Endothelial cells in portal vein thrombosis

Virginia Hernández-Gea

Liver Unit. Hospital Clinic Barcelona-IDIBAPS

Liver Disease & the Vascular System LAB

LiVas

Clínic Barcelona | Universitat de Barcelona

IDIBAPS Institut D'Investigacions Biomèdiques August Pi i Sunyer

ciber | EHD

cost European Cooperation in Science & Technology

national institute of gastroenterology de Bellis - Castellana Grotte IRCCS

Ministero della Salute

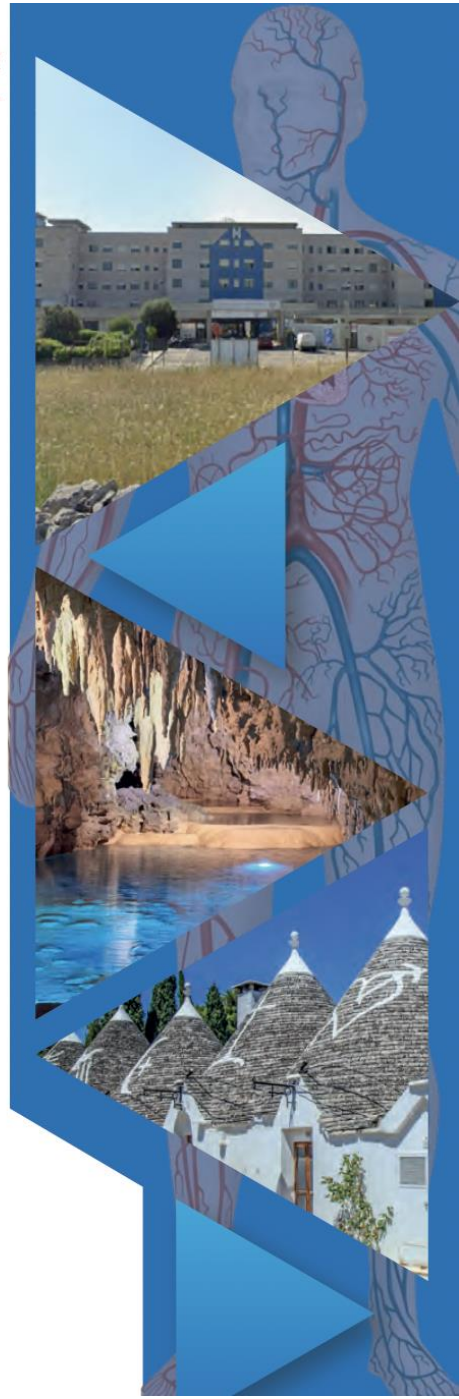
EASL The Home of Hepatology

AISF

International Congress on Coagulopathy in Liver Disease

Hemostasis and Thrombosis in Liver Disease: from Bench to Bedside

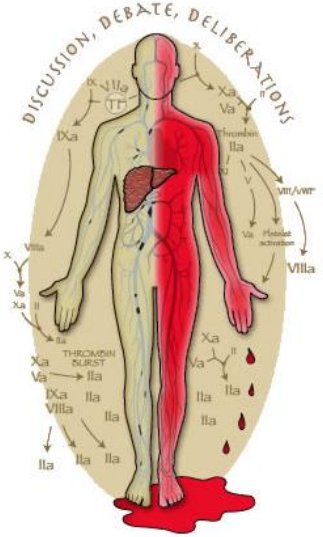
Castellana Grotte (BA)
8-10 April, 2026



8th International Symposium on Coagulation in Liver Disease

Discussion, Debates, and Deliberations

September 27 & 28, 2019



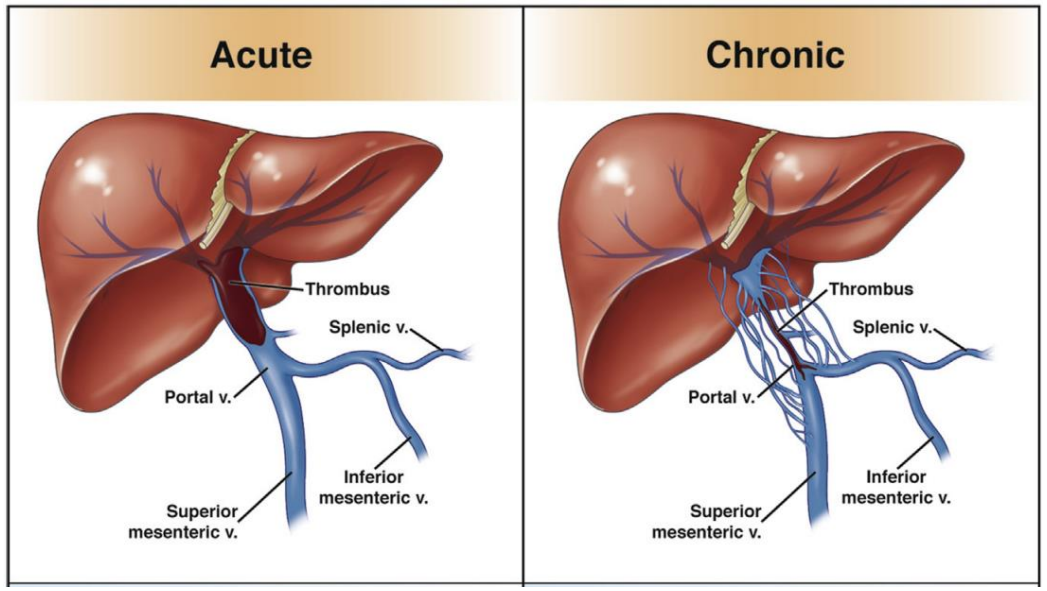
The endothelium in cirrhotic thrombosis

Virginia Hernández-Gea

Barcelona Hepatic Hemodynamic Unit, Liver Unit.

Hospital Clinic, IDIBAPS and CIBERehd

Portal vein thrombosis (PVT)



Intagliata NM et al. Gastroenterology. 2019

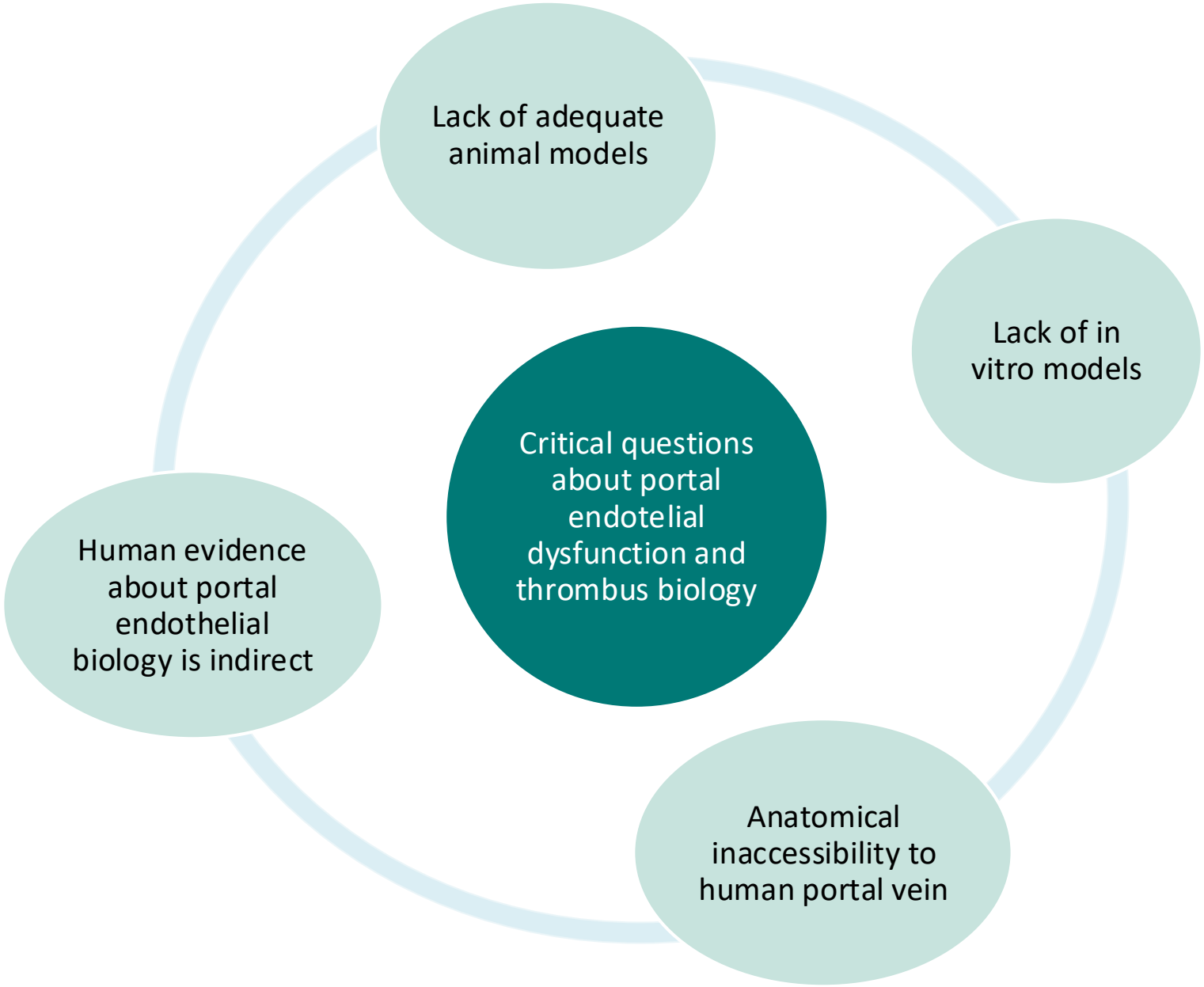
PVT is rare in the general population (global prevalence of 1%) but occurs in 5-35% of patients with cirrhosis, increasing with disease severity

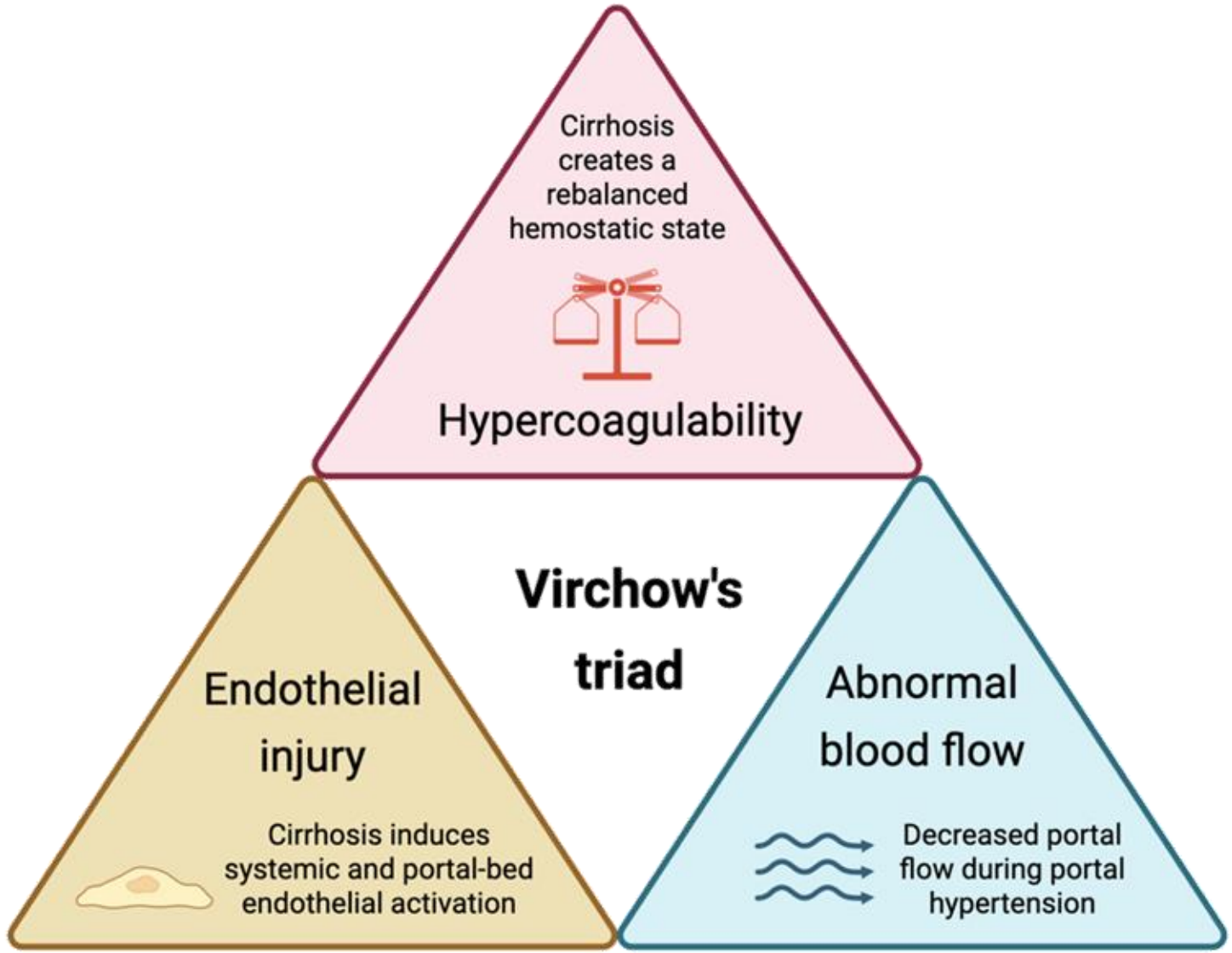
PVT contribution to disease progression is controversial. Negative impact in the setting of liver transplantation.

TREATMENT:

- Anticoagulation
- Shows attenuated response: **up to 60% fail** to complete recanalization
- If recanalization occurs, re-thrombosis rate is high

Challenges in the study of PVT

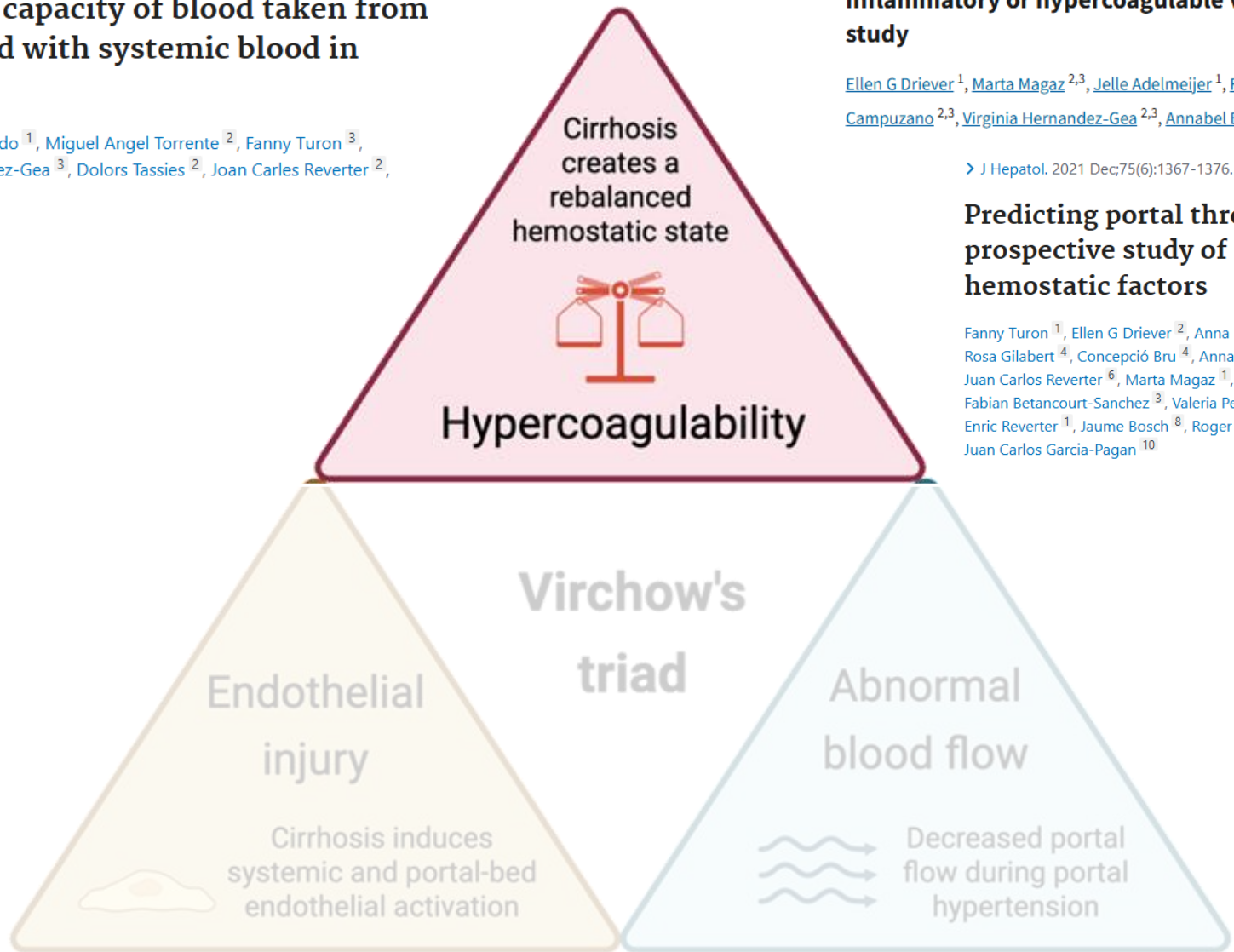



Cirrhosis creates a rebalanced hemostatic state
Hypercoagulability
Virchow's triad
Endothelial injury
Cirrhosis induces systemic and portal-bed endothelial activation
Abnormal blood flow
Decreased portal flow during portal hypertension

Res Pract Thromb Haemost. 2024 Oct 9;8(7):102583. doi: 10.1016/j.rpth.2024.102583. eCollection 2024 Oct.

Comparable hemostatic capacity of blood taken from the portal vein compared with systemic blood in patients with cirrhosis

Annabel Blasi [1], Andrea Calvo [1], Ricard Mellado [1], Miguel Angel Torrente [2], Fanny Turon [3], Juan Carlos Garcia-Pagan [3], Virginia Hernandez-Gea [3], Dolors Tassies [2], Joan Carles Reverter [2], Ton Lisman [4]



J Thromb Haemost. 2022 Jul 11;20(9):2075–2082. doi: 10.1111/jth.15797

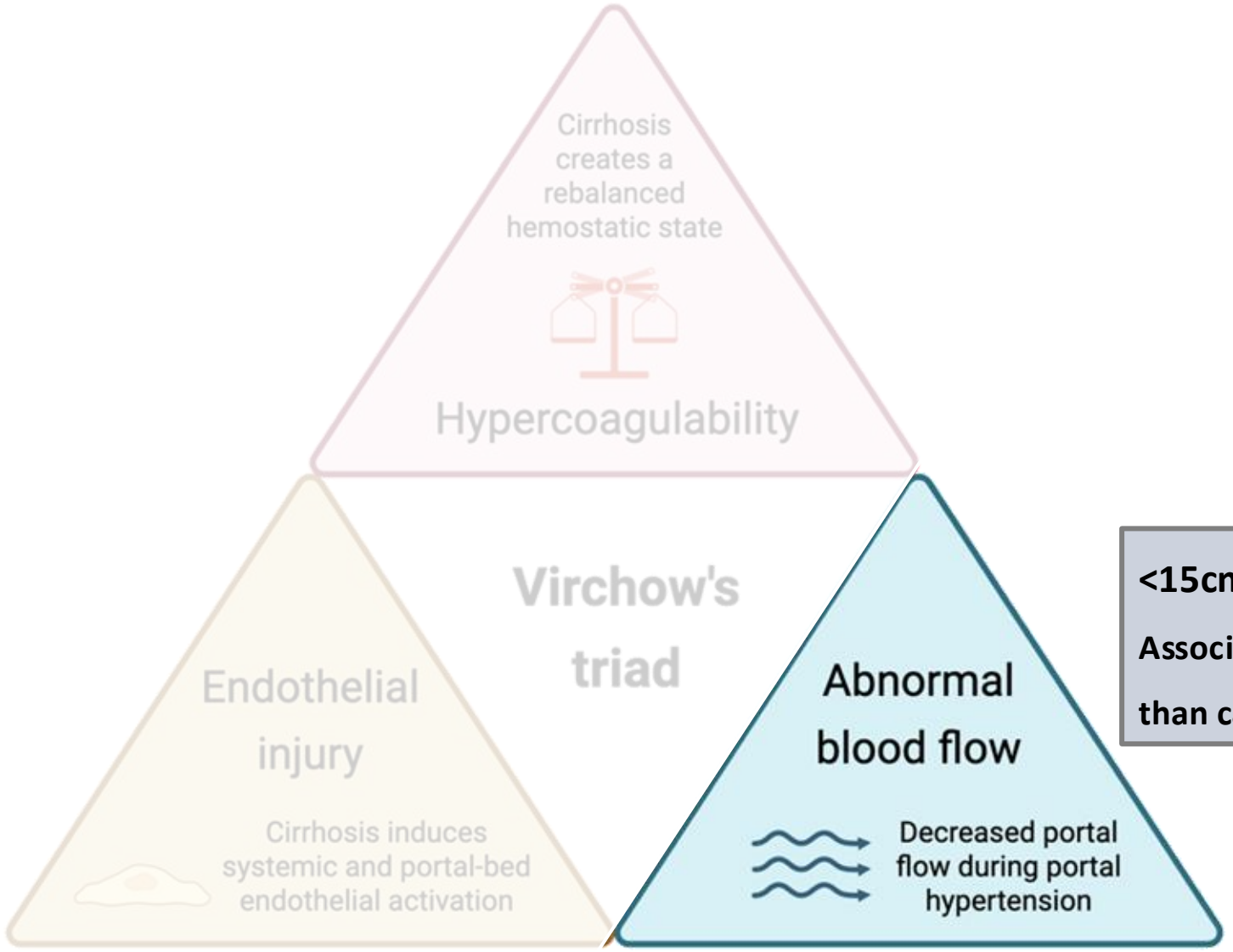
The portal vein in patients with cirrhosis is not an excessively inflammatory or hypercoagulable vascular bed, a prospective cohort study

Ellen G Driever [1], Marta Magaz [2,3], Jelle Adelmeijer [1], Fanny Turon [2,3], Anna Baiges [2,3], Pol Olivas [2,3], Valeria Pérez-Campuzano [2,3], Virginia Hernandez-Gea [2,3], Annabel Blasi [4], Juan-Carlos Garcia-Pagan [2,3], Ton Lisman [1,✉]

J Hepatol. 2021 Dec;75(6):1367-1376. doi: 10.1016/j.jhep.2021.07.020. Epub 2021 Jul 30.

Predicting portal thrombosis in cirrhosis: A prospective study of clinical, ultrasonographic and hemostatic factors

Fanny Turon [1], Ellen G Driever [2], Anna Baiges [1], Eira Cerda [3], Ángeles García-Criado [4], Rosa Gilabert [4], Concepció Bru [4], Annalisa Berzigotti [5], Isabel Nuñez [4], Lara Orts [1], Juan Carlos Reverter [6], Marta Magaz [1], Genis Camprecios [1], Pol Olivas [3], Fabian Betancourt-Sanchez [3], Valeria Perez-Campuzano [3], Annabel Blasi [7], Susana Seijo [3], Enric Reverter [1], Jaume Bosch [8], Roger Borràs [9], Virginia Hernandez-Gea [1], Ton Lisman [2], Juan Carlos Garcia-Pagan [10]



<15cm/s

Associative relationship rather than casual

Not much research has been dedicated to the portal vein endothelium

› Thromb Haemost. 2020 Aug;120(8):1173-1181. doi: 10.1055/s-0040-1713169. Epub 2020 Jun 30.

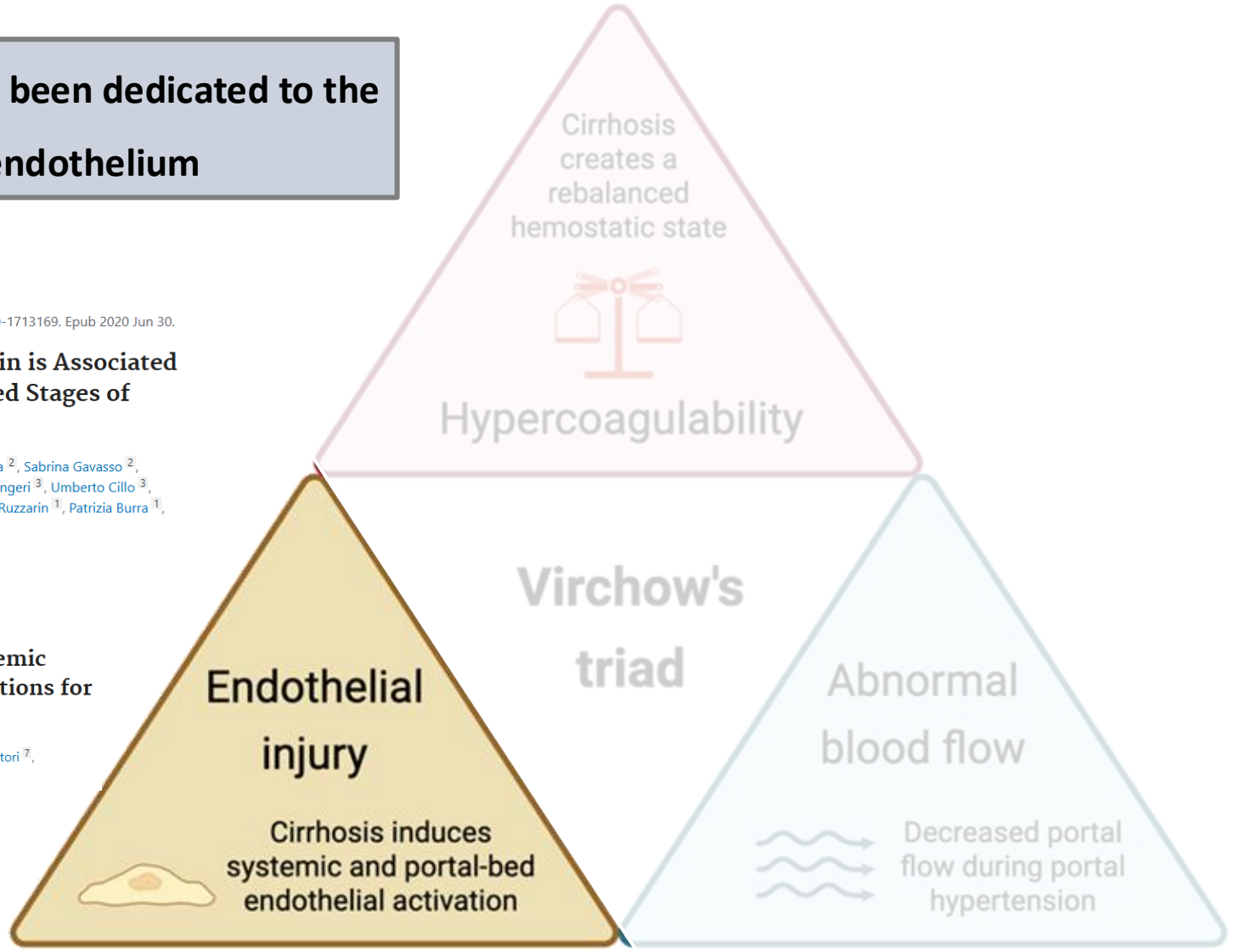
Endothelial Damage of the Portal Vein is Associated with Heparin-Like Effect in Advanced Stages of Cirrhosis

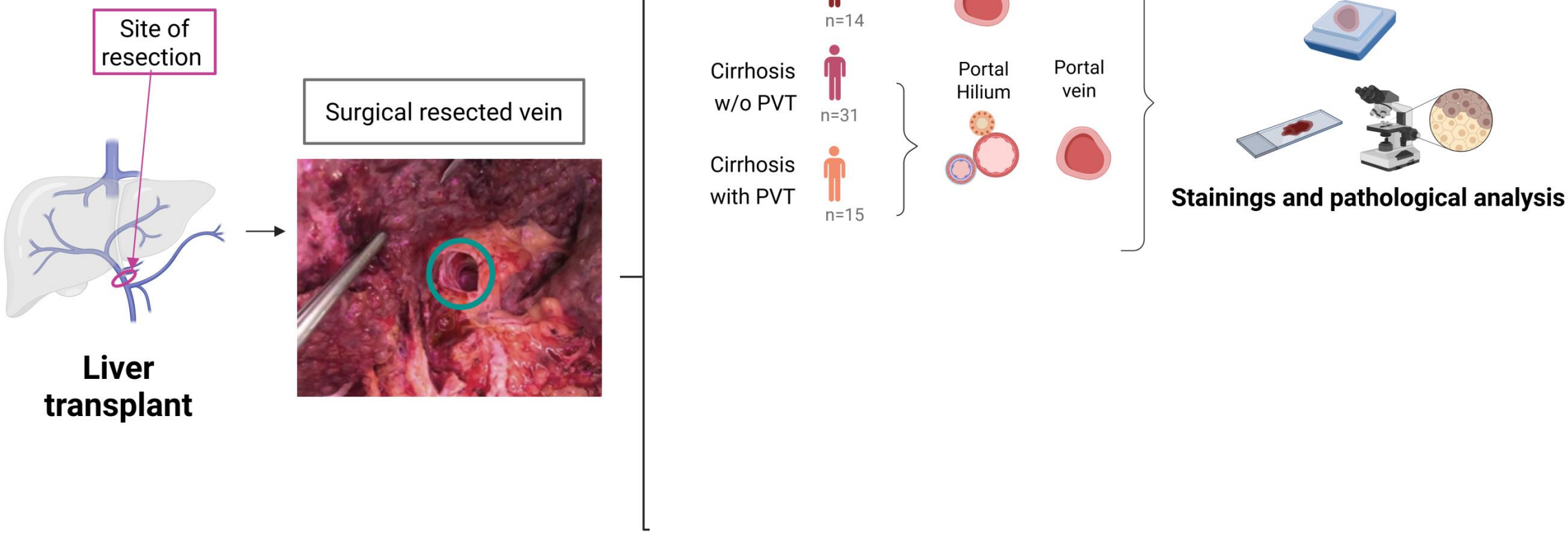
Sarah Shalaby [# 1], Paolo Simioni [# 2], Elena Campello [2], Luca Spiezia [2], Sabrina Gavasso [2], Debora Bizzaro [1], Romilda Cardin [1], Francesco D'Amico [3], Enrico Gringeri [3], Umberto Cillo [3], Giulio Barbiero [4], Michele Battistel [4], Alberto Zanetto [1], Alessandro Ruzzarin [1], Patrizia Burra [1], Marco Senzolo [1]

Observational Study › Clin Transl Gastroenterol. 2020 Feb;11(2):e00123. doi: 10.14309/ctg.0000000000000123.

Von Willebrand and Factor VIII Portosystemic Circulation Gradient in Cirrhosis: Implications for Portal Vein Thrombosis

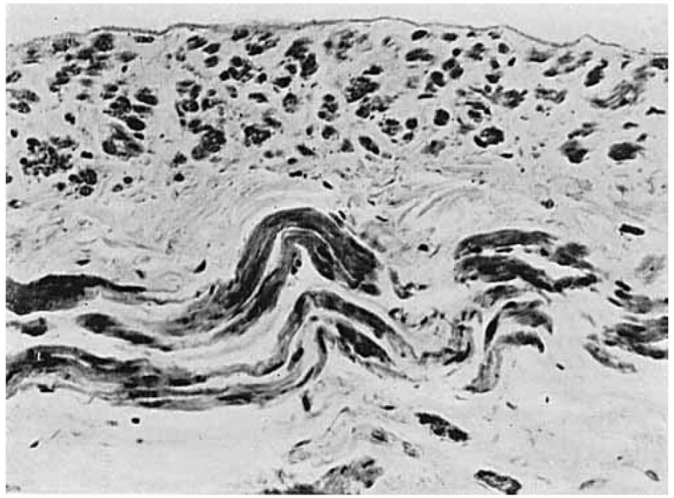
Michael Praktiknjo [1], Jonel Trebicka [2 3 4], Roberto Carnevale [5 6], Daniele Pastori [7], Alexander Queck [2], Evaristo Ettorre [8], Francesco Violi [6 7]




Site of resection
Liver transplant
Surgical resected vein
Donors
n=14
Portal vein
Cirrhosis w/o PVT
n=31
Cirrhosis with PVT
n=15
Portal Hilium
Portal vein
Stainings and pathological analysis

Histopathology of PVT

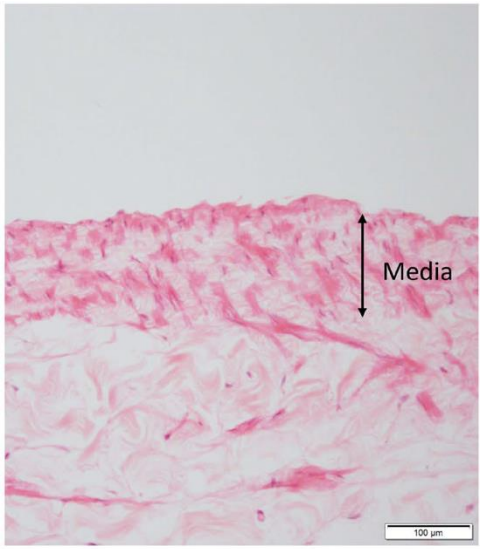
Normal portal vein



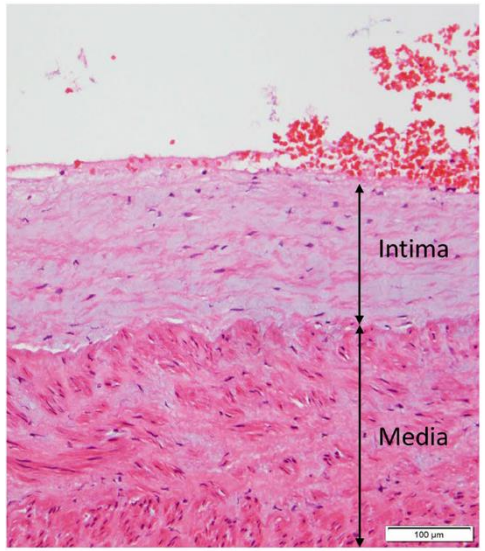
Portal vein in cirrhosis

Pei-Lin Li. Journal of Pathology 1940

Portal vein from donor

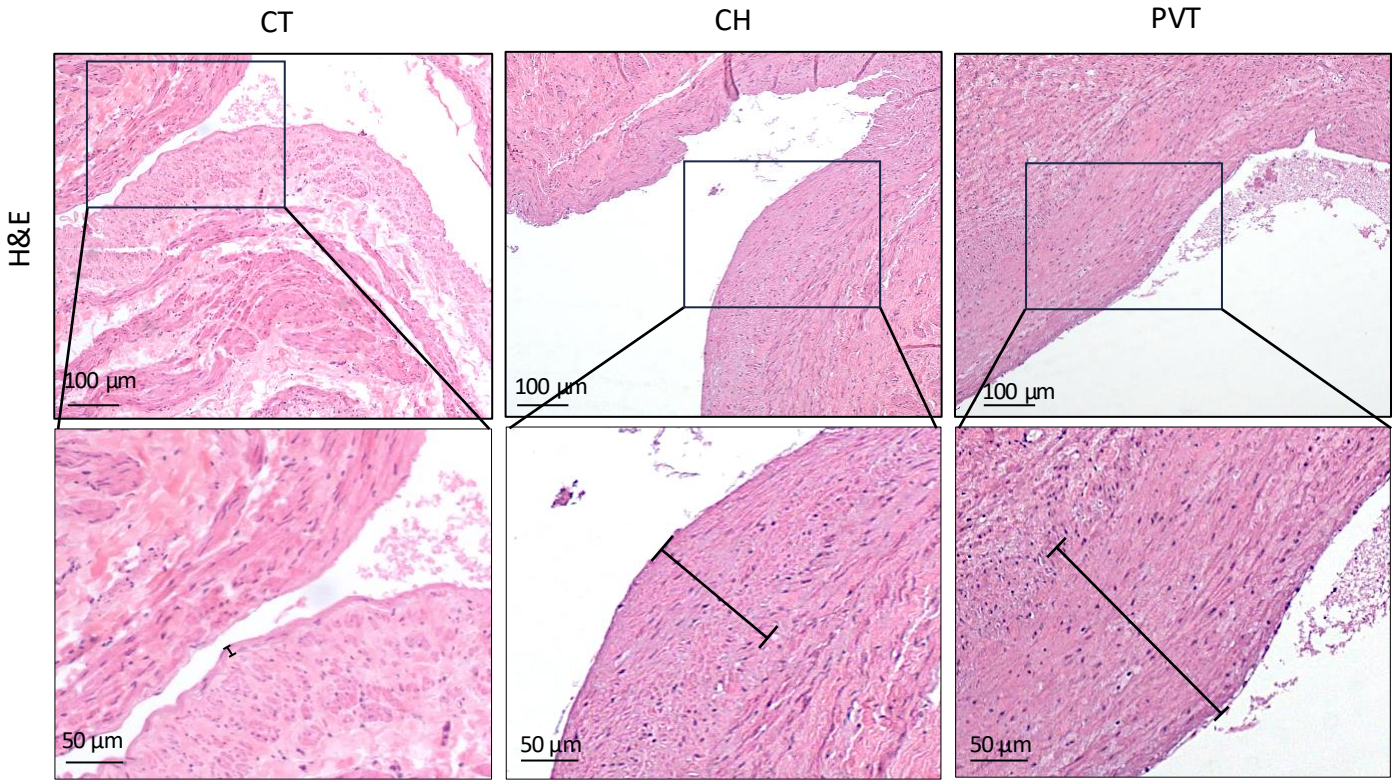


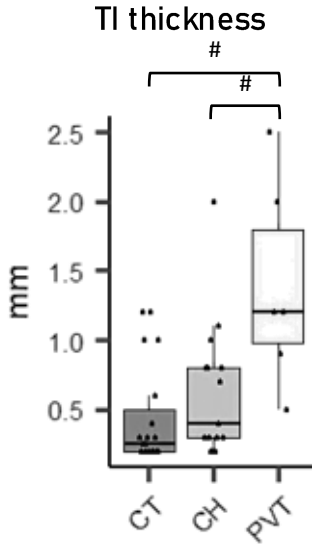
Portal vein from PVT

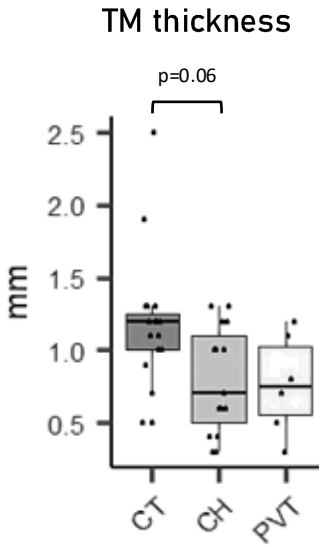


Driever et al. Hepatology. 2022

Cirrhosis remodels portal vein wall



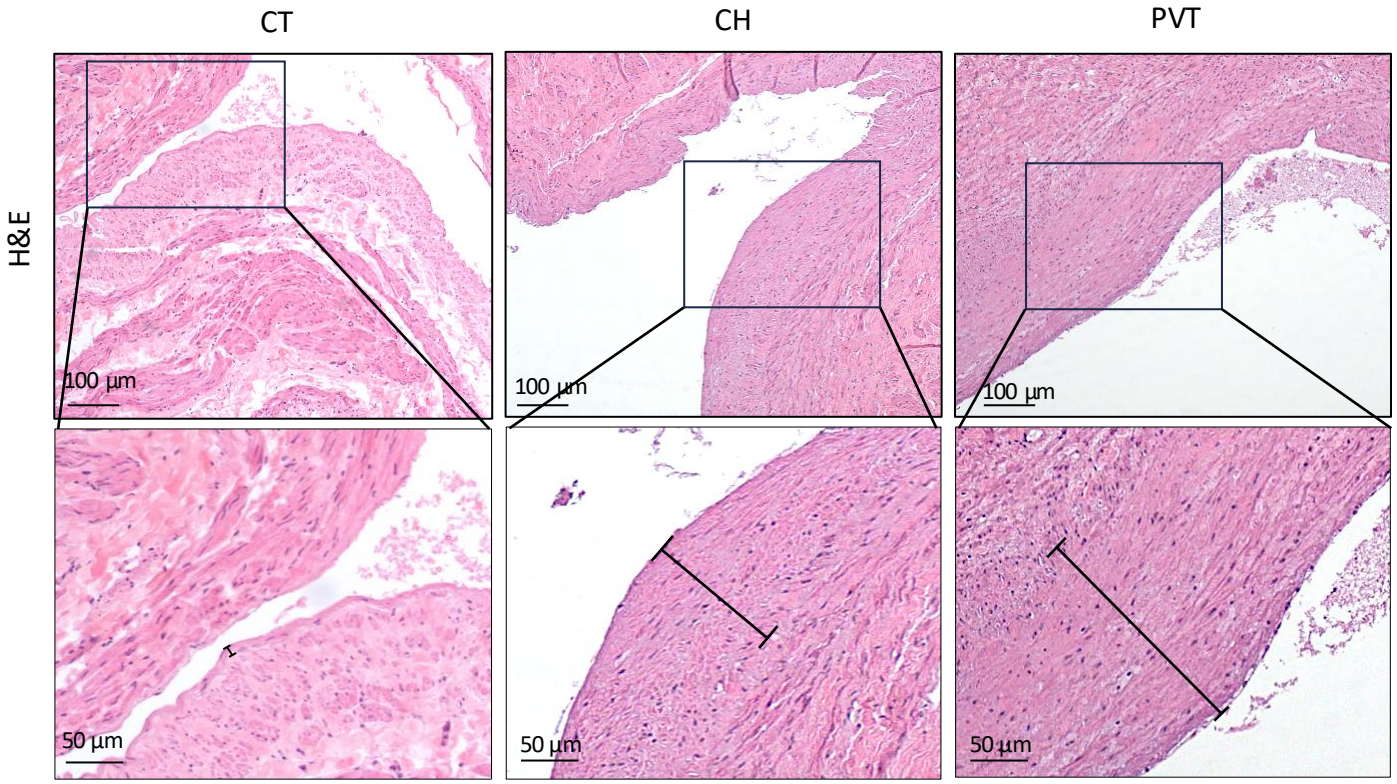


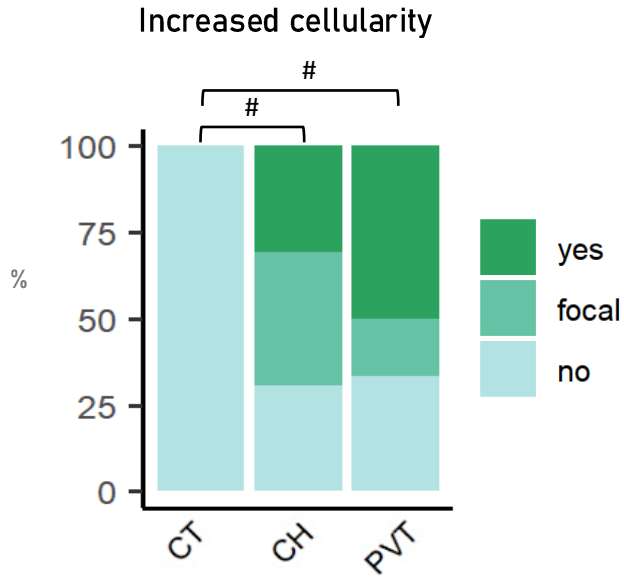


Anatomic changes of portal vein during cirrhosis:

- Increase tunica intima (TI) thickness with a decrease the thickness of tunica media (TM)

Cirrhosis remodels portal vein wall

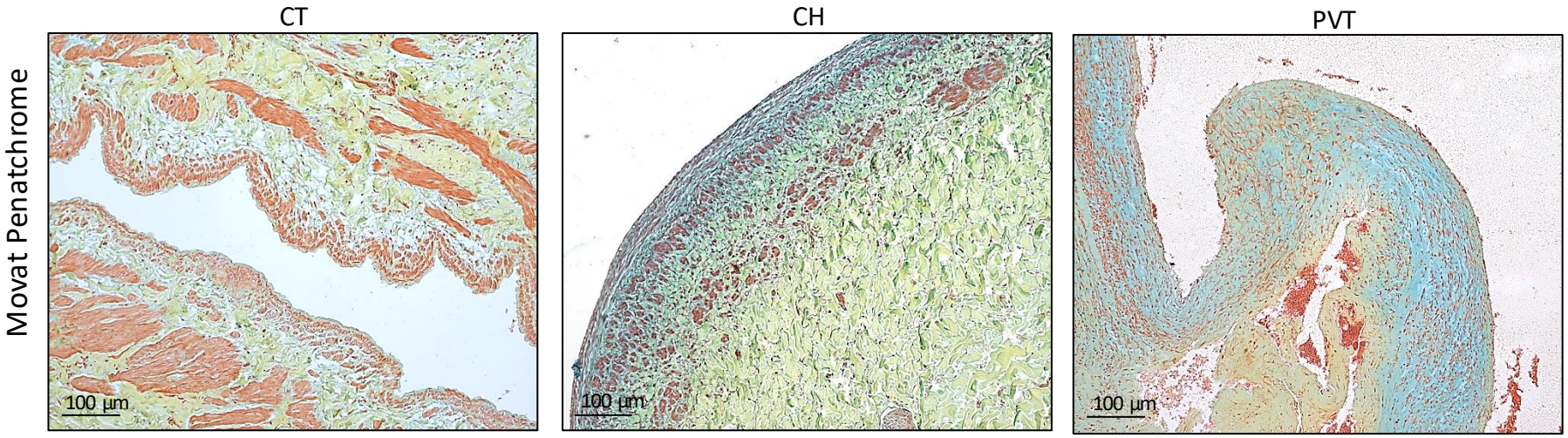




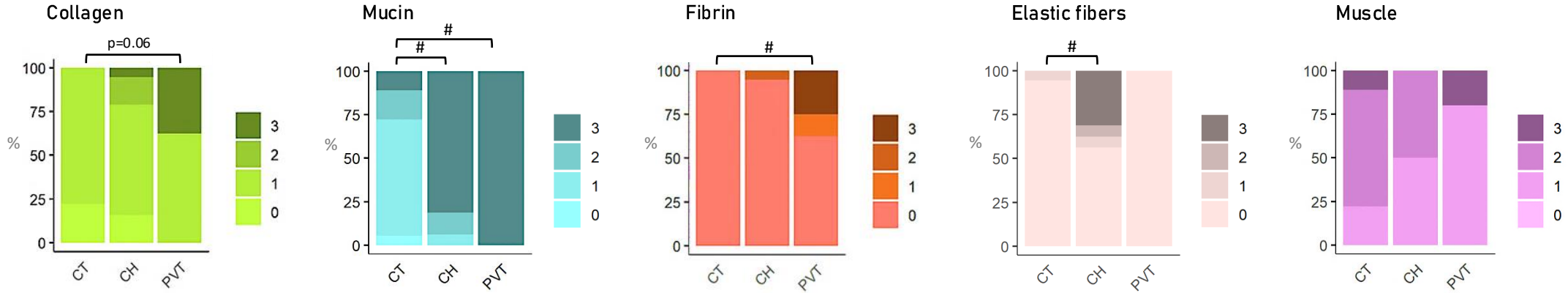
Anatomic changes of portal vein during cirrhosis:

- Increase tunica intima (TI) thickness with a decrease the thickness of tunica media (TM)
- Increase cellularity in the TI
- Acellular material

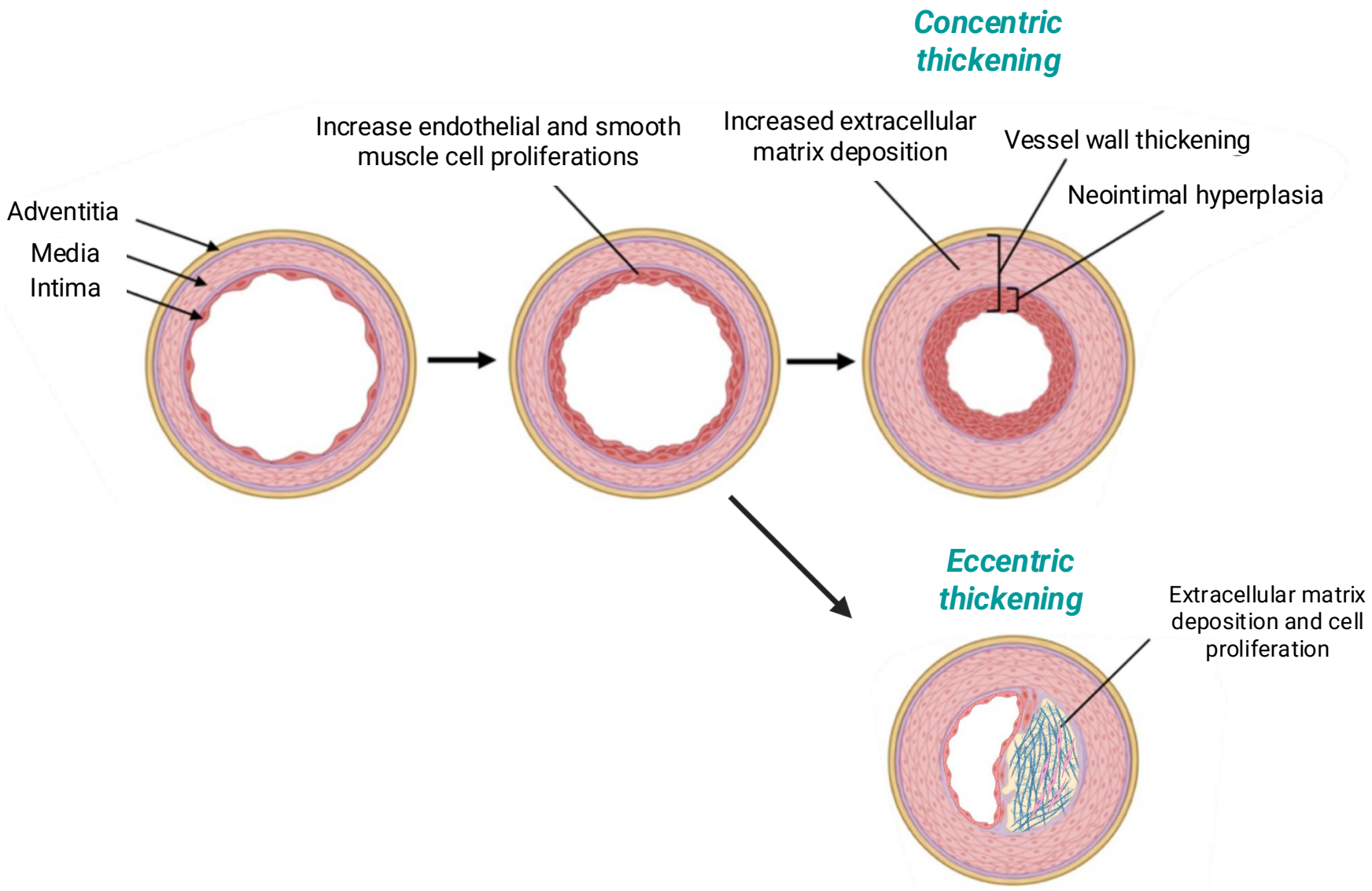
Cirrhosis remodels portal vein wall



Prominent mucin accumulation with changes in collagen, fibrin, elastin content in the subendothelial layer

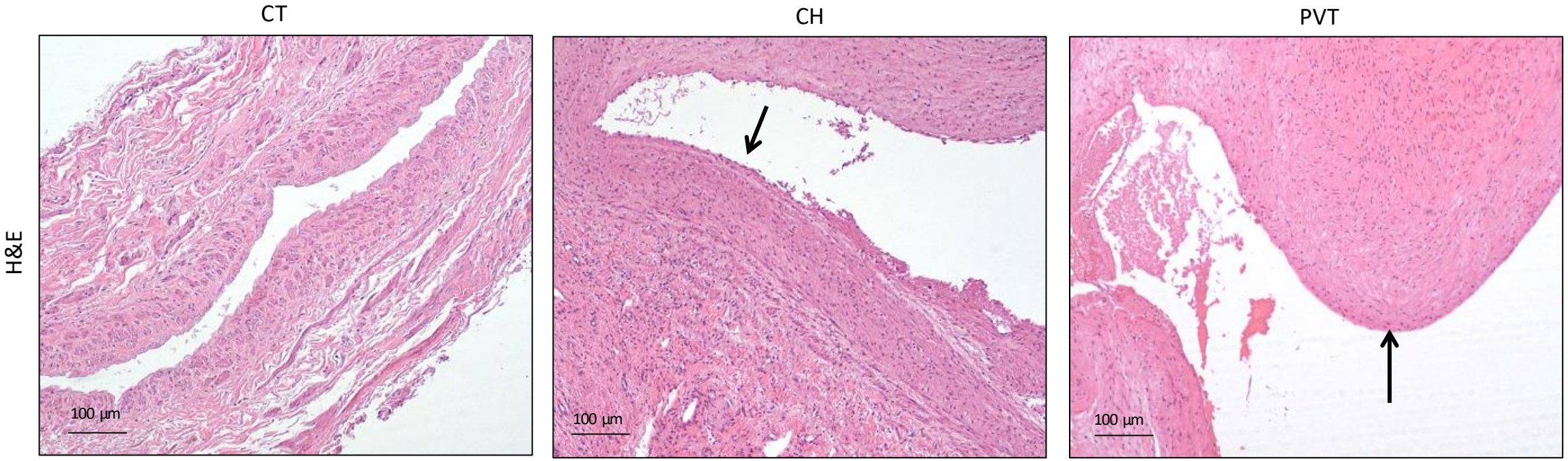


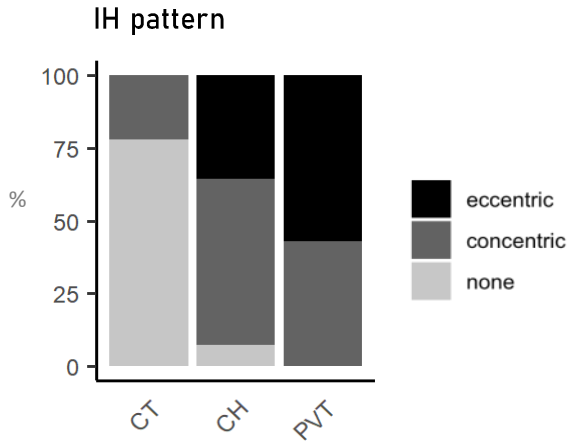
Vascular remodeling: the pattern of intimal hyperplasia



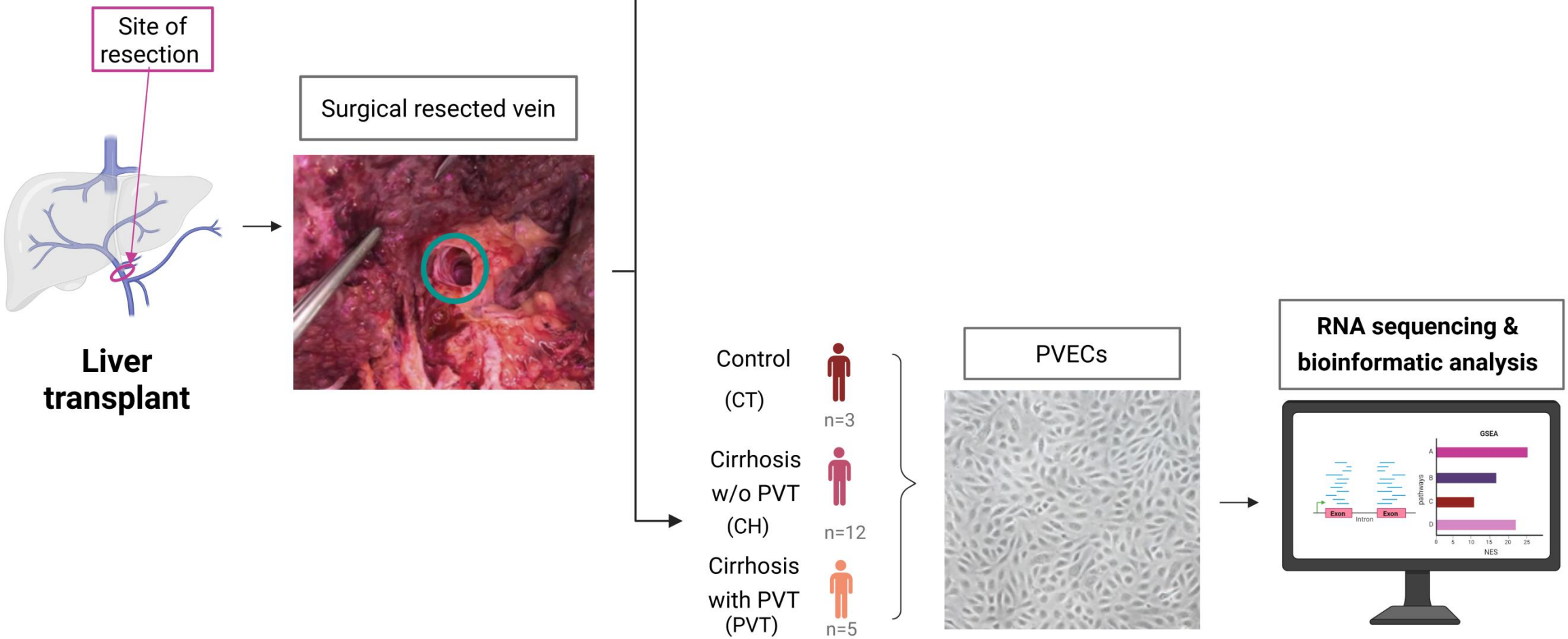
Adapted from Heng EE, et al. Vessel Plus. 2023

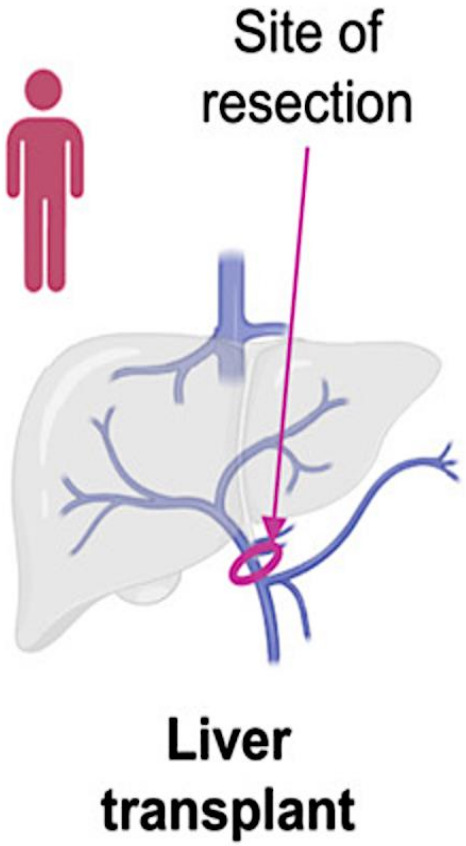
PV showed an eccentric intimal hyperplasia



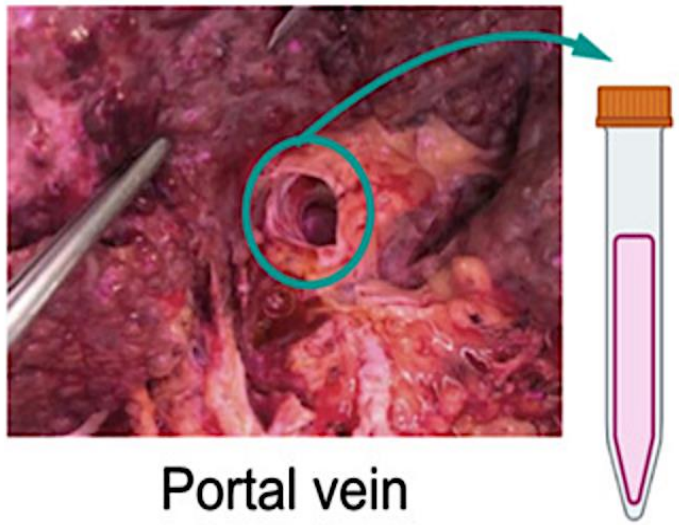


PVT: more advanced stage with more pronounced anatomical changes and eccentric thickening


Site of resection
Liver transplant
Surgical resected vein
Control (CT)
n=3
Cirrhosis w/o PVT (CH)
n=12
Cirrhosis with PVT (PVT)
n=5
PVECs
RNA sequencing & bioinformatic analysis
GSEA
Exon
Intron
Exon
pathways
A
B
C
D
0
5
10
15
20
25
NES



Surgically resected vein

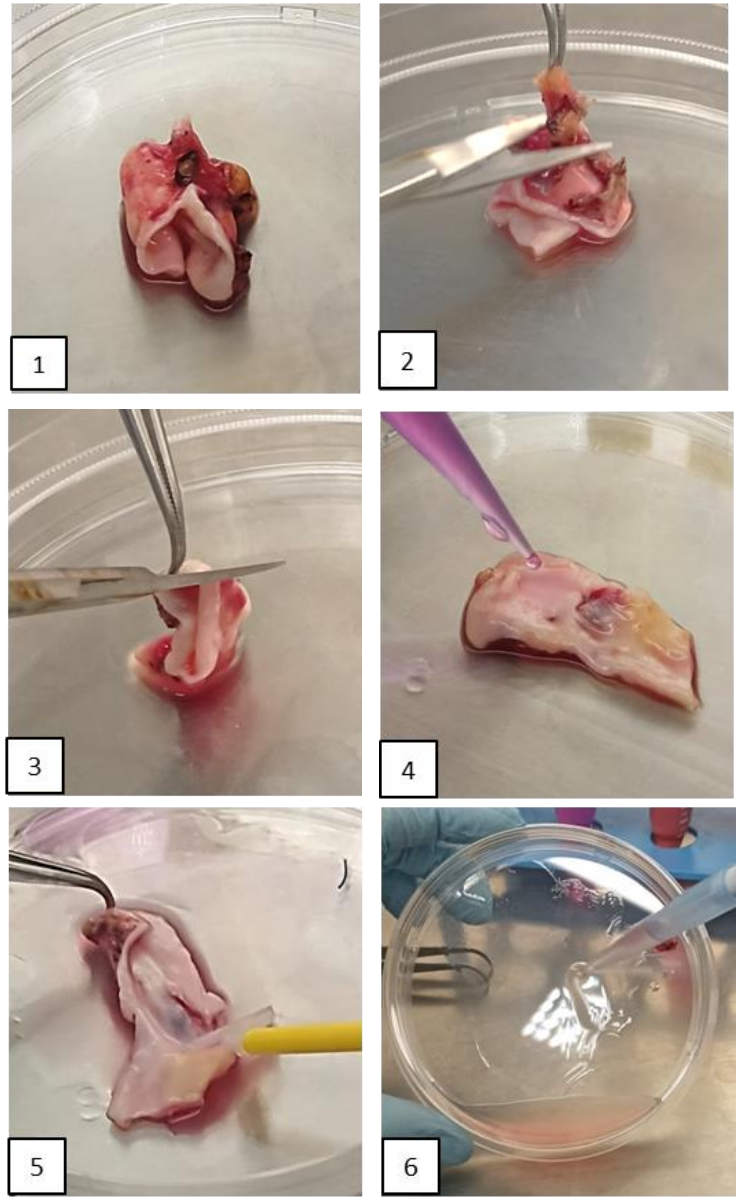


Portal vein

&

Inferior cava vein

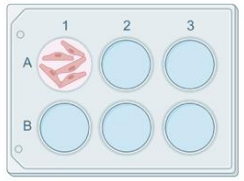
Isolation of cells from
human portal vein tissue



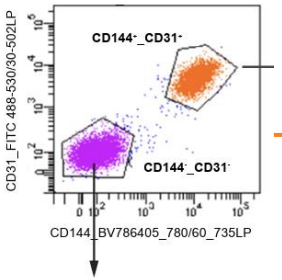
Human PVECs isolation

Trypsinization and cell scrapping

Cell expansion

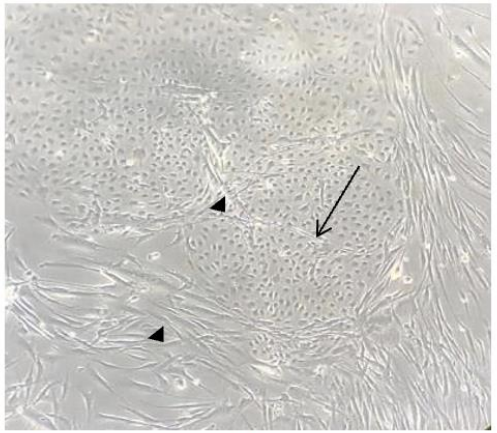


Endothelial cell purification by FACS sorting

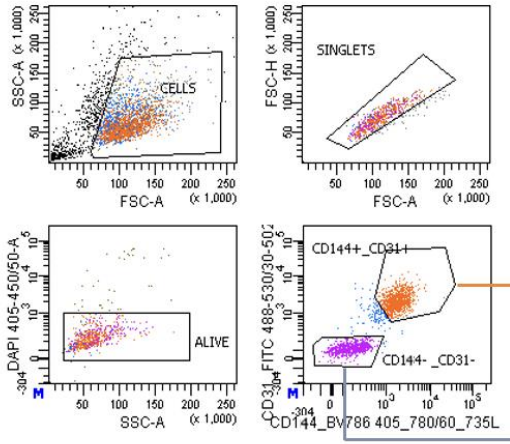


Non-EC

Mix of cells after isolation

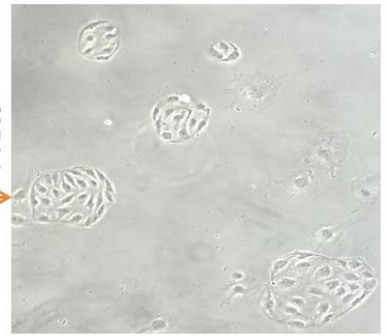


Purification by FACS

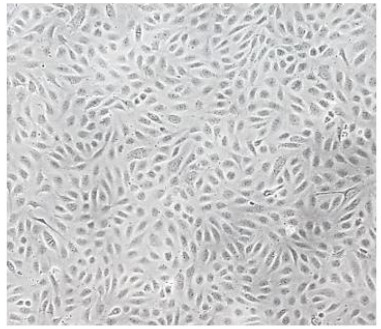


CD144, CD31

PVECs growing in small colonies

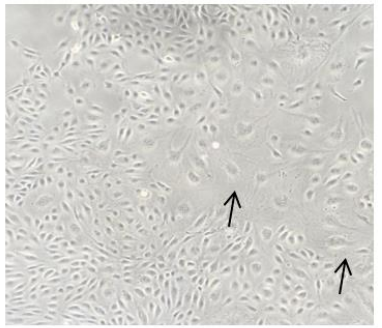


Monolayer of PVECs passage 1

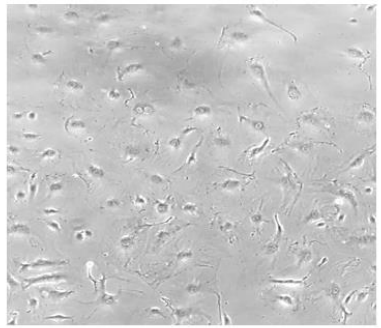


PVECs

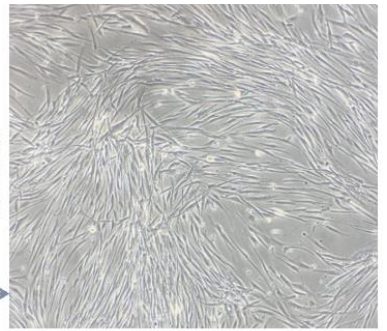
PVECs passage 6 - senescence onset



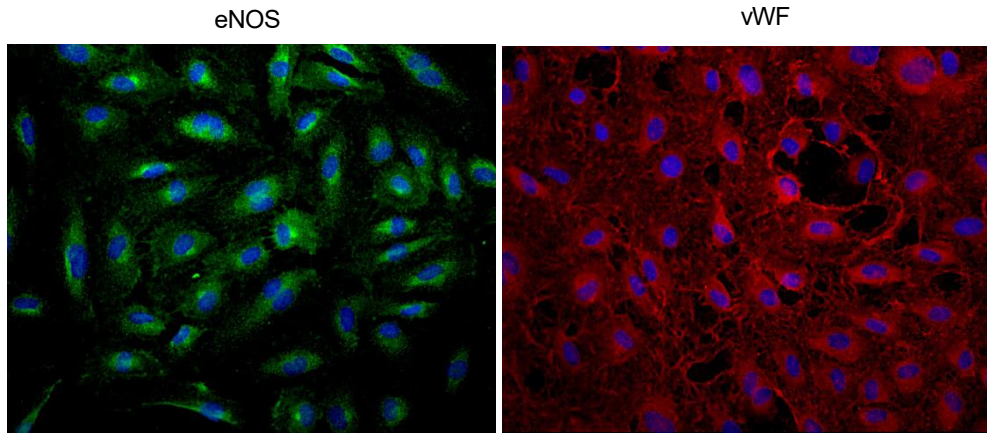
PVECs passage 9 - senescence

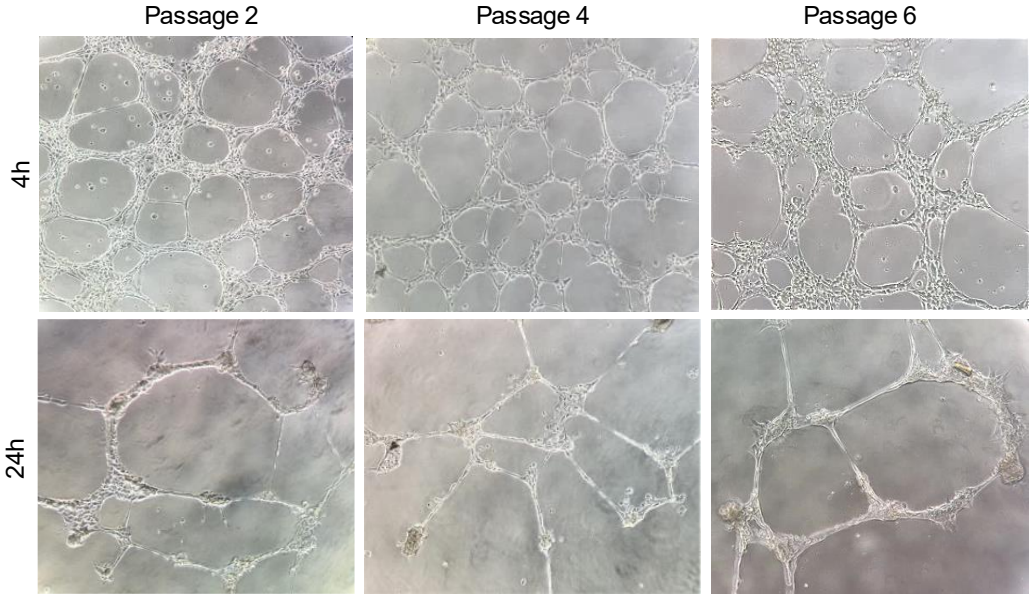


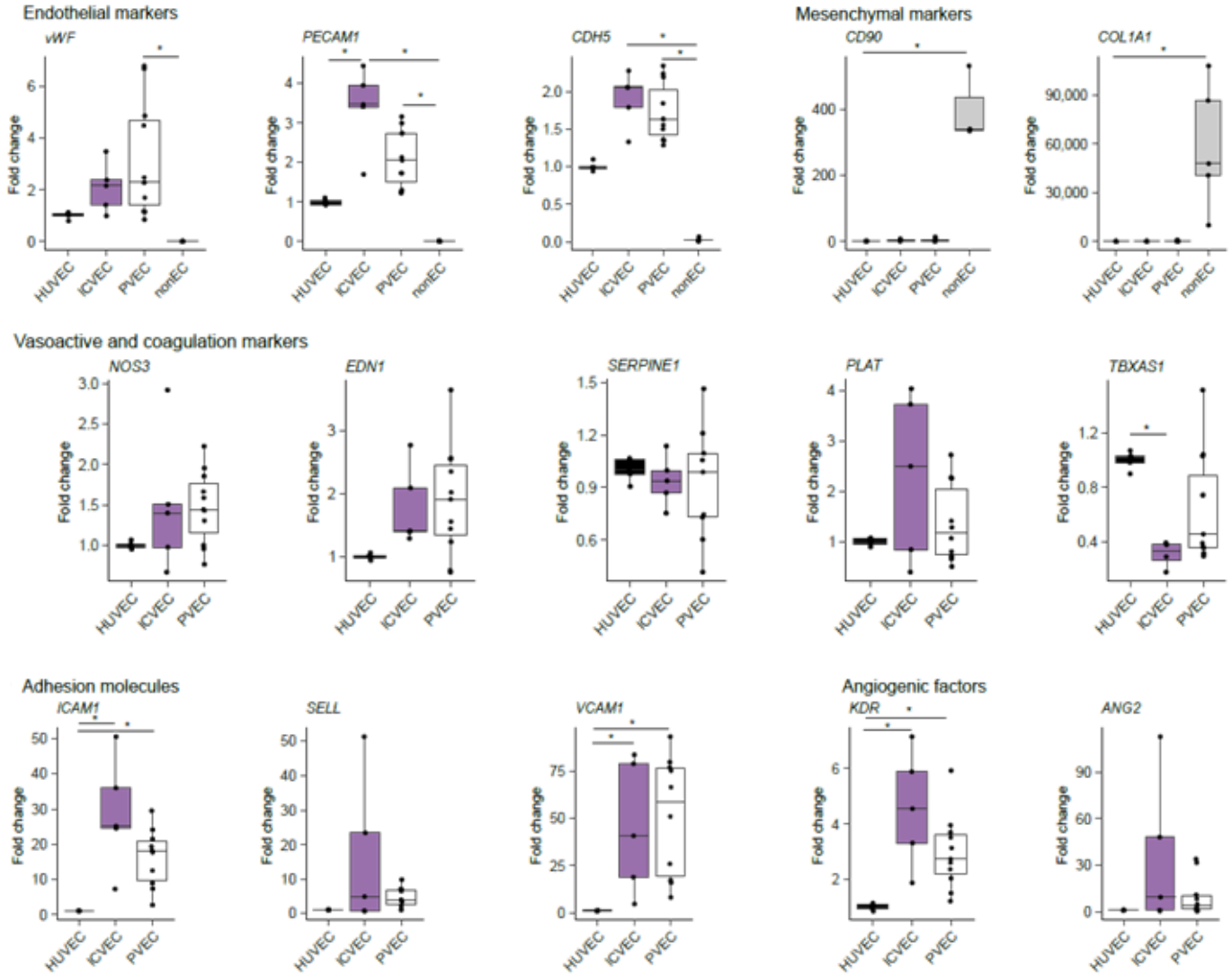
non-ECs



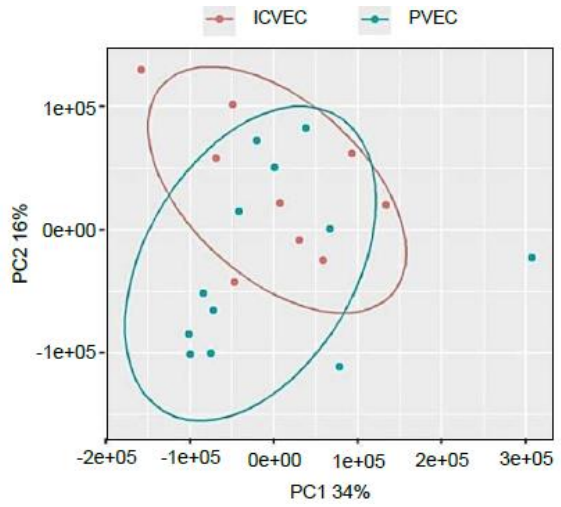
Isolated human PVECs display characteristic endothelial features

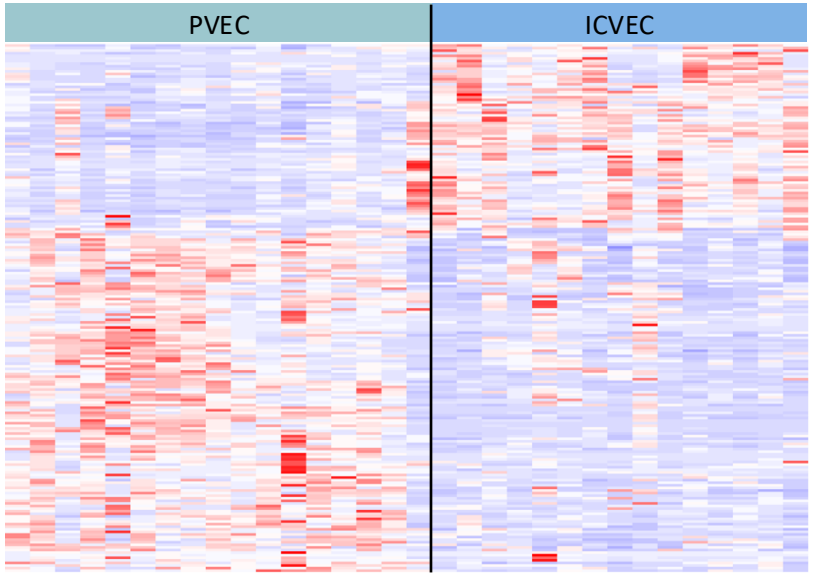




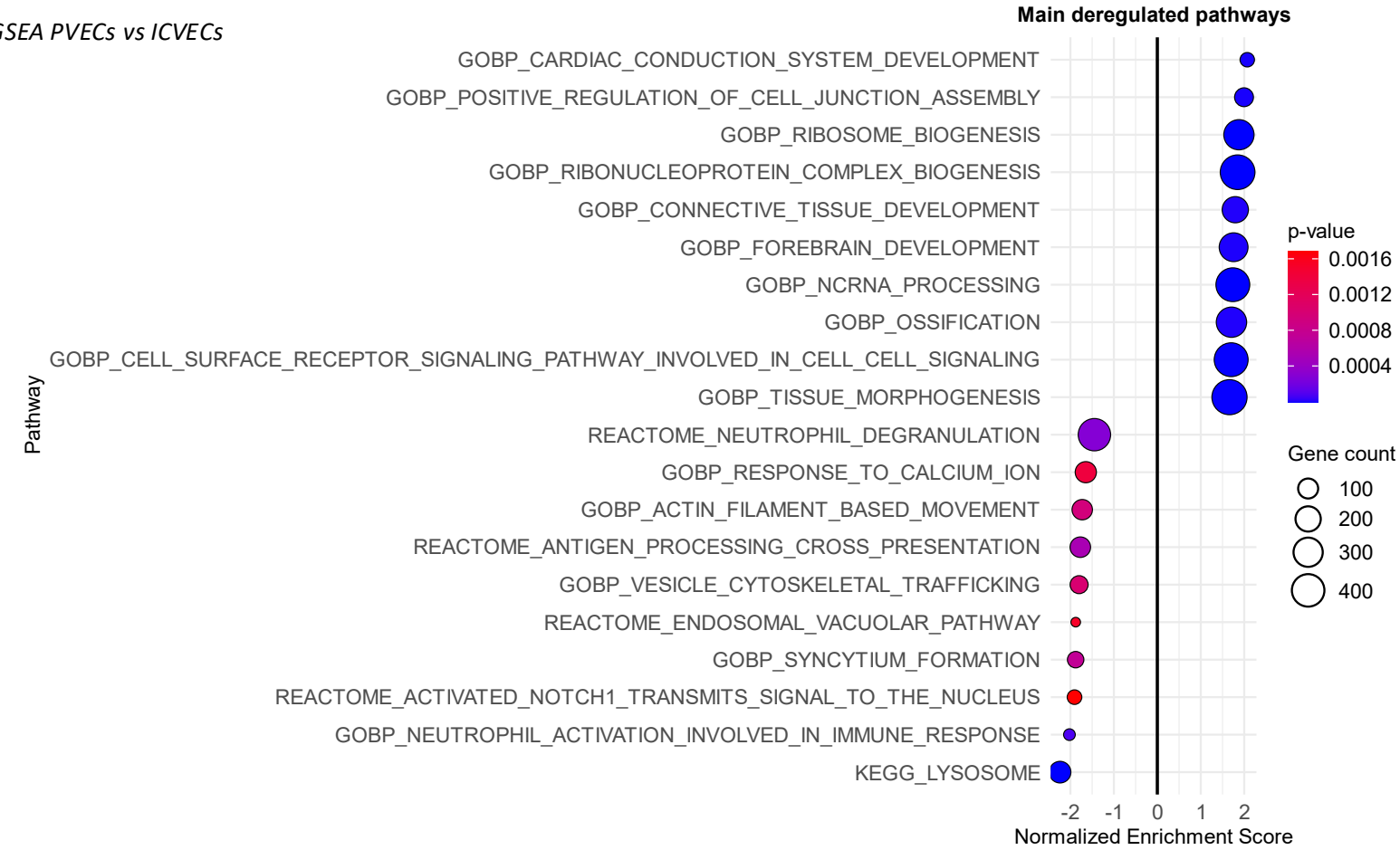


RNAseq:
PVECs are transcriptomically distinct from systemic venous ECs



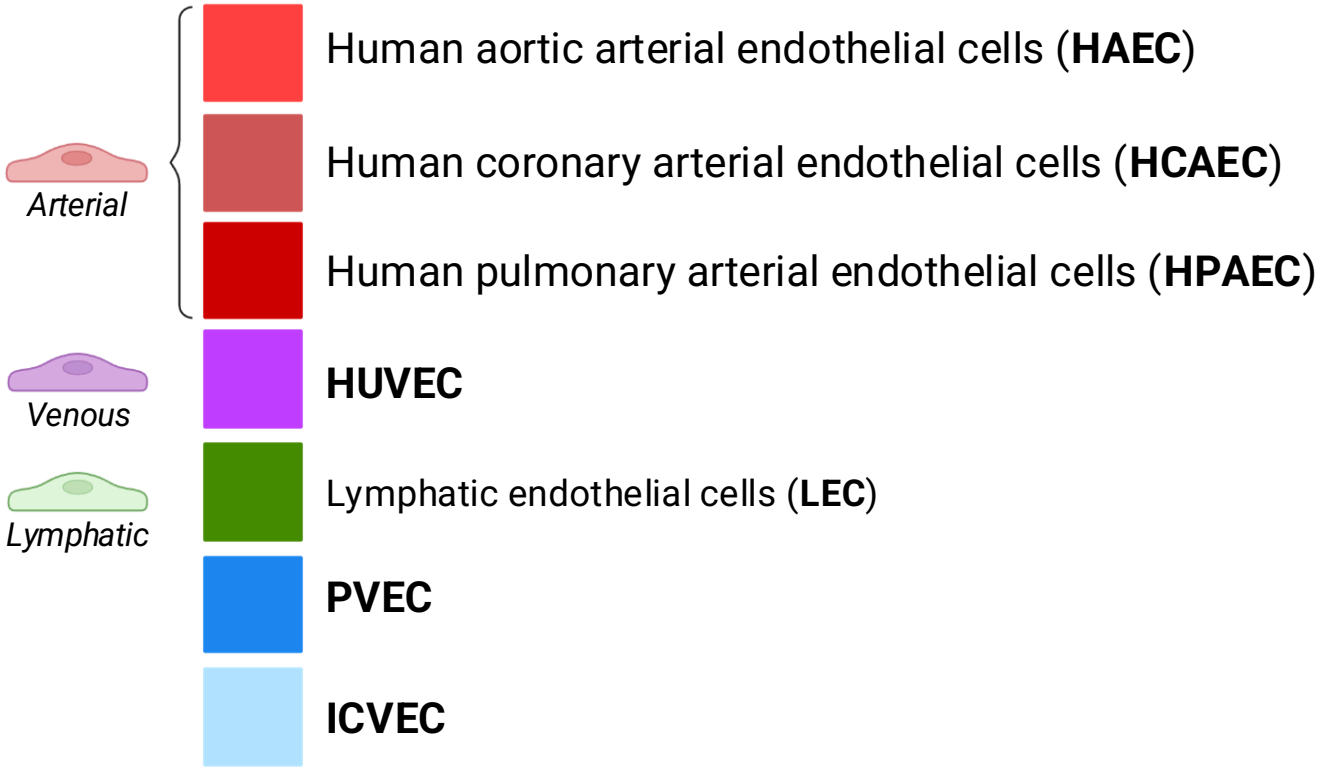


GSEA PVECs vs ICVECs

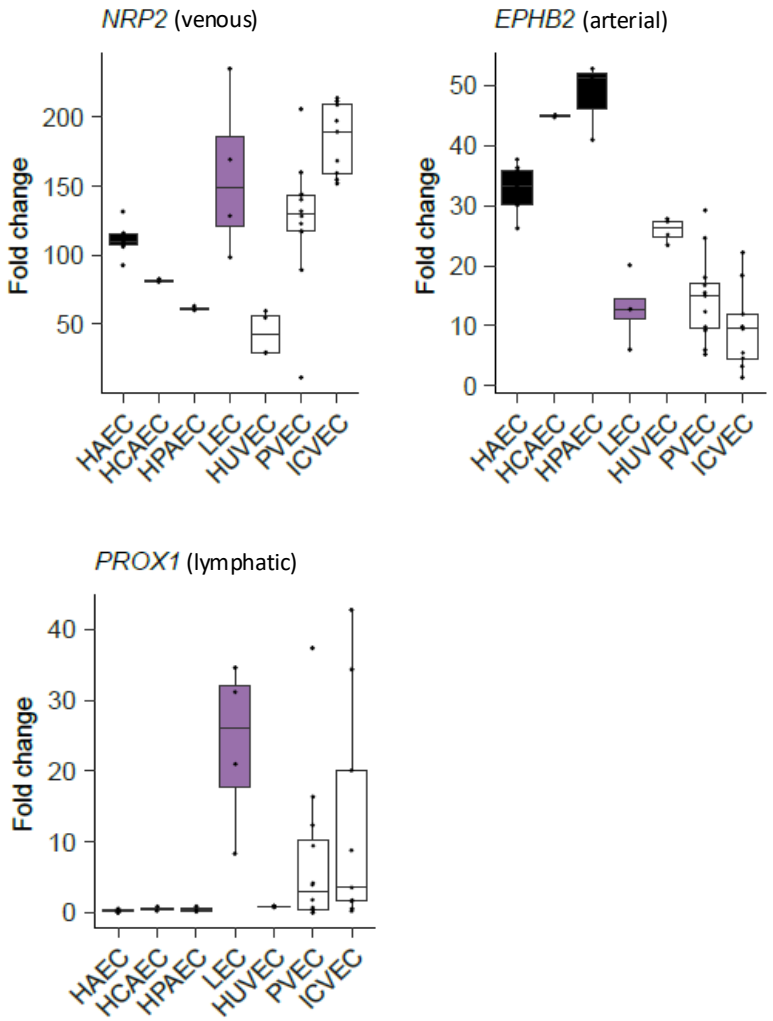


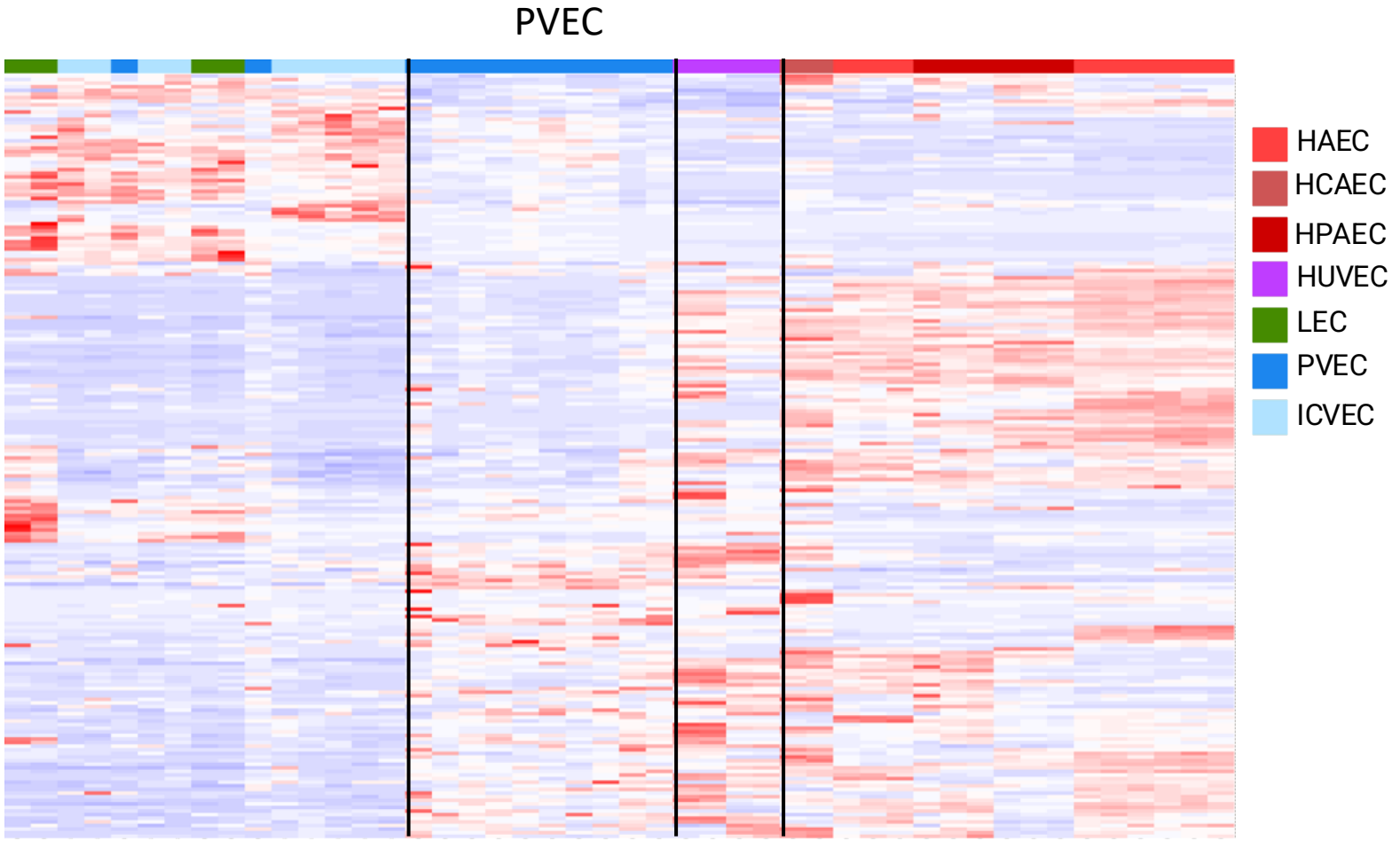
Enriched pathways in PVECs: biosynthesis, structural remodelling and repair, stress response and immunity

Positioning PVECs across vascular beds



Positioning PVECs across vascular beds

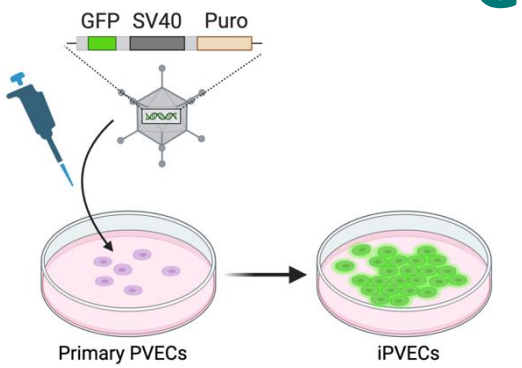




DEG heatmap across beds:

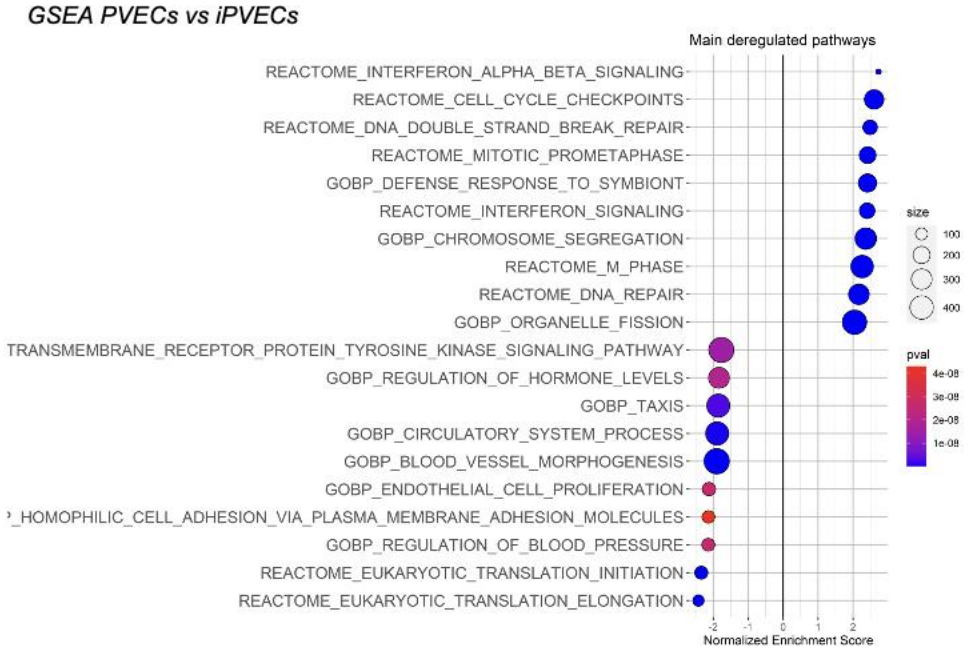
- Arterial ECs cluster together
- LECs and ICVECs cluster together
- PVECs cluster closest to HUVEC and as intermediate cluster

Generation of iPVECs: Novel biological tool for the study of splanchnic pathophysiology

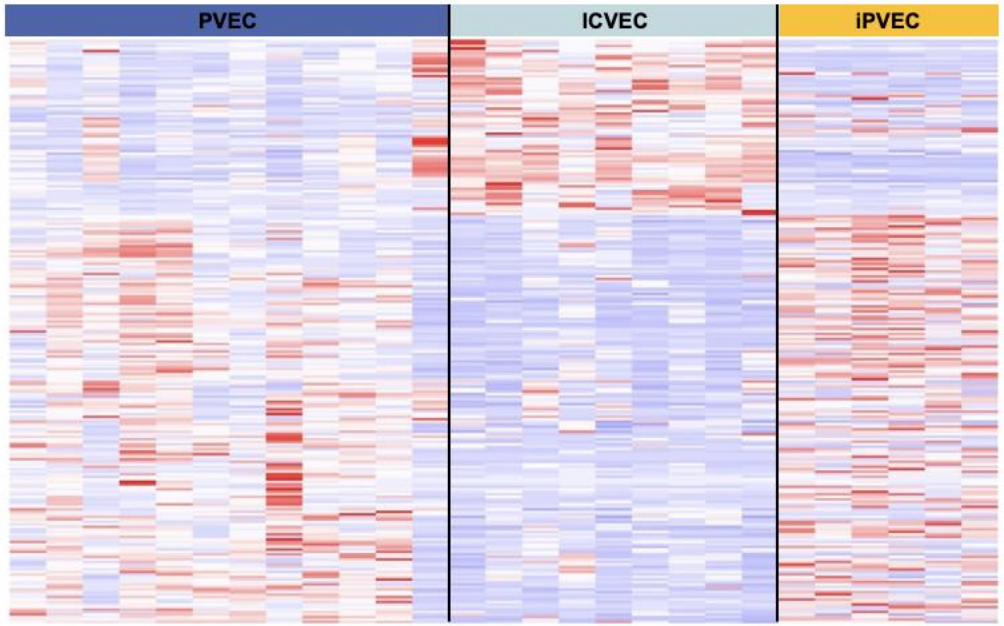


iPVECs preserve EC identity and key functions
iPVECs maintain their distinctive gene expression profile

Immortalization-associated shifts enriched for cell cycle/ DNA repair /maintenance



PVEC vs ICVEC DEG set: iPVECs mirror PVEC profile and remain distinct from ICVEC

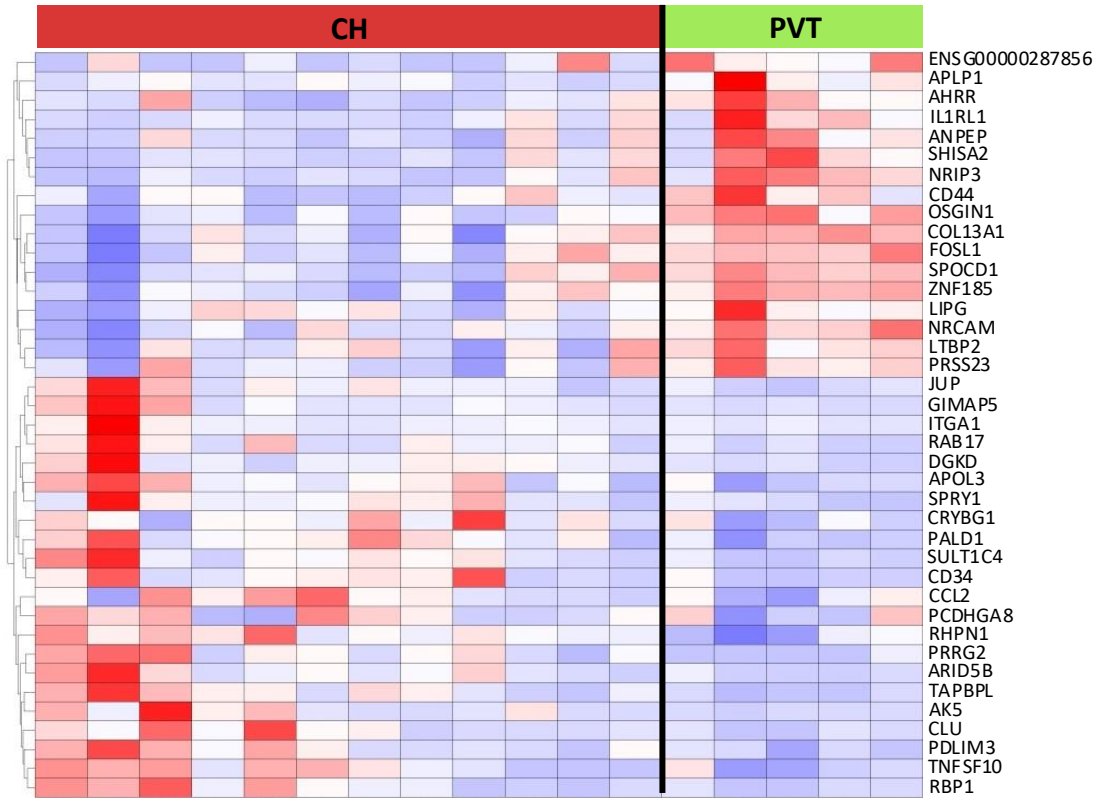


Anton A et al. JHEP Reports 2025

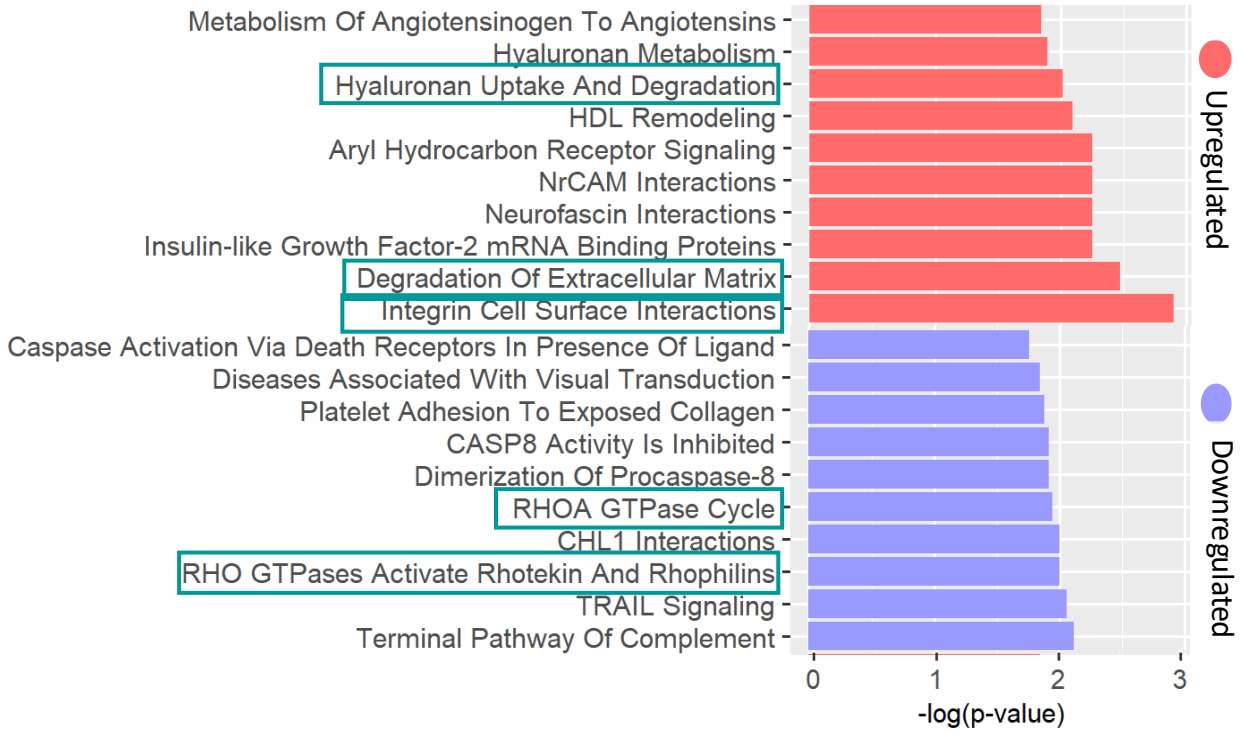
Are there transcriptomic differences between patients with and without PVT?

PVECs transcriptomic differences in PVT

DEGs



Enrichr

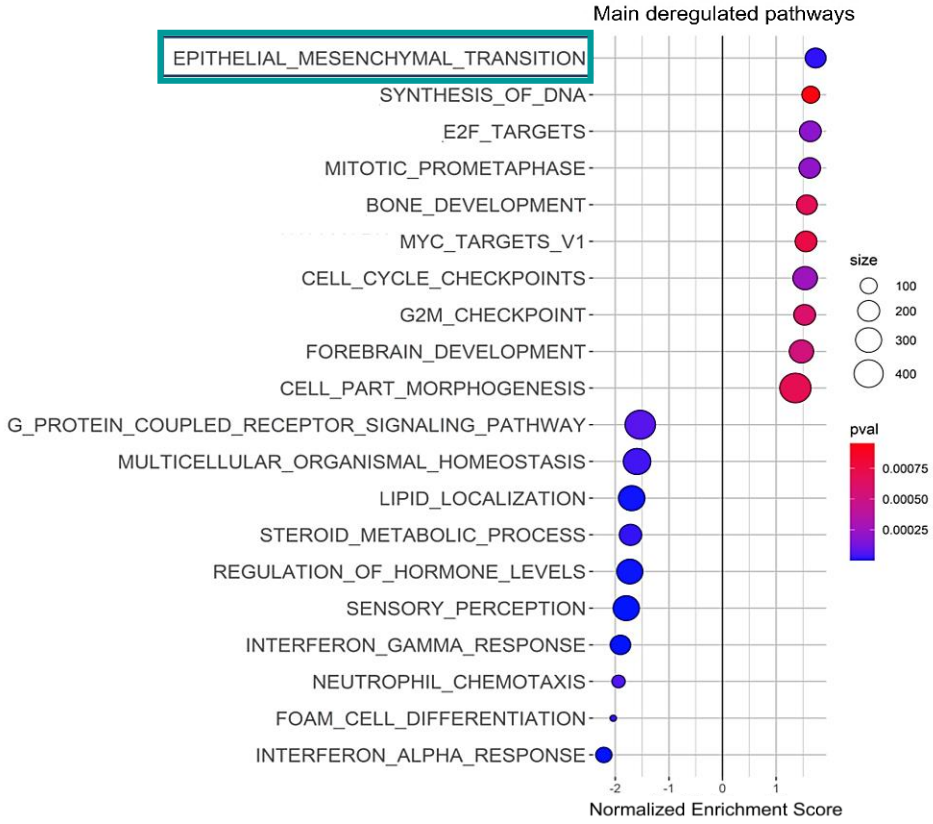


PVECs from patients with PVT present alterations in pathways and genes related with:

- ECM remodeling
- GTPase for cytoskeleton reorganization and vascular integrity

PVECs undergo EndMT in PVT

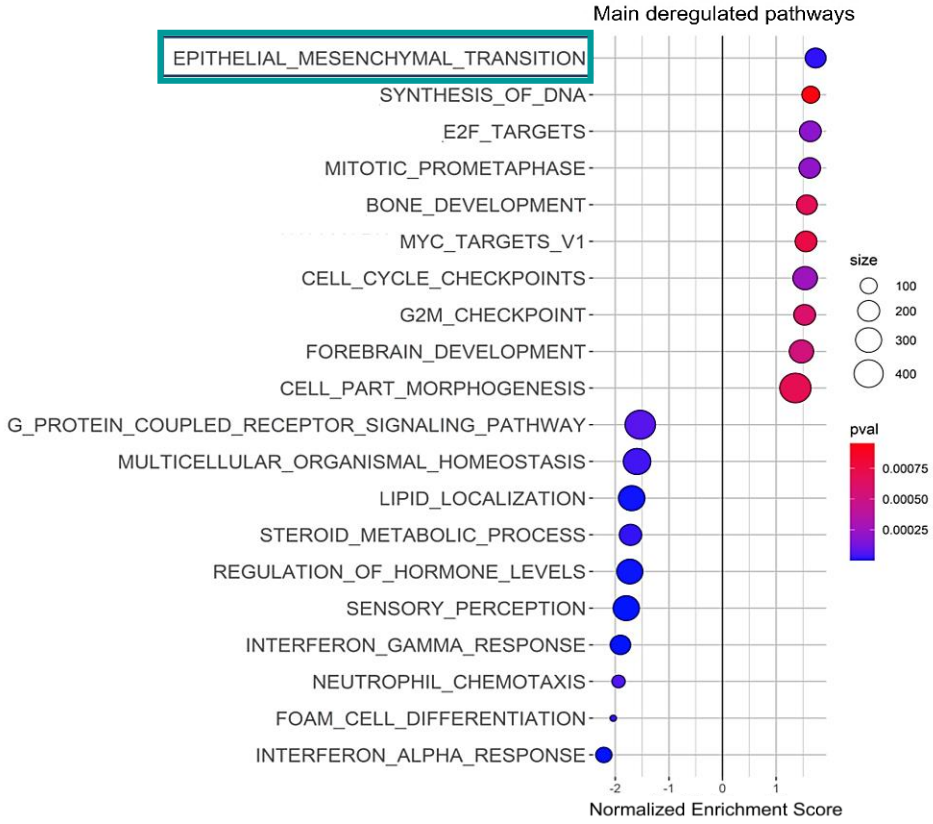
GSEA PVT cv CH:

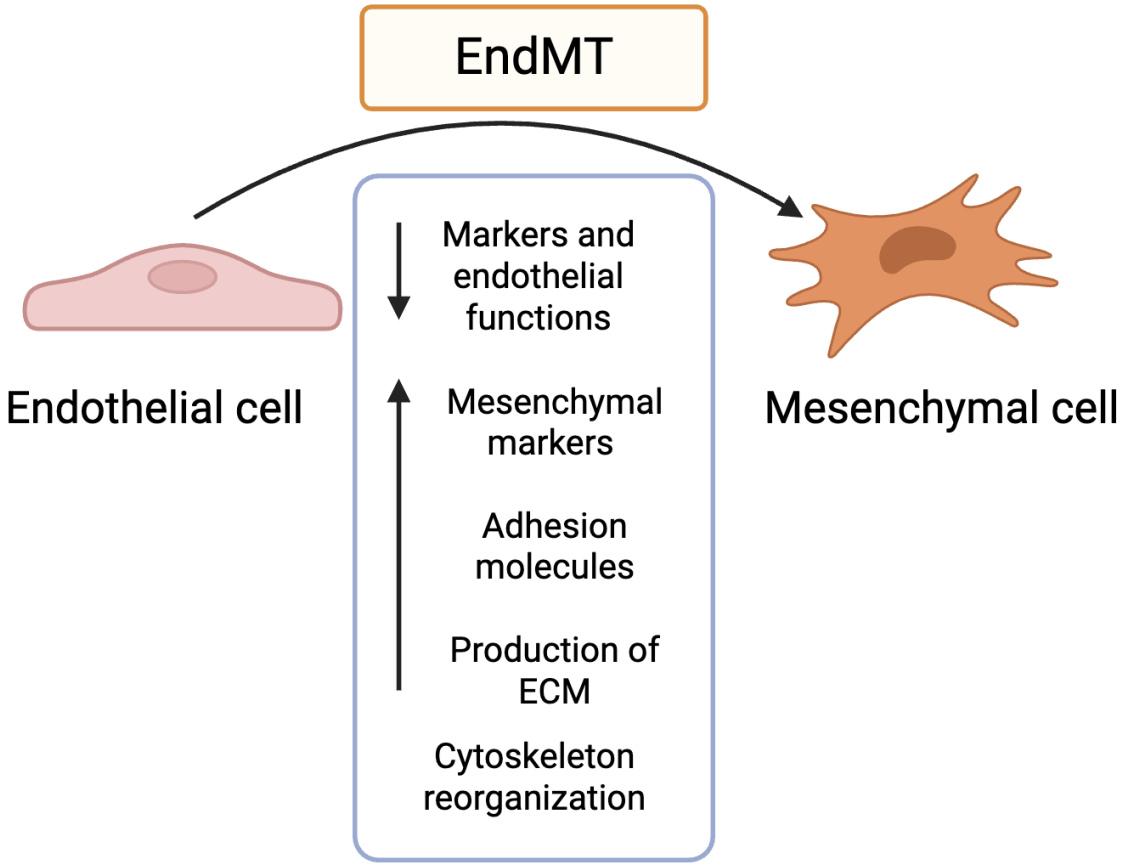


No alterations in hemostatic or coagulation factors were detected

PVECs undergo EndMT in PVT

GSEA PVT cv CH:





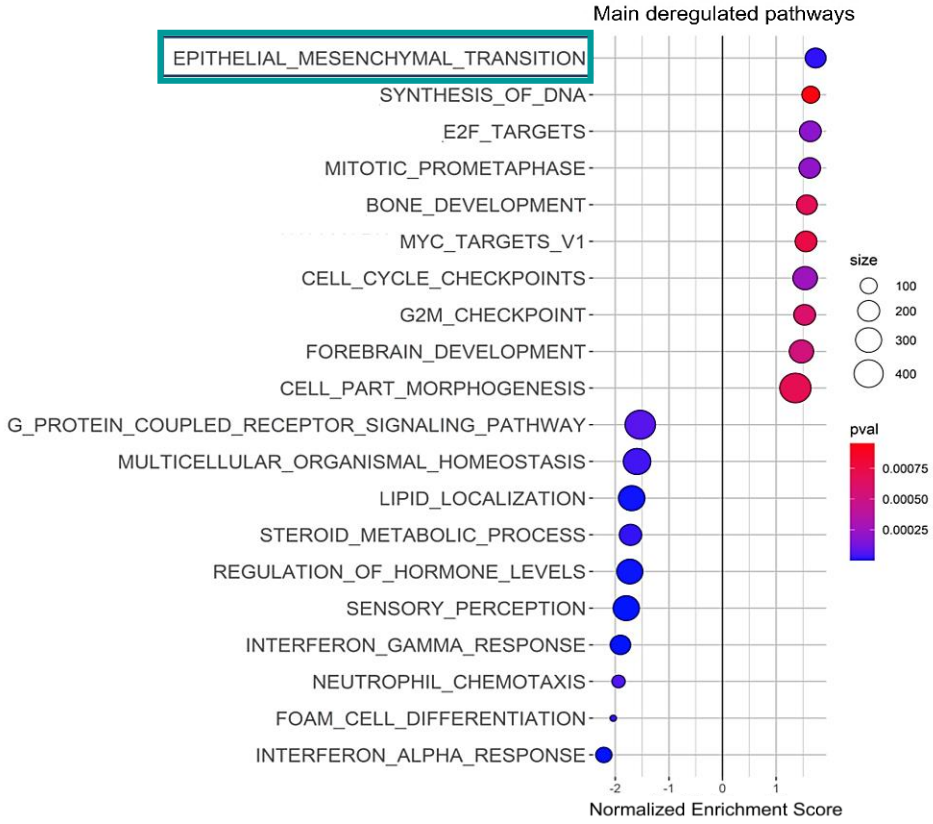
No alterations in hemostatic or coagulation factors were detected

No universal definition

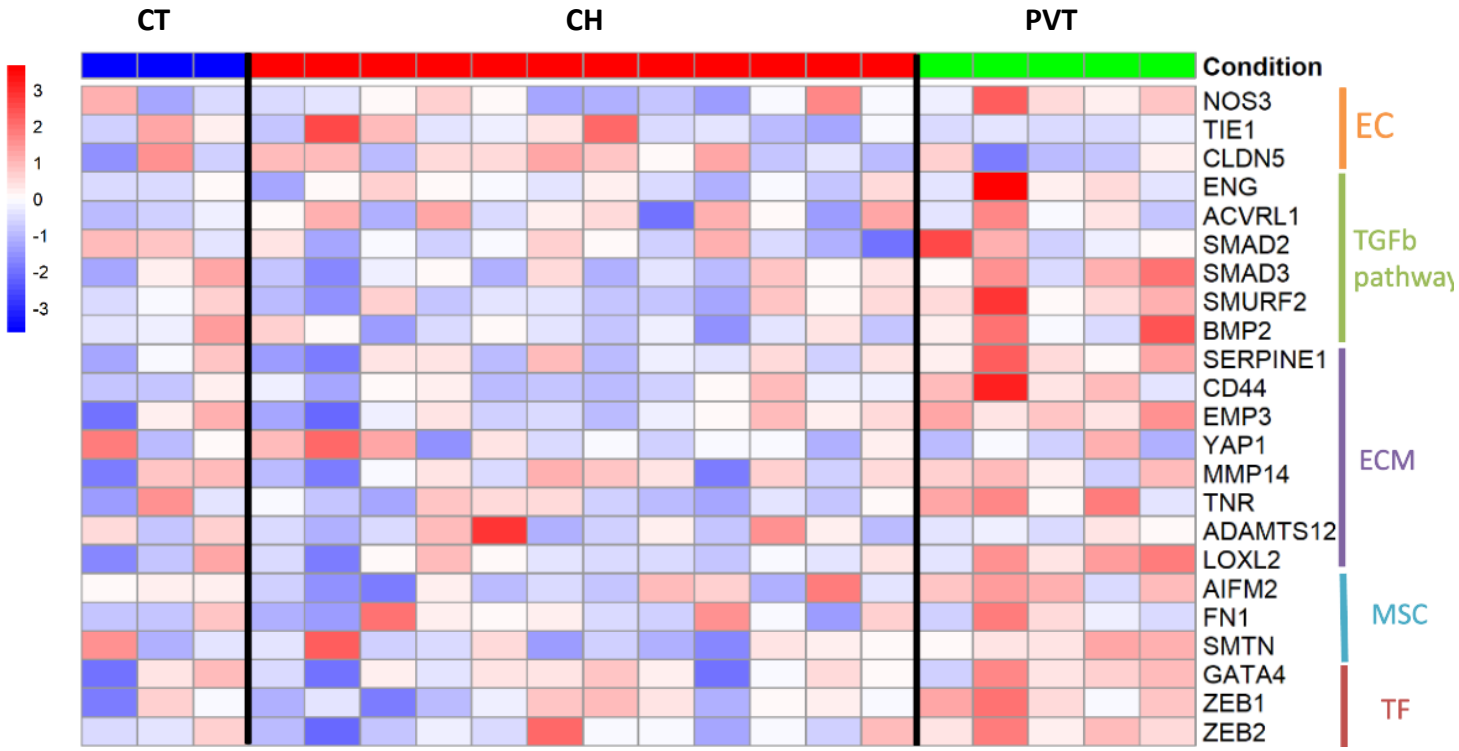
Transitioning state with multi-step changes

PVECs undergo EndMT in PVT

GSEA PVT cv CH:

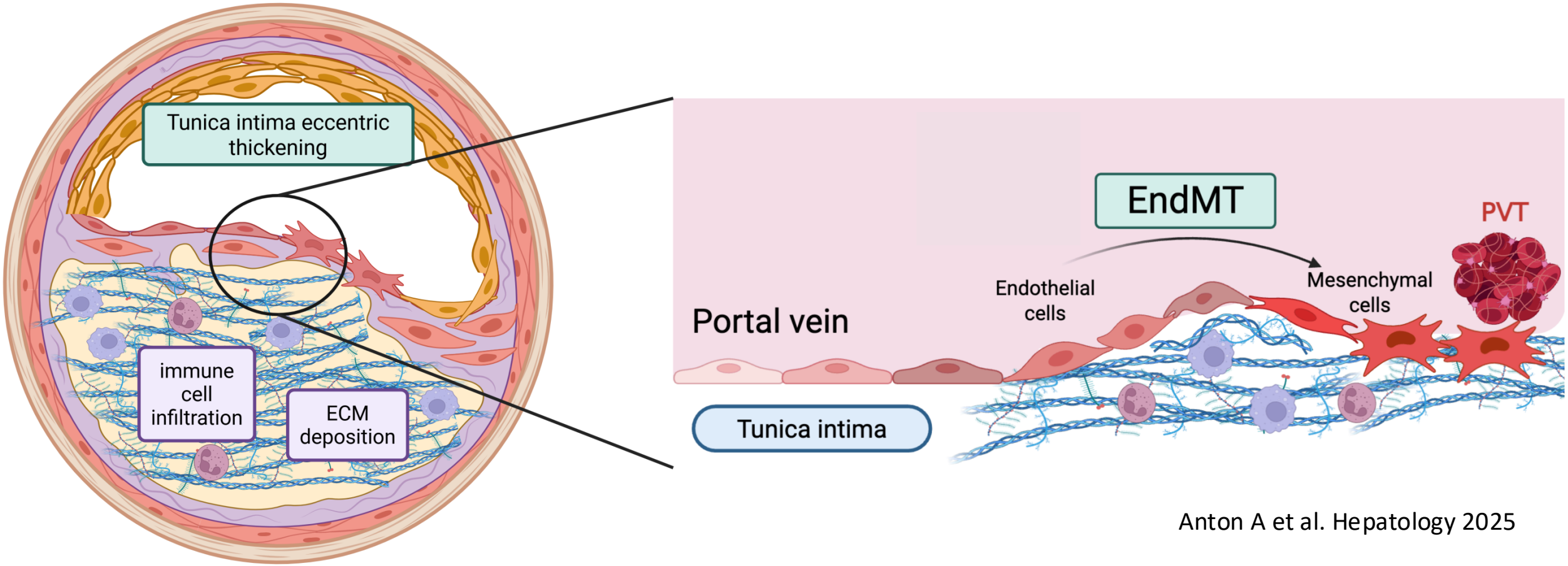


EndMT-associated genes



No alterations in hemostatic or coagulation factors were detected

Portal vein during cirrhosis and PVT



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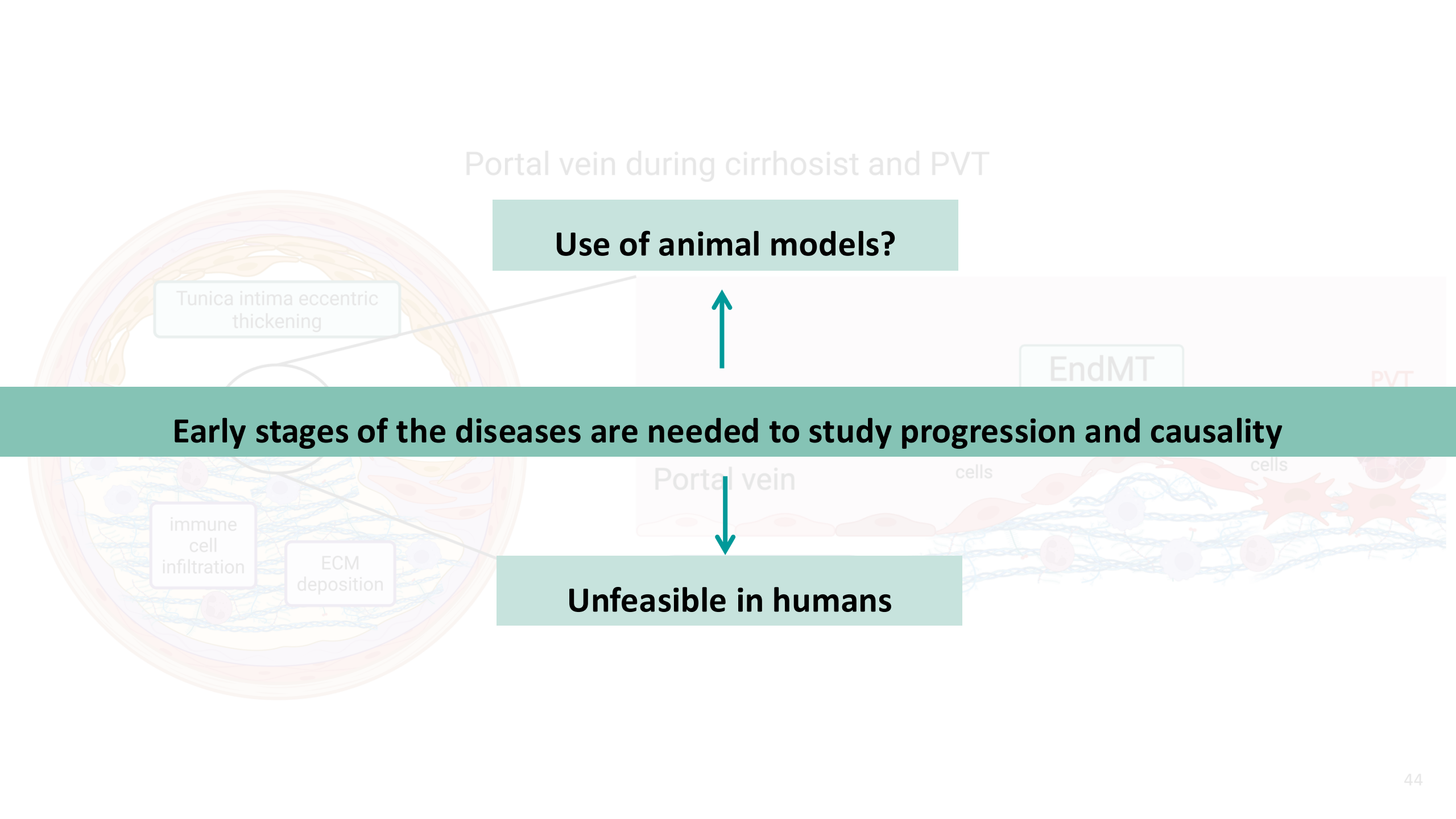
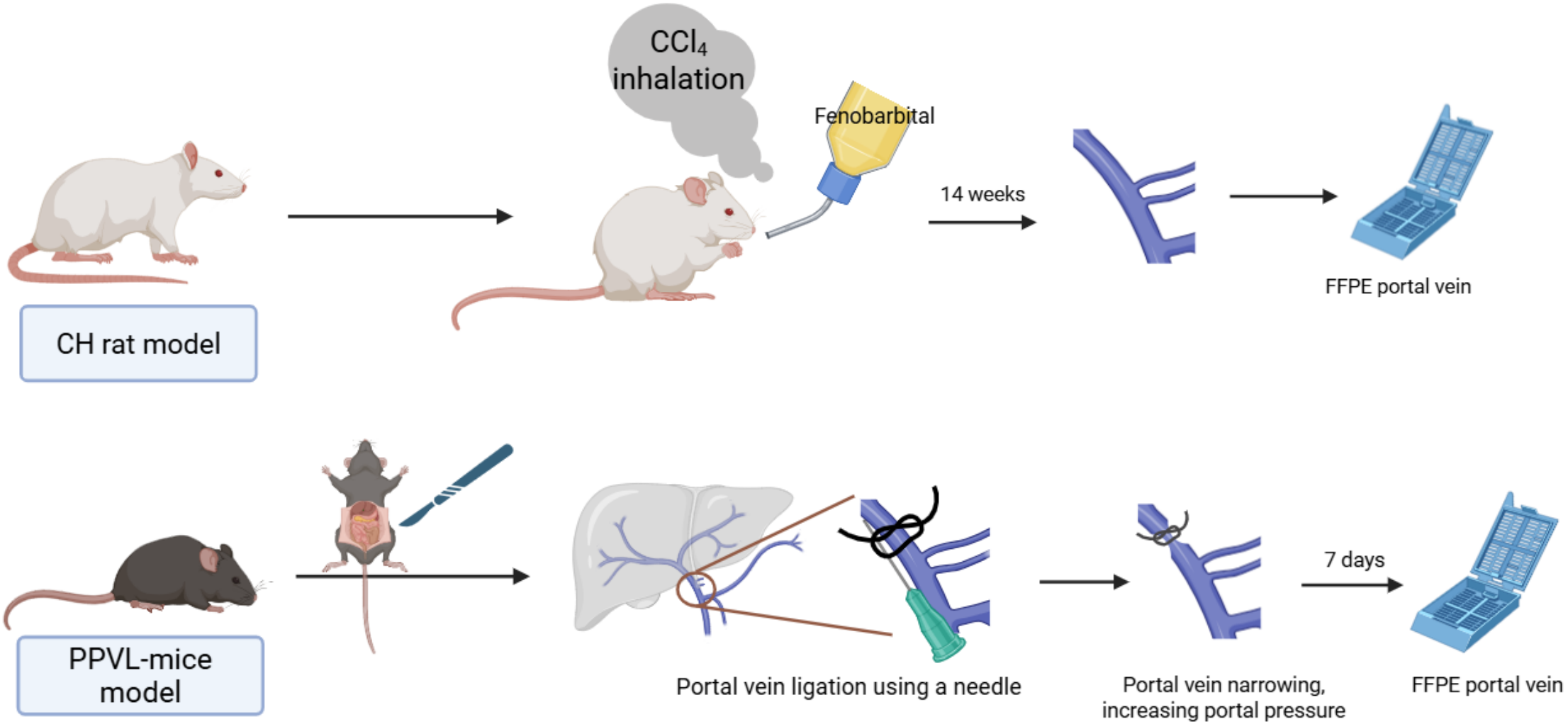
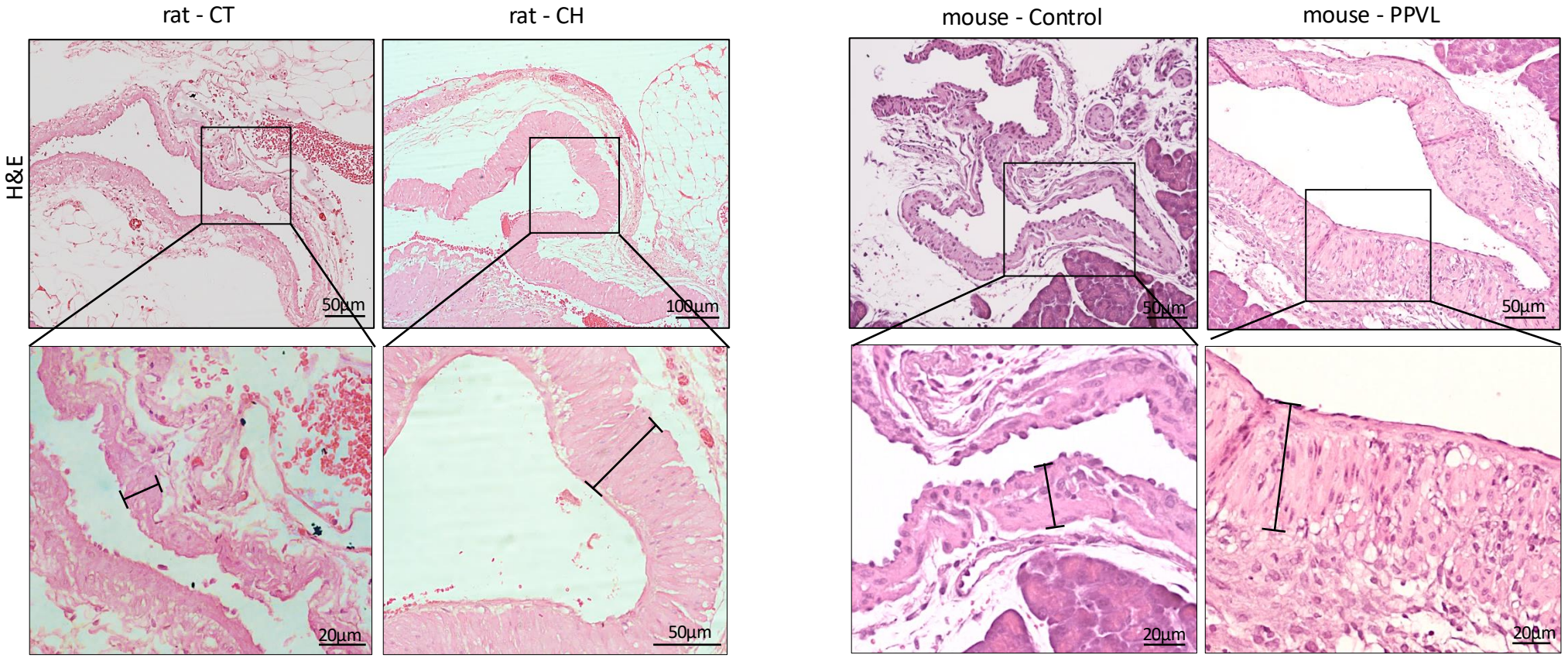

Portal vein during cirrhosist and PVT
Use of animal models?
Tunica intima eccentric thickening
EndMT
PVT
Early stages of the diseases are needed to study progression and causality
Portal vein
cells
cells
immune cell infiltration
ECM deposition
Unfeasible in humans

Rodent models of portal hypertension

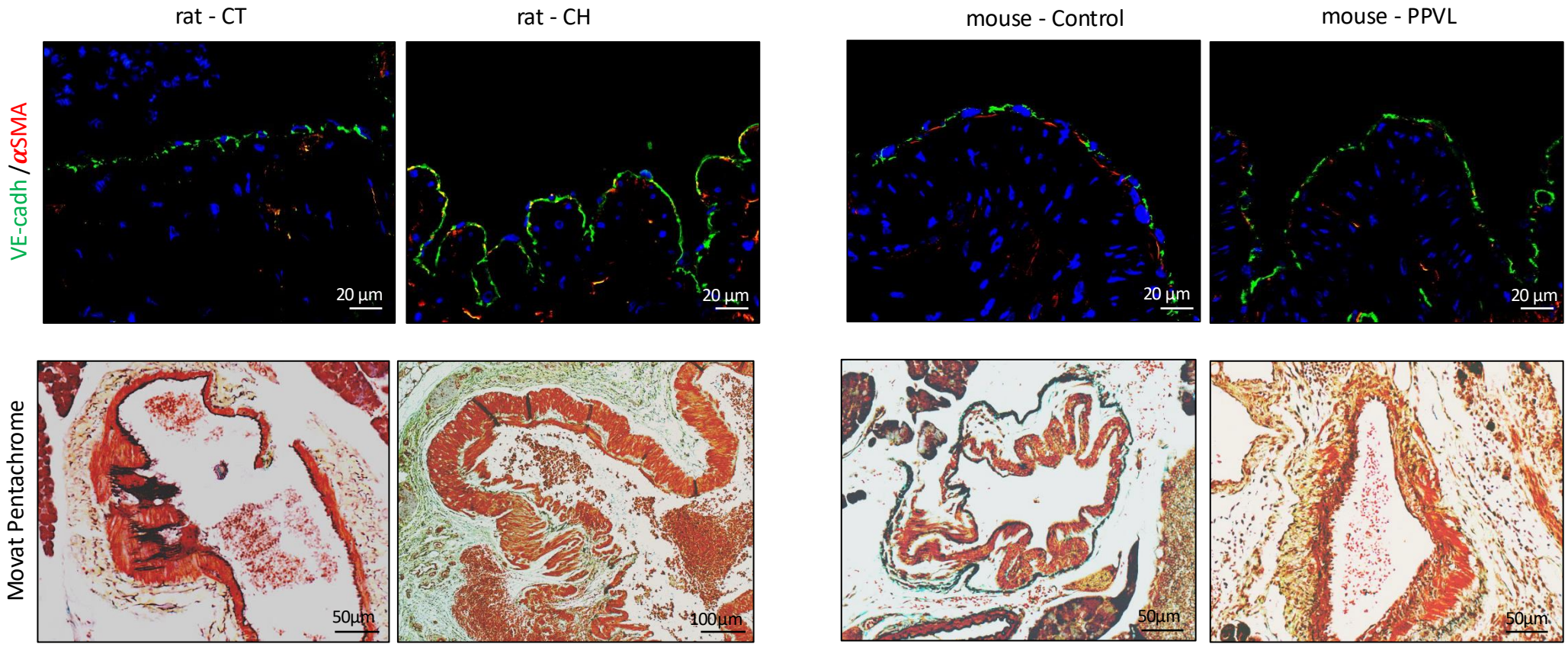


Rodent portal hypertension models do not reproduce human PV phenotype



- Concentric remodeling with no tunica intima thickening → remodeling dominated by muscular hypertrophy

Rodent portal hypertension models do not reproduce human PV phenotype

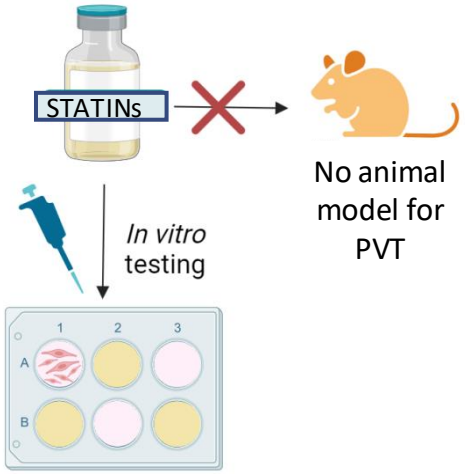


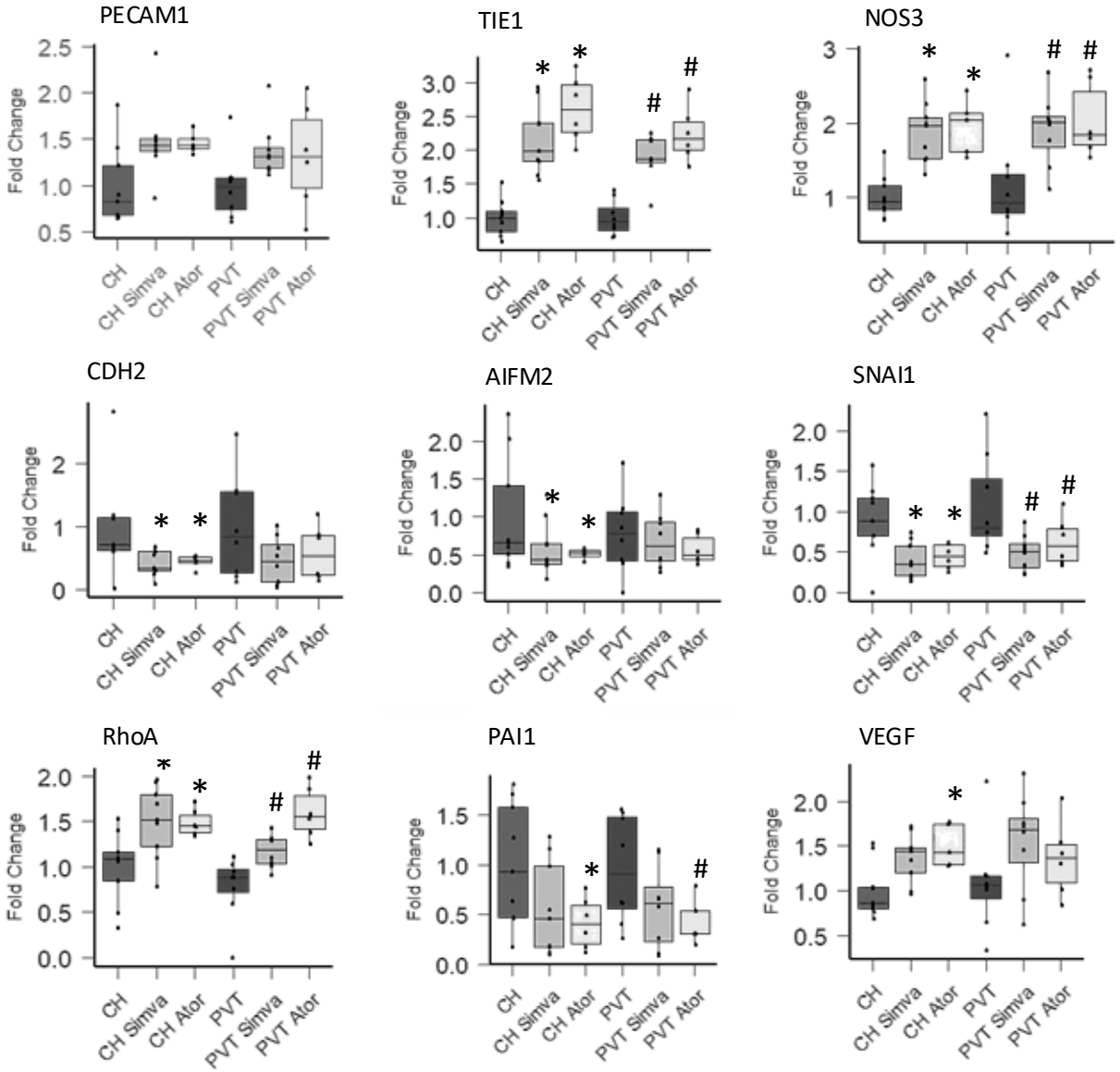
- Concentric remodeling with no tunica intima thickening → remodeling dominated by muscular hypertrophy
- No EC proliferation nor mesenchymal cells in the tunica intima → no EndMT
- No mucin or ECM accumulation in intima

Statins as potential disease modifiers in PVT

Drug-repurposing analysis

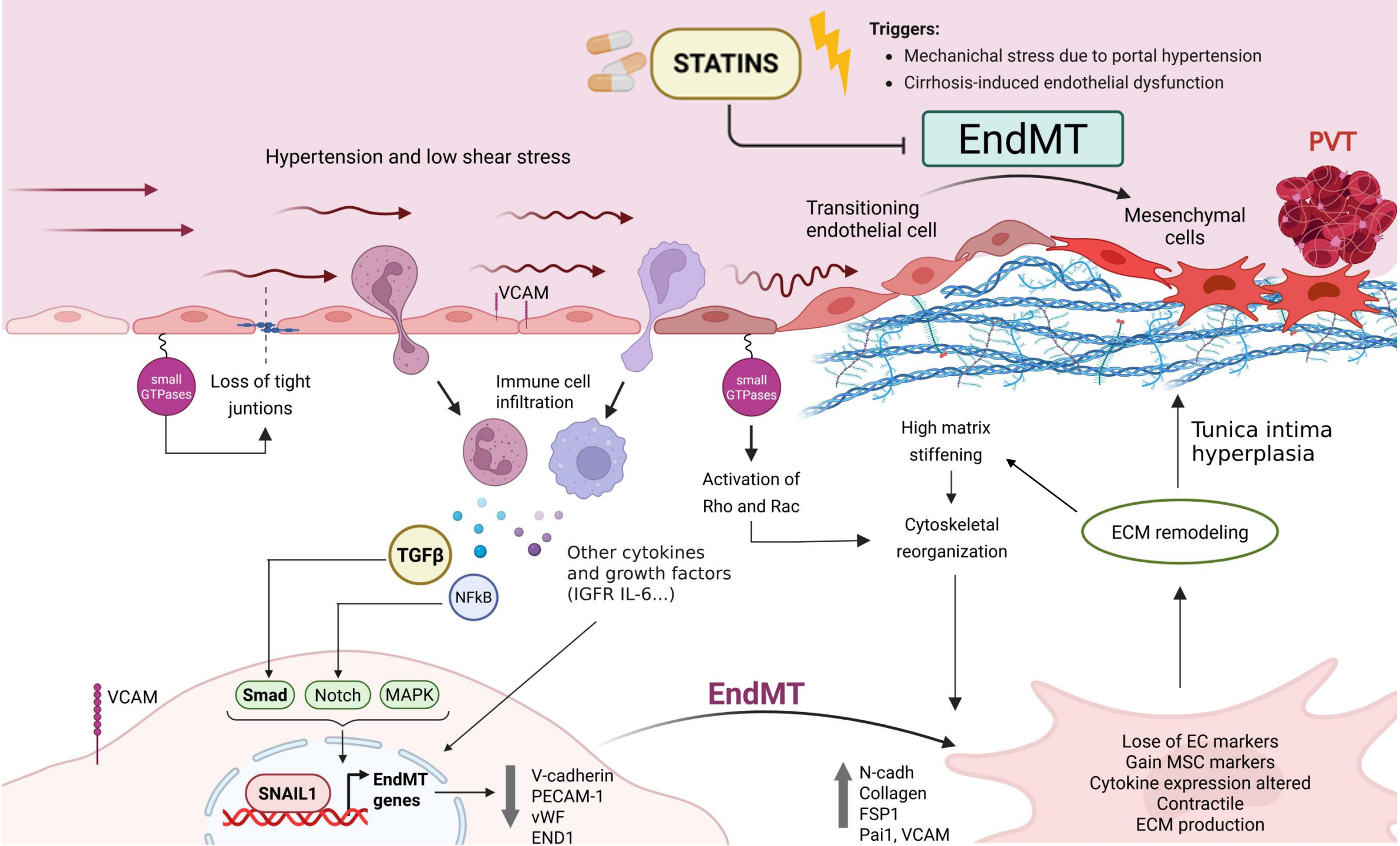
	pathway	p-val
1	**Atorvastatin**	0.0054
2	Isoproterenol	0.0092
3	Fenofibrate	0.0150
4	**Pravastatin**	0.0163
5	Triamterene	0.0184
6	Azathioprine	0.0223
7	Nevirapine	0.0230
8	5-fluorouracil	0.0259
9	Methimazole	0.0280
10	Bortezomib	0.0301
	[...]	
24	**Simvastatin**	0.0819





In PVECs *in vitro*, Atorvastatin and Simvastatin are able to:

- Increase EC markers
- Reduce mesenchymal markers
- Decrease the principal transcriptomic factors of EndMT
- Reduce adhesion molecules


STATINS
Triggers:
Mechanichal stress due to portal hypertension
Cirrhosis-induced endothelial dysfunction
EndMT
PVT
Hypertension and low shear stress
Transitioning endothelial cell
Mesenchymal cells
VCAM
small GTPases
Loss of tight juntions
Immune cell infiltration
small GTPases
Activation of Rho and Rac
High matrix stiffening
Tunica intima hyperplasia
Cytoskeletal reorganization
ECM remodeling
TGFβ
NFkB
Other cytokines and growth factors (IGFR IL-6...)
VCAM
Smad
Notch
MAPK
EndMT
SNAIL1
EndMT genes
V-cadherin
PECAM-1
vWF
END1
N-cadh
Collagen
FSP1
Pai1, VCAM
Lose of EC markers
Gain MSC markers
Cytokine expression altered
Contractile
ECM production

THANKS

Vihernandez@clinic.cat

Clínic Barcelona | Universitat de Barcelona

IDIBAPS Institut D'Investigacions Biomèdiques August Pi i Sunyer

European Reference Networks

ciber | EHD

LiVas