

CONGRÈS
d'FRANÇAIS
d'HÉMOSTASE

10-12
MAI
2023



Palais des Congrès

SAINT-MALO

Le Grand Large



Groupe d'Étude de la Thrombose
de Bretagne Occidentale

UMR 1304



FACULTÉ
DE MÉDECINE &
SCIENCES DE LA SANTÉ

Inserm

La science pour la santé
From science to health

Importance du phénotype endothélial et des mécanismes inflammatoires dans la maladie veineuse thromboembolique



GRRC
GROUPE
DE RÉFLEXION
SUR LA RECHERCHE
CARDIOVASCULAIRE

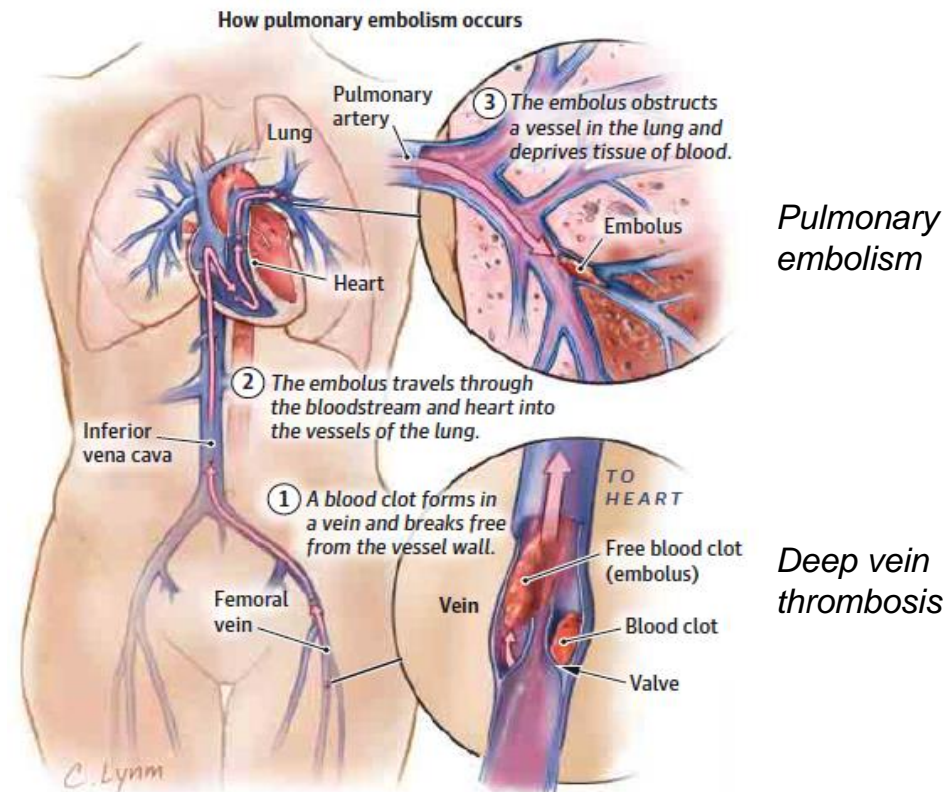


Société
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Venous thromboembolism – major public health issue



Pulmonary embolism

Deep vein thrombosis

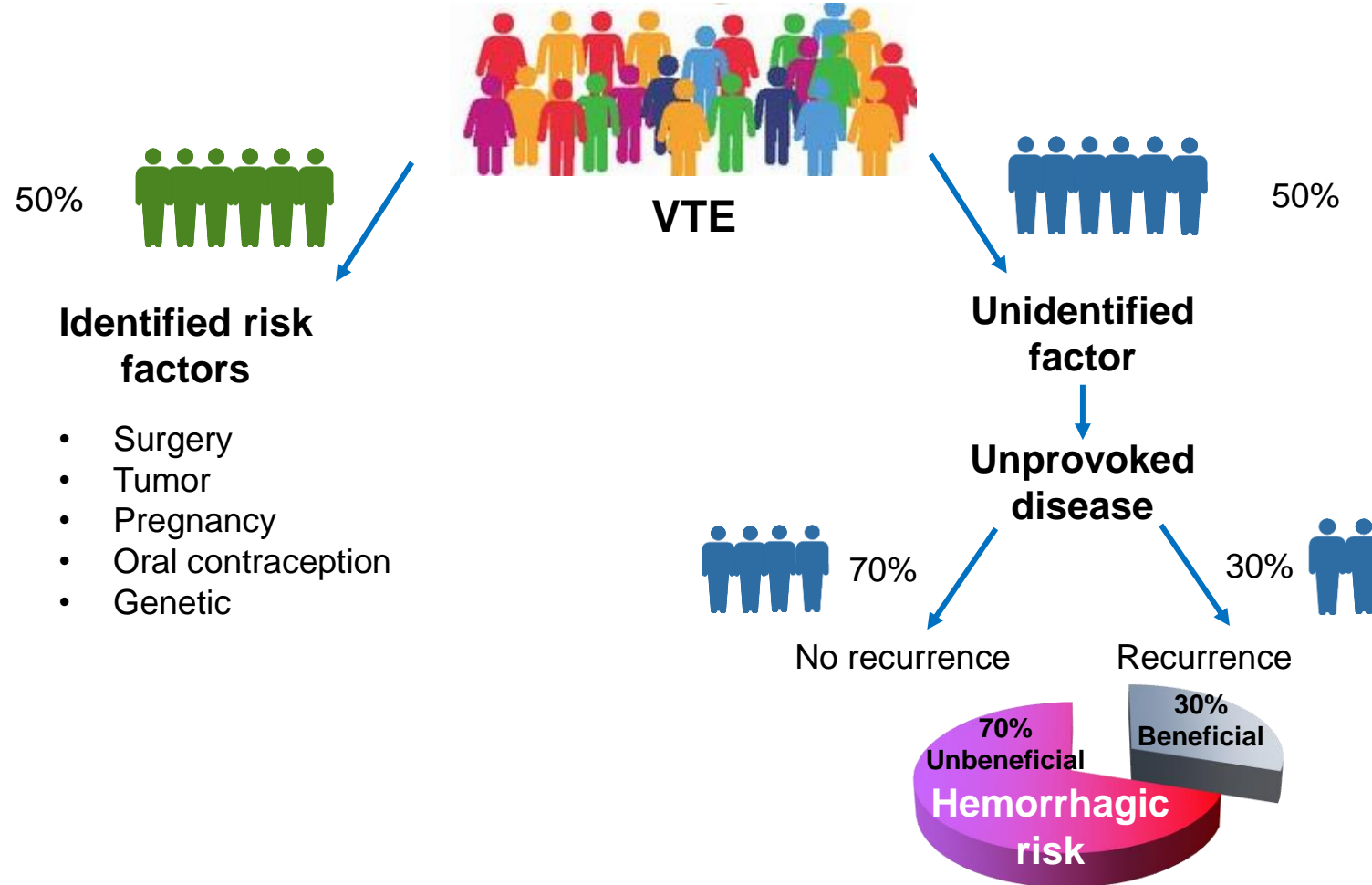
Incidence rate: 1 to 2 / 1000-person years

Risks:

- **Recurrence rate:** 5% to 40% at 5 years
- **Mortality:** 10% at 3 months if pulmonary embolism (2-fold higher than myocardial infarction; **3rd cardiovascular cause of death**)
- **Sequelae:** Chronic Thromboembolic pulmonary hypertension in 4% (median survival of 3 years)

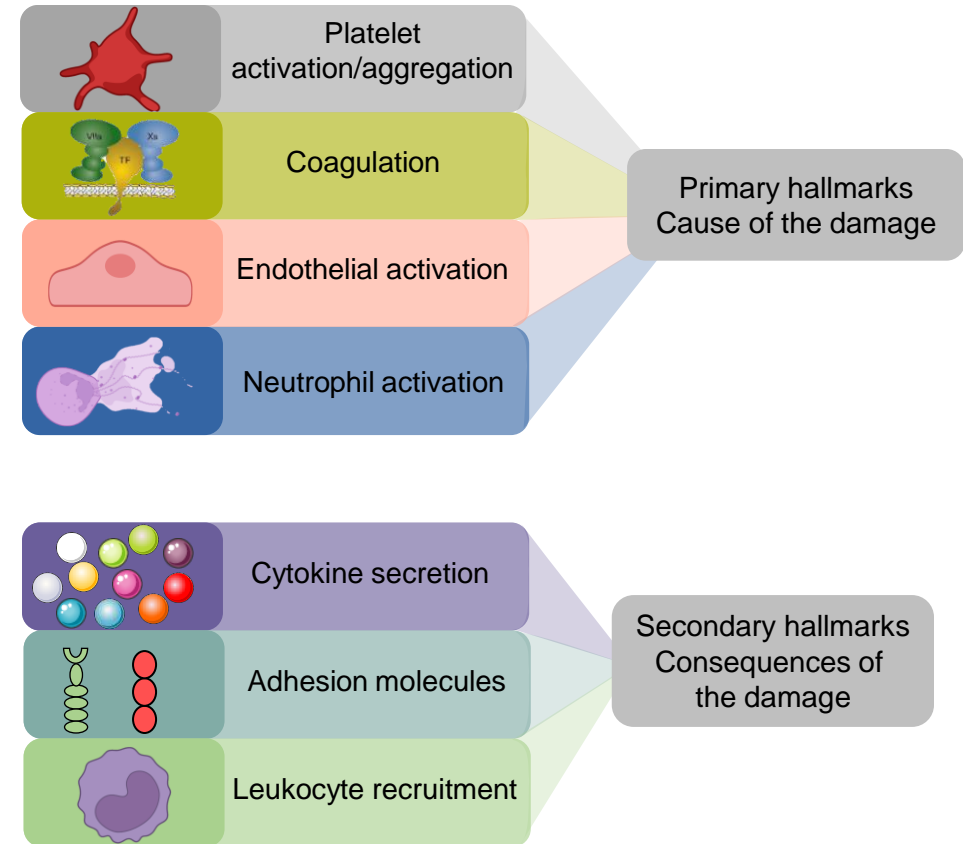
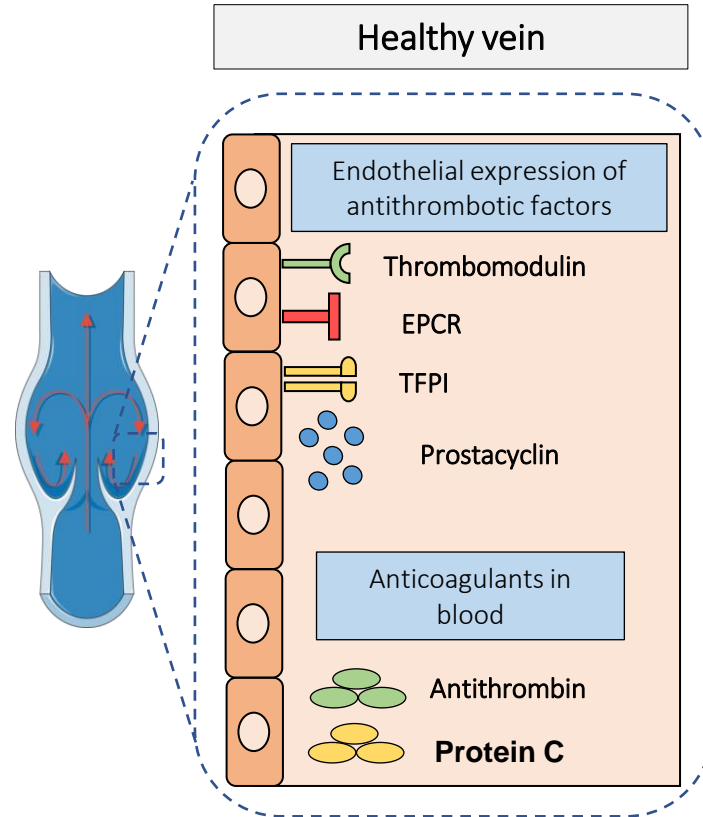
In hospital cost: 240 Millions Euros/y in France

Venous thromboembolism – major public health issue

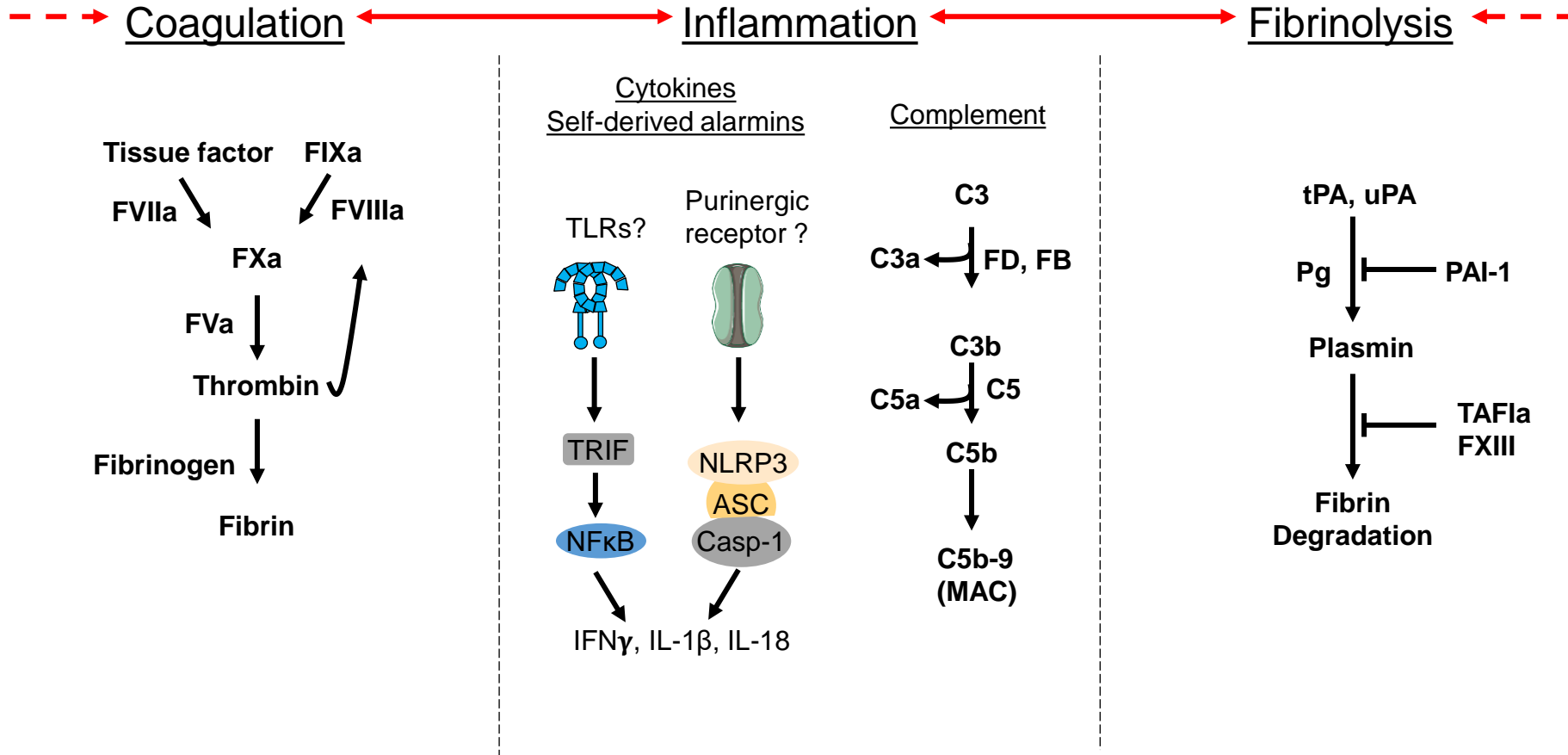


Need to identify patients with a risk of recurrence

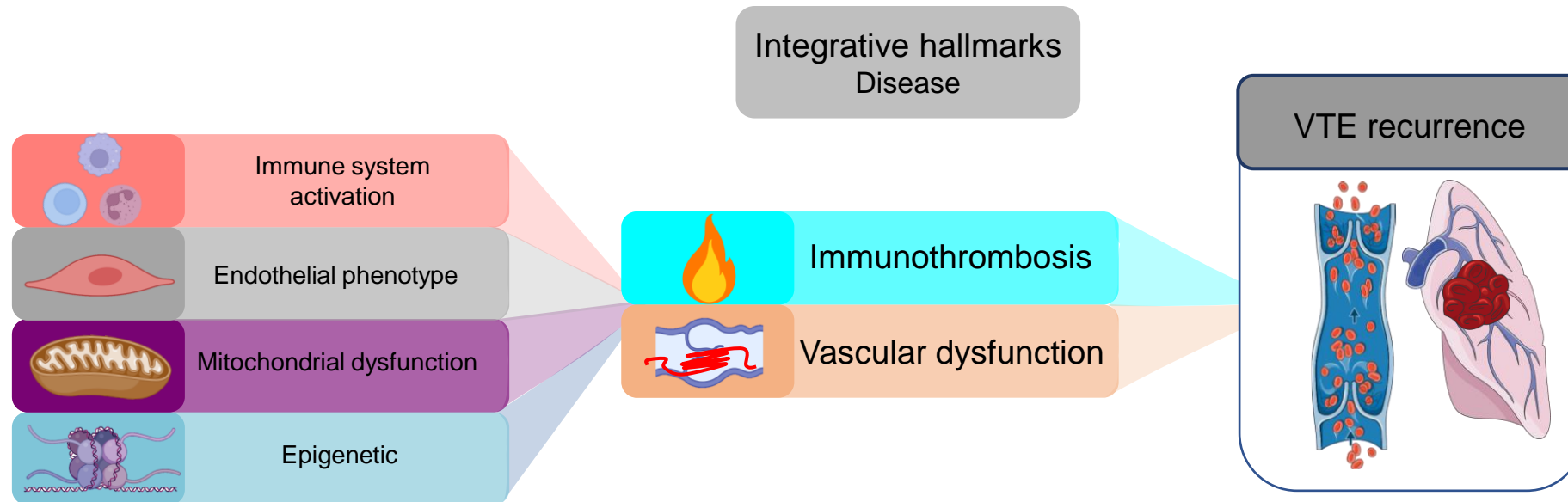
Hallmarks of venous thromboembolism



Coagulation, inflammation and fibrinolysis?

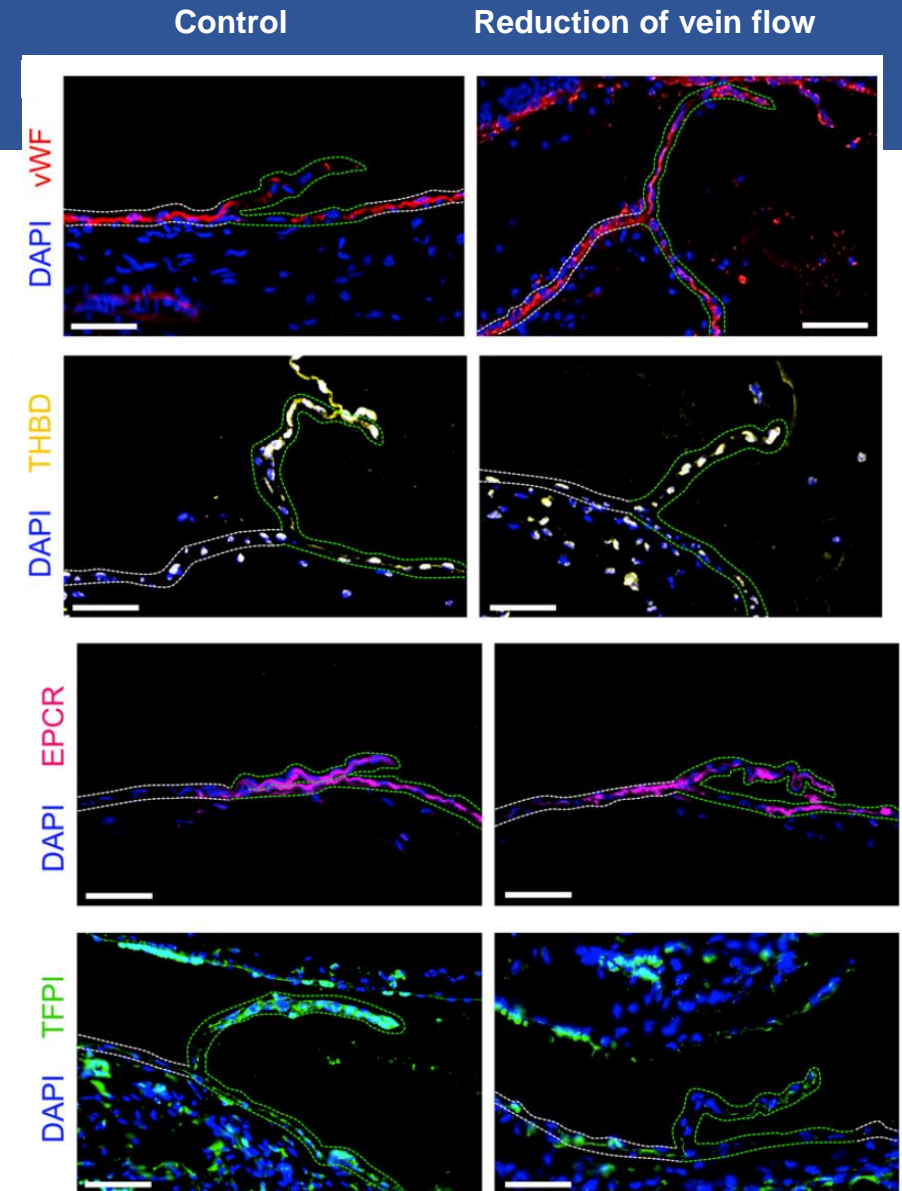
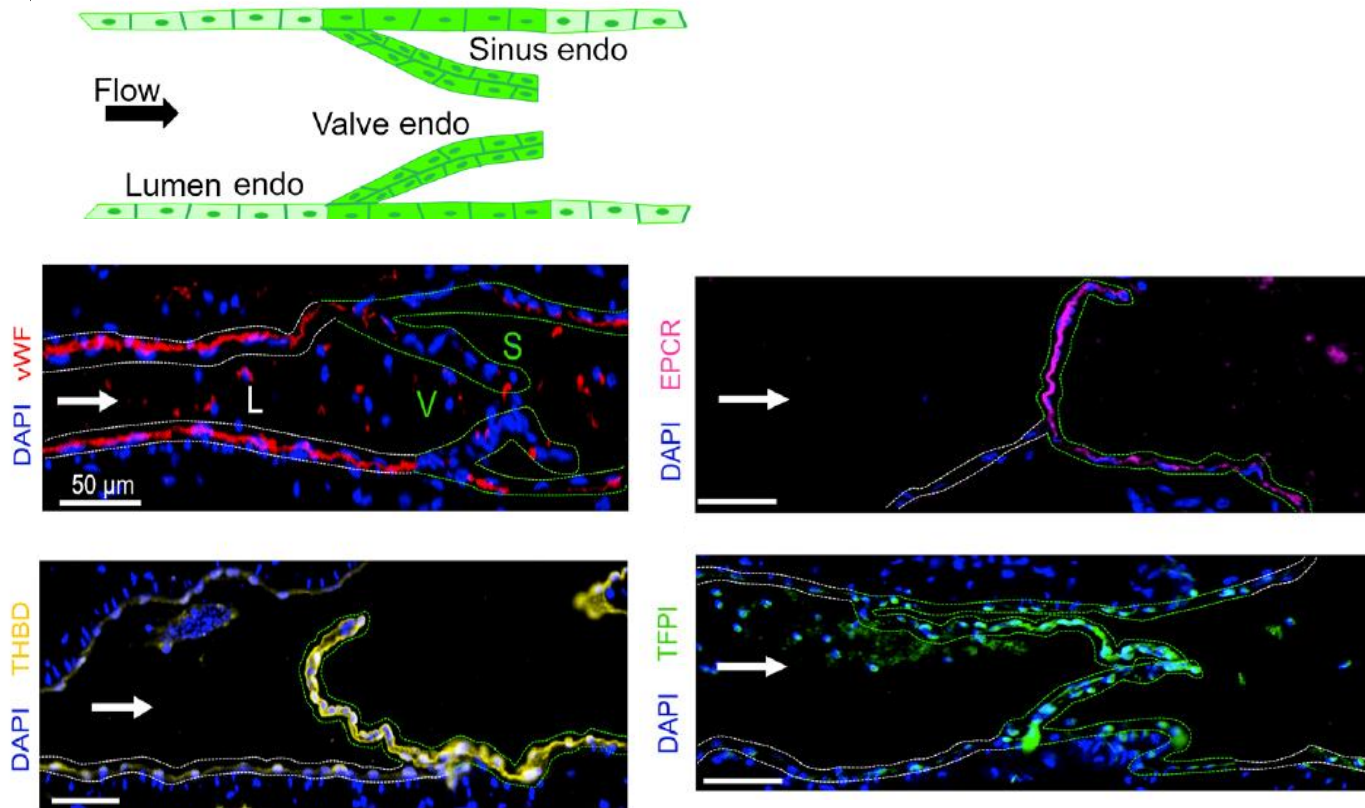


Endothelium, inflammation and fibrinolysis? → Chronic disease



↳ **How the endothelium drives VTE and recurrent VTE ?**

Endothelial dysfunction drives VTE ?



Endothelium and inflammation in VTE

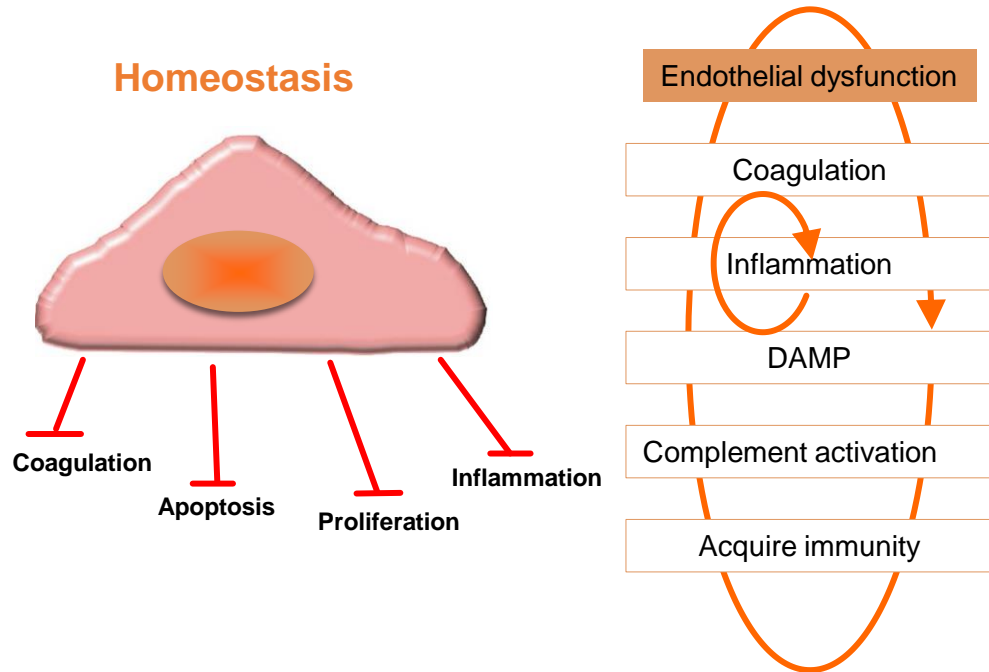


TABLE 2. ELISA Measurements for Cytokines and Chemokines in the Thrombosed Vein Walls Indexed to the Time From Clot Induction for All Time Points Including Baseline

Cytokine	Baseline	Day 1	Day 3	Day 6
Thrombosed veins (n=4)				
TNF	<50	127±46*	341±55†	610±212*
ENA-78	<50	<50	175±81	370±150*
MIP-1α	<50	<50	105±45	<50
Interleukin-6	<50	<50	328±187	445±243
JE/MCP-1	<50	2372±650*	3198±704†	12 914±7073
Shams (n=4)				
TNF		<50‡	<50§	<50‡
ENA-78		<50	<50	70±34
MIP-1α		<50	<50	<50
Interleukin-6		<50	<50	<50
JE/MCP-1		<50‡	<50§	50

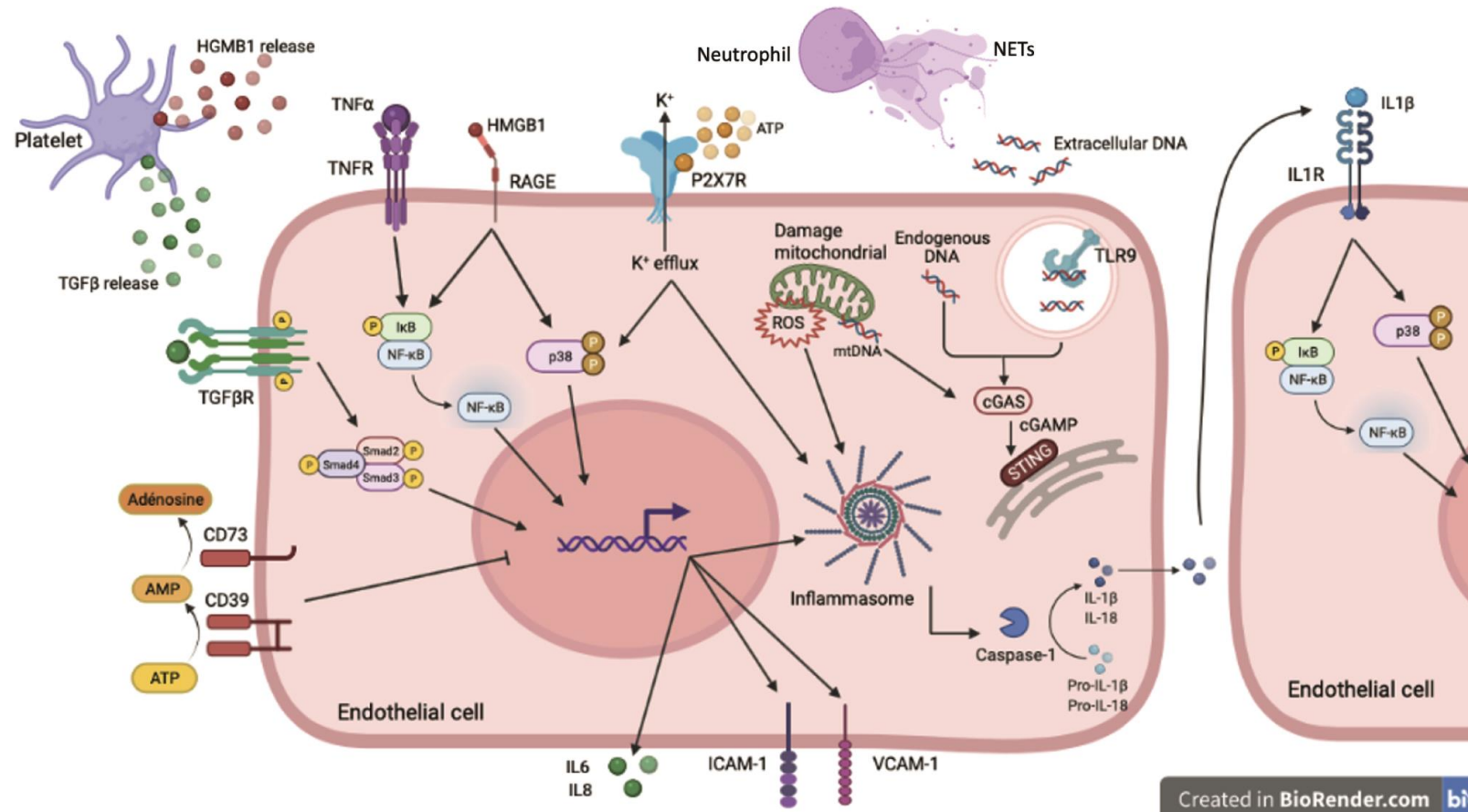
ELISA indicates enzyme-linked immunosorbent assay; TNF, tumor necrosis factor-α; epithelial neutrophil activating protein-78; MIP-1α, macrophage inflammatory protein-1α; and JE/monocyte chemoattractant protein-1. Measurements are expressed in picograms per milliliter.

* $P \leq .05$, † $P \leq .01$ compared with baseline.

‡ $P \leq .05$, § $P \leq .01$, shams compared with thrombosed veins.

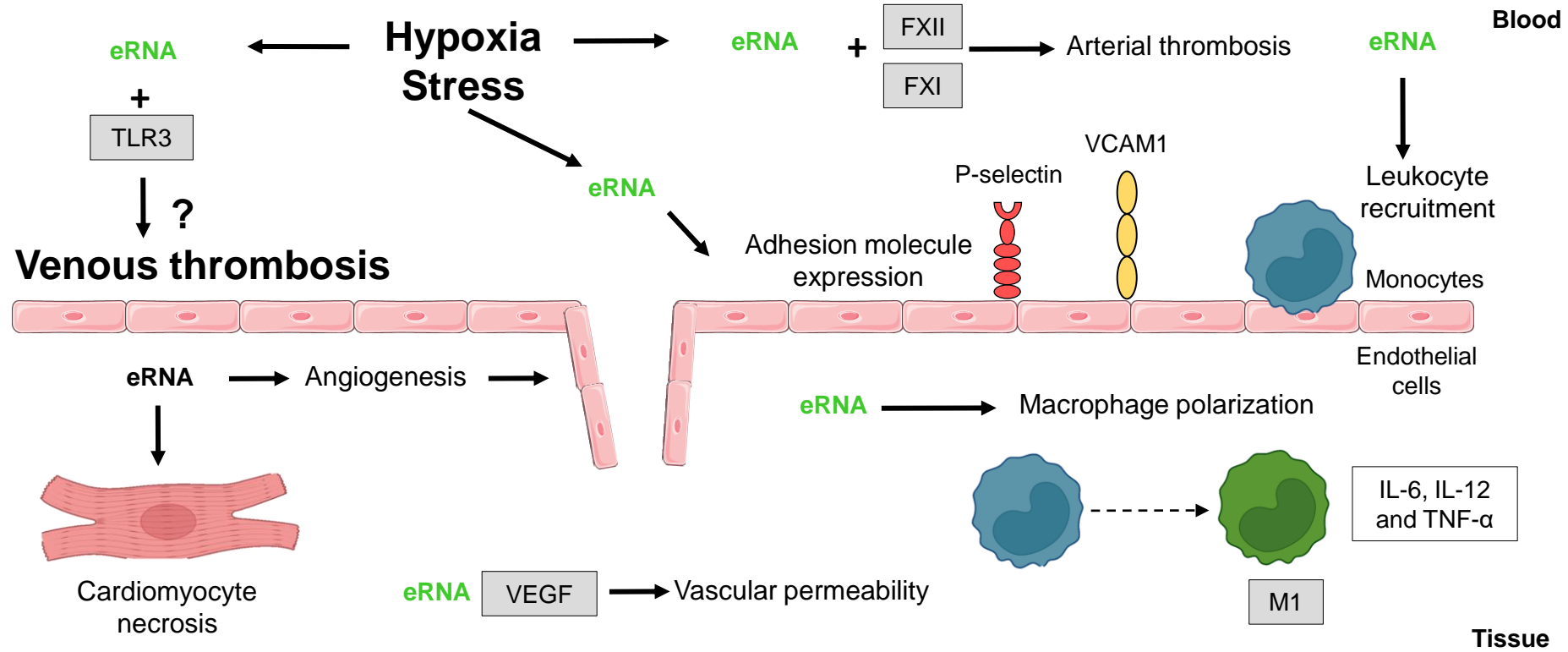
Environmental cues inducing *disruption of homeostasis*

Endothelial cell and inflammation



Marion Pilard, Estelle Ollivier, Virginie Gourdou-Latyszenok, Francis Couturaud and Catherine A. Lemarié. Frontiers in CV April 2022.

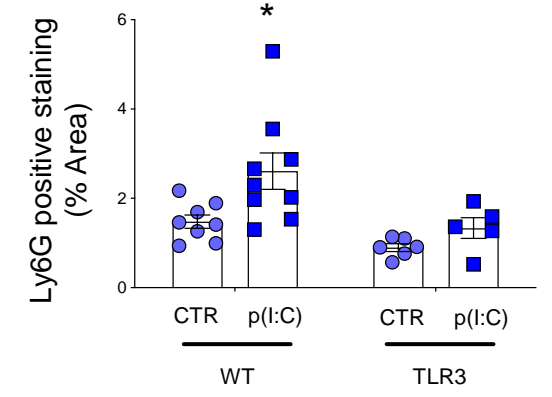
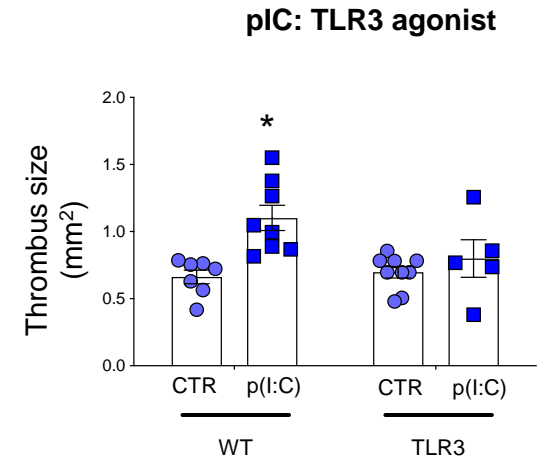
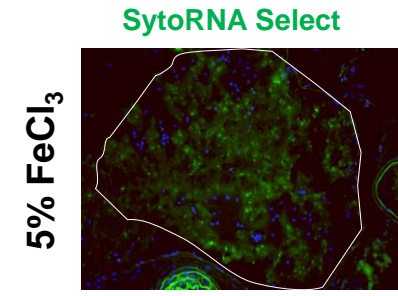
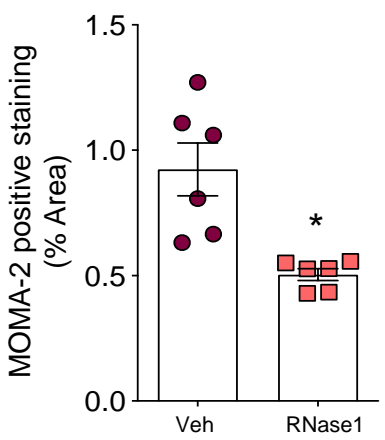
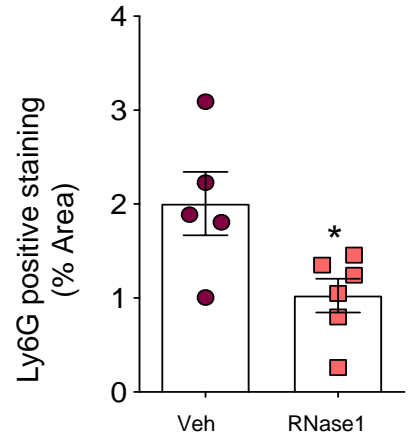
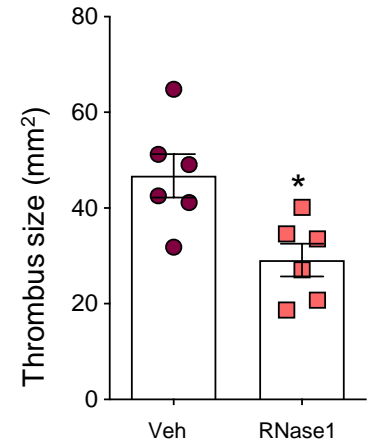
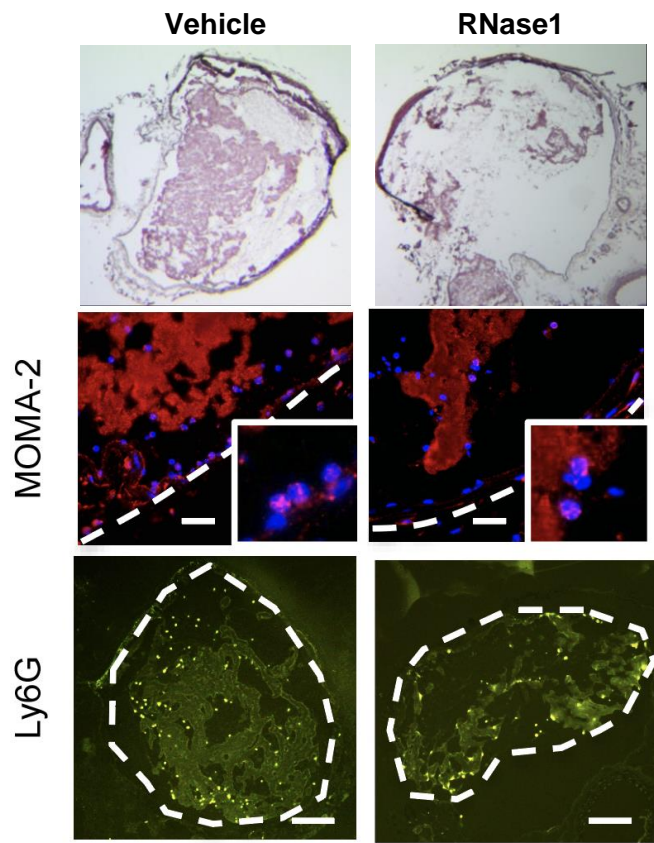
Environmental cues : extracellular RNA



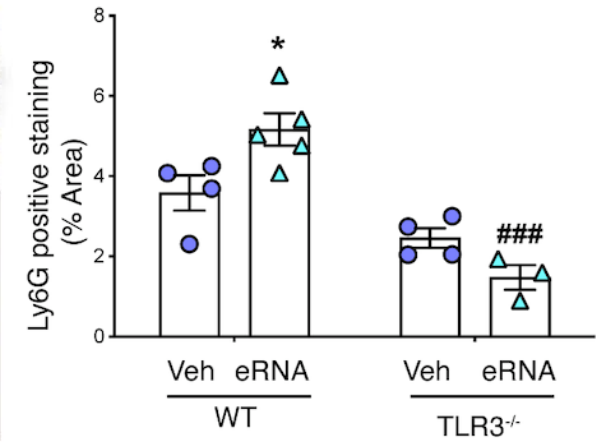
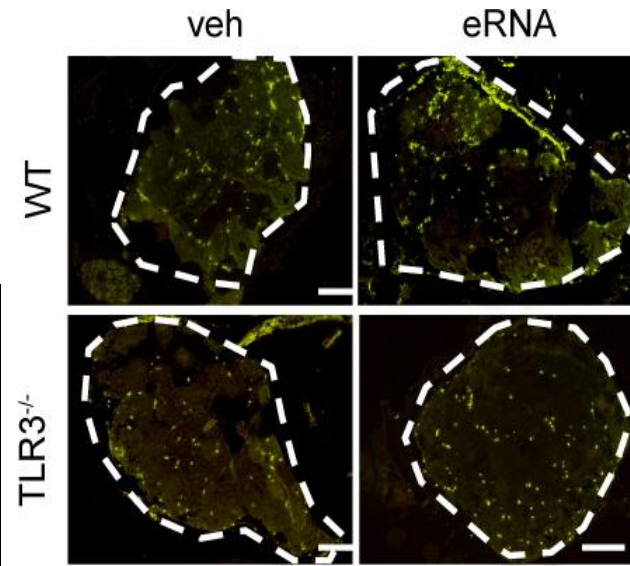
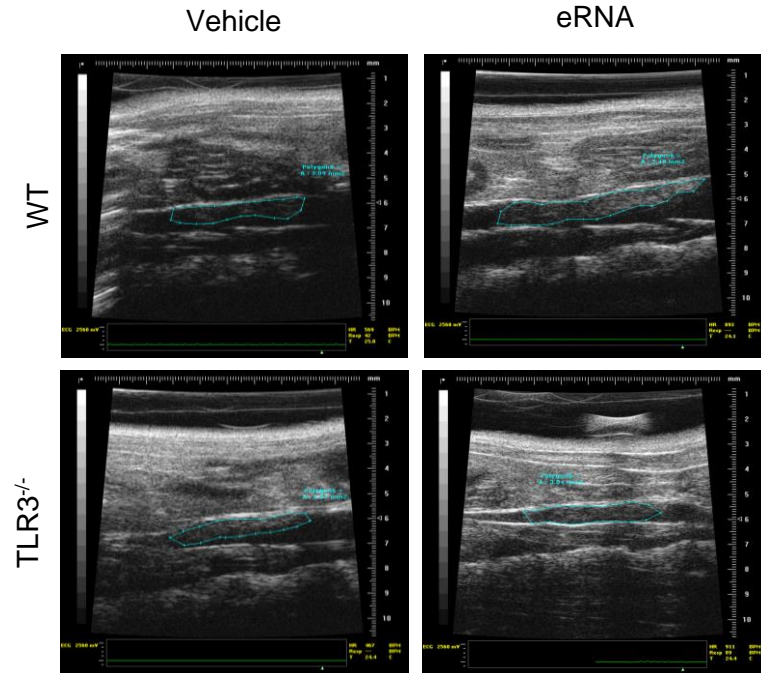
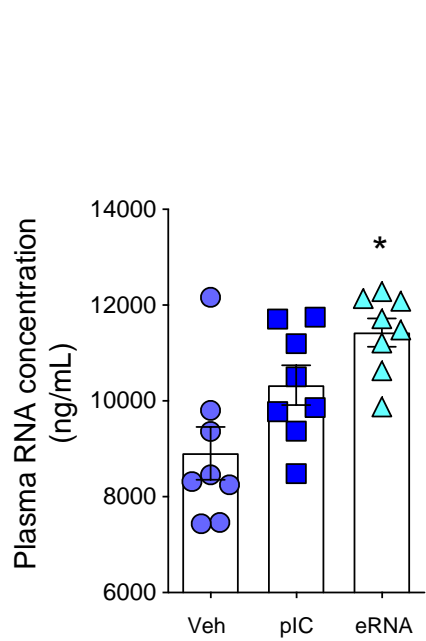
Environmental cues : extracellular RNA

Maria Najem, PhD

Hypothesis: eRNA promote the inflammatory development of venous thrombosis via endothelial TLR3.

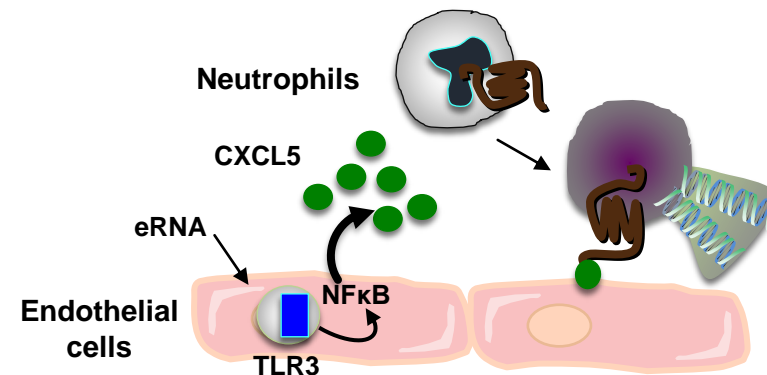
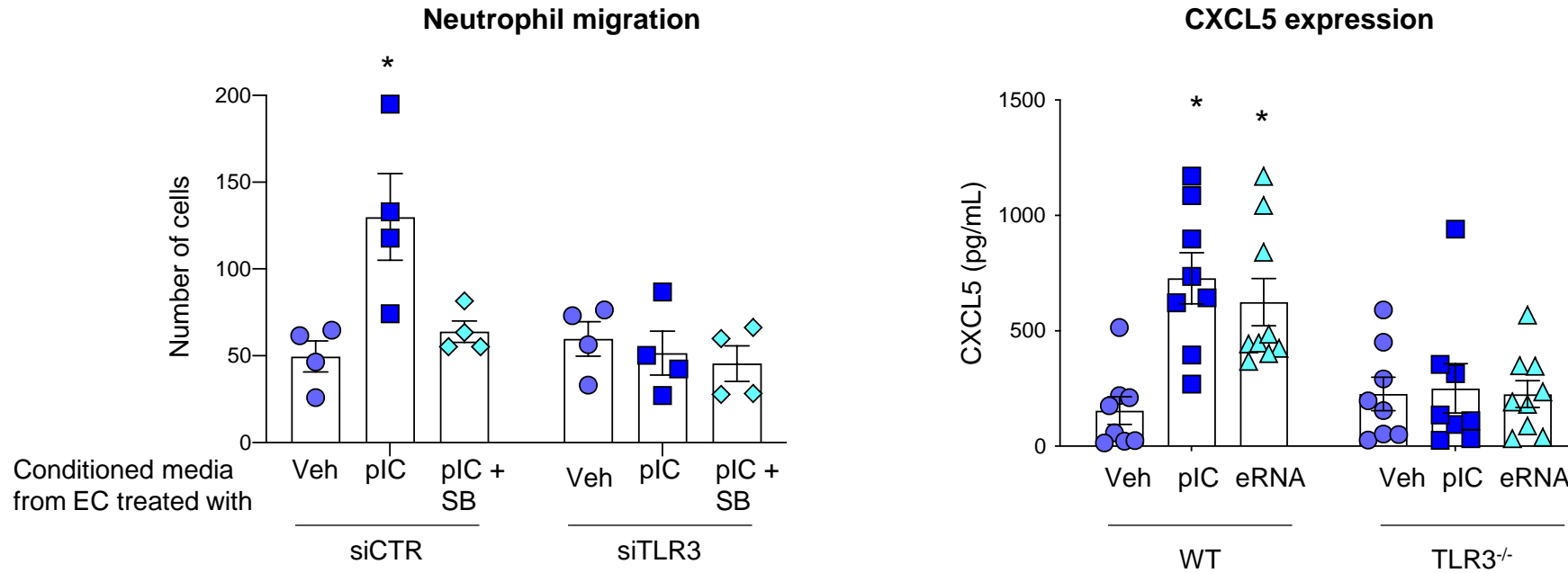


Environmental cues : extracellular RNA

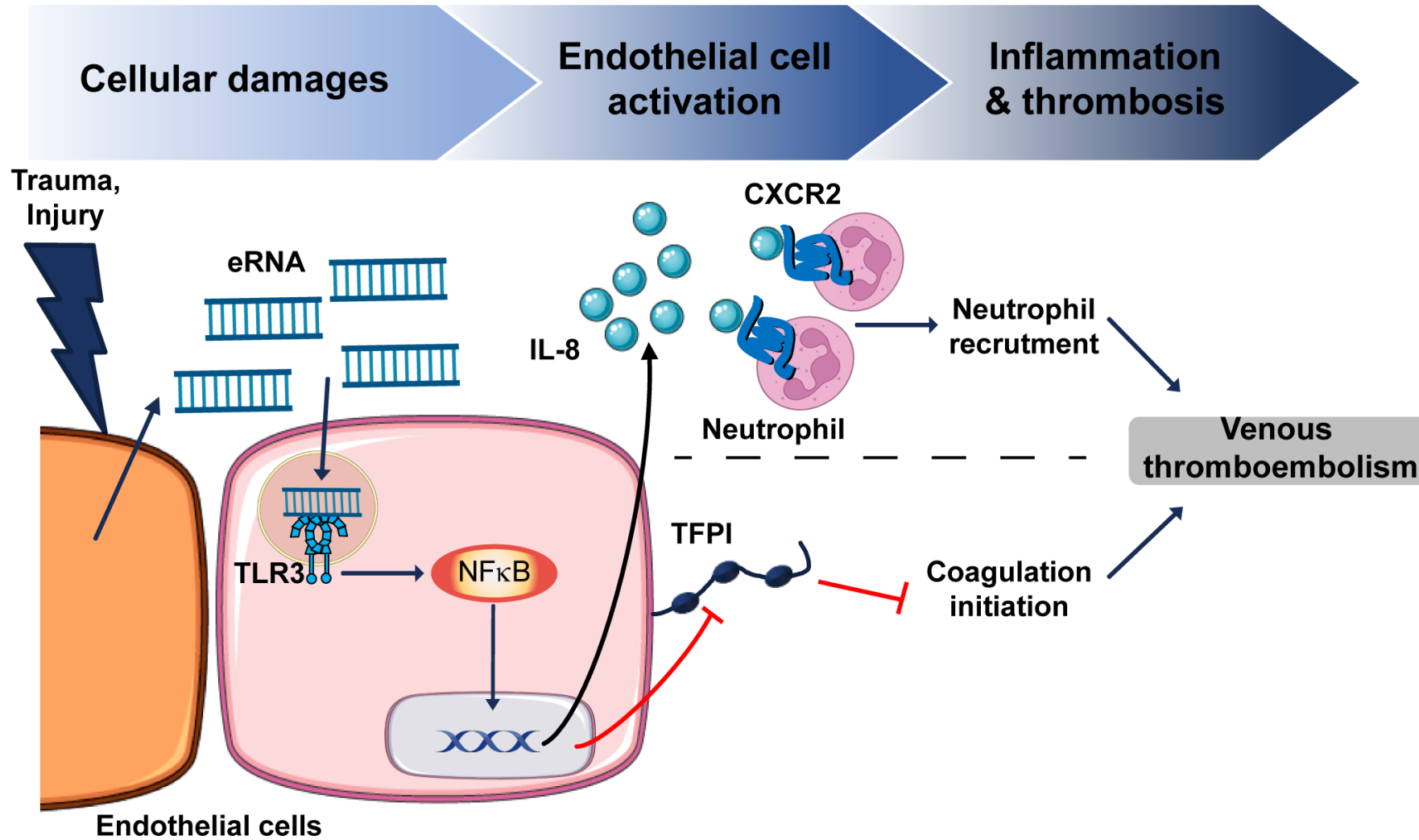


eRNA promote neutrophil recruitment

Environmental cues : extracellular RNA

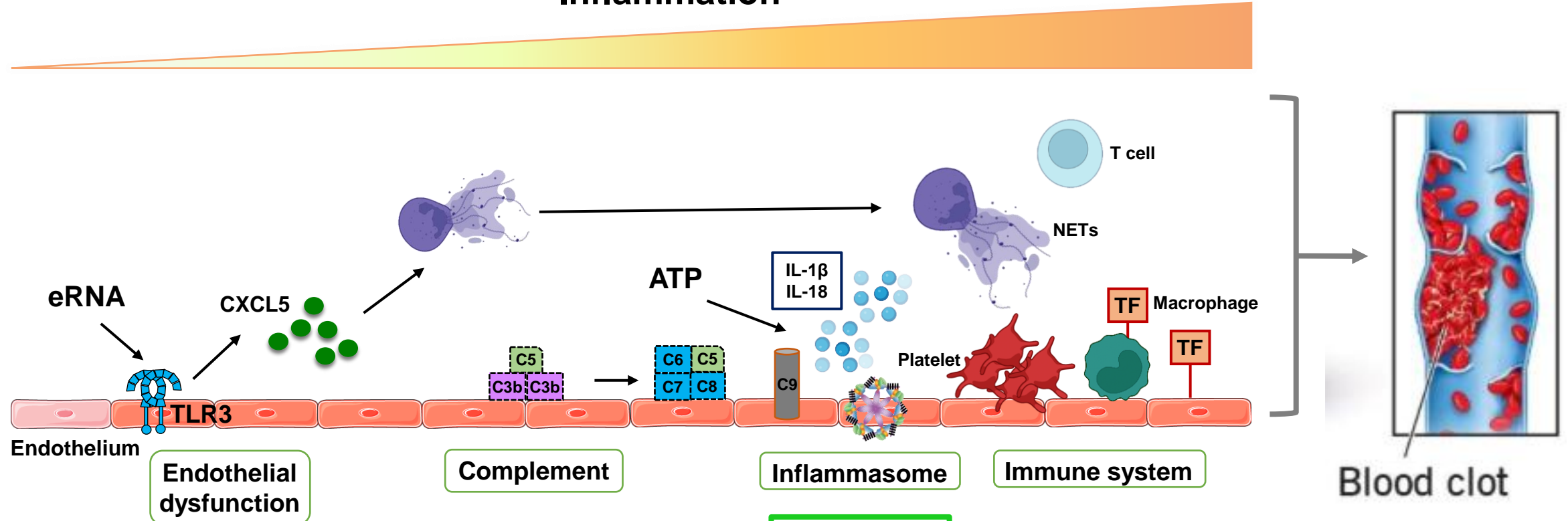


Environmental cues : extracellular RNA Endothelial dysfunction



Endothelium, inflammation and VTE occurrence

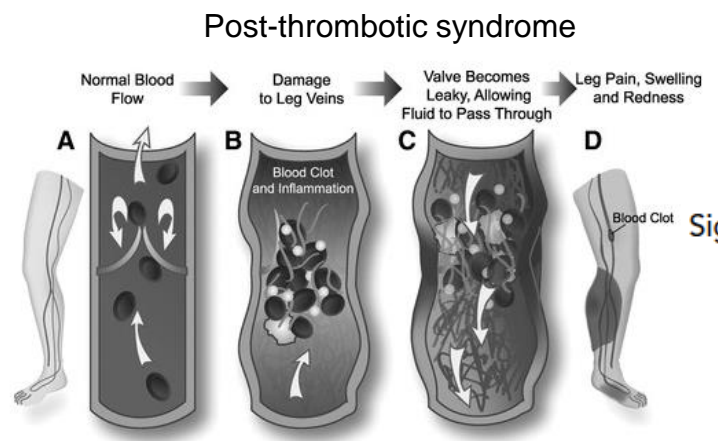
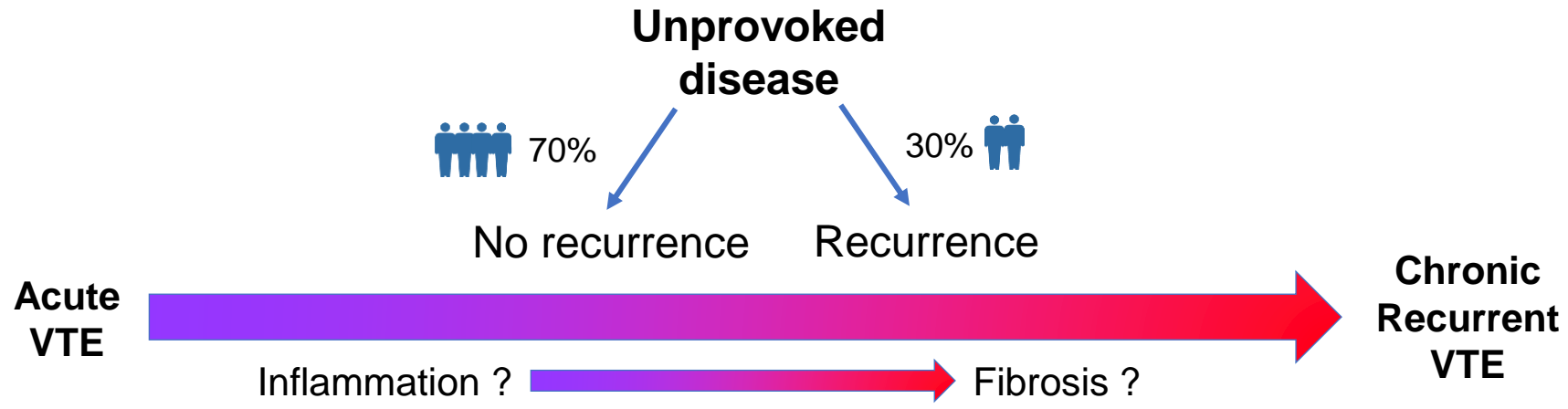
Inflammation



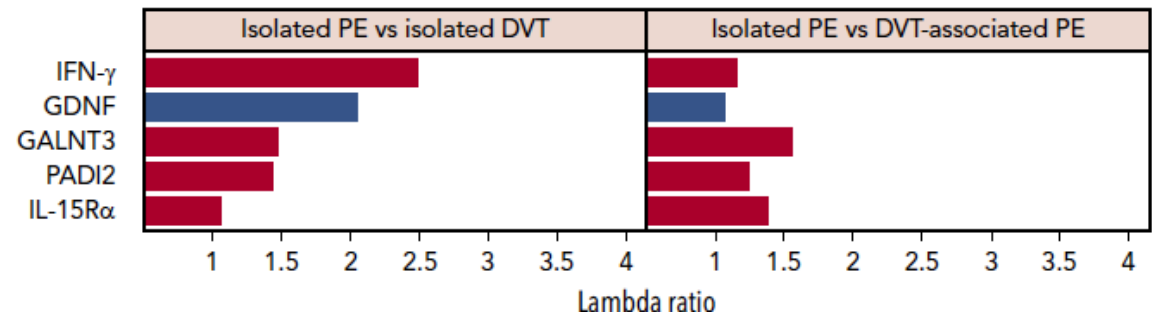
Estelle Ollivier,
PhD student

Poster # 0006

Mechanisms of VTE recurrence



Post-PE syndrome
 (residual vascular obstruction, dyspnea, CTEPH..)



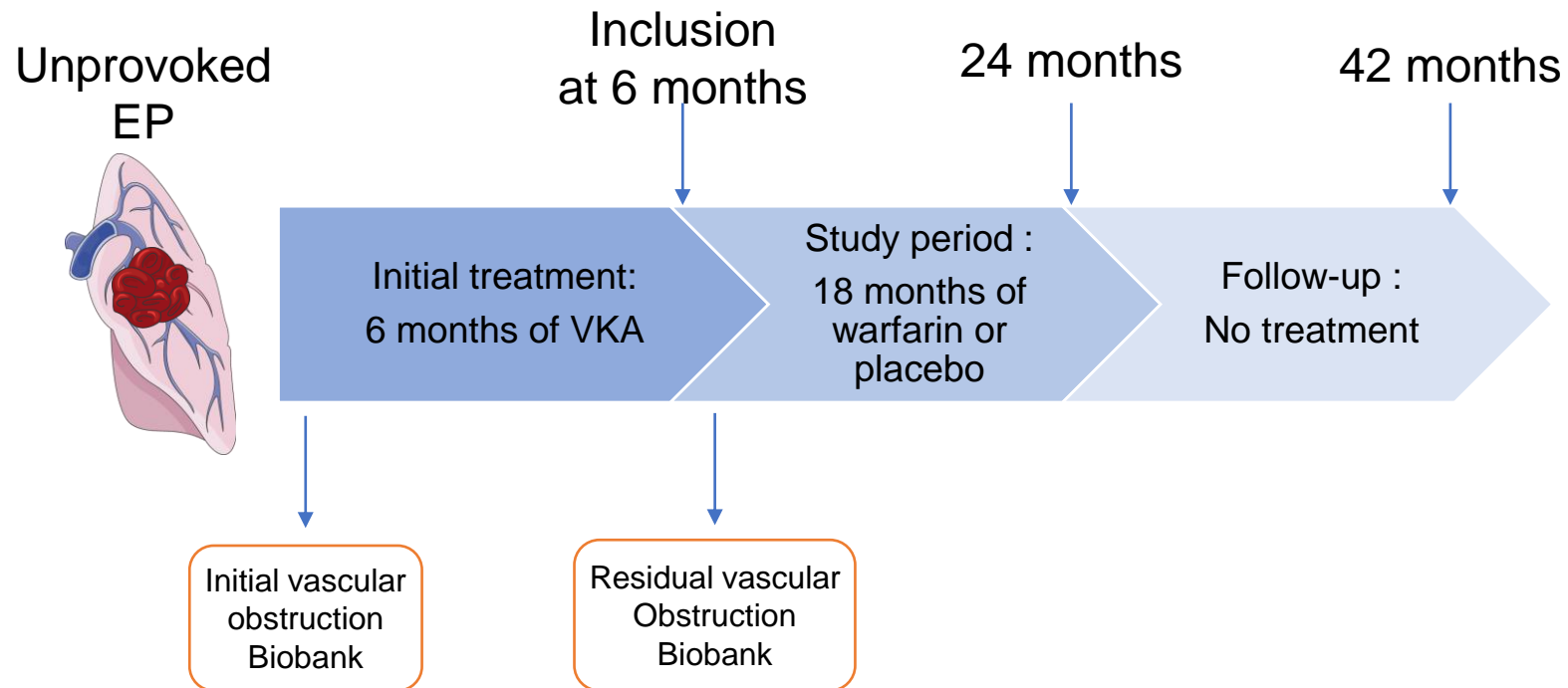
Residual vascular obstruction

Vasquez and Kahn Circulation. 2010;121:e217–e219.
 Cate et al. Blood. 2021;137:2681–2693.

Mechanisms involved in venous thromboembolism → Chronic disease

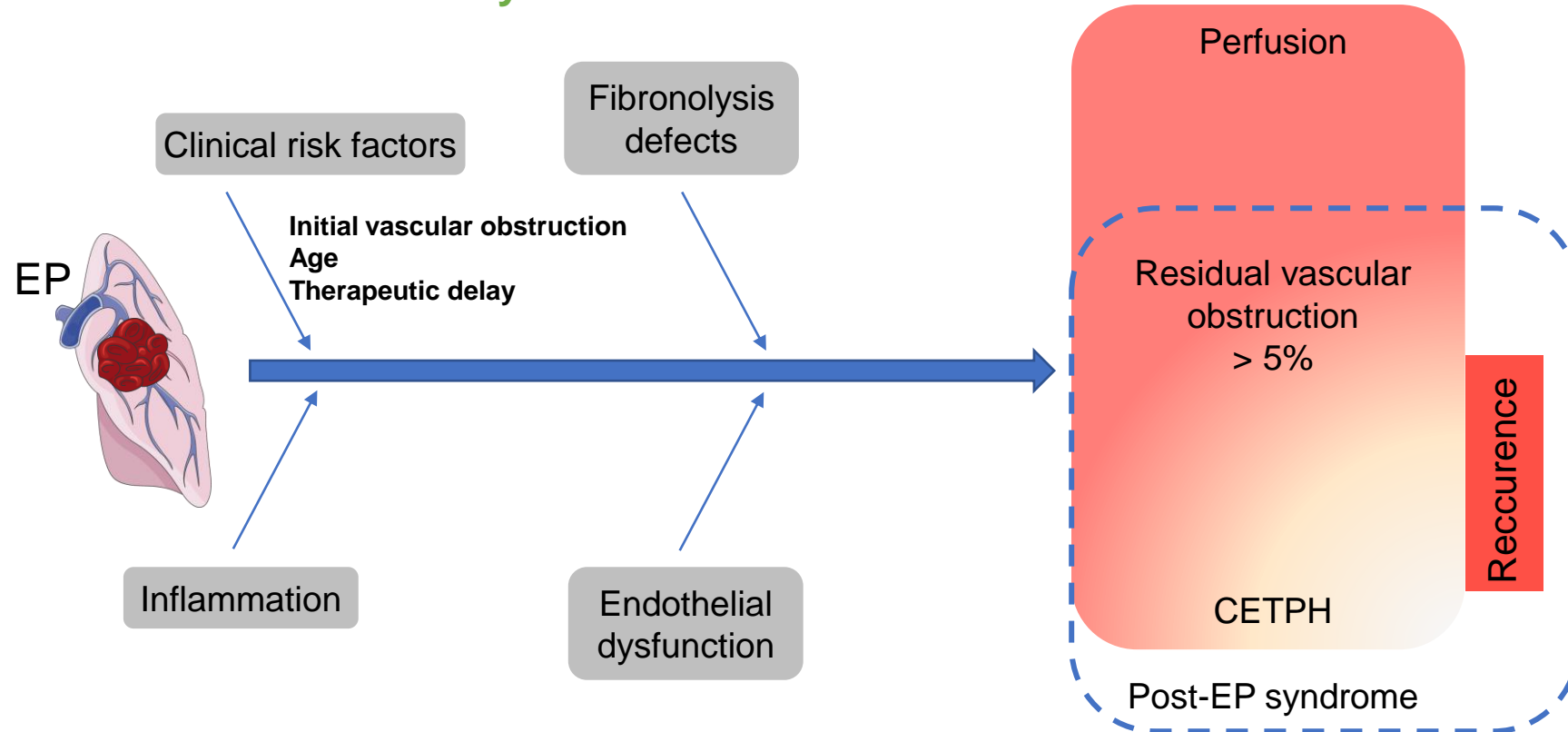
How VTE occurs and recurs?

PADIS-EP clinical study – Pr Francis Couturaud



Mechanisms involved in venous thromboembolism → Chronic disease

PADIS-EP clinical study



Mechanisms involved in venous thromboembolism → Chronic disease

PADIS-EP clinical study Residual vascular obstruction (RVO)

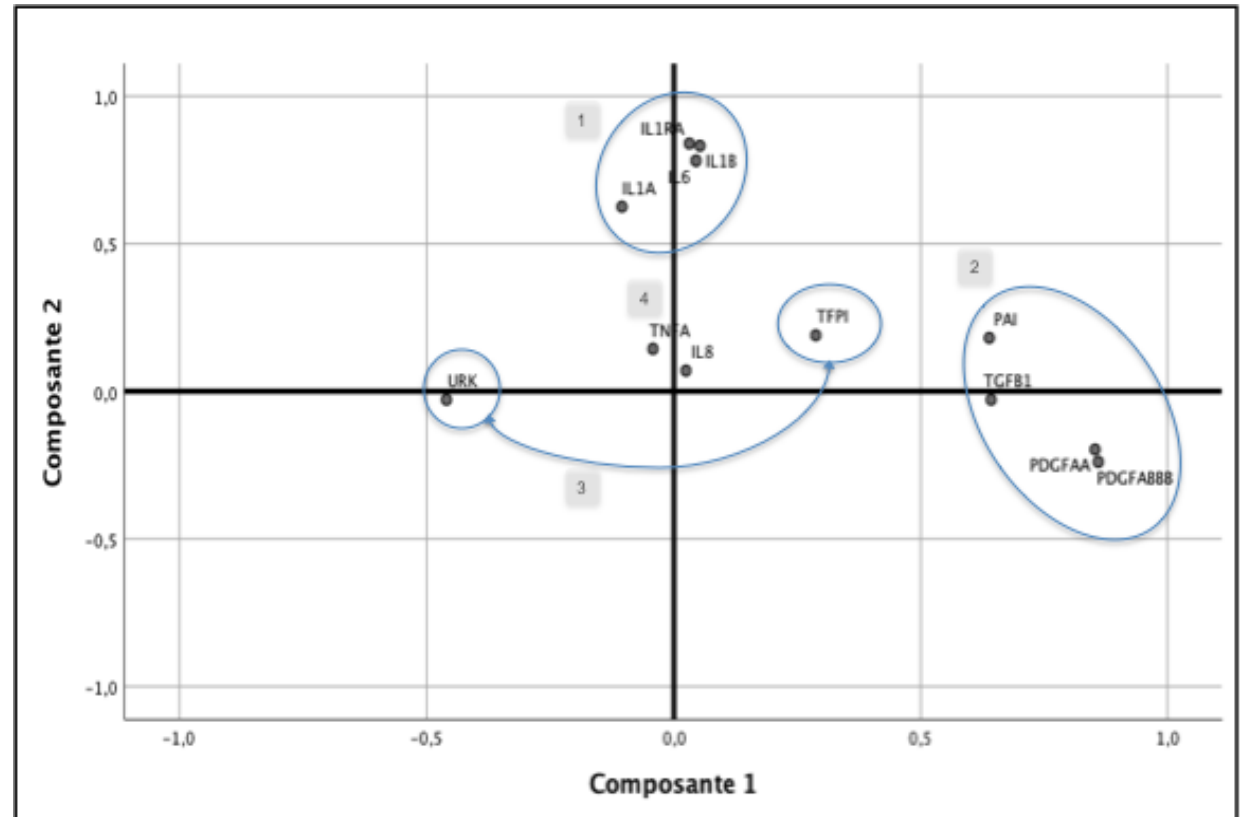
- group 1 : RVO < 5% without recurrence
- group 2 : RVO < 5% with recurrence
- group 3 : RVO > 5% without recurrence
- group 4 : RVO > 5% with recurrence

Results

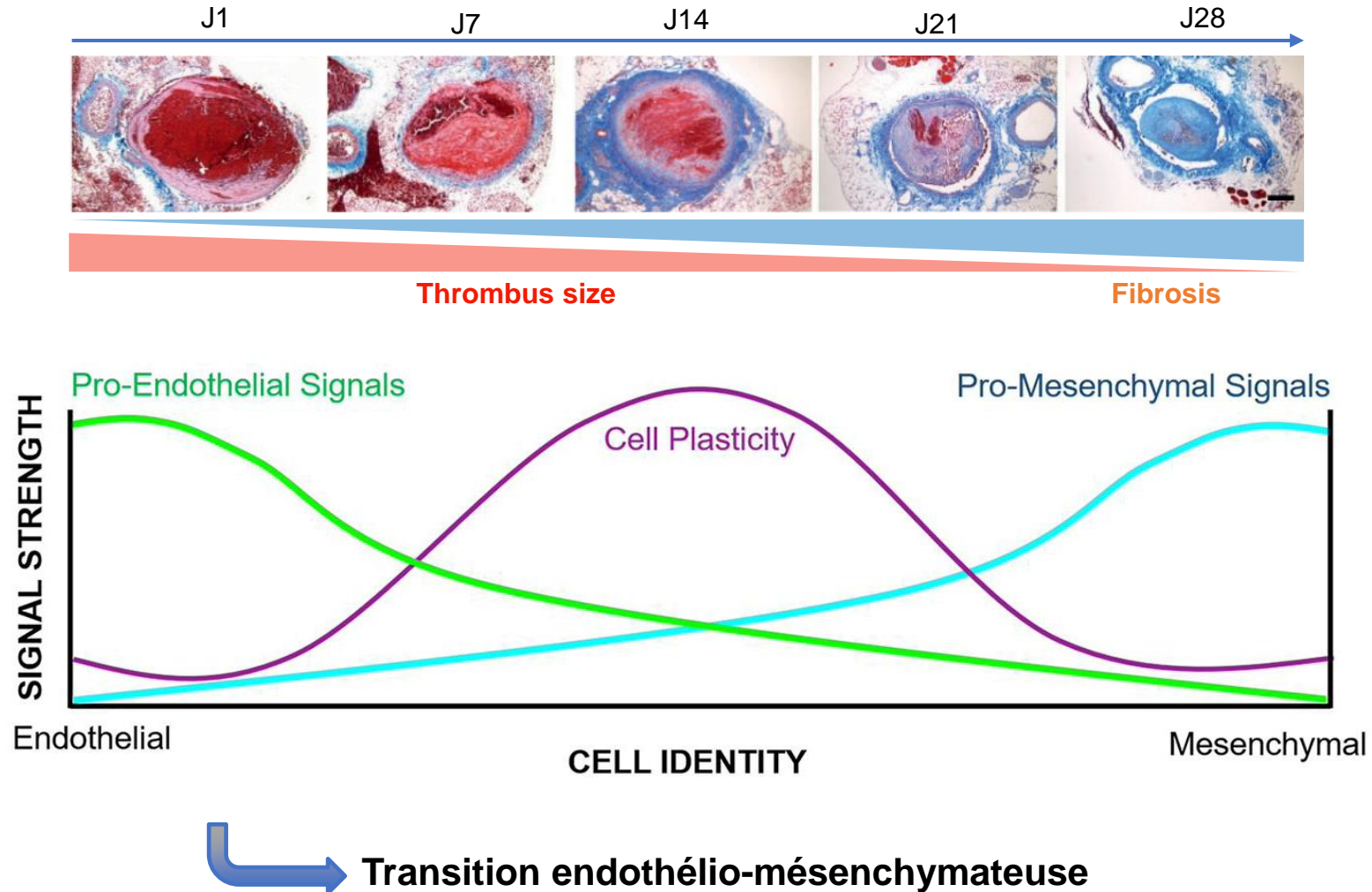
Markers of inflammation: higher
with RVO > 5%.

Markers of endothelial
dysfunction: higher with
recurrence.

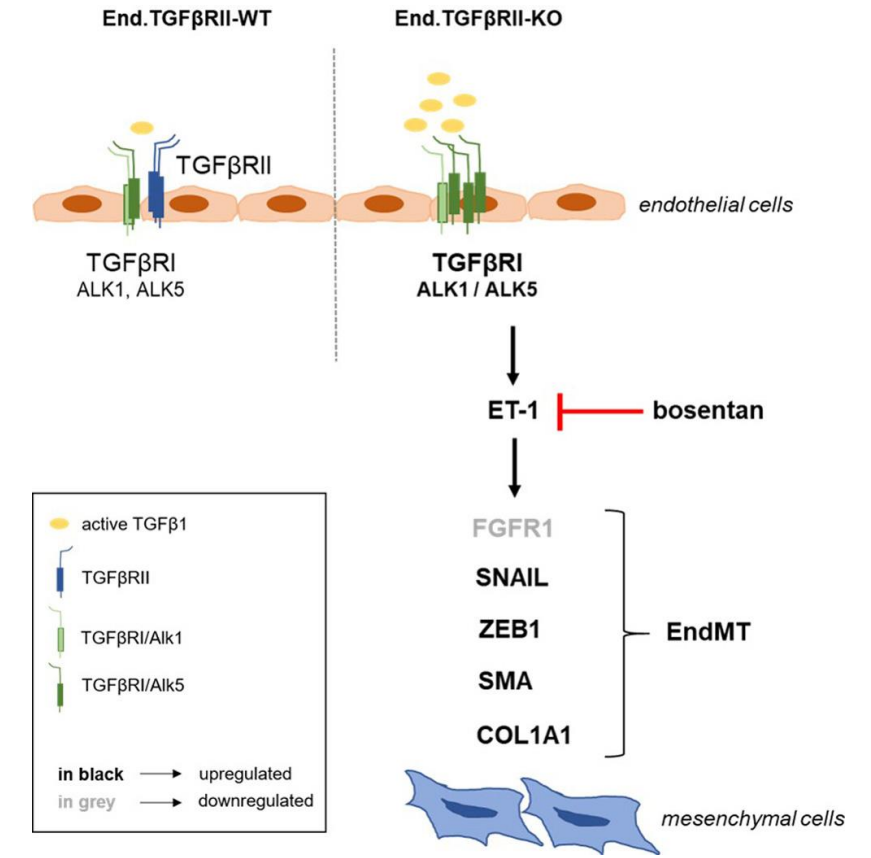
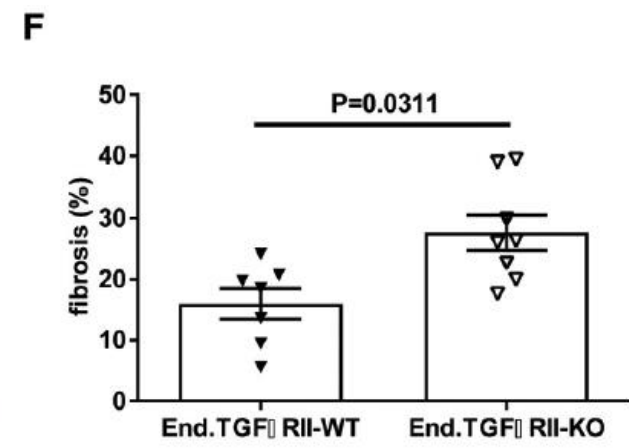
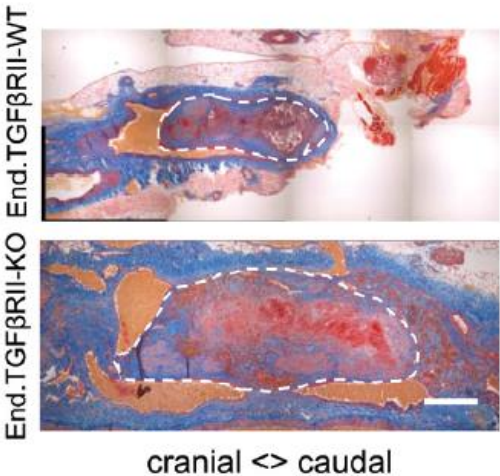
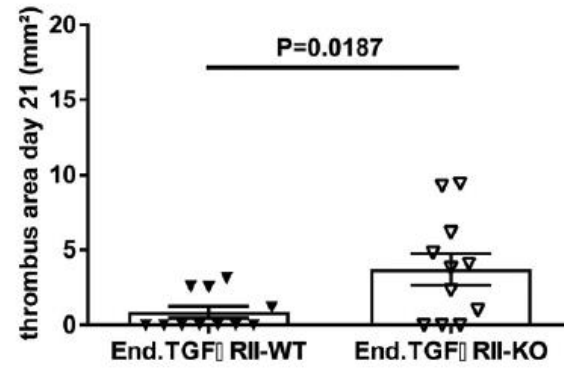
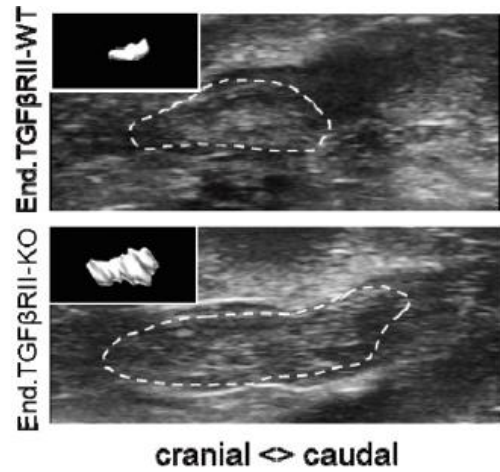
PAI-1 levels are associated with
RVO > 5%.



Endothelial cell response : mechanisms, regulation ?



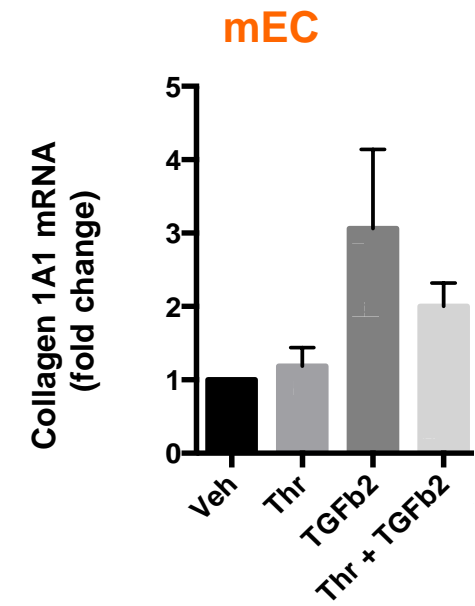
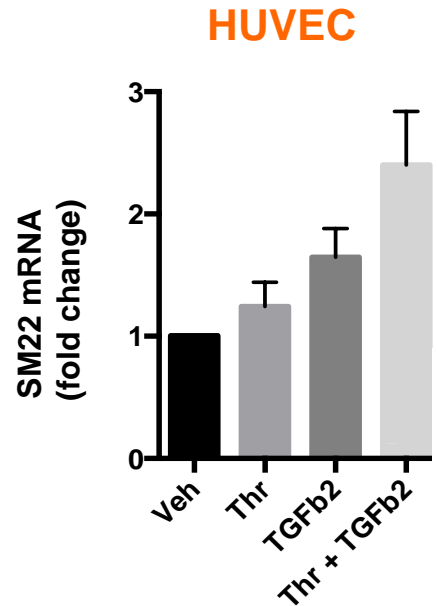
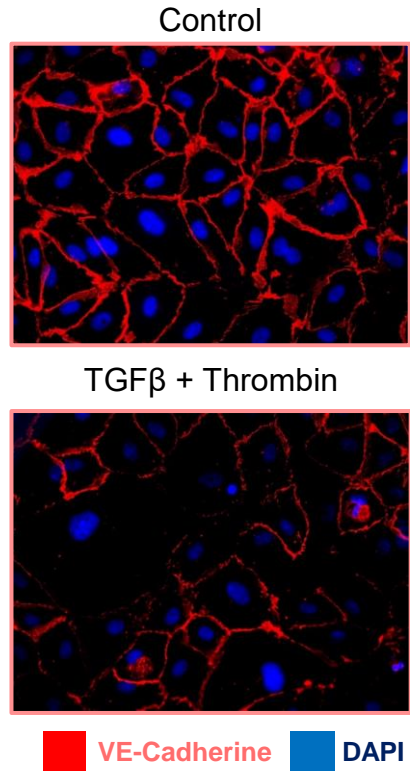
Endothelial cell response : mechanisms, regulation ?



Endothelial cell response : mechanisms, regulation ?

Hypothesis: Epigenetic regulation of EndMT in VTE: role in recurrent events?

Marion Pilard, PhD student

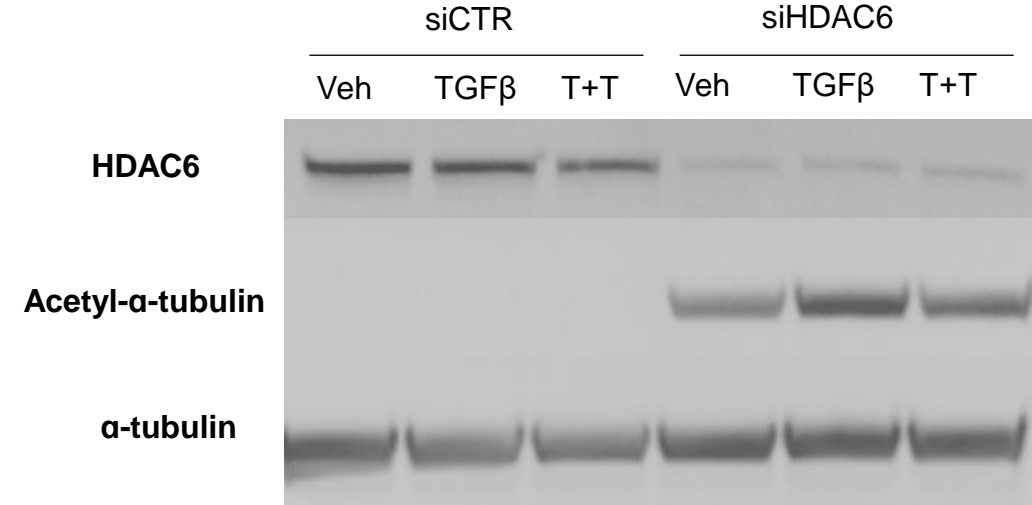
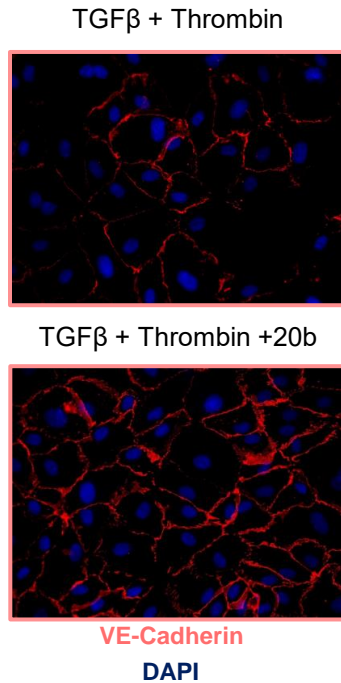
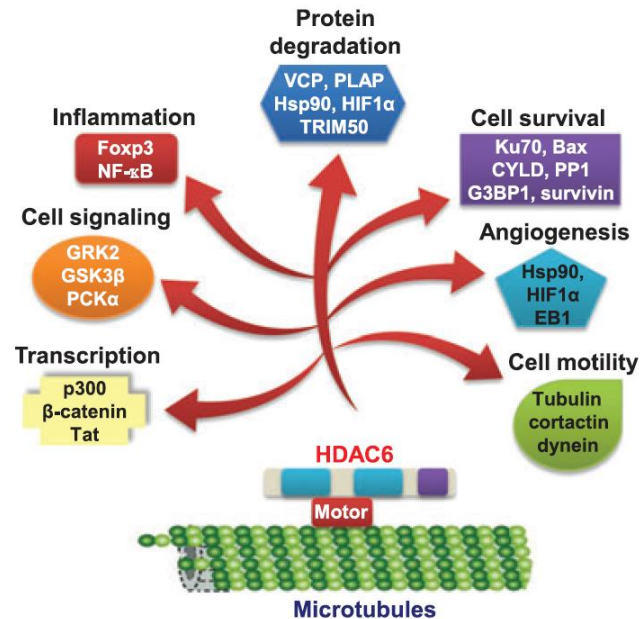


Mechanisms, regulation: HDACs?

Vascular remodeling, fibrosis, endothelial integrity and differentiation

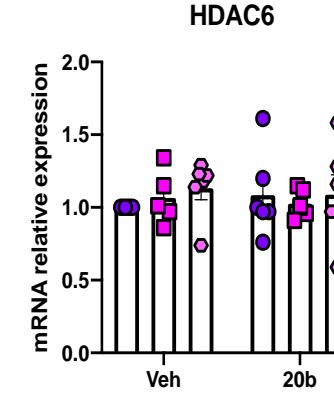
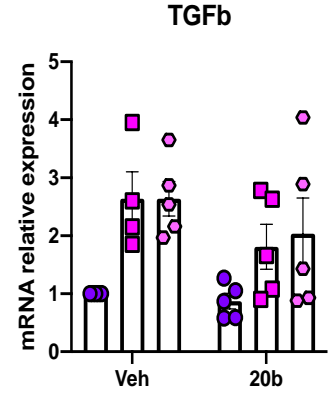
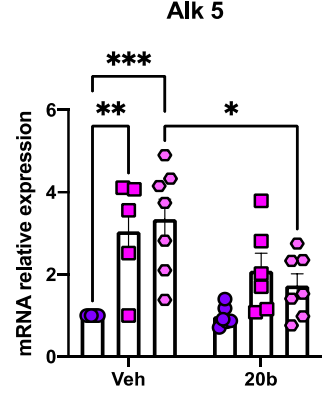
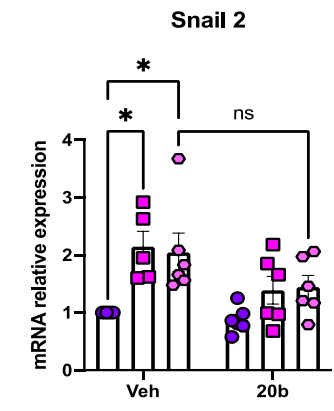
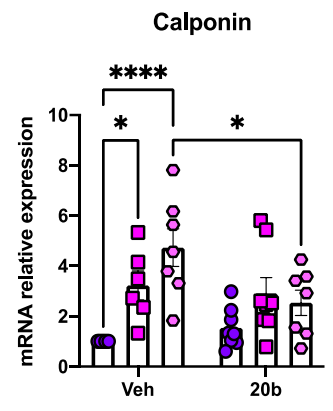
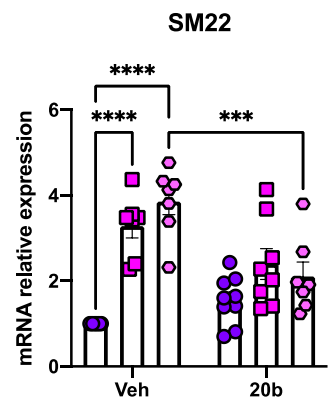
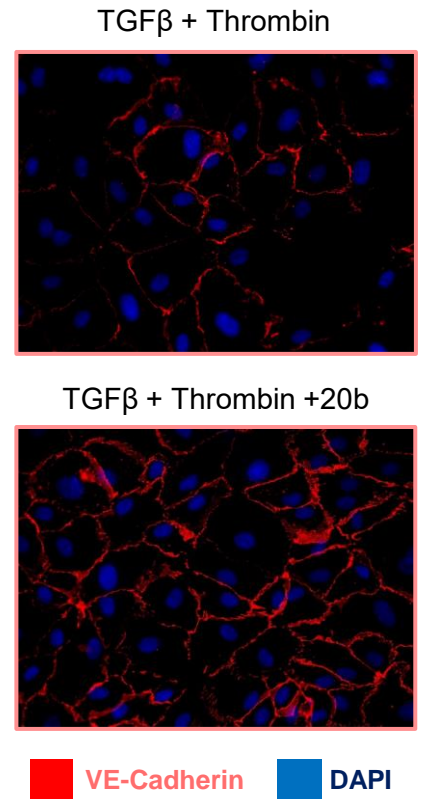
HDAC6 controls numerous processes, impacting cell migration, proliferation and survival

Lanig Civi, M2 student

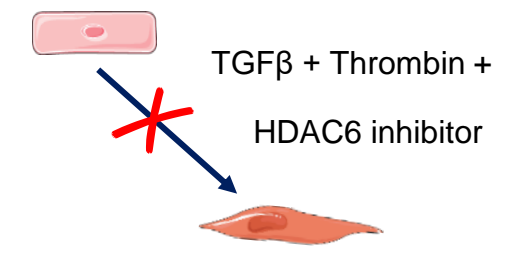


Endothelial cell response : endothelial-to-mesenchymal transition ?

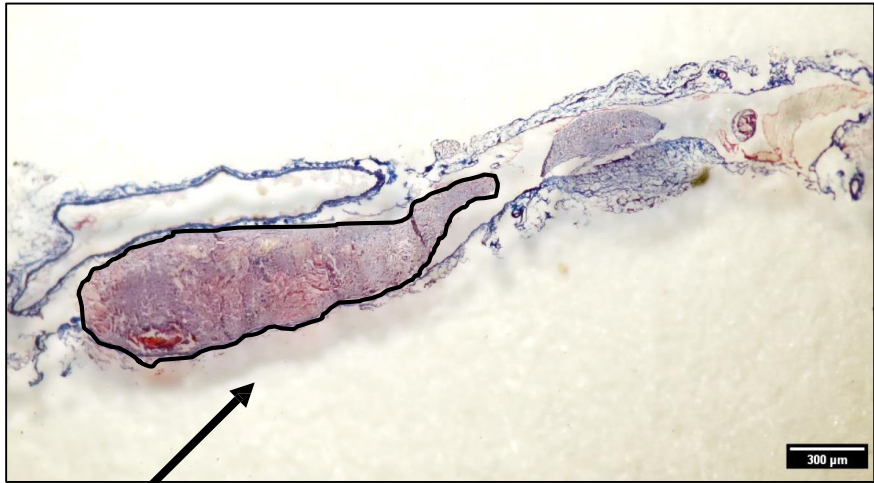
● CTR ■ TGFb ● T+T



↗ Endothelial markers
 ↘ Mesenchymal markers
 ↙ Genes involved in EndMT

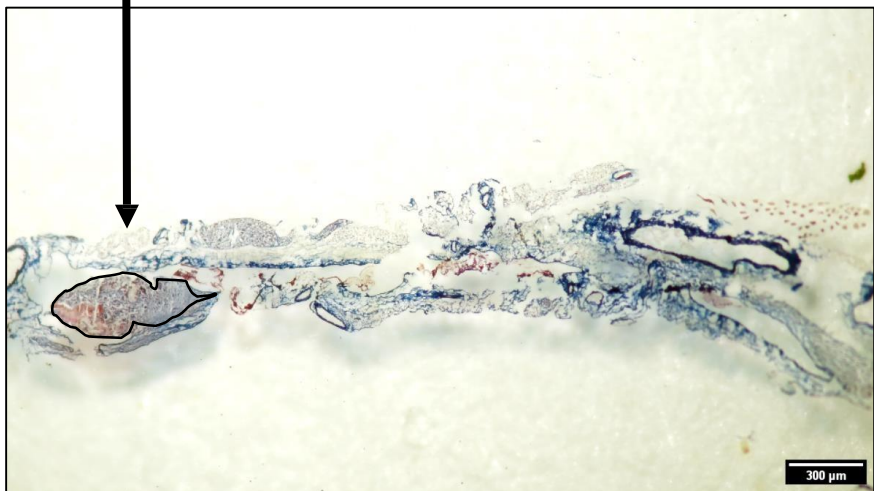


Mechanisms of endothelial-to-mesenchymal transition ?

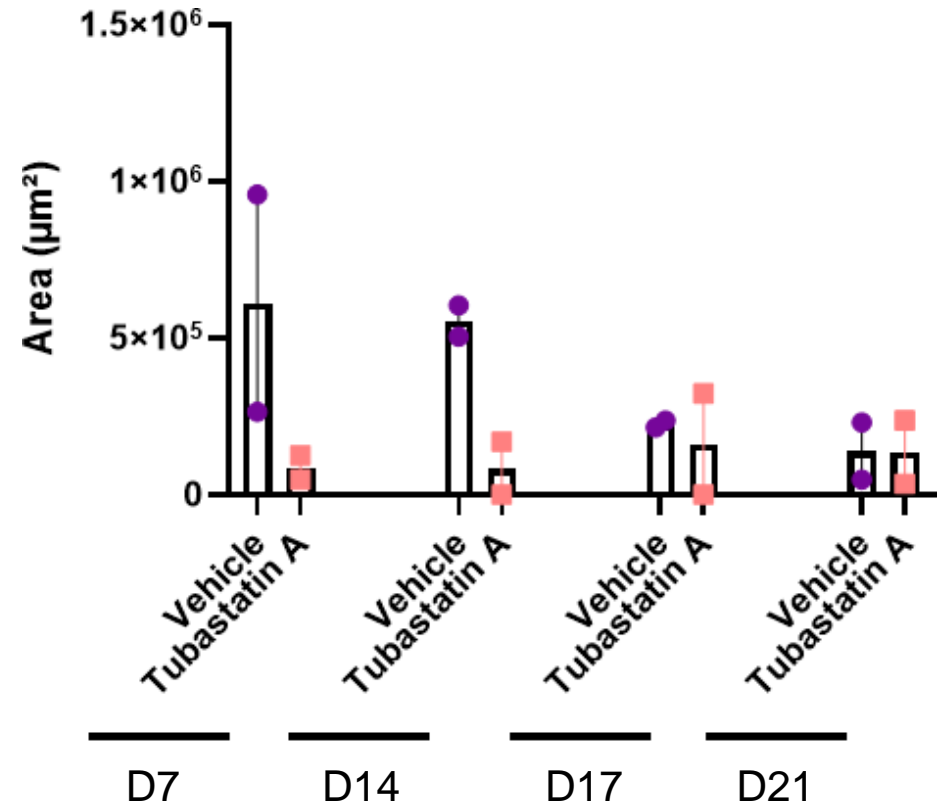


D7
Vehicle

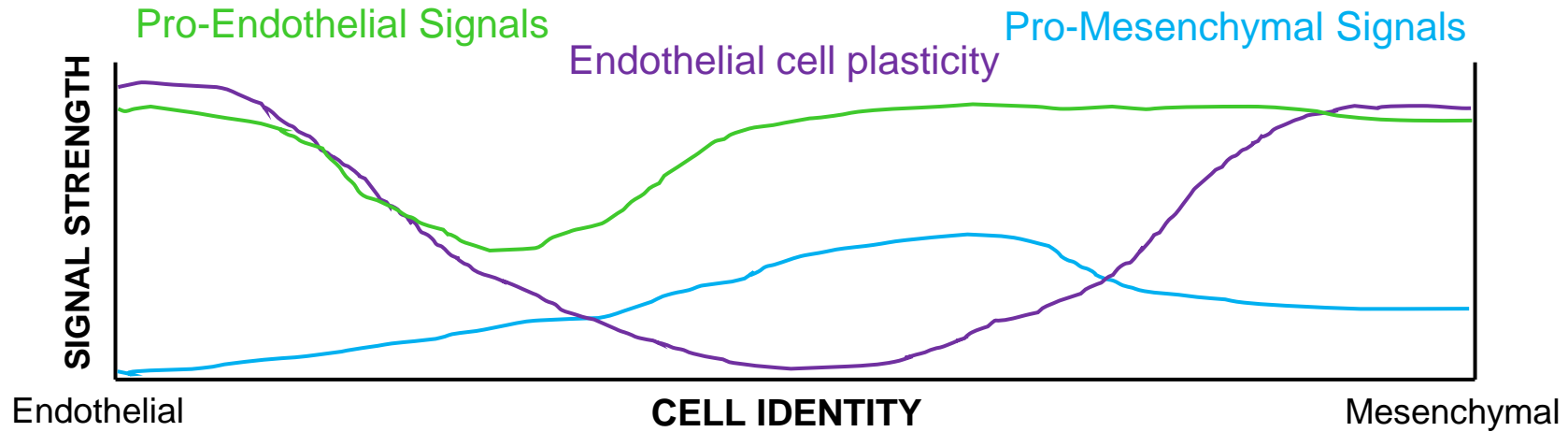
Thrombus



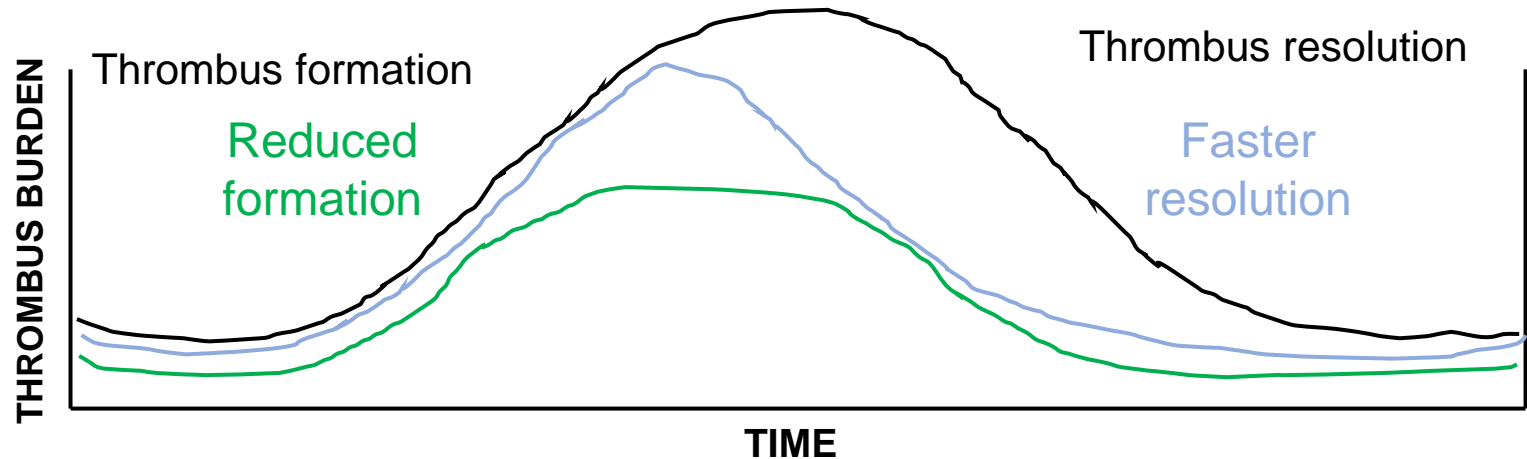
D7
Tubastatin A



Anti-endothelial dysfunction therapy ?



- P2X7R antagonists
- TLR3 antagonists
- Complement inhibition
- Interfiring with TGFβ
- HDAC inhibitors



Long term complications
 ↓
 Recurrence

Acknowledgements



Lab members

Rozenn Le Corre, MCF

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