Current Immunological trends in clinical topics

Thrombosis & fibrosis in inflammation

DEMOCRITUS UNIVERSITY OF THRACE

INFLATHRACE
ΔΗΜΟΚΡΙΤΕΙΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΡΑΚΗΣ
ΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΑΛΕΞΑΝΔΡΟΥΠΟΛΗΣ

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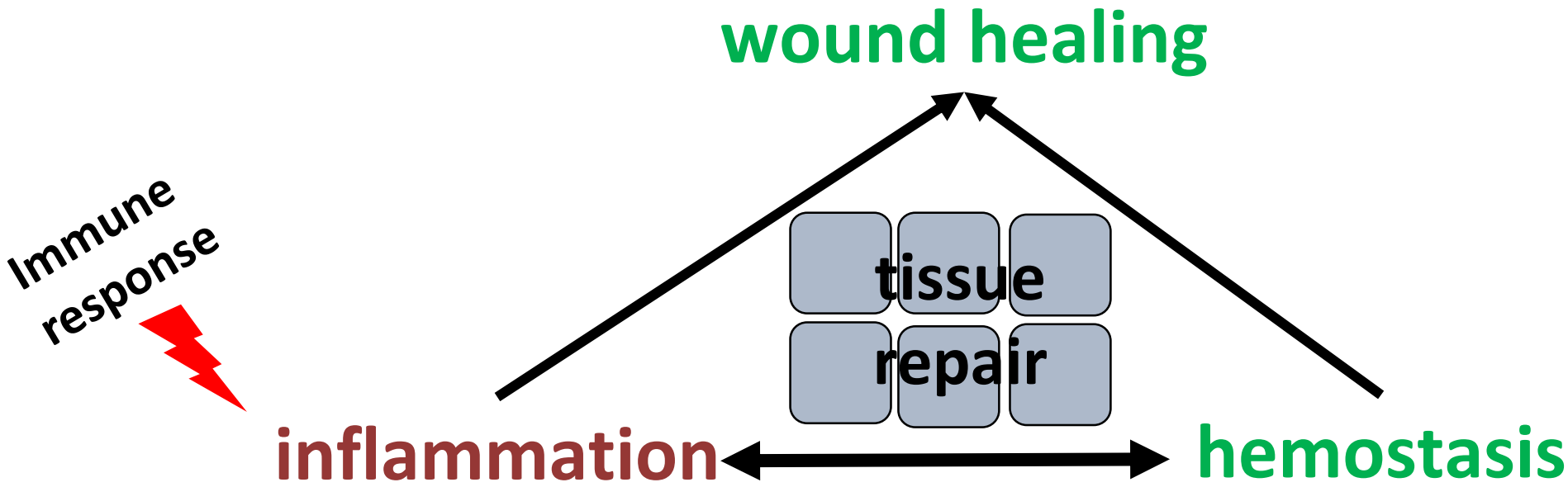
First Department of Internal Medicine
& Laboratory of Molecular Hematology
University Hospital of Alexandroupolis

Inflammation is linked with thrombosis and fibrosis in common human diseases

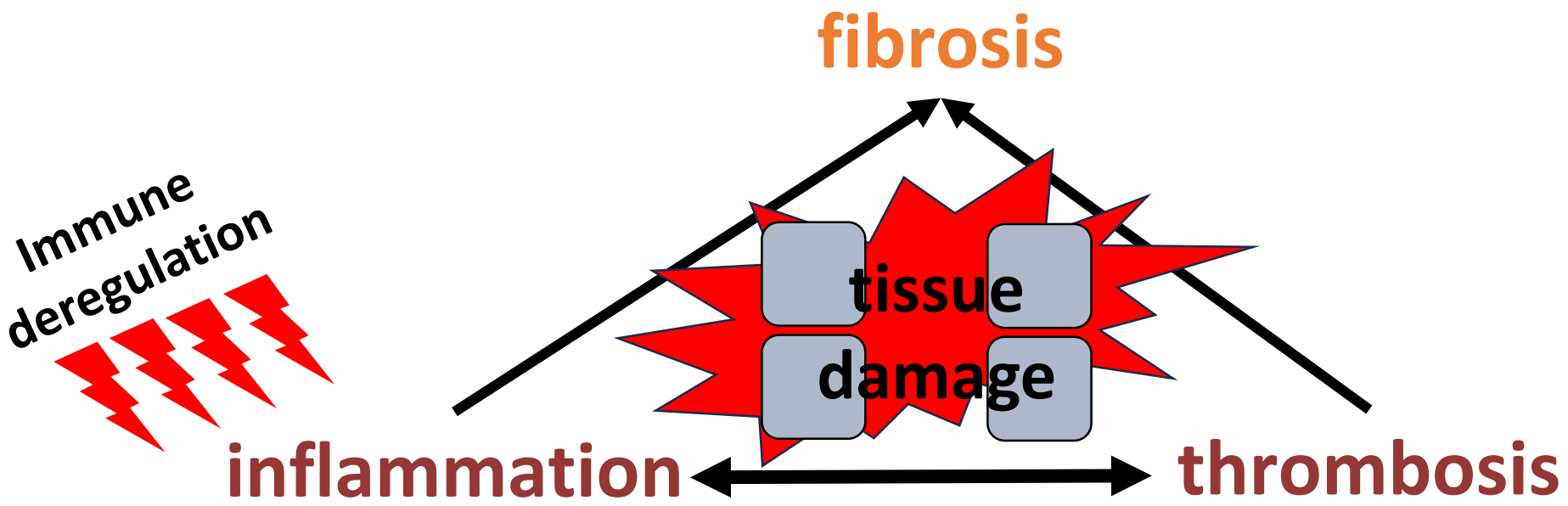
- Infectious inflammation (sepsis/SIRS) and thrombosis (DIC)
- Chronic inflammatory and autoimmune diseases are associated with high cumulative risk for atherosclerosis and thrombotic complications
- Metabolic syndrome and subclinical, low grade systemic inflammation
- Inflammatory process is considered to be one of the main steps leading to fibrosis in several autoinflammatory/autoimmune diseases (end-result of a chronic inflammatory process)

Homeostasis

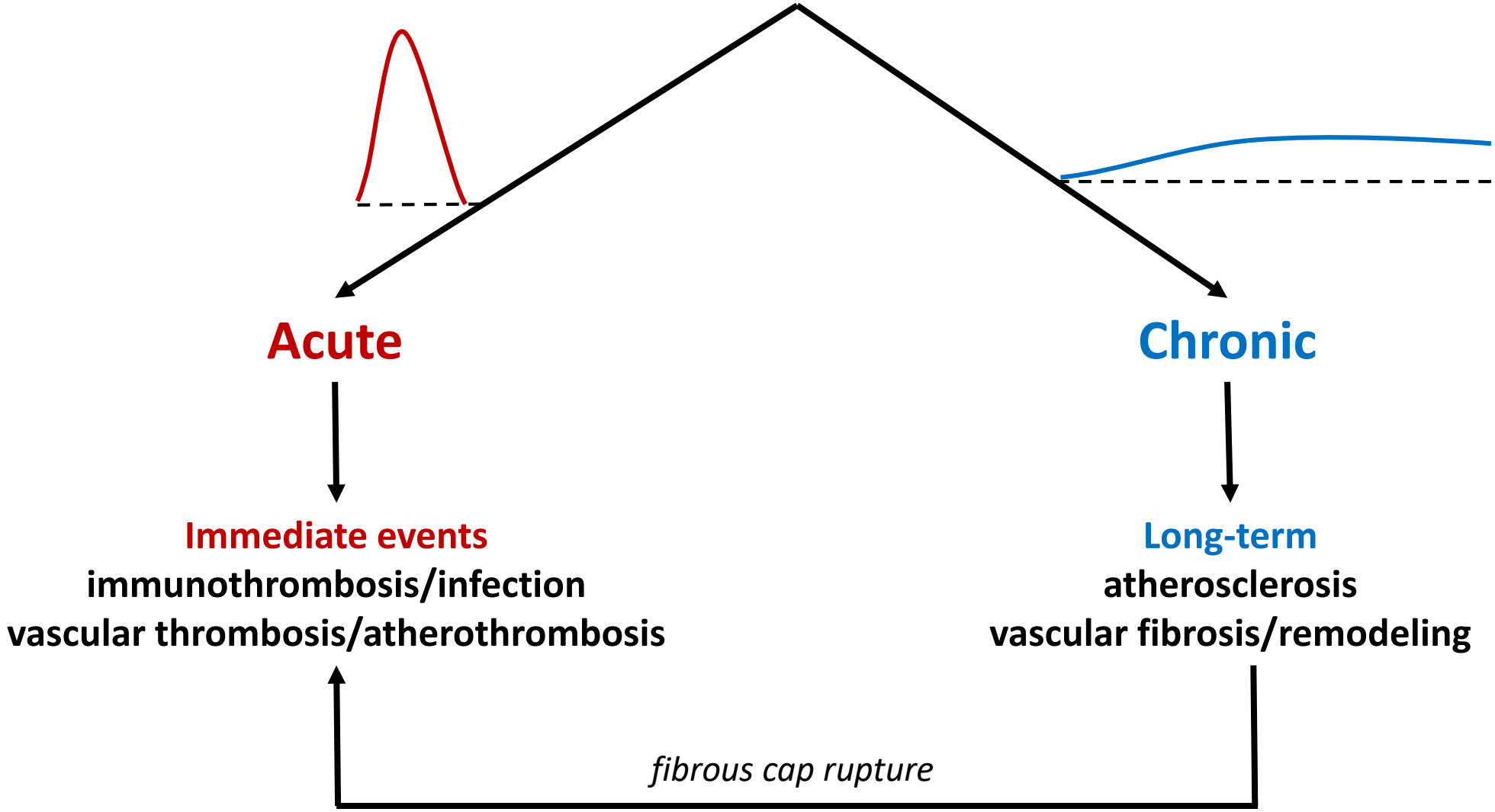


Disease

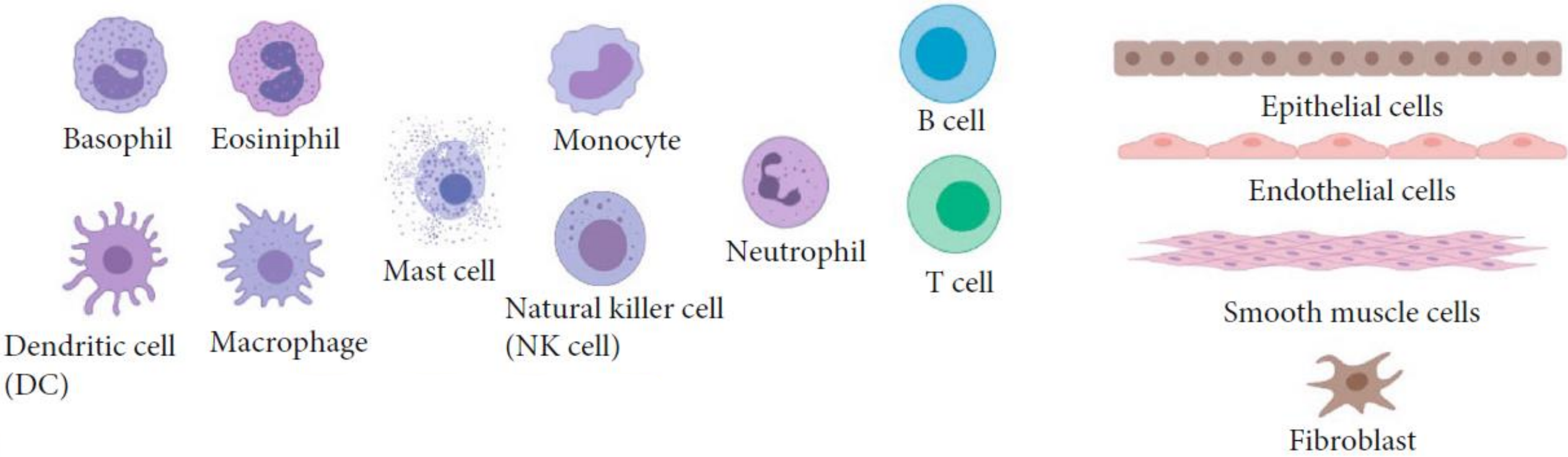
immunothrombosis and/or immunofibrosis



Thromboinflammation (CVDs example)



Different types of immune and non-immune cells



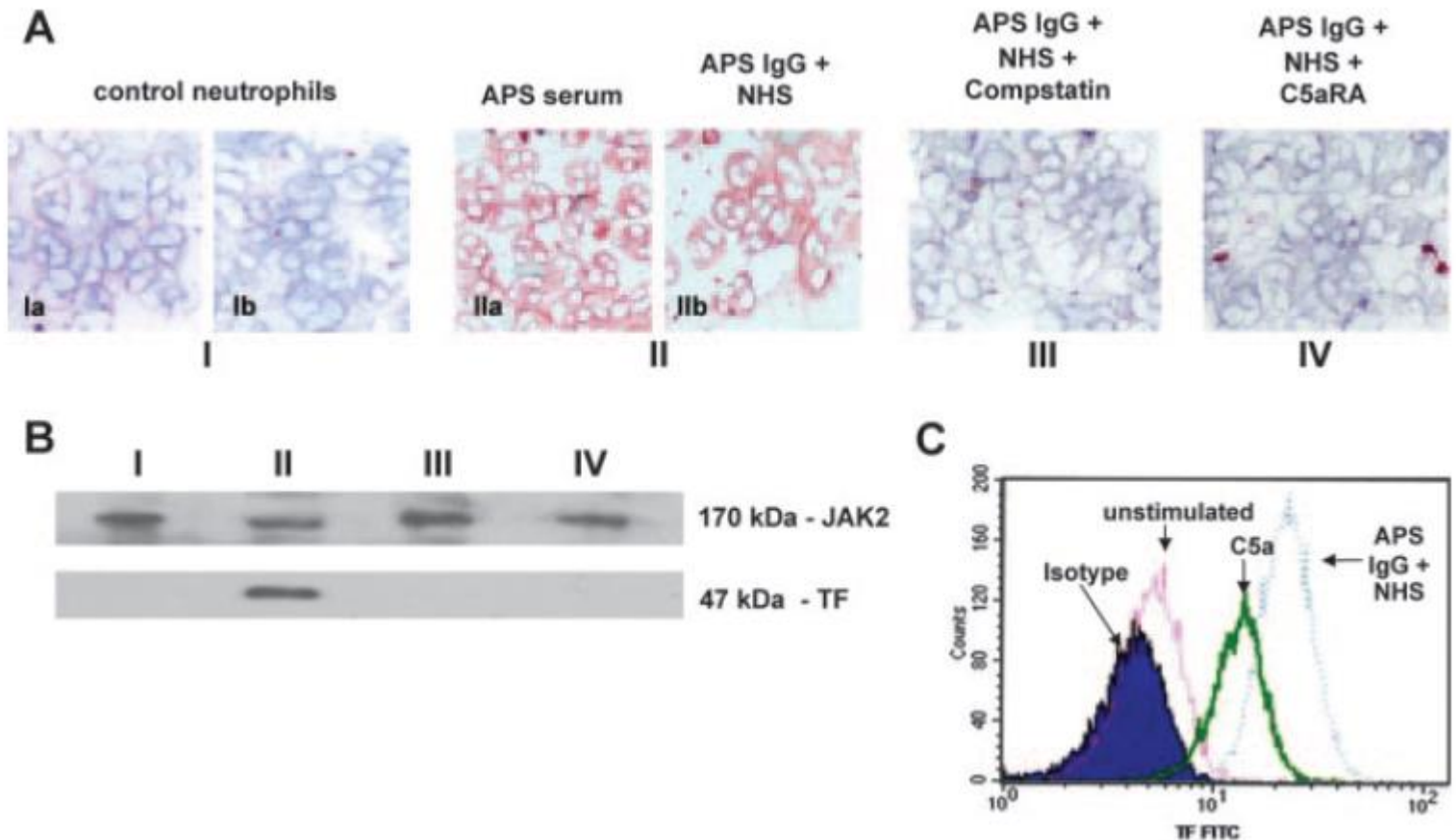
Innate and adaptive immune immune cells ⟷ ***Non-immune cells (tissue)***

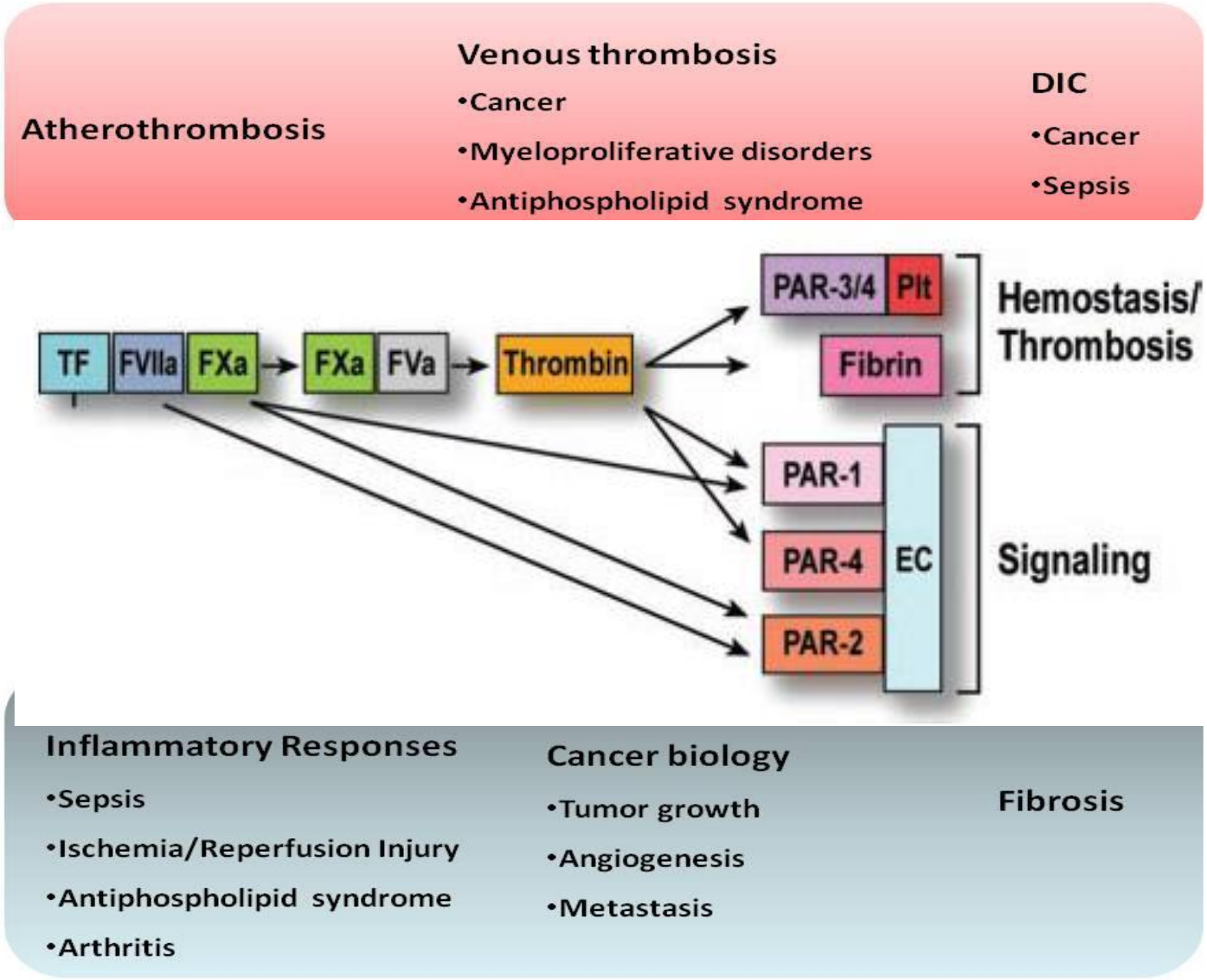
Modified from: Behzadi P, et al. J Immunol Res. 2021

The Journal of Immunology, 2006, 177: 4794–4802.

A Novel C5a Receptor-Tissue Factor Cross-Talk in Neutrophils Links Innate Immunity to Coagulation Pathways[1]

Konstantinos Ritis,[2]* Michael Doumas,* Dimitrios Mastellos,† Anastasia Micheli,* Stavros Giaglis,* Paola Magotti,‡ Stavros Rafail,* Georgios Kartalis,* Paschalis Sideras,† and John D. Lambris[2‡]





Mitroulis I, Kambas K, Anyfanti P, Doumas M, Ritis K. Expert Opin Ther Targets. 2011

Table 1. The characteristics of different PAR members [12].

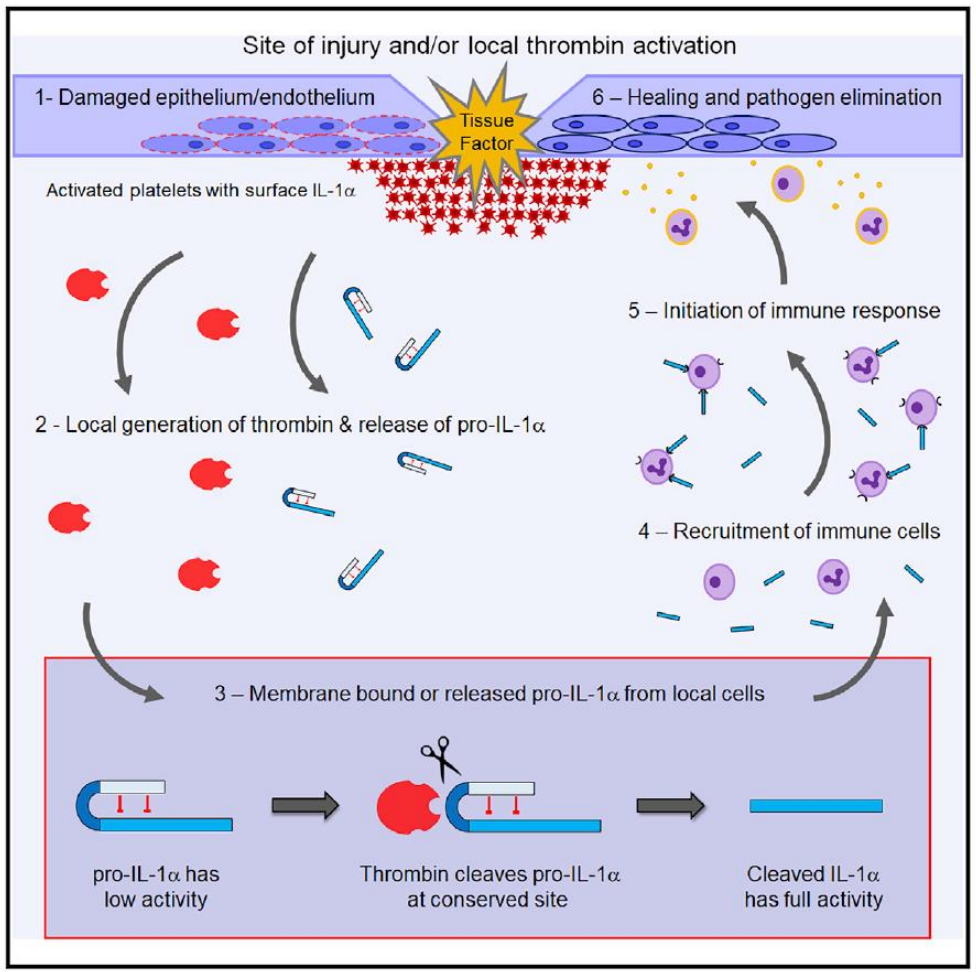
Receptor	Amino acids	Tethered ligands	Classical proteases
PAR1	425	h: SFFLR m: SFLLR	Thrombin [13]; MMPs [14]; Granzyme B [15]; Cathepsin G [16]; Neutrophil elastase (NE) [17]; Factor Xa [18]; Granzyme K [19]; Proteinase-3 [17]; Activated protein C (APC) [20]
PAR2	395	h: SLIGKV m: SLIGRL	Mast cell tryptase [23]; Thrombin [11]; Trypsin [24]; Matriptase [25]; Factor Xa [26]
PAR3	483	h: TFRGAP m: SFNGGP	Thrombin [30]; Activated protein C [31]; Factor Xa [32]
PAR4	385	h: GYPGQV m: GYPGKF r: GFPGKP	Thrombin [13]; Trypsin [34]; Cathepsin G [35]

Zhuo X, et al. FEBS J. 2022

Immunity

The Coagulation and Immune Systems Are Directly Linked through the Activation of Interleukin-1α by Thrombin

Graphical Abstract



Authors

Laura C. Burzynski, Melanie Humphry, Katerina Pyrillou, ..., Paul B. Martin, Martin R. Bennett, Murray C.H. Clarke

Correspondence

mchc2@cam.ac.uk

In Brief

Burzynski et al. reveal that the coagulation protease thrombin directly cleaves pro-interleukin (IL)-1α, rapidly activating the downstream inflammatory cascade. This cleavage site in IL-1α is conserved throughout mammals, suggesting that this link between coagulation and inflammation may be relevant in multiple disease settings.

Burzynski et al., 2019, Immunity *50*, 1033–1042

Thrombin proteolytically cleaves and activates C5 and C3

Ex-vivo/In-vitro experimental and human studies

Generation of C5a in the absence of C3: a new complement activation pathway

Markus Huber-Lang[1,6], J Vidya Sarma[2,6], Firas S Zetoune[2,6], Daniel Rittirsch[2], Thomas A Neff[2], Stephanie R McGuire[2], John D Lambris[3], Roscoe L Warner[2], Michael A Flierl[2], Laszlo M Hoesel[2], Florian Gebhard[1], John G Younger[4], Scott M Drouin[5], Rick A Wetsel[5] & Peter A Ward[2]

JUNE 2006 NATURE MEDICINE

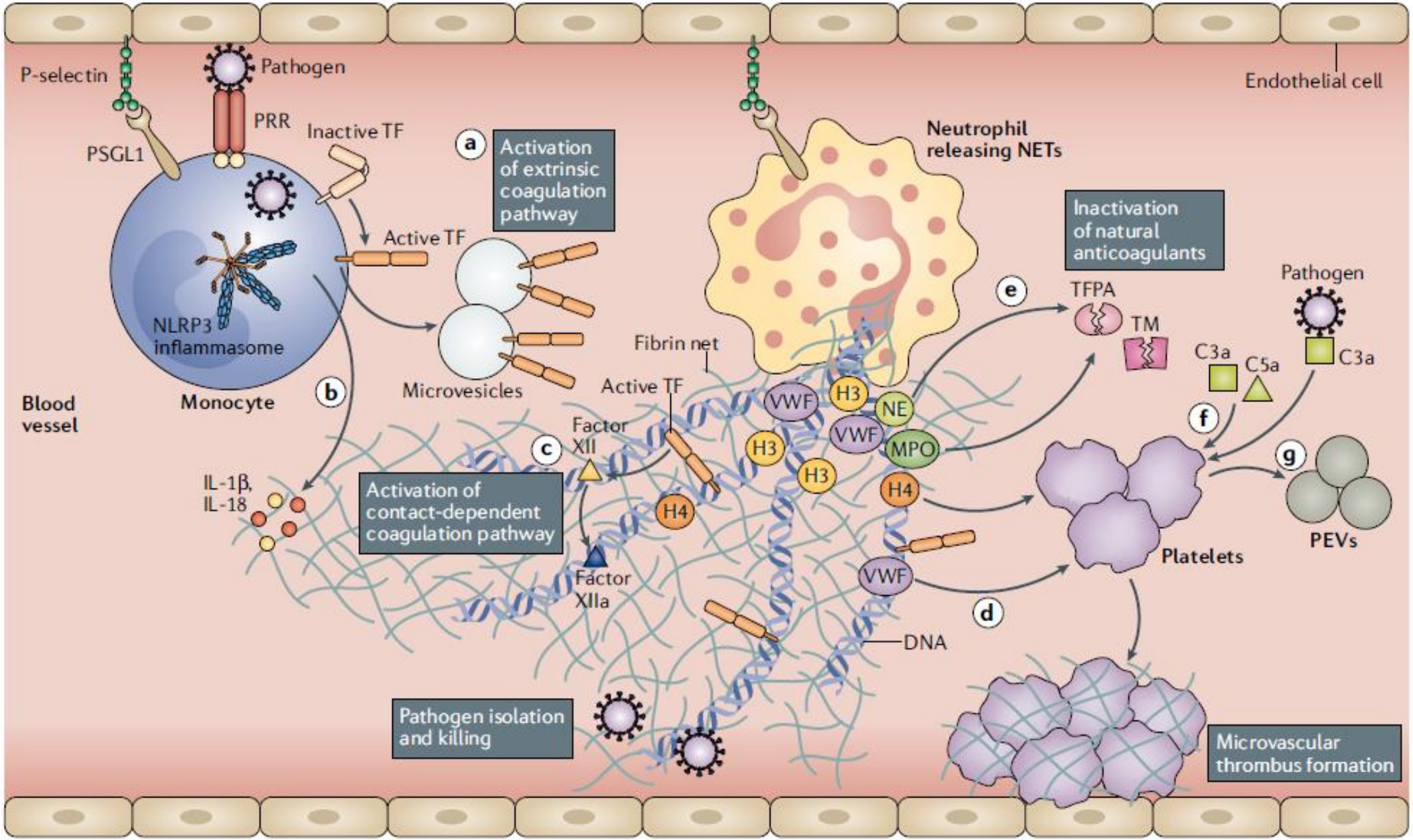
The Journal of Immunology

Molecular Intercommunication between the Complement and Coagulation Systems

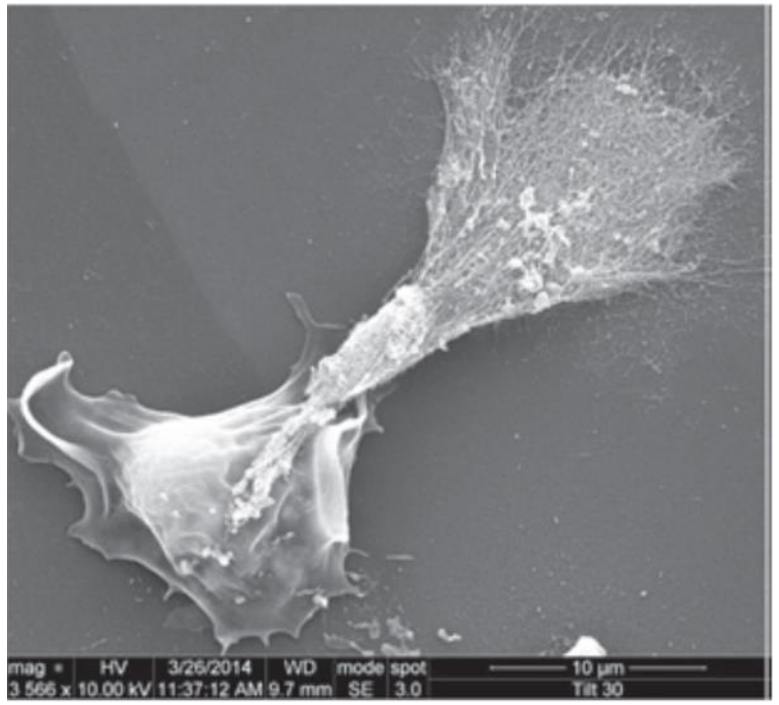
Umme Amara, Michael A. Flierl, Daniel Rittirsch, Andreas Klos, Hui Chen, Barbara Acker, Uwe B. Brückner, Bo Nilsson, Florian Gebhard, John D. Lambris and Markus Huber-Lang

J Immunol 2010; 185:5628-5636;

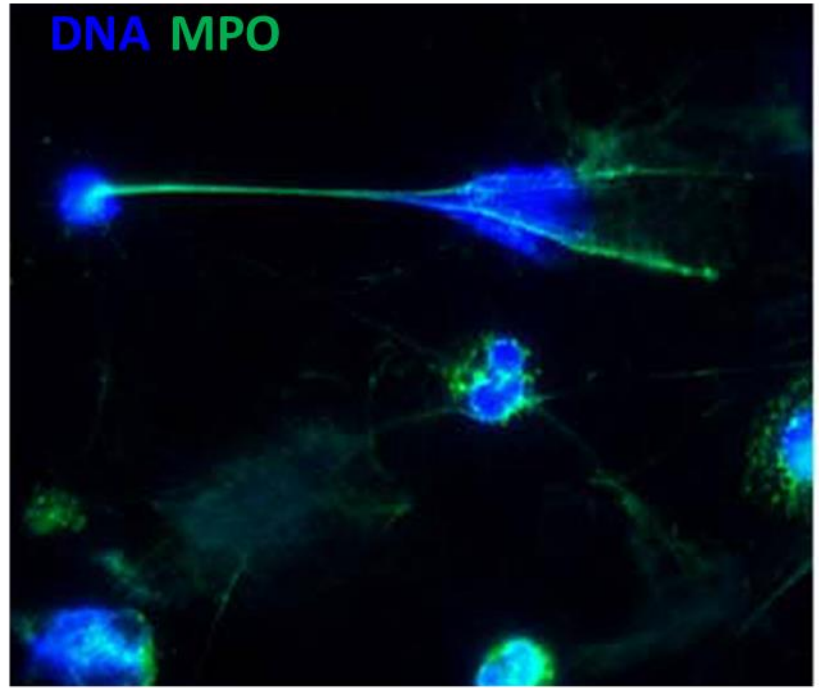
Immunothrombosis: a conserved mechanism of host defence



Bonaventura A et al Nat Rev Immunol 2021



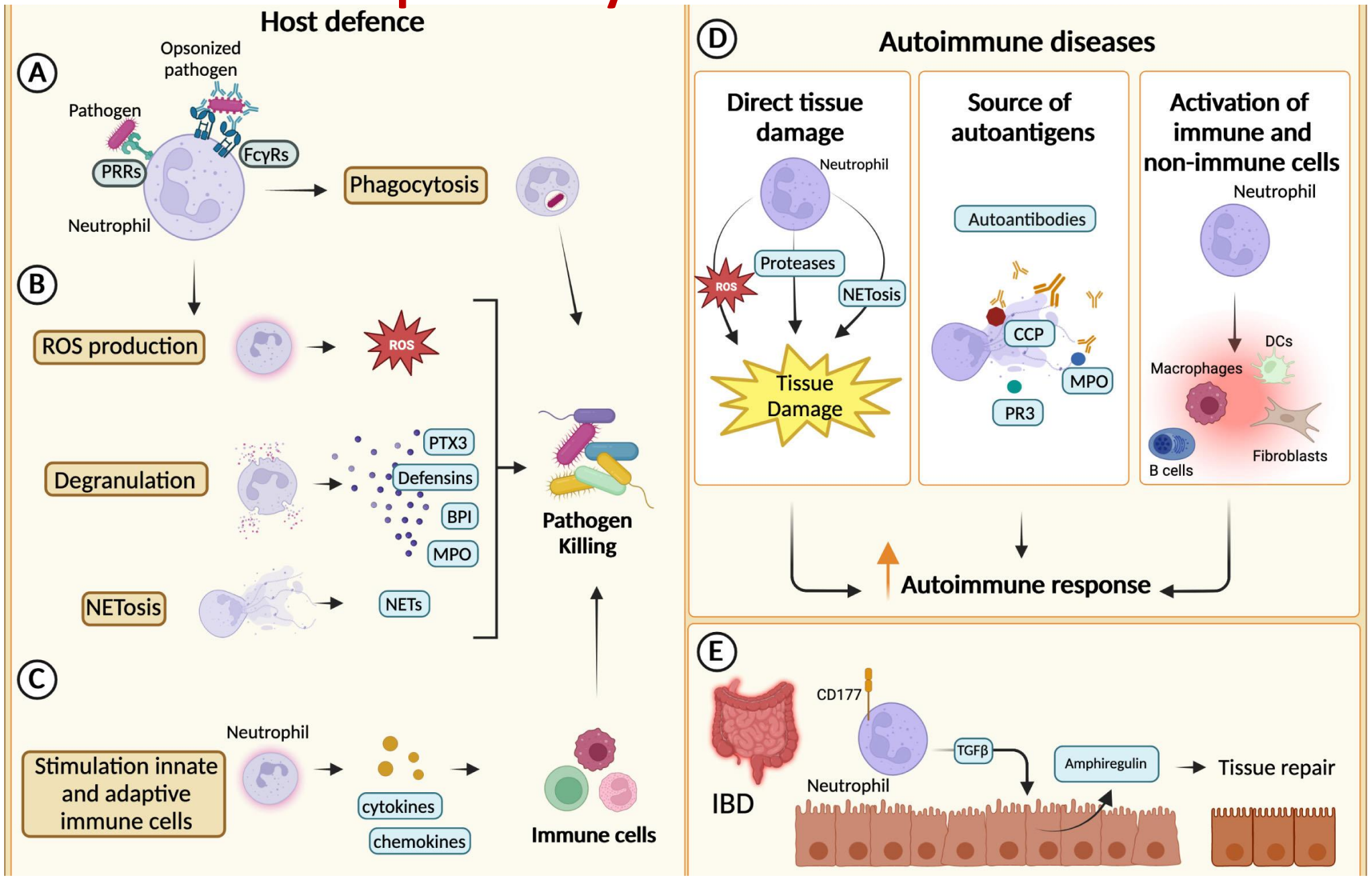
Barnado A et al. J. Leukoc. Biol. 2016



Laboratory of Molecular Hematology, DUTH, Alexandroupolis, Greece

Neutrophil/NETs: key player in inflammation

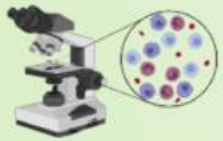
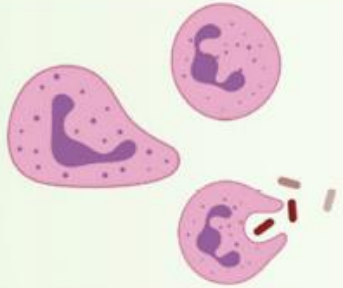
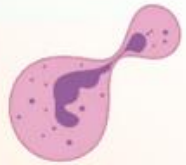
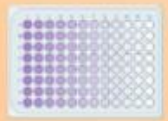
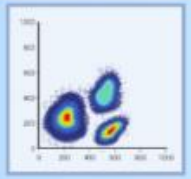
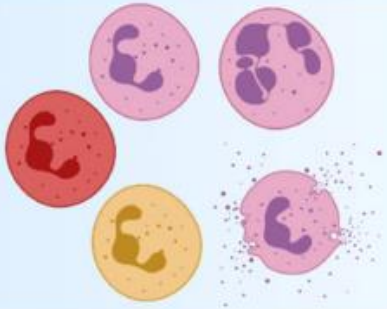
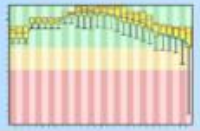
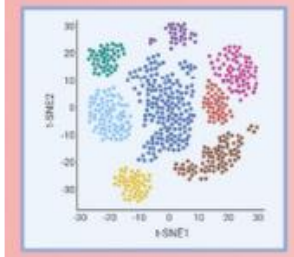
Neutrophils in systemic inflammation



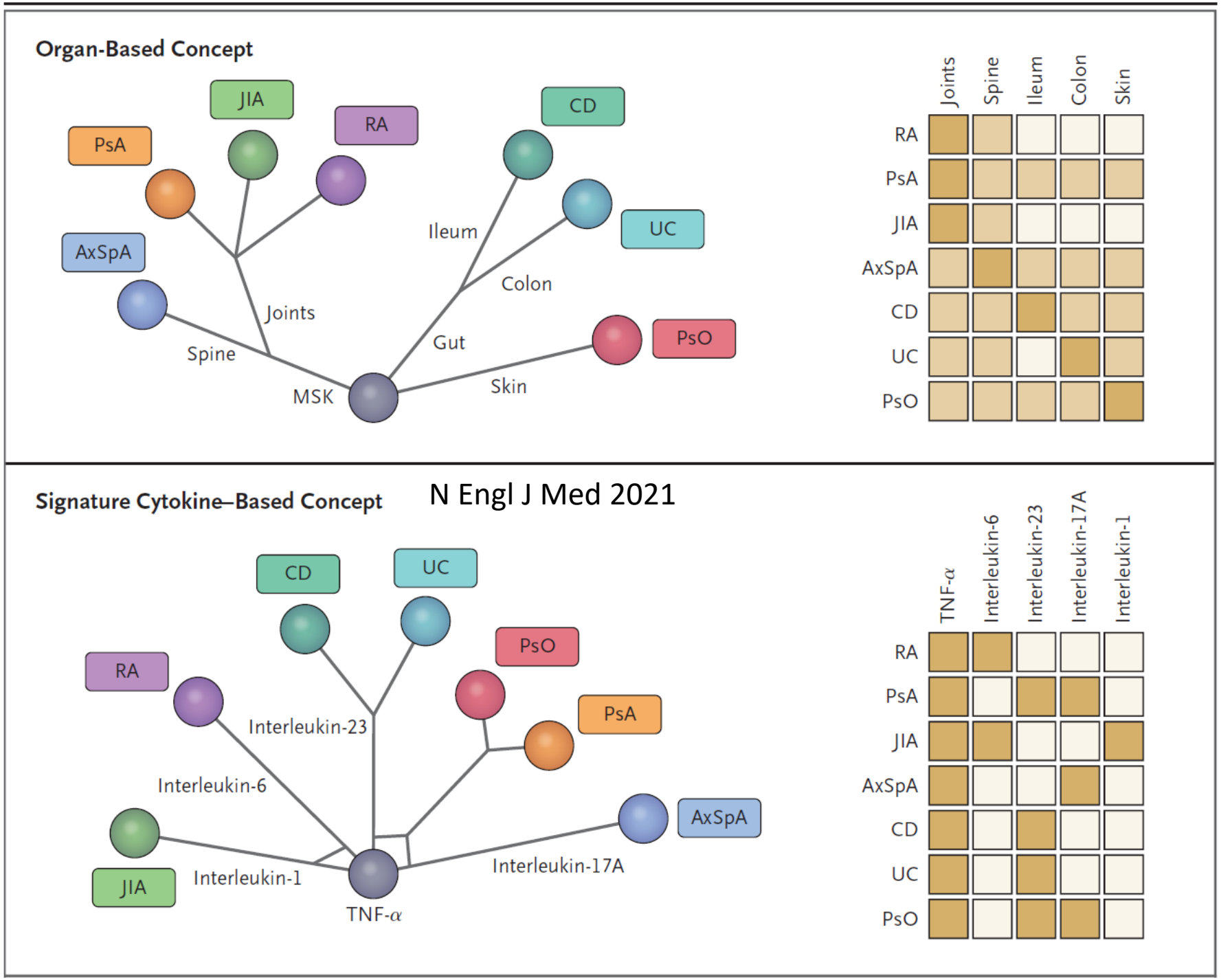
Carnevale S, et al Front. Immunol. 2023

Functional plasticity of immune cells

- the ability of cells to acquire a new function and adopt an alternative fate when exposed to different environmental conditions
- heterogeneous subsets of immune cells have been described during **homeostatic/steady-state** and **inflammatory conditions**
- **mRNA as a molecular readout**: bulk/single cell transcriptomics
- **proteins as molecular readout**: proteomics
- **functional validation**: in-vitro, ex-vivo assays
- **In-vivo "validation"**: genetic mutations of key immune pathways and monoclonal antibodies that target cytokines (monogenic autoinflammatory diseases as an excellent example)

Technology	Observations	Insights
Histology 	Unique nuclei morphology	 Central role in immunity against pathogens
Functional Assays 	Neutral stain	
	Kill bacteria	
	Generate reactive oxygen species	
  PCR	De novo protein synthesis	Capable of rapid, extreme deformability 
	Gene expression	
 Western Blot/ELISA	Regulation by miRNAs	Expel DNA to kill microbes
	Specialised nuclear envelope	Multiple neutrophil fates 
Flow Cytometry 	Dynamic surface marker profiles	 Subsets of protein expression (CD177, OLFM4)
	Gene networks vary across conditions	
RNAseq 	Roles for lncRNAs	Spectrum of phenotypes across diseases
 Super-res microscopy	Visualise nuclei structure	Complex roles for individual cells within phenotypes 
	Complex populations in tissues	
scRNAseq	Novel subsets by transcriptomics	Spectrum of phenotypes across diseases

Garratt LW. Cells 2021



N Engl J Med 2021

The NEW ENGLAND JOURNAL of MEDICINE

Transition from organ-based to molecular-based classification

Schett G et al. N Engl J Med 2021

Excess NET formation can drive a variety of severe pathologies

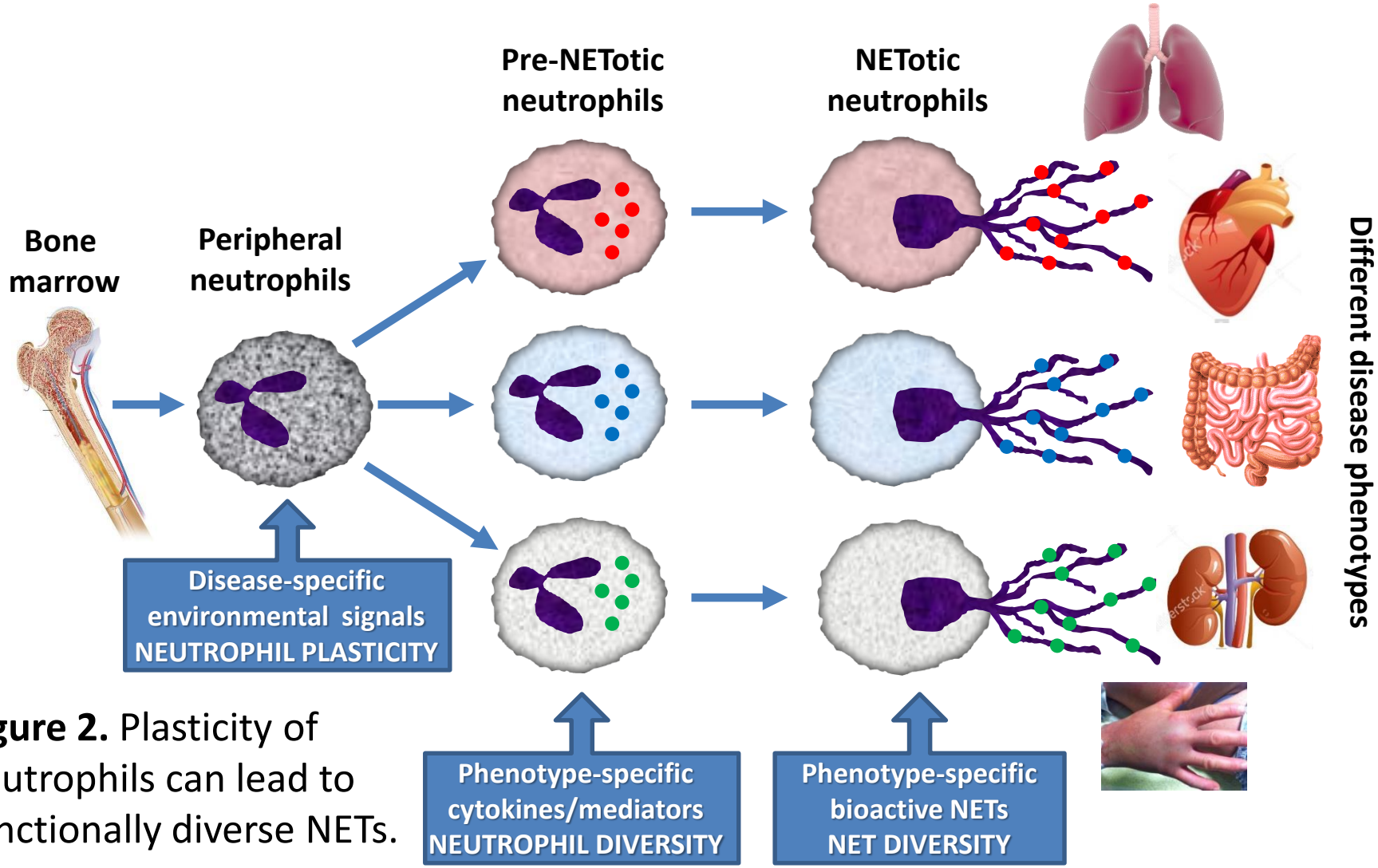
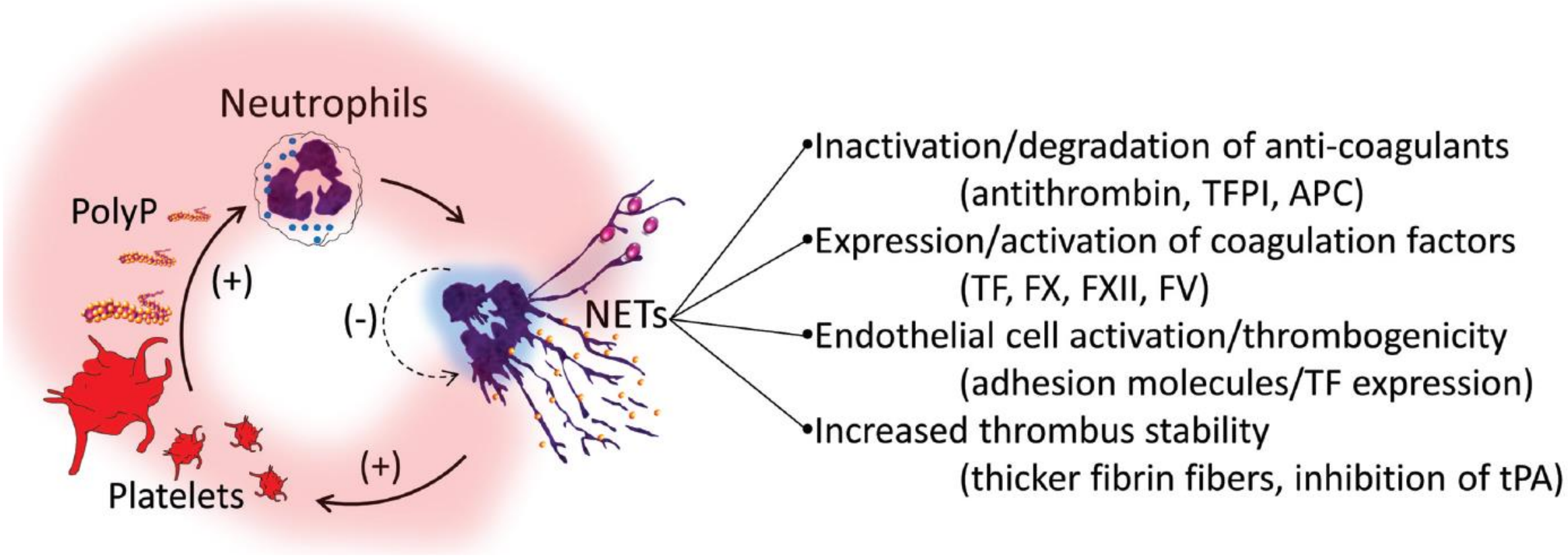


Figure 2. Plasticity of neutrophils can lead to functionally diverse NETs.

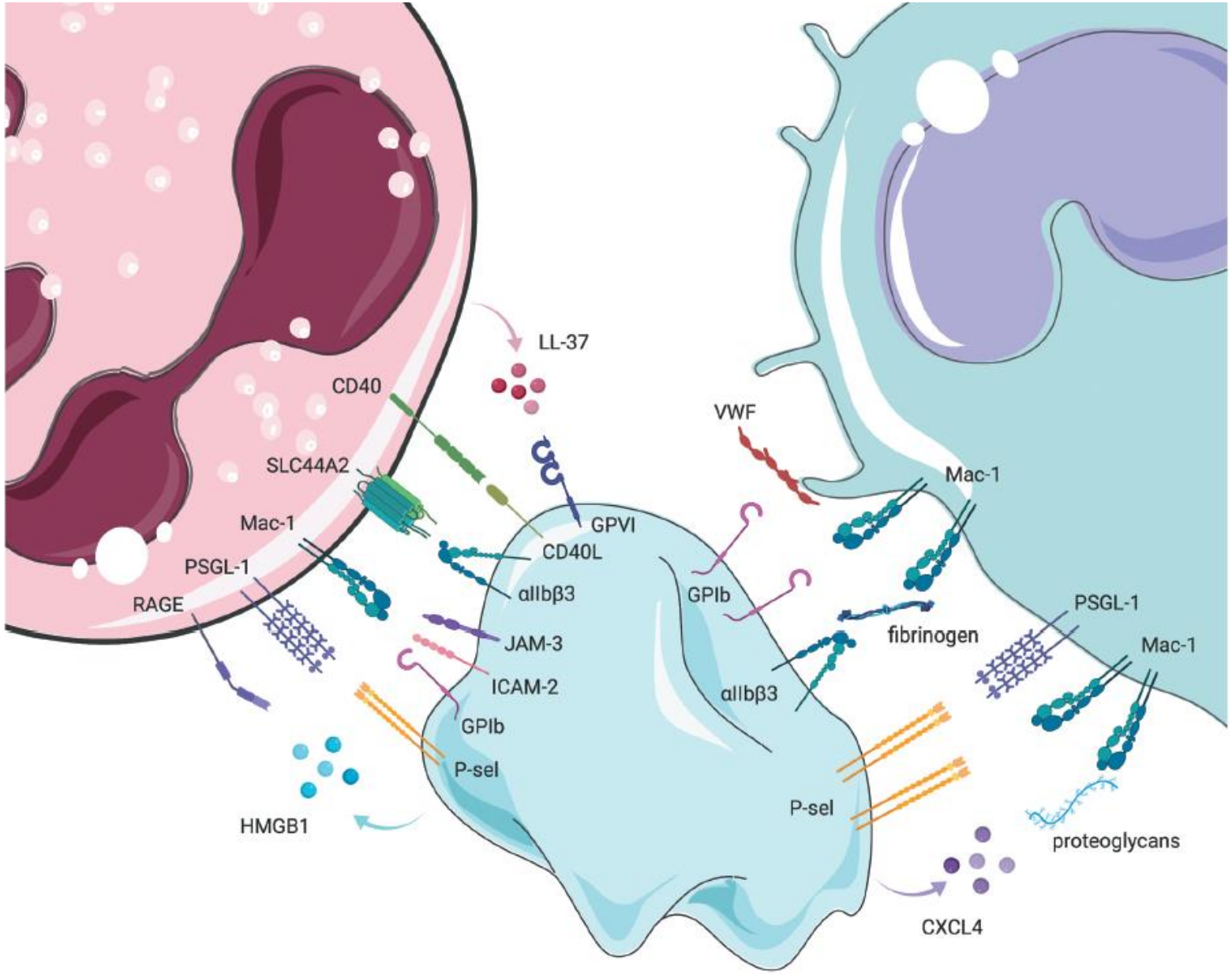
Skendros P et al. CYTONET Project

Mechanisms of neutrophil extracellular trap (NET) thrombogenicity

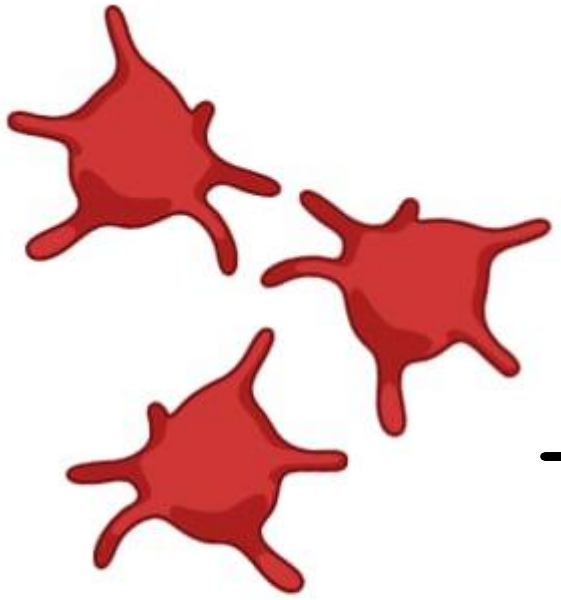


Stakos & Skendros. Thromb Haemost. 2020

Key interactions between platelets and neutrophils or macrophages



Martinod K, Deppermann C. Platelets. 2021



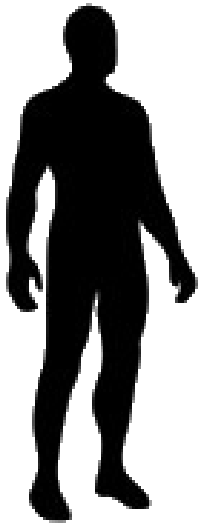
Platelets

Support/induce NET formation

Influence the migratory properties of neutrophils

Clark SR, et al. Nat Med. 2007- Chrysanthopoulou A, et al. J Pathol 2017 - Sreeramkumar, V. et al. Science 2014

Neutrophils/NETs are key factors linking inflammation to immunothrombosis & immunofibrosis in various clinical models



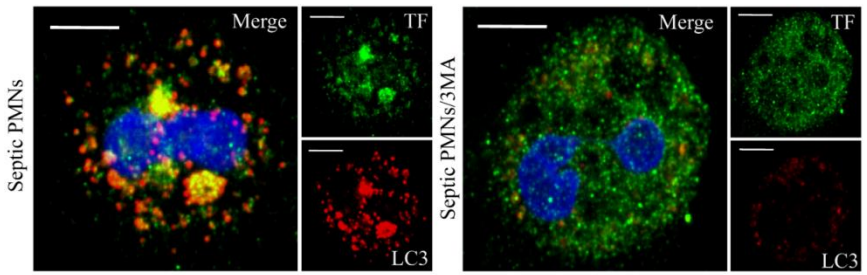
OPEN ACCESS Freely available online

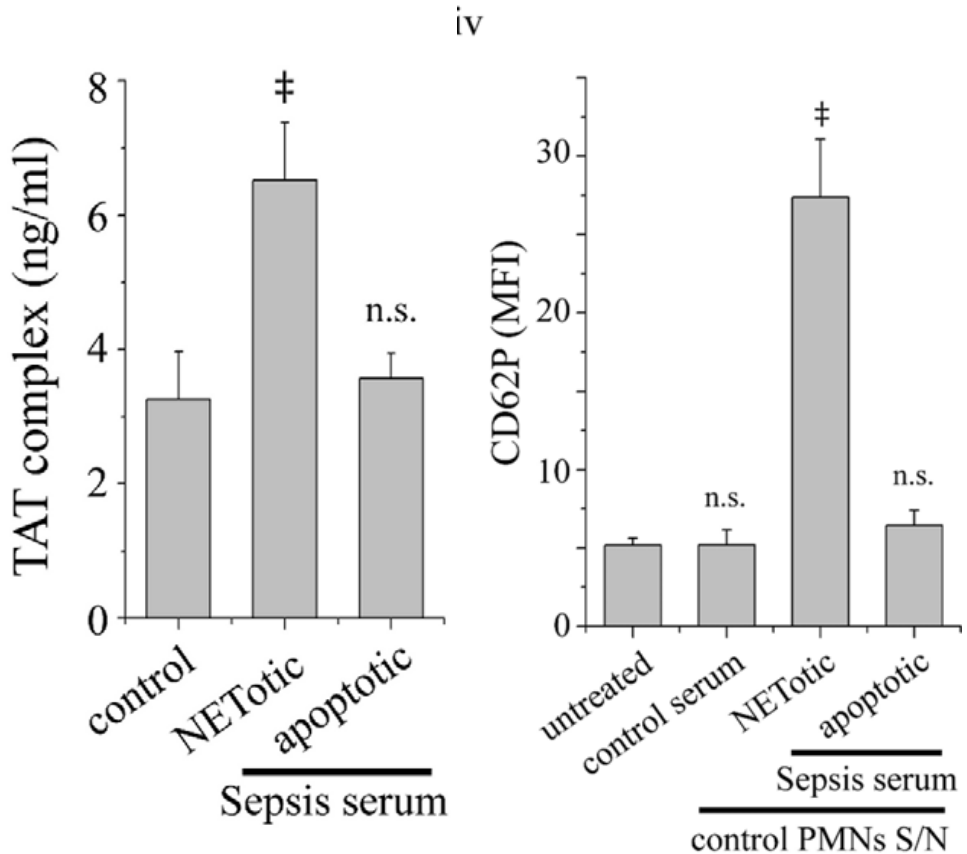
PLOS ONE

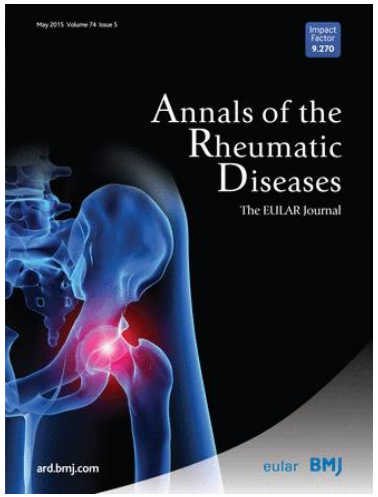
Autophagy Mediates the Delivery of Thrombogenic Tissue Factor to Neutrophil Extracellular Traps in Human Sepsis

PLoS One. 2012;7(9):e45427

Konstantinos Kambas[1☯], Ioannis Mitroulis[1☯], Eirini Apostolidou[1], Andreas Girod[2], Akrivi Chrysanthopoulou[1], Ioannis Pneumatikos[3], Panagiotis Skendros[1], Ioannis Kourtzelis[4], Maria Koffa[5], Ioannis Kotsianidis[6], Konstantinos Ritis[1*]







Ann Rheum Dis 2014

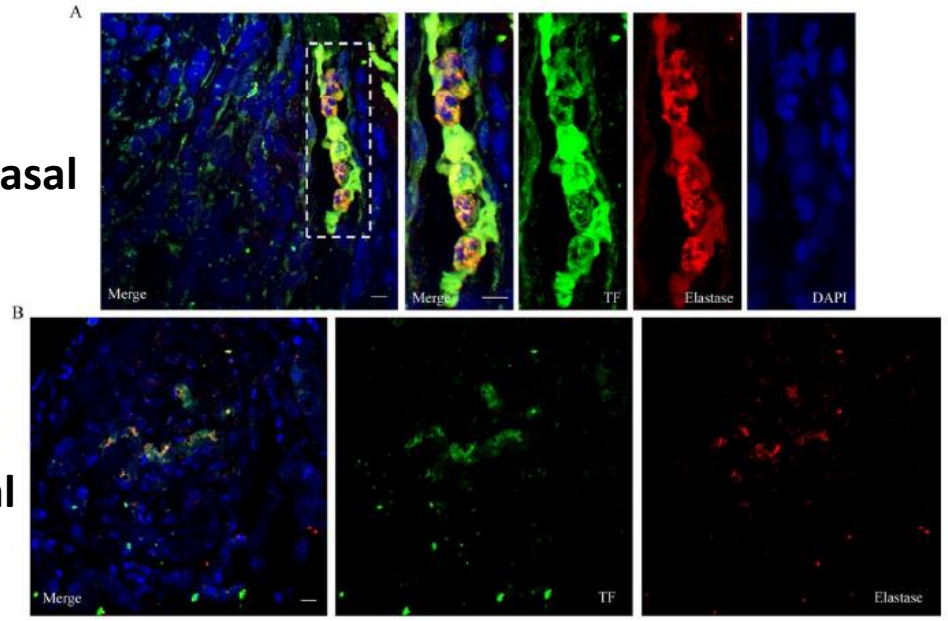
EXTENDED REPORT

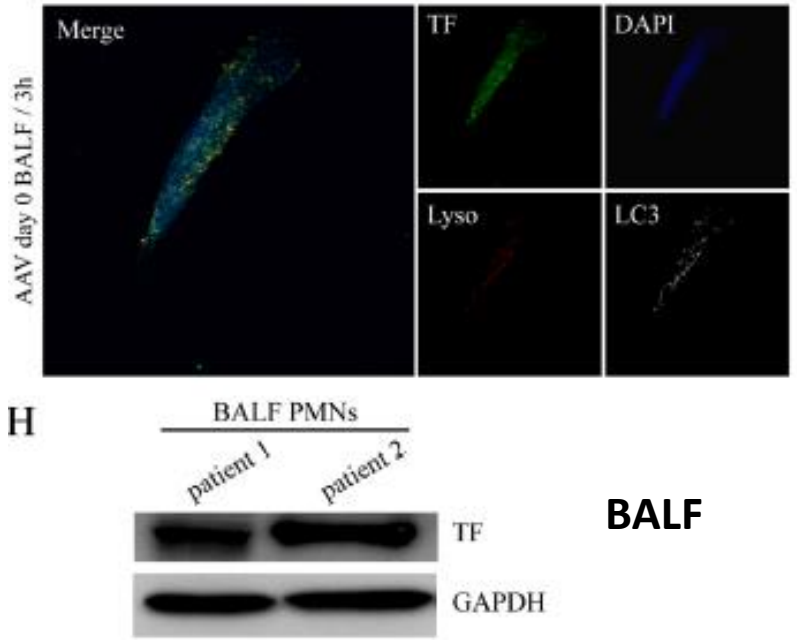
Tissue factor expression in neutrophil extracellular traps and neutrophil derived microparticles in antineutrophil cytoplasmic antibody associated vasculitis may promote thromboinflammation and the thrombophilic state associated with the disease

Konstantinos Kambas,[1] Akrivi Chrysanthopoulou,[1] Dimitrios Vassilopoulos,[2] Eirini Apostolidou,[1] Panagiotis Skendros,[3] Andreas Girod,[4] Stella Arelaki,[1] Marios Froudarakis,[5] Lydia Nakopoulou,[6] Alexandra Giatromanolaki,[7] Prodromos Sidiropoulos,[8] Maria Koffa,[9] Dimitrios T Boumpas,[10,11] Konstantinos Ritis,[1,3] Ioannis Mitroulis[1,3,12]

nasal

renal





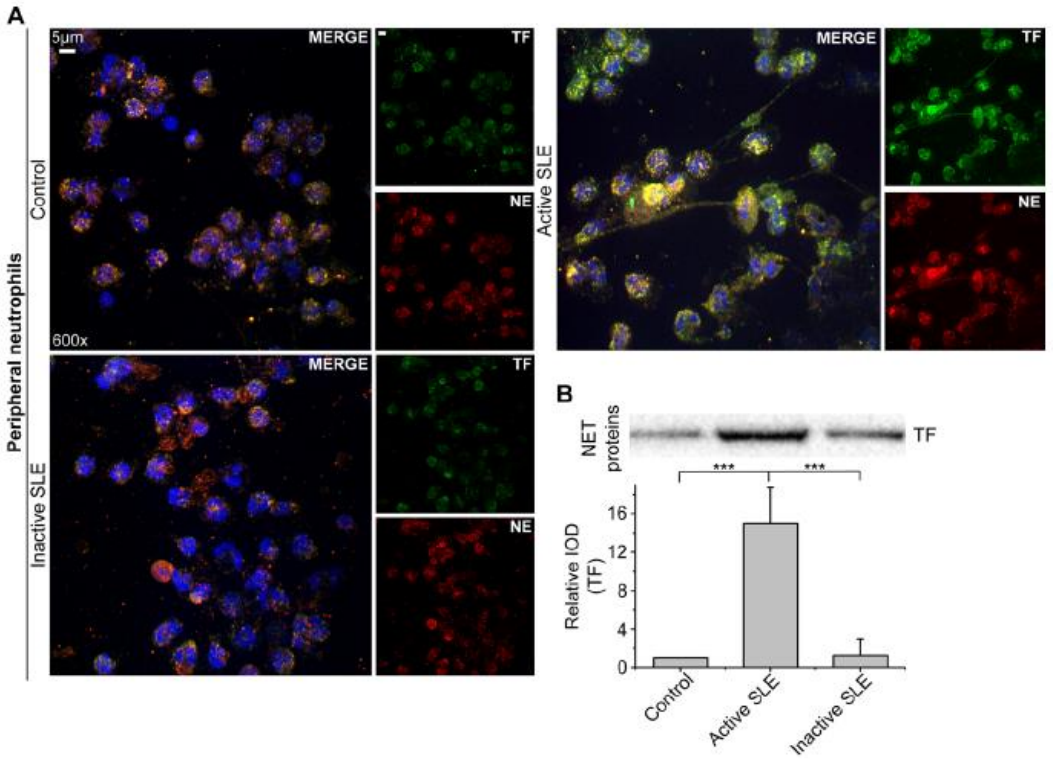
BALF

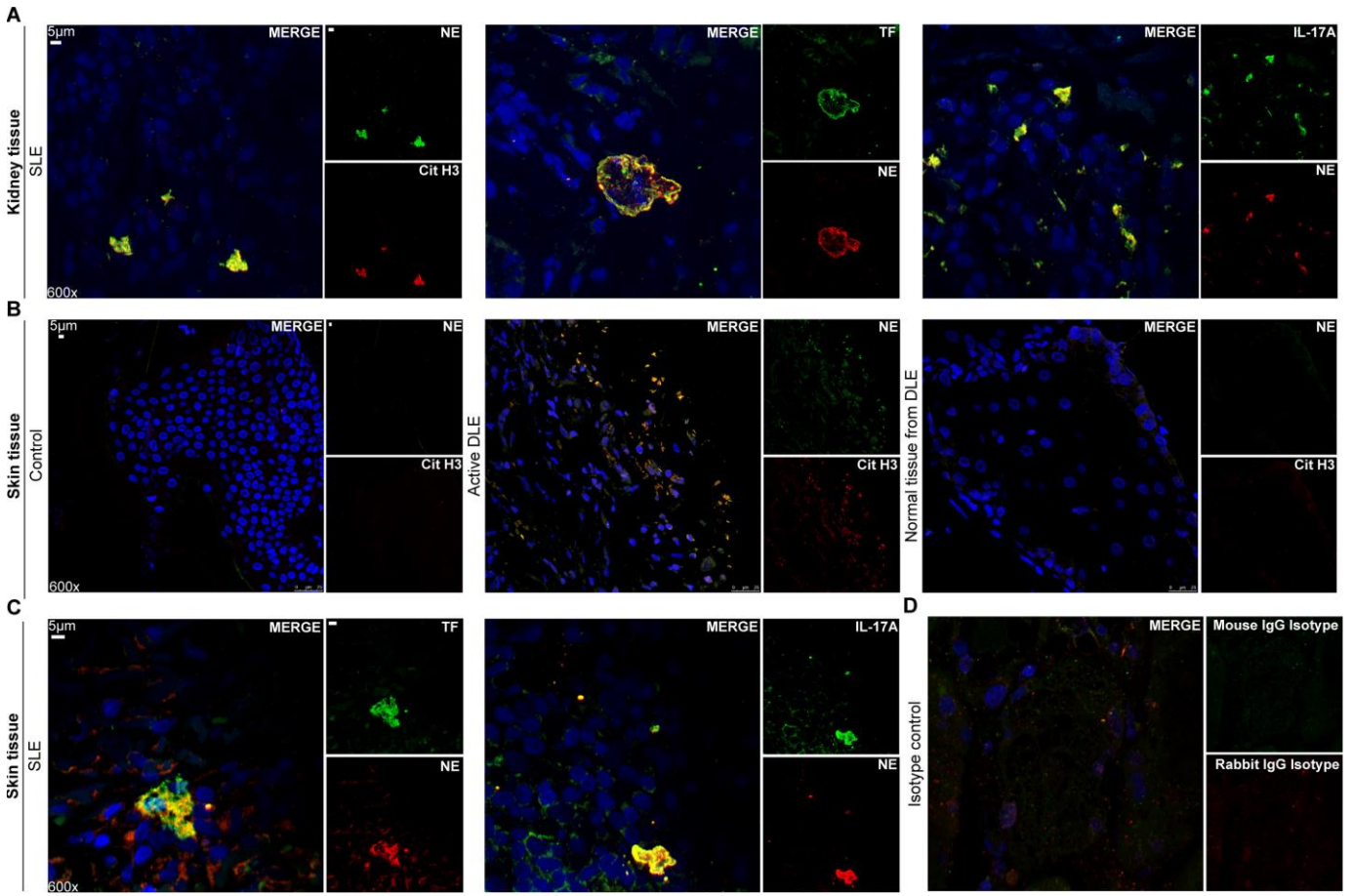
TRANSLATIONAL SCIENCE

Ann Rheum Dis 2019

REDD1/autophagy pathway promotes thromboinflammation and fibrosis in human systemic lupus erythematosus (SLE) through NETs decorated with tissue factor (TF) and interleukin-17A (IL-17A)

Eleni Frangou,[1,2,3] Akrivi Chrysanthopoulou,[4] Alexandros Mitsios,[4] Konstantinos Kambas,[4] Stella Arelaki,[5] Iliana Angelidou,[4] Athanasios Arampatzioglou,[4] Hariklia Gakiopoulou,[6] George K Bertsias,[7] Panayotis Verginis,[1] Konstantinos Ritis,[4,8] Dimitrios T Boumpas[1,2,9,10]





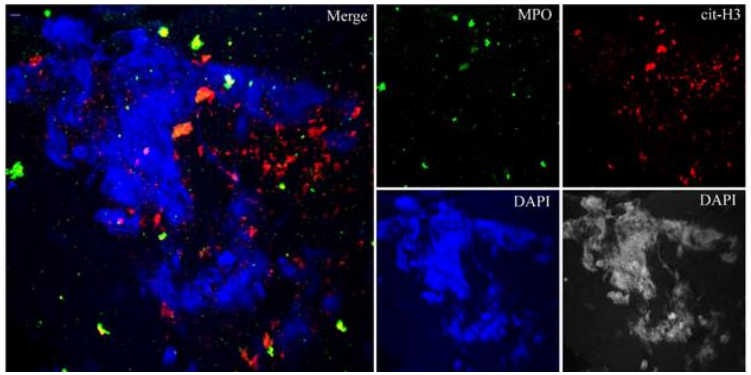
European Heart Journal Advance Access published February 7, 2015

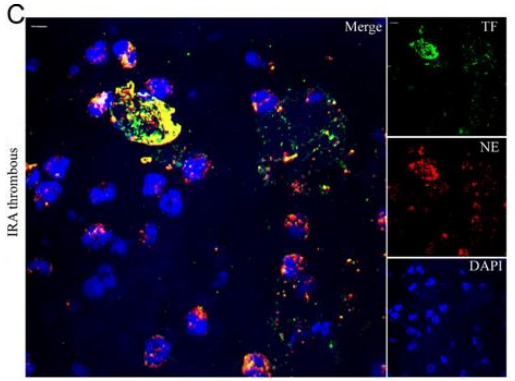
European Heart Journal
doi:10.1093/eurheartj/ehv007

BASIC SCIENCE

Expression of functional tissue factor by neutrophil extracellular traps in culprit artery of acute myocardial infarction

Dimitrios A. Stakos[1†], Konstantinos Kambas[2†], Theocharis Konstantinidis[2], Ioannis Mitroulis[3], Eirini Apostolidou[2], Stella Arelaki[4], Victoria Tsironidou[2], Alexandra Giatromanolaki[4], Panagiotis Skendros[2], Stavros Konstantinides[1,5], and Konstantinos Ritis[2*]





Translational perspective

Neutrophils are involved in the pathophysiology of infracted coronary arteries in STEMI via NET structures. Platelets, activated by thrombin, are required for NET formation, while the integrity of NET scaffold contributes to the functionality of NET-bound TF. The blockage of NET formation or local neutralization of NET-mediated TF signalling constitutes candidate therapeutic targets.

European Heart Journal (2016) **37**, 1538–1549
doi:10.1093/eurheartj/ehv419

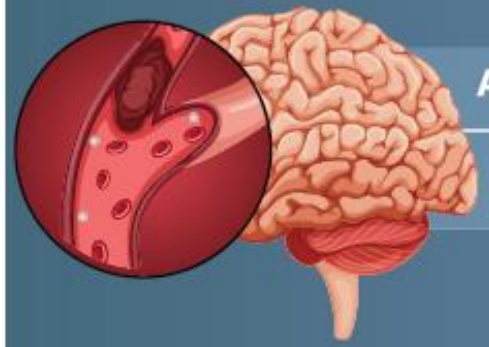
Histopathological evaluation of thrombus in patients presenting with stent thrombosis. A multicenter European study: a report of the prevention of late stent thrombosis by an interdisciplinary global European effort consortium†

PRESTIGE Investigators

Results Overall 253 thrombus specimens were analysed; 79 (31.2%) from patients presenting with early ST, 174 (68.8%) from late ST; 79 (31.2%) were from bare metal stents, 166 (65.6%) from drug-eluting stents, 8 (3.2%) were from stents of unknown type. Thrombus specimens displayed heterogeneous morphology with platelet-rich thrombus and fibrin/fibrinogen fragments most abundant; mean platelet coverage was 57% of thrombus area. Leukocyte infiltrations were hallmarks of both early and late ST (early: 2260 $\pm$ 1550 per mm^2 vs. late: 2485 $\pm$ 1778 per mm^2; $P = 0.44$); neutrophils represented the most prominent subset (early: 1364 $\pm$ 923 per mm^2 vs. late: 1428 $\pm$ 1023 per mm^2; $P = 0.81$). Leukocyte counts were significantly higher compared with a control group of patients with thrombus aspiration in spontaneous myocardial infarction. Neutrophil extracellular traps were observed in 23% of samples. Eosinophils were present in all stent types, with higher numbers in patients with late ST in sirolimus-and everolimus-eluting stents.

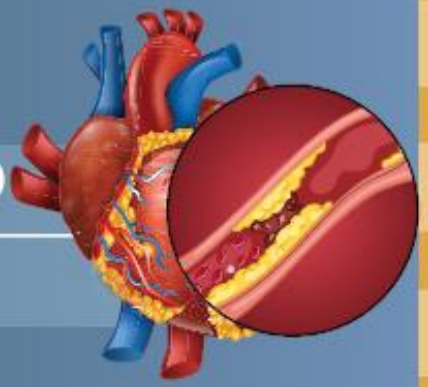
Conclusion In a large-scale study of histological thrombus analysis from patients presenting with ST, thrombus specimens displayed heterogeneous morphology. Recruitment of leukocytes, particularly neutrophils, appears to be a hallmark of ST. The presence of NETs supports their pathophysiological relevance. Eosinophil recruitment suggests an allergic component to the process of ST.

Thrombus Immune Cell Composition Differences between Acute Ischemic Stroke and Acute Myocardial Infarction



Acute ischemic stroke (AIS)

Thromboembolic occlusion of a cerebral vessel



Acute myocardial infarction (AMI)

Coronary artery occlusion after atheromatous plaque rupture

Patients with

AIS = 71

AMI = 72

Immunohistological analysis of immune cell composition and NET prevalence in thrombus

Clinical outcomes

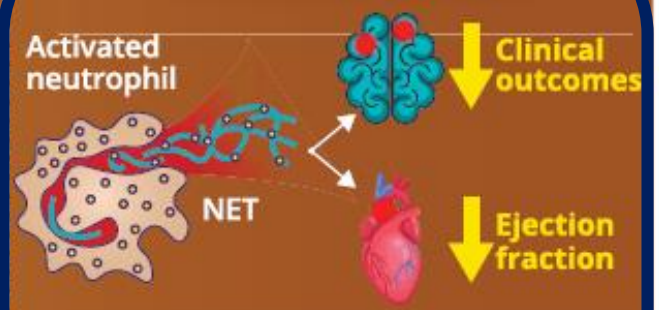
Cardiac function

Thrombus composition

Leukocyte and neutrophil counts were similar in AIS and AMI thrombi

	AIS	AMI
Monocytes		
Eosinophils		
B and T cells		

Formation of NETs



Prevalence of NETs

Study question

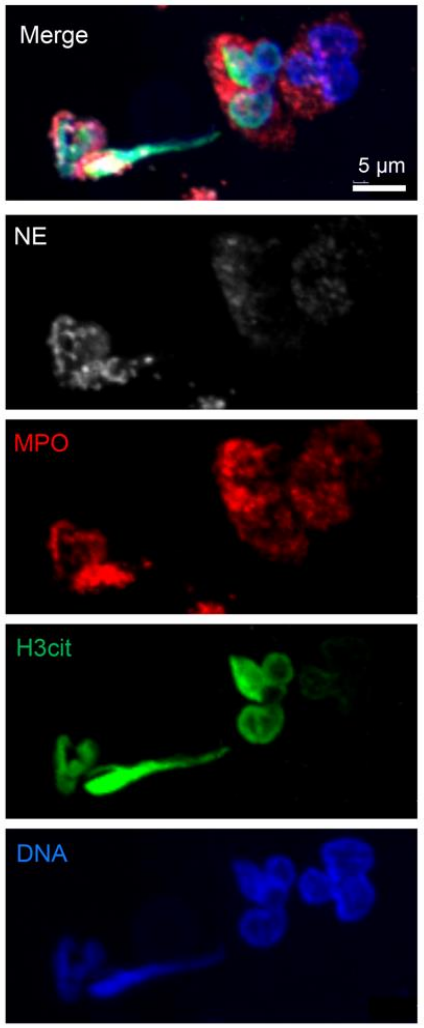
Are there differences in immune cell composition and prevalence of NETs in patients with AIS and AMI?

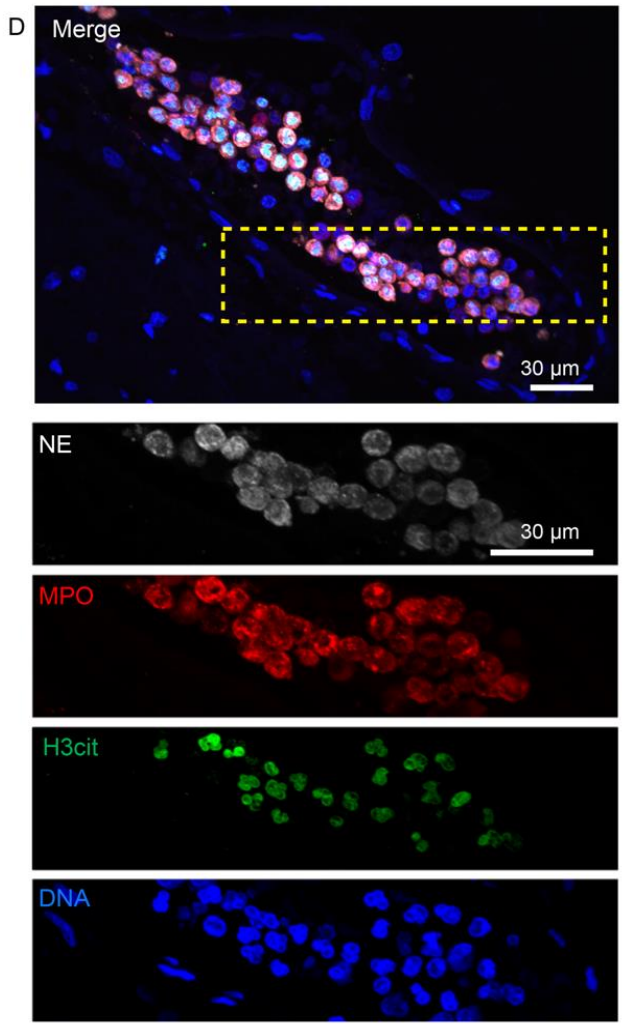
Thrombus NET composition is different in patients with AIS and AMI, with implications for clinical outcomes

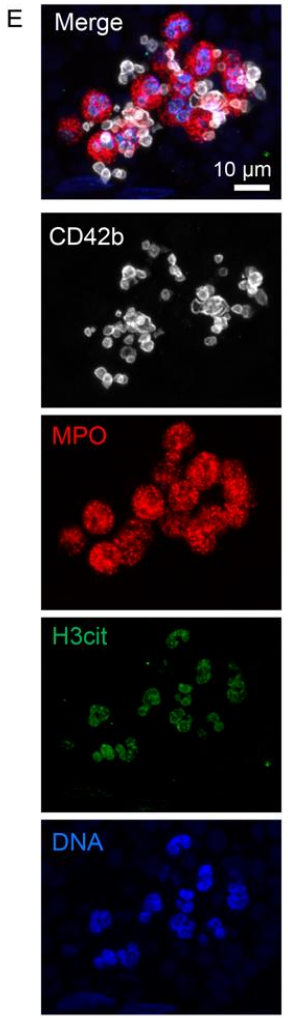
doi:10.1212/WNL.0000000000009532

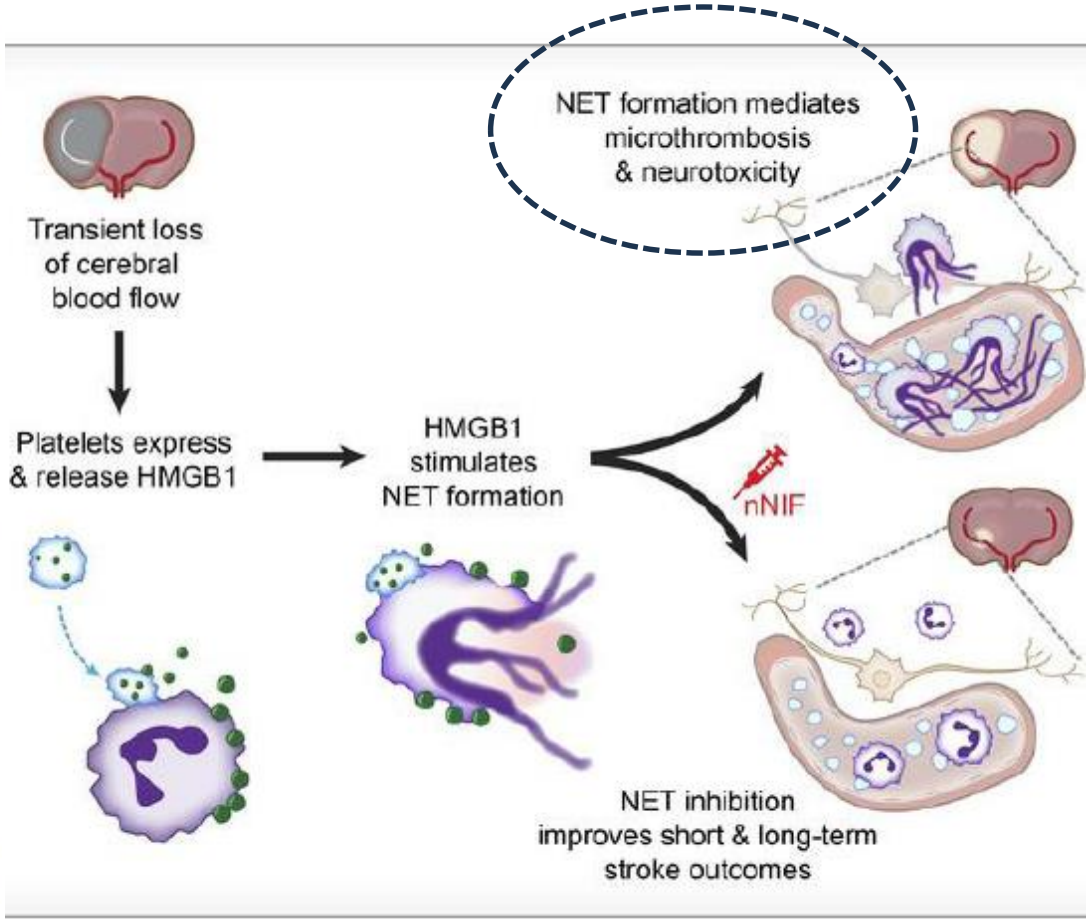
Neurology®

Neutrophil Extracellular Traps (NETs) are found in ipsilesional brain tissue from ischemic stroke patients









Denorme F et al. J Clin Invest 2022

EClinicalMedicine 29–30 (2020) 100639

Contents lists available at ScienceDirect

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journal homepage: https://www.journals.elsevier.com/eclinicalmedicine

Research Paper

Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis

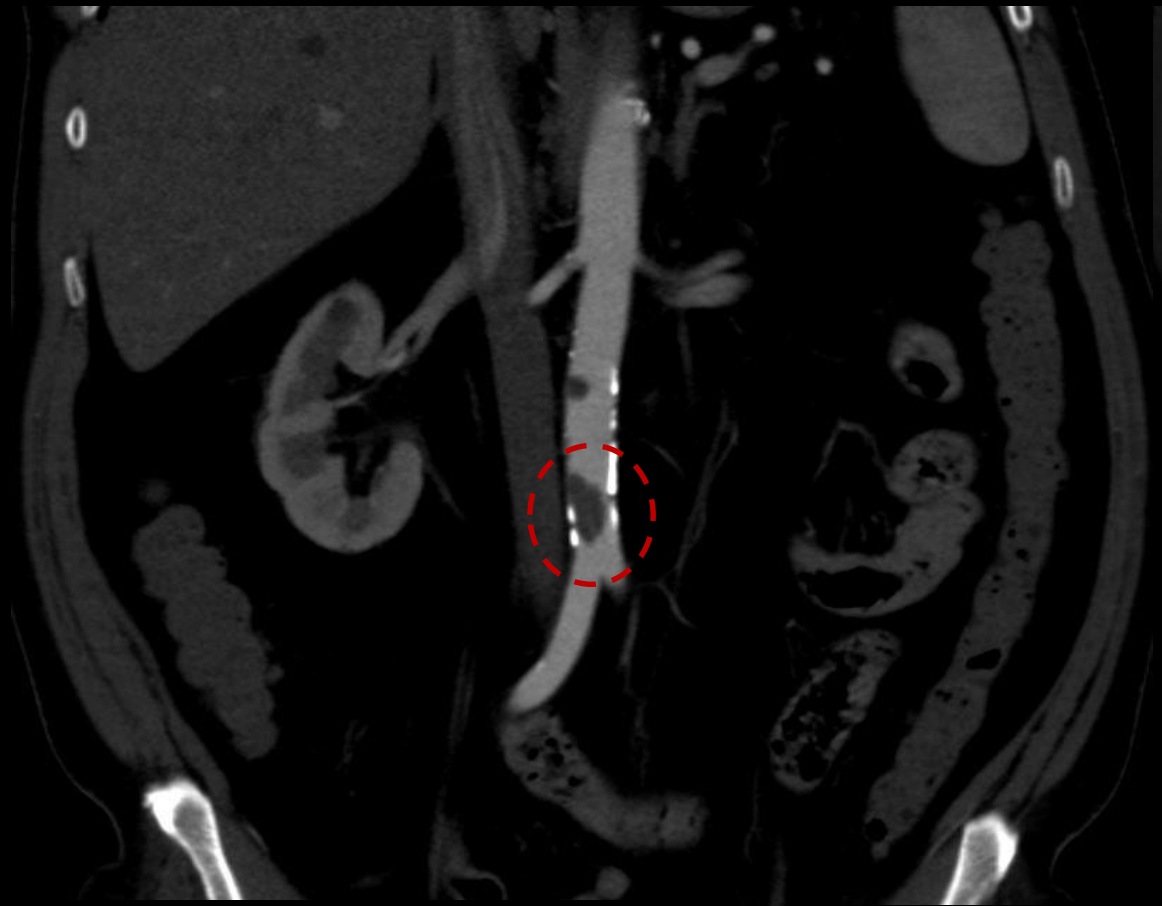
Mahmoud B. Malas[1,*], Isaac N. Naazie[1], Nadin Elsayed, Asma Mathlouthi, Rebecca Marmor, Bryan Clary

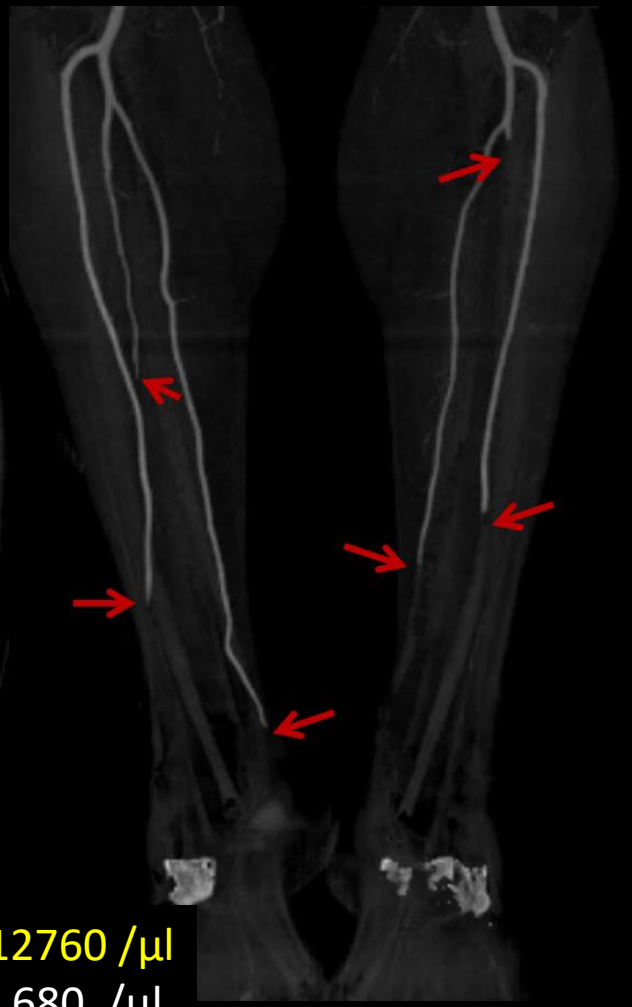
Department of Surgery, University of California San Diego Health System, San Diego, CA 92093, United States

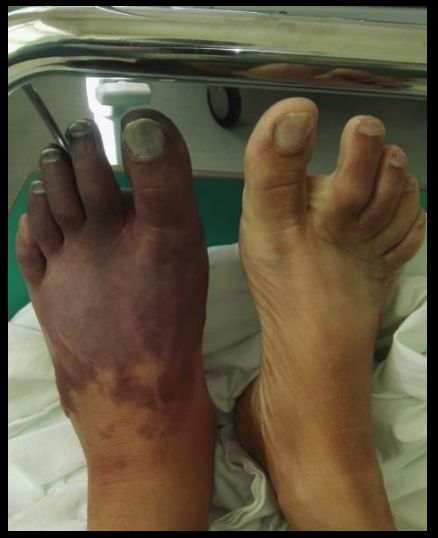
42 studies/8271 patients

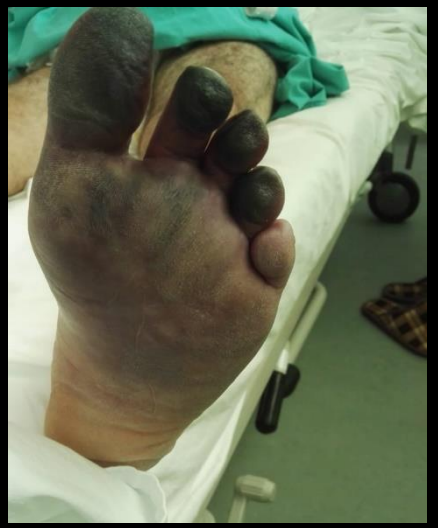
Findings: Of 425 studies identified, 42 studies enrolling 8271 patients were included in the meta-analysis. Overall venous TE rate was 21% (95% CI:17–26%): ICU, 31% (95% CI: 23–39%). Overall deep vein thrombosis rate was 20% (95% CI: 13–28%): ICU, 28% (95% CI: 16–41%); postmortem, 35% (95% CI:15–57%). Overall pulmonary embolism rate was 13% (95% CI: 11–16%): ICU, 19% (95% CI:14–25%); postmortem, 22% (95% CI:16–28%). Overall arterial TE rate was 2% (95% CI: 1–4%): ICU, 5% (95%CI: 3–7%). Pooled mortality rate among patients with TE was 23% (95%CI:14–32%) and 13% (95% CI:6–22%) among patients without TE. The pooled odds of mortality were 74% higher among patients who developed TE compared to those who did not (OR, 1.74; 95%CI, 1.01–2.98; $P = 0.04$).

Severe thrombotic complication in a COVID-19 patient





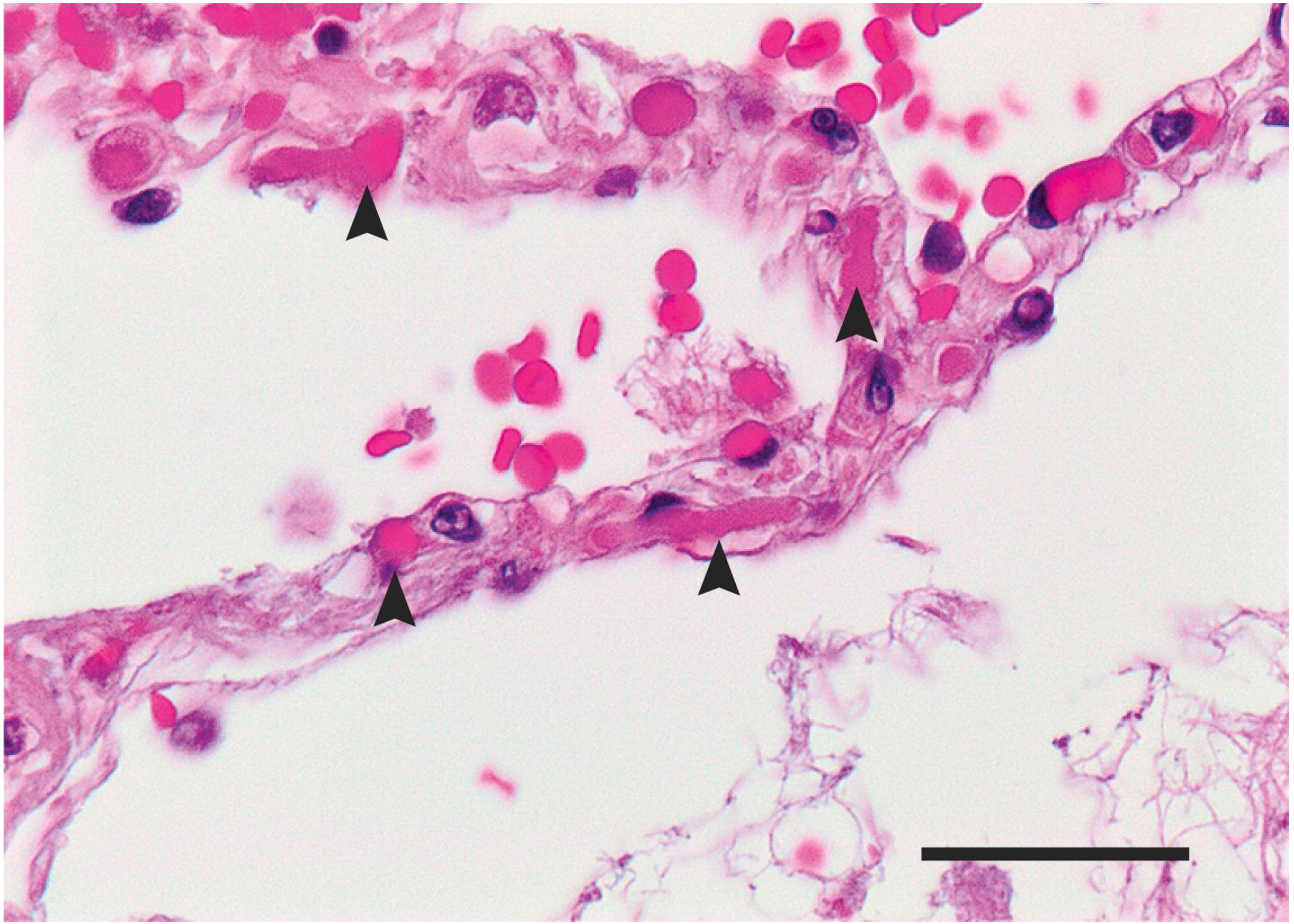




- Male, 58 yrs
- 16th day of disease
- SpO_2 = 97%, FiO_2 35%
- No smoking, BMI 25
- Well-controlled hypertension
- No history of CVD event

- Neutrophils: 12760 /μl
- Lymphocytes: 680 /μl
- CRP: 7.71 mg/dl
- LDH: 1057 U/L
- D-Dimers: 976 ng/ml

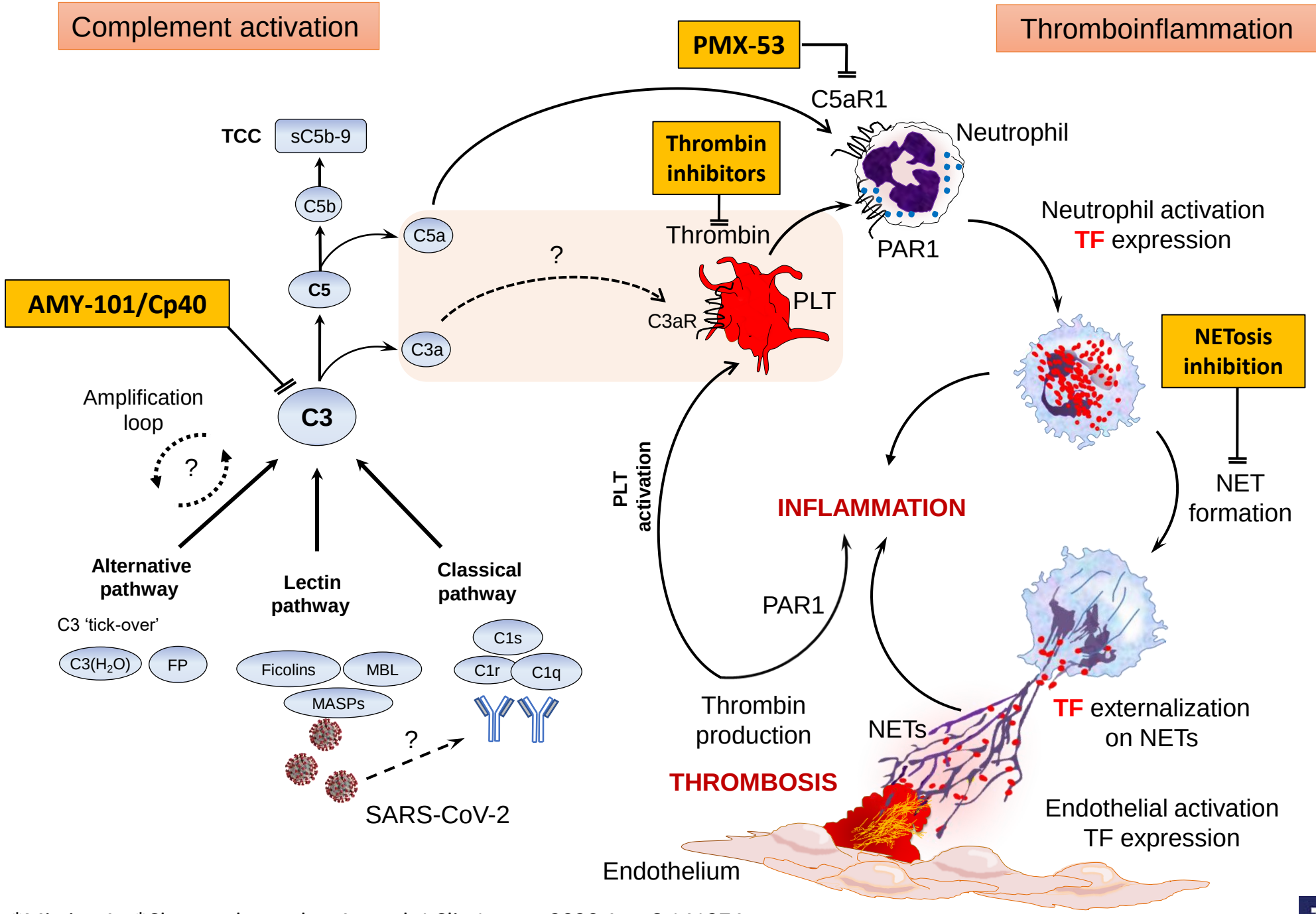
COVID-19 2nd Wards, First Department of Internal Medicine, University Hospital of Alexandroupolis



Micro-CLOTs

Microthrombi in the alveolar capillaries (arrowheads)

Ackermann M, et al. N Engl J Med. 2020



*Skendros P, *Mitsios A, *Chrysanthopoulou A. et al. J Clin Invest. 2020 Aug 6:141374

JCI The Journal of Clinical Investigation

CORONAVIRUS

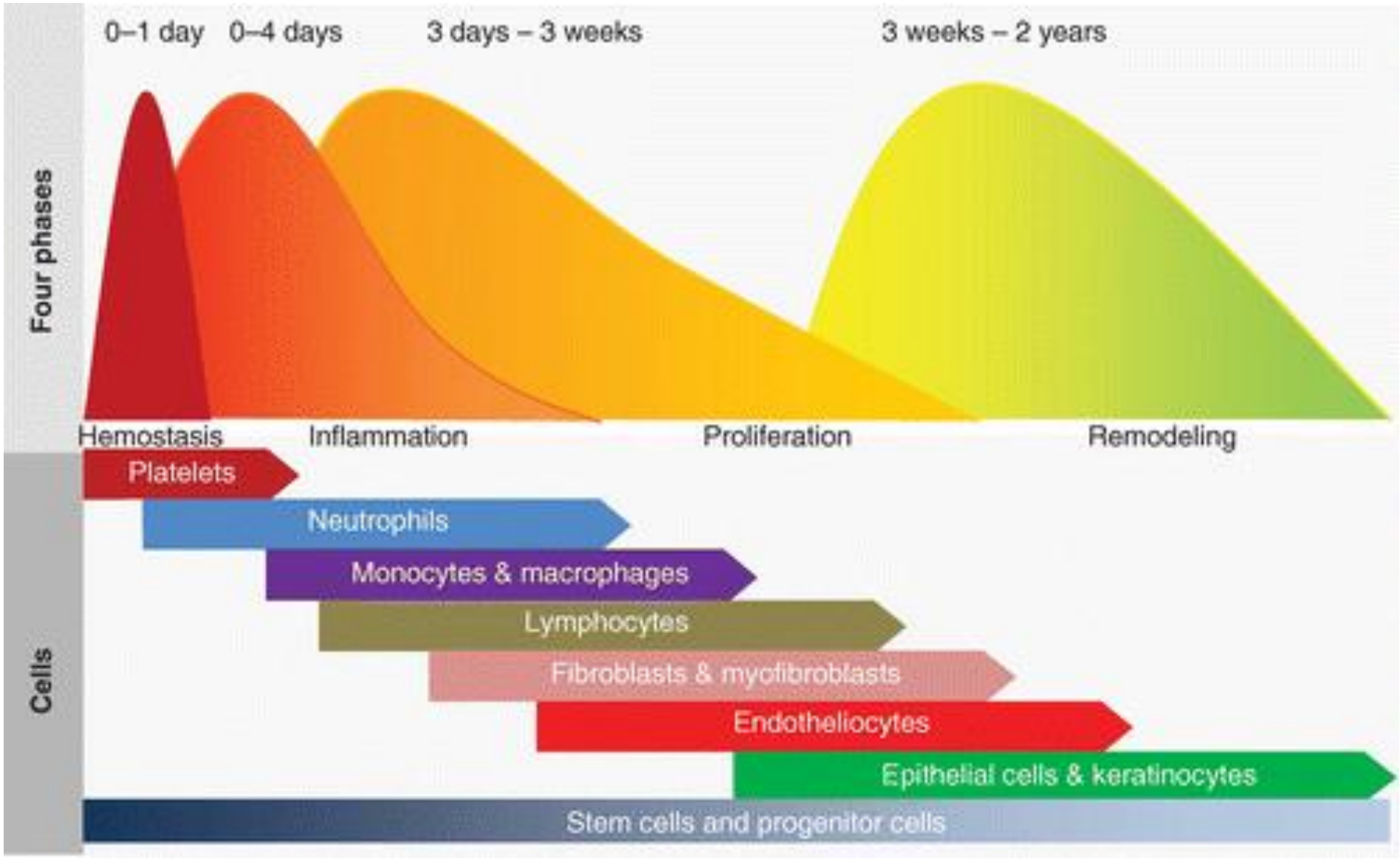
Complement C3 inhibition in severe COVID-19 using

Complement C3 activation contributes to COVID-19 pathology, and C3 targeting has emerged as a promising therapeutic strategy. We provide interim data from ITHACA, the first randomized trial evaluating a C3 inhibitor, AMY-101, in severe COVID-19 ($PaO_2/FiO_2 \leq 300$ mmHg). Patients received AMY-101 ($n = 16$) or placebo ($n = 15$) in addition to standard of care. AMY-101 was safe and well tolerated. Compared to placebo (8 of 15, 53.3%), a higher, albeit nonsignificant, proportion of AMY-101–treated patients (13 of 16, 81.3%) were free of supplemental oxygen at day 14. Three nonresponders and two placebo-treated patients succumbed to disease-related complications. AMY-101 significantly reduced CRP and ferritin and restrained thrombin and NET generation. Complete and sustained C3 inhibition was observed in all responders. Residual C3 activity in the three nonresponders suggested the presence of a convertase-independent C3 activation pathway overriding the drug's inhibitory activity. These findings support the design of larger trials exploring the potential of C3-based inhibition in COVID-19 or other complement-mediated diseases.

- ✓ ***Thrombin and Kallikrein/kinin systems are strongly activated in severe COVID-19***
- ✓ ***Linkage between the complement and coagulation systems may represent a new pathway of complement activation***

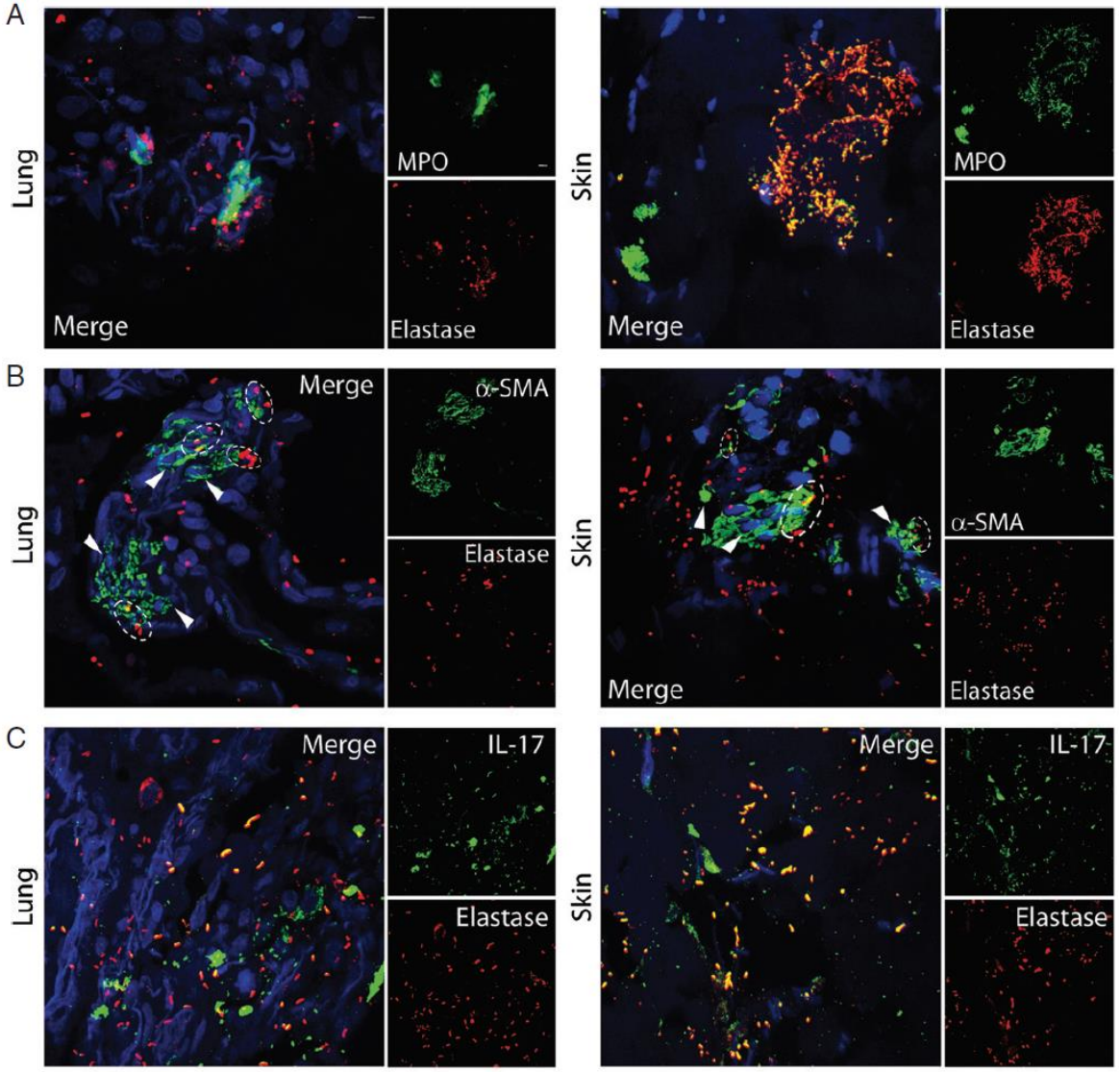
Skendros et al. Science Advances 2022

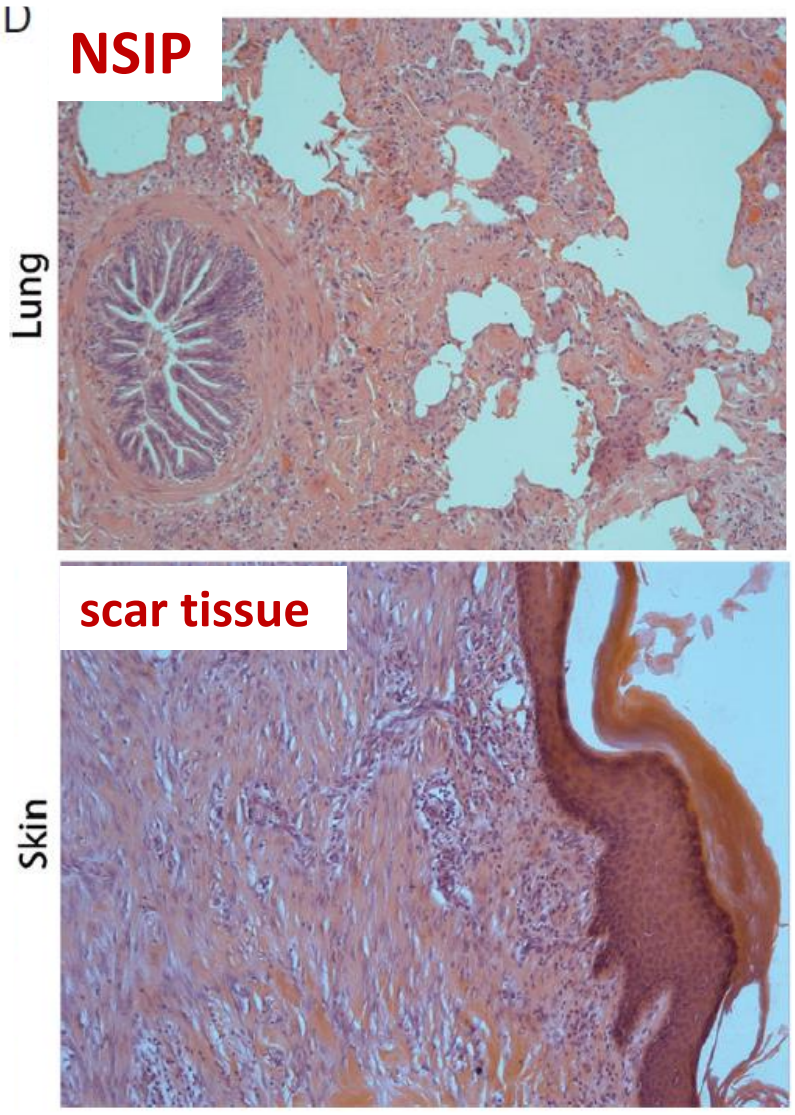
The biological processes during wound healing



Fan Yang, et al. Regenerative Medicine 2021

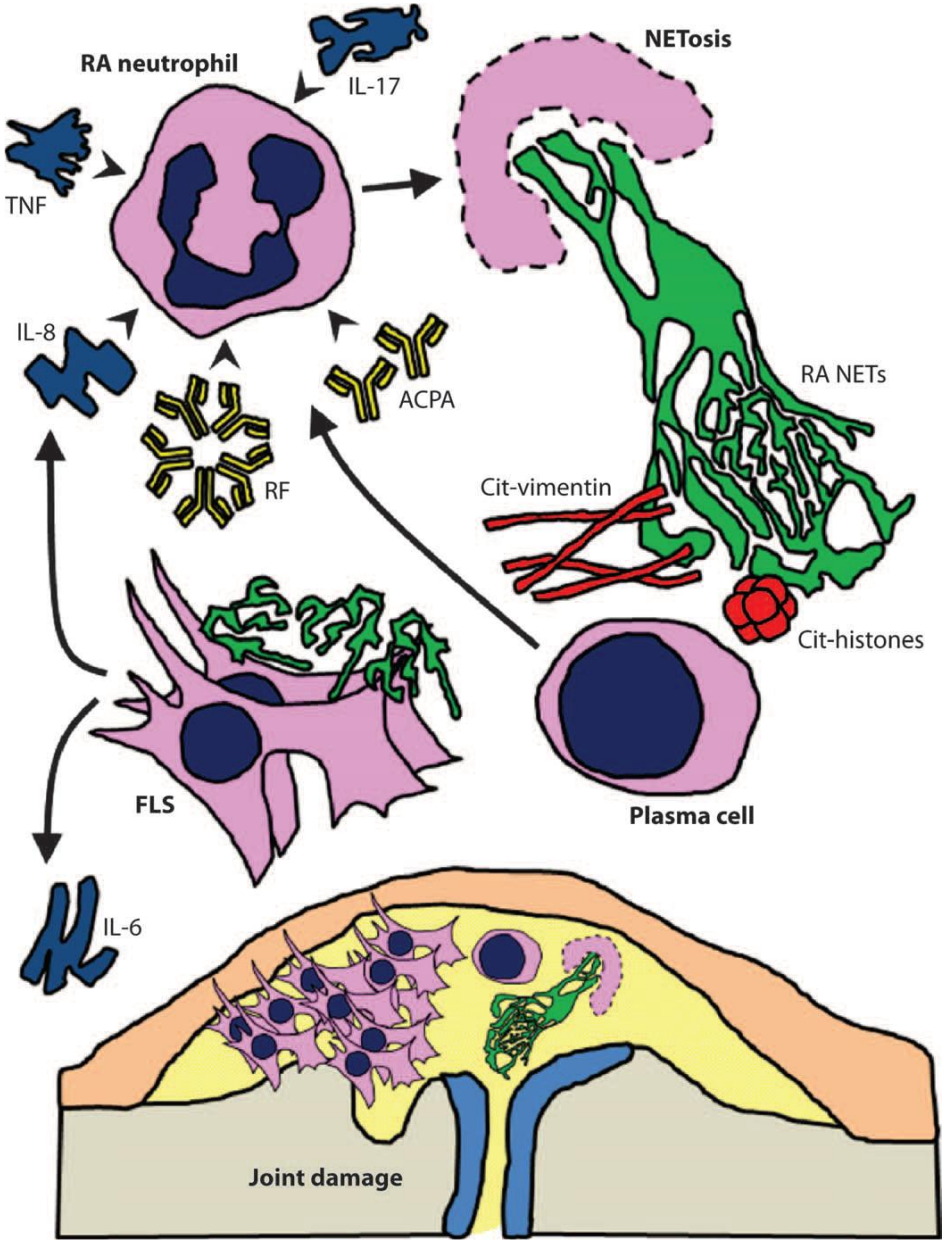
Neutrophil extracellular traps promote differentiation and function of fibroblasts

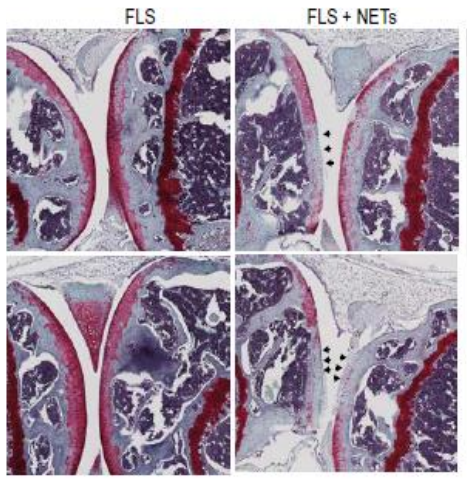


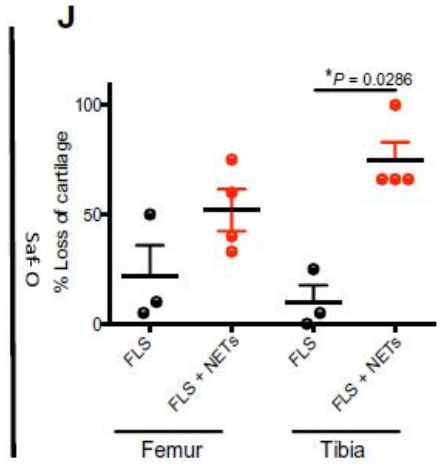


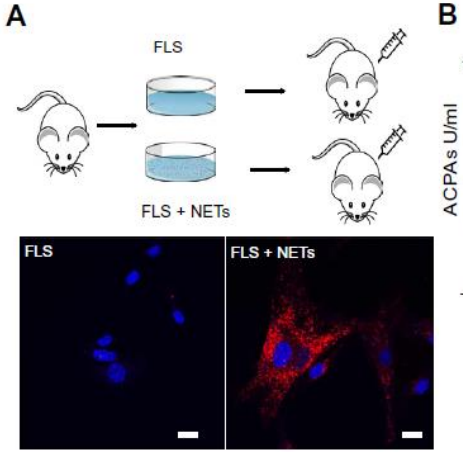
NETs IL-17+ were identified in close proximity to α-SMA-positive fibrocytes in lung and skin biopsy specimens

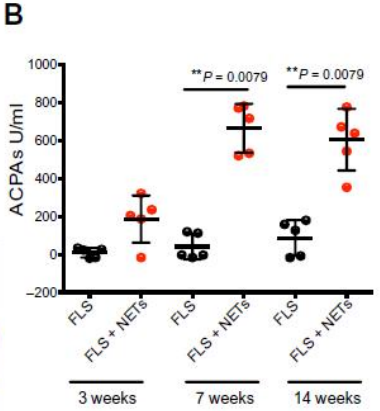
Chrysanthopoulou A, Mitroulis I, et al. J Pathol. 2014









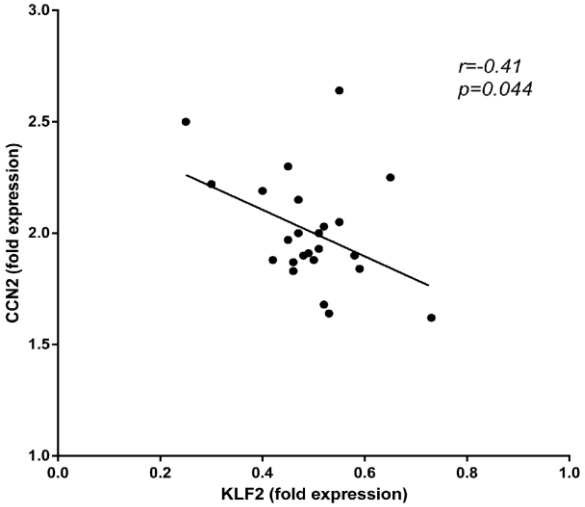


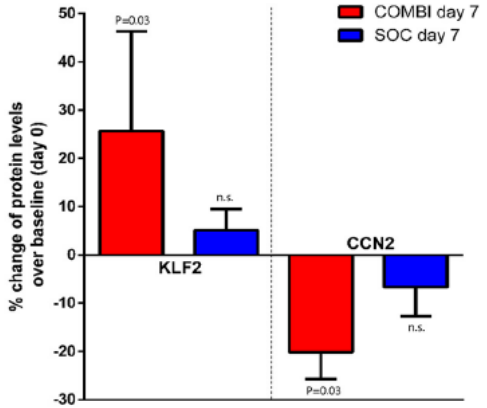
- **NETs are a source of citrullinated autoantigens and activate RA synovial fibroblast**
- **Synovial fibroblast-neutrophil interactions promote pathogenic adaptive immunity in RA**

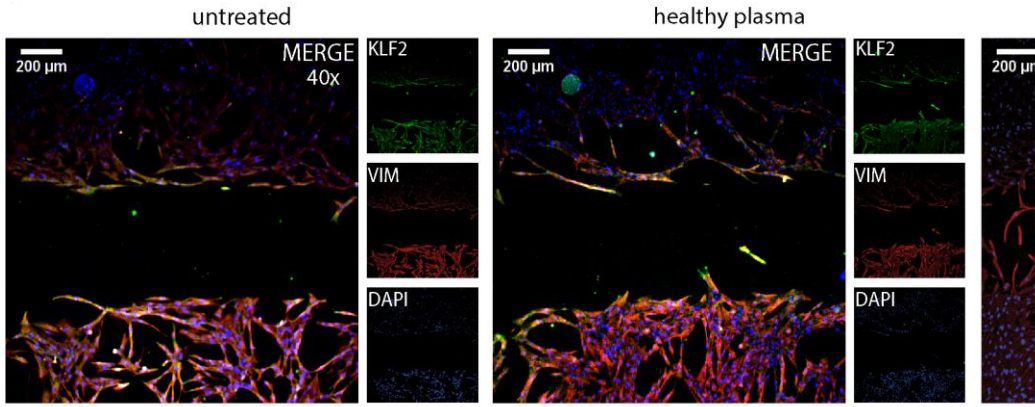
Khandpur R, et al. Sci Transl Med. 2013 - Carmona-Rivera C, et al. Sci Immunol. 2020

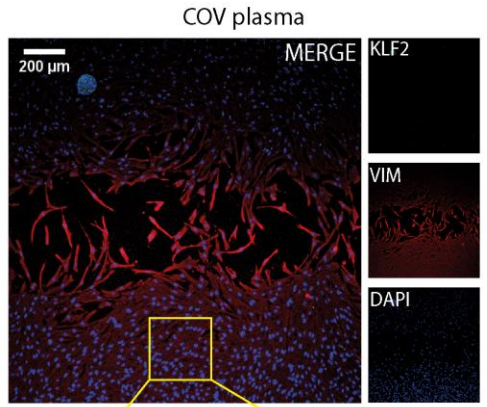
Down-regulation of KLF2 in lung fibroblasts is linked with COVID-19 immunofibrosis and restored by combined inhibition of NETs, JAK-1/2 and IL-6 signaling

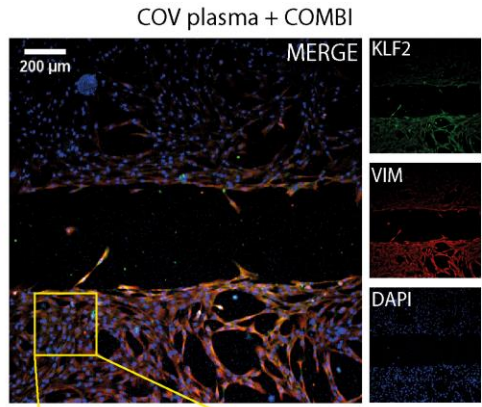
low expression levels of KLF2 in human lung fibroblasts is correlated with their fibrotic activity

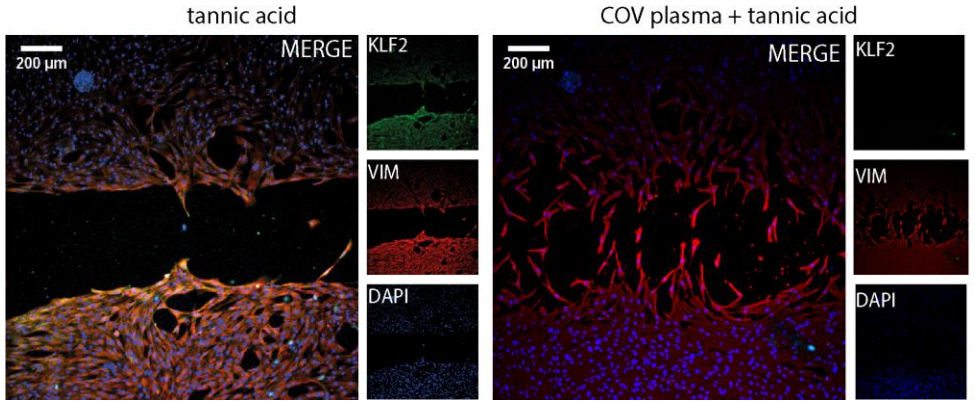


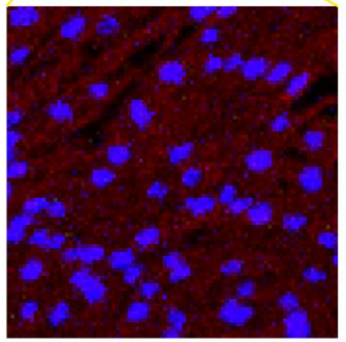


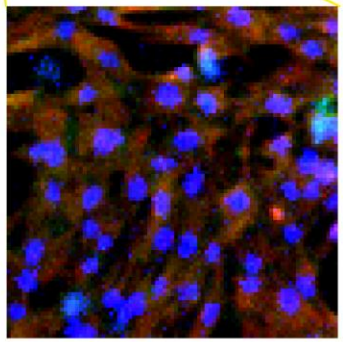




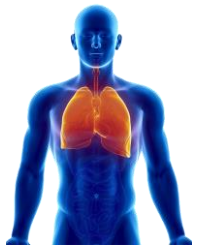


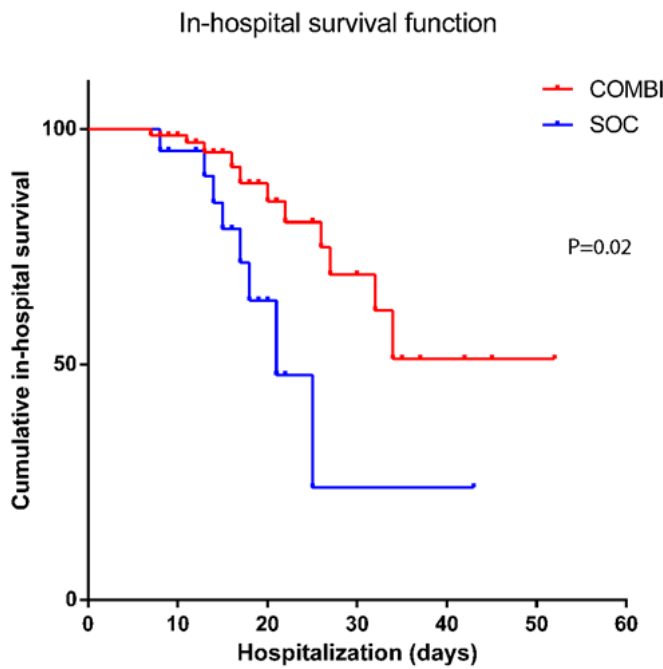


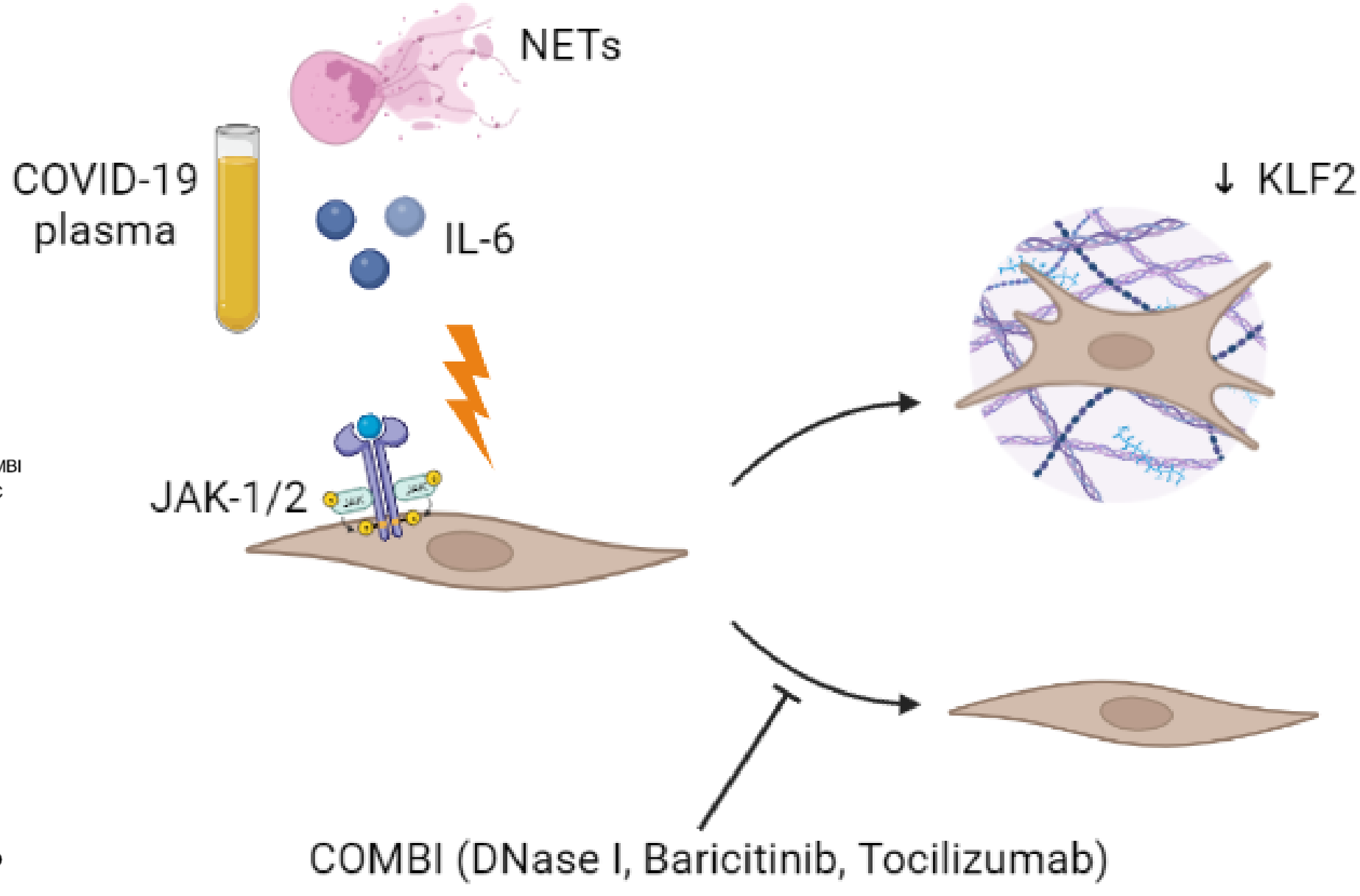




Chrysanthopoulou A*, Antoniadou C*, Natsi AM*, et al. Clin Immunol. 2023



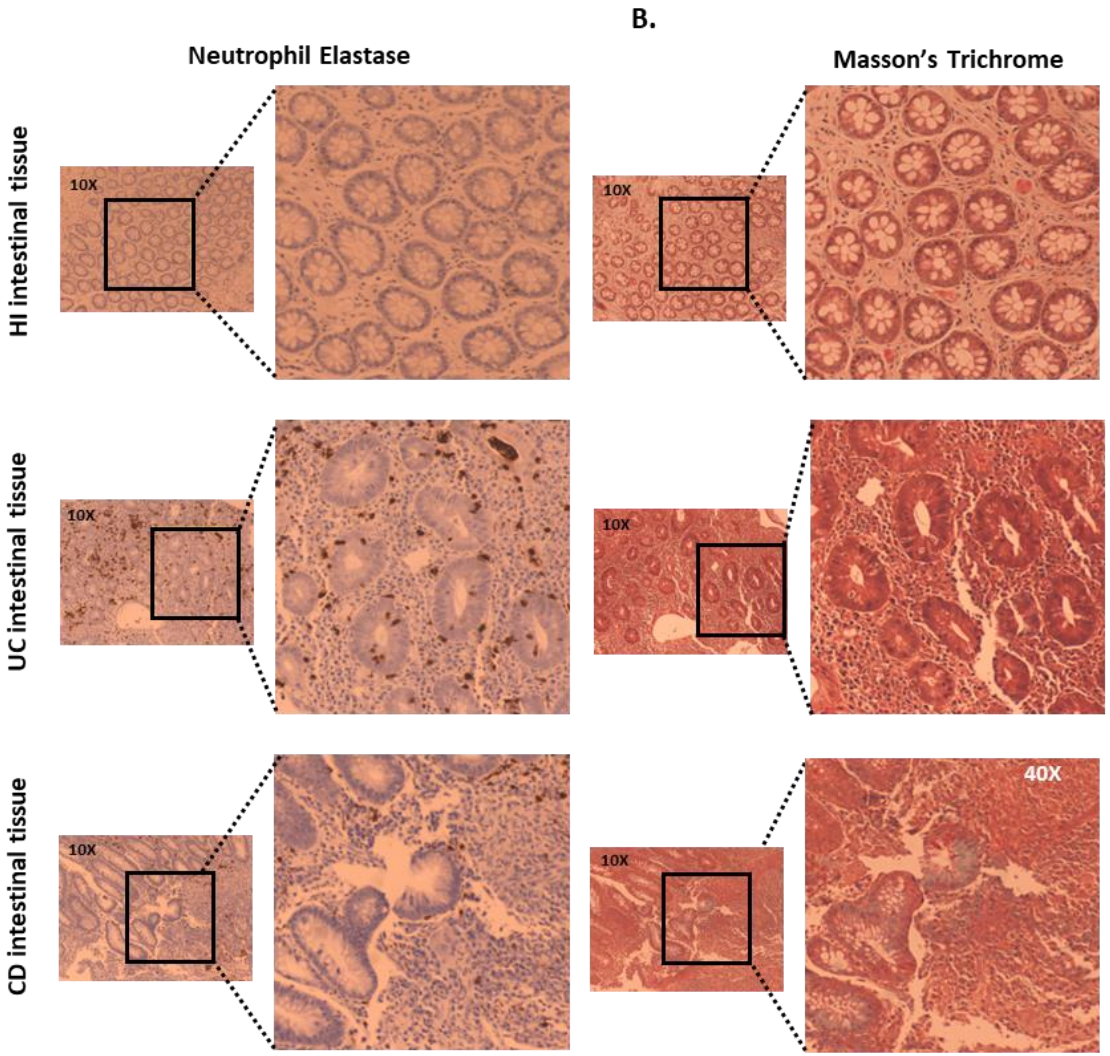


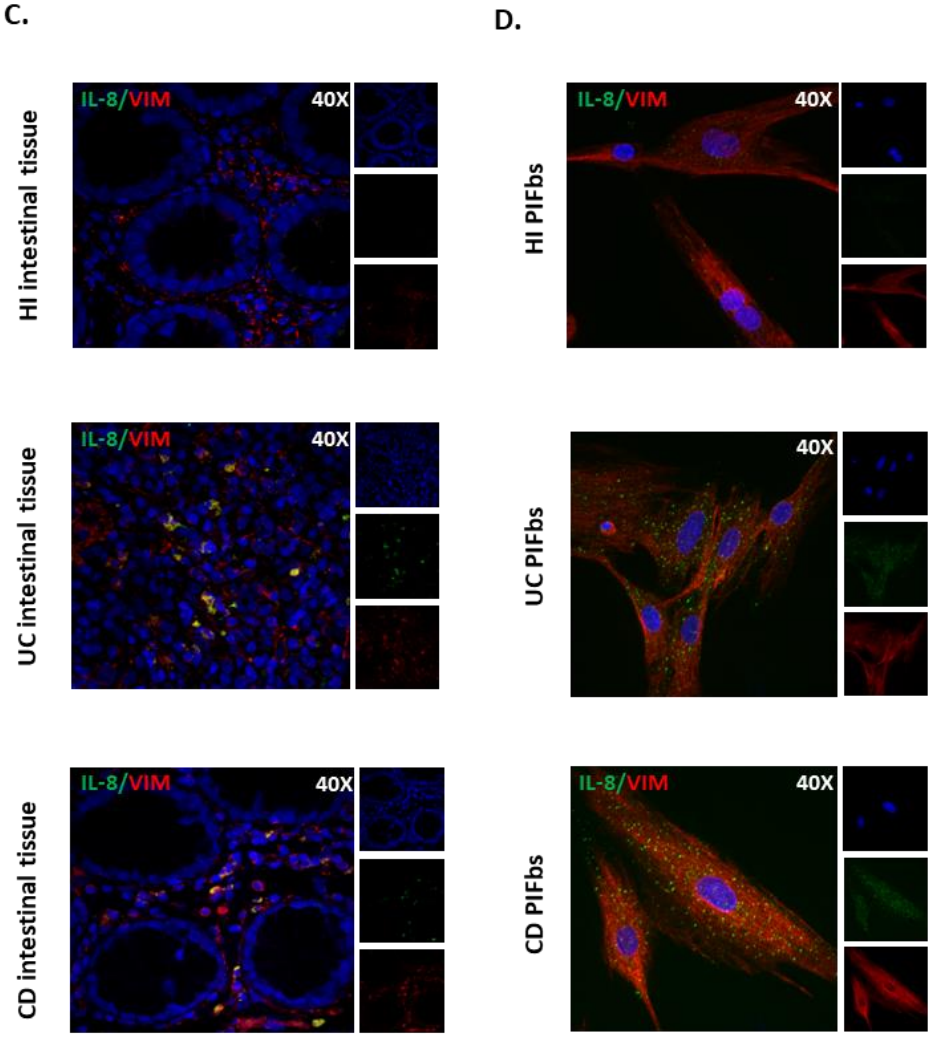


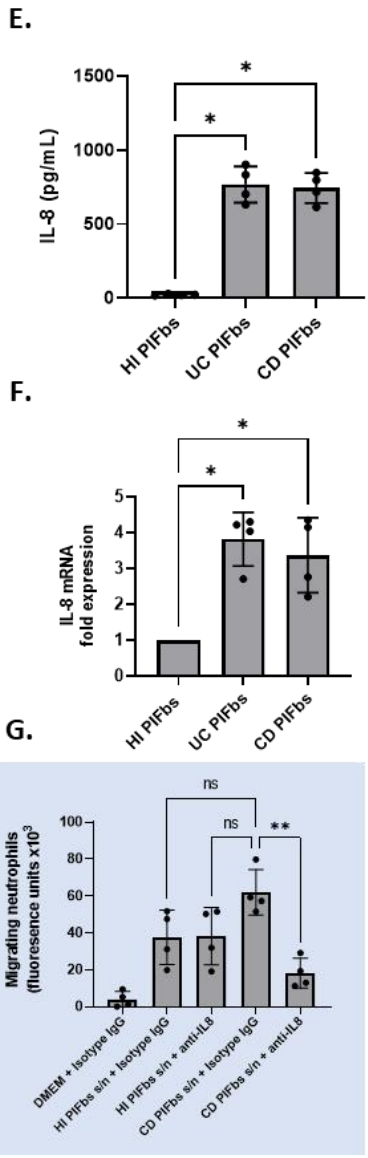
Chrysanthopoulou A*, Antoniadou C*, Natsi AM*, et al. Clin Immunol. 2023

Neutrophil-fibroblast interaction in immunofibrosis of Crohn's disease

Fig. 2

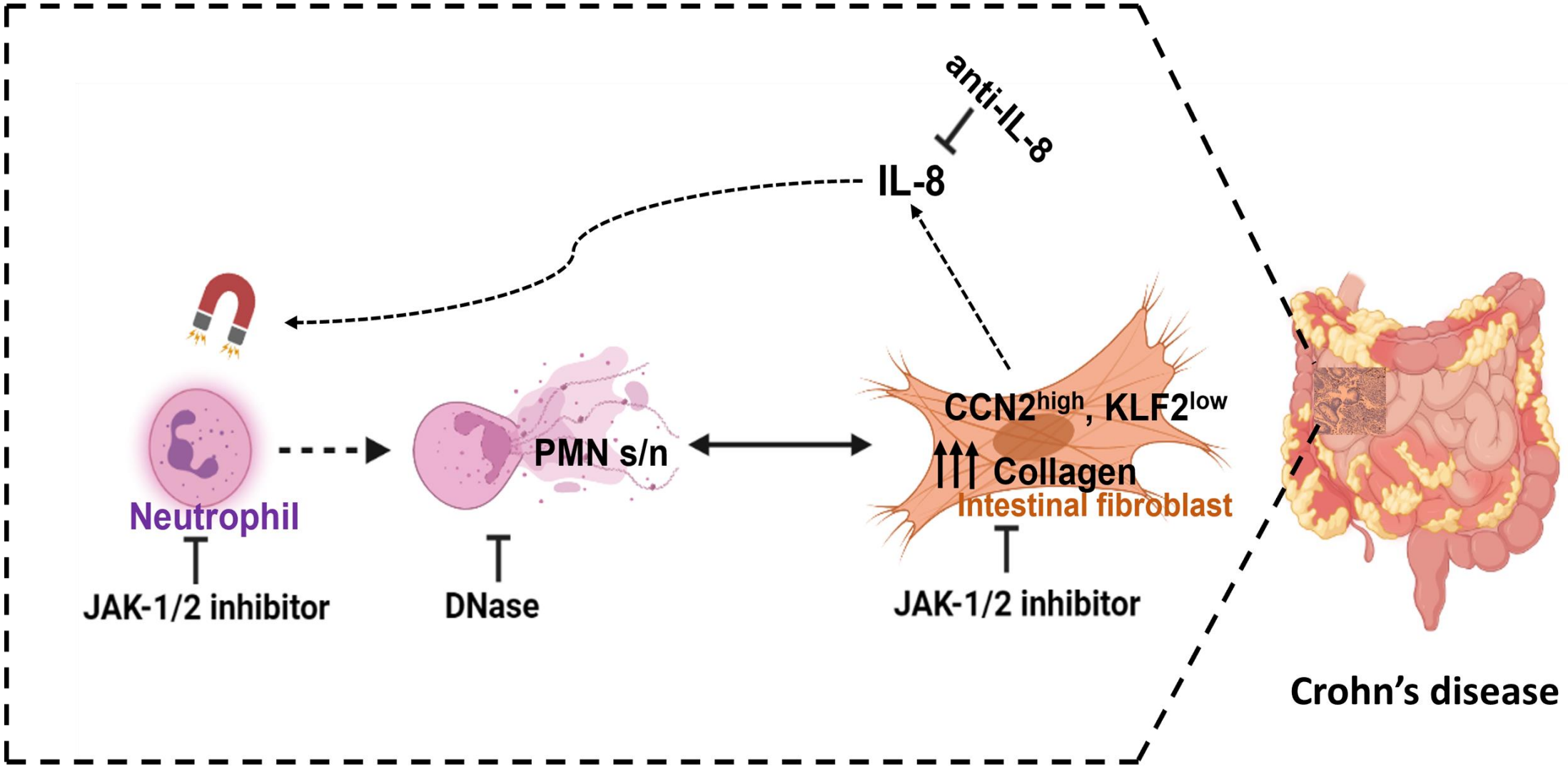






Paper in preparation

Neutrophil-fibroblast interaction in immunofibrosis of Crohn's disease



Paper in preparation

ΠΑΝΕΠΙΣΤΗΜΙΟ ΚΡΗΤΗΣ
UNIVERSITY OF CRETE

ΙΑΤΡΙΚΗ ΣΧΟΛΗ
SCHOOL OF MEDICINE

Delineation of fibroblast-like synoviocyte-mediated immune responses in the pathogenesis of rheumatoid arthritis

Neofotistou-Themeli E.[1,2], Chanis T.[1,2], Semitekolou M.[1,2], Sevdali E.[1,2], Papadaki G.[1,2], Goutakoli P.[1,2], Drakos E.[3], Bertsias G.[1,2,4], Verginis P.[1,2,5], Sidiropoulos P.[1,2,4]

1 Laboratory of Rheumatology, Autoimmunity & Inflammation, Medical School, University of Crete; 2 Infections and Immunity, Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology - Hellas (FORTH), Crete; 3 Department of Pathology, Medical School, University of Crete; 4 Clinic of Rheumatology, Clinical Immunology, University Hospital of Heraklion, Crete; 5 Laboratory of Immune Regulation and Tolerance, Medical School, University of Crete

JAK inhibitor Baricitinib alters the profile of FLS *ex vivo*

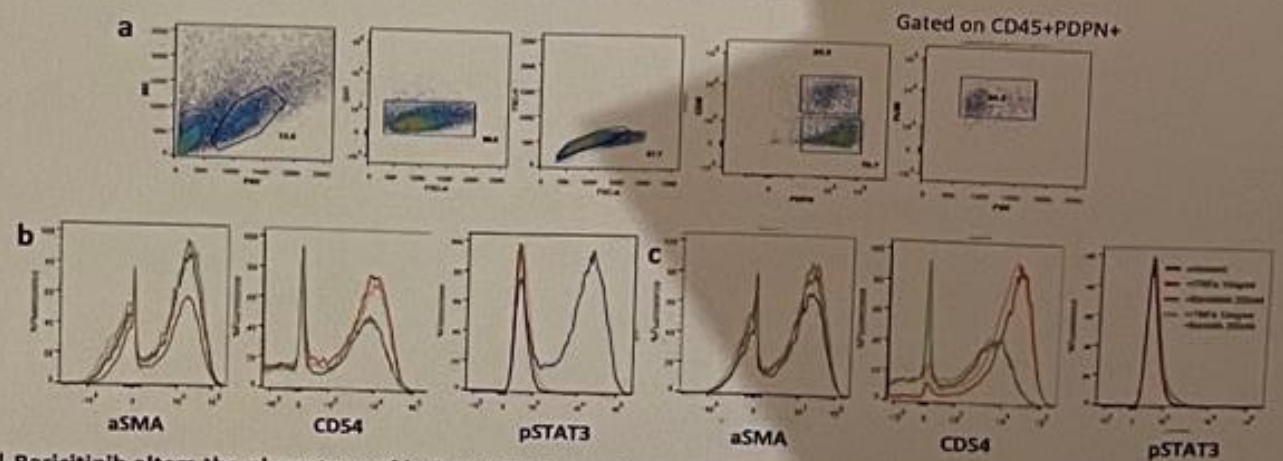
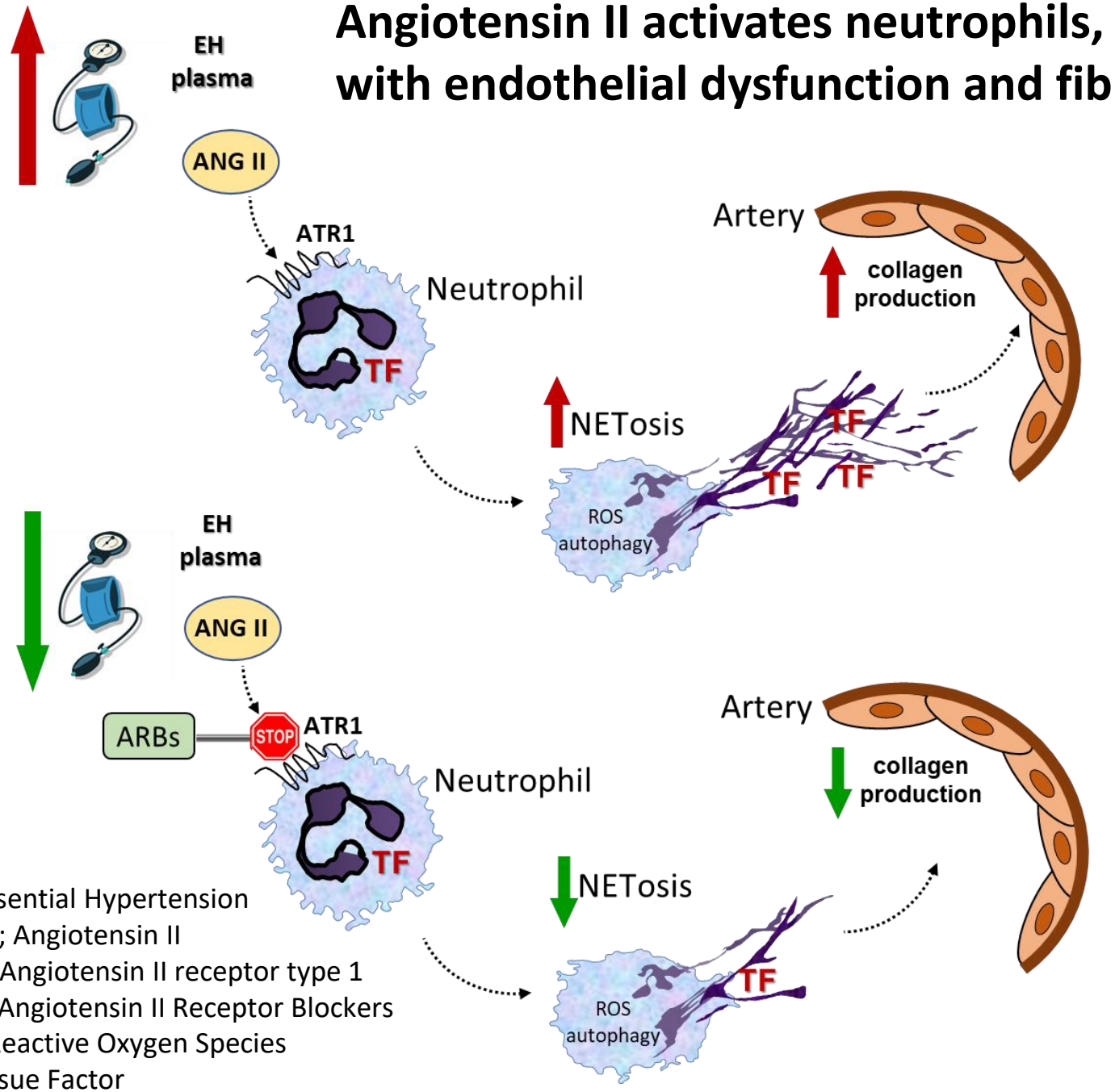


Fig. 4 | Baricitinib alters the phenotype of isolated FLS in *ex vivo* cultures. (a) Gating strategy for isolating FLS and macrophages from bulk synovium cultures of K/BxN arthritic mice using FACS sorting. Upon activation with recombinant TNFα (10ng/ml) and addition of JAK1/2 inhibitor baricitinib (Olumiant, 250nM), we observed alterations in the expression of the myofibroblast activation marker aSMA and the adhesion molecule CD54 at **(b)** 2 and **(c)** 24 hours of treatment.

Angiotensin II activates neutrophils, linking thromboinflammation with endothelial dysfunction and fibrosis in essential hypertension



Induction of Atherothrombosis/ Atherosclerosis

Protection from Atherothrombosis/ Atherosclerosis

EH; Essential Hypertension
ANG II; Angiotensin II
ATR1; Angiotensin II receptor type 1
ARBs; Angiotensin II Receptor Blockers
ROS; Reactive Oxygen Species
TF; Tissue Factor

Chrysanthopoulou A, et al JCI Insight 2021

Presence of NETotic neutrophils expressing TF in the fibrotic renal and aneurysmal aortic tissue of patients with essential hypertension

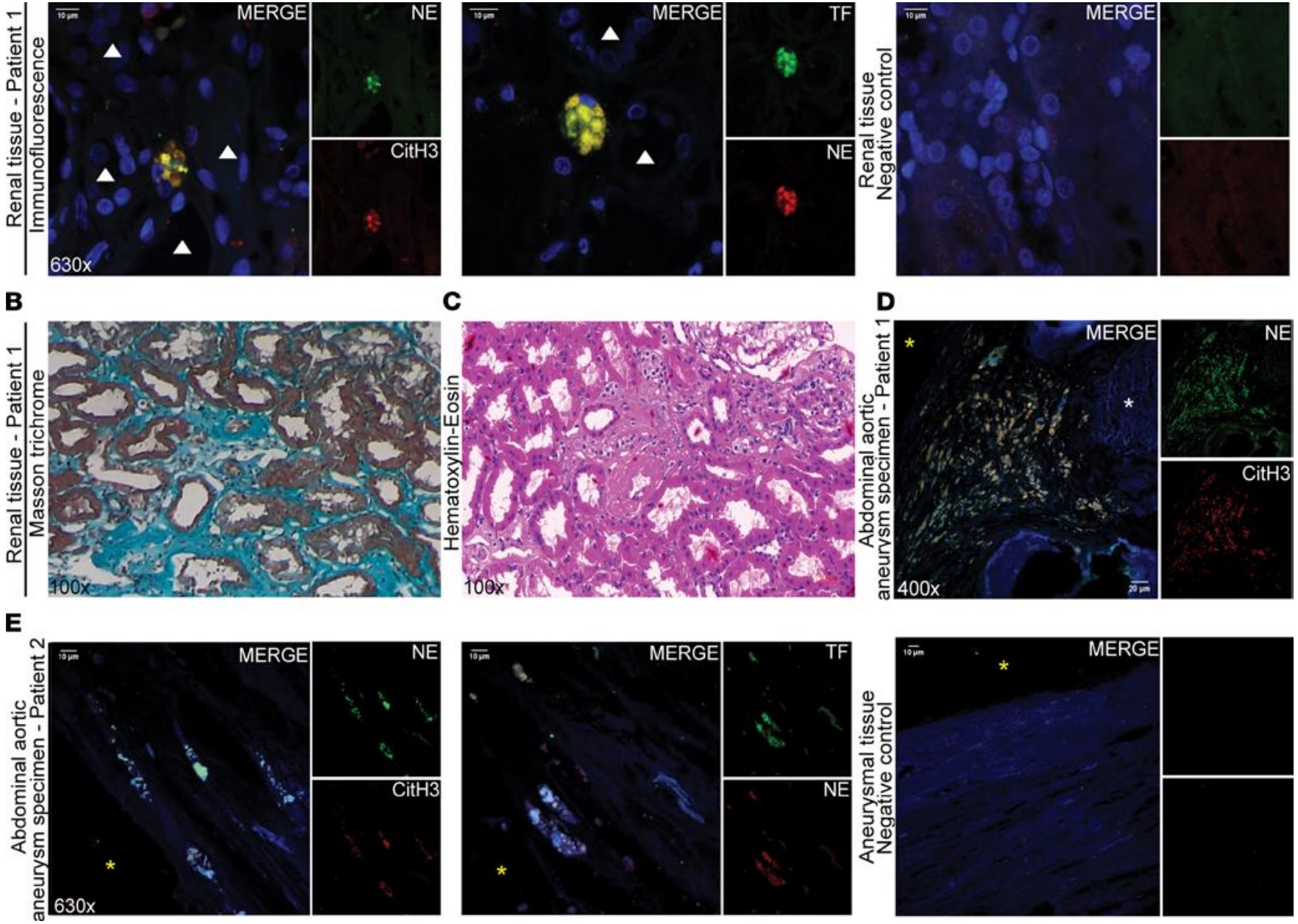


Table 2 | **New anti-inflammatory approaches for the prevention of atherosclerosis and thrombosis**

Study name (year)	Medications	Clinical setting	Ischaemic events	Infections	All-cause mortality
CANTOS (2017)	Canakinumab (150 mg) versus placebo	Secondary prevention of MI	↓Non-fatal MI, non-fatal stroke or cardiovascular death: HR 0.85, 95% CI 0.74–0.98, $P = 0.021$; MI: HR 0.76, 95% CI 0.62–0.92; any stroke: HR 0.98, 95% CI 0.71–1.35	↑Fatal infections and sepsis	↔HR 0.92, 95% CI 0.78–1.09
CIRT (2019)	Low-dose methotrexate versus placebo	Secondary prevention of MI or multivessel coronary artery disease	↔Non-fatal MI, non-fatal stroke, cardiovascular death or hospitalization for unstable angina that led to urgent revascularization: HR 0.96, 95% CI 0.79–1.16, $P = 0.67$	↔Serious infection events	↔HR 1.16, 95% CI 0.87–1.56
COLCOT (2019)	Low-dose colchicine versus placebo	Treatment within 30 days of an MI	↓MI: HR 0.91, 95% CI 0.68–1.21; stroke: HR 0.26, 95% CI 0.10–0.70; VTE: HR 1.43, 95% CI 0.54–3.75	↑Pneumonia	↔HR 0.98, 95% CI 0.64–1.49
LoDoCo2 (2020)	Low-dose colchicine versus placebo	Chronic coronary artery disease	↓Cardiovascular death, MI, ischaemic stroke or ischaemia-driven coronary revascularization: HR 0.69, 95% CI 0.57–0.83; cardiovascular death, MI or ischaemic stroke: HR 0.72, 95% CI 0.57–0.92, $P = 0.007$; MI: HR 0.70, 95% CI 0.53–0.93; ischaemic stroke: HR 0.66, 95% CI 0.35–1.25; VTE: HR 1.06, 95% CI 0.53–2.10	↔Hospitalizations for infection	↔HR 1.21, 95% CI 0.86–1.71

Stark K, Massberg S. Nat Rev Cardiol. 2021

EULAR recommendations for cardiovascular risk management in rheumatic and musculoskeletal diseases, including systemic lupus erythematosus and antiphospholipid syndrome

8. In patients with SLE, treatment with ***hydroxychloroquine*** *(which is recommended for all SLE patients, unless contraindicated)* ***should be considered to also reduce the risk of cardiovascular events****. (LoE: 2b, GoR: B)*

Drosos GC, Vedder D, Houben E et al. Ann Rheum Dis. 2022 Feb

Table 1 | **Anti-inflammatory effects of antithrombotic medications**

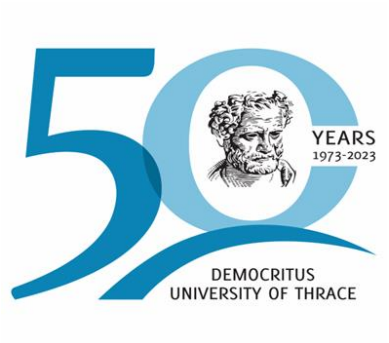
Medication	Antithrombotic effects	Anti-inflammatory effects
Heparin	Inhibition of coagulation	Disruption of neutrophil extracellular traps
		Neutralization of histones
Low-dose aspirin	Inhibition of platelet activation	Increased synthesis of the pro-resolution mediator 15-epi-lipoxin A4
$P2Y_{12}$ receptor inhibitors	Inhibition of platelet activation	Decreased pro-inflammatory mediator release
Direct-acting oral anticoagulants	Inhibition of coagulation	Inhibition of protease-activated receptors, which induce the expression of chemokines, cytokines and adhesion molecules

Stark K, Massberg S. Nat Rev Cardiol. 2021

- ✓ **Dysregulated innate immunity leading to excessive inflammation is involved in the whole spectrum of cardiovascular pathology implicating immune and non-immune cells (tissue)**

- ✓ **Inflammation emerges as a promising candidate therapeutic target in addition to optimizing risk factors and targeting platelets and the coagulation system**

Many thanks!



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