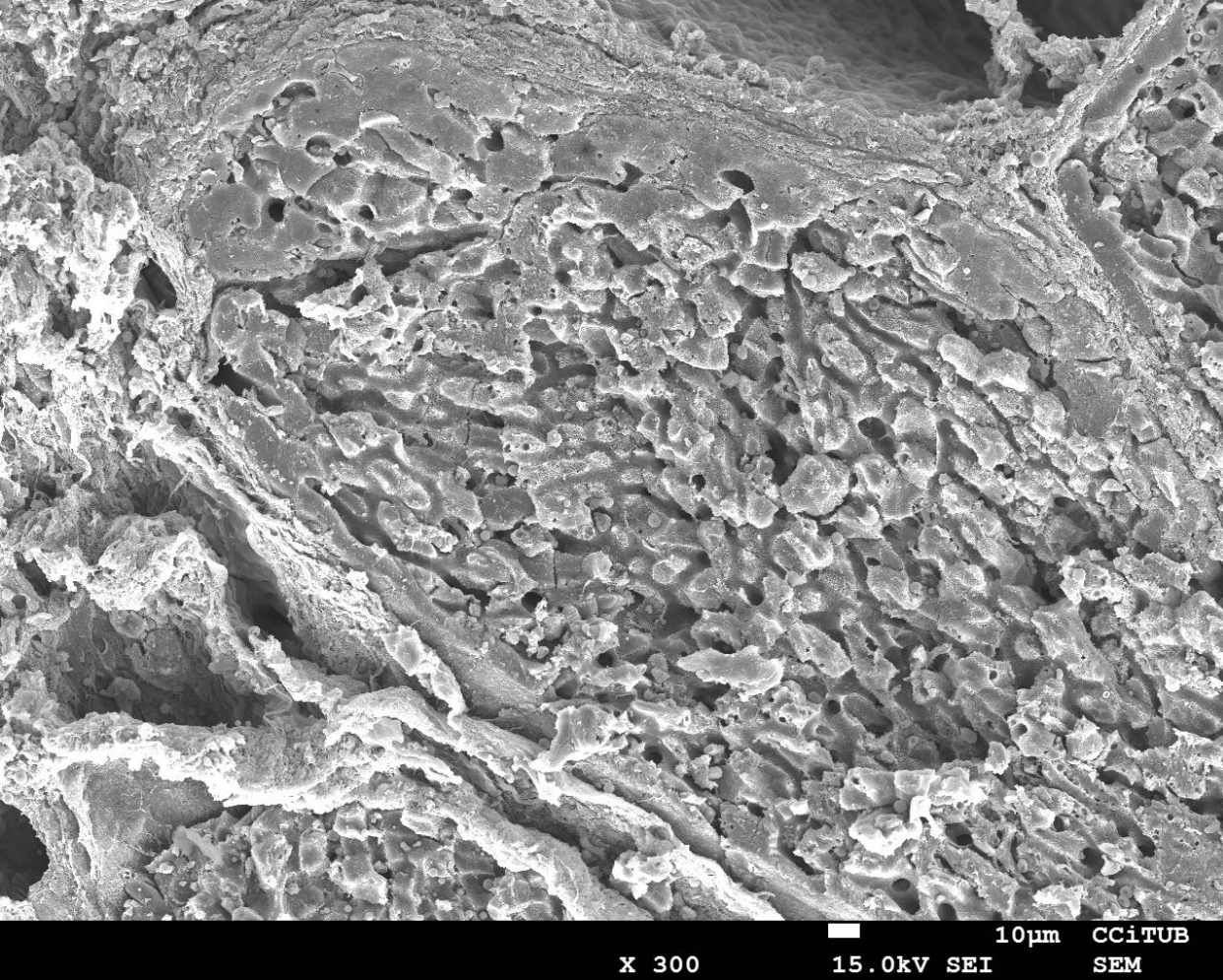
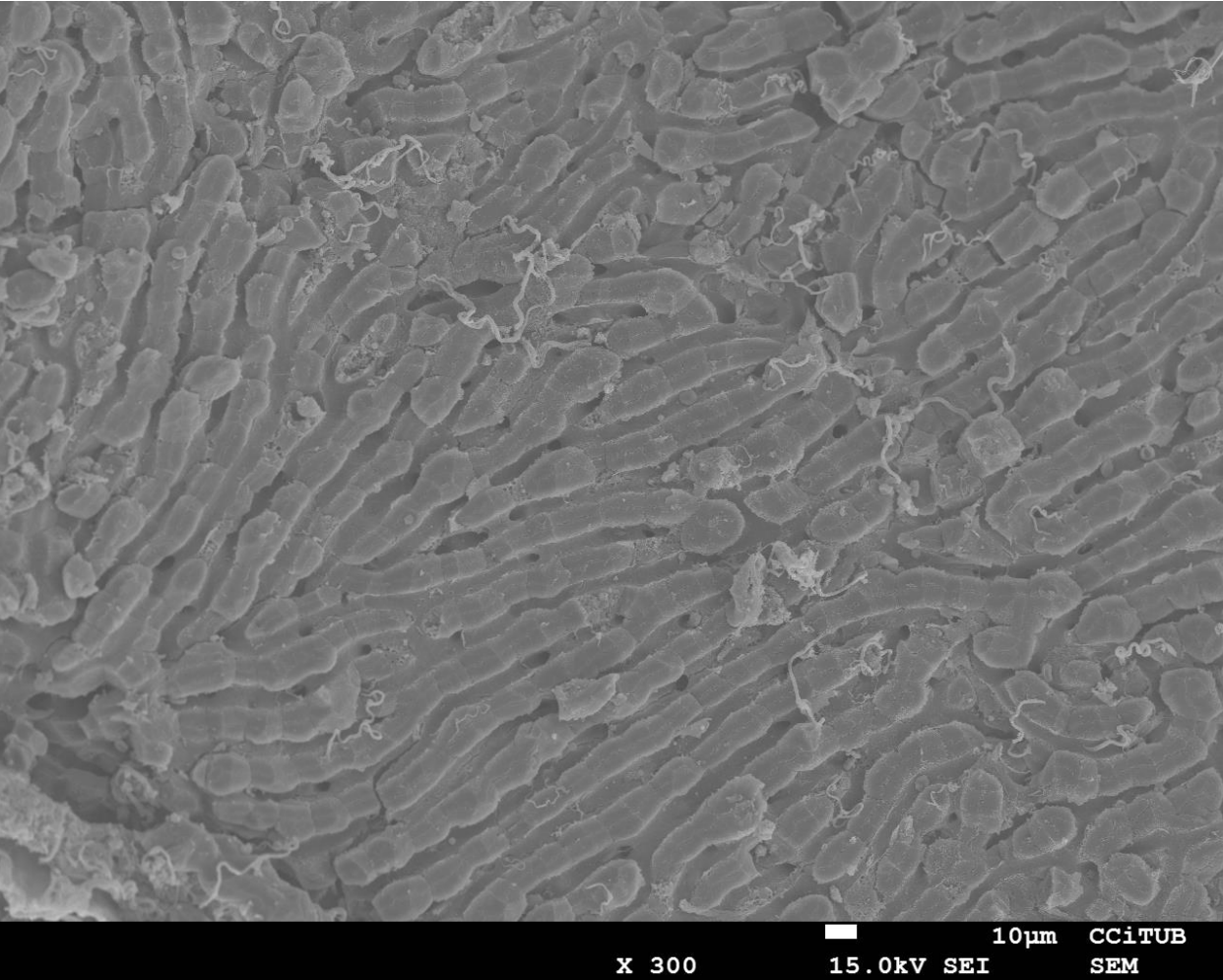


# The liver sinusoid during CLD progression

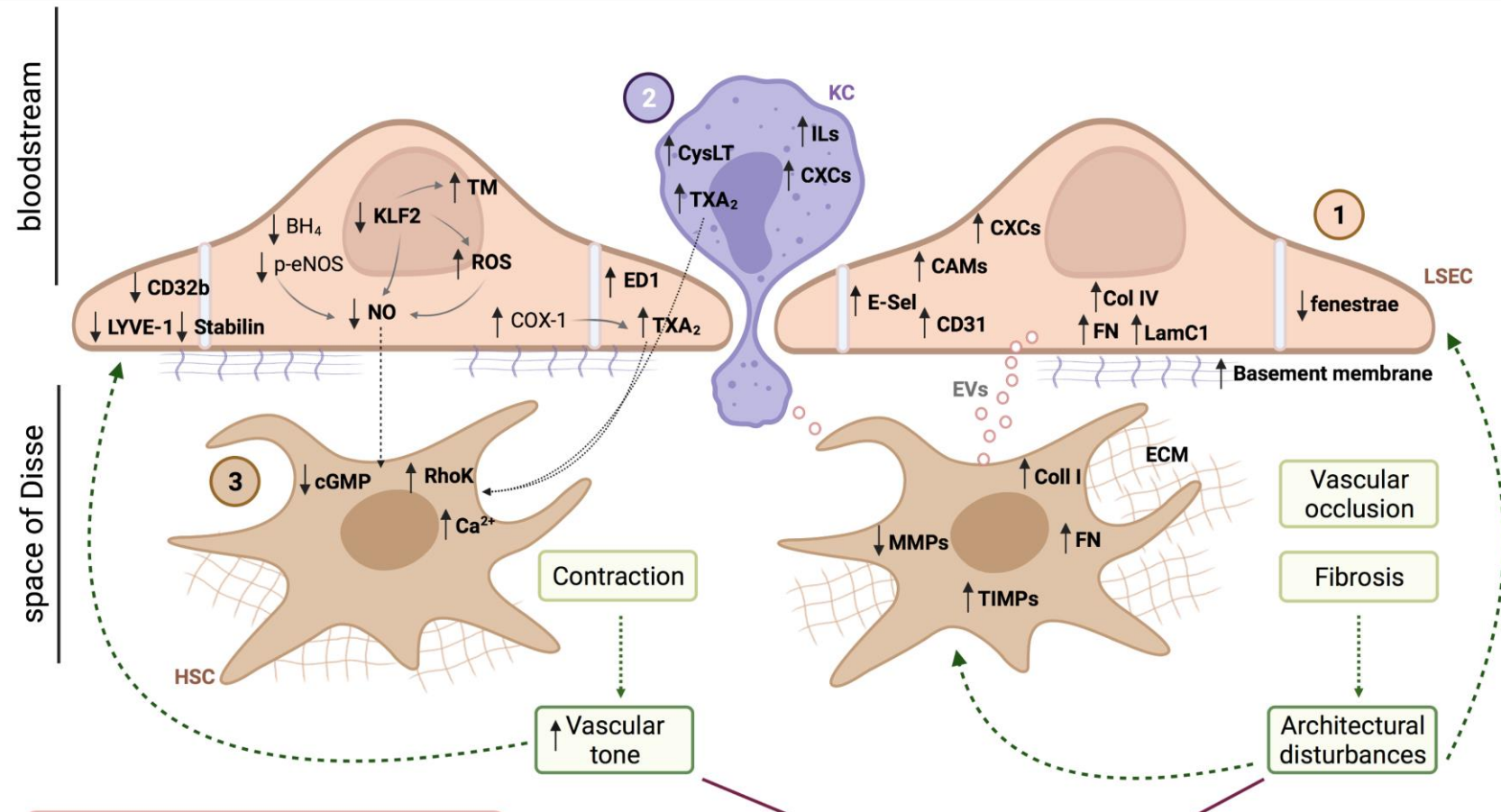


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# The liver sinusoid in CLD



# Hepatic microcirculatory dysfunction in CLD



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

↑ Hepatic vascular resistance

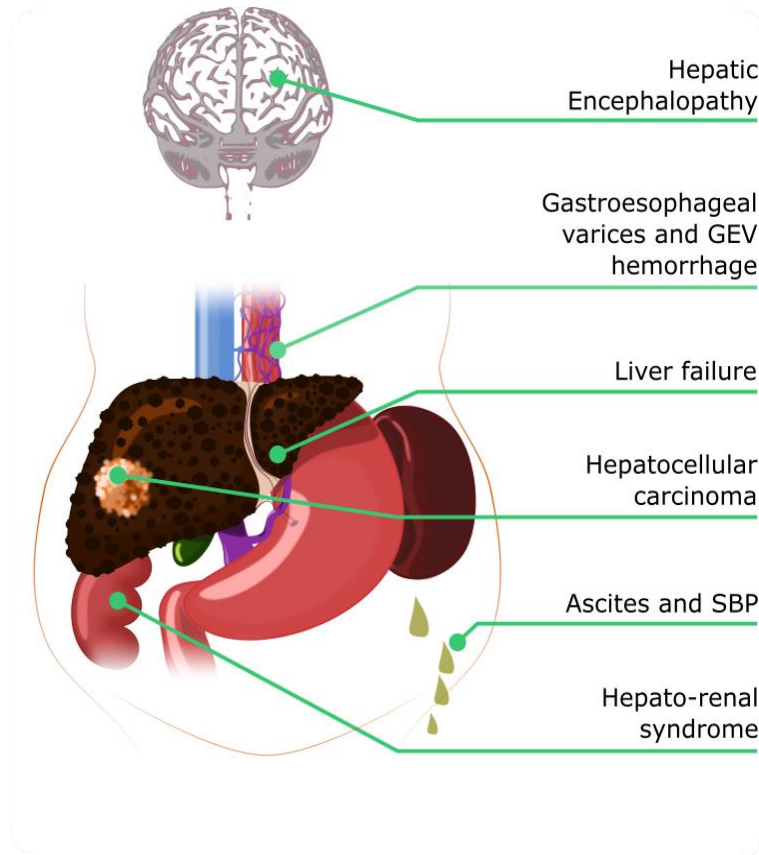
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# Portal hypertension



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

## Consequences

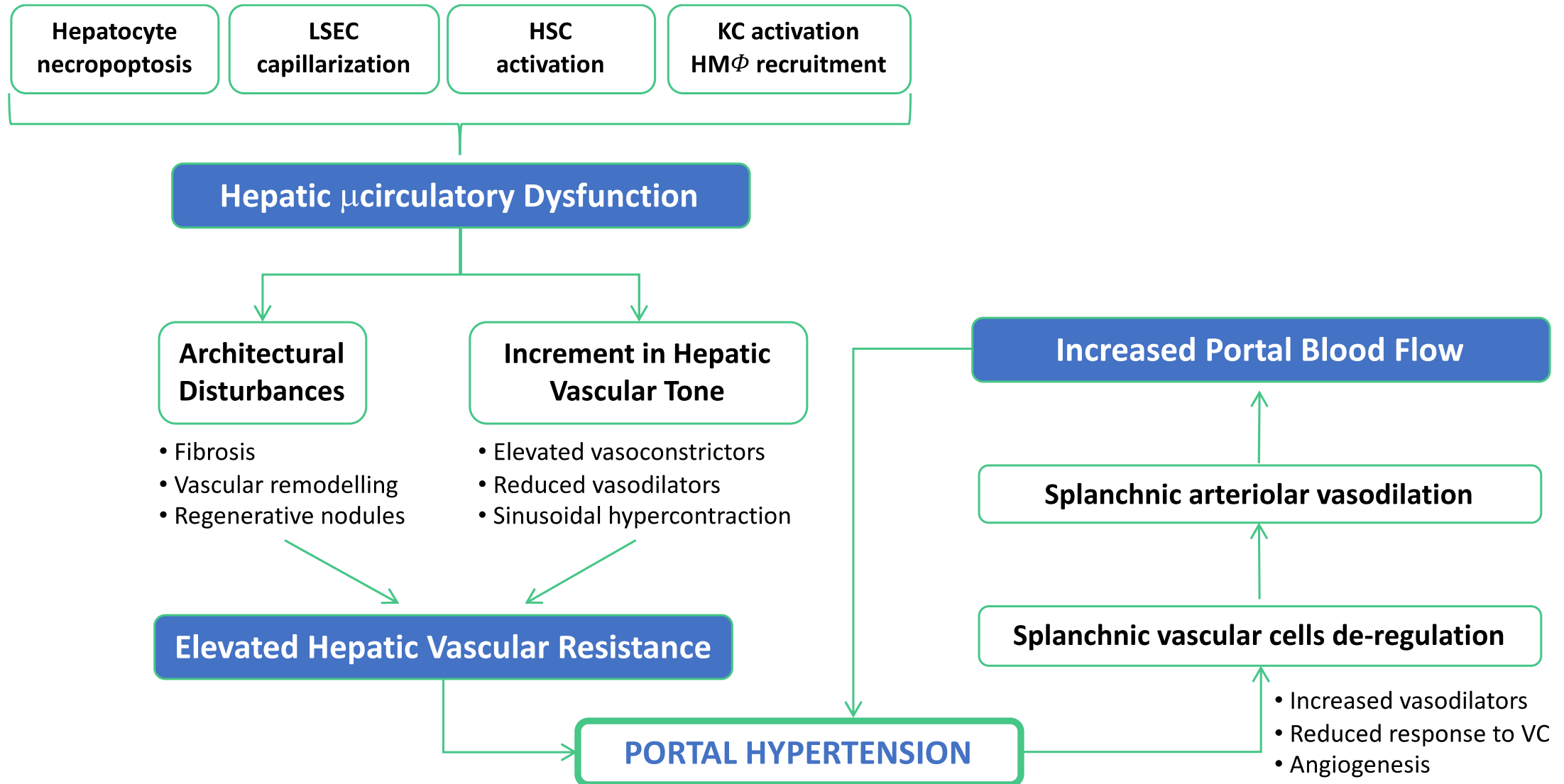


**Reversible by decreasing portal pressure**

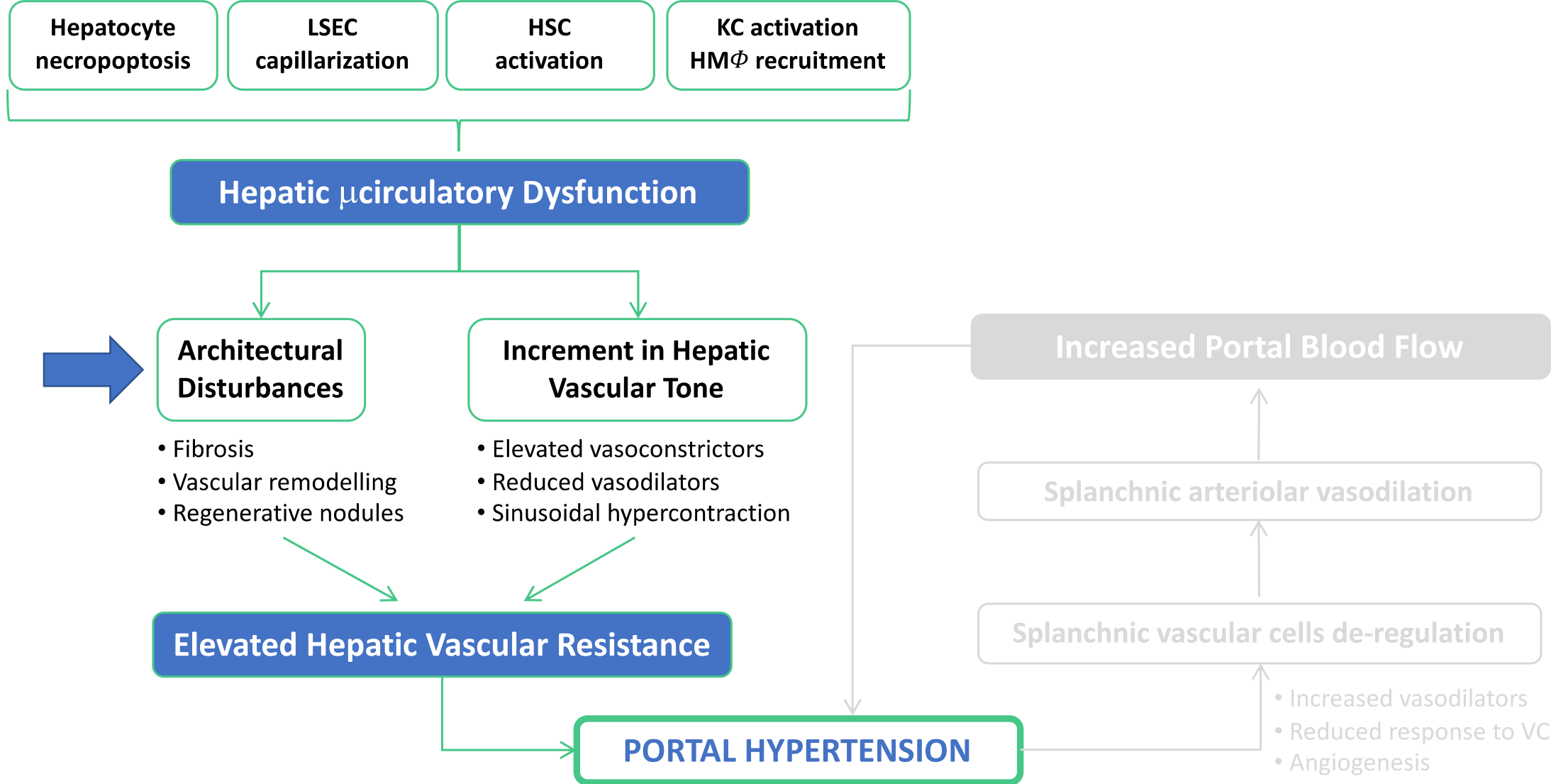
**170.000 deaths/year in the EU**

**1.300.000 deaths/year worldwide**

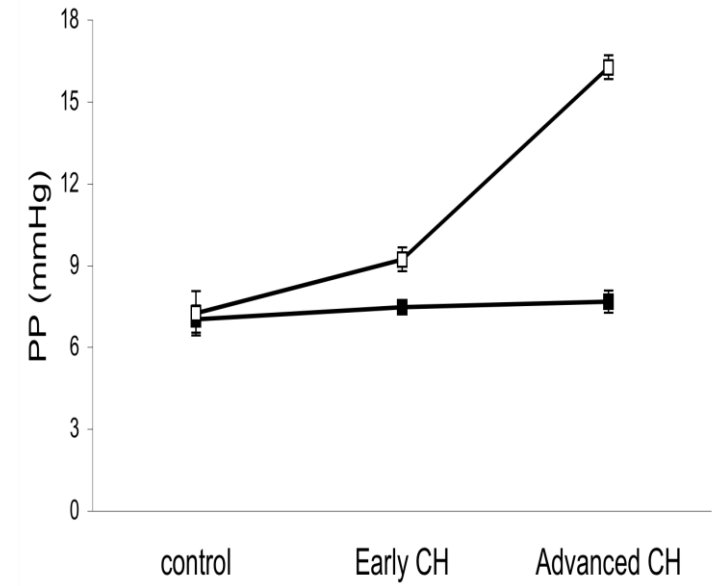
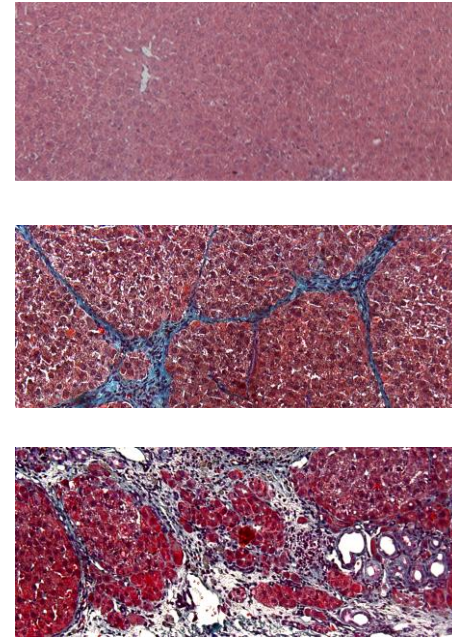
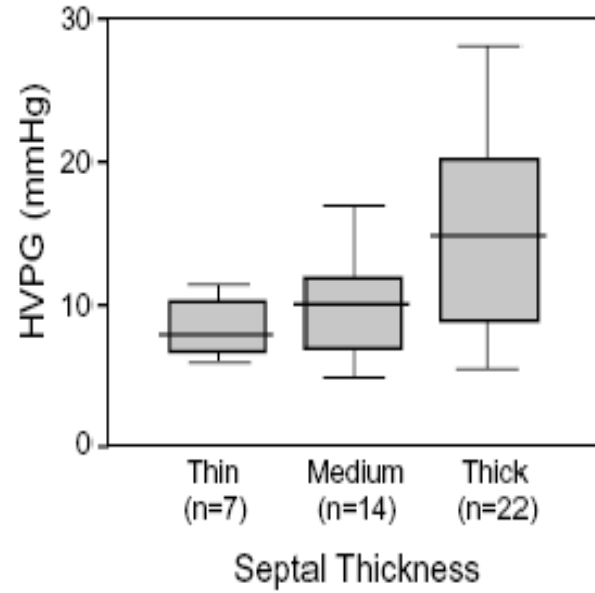
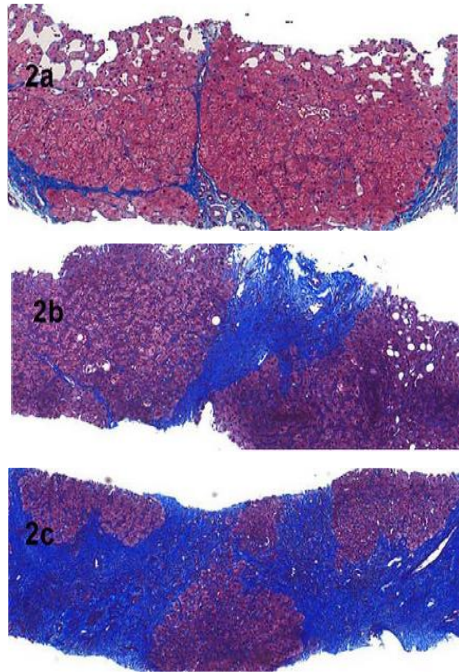
# Hepatic microcirculatory dysfunction in PH



# Hepatic microcirculatory dysfunction in PH



# Hepatic microcirculatory dysfunction - fibrosis

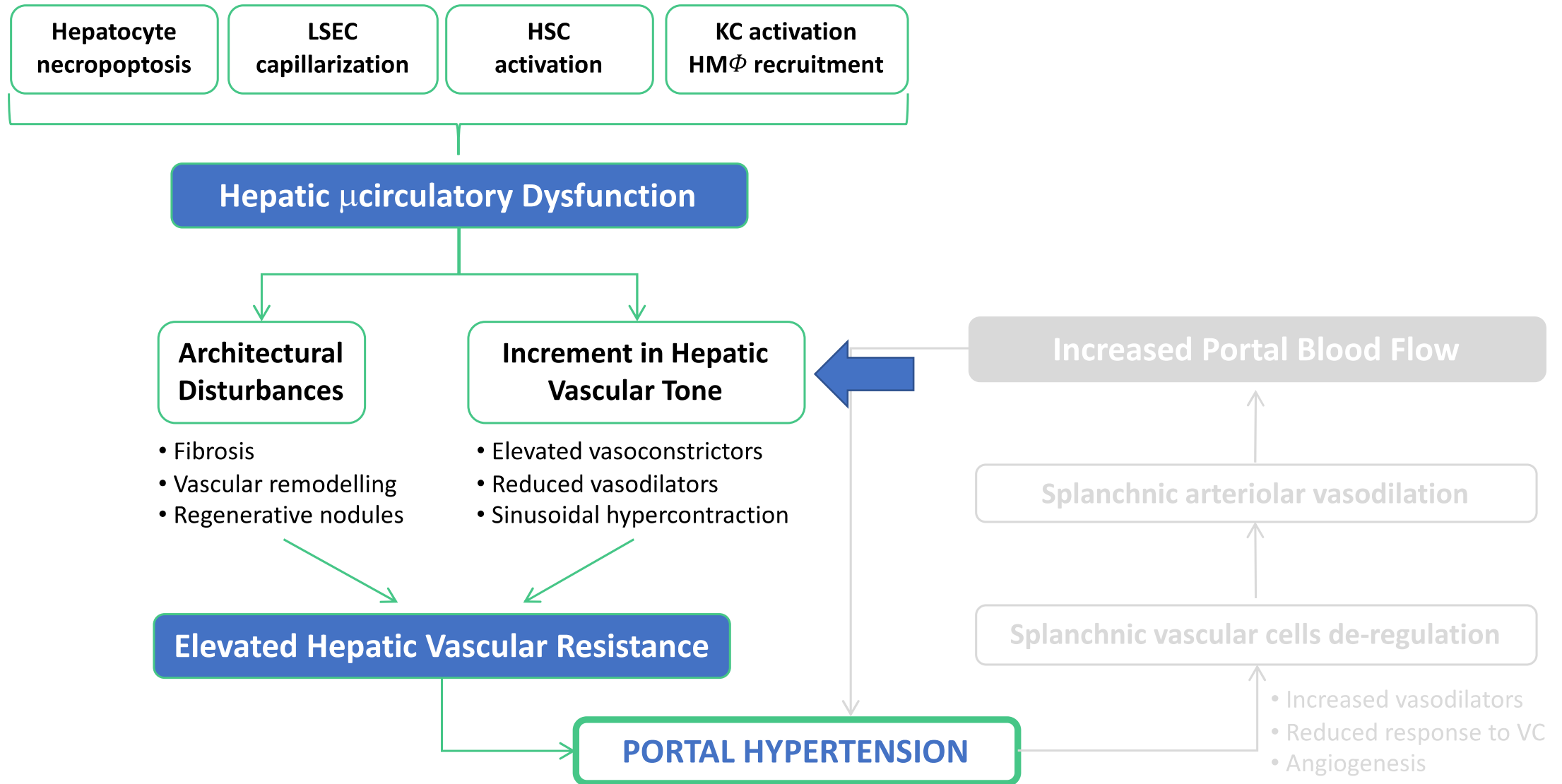


Nagula et al. J Hepatol 2006

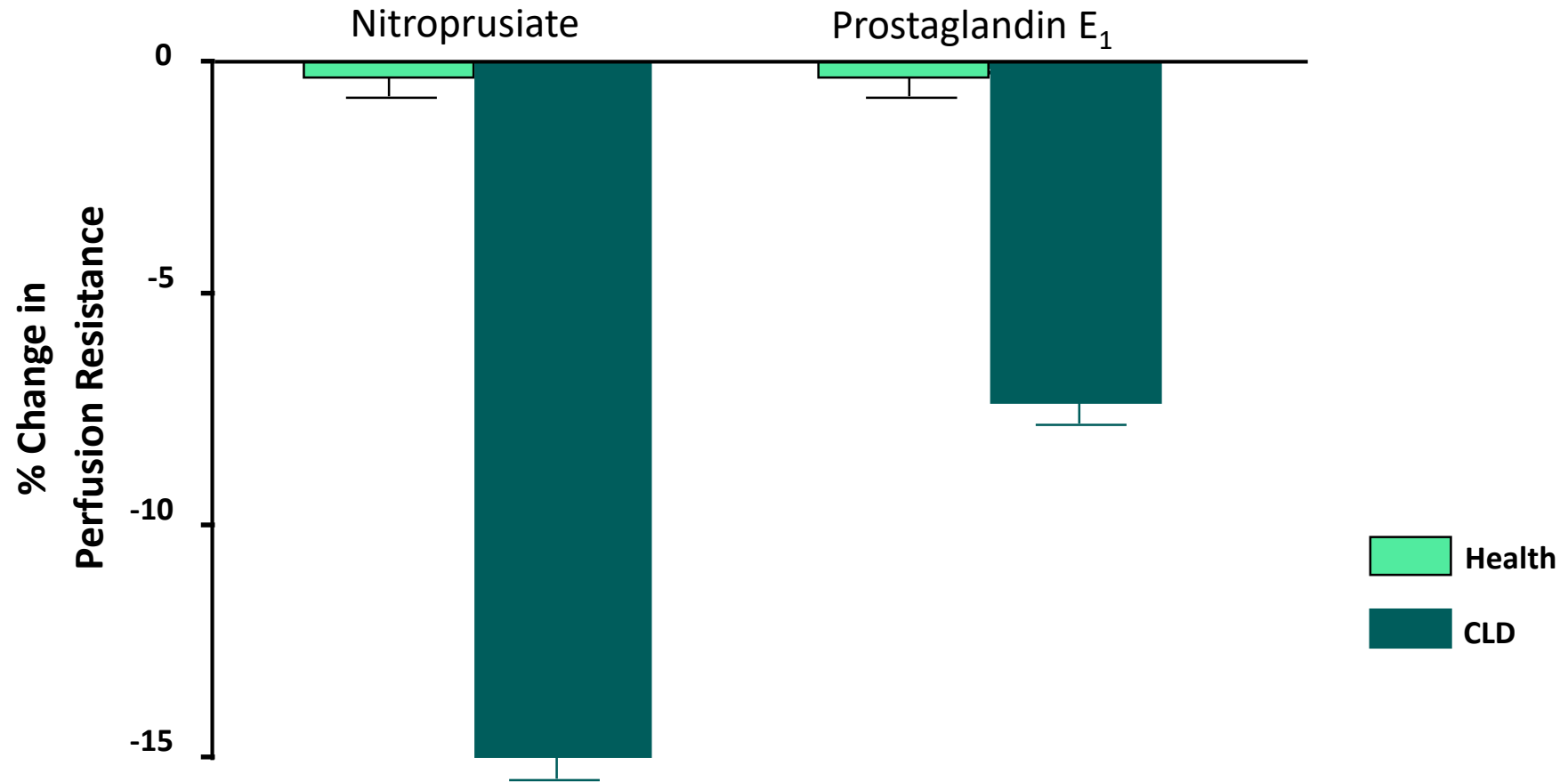
Gracia-Sancho et al. Gut 2011



# Hepatic microcirculatory dysfunction in PH



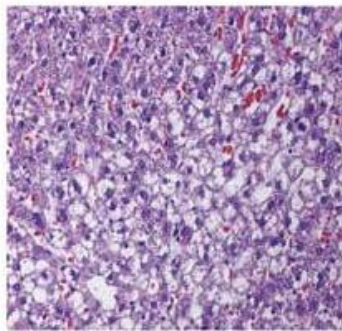
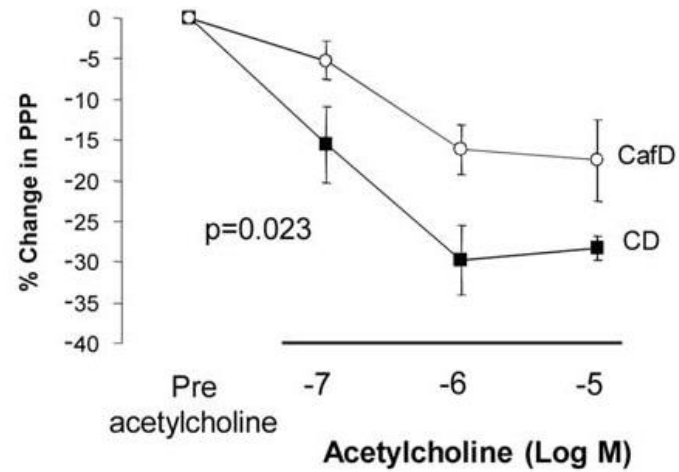
# Hepatic microcirculatory dysfunction – vascular tone



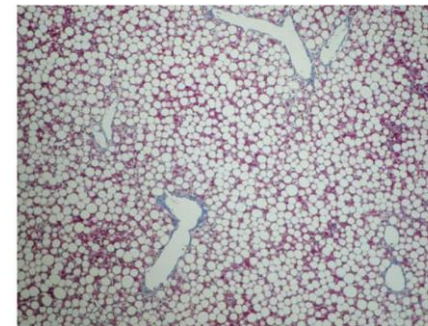
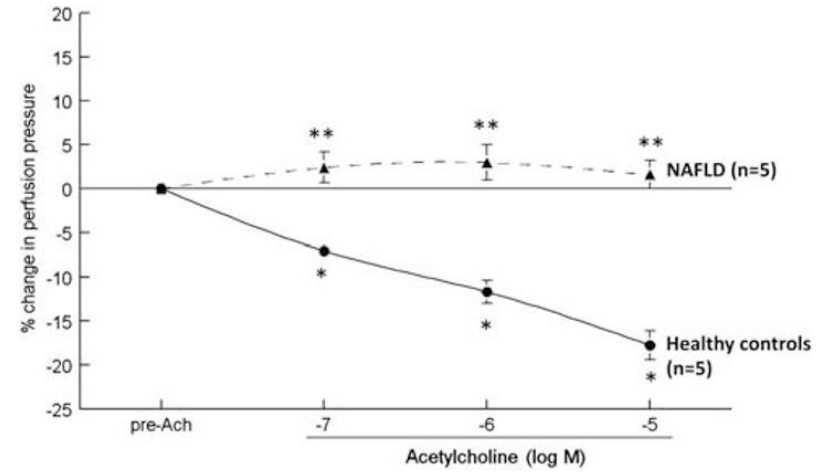
# Hepatic microcirculatory dysfunction – NAFLD



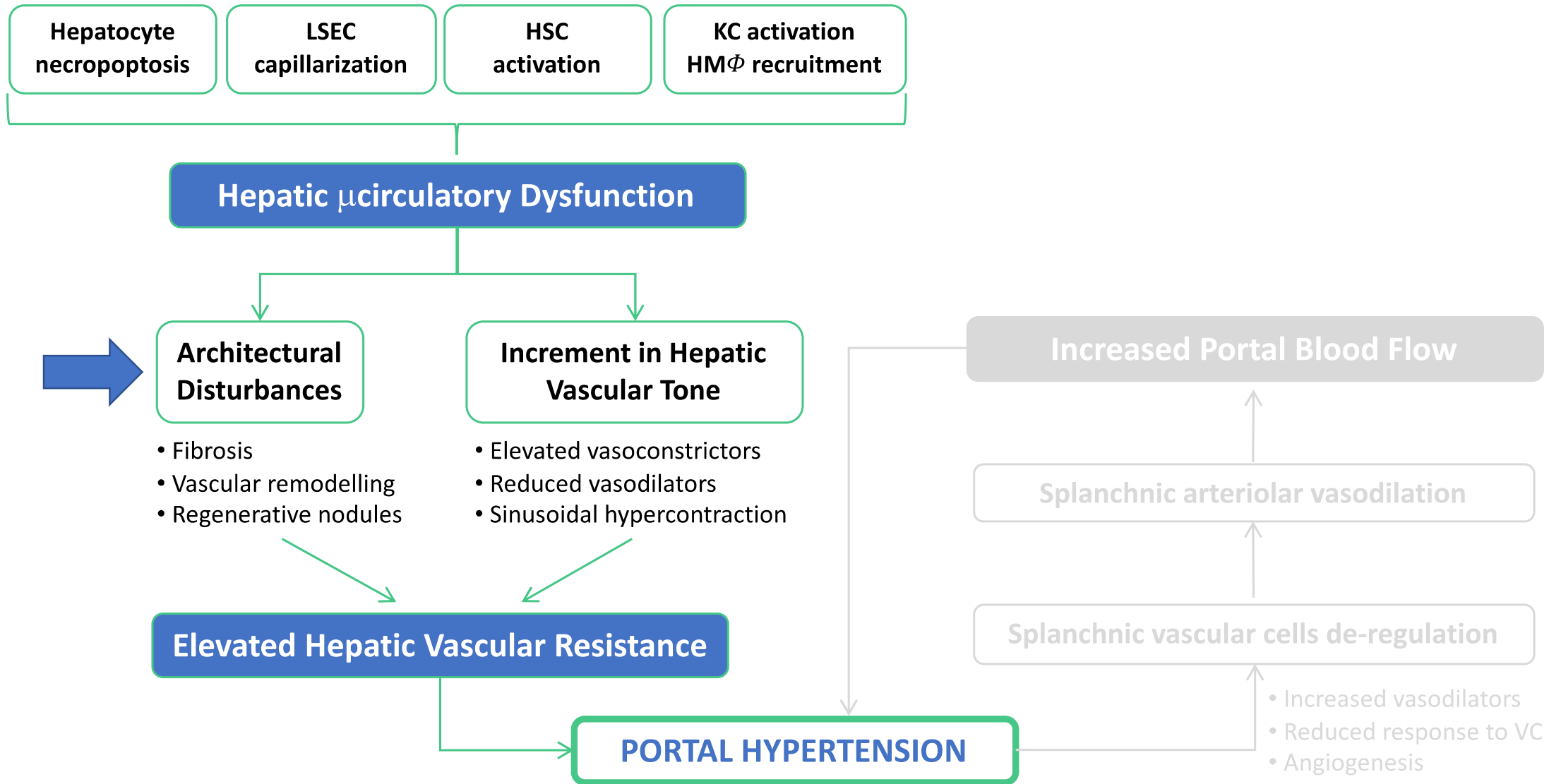
4w CafD



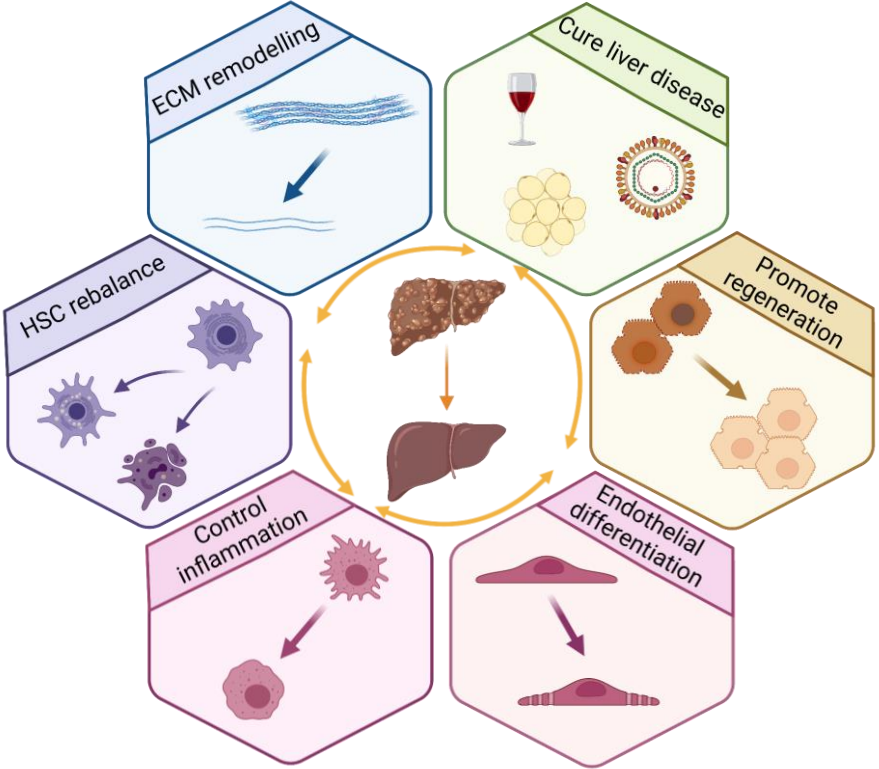
4w MCD



# Hepatic microcirculatory dysfunction in PH

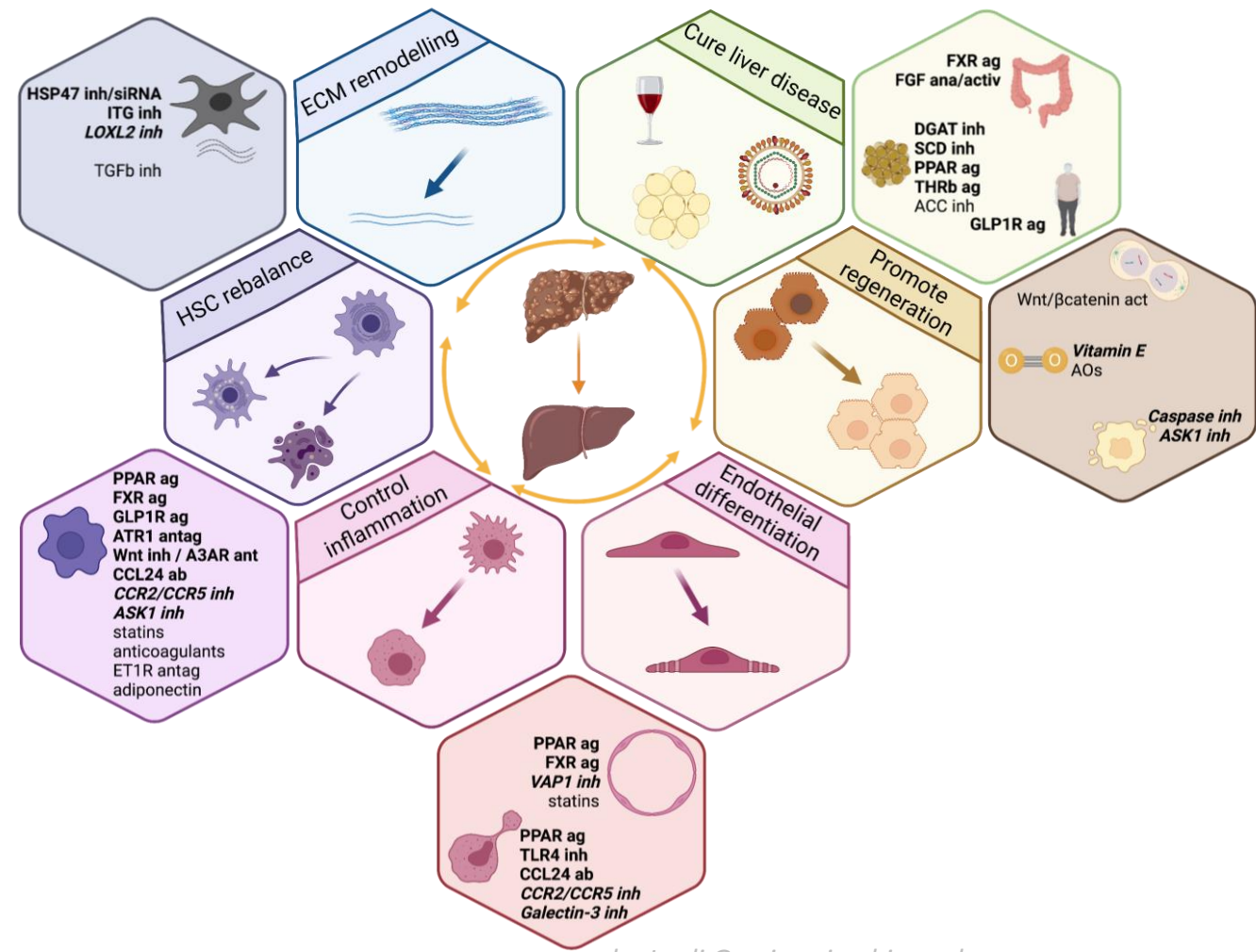


# Targeting liver fibrosis



by Jordi Gracia using biorender.com

# Targeting liver fibrosis



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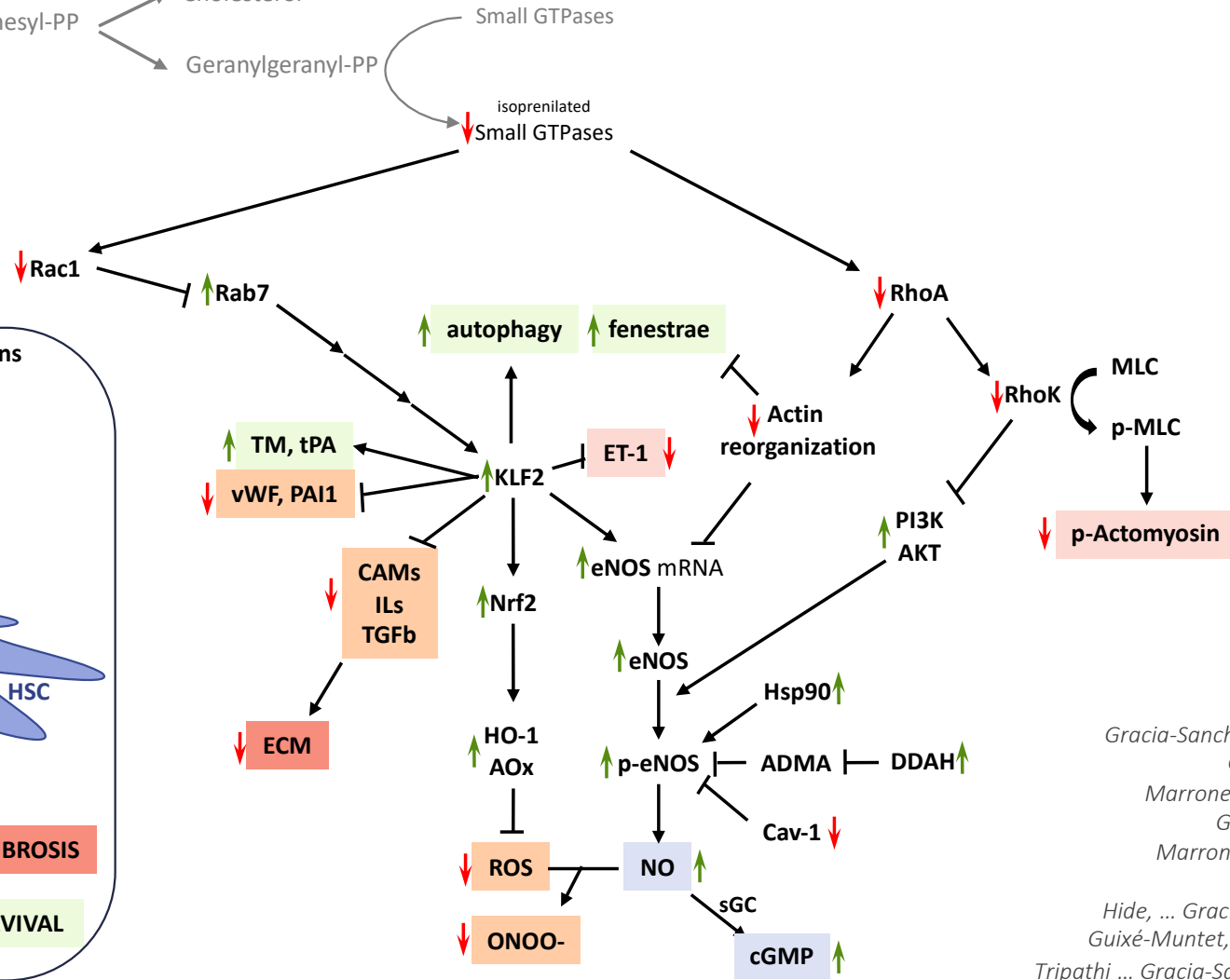
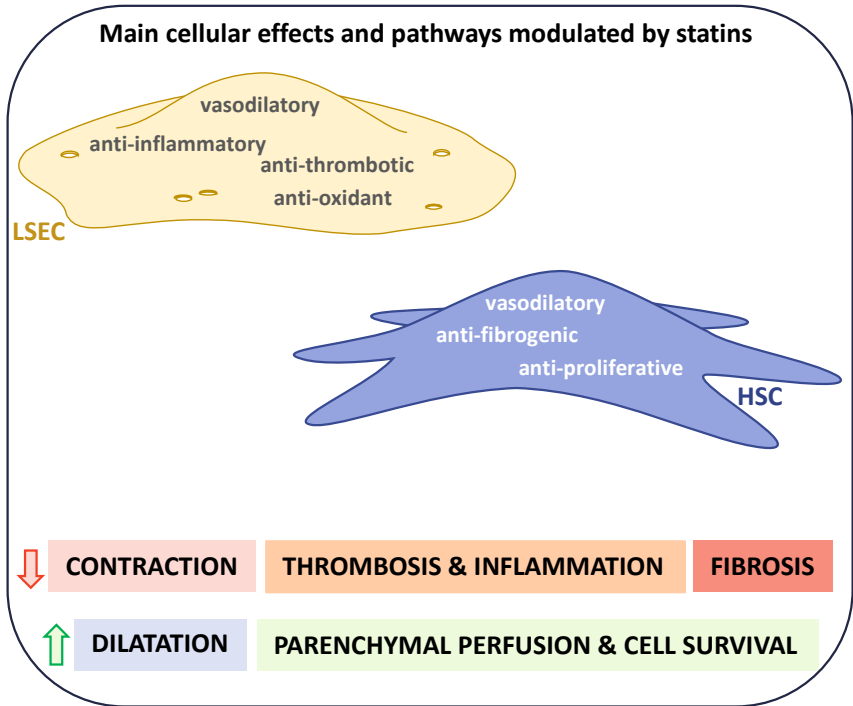
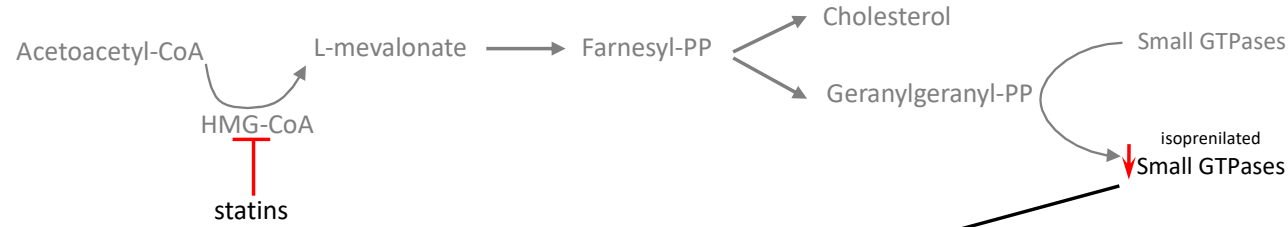
**Bold:** positive or ongoing CT  
*Italics:* negative CT  
 standard: pre-clinical research

# Statins as therapeutic option



		Acute liver injury		Chronic liver disease		Acute on chronic liver failure
		ischaemia/reperfusion 24h - 3days	infection 24h - 3days	24h - 3days	7-14days	cirrhosis + infection 24h - 3days
LIVER PATHOBIOLOGY	type of injury treatment length					
	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
EVIDENCE	Preclinical models	Cold preservation lean & steatotic grafts - <i>simvastatin</i> - Warm ischaemia young & aged animals - <i>simvastatin</i> - Haemorrhagic shock healthy & cirrhotic animals - <i>simvastatin</i> -	acute LPS healthy animals - <i>simvastatin</i> -	chronic CCl <sub>4</sub> chronic TAA BDL - <i>simvastatin</i> - - <i>atorvastatin</i> -	chronic CCl <sub>4</sub> aged animals BDL - <i>simvastatin</i> -	chronic CCl <sub>4</sub> + LPS chronic TAA + LPS compensated & decompensated cirrhosis BDL + LPS - <i>simvastatin</i> -
	Clinical evidence	Observational studies - <i>diverse statins</i> -		Observational studies - <i>diverse statins</i> - Proof-of-concept RCTs - <i>simvastatin</i> - RCT with clinical end points - <i>simvastatin</i> -		Ongoing phase III RCT - <i>simvastatin</i> -

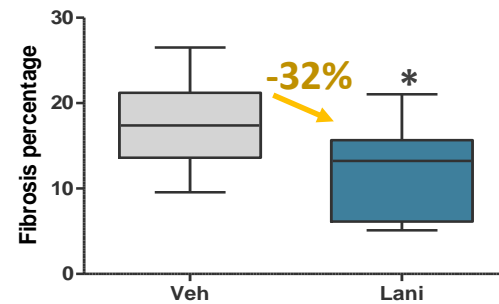
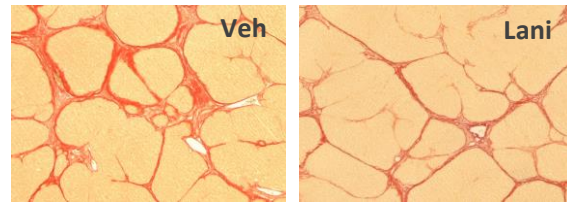
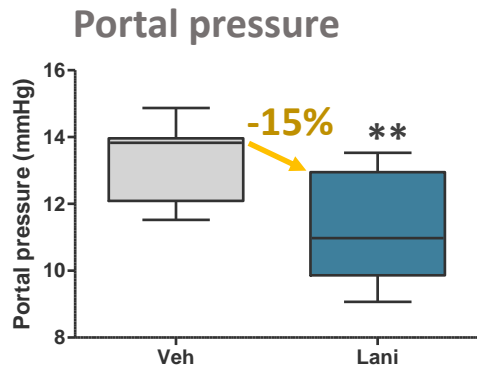
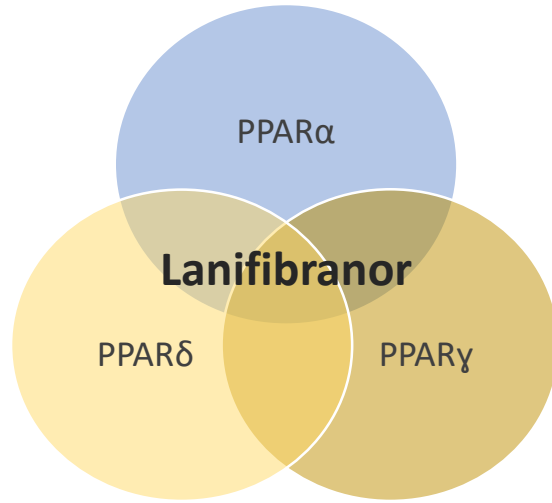
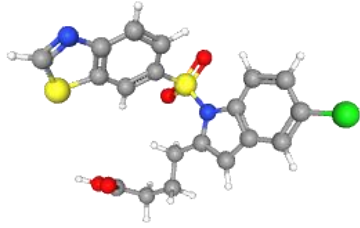
# Statins as therapeutic option



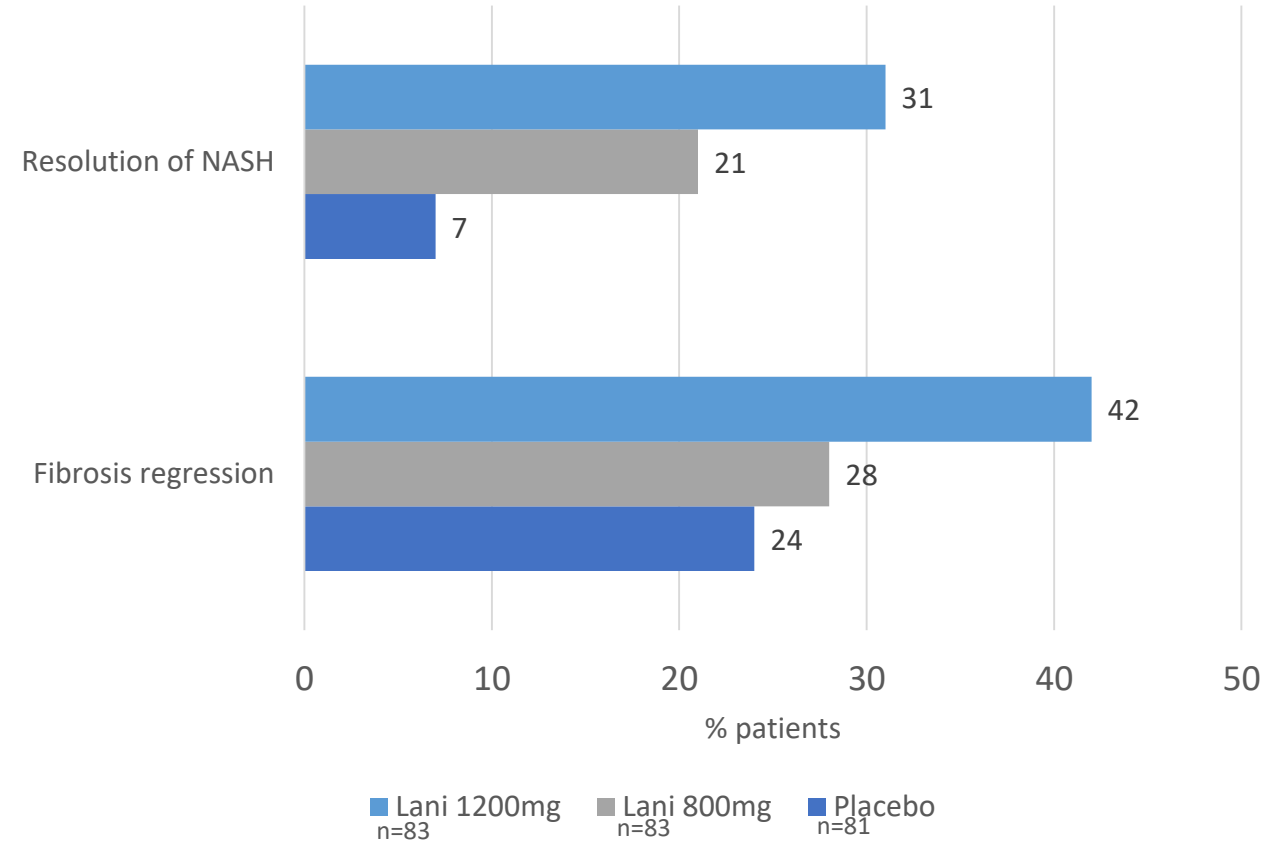
Gracia-Sancho et al, Transplantation 2010  
 Gracia-Sancho et al, Gut 2011  
 Marrone ... Gracia-Sancho, JHep 2013  
 Gracia-Sancho et al, JHep 2013  
 Marrone ... Gracia-Sancho, Gut 2015  
 Trebicka et al, JHep 2010  
 Hide, ... Gracia-Sancho, Scientific Rep 2016  
 Guixé-Muntet, ... Gracia-Sancho, 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



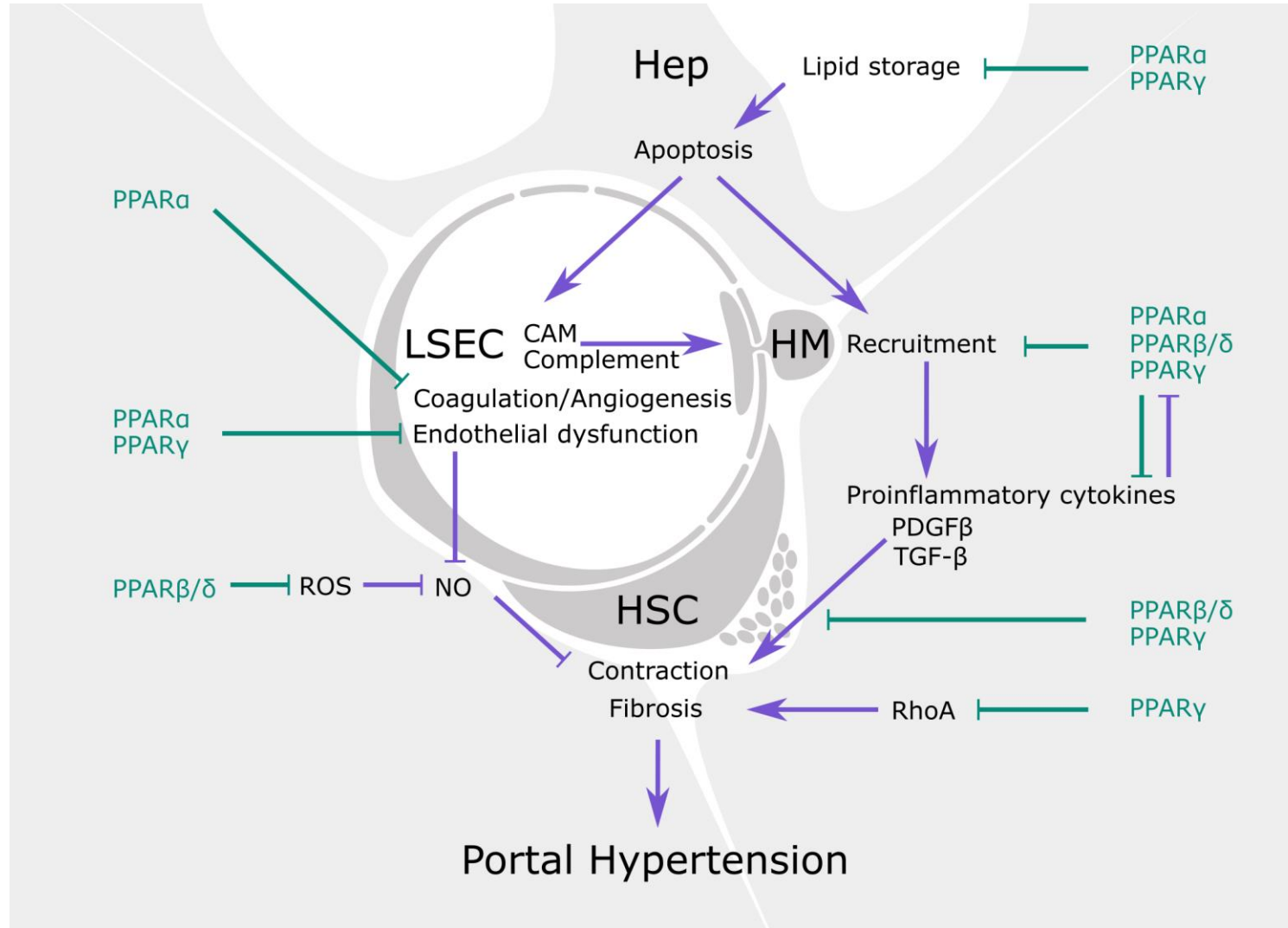
# PPAR agonist as therapeutic option



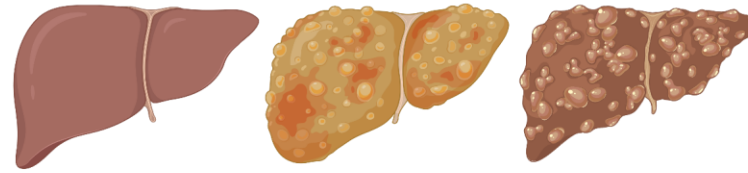
## Lanifibranor 24w



# PPAR agonist as therapeutic option



# Studying fibrosis – in vitro models



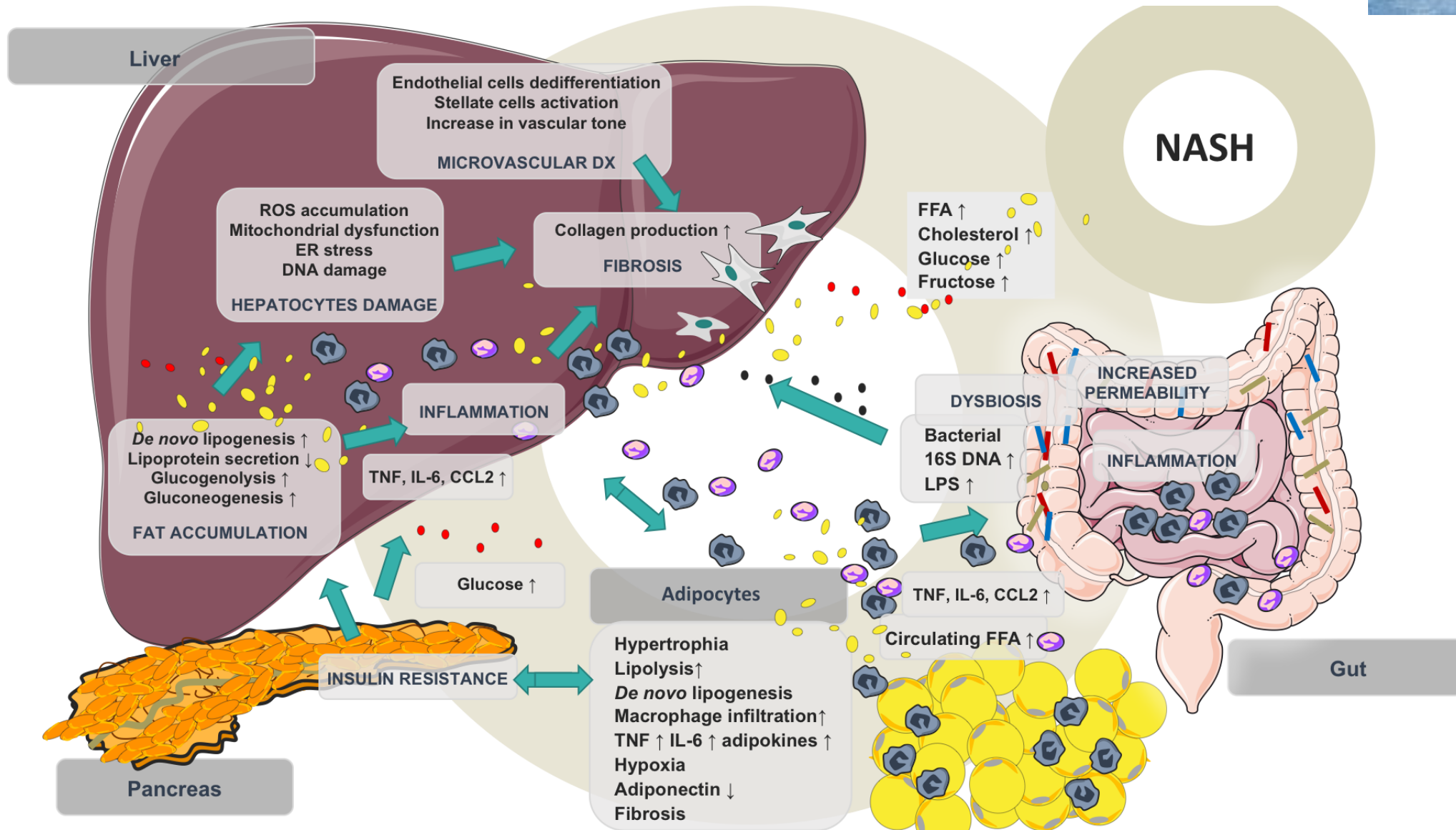
	2D cell culture	2D cell co-culture	Liver on a chip	PCLS	Organoid/spheroid
Accessibility	+++	+++	+	+	++
Complexity	+	+	+++	++	+++
Reproducibility	+++	+++	++	++	++
Relevance	+	++	+++	+++	+++
Human-derived	primary cells	primary cells	primary cells	fresh tissue	human like cells
Disease models	in vivo, in vitro	in vivo, in vitro	in vivo, in vitro	in vivo	in vitro
Biomechanical stimuli	stiffness	stiffness (bottom well)	stiffness, controlled shear stress, pressure	intrinsic matrix stiffness	stiffness, perfusion

# Studying fibrosis – in vivo models

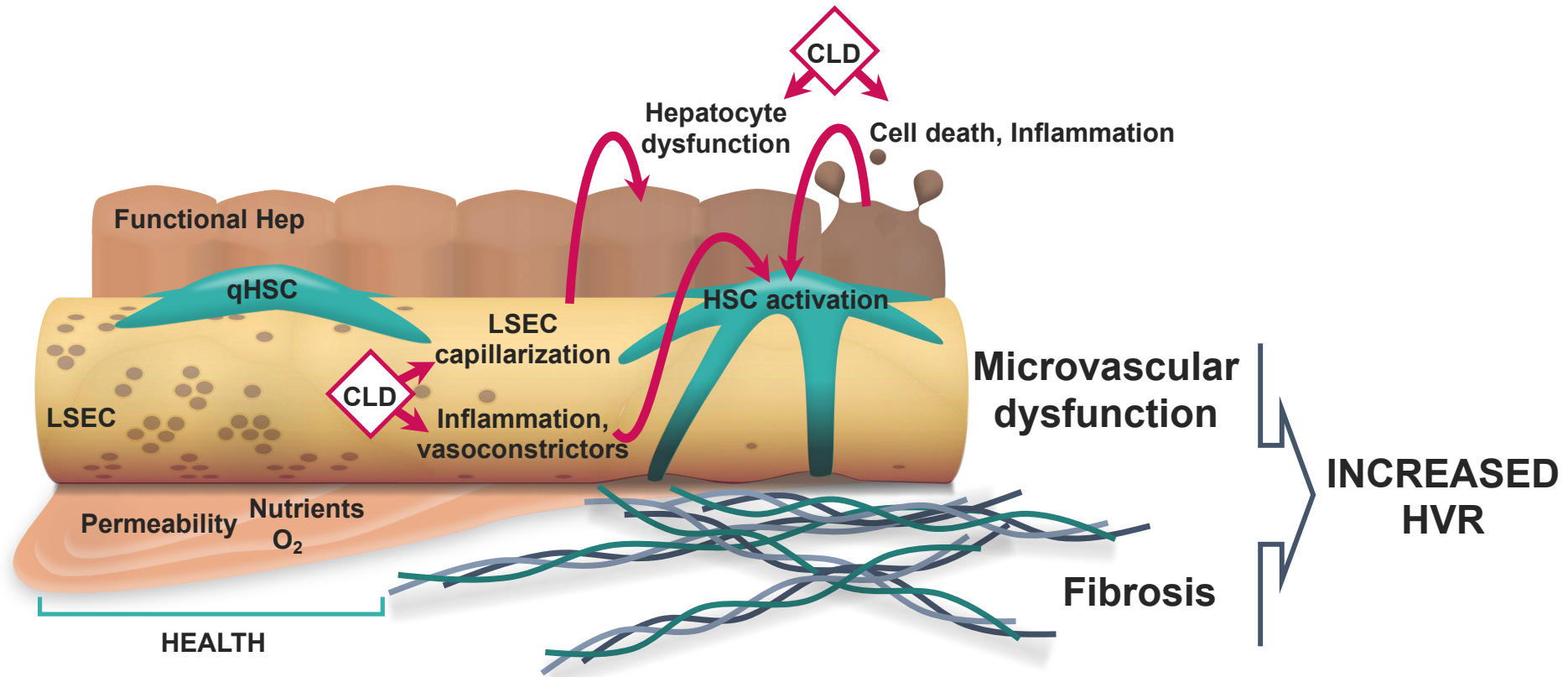


Model	Administration route	Administration duration (weeks)	Ascites	Portal pressure (mmHg)	Portal blood flow (ml/min)	IHVR (mmHg•min/ml)	Mean arterial pressure (mmHg)	Fibrosis (% sirius red staining)
Sham	NA	NA	–	6–8	10–13	0.6–0.7	>110	0–1
CCl <sub>4</sub>	Inhalation	14–16	+++	14.3 ± 0.3	14.3 ± 0.6	1.10 ± 0.04	93.3 ± 2.2	20–30
TAA	Intraperitoneal	12	++	14.2 ± 0.5	16.7 ± 2.0	0.98 ± 0.12	100.9 ± 5.7	20–30
cBDL	Bile duct ligation	4	–	15.7 ± 0.3	17.1 ± 1.2	1.02 ± 0.07	89.2 ± 2.3	30–35

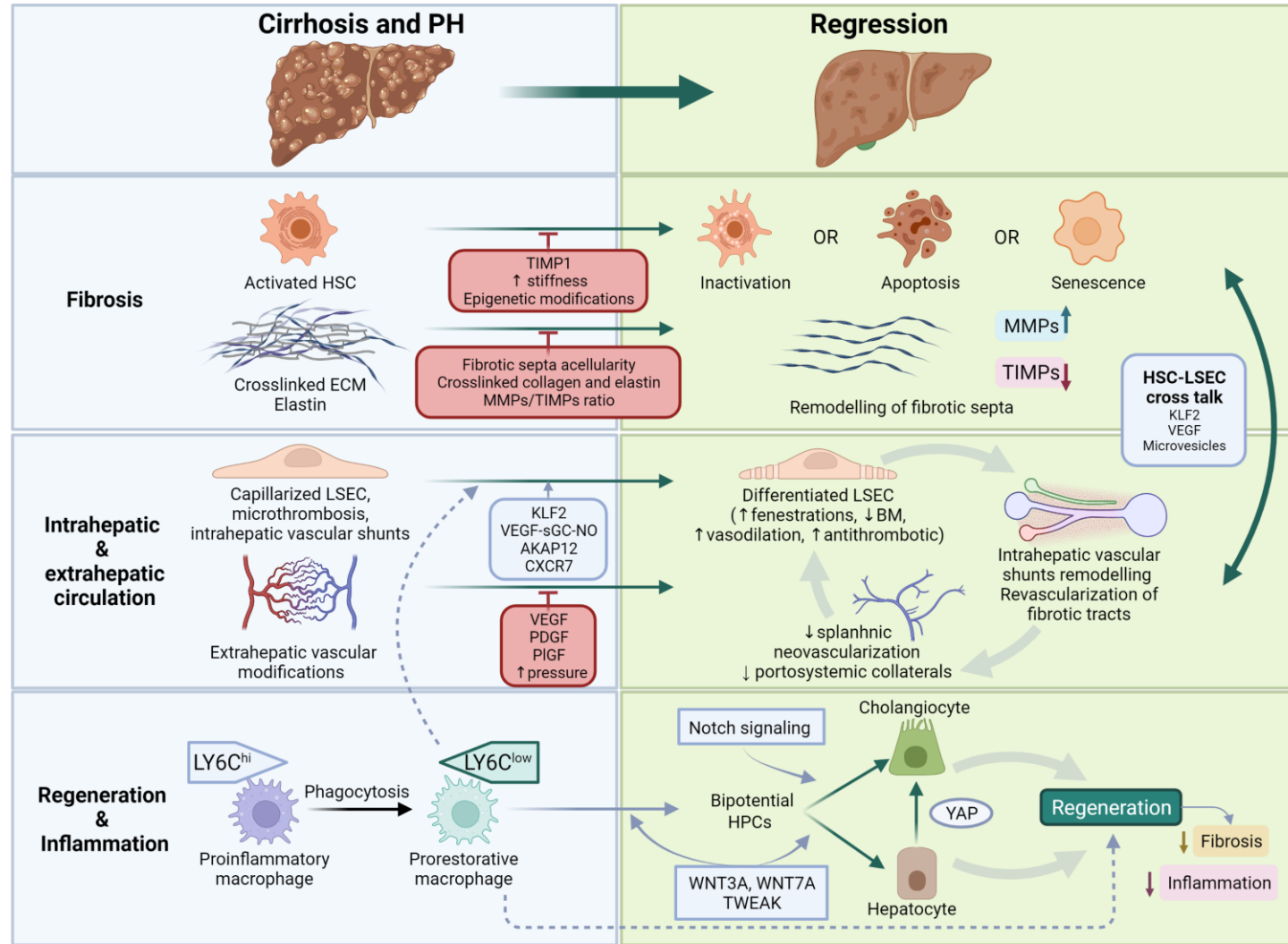
# Studying fibrosis – in vivo models



# Take home messages (1)

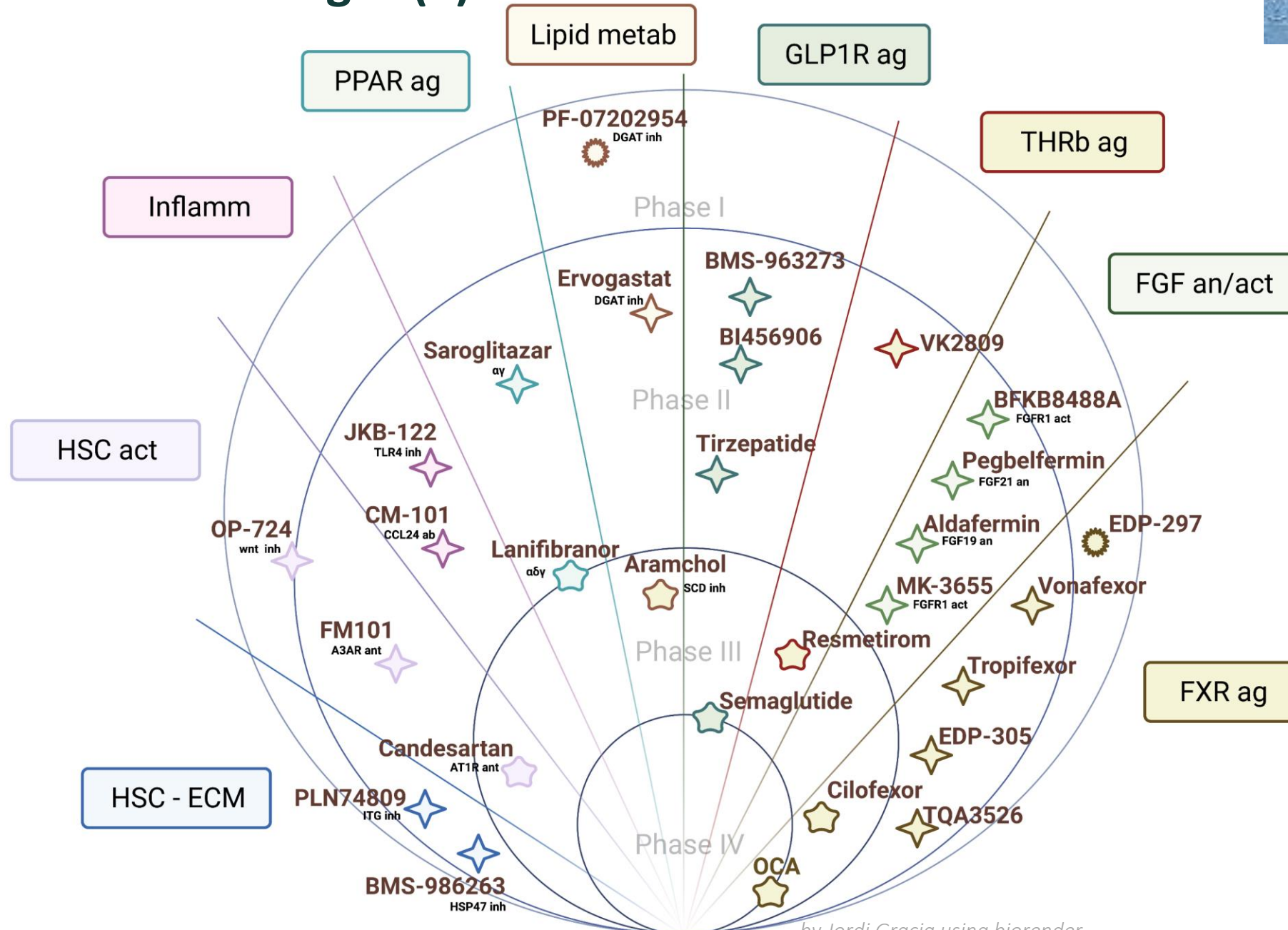


# Take home messages (2)



Mendoza Y, Selicean S, Gracia-Sancho J

# Take home messages (3)



by Jordi Gracia using biorender





**Anabel Fernández**  
**Sergi Guixé**  
**Eric Felli**  
**Albert Gibert**  
**Zoe Boyer**  
**Peio Aristu**  
**Laia Abad**  
**María de Andrés**  
**Cong Wang**  
**David Sanfeliu**  
**Sonia Selicean**  
**Ana Martínez**  
**Chaonan Jin**  
**Yeldos Nulan**  
**Raul Pastó**

## Collaborations

JC García-Pagán  
Agustín Albillos (IRYCIS)  
Rafa Bañares (IISGM)  
Manuel Romero (IBIS)  
Javier Cubero (UCM)  
Rubén Francés (UMH)  
Carmen Peralta (IDIBAPS)  
Rosa Villa (CNM-CSIC)  
JuanMa Falcón (CICbioGUNE)  
Pere Roca-Cusachs (IBEC)  
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Giada Pietrosi (ISMETT)  
Jarbas Rodrigues (PUCRS Brasil)  
Zhi-Ren Liu (GSU-Atlanta)  
Jonel Trebicka (Frankfurt)





**APASL STC**

**Cairo, July 30<sup>th</sup> 2022**

# **Liver vascular dysfunction as trigger of fibrosis**

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