

VI Foro Stago Academy



# Fisiopatología y consecuencias clínicas de los procesos de inmunotrombosis

**Dr. José Antonio Páramo.**

**Clínica Universidad de Navarra**

**Pamplona**

26/05/23



# DECLARACIÓN CONFLICTO DE INTERES

Items	Casa Comercial
Fondos para investigación	no
Empleado	no
Acciones	no
Consultorías o Asesorías	no
Conferencias	Boehringer, Daiichi-Sankyo, Rovi, Octapharma Stago
Becas	no
Comité de ética	no
Invitación a eventos Nacionales/Internacionales	Rovi



## Inflammation and Thrombosis: a bidirectional relationship

Infection/inflammation



Prothrombotic state (thromboinflammation)

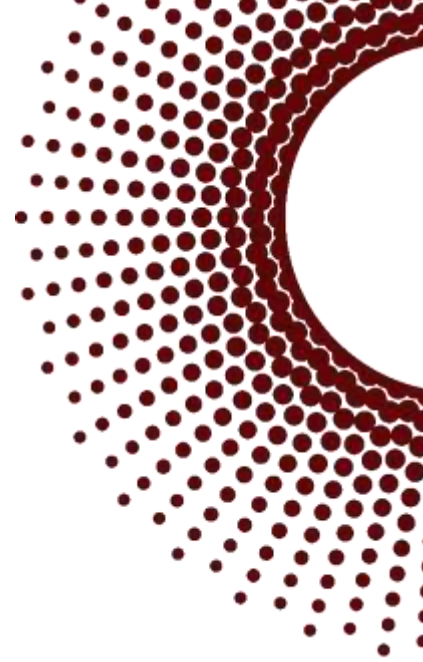


Microvascular  
thrombosis

Macrovascular  
thrombosis



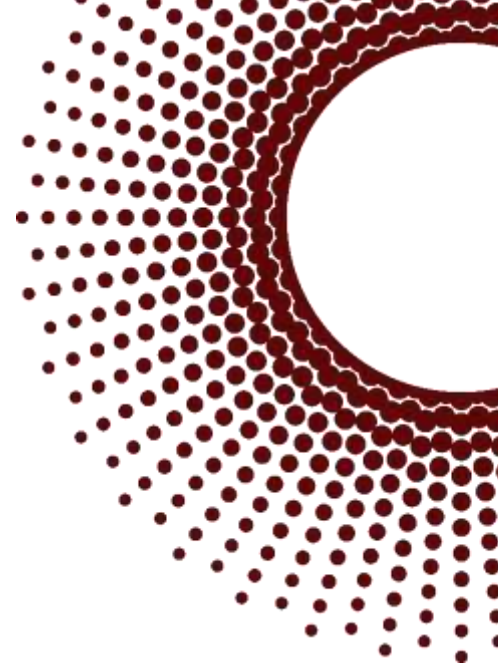
Increased morbidity and mortality





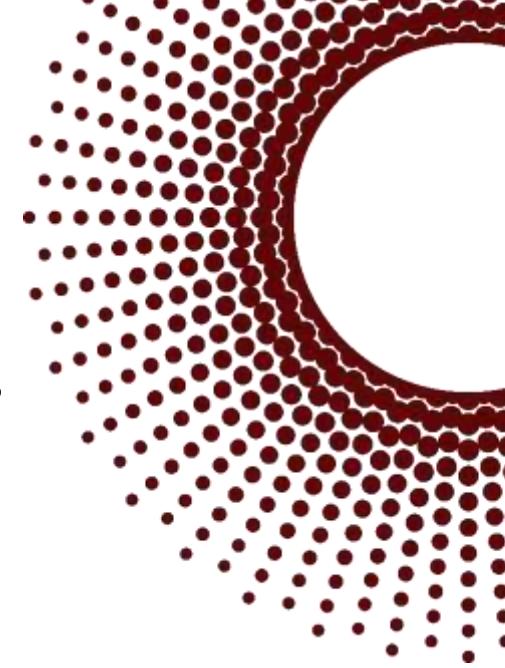
## Outline

- Concept of microvascular thrombosis and anatomy of the microcirculation
- Regulatory mechanisms of the vascular endothelium that prevent thrombosis
- Thromboinflammation or immunothrombosis: role of inflammasome
- Diseases accompanied by microvascular thrombosis
- Modulation of microvascular thrombosis

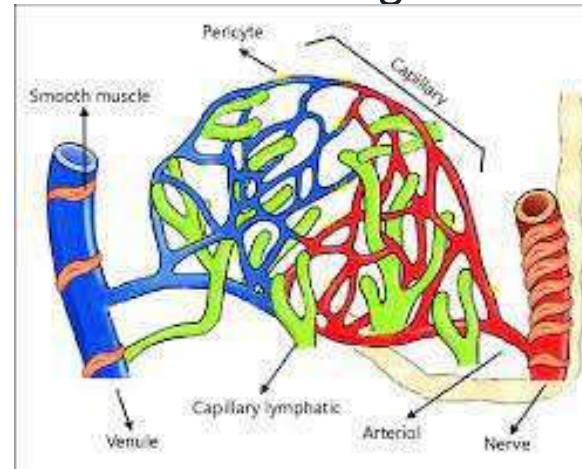




## Microvascular thrombosis: Concept and anatomy of microcirculation



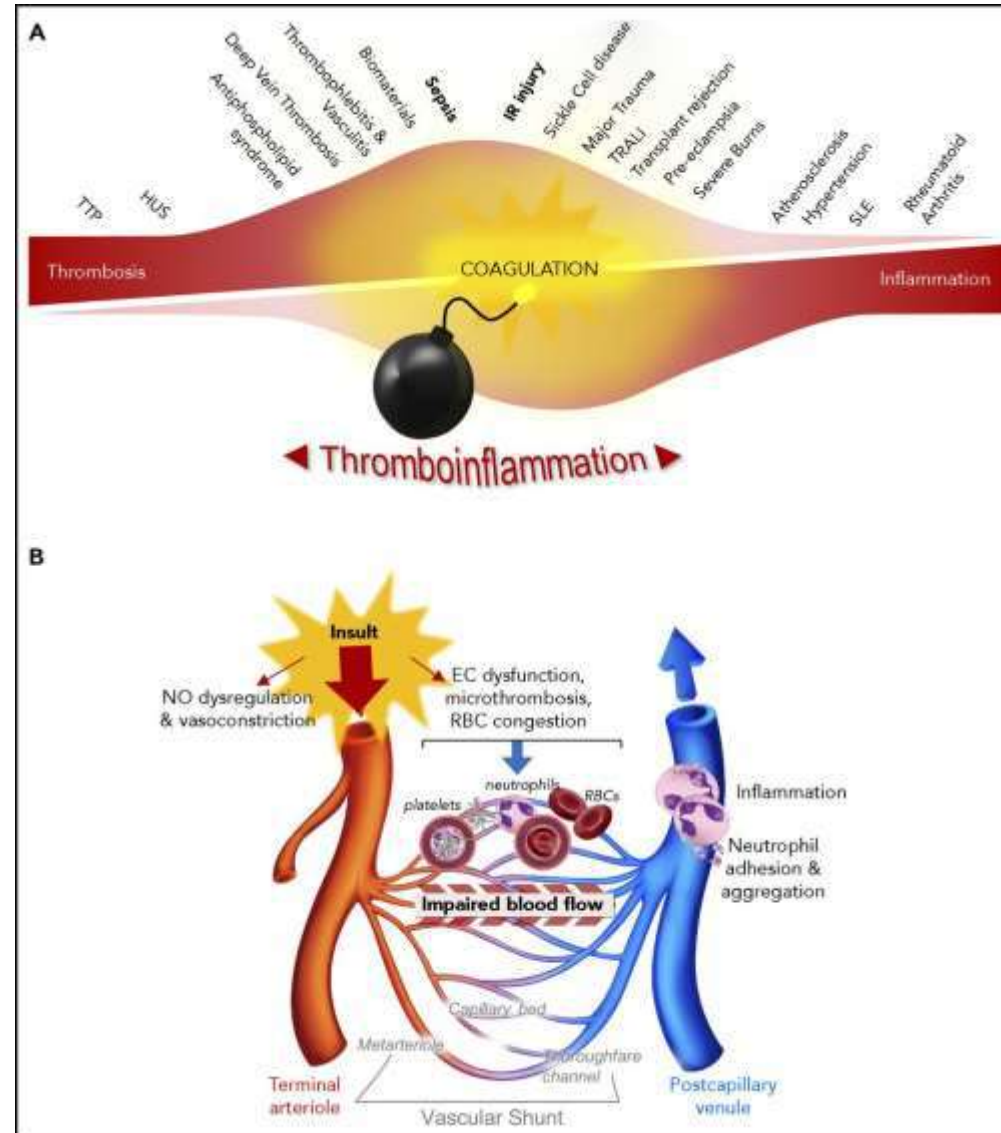
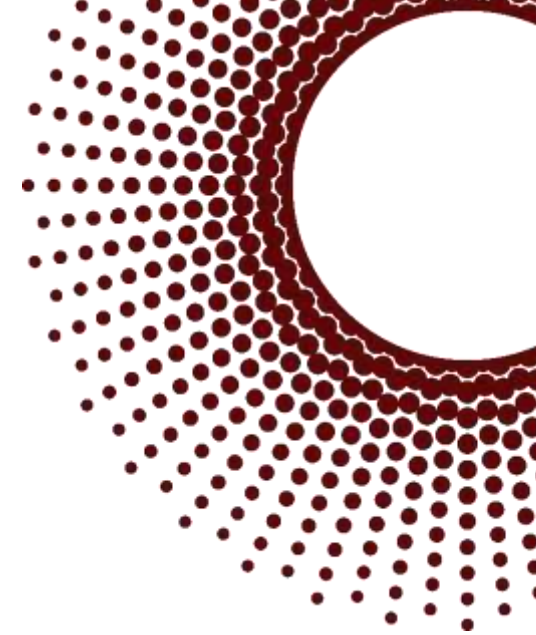
- In a simplified manner, the microcirculation may be defined as those blood vessels that cannot be observed clearly by the human eye without assistance
- The microvasculature is subdivided into 3 main categories of blood vessels:
  - Arterioles
  - Capillaries
  - Venules



- Distinguished by location, function and structure
- The sum of capillary surface area is larger than the area of a tennis court for doubles matches (nearly 261m<sup>2</sup>)
- Microvessels are subjected to significantly increased wall shear stress

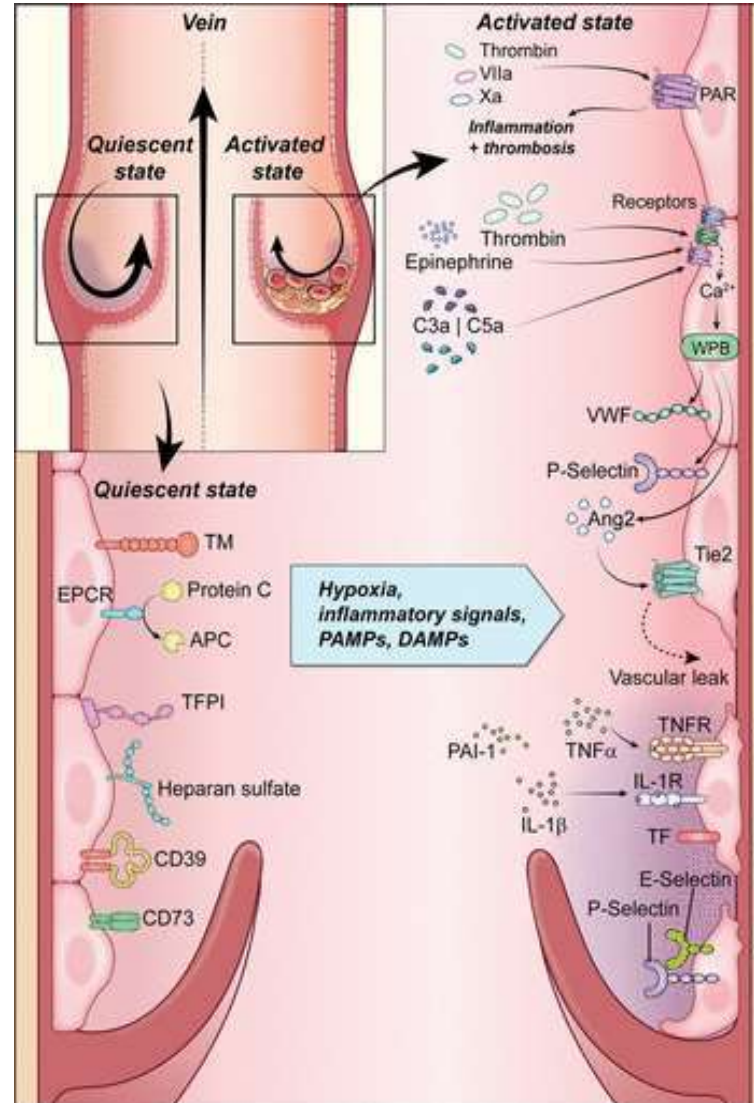
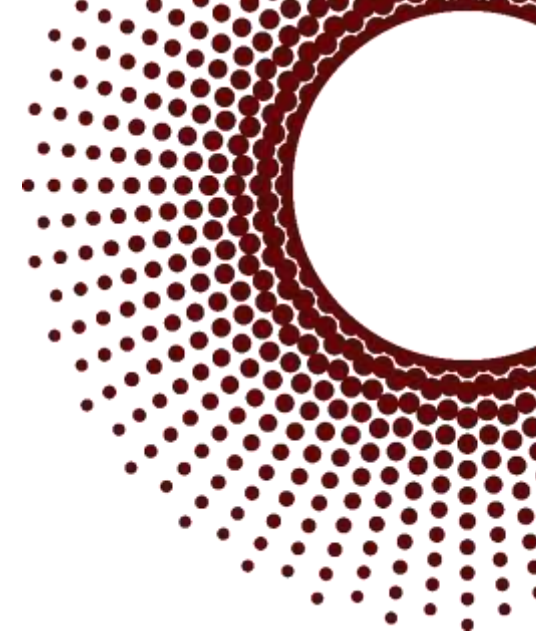


# Thromboinflammation: an important pathogenic process linked to a diverse range of human diseases





# Antithrombotic function of endothelial cells





# ¿Qué hay de nuevo en los mecanismos de trombosis?

Med Clin (Barc). 2019;153(2):78-81

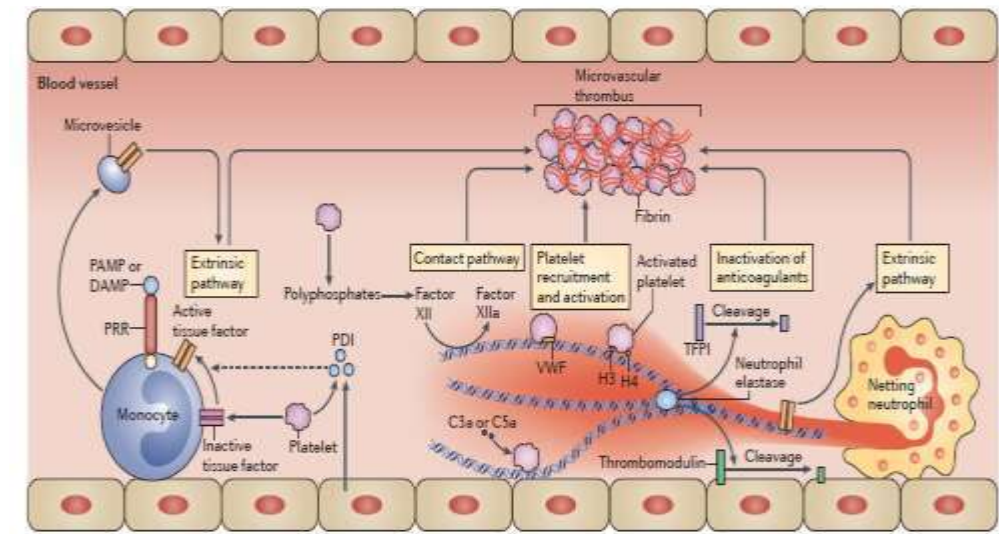
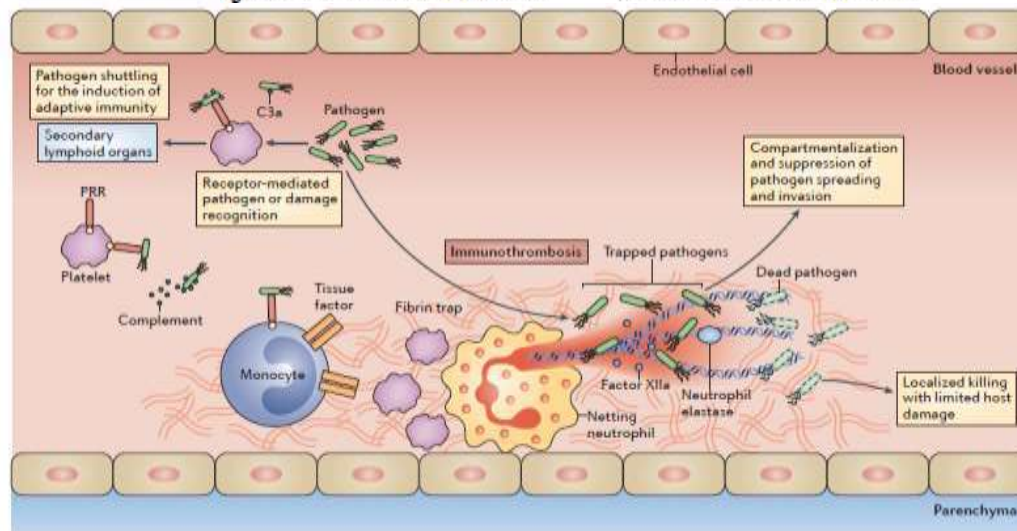


Special article

## New mechanisms in venous thrombosis: Immunothrombosis<sup>☆</sup>

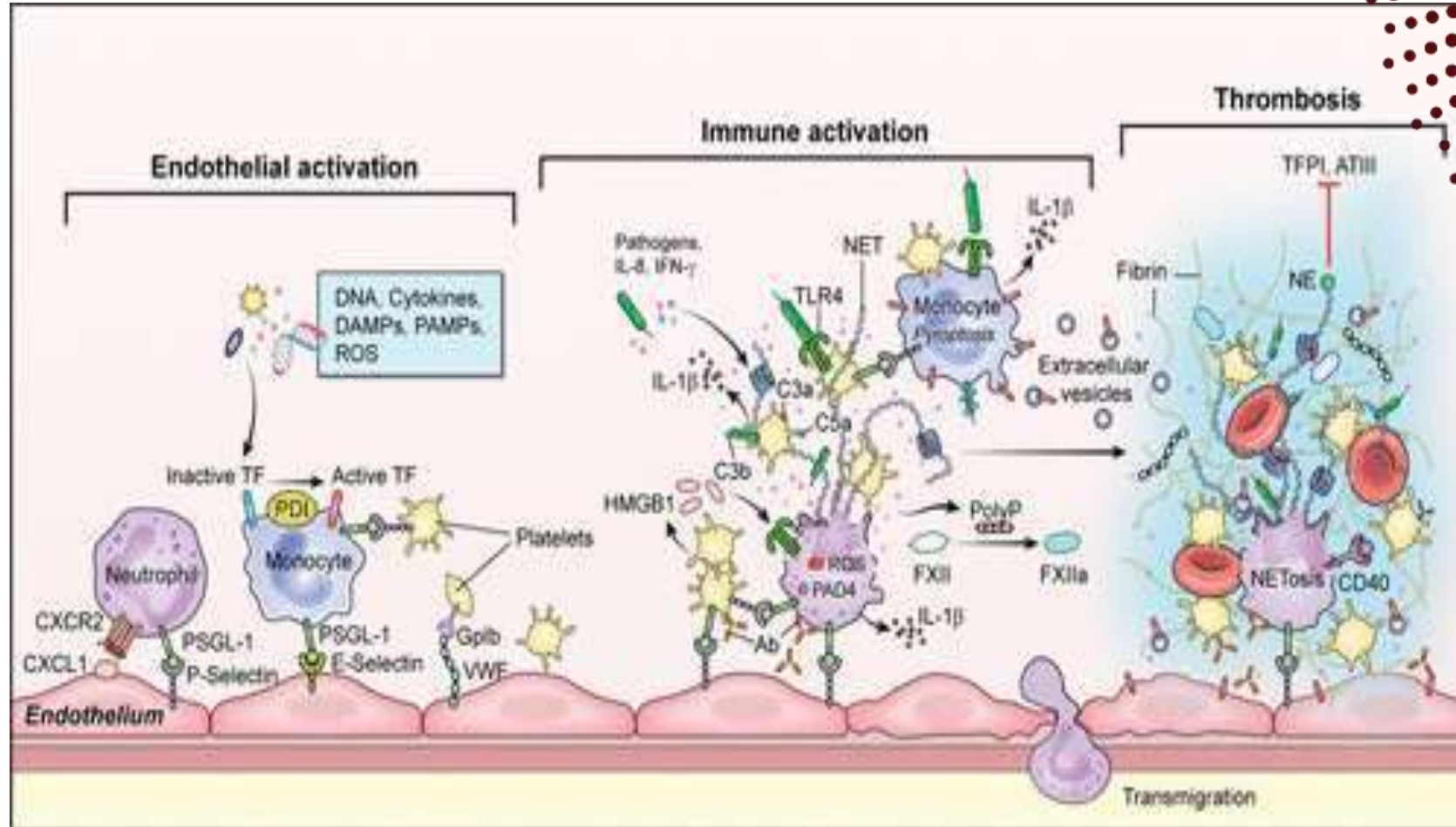
### Nuevos mecanismos en la trombosis venosa: inmunotrombosis

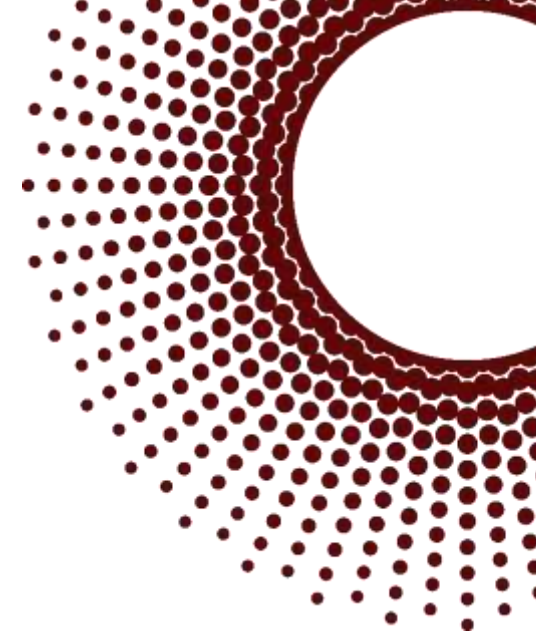
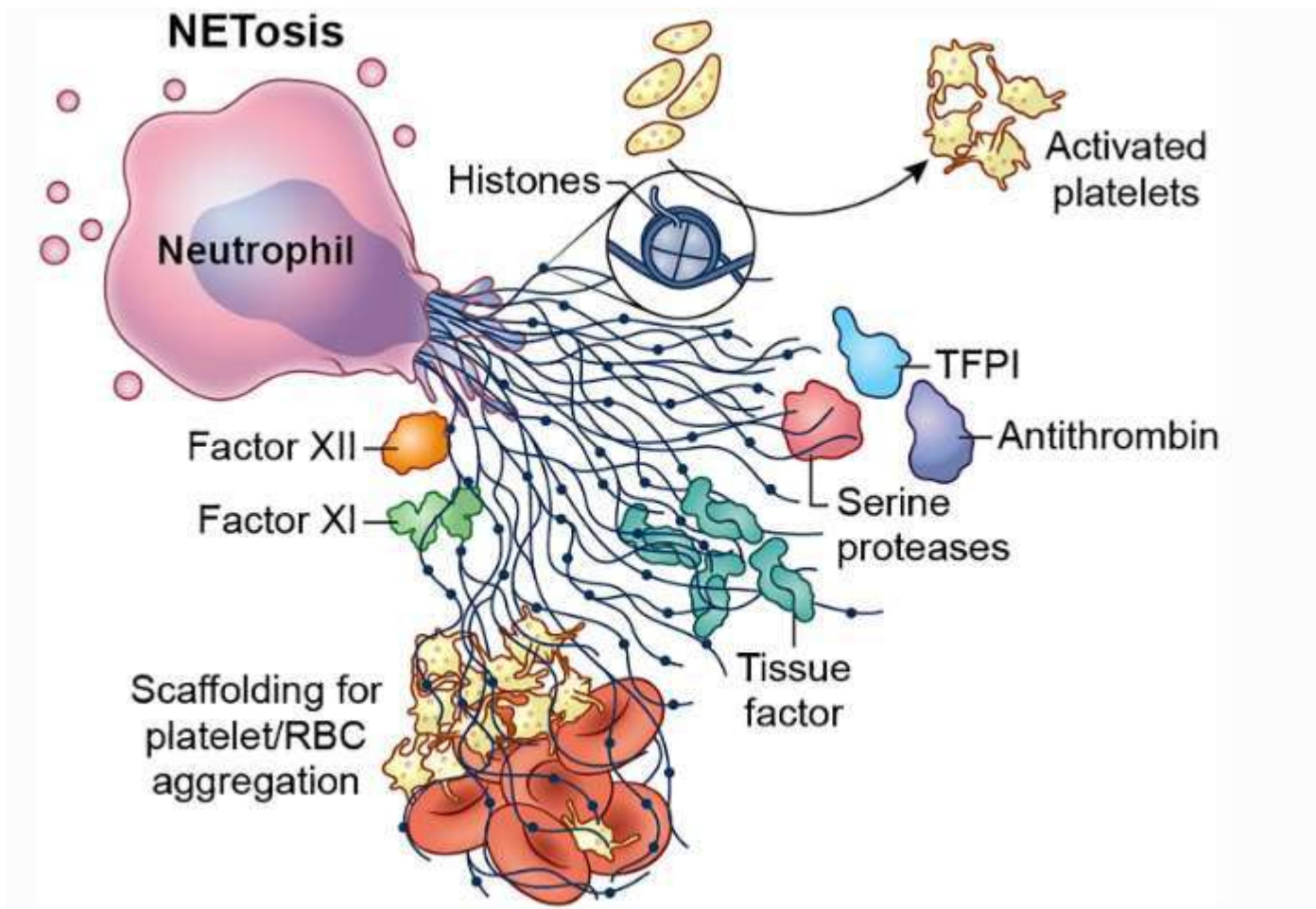
José Antonio Páramo<sup>a,b,c,\*</sup>, Ramón Lecumberri<sup>a,b,c</sup>



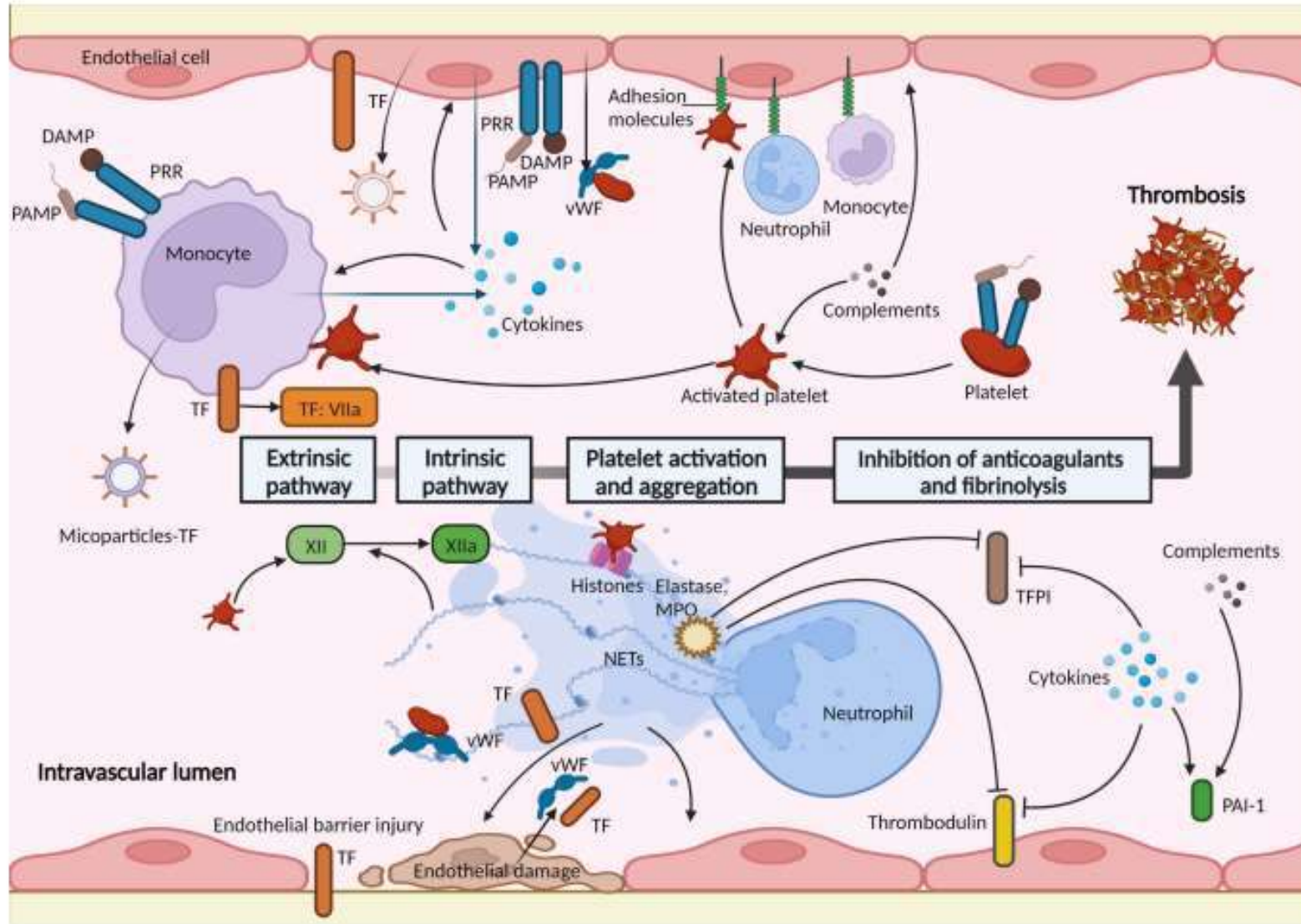


# Proinflammatory and prothrombotic function of inflamed endothelial cells

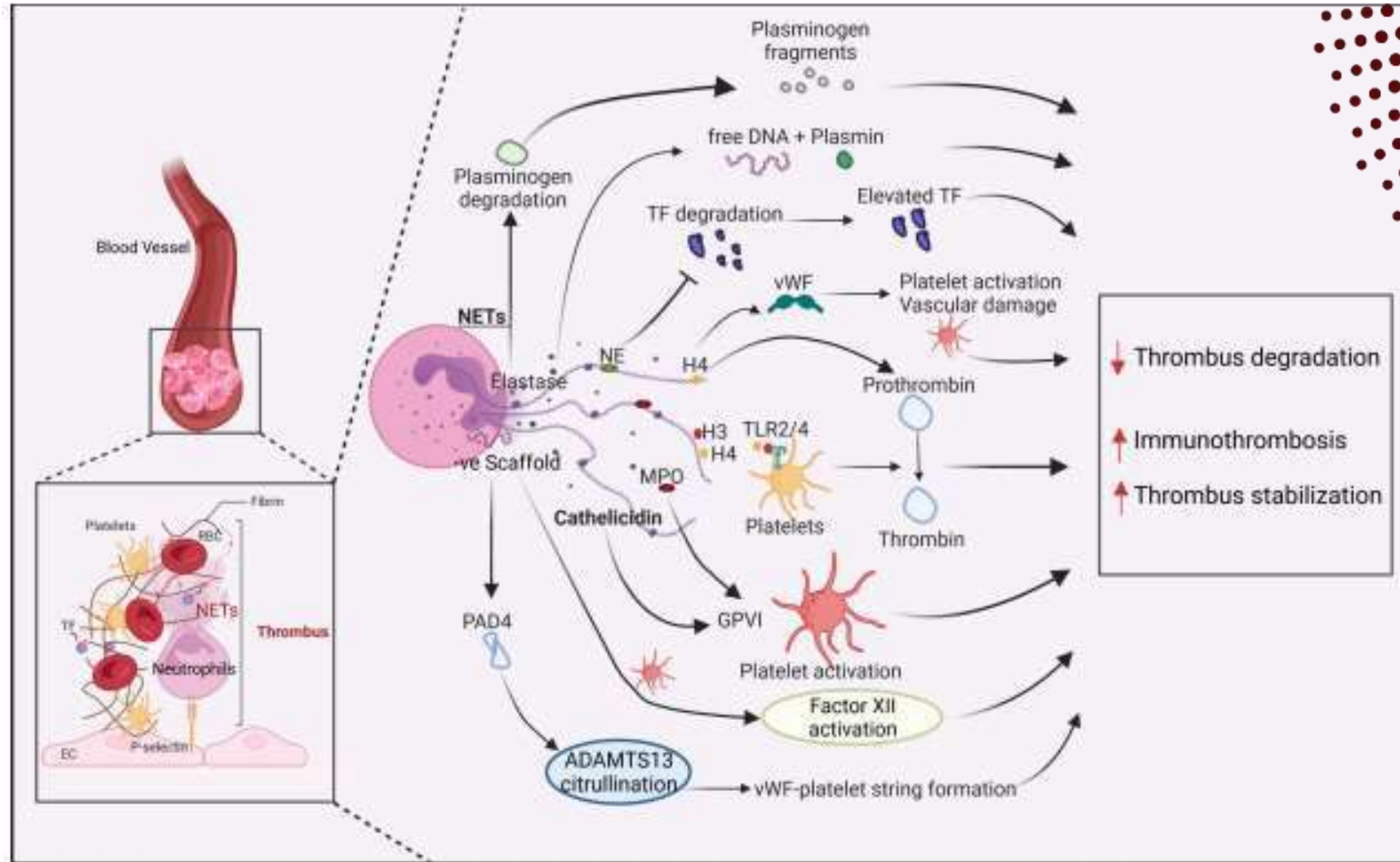


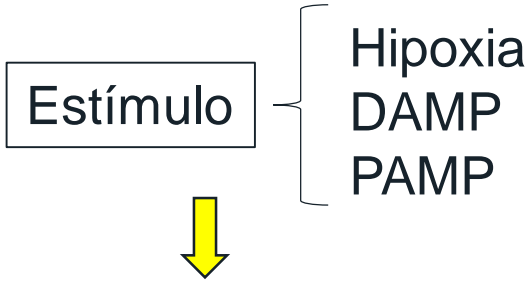


# Immunothrombosis as the final outcome in pathogen-induced neutrophil activation

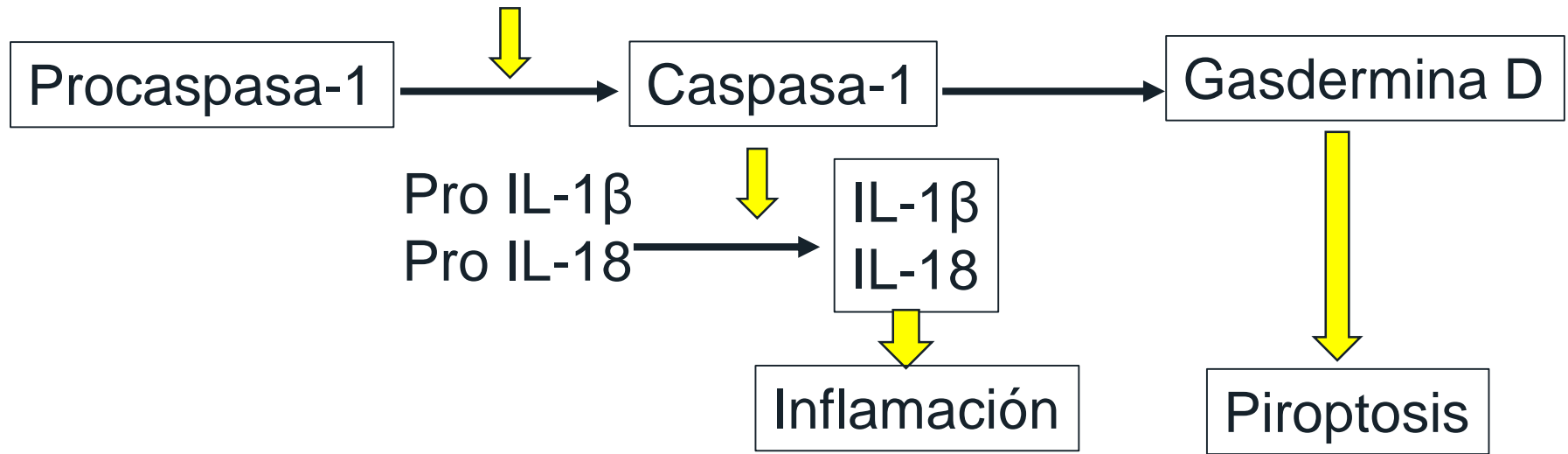


# NETs (neutrophil extracellular traps) components induce immunothrombosis





**Activación inflammasoma (NLRP3)**



DAMP: Patrón molecular asociado a daño  
PAMP: Patrón molecular asociado a patógenos

Reumatol Clin. 2020;xxx(xx):xxx-xxx.

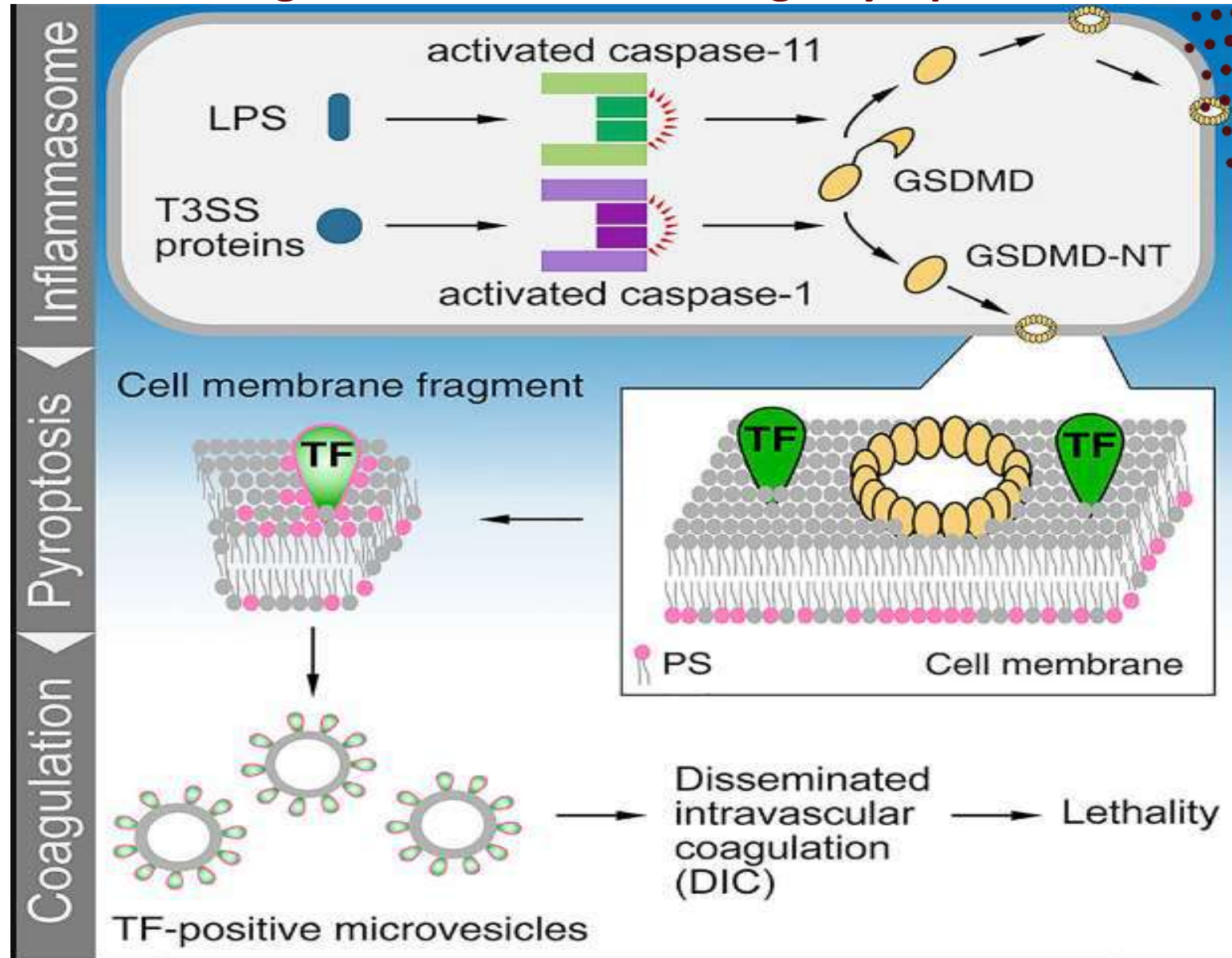
# Reumatología Clínica

www.reumatologiaclinica.org

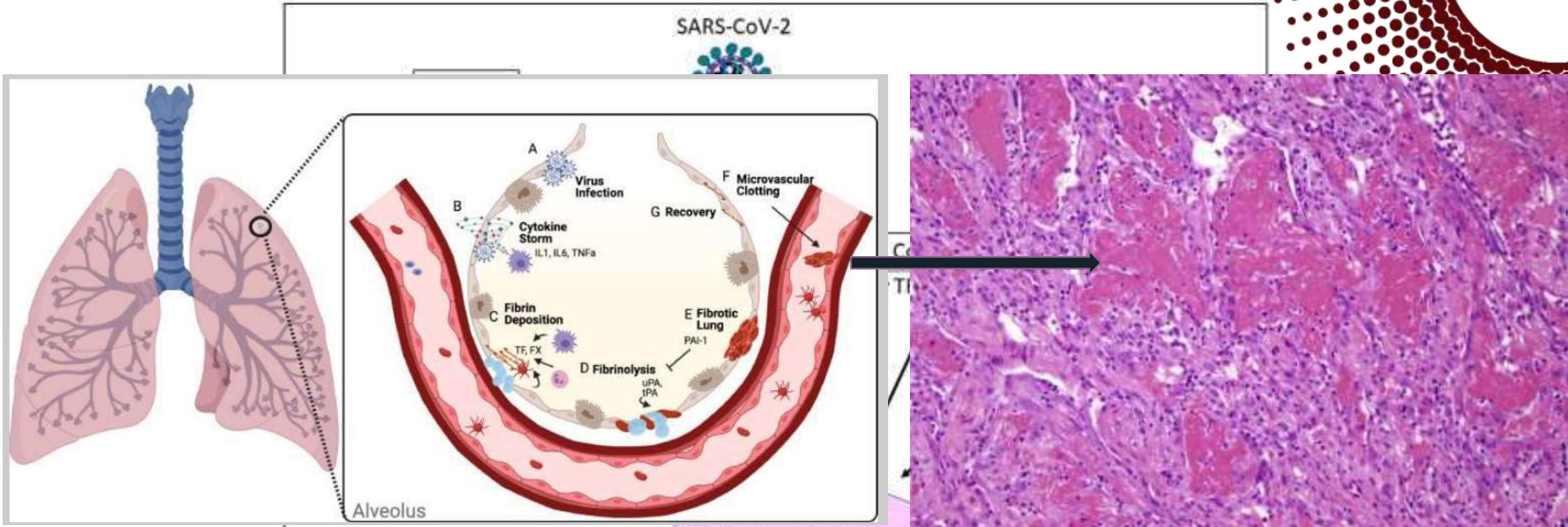
Artículo especial  
Respuesta inflamatoria en relación con COVID-19 y otros fenotipos protrombóticos  
José A. Páramo  
Servicio de Hematología, Clínica Universidad de Navarra. IDISNA. CIBERCV, Pamplona, España

- Sepsis, COVID-19
- Behcet
- Vasculitis
- LES, AR
- Enfermedad inflamatoria intestinal
- Síndrome antifosfolípido
- Fiebre Mediterránea familiar

# Inflammasome Activation Triggers Blood Clotting and Host Death through Pyroptosis



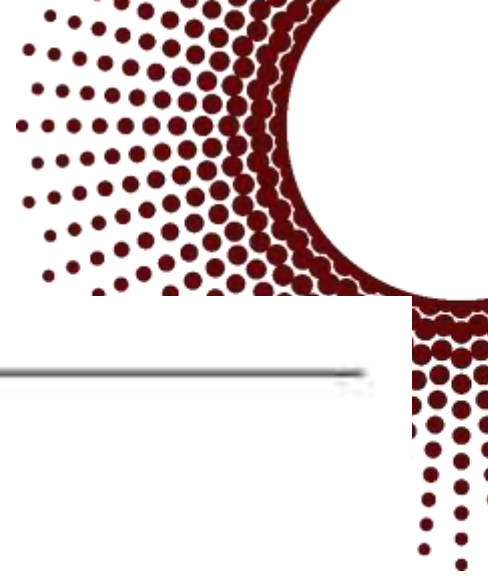
# COVID-19 and microvascular thrombosis



Venous and Arterial  
Thromboembolism  
Microvascular  
thrombosis



COVID-19: an example of microvascular thrombosis



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# Endothelial dysfunction and immunothrombosis as key pathogenic mechanisms in COVID-19

Nature Rev immunol 2021

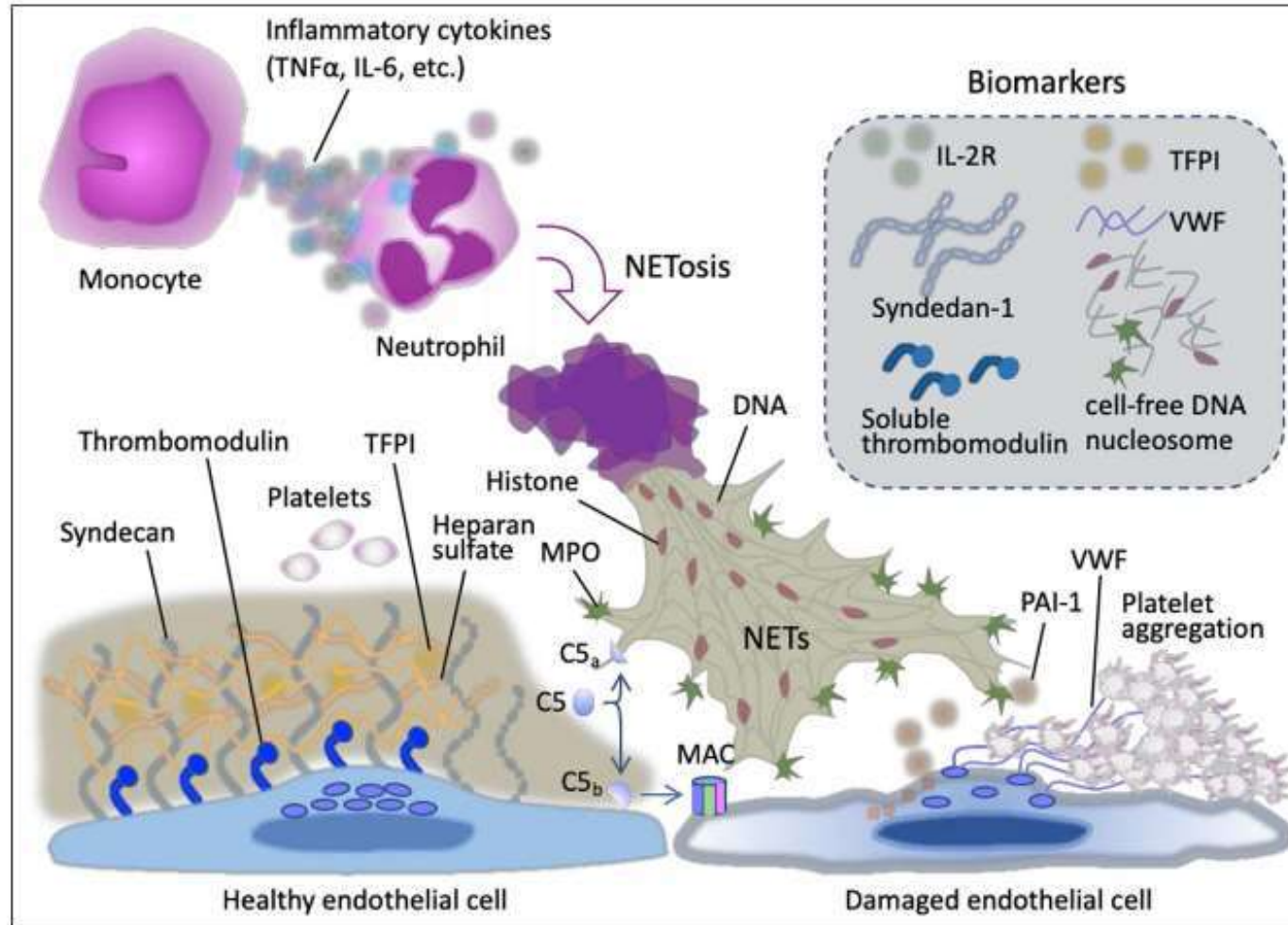
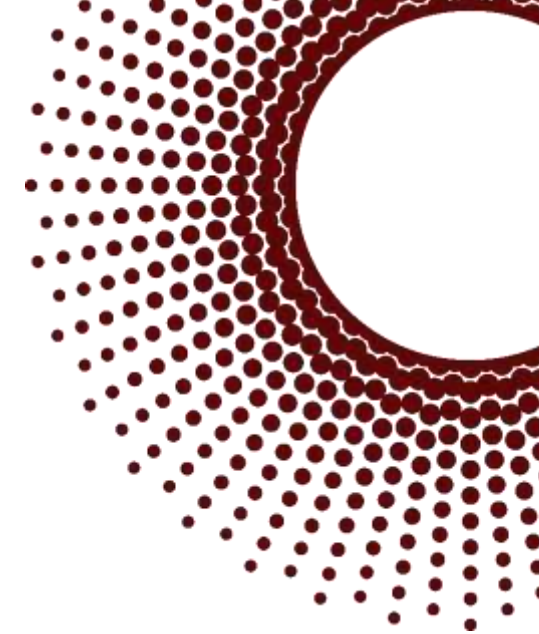
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*Aldo Bonaventura<sup>1</sup>, Alessandra Vecchi<sup>2</sup>, Lorenzo Dagna, Kimberly Martinod<sup>3</sup>,  
Dave L. Dixon, Benjamin W. Van Tassel, Francesco Dentali,  
Fabrizio Montecucco<sup>4</sup>, Steffen Massberg<sup>5</sup>, Marcel Levi and Antonio Abbate*





# Damage to the endothelium could underpin the thrombosis and inflammation induced by COVID-19

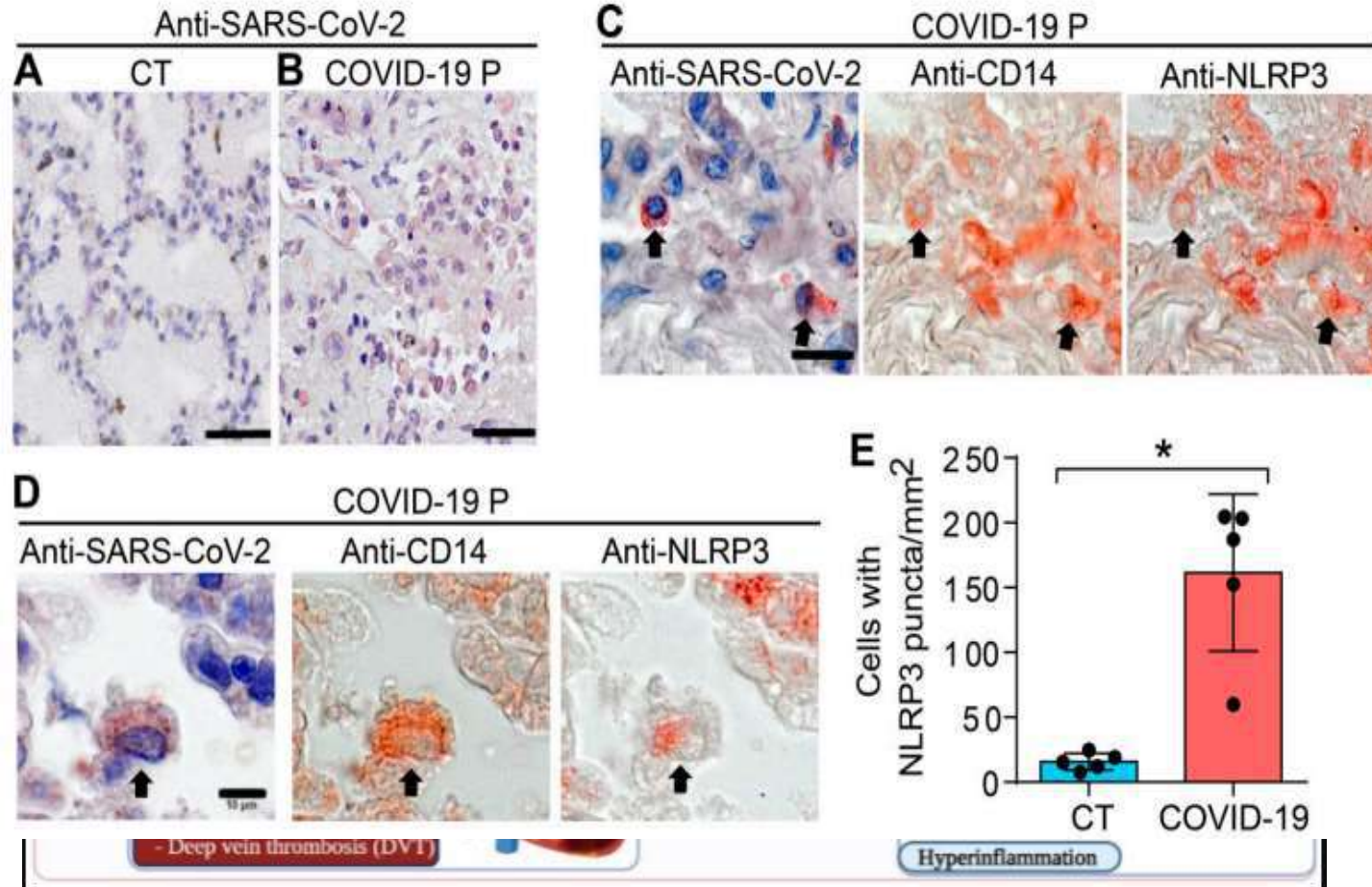


**Endothelial cells orchestrate COVID-19 coagulopathy**

BRIEF DEFINITIVE REPORT

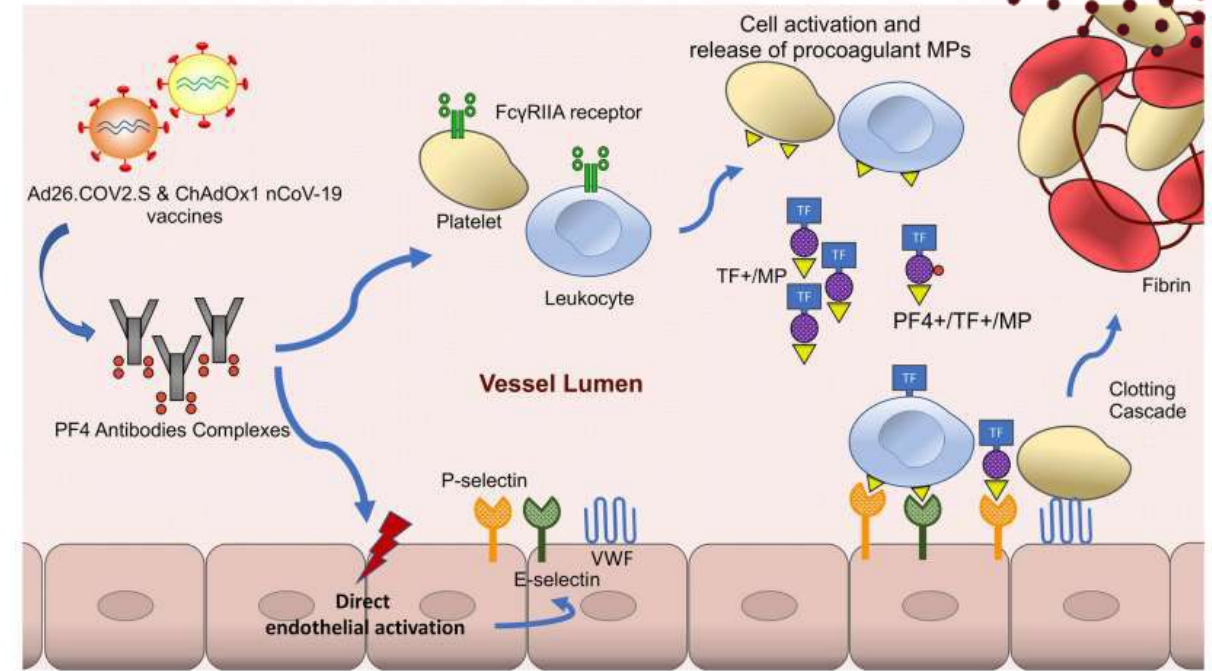
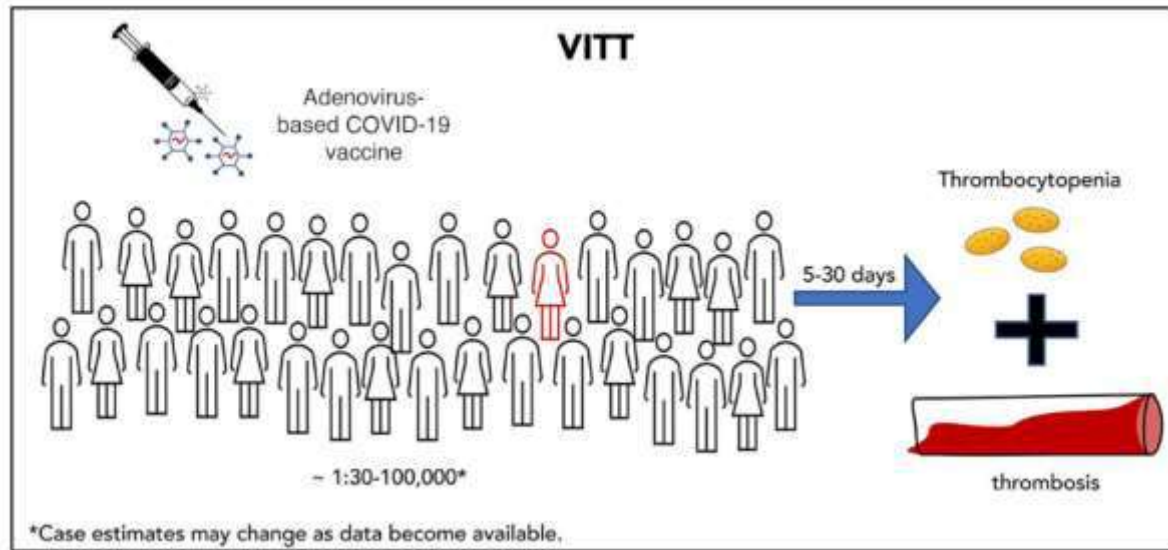
# Inflammasomes are activated in response to SARS-CoV-2 infection and are associated with COVID-19 severity in patients

Tamara S. Rodrigues<sup>1</sup>, Keyla S.G. de Sá<sup>1</sup>, Adriene Y. Ishimoto<sup>1</sup>, Amanda Becerra<sup>1</sup>, Samuel Oliveira<sup>1</sup>, Leticia Almeida<sup>1,2</sup>





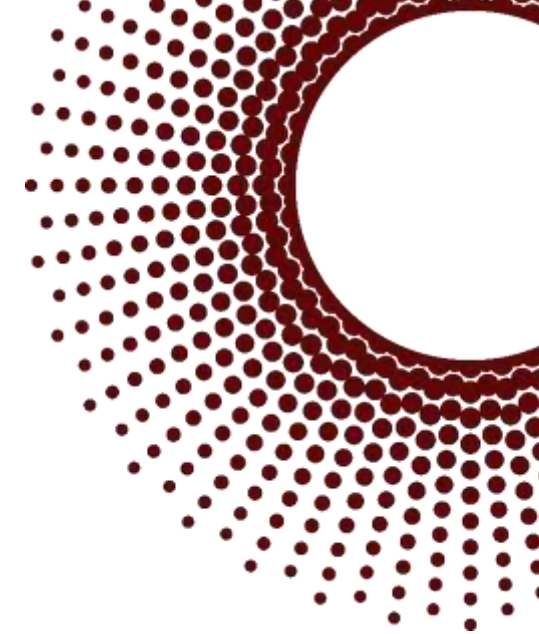
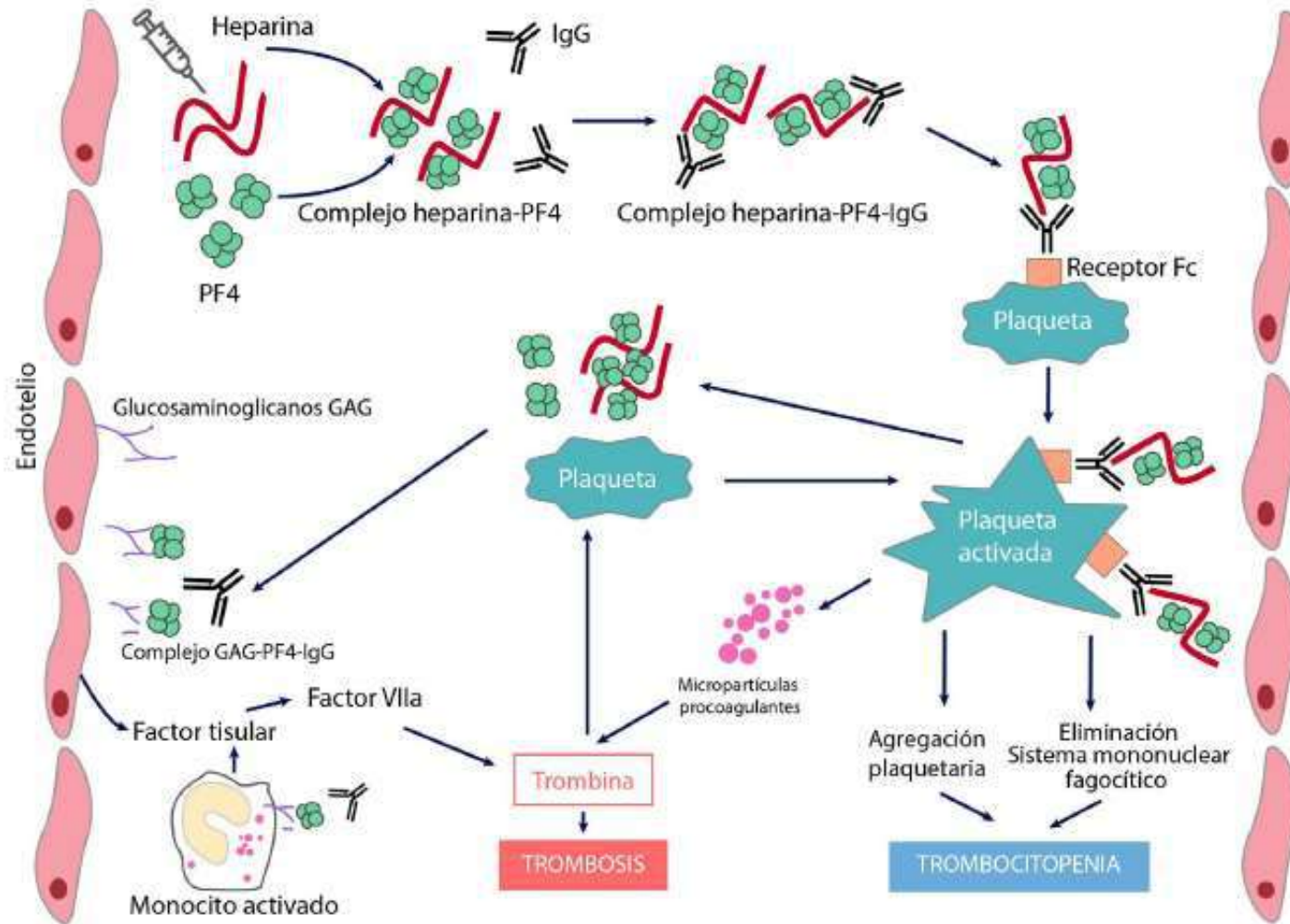
# Proposed mechanisms for thrombosis in vaccine-induced immune thrombocytopenia (VITT)



Cerebral vein thrombosis  
Splanchnic thrombosis  
Microvascular thrombosis

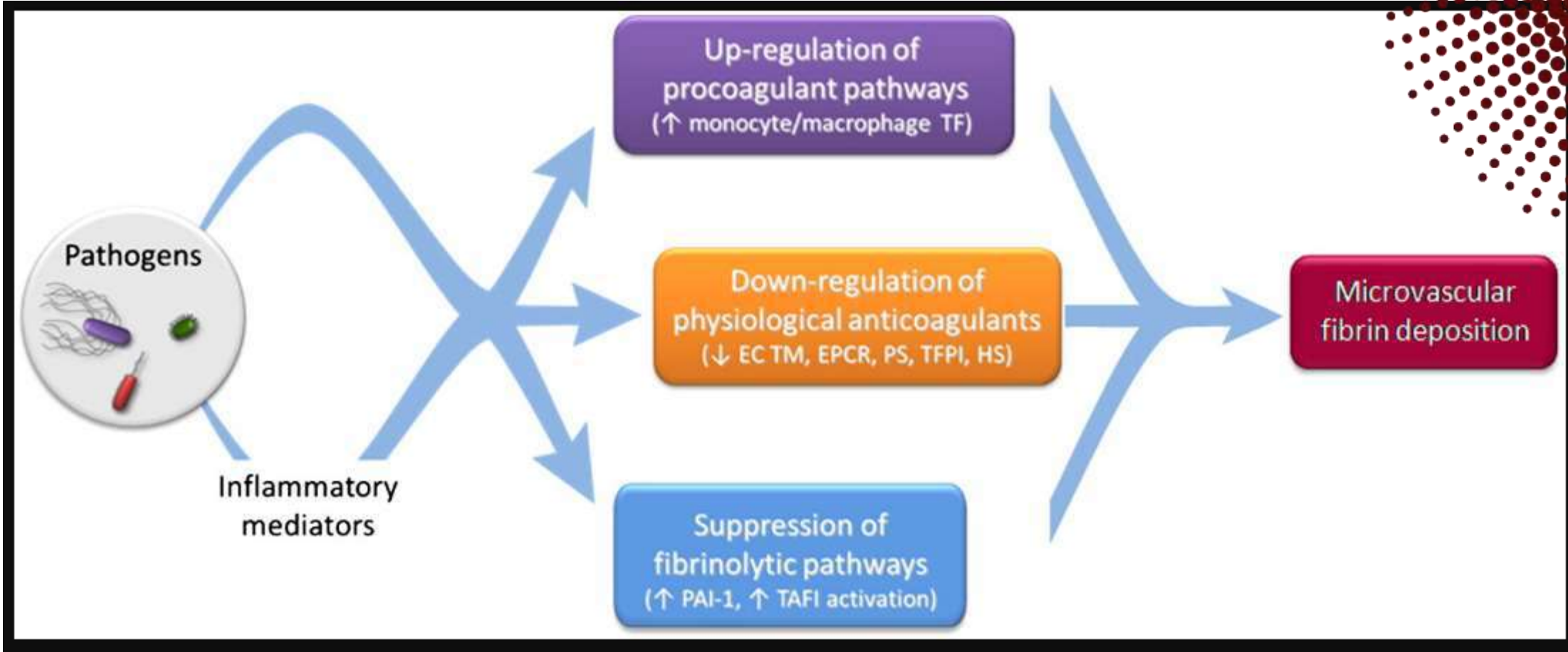


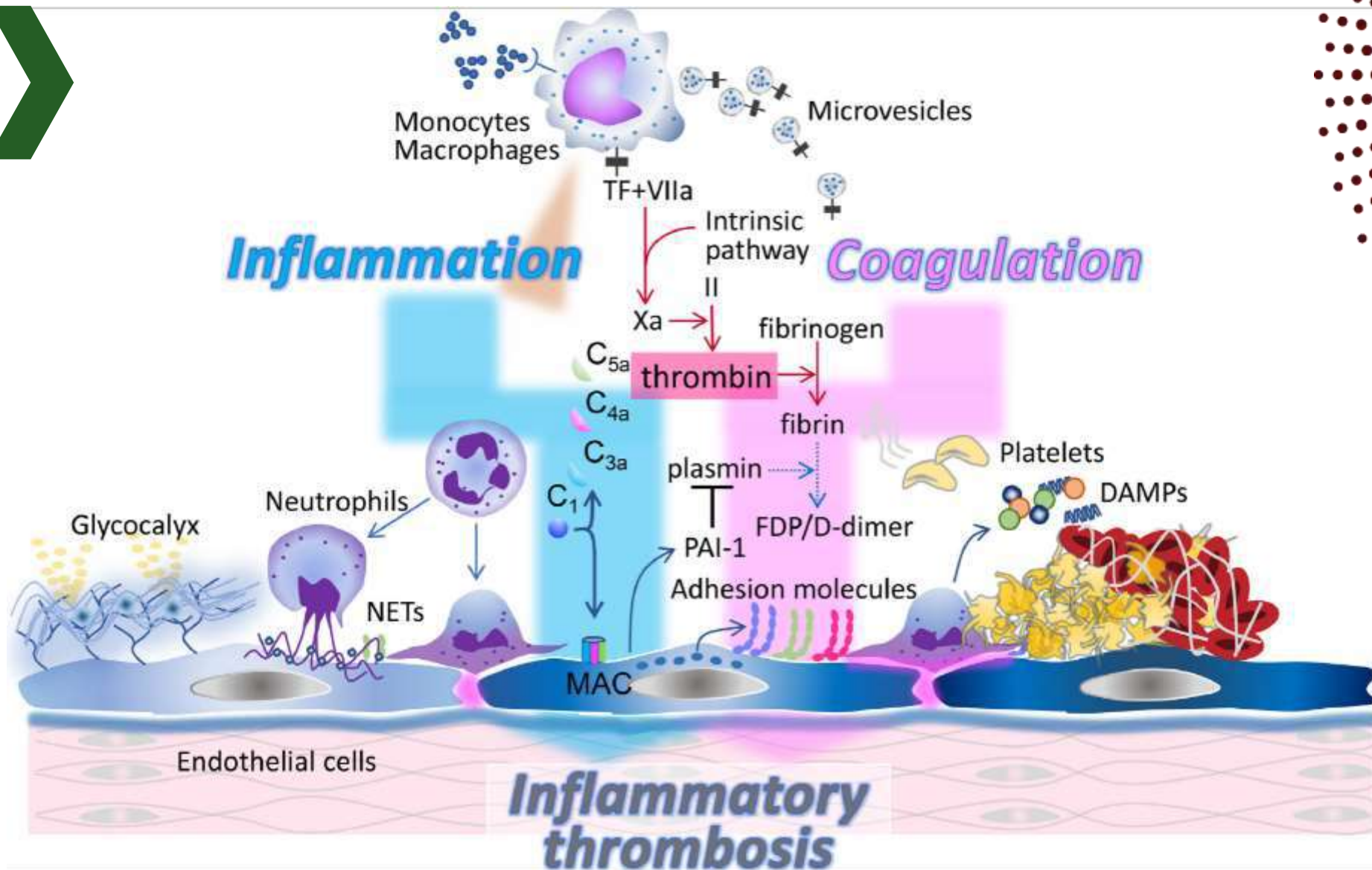
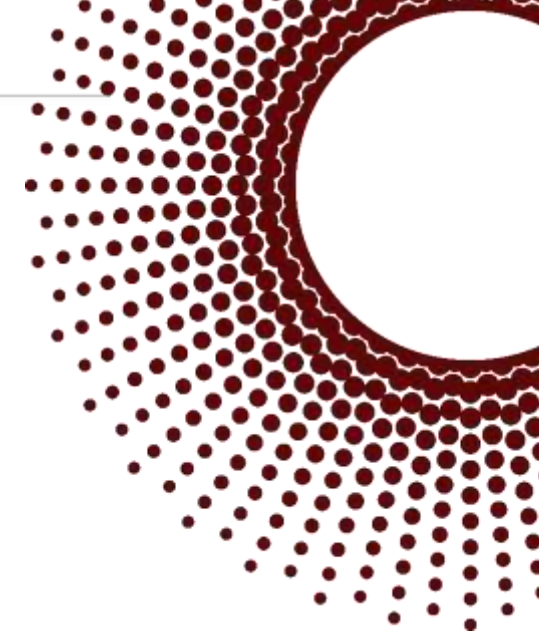
# Heparin-induced thrombocytopenia (HIT)



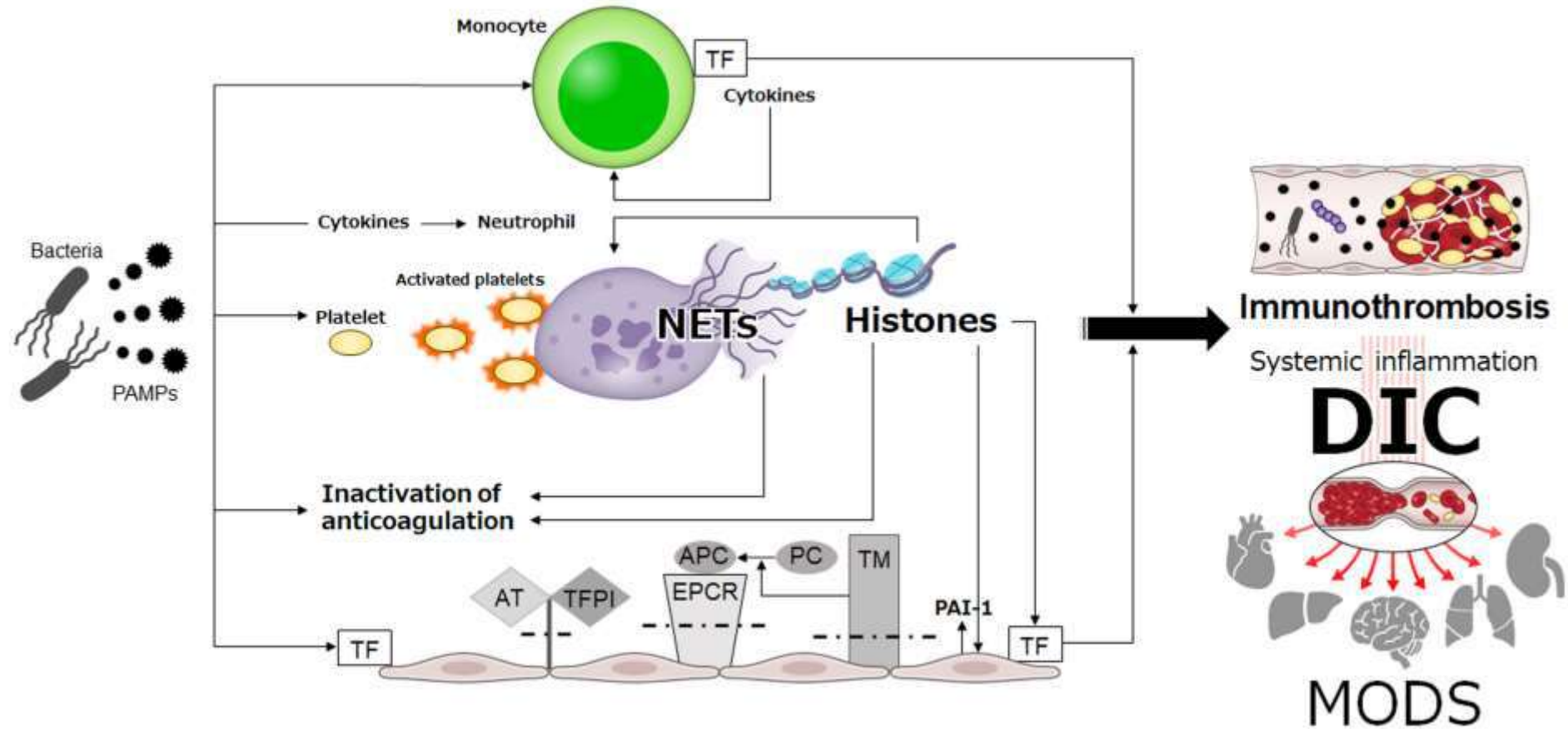
Macrovascular thrombosis  
Microvascular thrombosis

# Sepsis-associated coagulopathy

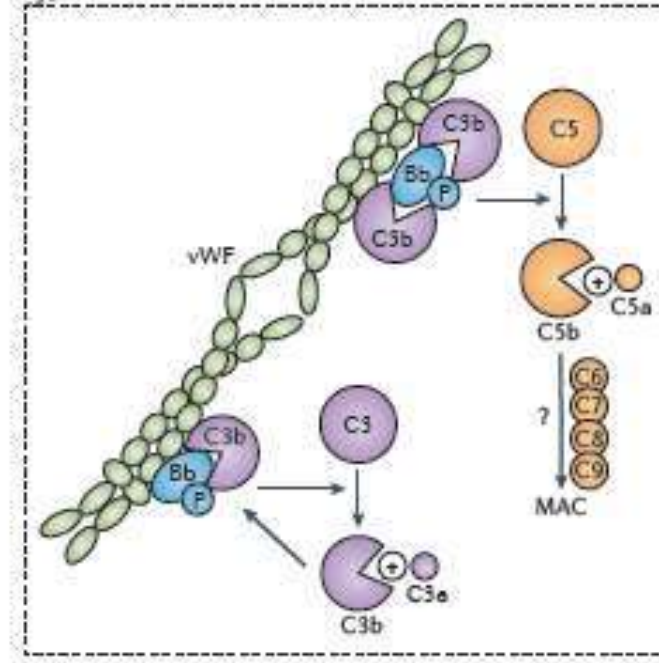
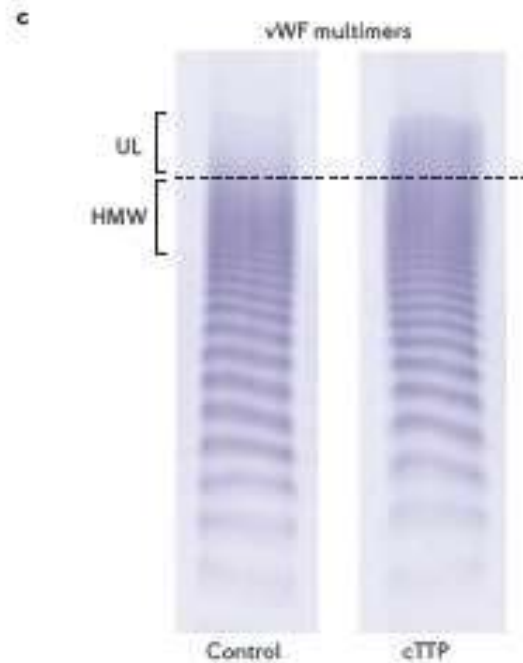
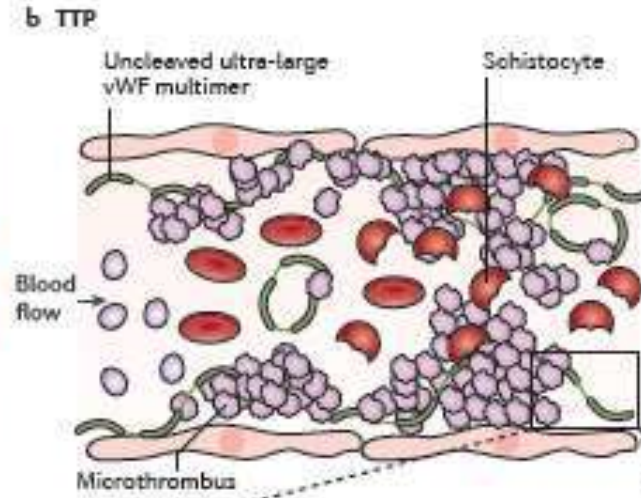
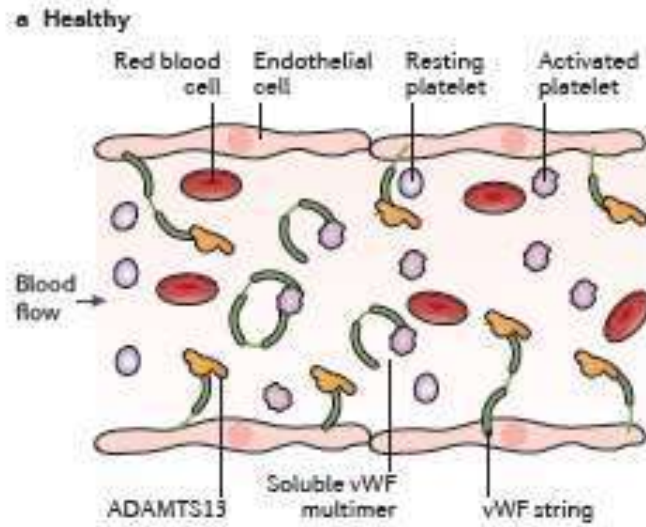
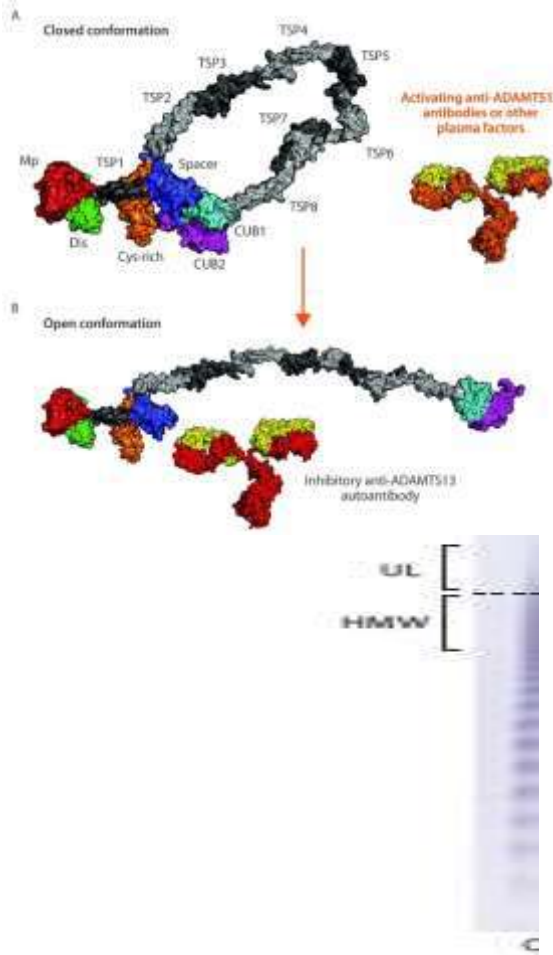




# Sepsis, DIC and immunothrombosis

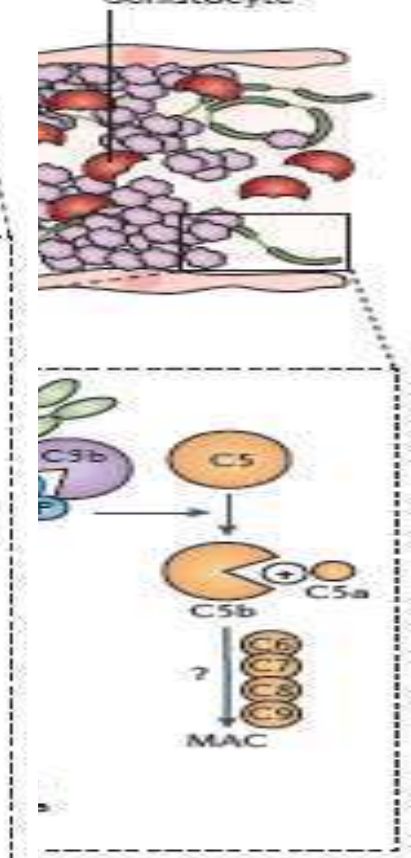


# Immune-mediated TTP: Pathophysiology



Interaction between ULVWF, platelets and RBC

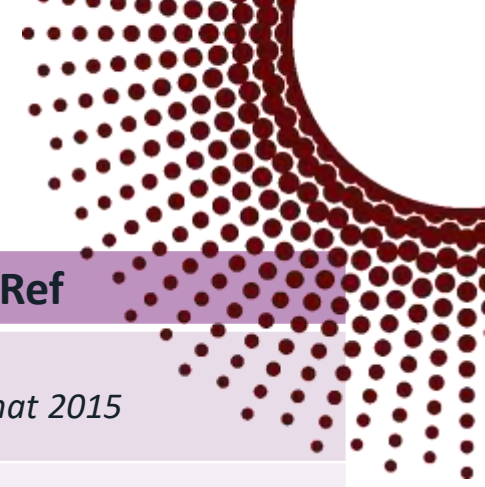
Widespread microvascular thrombosis and hemolysis







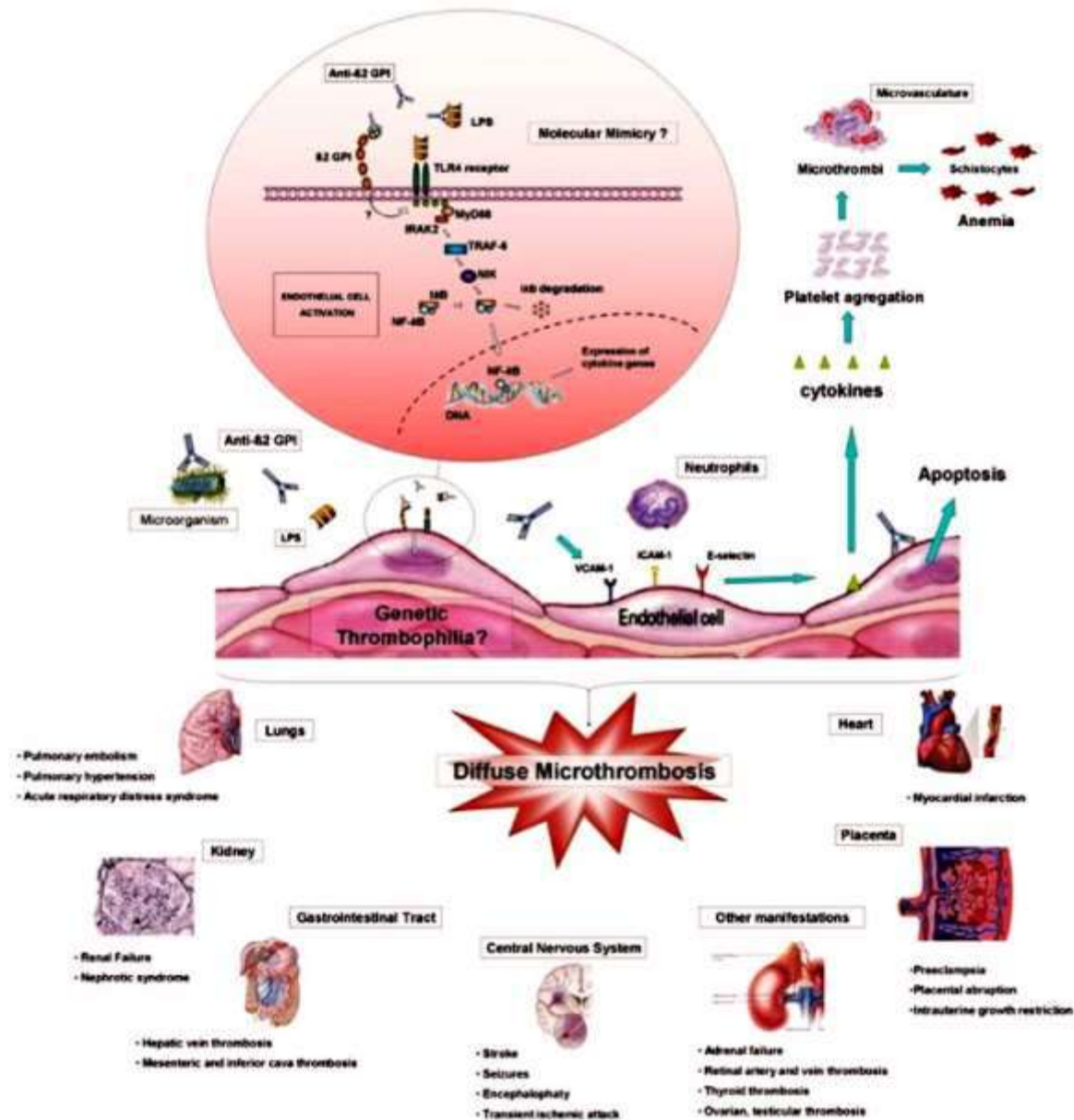
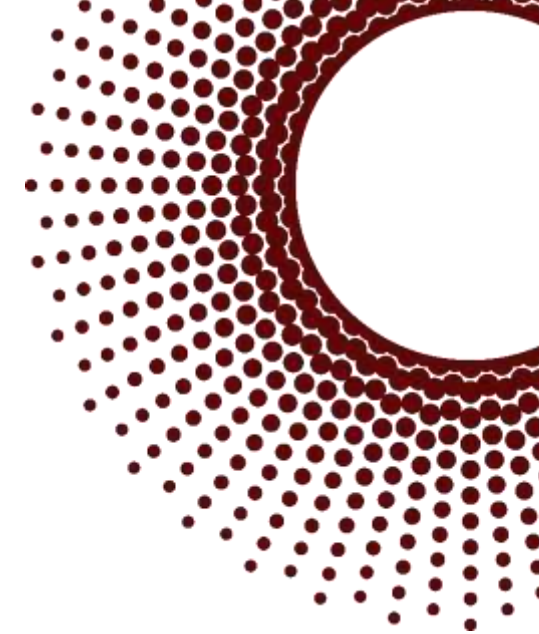
## Microvascular thrombosis associated with other inflammatory disorders

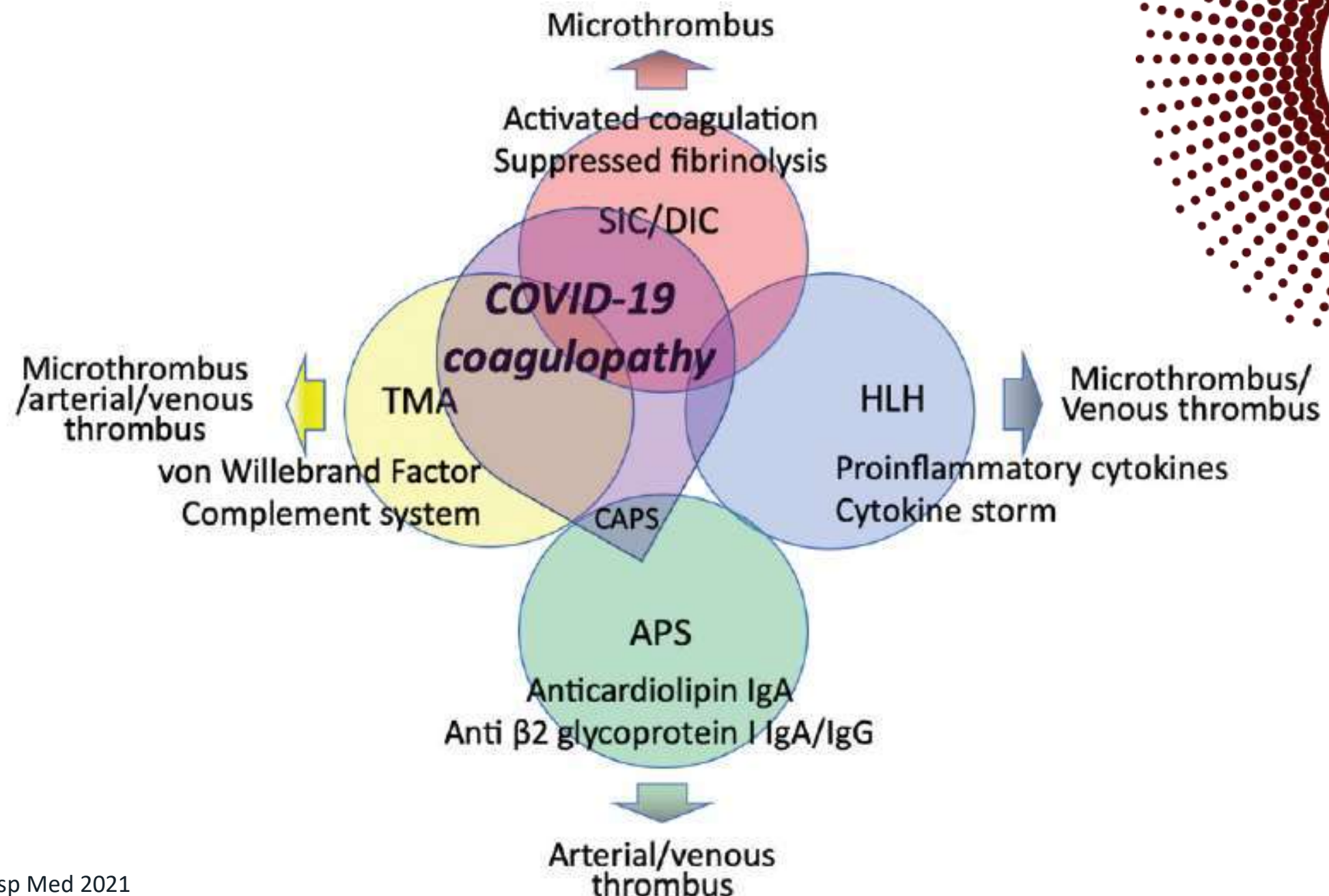
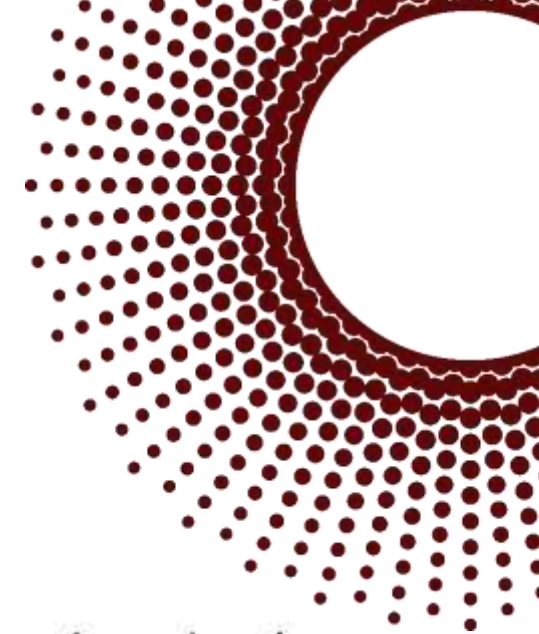


	Thrombosis pathophysiology	Ref
Behcet disease	Mostly VTE due to endothelial injury Increased expression of <b>NLRP3</b> and IL-1B	<i>Kim EH, J Inflamm 2015</i>
SLE/RA	Both arterial and venous types Hypercoagulability, Hyperhomocysteinemia Increased expression of VCAM-1, vWF and <b>NLRP3</b>	<i>Grandemange S, Ann Rheum Dis 2017</i> <i>Shen H, Autoimmune Rev 2018</i>
Inflammatory bowel disease	Both arterial and venous types Hypercoagulability, Hyperhomocysteinemia Increased expression of <b>NLRP3</b> and IL1-B	<i>Mao I, Front Immunol 2018</i>
Familial mediterranean fever	Both arterial and venous types due to endothelial injury Hypercoagulability, Hyperhomocysteinemia Increased expression of <b>NLRP3</b> and IL1-B	<i>Migita K, Immunol Med 2018</i>
ANCA-associated vasculitis	Mostly VTE Increased expression of TNF-IL-1B, TF and <b>NLRP3</b>	<i>Wang L, J Transl Med 2019</i>



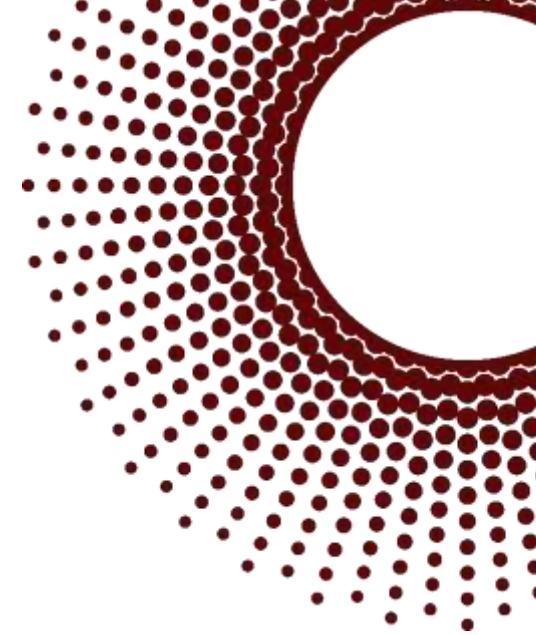
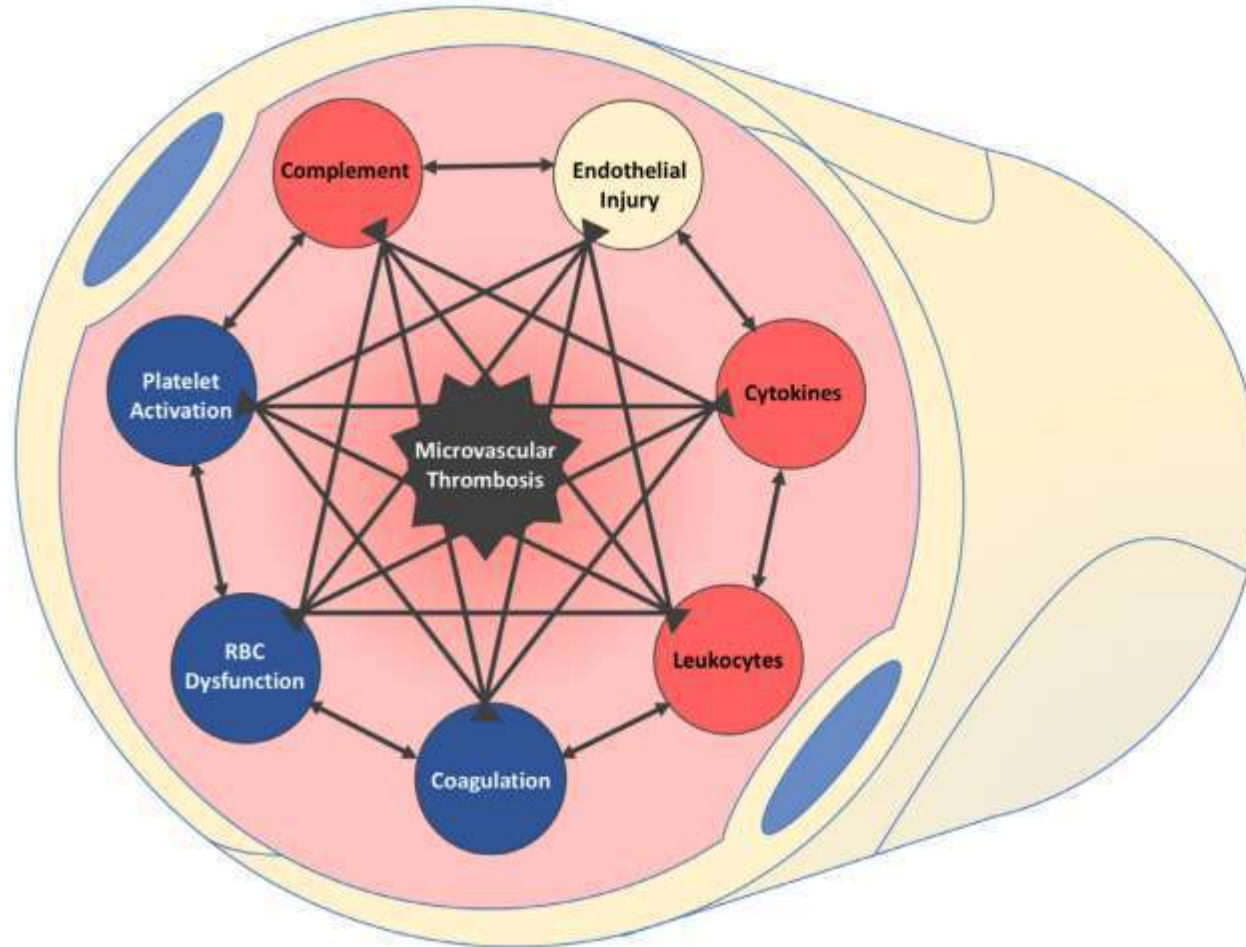
# Catastrophic antiphospholipid syndrome (CAPs)



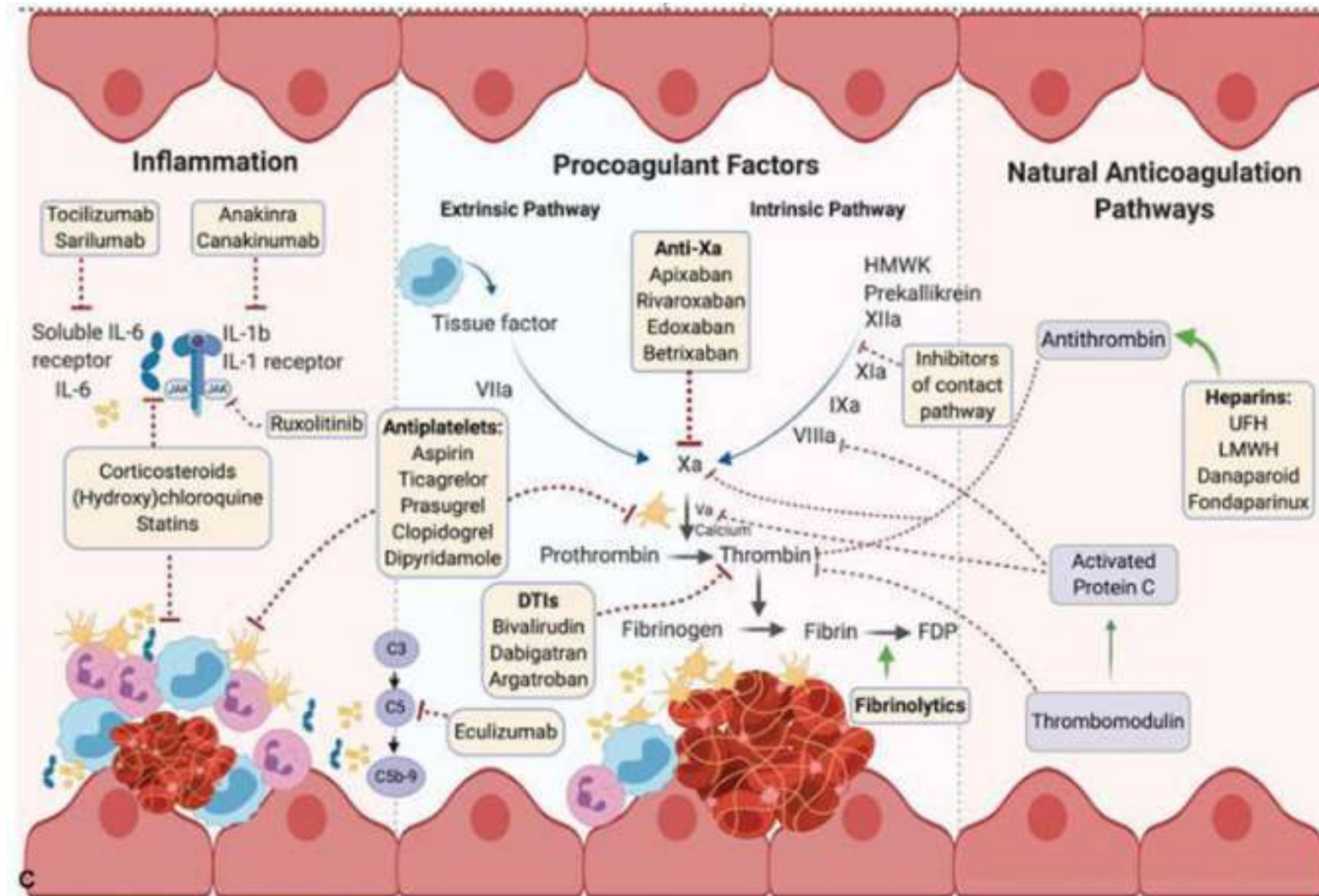




## Schematic of inter-related pathways that contribute to the clinical conditions associated with microvascular thrombosis



# Preventing the development of microvascular thrombosis





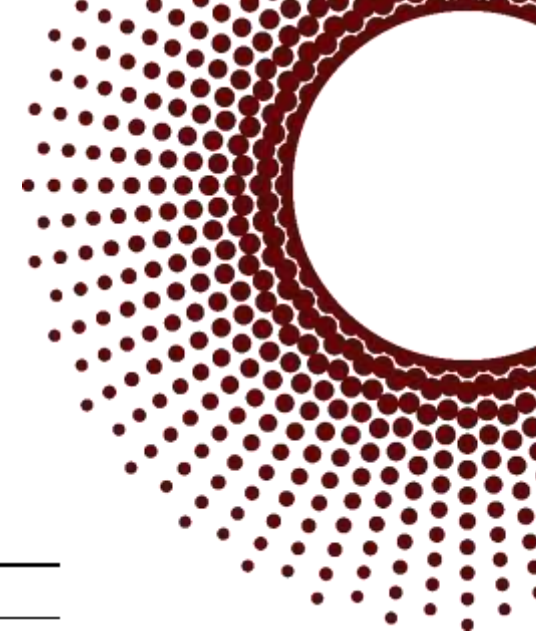
# Therapeutic strategies in immunothrombosis

*Perspective*

## Immunothrombosis: Molecular Aspects and New Therapeutic Perspectives

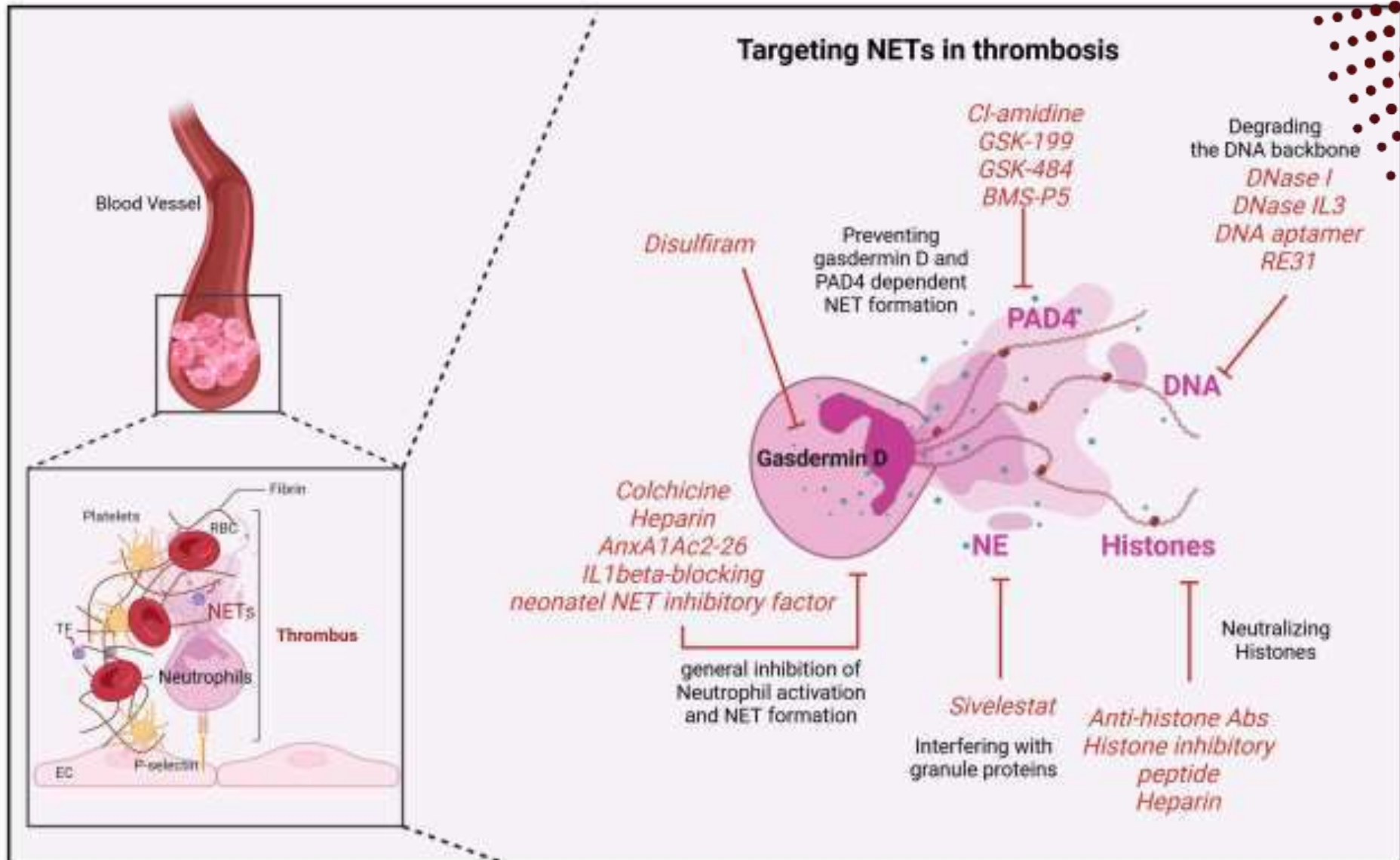
María Marcos-Jubilar <sup>1</sup>, Ramón Lecumberri <sup>1,2</sup> and José A. Páramo <sup>1,3,\*</sup>

Target	Drugs
Coagulation	
Anticoagulant	Low molecular weight heparin [66], fondaparinux [76].
Antiplatelets	Aspirin [77], ticagrelor [78].
NETS	Colchicine [73,74], heparin [79], aspirin [77], ticagrelor [78], DNASEs [26].
Inflammation	
JAK-STAT pathway inhibitors	Baricitinib, ruxolitinib, tofacitinib [80].
STING inhibitors	Nitrofurans, acrylamides, indole ureas [68].
Inflammasome inhibitors (NLRP3)	MCC950 [71], colchicine [73,74].
Gasdermin D inhibitors	Dimetil fumarate [70,71].
HMGB1 inhibitors	Peptide p5779, m2G7, metformin, thrombomodulin [72].
Complement	Eculizumab [75].





# NETs (neutrophil extracellular traps) targeting in thrombosis



# Drugs targeting sepsis-related immunothrombosis in clinical trials

## REPURPOSING OF FDA APPROVED DRUGS UNDER INVESTIGATION IN SEPSIS

### Anticoagulants

Unfractionated heparin  
Low molecular weight heparin

### Antithrombin

PAR-1 antagonist  
Vorapaxar

### Defibrotide

**Antiplatelets**  
P2Y12 inhibitors  
(clopidogrel, ticagrelor)  
GP IIb/IIIa inhibitors  
(eptifibatide, tirofiban)

## NON FDA APPROVED DRUGS UNDER INVESTIGATION IN SEPSIS

DNase (NCT05453695)

### Thrombomodulin

Activated protein C

Tissue factor pathway inhibitor

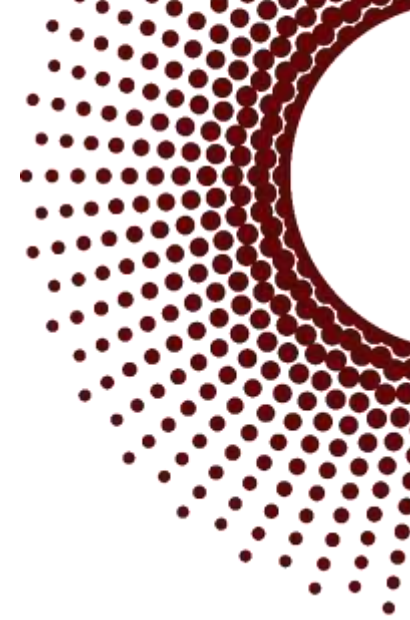
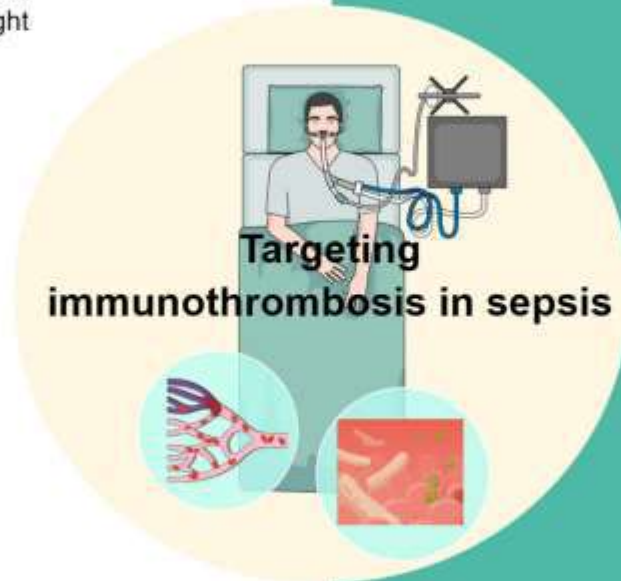
Anti-IL-6 mAb  
B-E8

Anti-CD14 mAb  
IC14

IL-10

Pan-selectin antagonist  
Bimosiamose

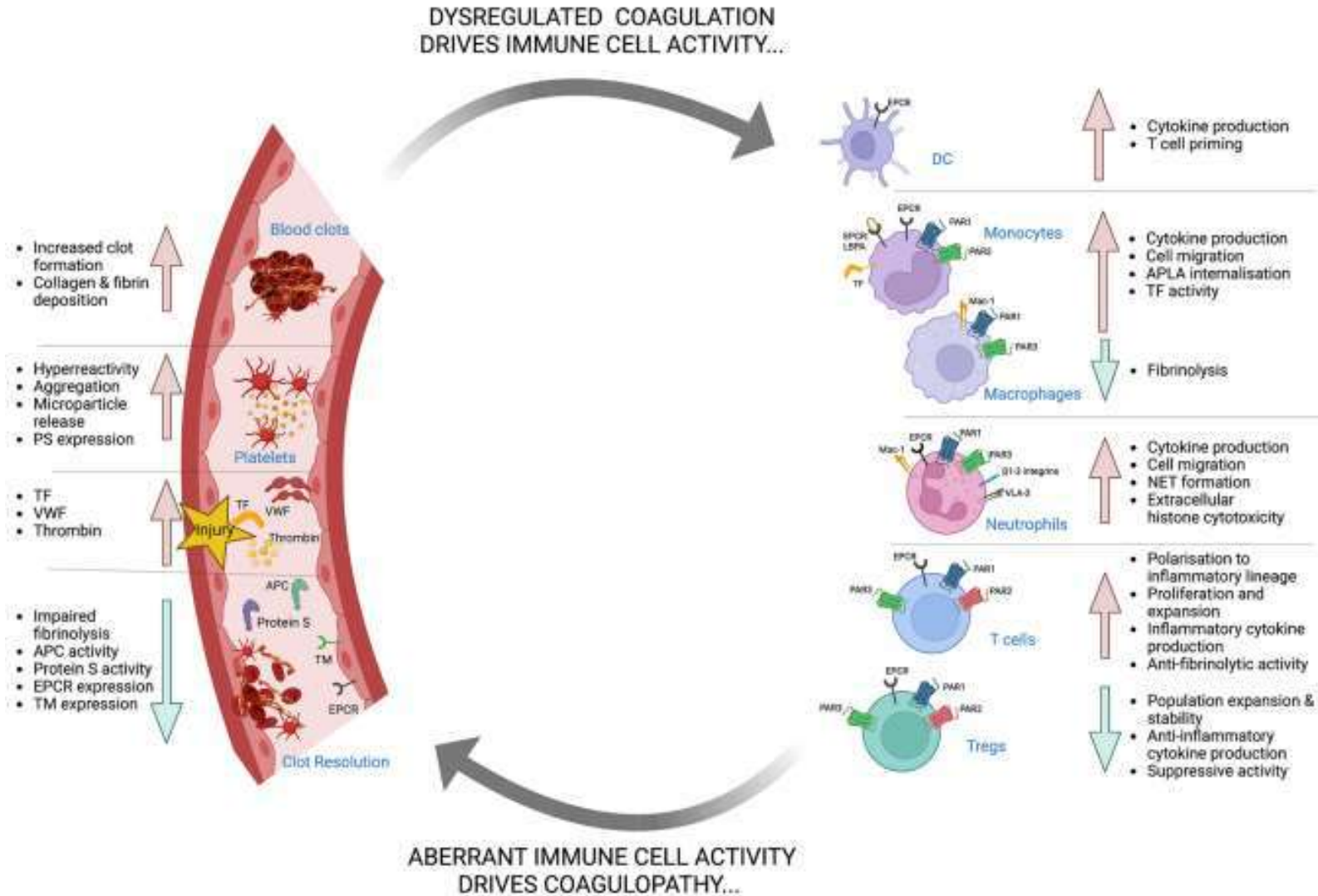
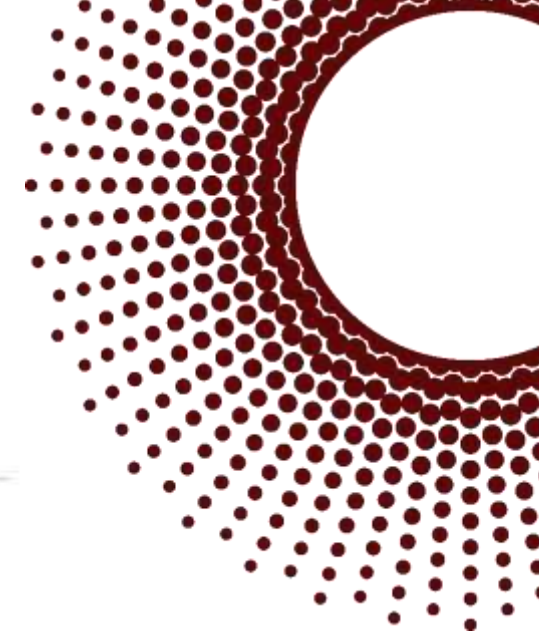
Active site-inhibited  
factor VIIa





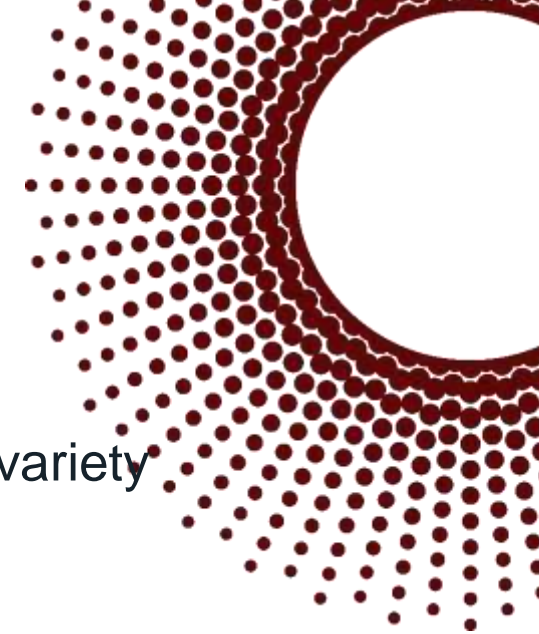


# Cellular and molecular mechanisms in immunotrombosis





## Take home messages



- The diseases characterized by microvascular thrombosis span a wide variety of medical specialties
- Microvascular thrombosis is accompanied by inflammation, an association referred to as thromboinflammation or immunothrombosis
- These pathways are often viewed separately in different clinical disciplines
- It is helpful to conceptualize inflammation and thrombosis as interconnected
- A greater understanding of thromboinflammation in the circulation will provide new therapeutic targets for patients with diseases associated with microvascular thrombosis



**GRACIAS!!!!**