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thématiques



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Institut national
de la santé et de la recherche médicale

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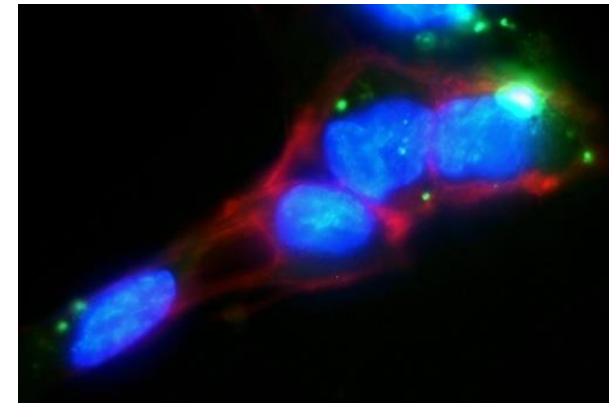
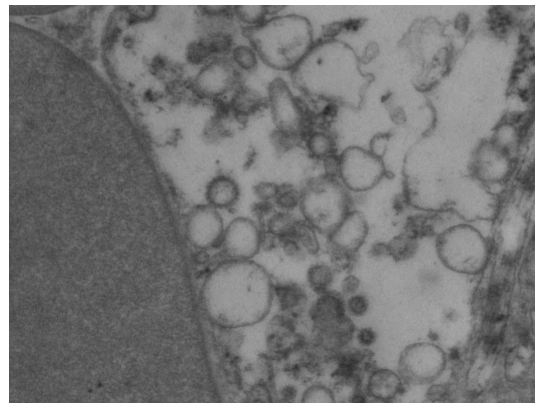
CRi
CENTRE de RECHERCHE
sur l'INFLAMMATION



Les vésicules extracellulaires : des biomarqueurs sanguins prédictif d'évolution des malades atteints de cirrhose

Pierre-Emmanuel RAUTOU

Inserm UMR-1149, Research center on Inflammation, Paris
Service d'hépatologie, Hôpital Beaujon, Clichy, France



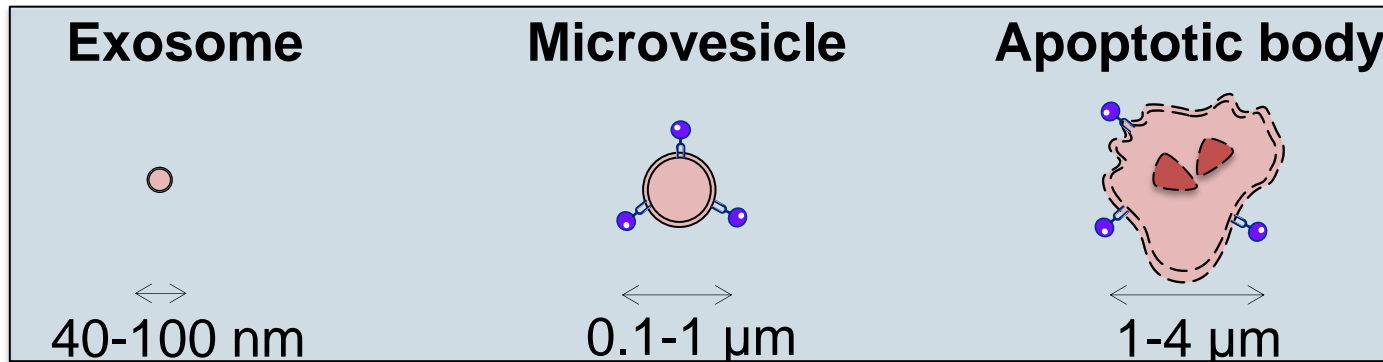
Extracellular vesicles in cirrhosis

- What are extracellular vesicles?
- Microvesicles: role in cirrhosis
- Microvesicles: promising biomarkers

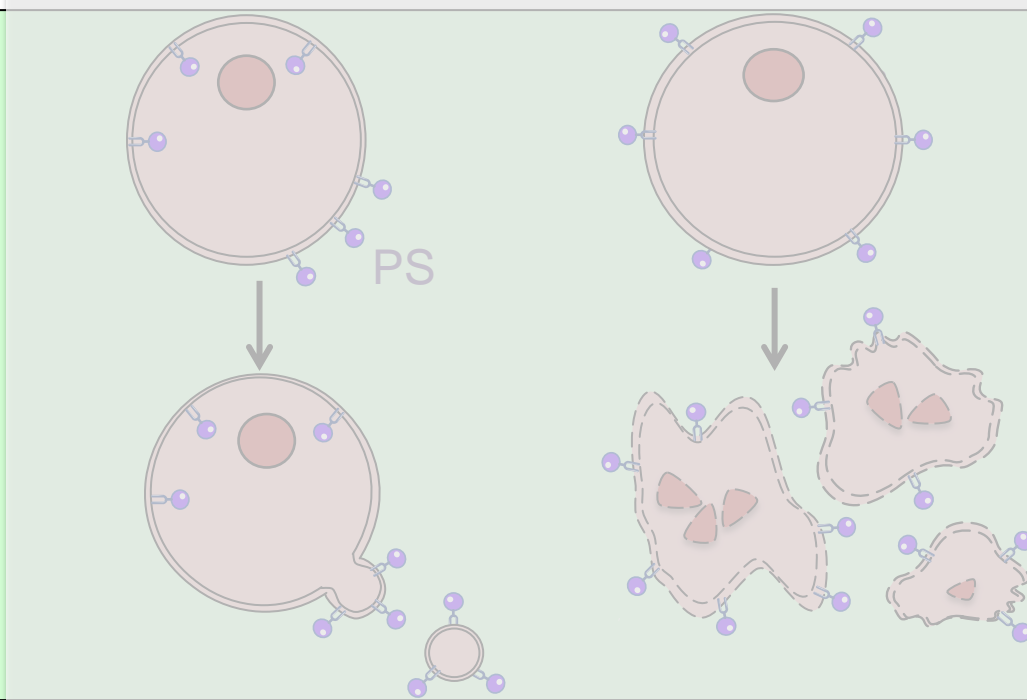
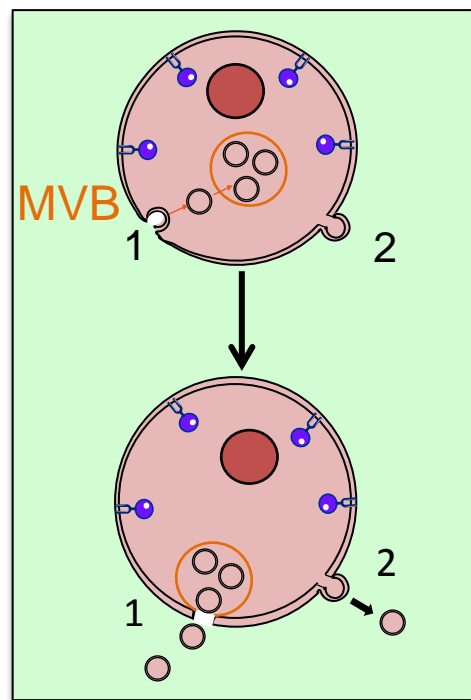
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Extracellular vesicles



Extracellular
Vesicles



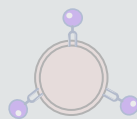
Cells

Exosome



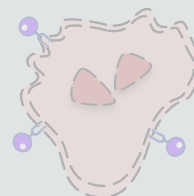
↔
40-100 nm

Microvesicle



↔
0.1-1 μm

Apoptotic body



↔
1-4 μm

Extracellular
Vesicles



Virus

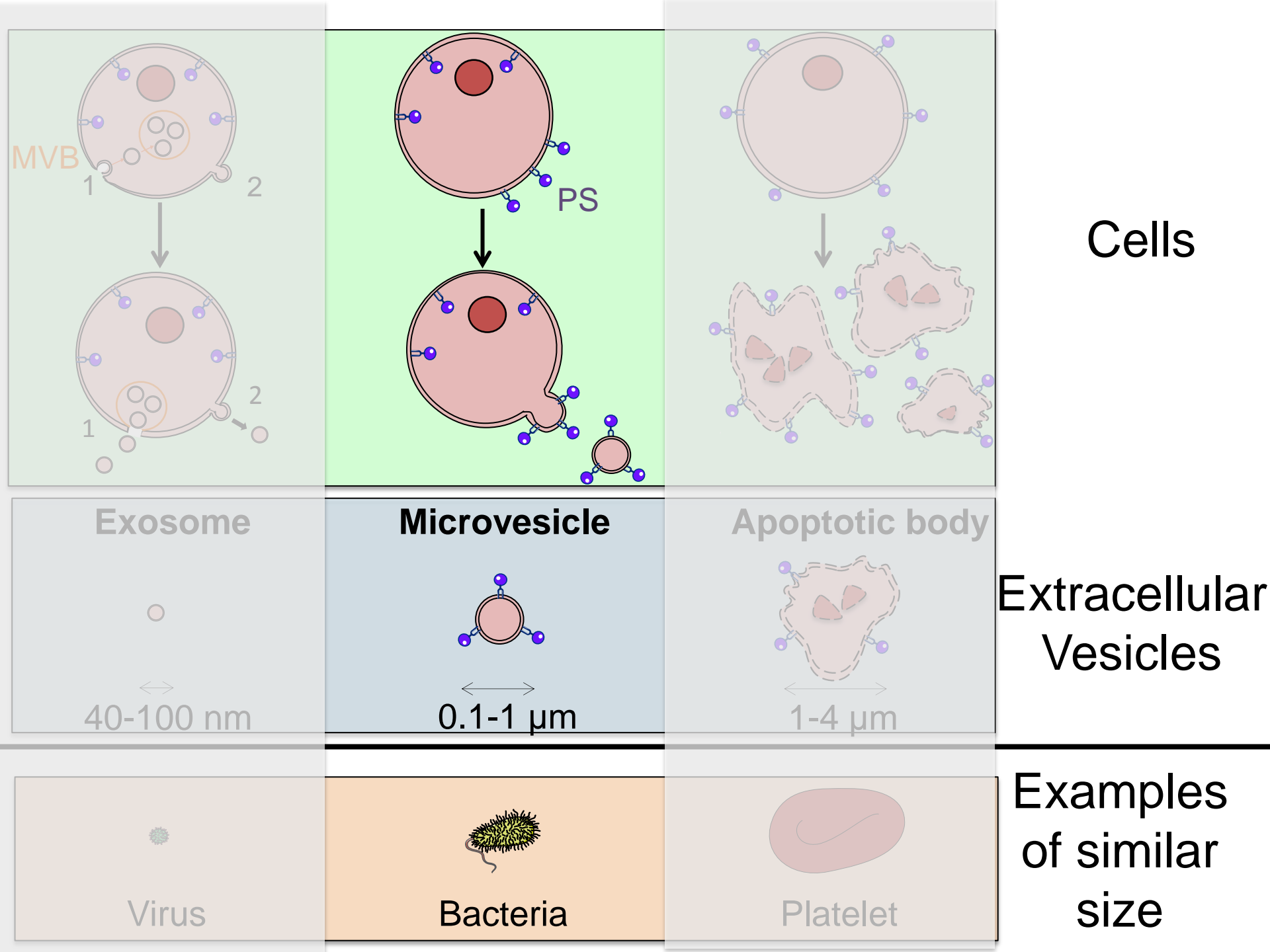


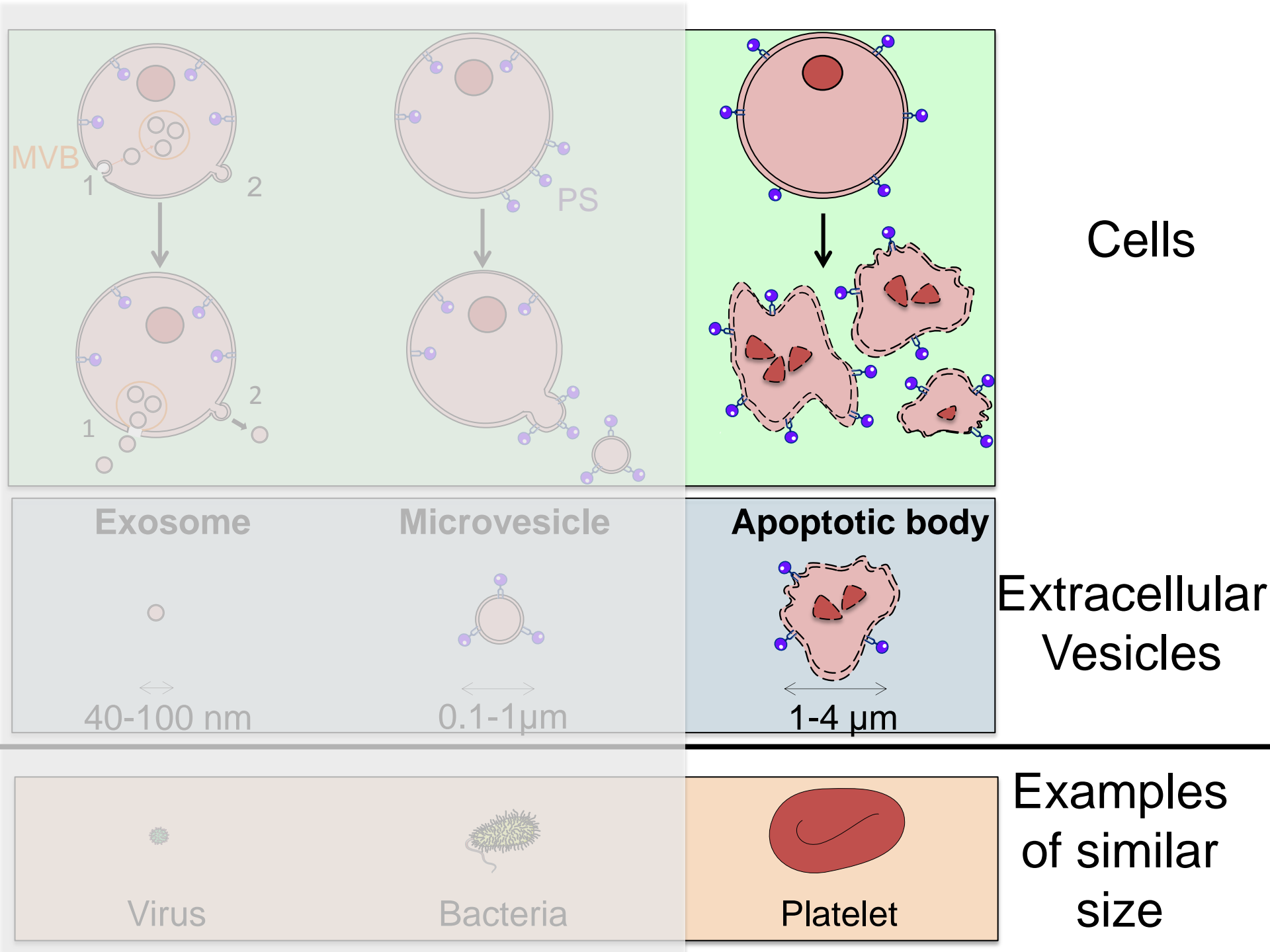
Bacteria



Platelet

Examples
of similar
size





Cells

Exosome

Microvesicle

Apoptotic body

Extracellular Vesicles

40-100 nm

0.1-1 μm

1-4 μm

Virus

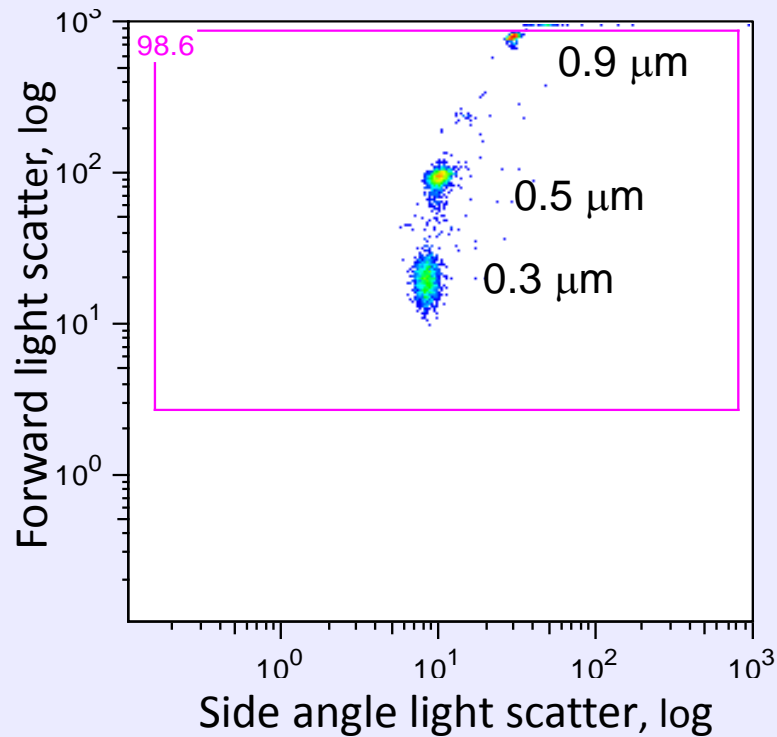
Bacteria

Platelet

Examples of similar size

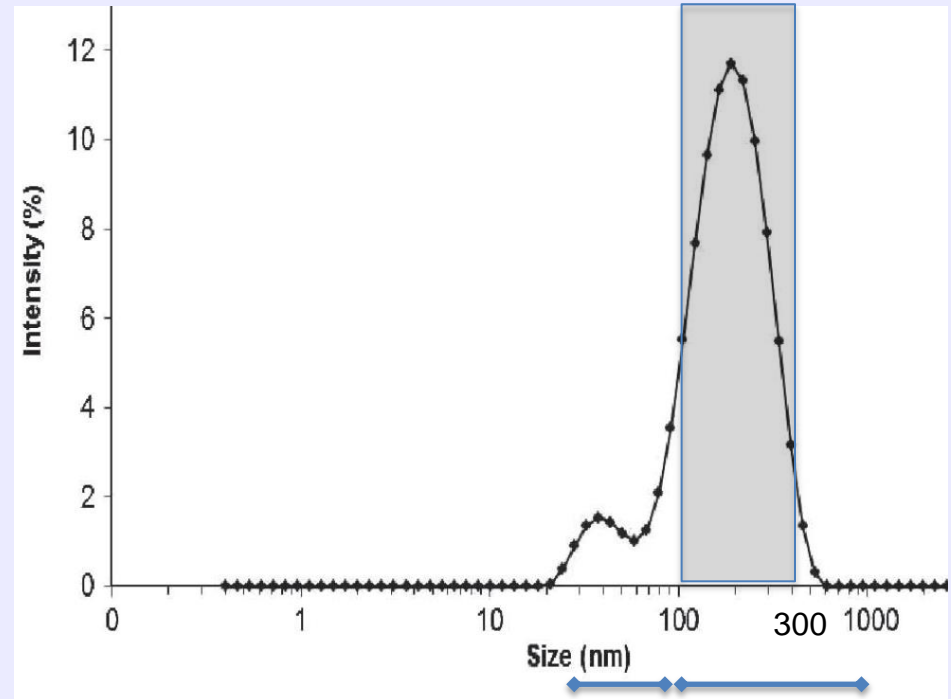
Techniques and names

Flow cytometry



Rautou, Circ Res 2011

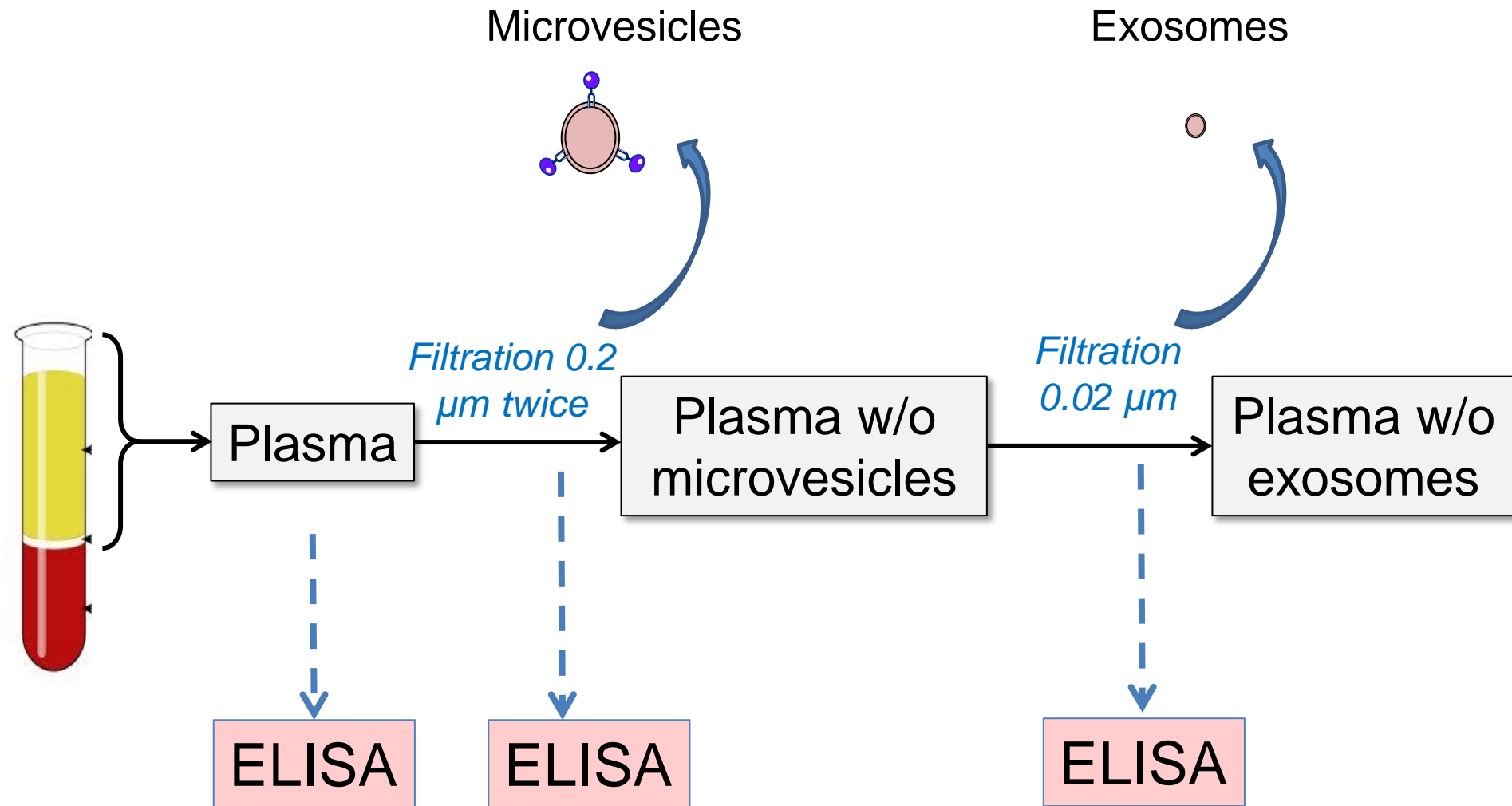
Dynamic light scattering



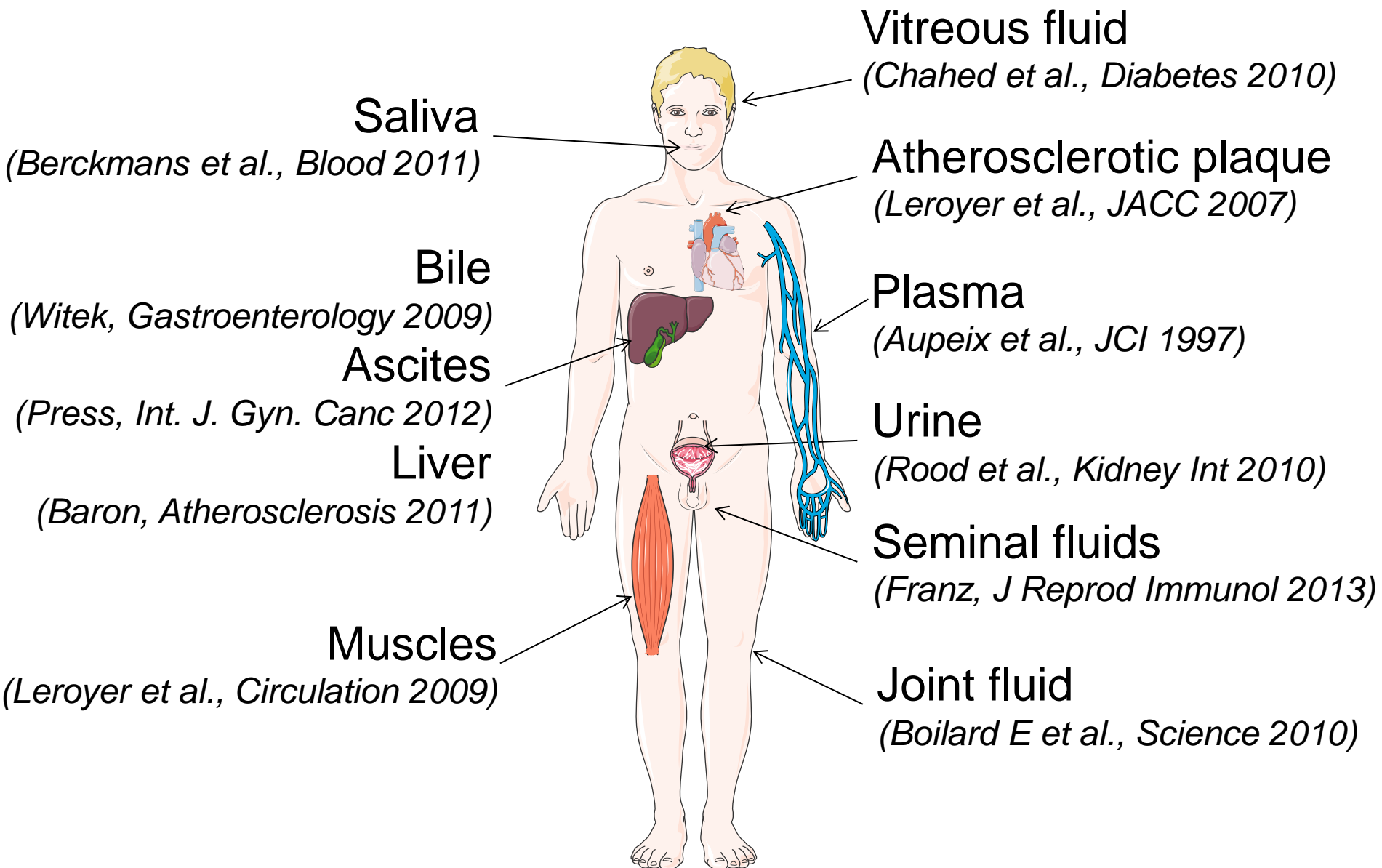
Exos MVs

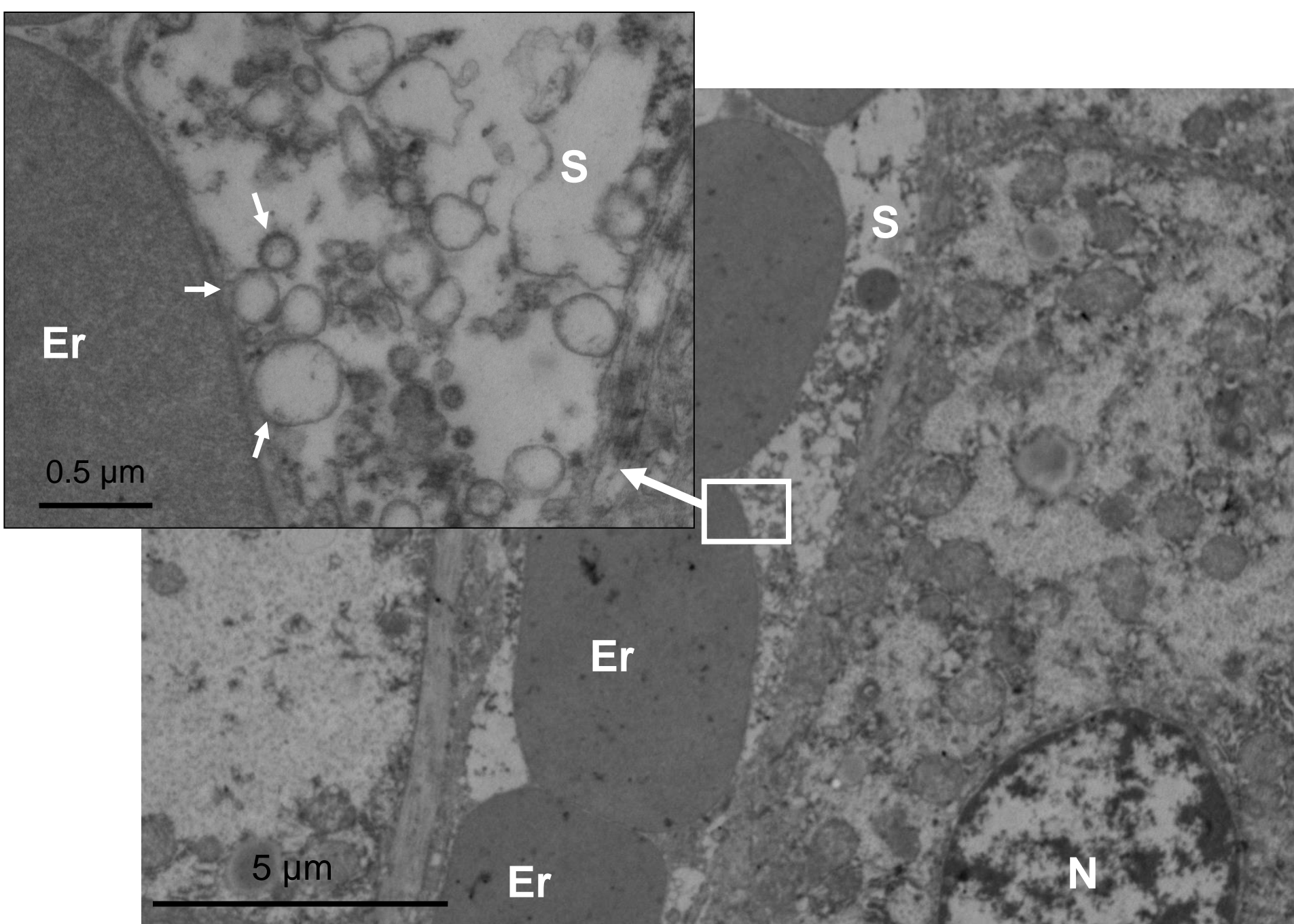
Povero, Sci Signal 2013

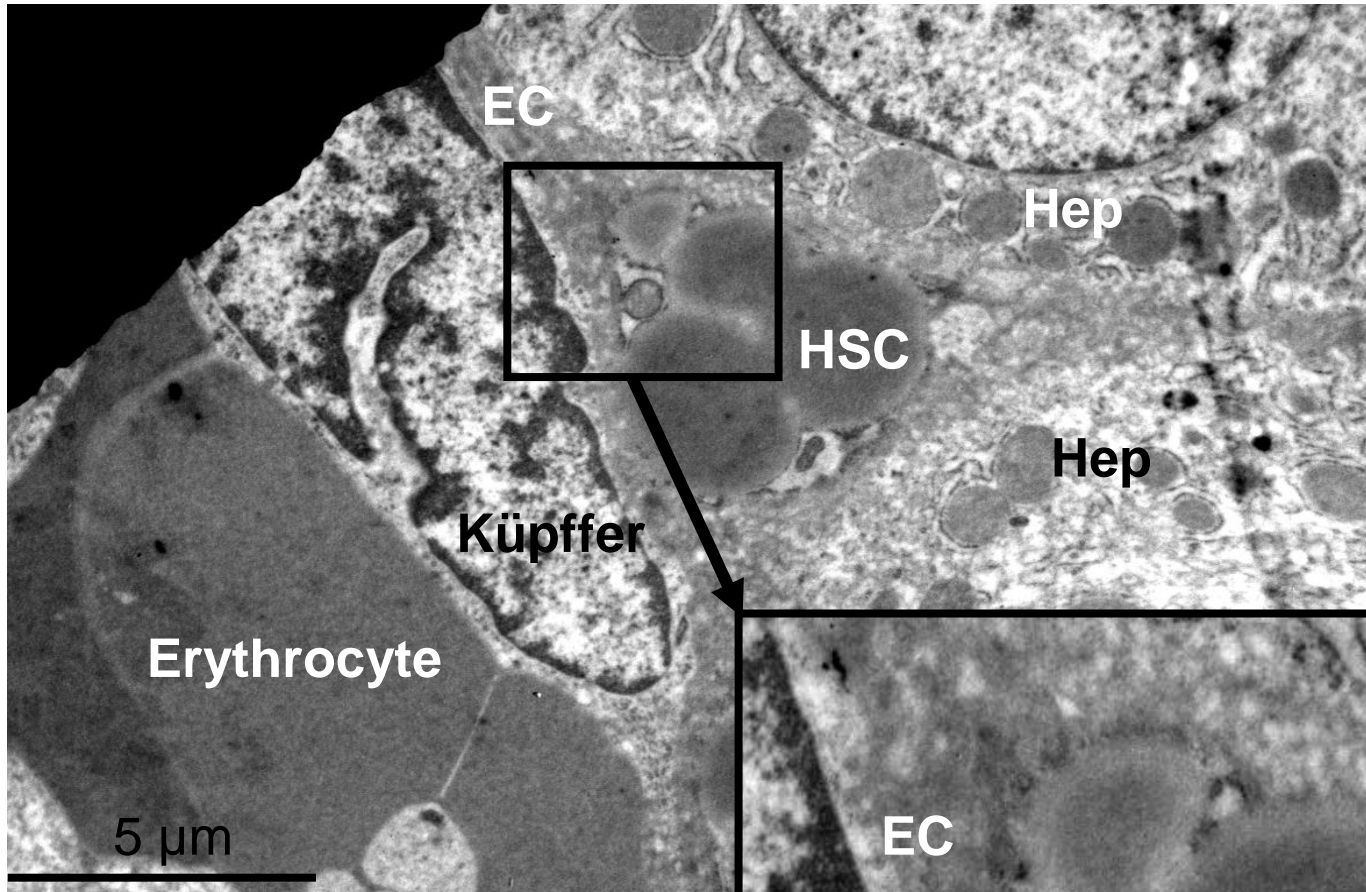
Techniques and names



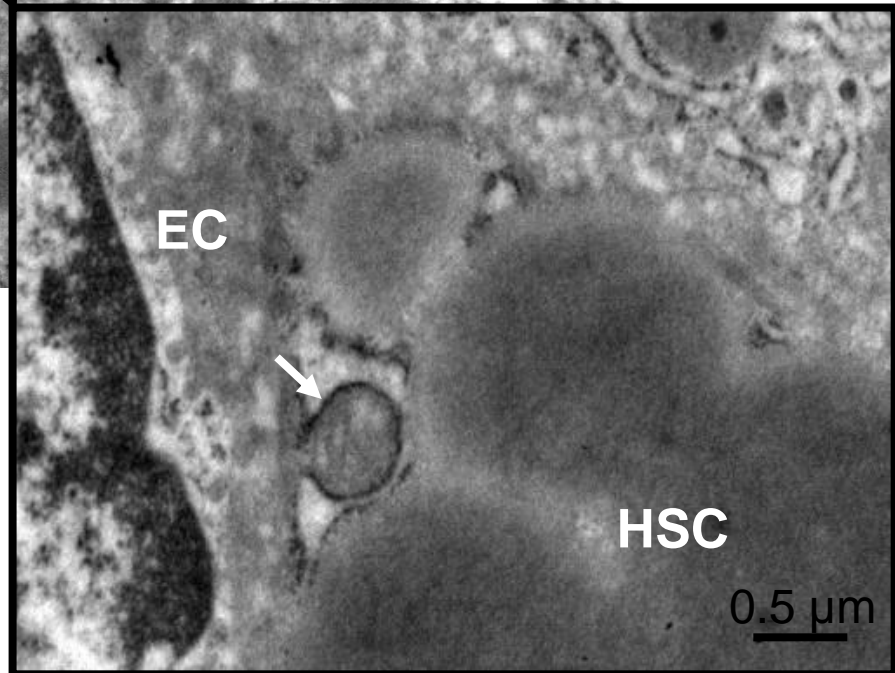
Extracellular vesicles in tissues







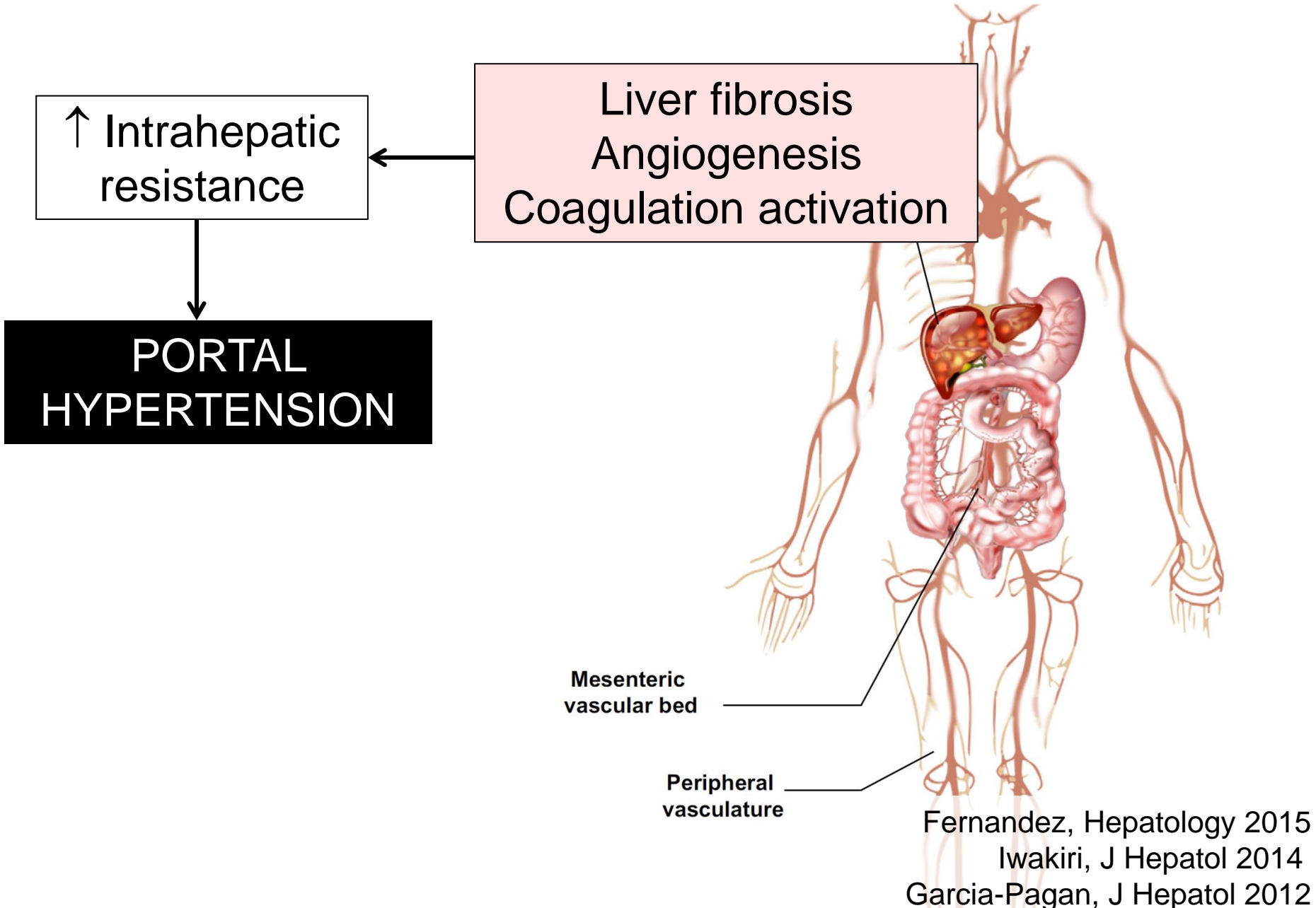
Lemoinne S *et al.* Hepatogastro 2013



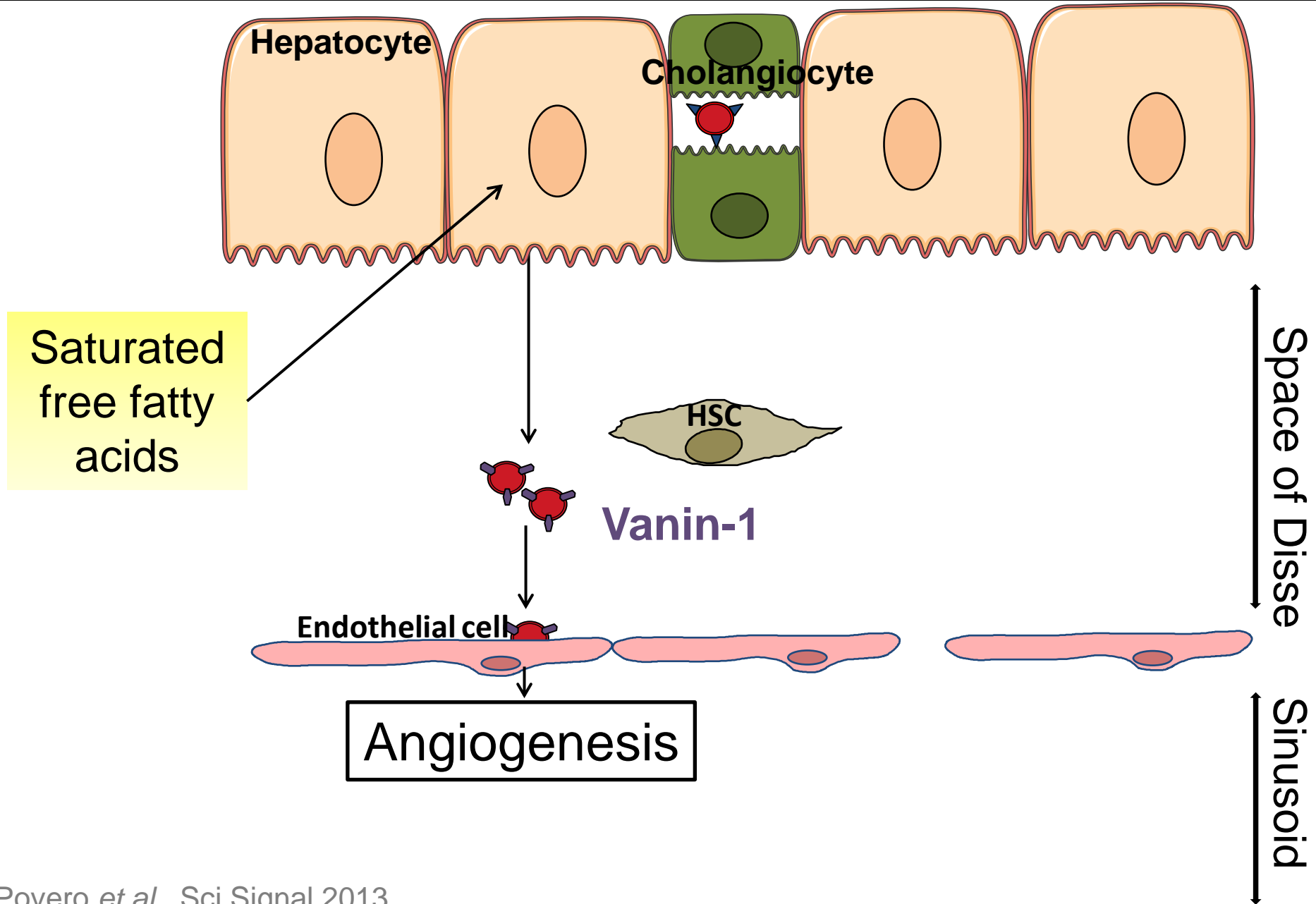
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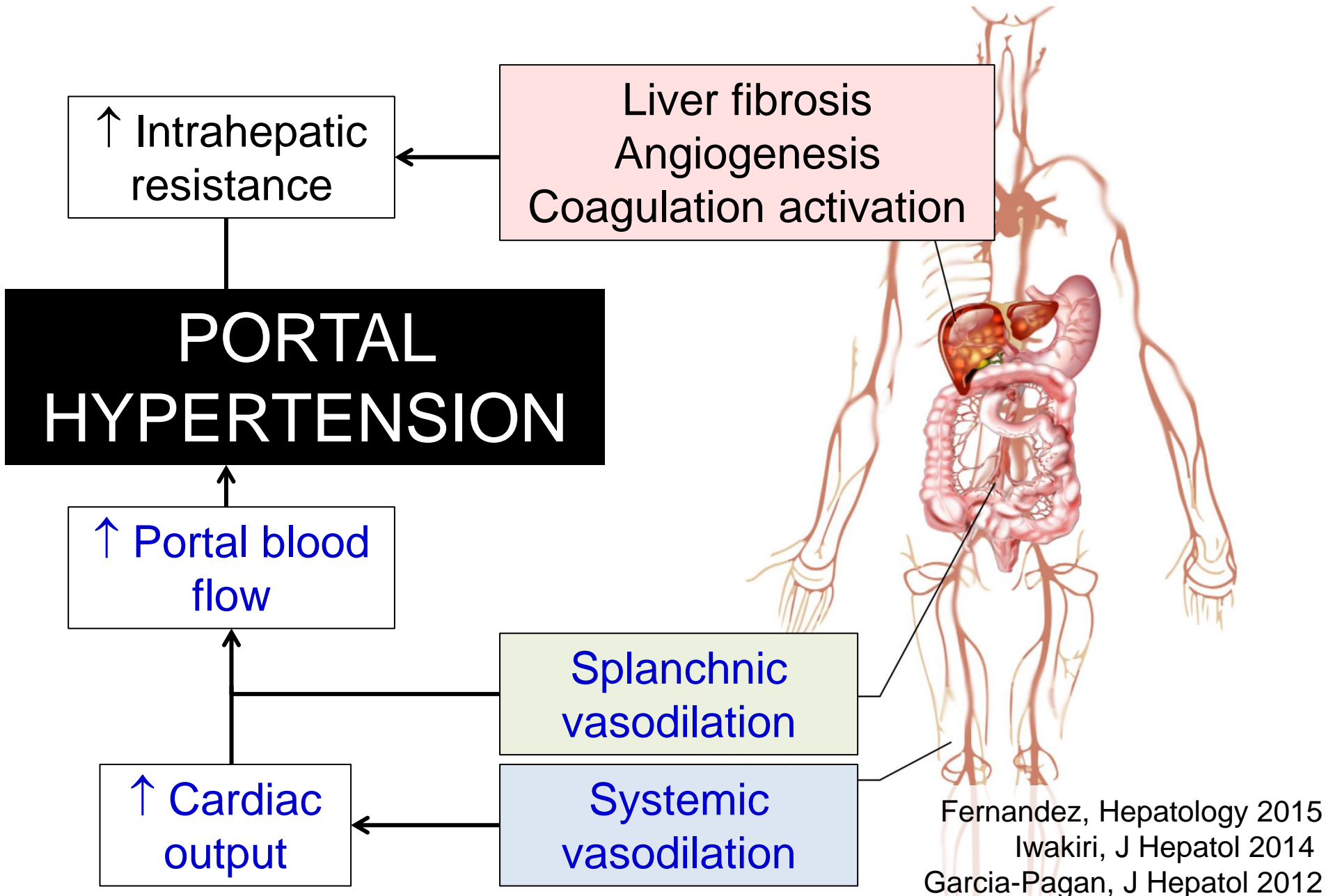
Portal hypertension



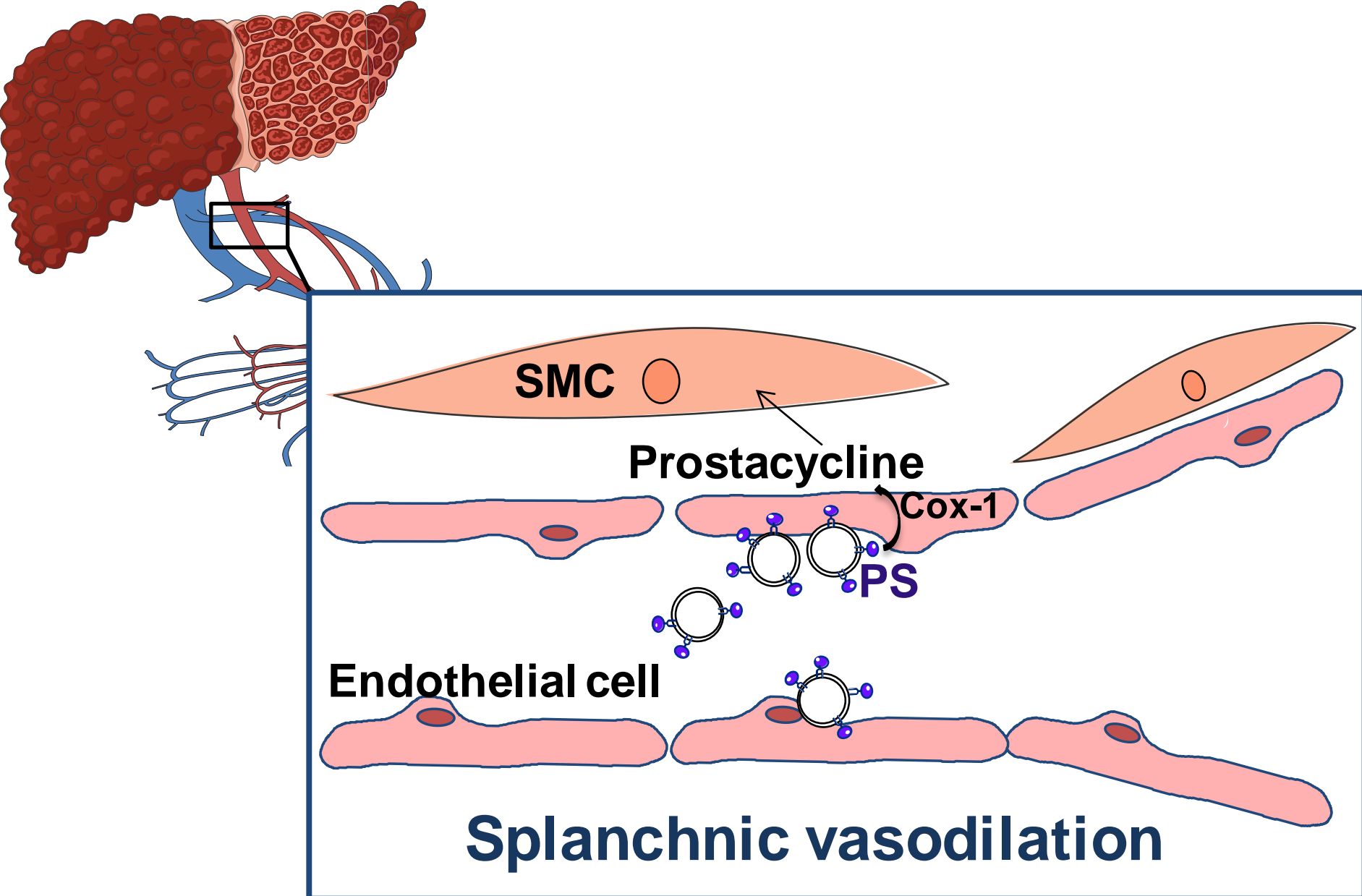
Microvesicles promote liver angiogenesis



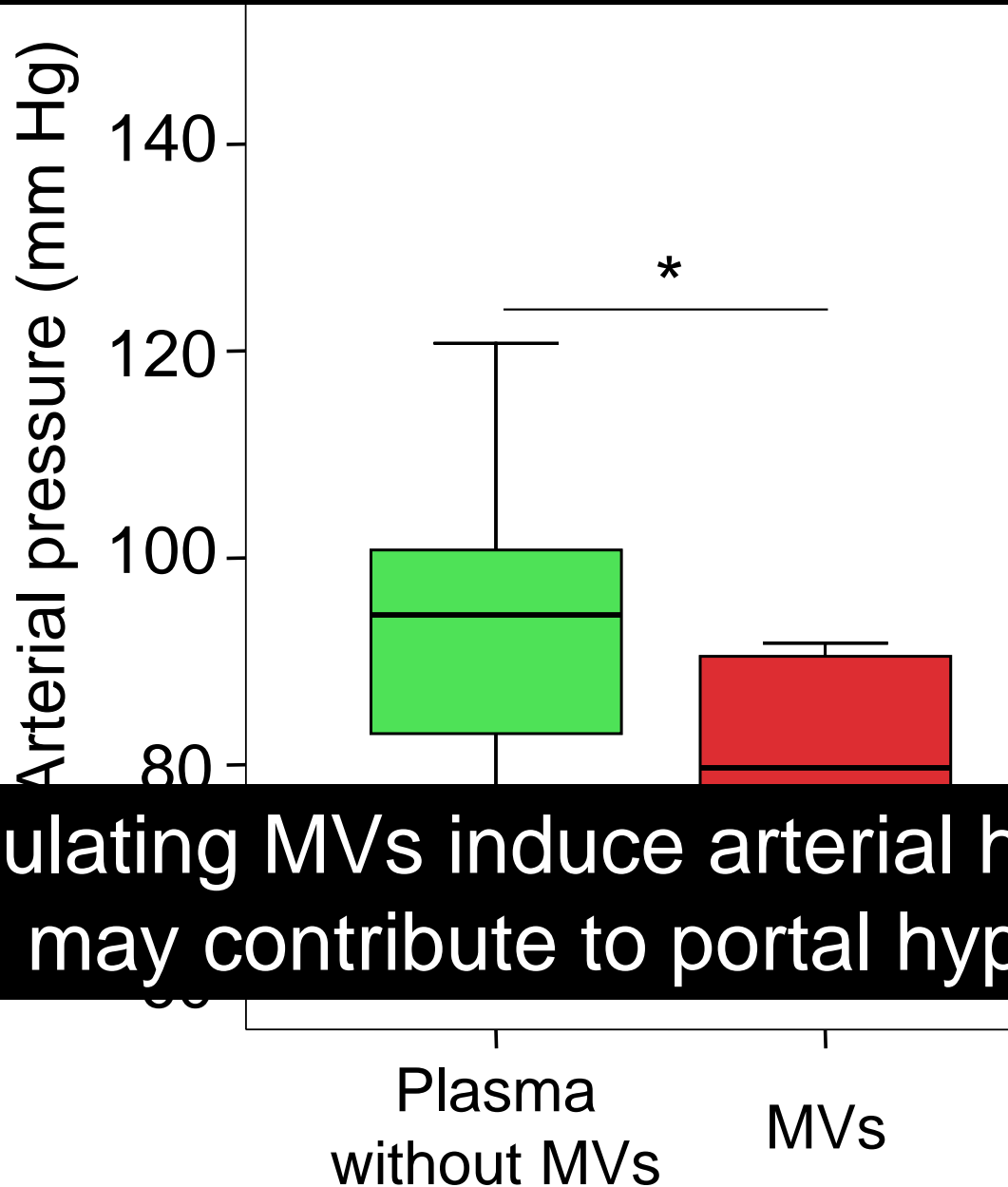
Portal hypertension



Microvesicles enhance systemic vasodilation



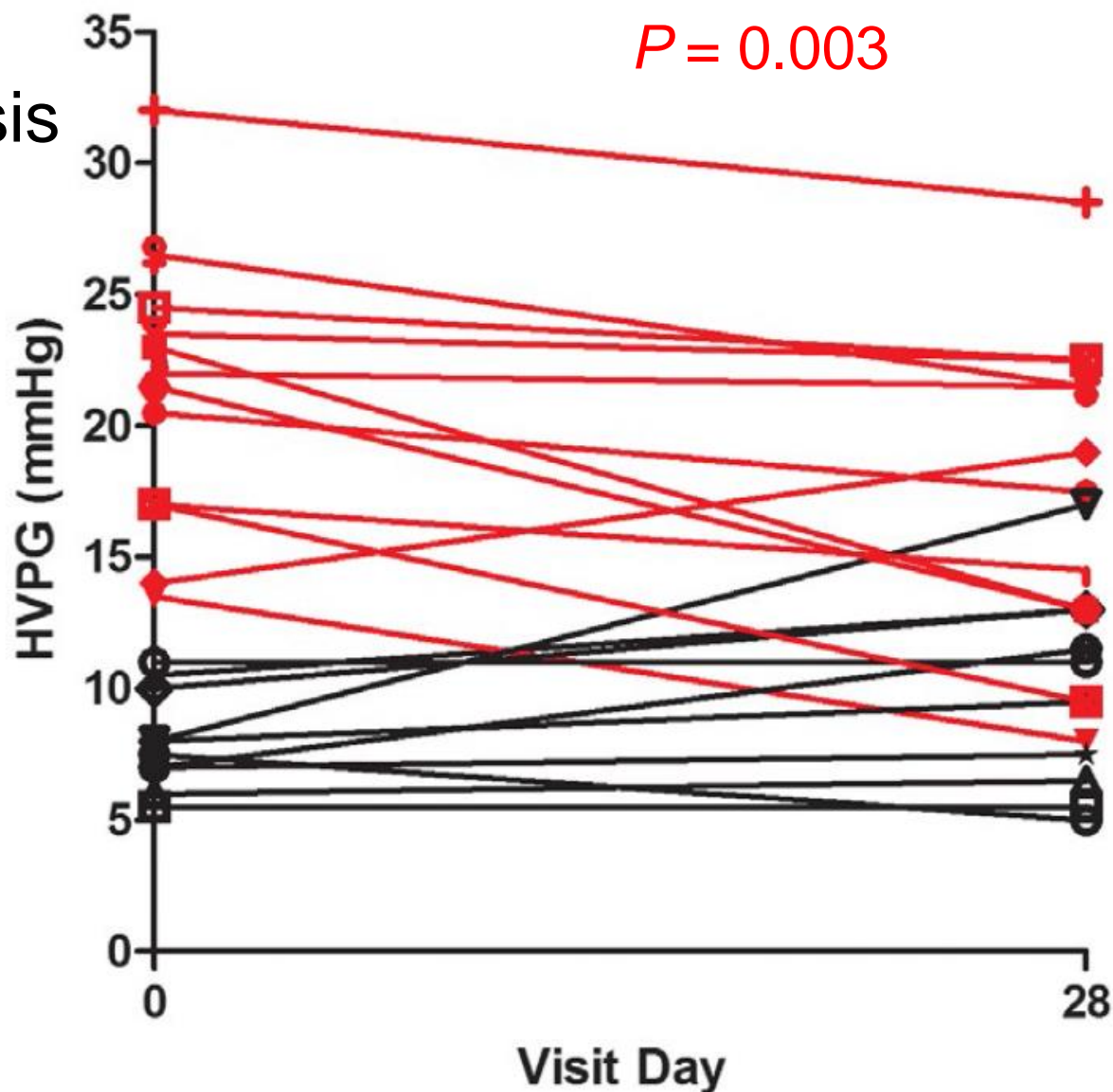
Microvesicles enhance systemic vasodilation



→ Circulating MVs induce arterial hyporeactivity and may contribute to portal hypertension

Emricasan: an “anti-microvesicles” drug?

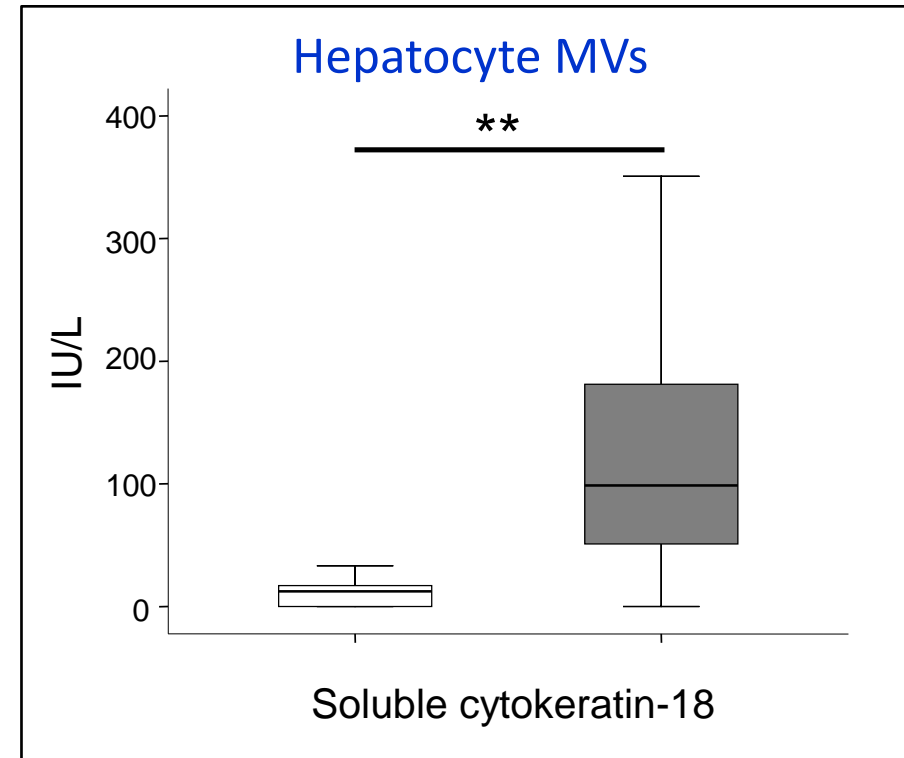
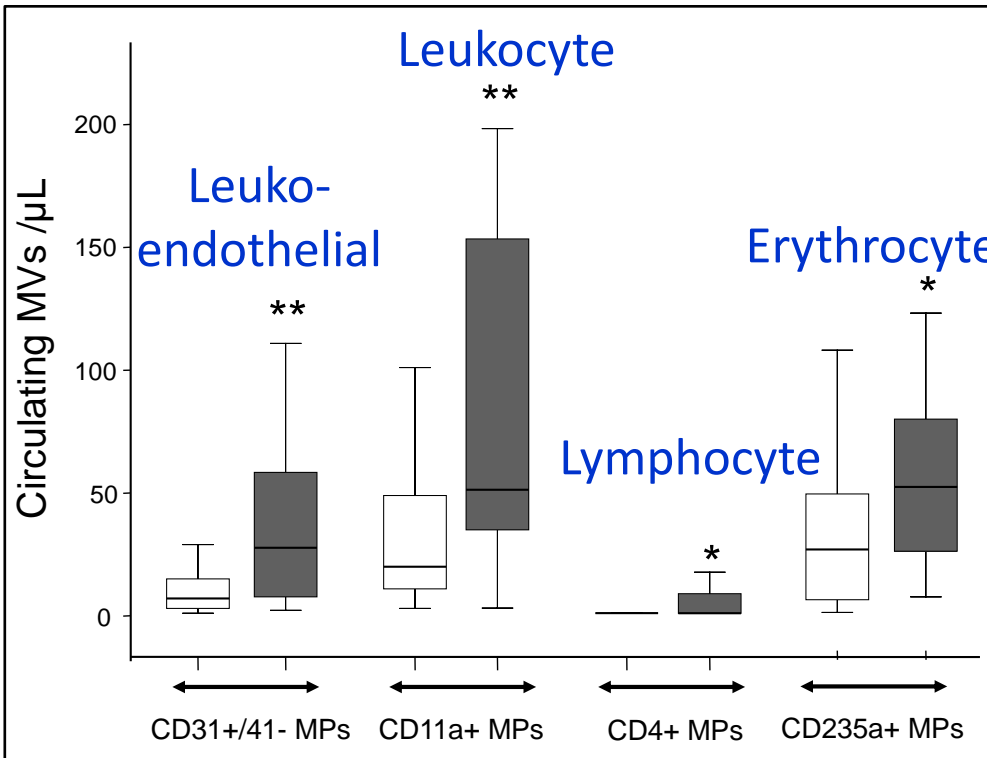
23 patients with compensated cirrhosis



Extracellular vesicles in cirrhosis

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Increased levels of subpopulations of MVs in cirrhosis

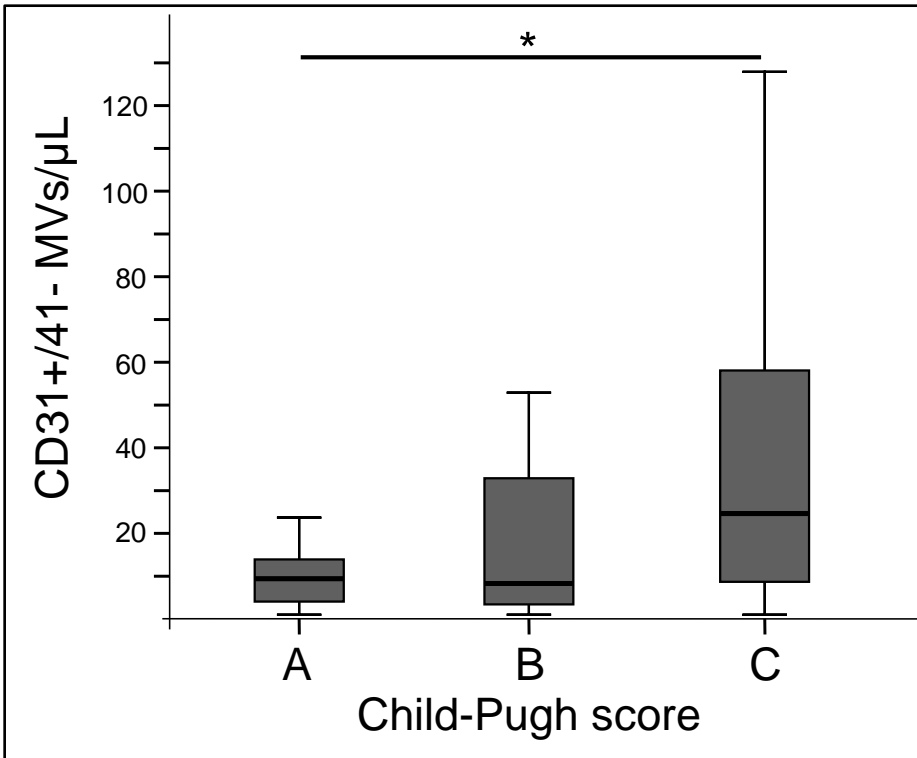


□ Controls (n=30)

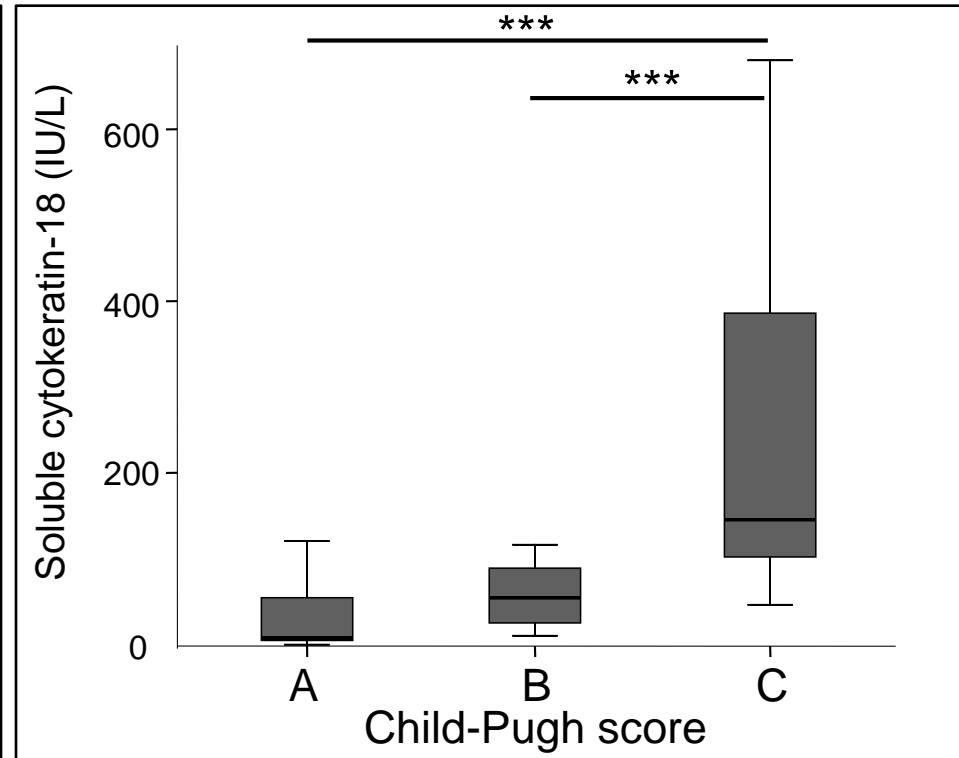
■ Patients with cirrhosis (n=91)

Increased levels of subpopulations of MVs in cirrhosis

Leuko-endothelial MVs in cirrhosis



Hepatocyte MVs in cirrhosis

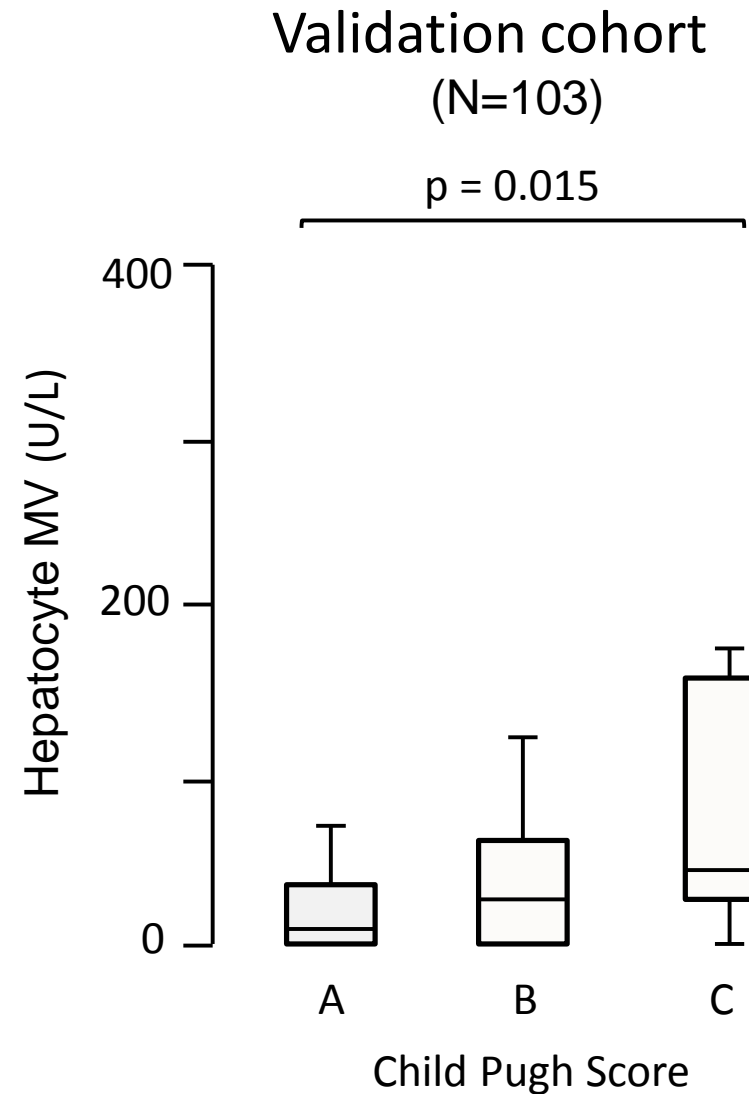
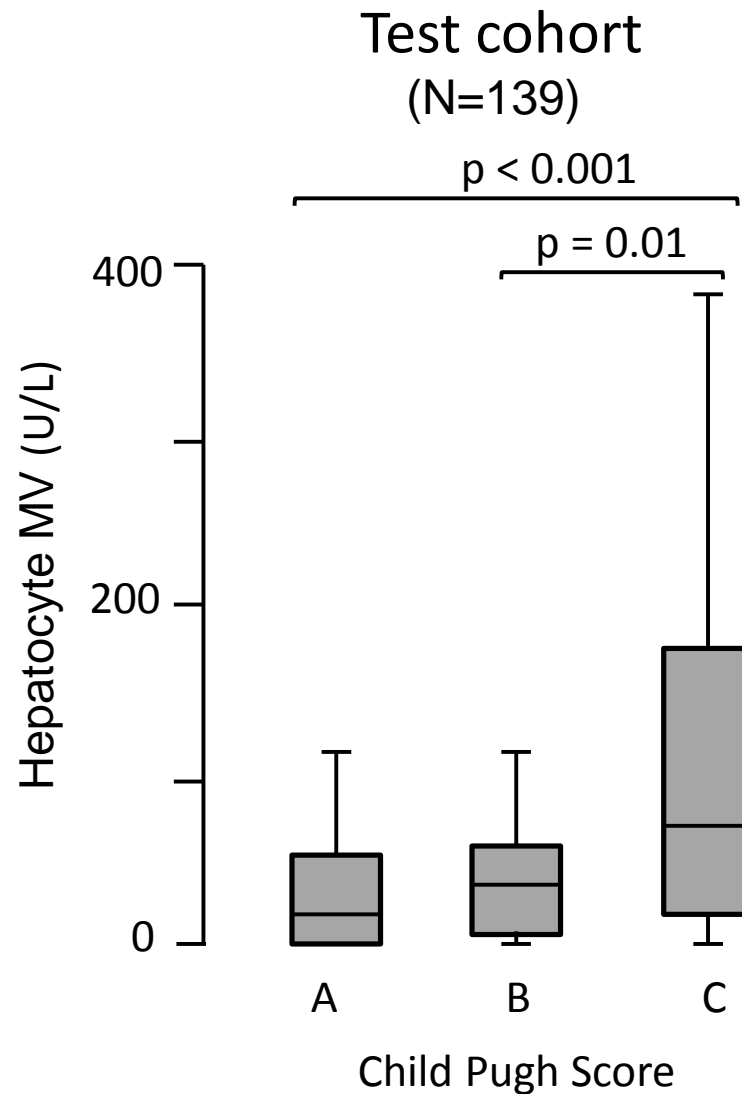


CD31+/41- MVs associated with survival independently of Child-Pugh score

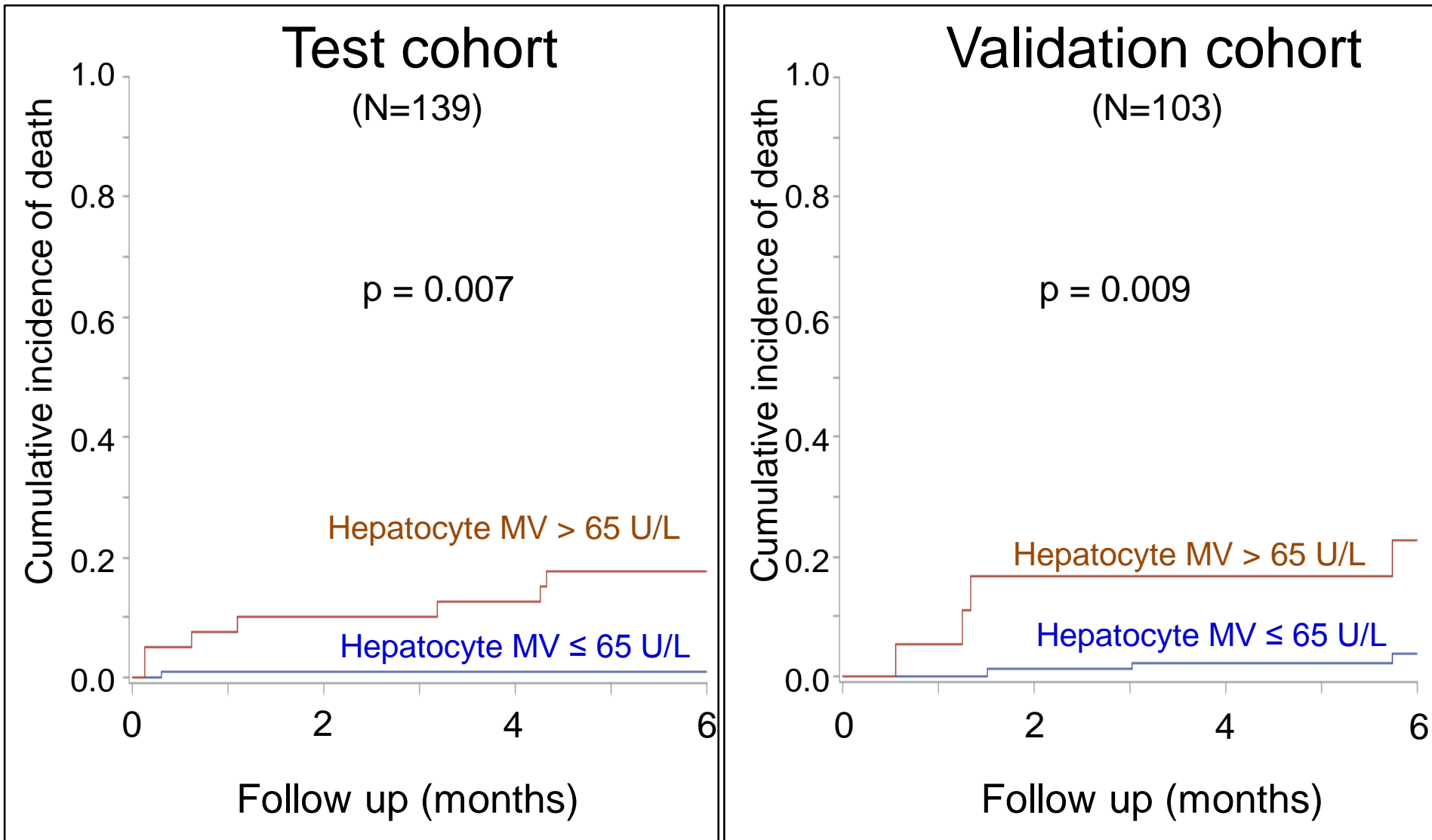
Extracellular vesicles in cirrhosis

	Test (n = 139)	Validation (n=103)
Causes of cirrhosis (%)		
Alcohol	48%	18%
NASH	30%	3%
Hepatitis C / B	29% / 8%	75% / 4%
Ascites -N (%)	55%	22%
HCC (%)	31%	19%
Child Pugh A/B/C	31% / 37% / 32%	64% / 28% / 8%
MELD	13 (9 - 17)	11 (8 - 14)

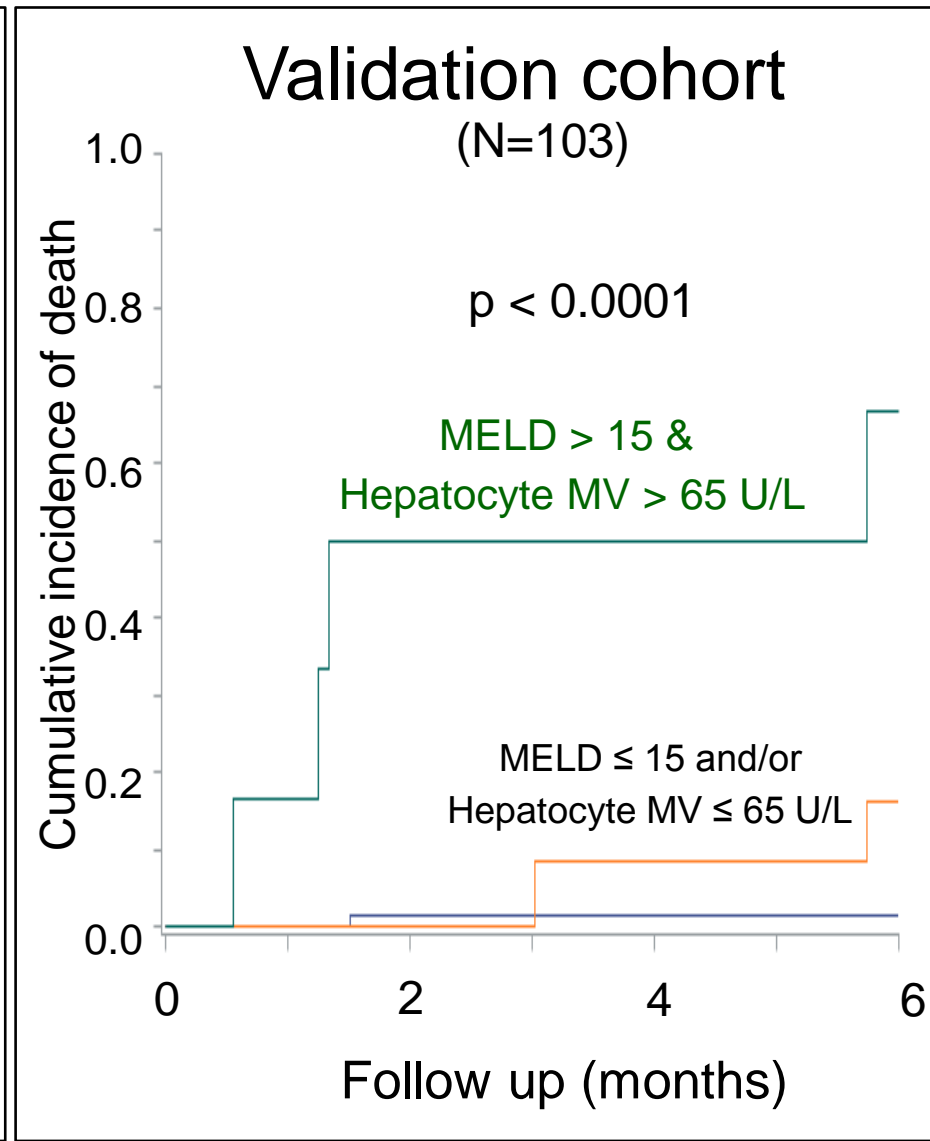
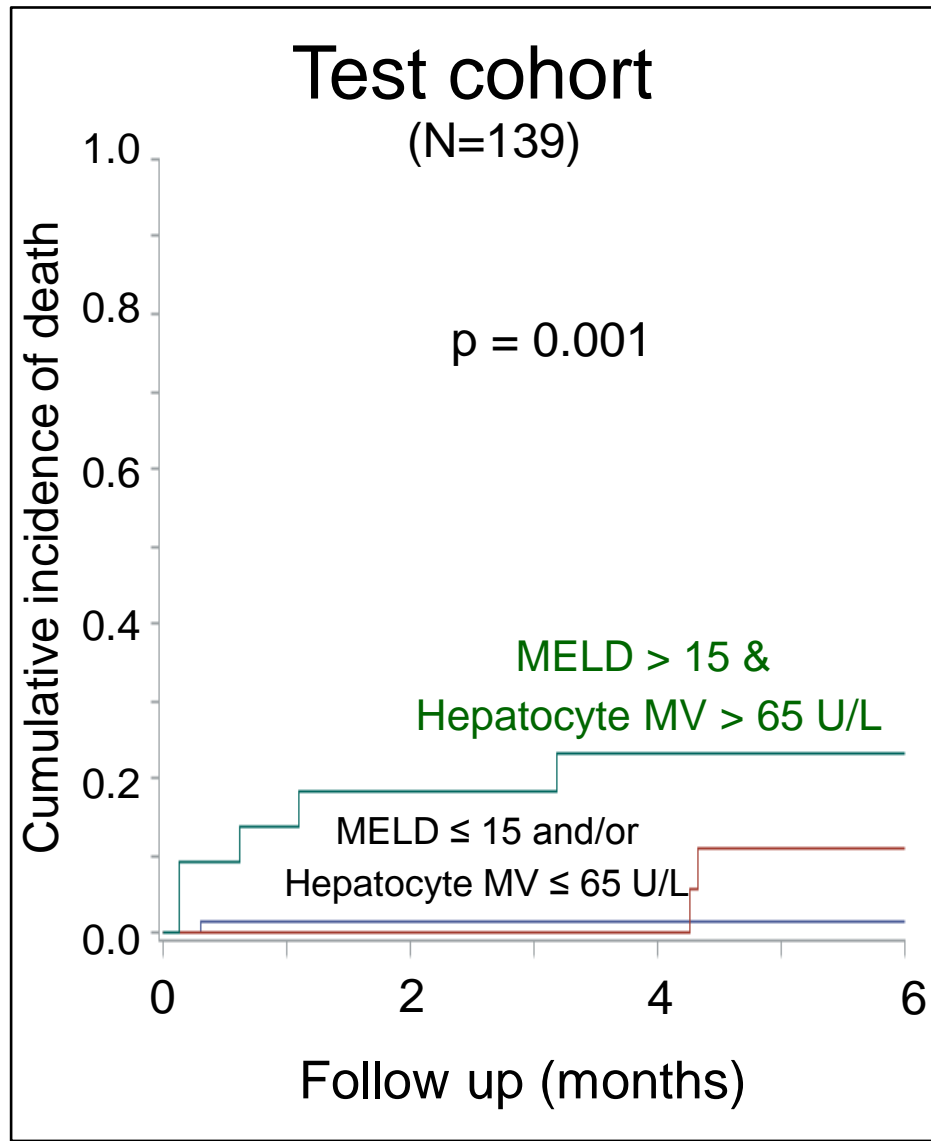
Increased levels of hepatocyte MVs in cirrhosis



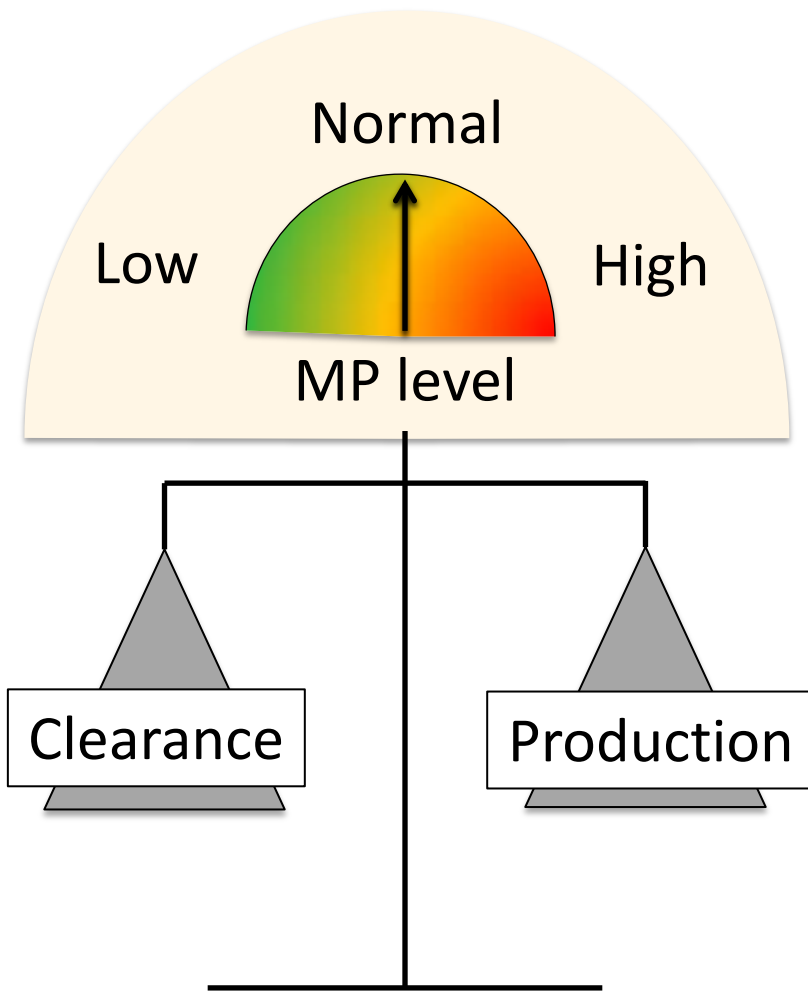
Hepatocyte MVs predict patients' survival



Hepatocyte MVs predict patients' survival

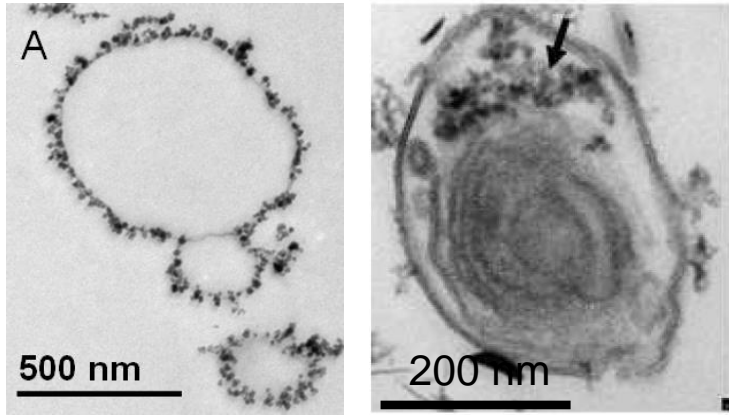


Why are MV levels increased in cirrhosis?



Healthy individual

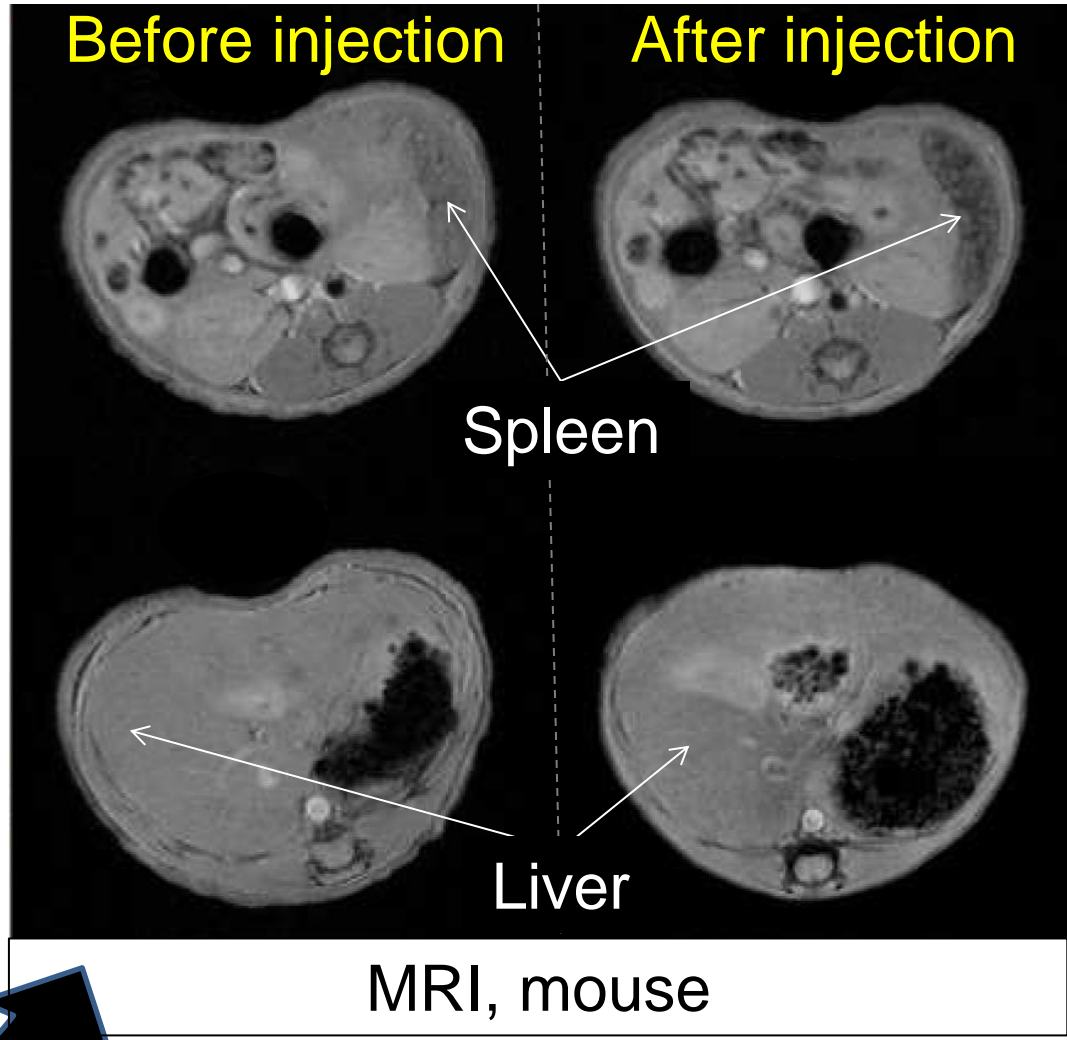
MVs are cleared in the spleen liver and lungs



External

Internal

MP labeling
using nanoparticles



Before injection

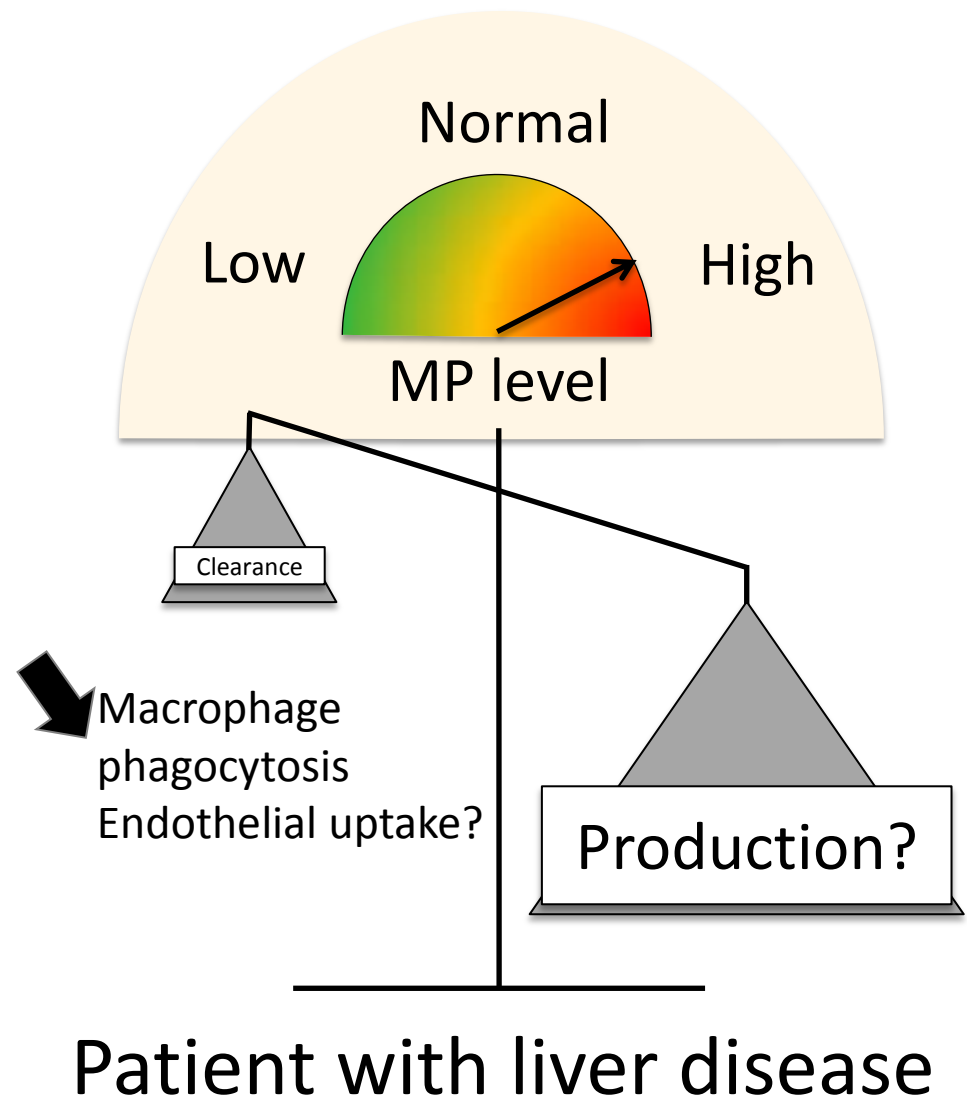
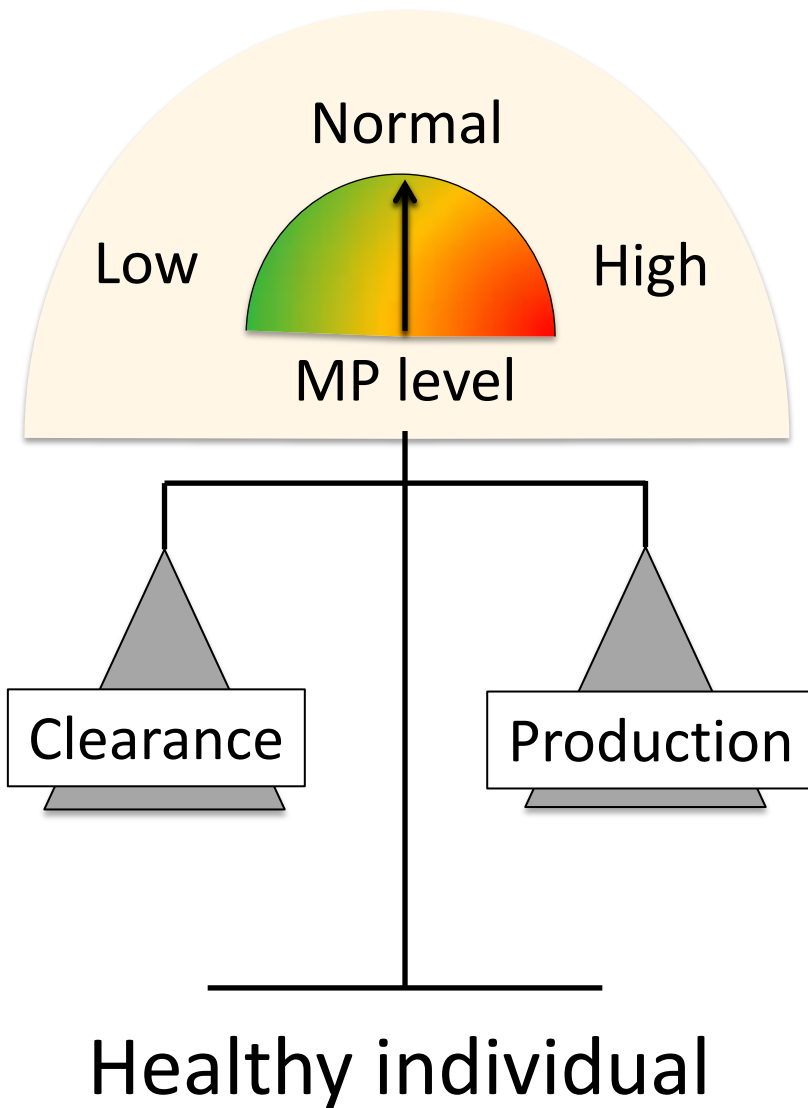
After injection

Spleen

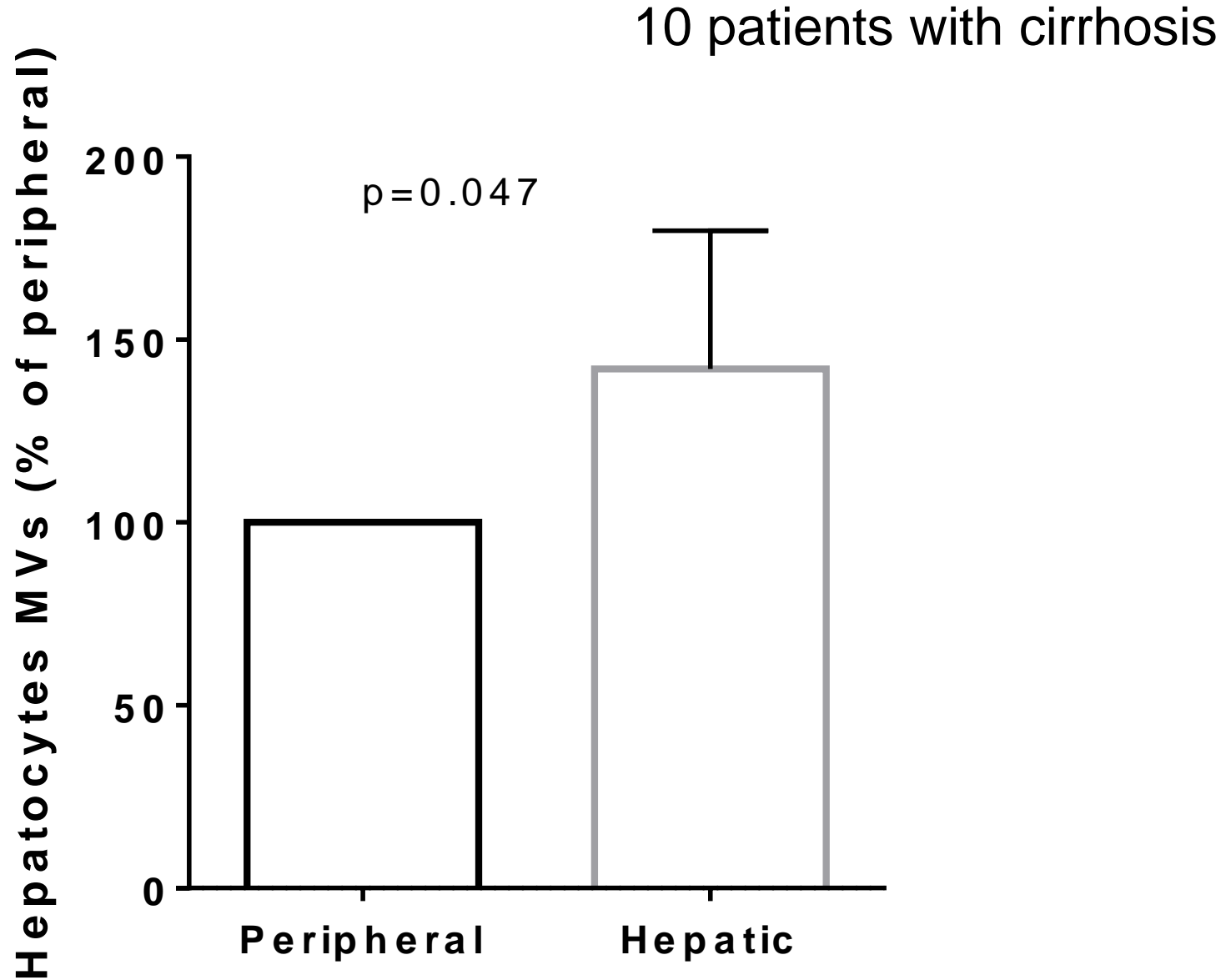
Liver

MRI, mouse

Why are MV levels increased in cirrhosis?

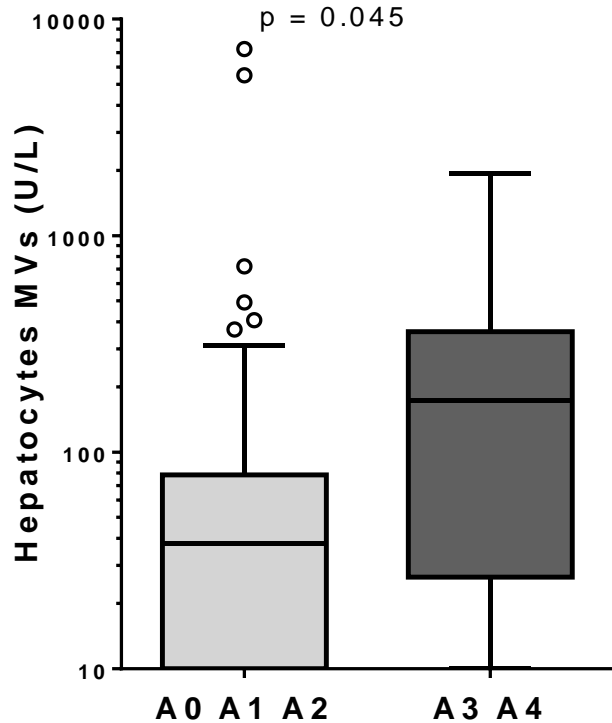


Hepatocyte MV levels in hepatic veins

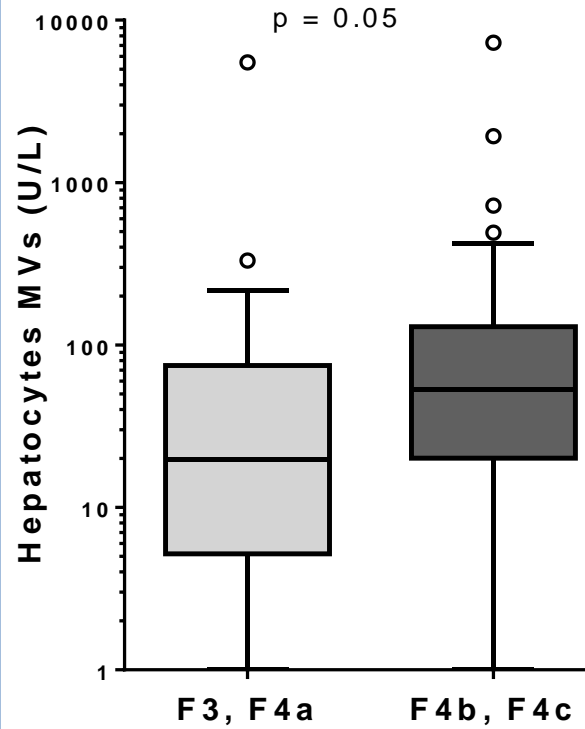


Factors influencing hepatocyte MV levels

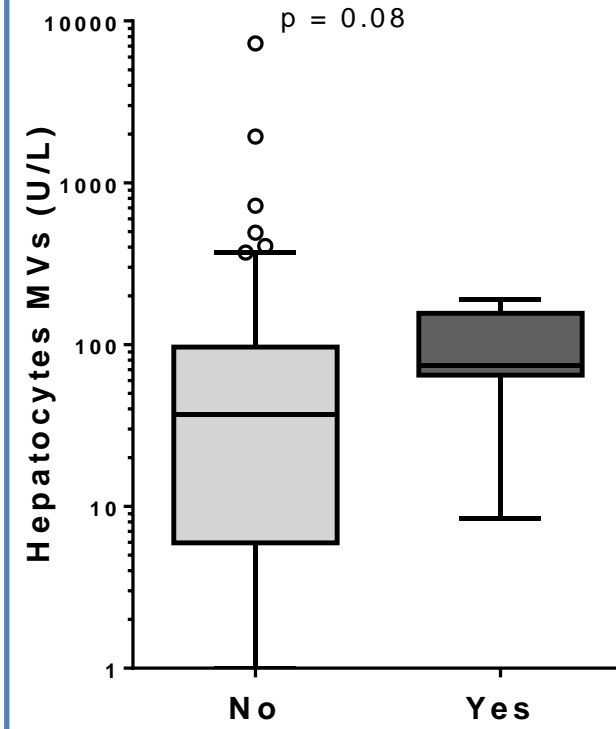
Histological activity



Fibrosis

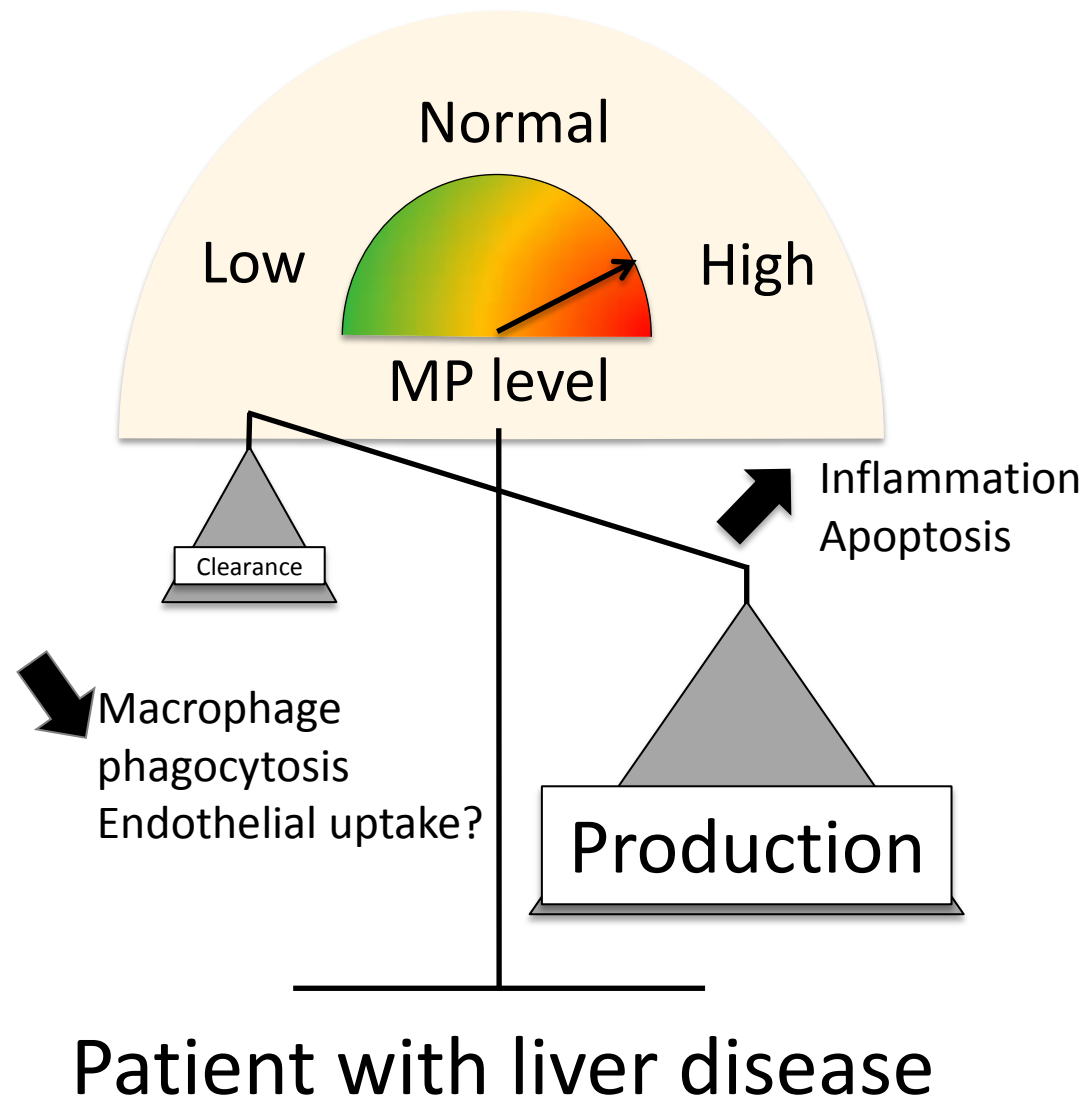
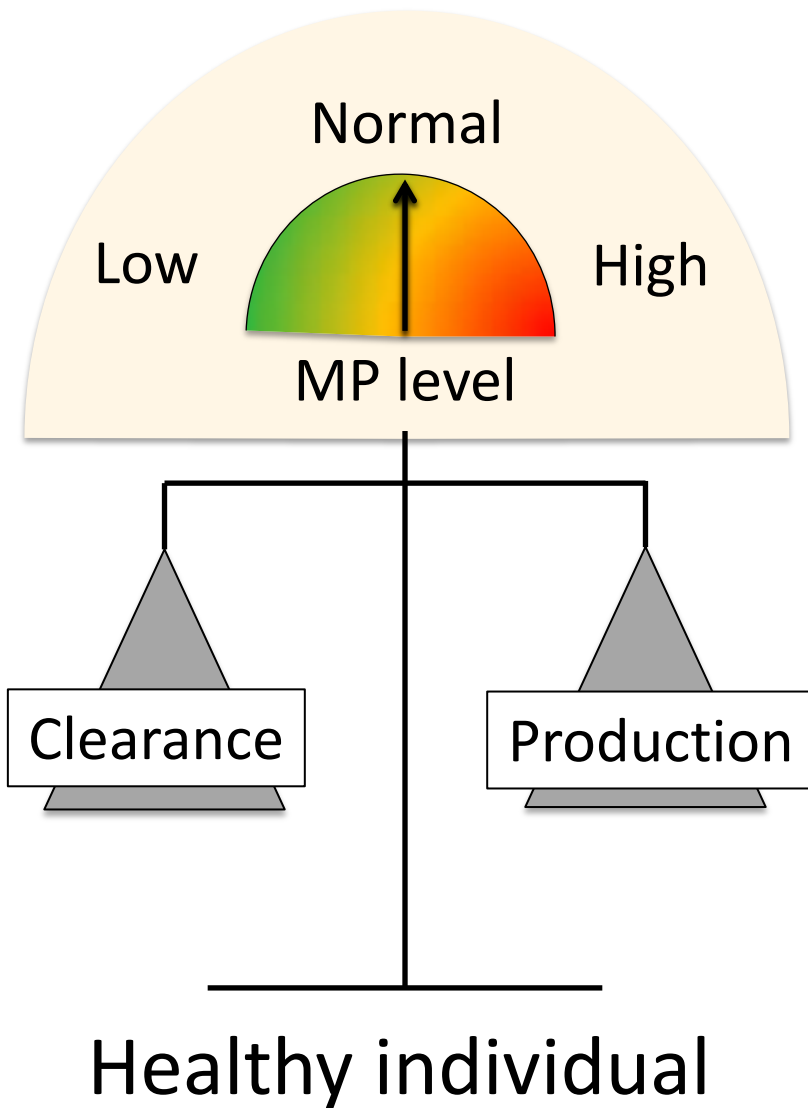


Apoptosis



76 patients from the test cohort
Collab V. Paradis

Why are MV levels increased in cirrhosis?



Current directions: extended populations



Les Programmes Hospitaliers de Recherche Clinique (PHRC)

RHU QUID

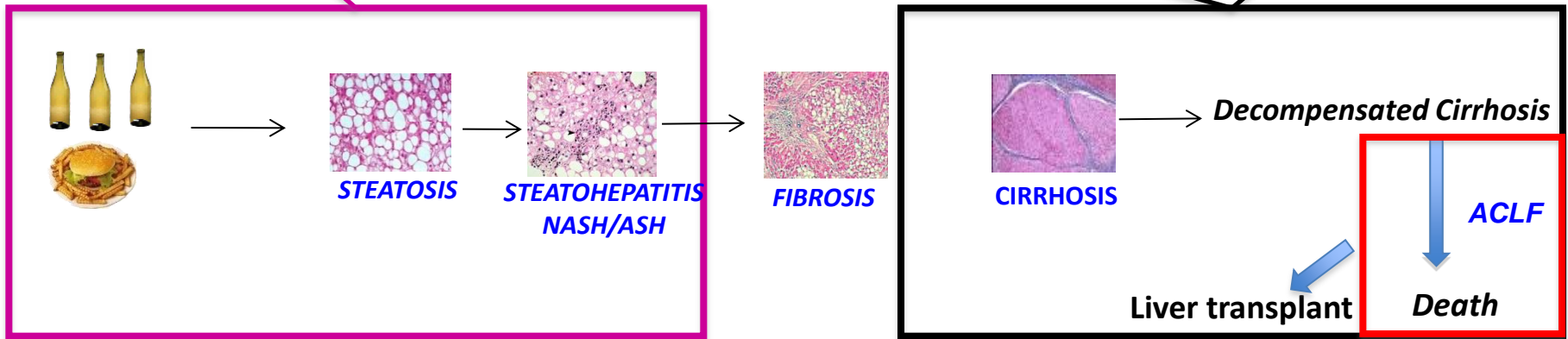
700 patients with diabetes and ↑ ALT levels

Booster Innovation

650 patients with compensated cirrhosis

PHRC PROMICE

335 patients with survival



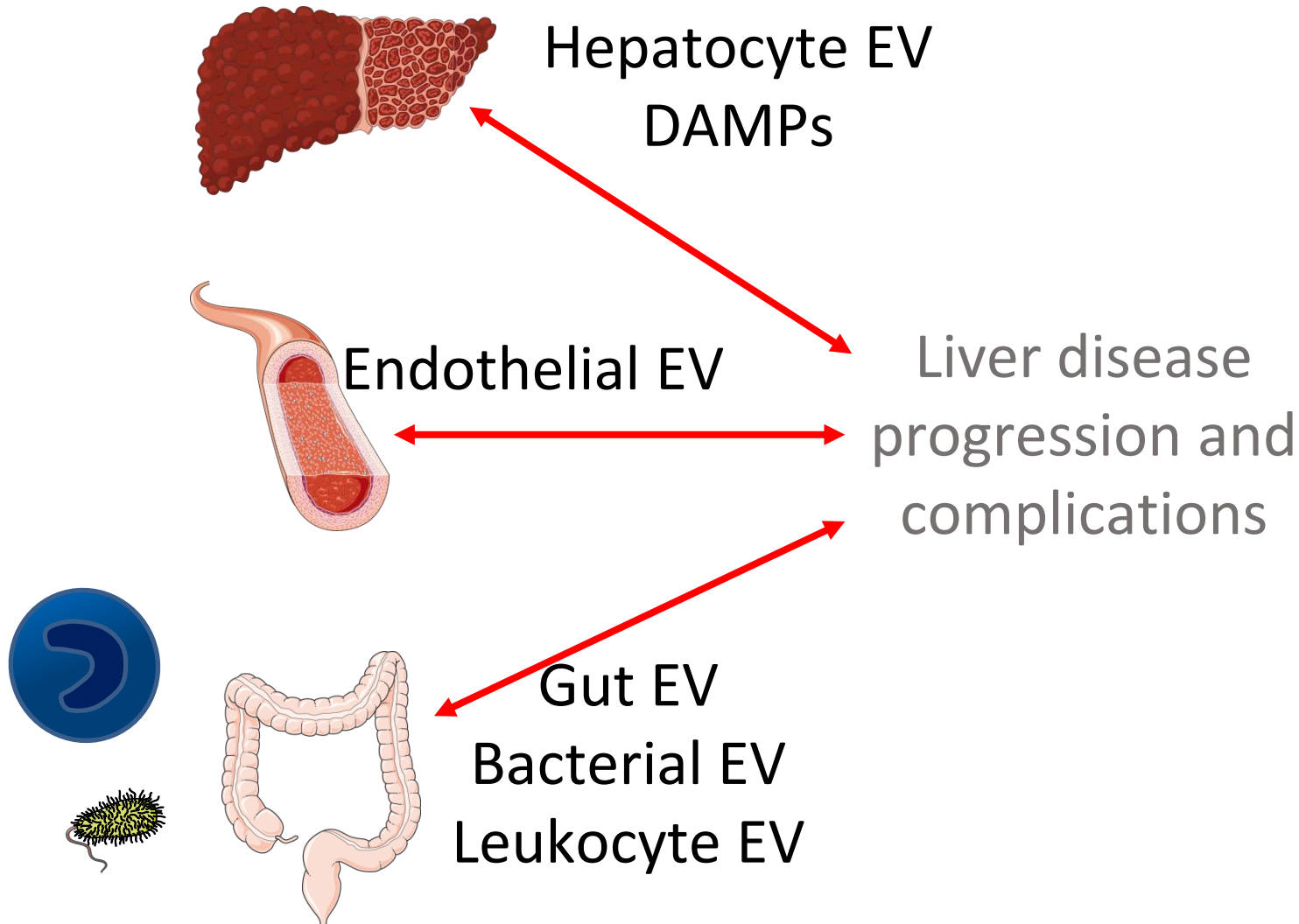
CANONIC

800 patients with decompensated cirrhosis

ALADDIN : 340 patients with ACLF

GRIFOLS

Current directions: an MV signature



Conclusion

- MVs are implicated at many stages of liver disease progression, including fibrogenesis, portal hypertension
- Circulating levels of several subpopulations of MVs are increased in patients with cirrhosis
- MVs might reflect ongoing liver injury and thereby predict patients' outcome



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CENTRE de RECHERCHE
sur l'INFLAMMATION

Hepatology unit, Beaujon Hospital
Reference center for vascular liver diseases



Inserm U1149
Research center on inflammation



Société Nationale Française
de Gastro-Entérologie
SNFGE

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