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CAPLANET:
il network italiano della TTP
Gestione multidisciplinare

sanofi

MAT-IT-2401916

Stimolazione del sistema immunitario: effetti sulle TMA immunomediate

Marco Marietta – Modena
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Relazioni con soggetti portatori di interessi commerciali in campo sanitario

Io sottoscritto **Marco Marietta,** in qualità di relatore all'evento "***CAPLANET: il network italiano della TTP***", ai sensi dell'art. 3.3 sul Conflitto di Interessi, dell'Accordo Stato-Regione del 19 aprile 2012,

dichiaro

che negli ultimi due anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- **Consulenza per attività formativa e relazioni a convegni per le ditte:**
  - **KEDRION**
  - **NOVO-NORDISK**
  - **OCTAPHARMA**
  - **SANOFI**
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Speaker will receive compensation from Sanofi for participation in this event

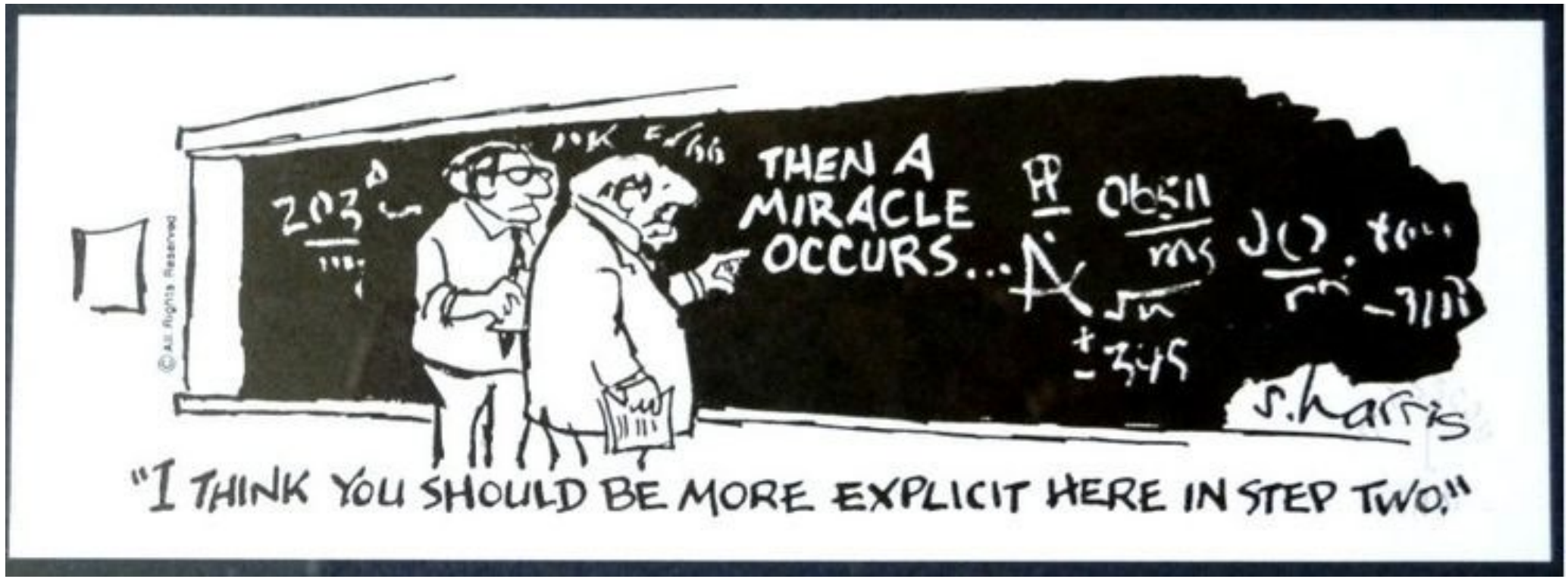
Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies

immune mediated ttp (iTTP)

Primary iTTP This refers to acquired autoimmune TTP for which there is no obvious underlying precipitating cause/disease, and there is ADAMTS-13 activity of < 10% with the presence of ADAMTS-13 autoantibodies. Primary iTTP accounts for the majority of cases of TTP.

Secondary iTTP This refers to acquired autoimmune TTP for which a defined underlying disorder or trigger can be identified, including connective tissue disease (such as systemic lupus erythematosus [SLE]), HIV infection, cytomegalovirus infection, and/or a specific precipitating factor (e.g. pregnancy or drugs). Treatment of the underlying disorder and/or removal of the underlying precipitant may be required, as well as standard TTP therapy.

Scully M et al. J Thromb Haemost 2017; 15: 312–22



Haematologica 2018
Volume 103(2):1099-1109

Dissecting the pathophysiology of immune thrombotic thrombocytopenic purpura: interplay between genes and environmental triggers

Johana Hrdinová,[1,2,3] Silvia D'Angelo,[4,5] Nuno A. G. Graça,[1,6] Bogac Ercig,[1,2,3] Karen Vanhoorelbeke,[4] Agnès Veyradier,[7,8] Jan Voorberg [1]and Paul Coppo[8,9,10]

EUROPEAN HEMATOLOGY ASSOCIATION

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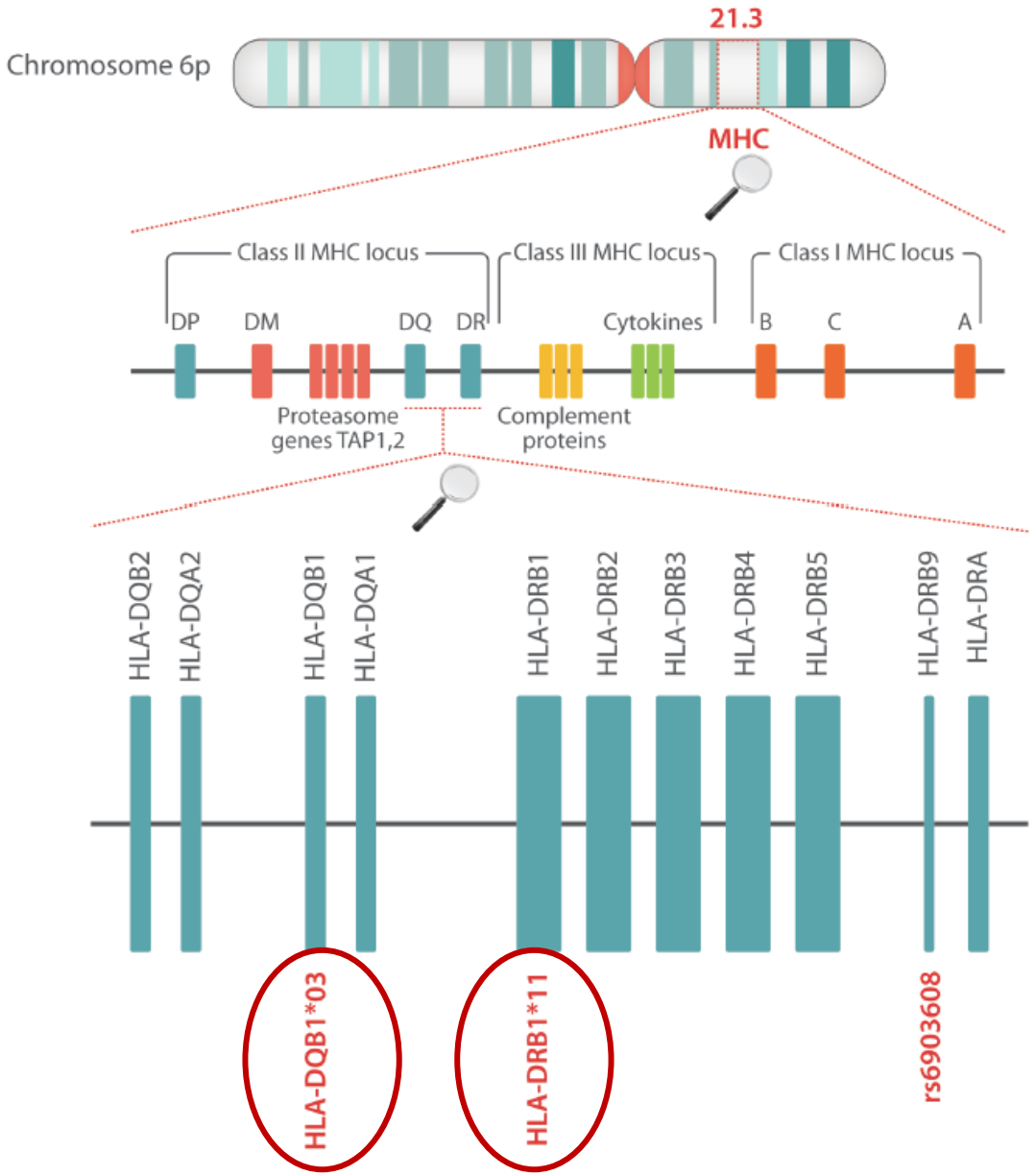
Sei personaggi in cerca d'autore
Luigi Pirandello, 1921

Six characters involved in iTTP

1. Genetic risk factors: HLA alleles and sNP
2. ADAMTS-13 structure and peptides
3. Autoreactive CD4 T cells
4. Molecular mimicry phenomenon
5. Endothelium
6. Immature platelets

Dissecting the pathophysiology of immune thrombotic thrombocytopenic purpura: interplay between genes and environmental triggers



PREDISPOSING HLA APLOTYPES / SNP

- ✓ HLA-B18
- ✓ DRB3*
- ✓ DRB1*15-DQB1*06
- ✓ DRB 1*08:03
- ✓ HLA-DRB1*08:03
- ✓ HLA- DQB1*02:02
- ✓ HLA variant rs6903608 (↑ risk of onset and relapse)

PROTECTIVE HLA APLOTYPES / SNP

- HLA-DRB1*04 and associated serotype HLA-DR53
- HLA-DRB1*07
- HLA- DQB1*02

- SNP rs9884090 (↓ POGLUT1=↓ O-glycosilation)

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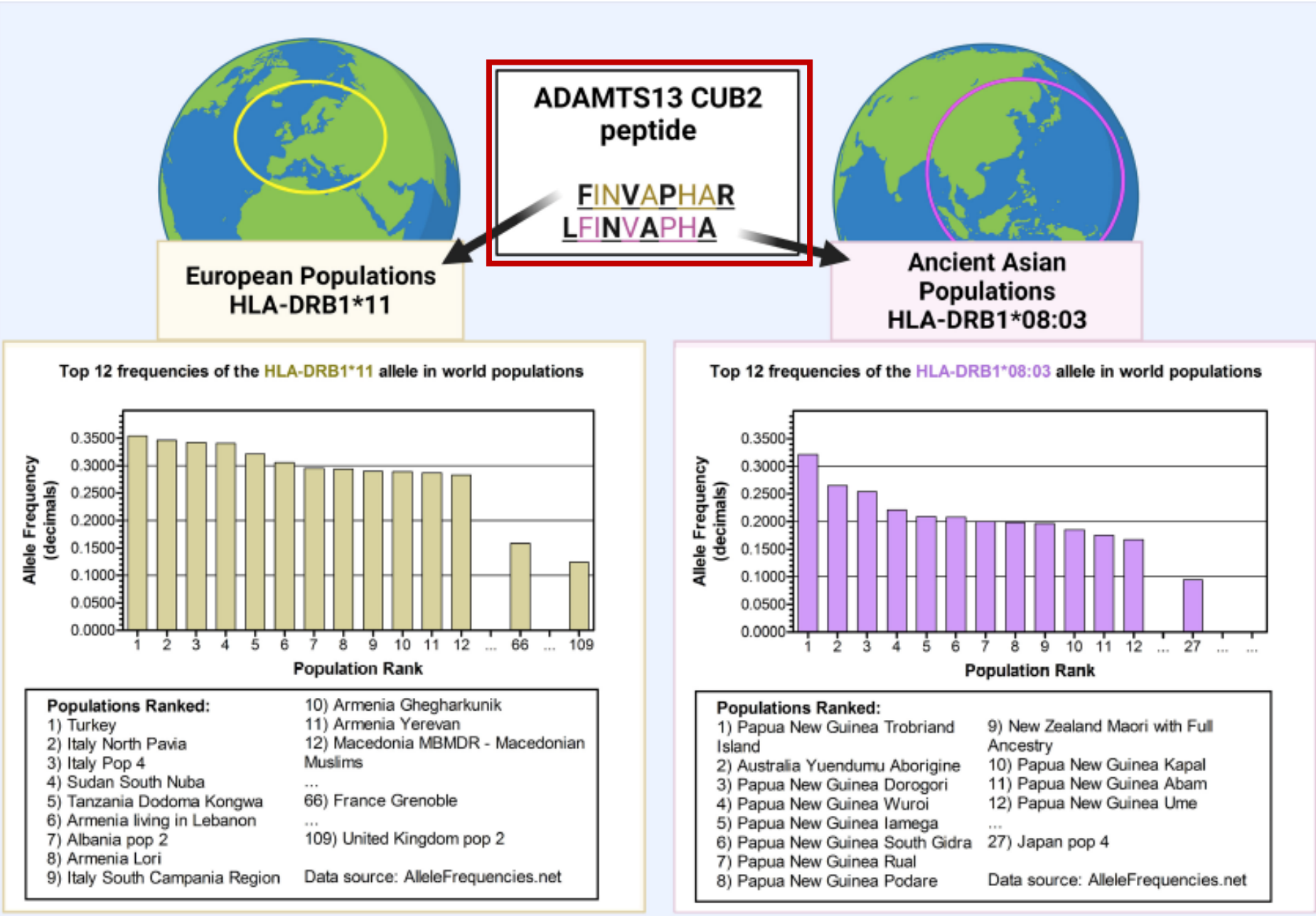
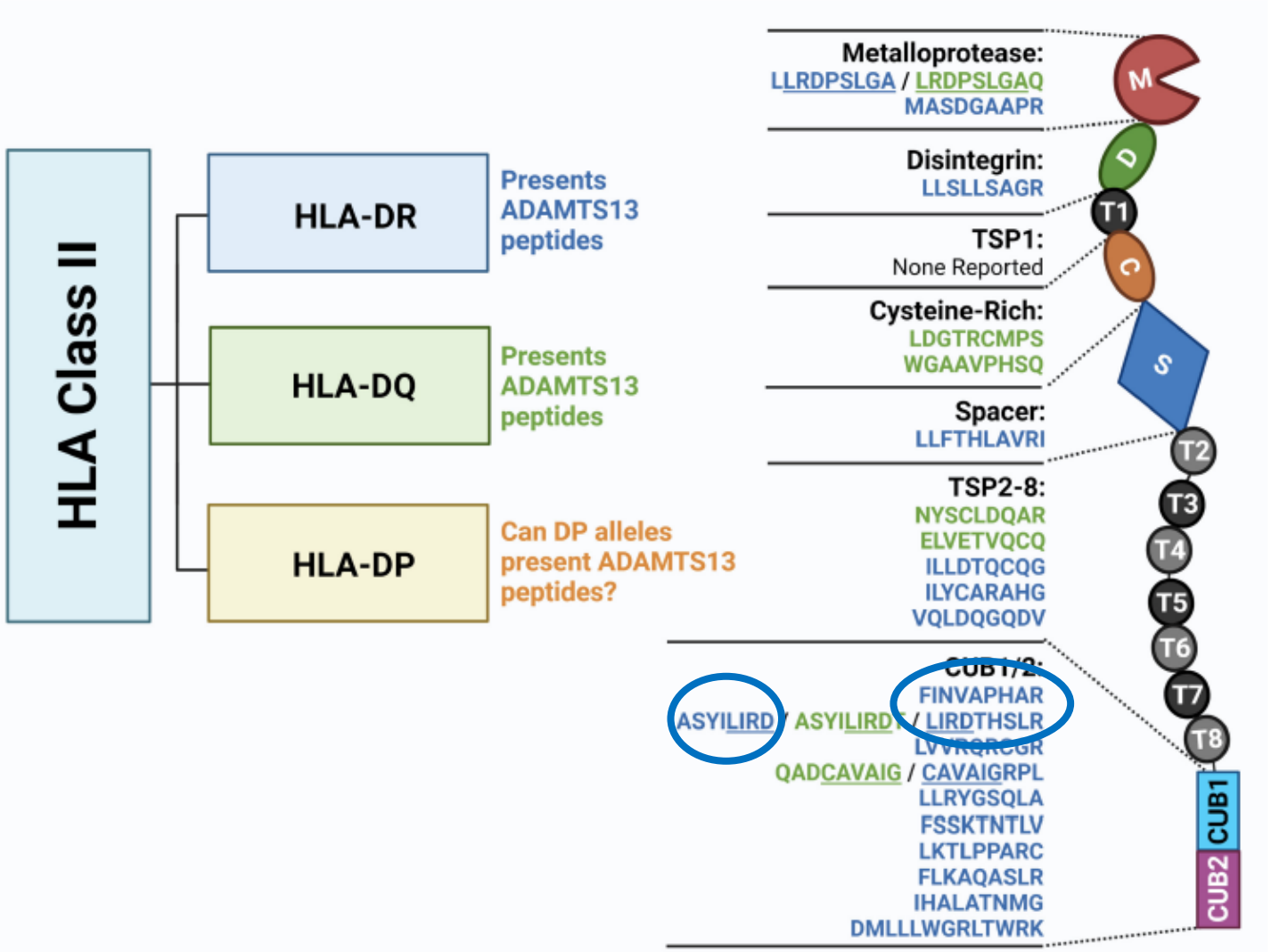
Hrdinová J et al. Haematologica 2018; 103:1099; Mancini I et al. J Clin Med 2020;9:337; Stubbs MJ et al. Haematologica 2022; 107:504



Laghmouchi A et al. Front Immunol 2021; 12:757192.

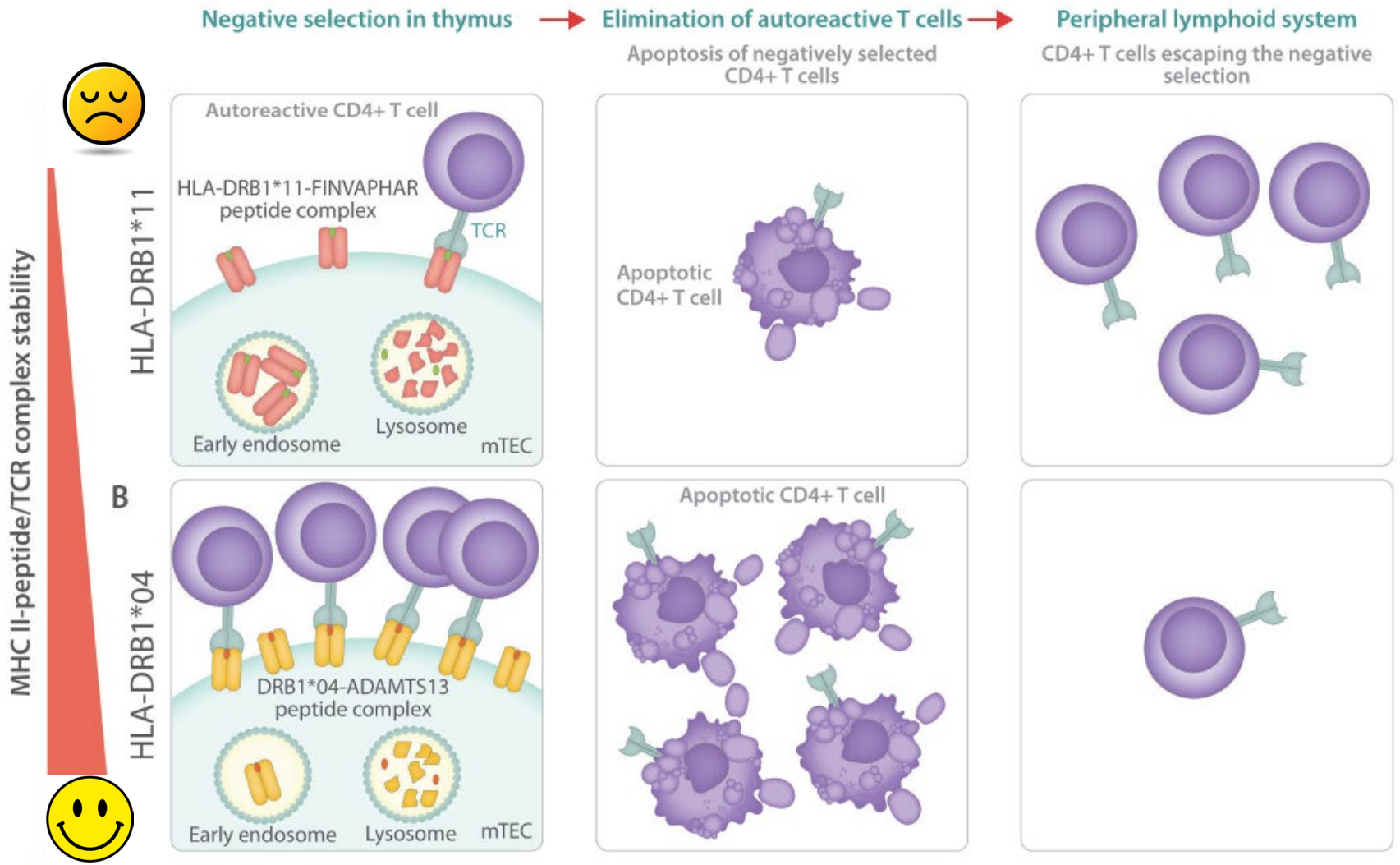
The ADAMTS13 peptidome presented by HLA Class II molecules



- ✓ The presentation of antigens by HLA-class II molecules is required for the induction of adaptive immune responses.
- ✓ One HLA-II molecule binds many different peptides.
- ✓ On the other hand, peptides have also been found to show a degree of promiscuity towards HLA-II molecules
- ✓ Some HLA-class II restricted T-cell receptors are capable of recognizing more than one HLA class II-peptide complex with different affinities

Laghmouchi A et al. Front Immunol 2021; 12:757192.

Dissecting the pathophysiology of immune thrombotic thrombocytopenic purpura: interplay between genes and environmental triggers



- ✓ Instability of HLA-DRB1*11/peptide complexes results in inefficient removal of self-reactive CD4+ T cells in the thymus, and the appearance of potentially self-reactive CD4+ T cells in the peripheral lymphoid system.
- ✓ Intrinsically stable HLA-DRB1*04 molecules are retained for prolonged periods of time on the surface of mTEC > only few self-reactive CD4+ T cells escaping the negative selection in thymus

Hrdinová J et al. Haematologica 2018; 103(2):1099-1109

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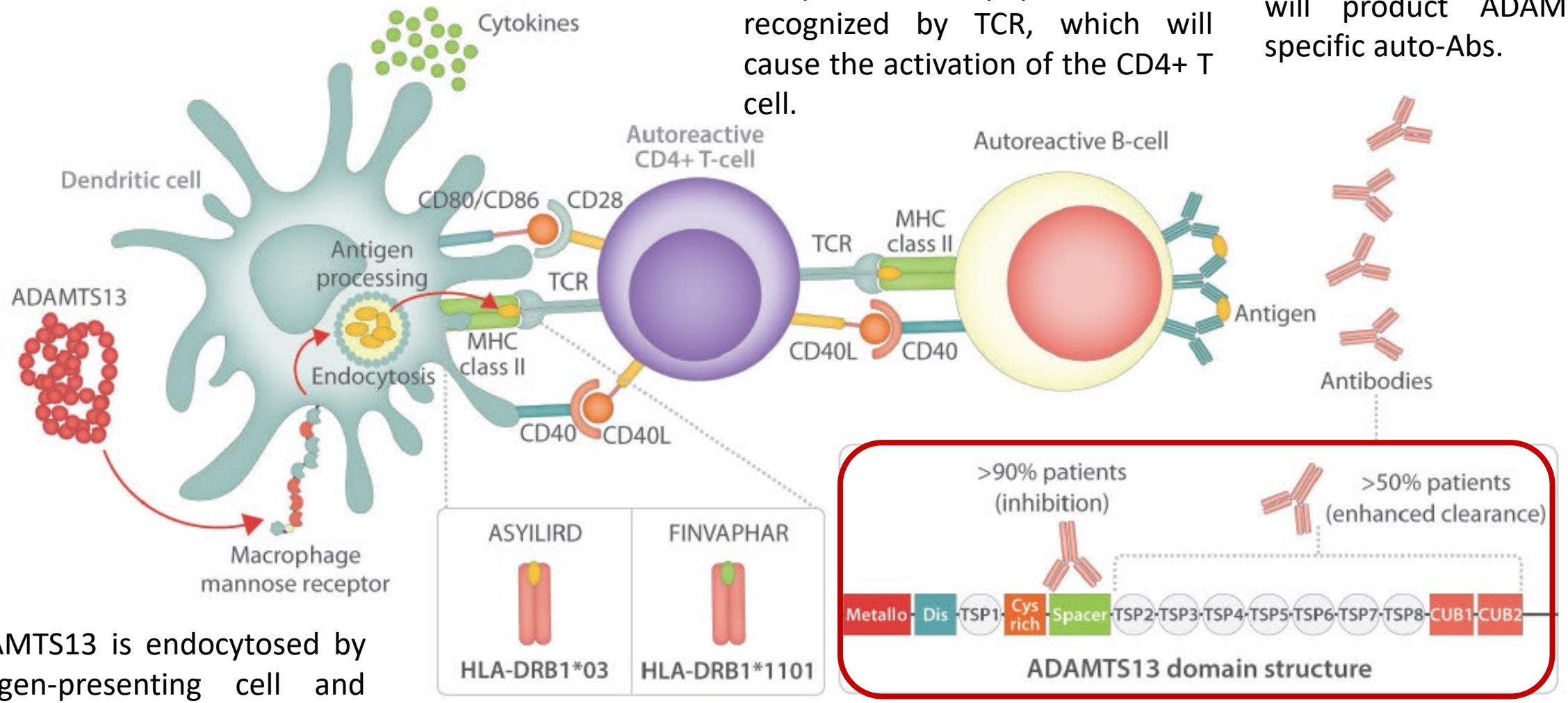
Dissecting the pathophysiology of immune thrombotic thrombocytopenic purpura: interplay between genes and environmental triggers

In case of presence of autoreactive CD4+ T cells, the complex MHC-II/peptide will be recognized by TCR, which will cause the activation of the CD4+ T cell.

Activated CD4+ T cells will then provide help to autoreactive B cells that will product ADAMTS13-specific auto-Abs.



ADAMTS13 is endocytosed by antigen-presenting cell and processed to peptides loaded on MHC-II molecules.

Hrdinová J et al. Haematologica 2018; 103(2):1099-1109

Dissecting the pathophysiology of immune thrombotic thrombocytopenic purpura: interplay between genes and environmental triggers

- ✓ Anti-ADAMTS13 Abs result in a profound deficiency in ADAMTS13 activity by two main mechanisms:
  - Inhibitory Abs targeting the spacer domain of ADAMTS13 block the proteolytic activity of ADAMTS13 towards VWF ➞ majority of auto-Ab
  - Non-inhibitory Abs targeting the carboxyterminal domains increase ADAMTS13 clearance by forming I.C. ➞ activation of the complement system and binding to cellular Fc receptors?
- ✓ IgG4 =90%, IgG1 =53%, IgG2 =50%, IgG3 =33%
- ✓ IgM and IgA = 10% of patients, mainly in association with IgG
- ✓ Anti-ADAMTS13 IgG have been reported to be present in 5% of healthy individuals, BUT they are noninhibitory, probably because of a lower affinity to the protein ➞risk factor for iTTP?

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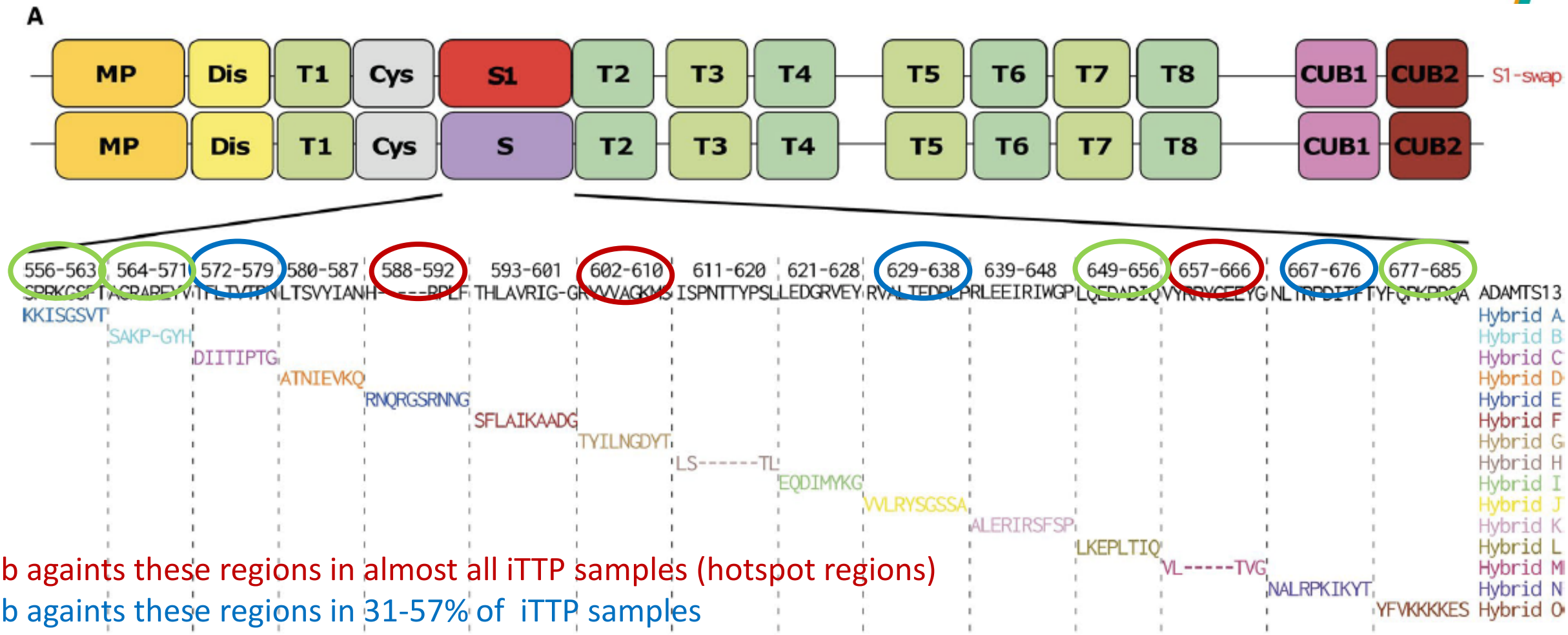
Hrdinová J et al. Haematologica 2018; 103(2):1099-1109

Immunogenic hotspots in the spacer domain of ADAMTS13 in immune-mediated thrombotic thrombocytopenic purpura



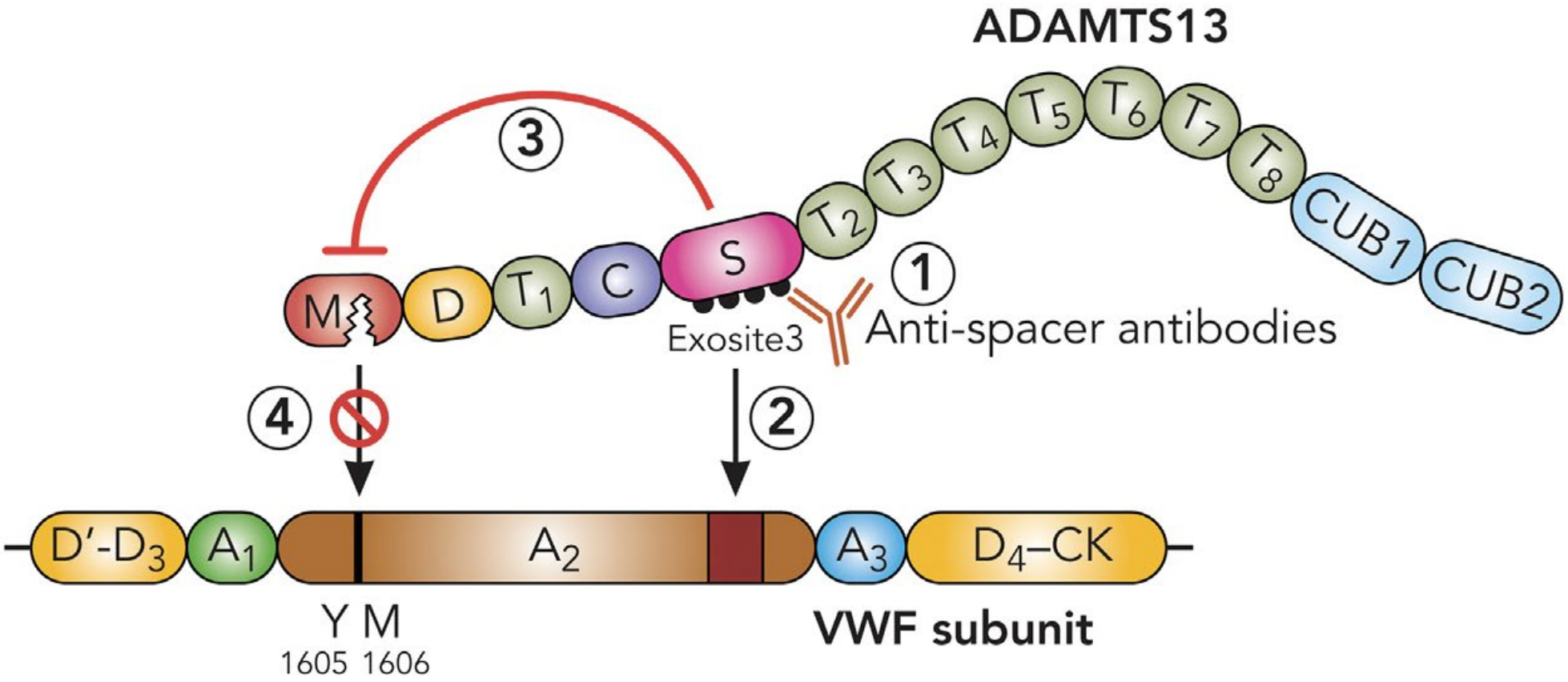
Ab againts these regions in almost all iTTP samples (hotspot regions)

Ab againts these regions in 31-57% of iTTP samples

NO Ab againts these regions in 31-57% of iTTP samples

Velásquez Preira LC et al. J Thromb Haemost 2021;19:478-488

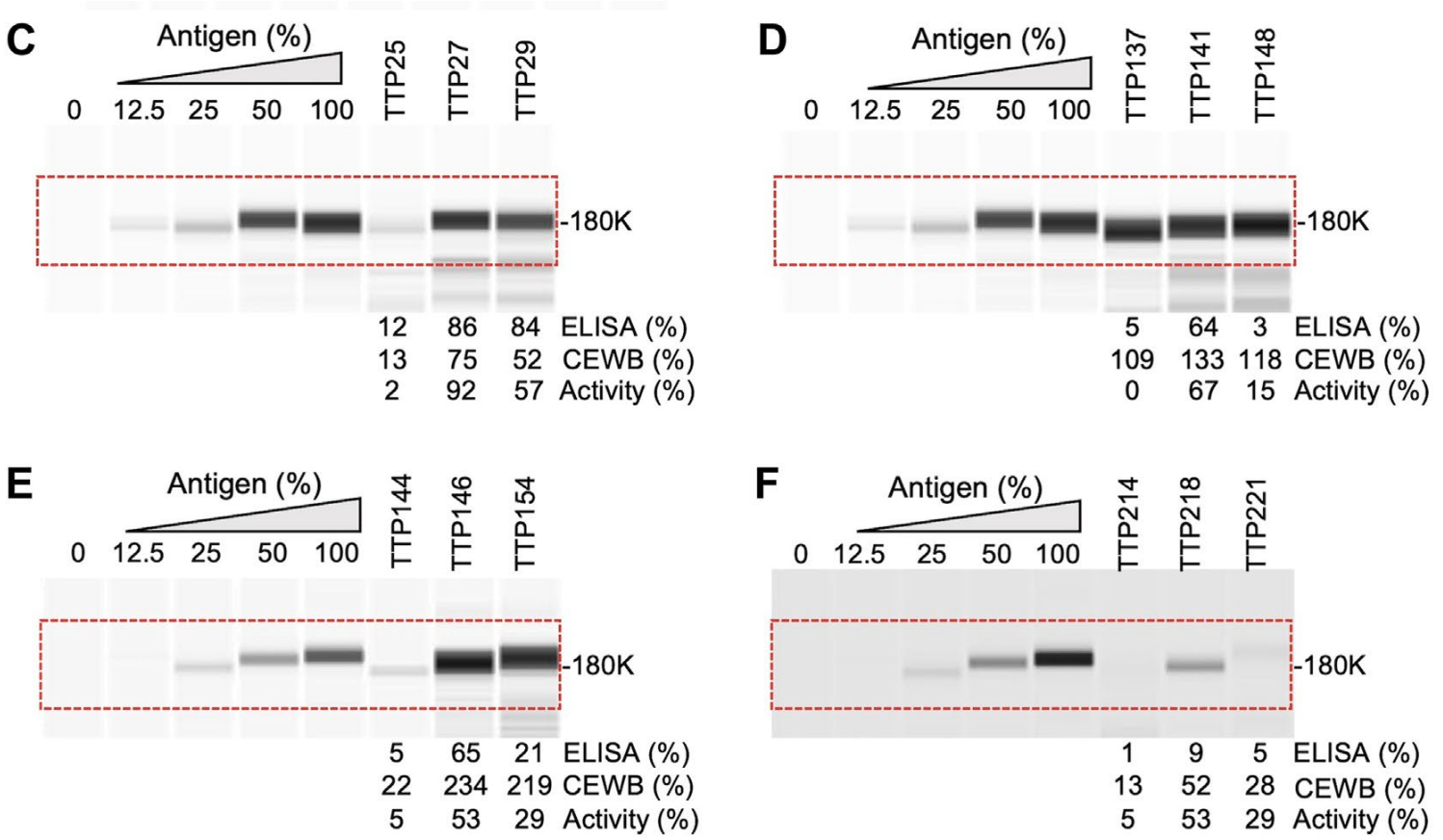
Mechanisms of inhibition of human monoclonal antibodies in immune thrombotic thrombocytopenic purpura



Halkidis K et al. Blood 2023; 141: 2993-3005

Mechanism underlying severe deficiency of plasma ADAMTS-13 activity in immune thrombotic thrombocytopenic purpura

The capillary electrophoresis–based Western blotting (CEWB) assay eliminated the potential interference from autoantibody associated shielding, competition, and conformational changes of antigenic epitopes of ADAMTS-13



Severe deficiency of plasma ADAMTS-13 activity primarily resulted from antibody-mediated inhibition, but the accelerated clearance of plasma ADAMTS-13 antigen via immune complexes may also contribute significantly in a subset of patients with acute iTTP.

Long Xhen X. J Thromb Haemost. 2024;22:1358–1365

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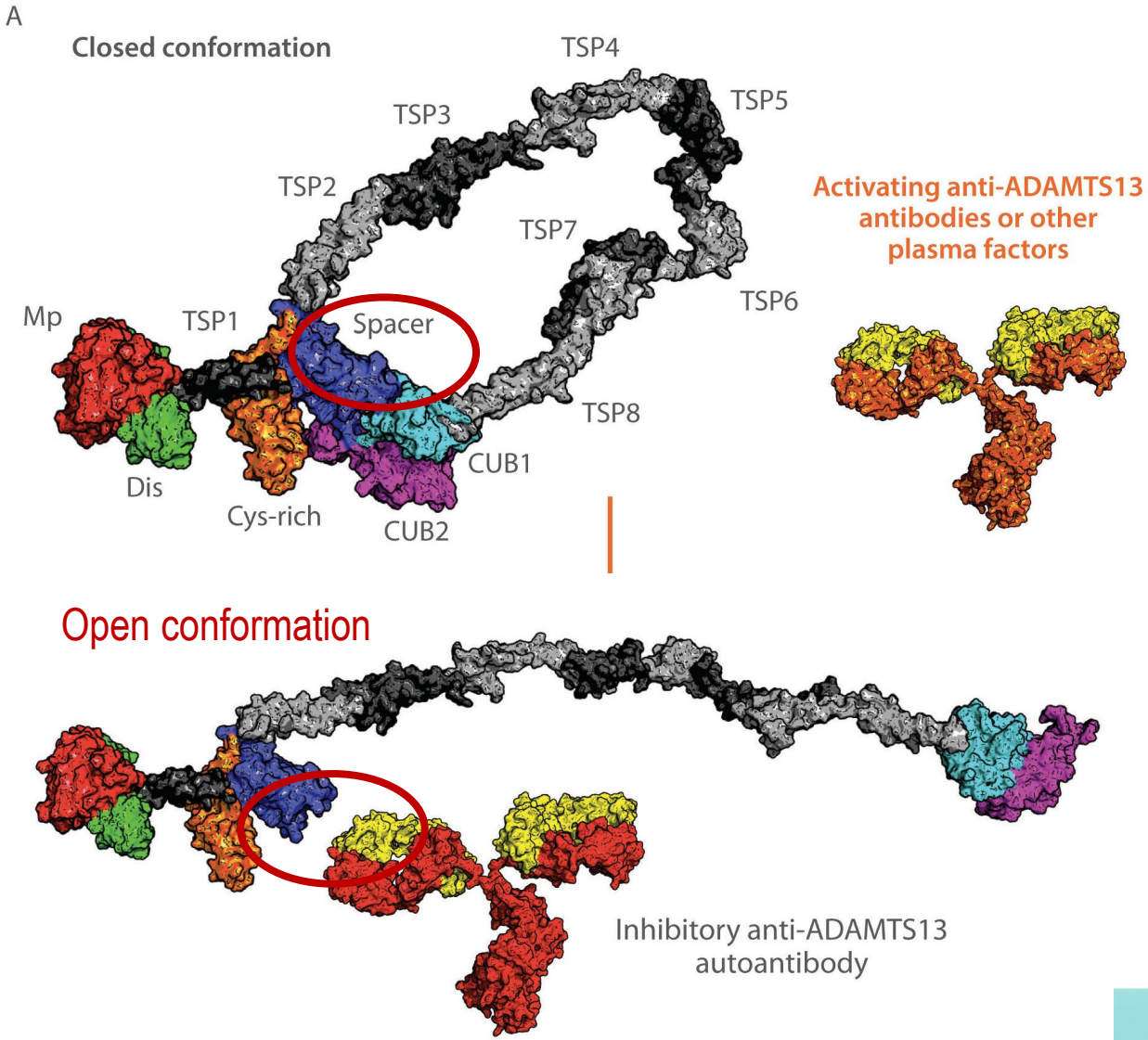
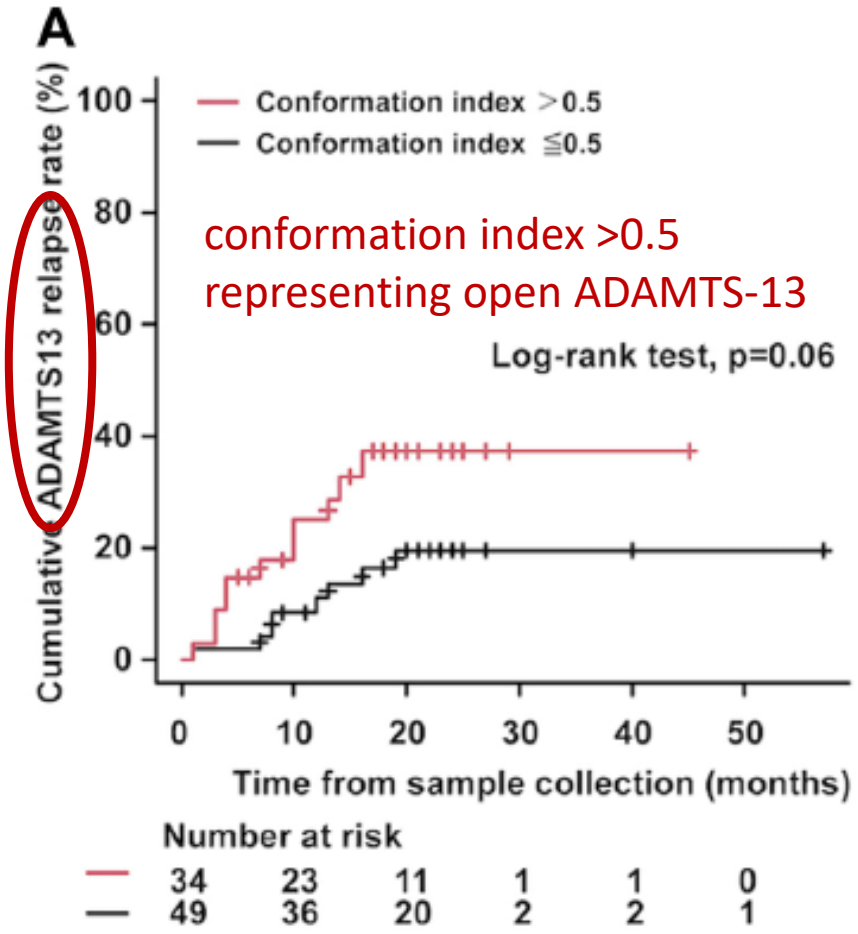


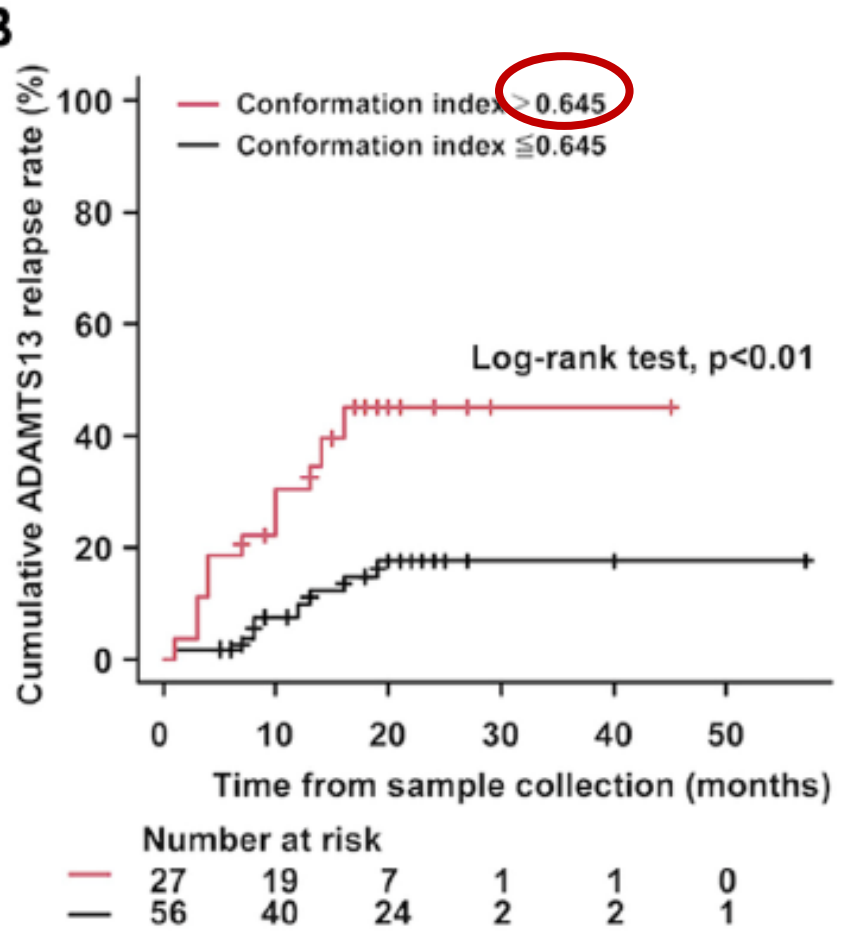
- ✓ In healthy individuals and iTTP pts. in remission ADAMTS13 is present in closed conformation with CUB1/2 domains covering the spacer domain.
- ✓ Binding of plasma factors (e.g. VWF, or activating anti-ADAMTS13 auto-Abs against the TSR5-8-CUB1/2 domains) results in the conversion of the ADAMTS13 from a closed to an open configuration
- ✓ Open conformation of ADAMTS13 exposes the B-cell epitope localized in the spacer domain, making it accessible for additional anti-ADAMTS13 Abs.

Hrdinová J et al. Haematologica 2018; 103(2):1099-1109

Open ADAMTS-13 conformation index predicts earlier relapse in immune-mediated thrombotic thrombocytopenic purpura



HR	95% CI	p-value
2.3	0.9-5.8	0.07

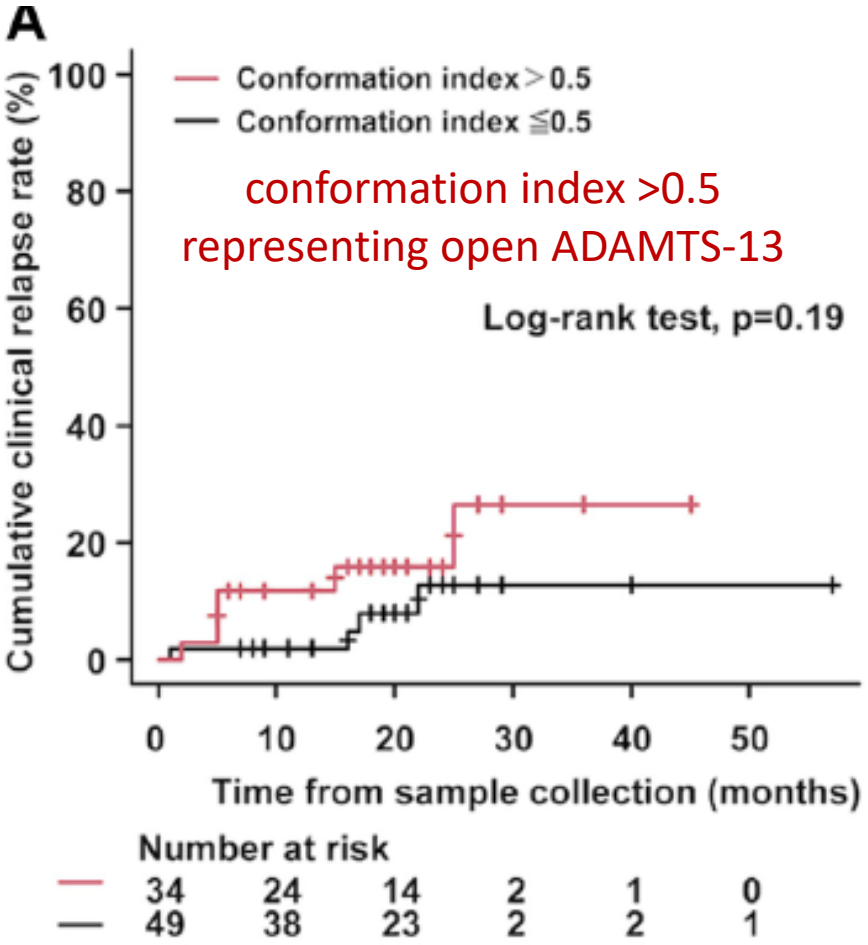


HR	95% CI	p-value
3.3	1.3-8.3	0.01

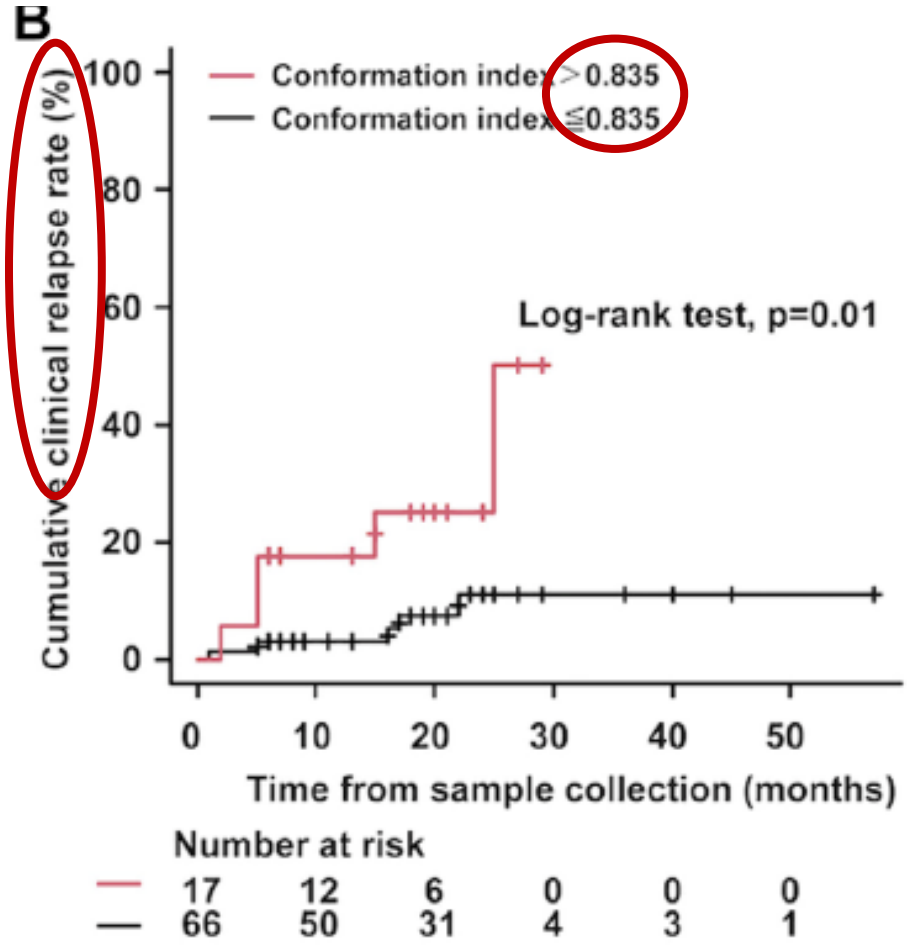
Cohort of 91 patients with iTTP in remission with restored A13 activity >50%

De Waele L, Sakai K, Mancini I et al. J Thromb Haemost. 2024;22:493–502

Open ADAMTS-13 conformation index predicts earlier relapse in immune-mediated thrombotic thrombocytopenic purpura



HR	95% CI	p-value
2.3	0.6-8.0	0.21



HR	95% CI	p-value
4.4	1.3-15.3	0.02

Cohort of 91 patients with iTTP in remission with restored A13 activity >50%

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Molecular mimicry (Mm)

- ✓ The term refers to the process of activation of autoreactive T or B cells in genetically susceptible individuals by pathogen peptides similar to the self-ones
- ✓ Molecular Mimicry should conceivably require the fulfilment of 4 major criteria:
  - i. similarities between pathogen-derived and self-antigens;
  - ii. detection of antibodies or T cells cross-reacting with both epitopes;
  - iii. an epidemiological correlation/association between infection and onset of autoimmunity
  - iv. Reproducibility of the autoimmune disease in an animal model by exposing the animal to the pathogen-derived cross-reactive antigen

Only Guillain-Barré syndrome resulting from C. jejuni infection fulfill all four criteria

Laghmouchi A et al. Front Immunol 2021; 12:757192.

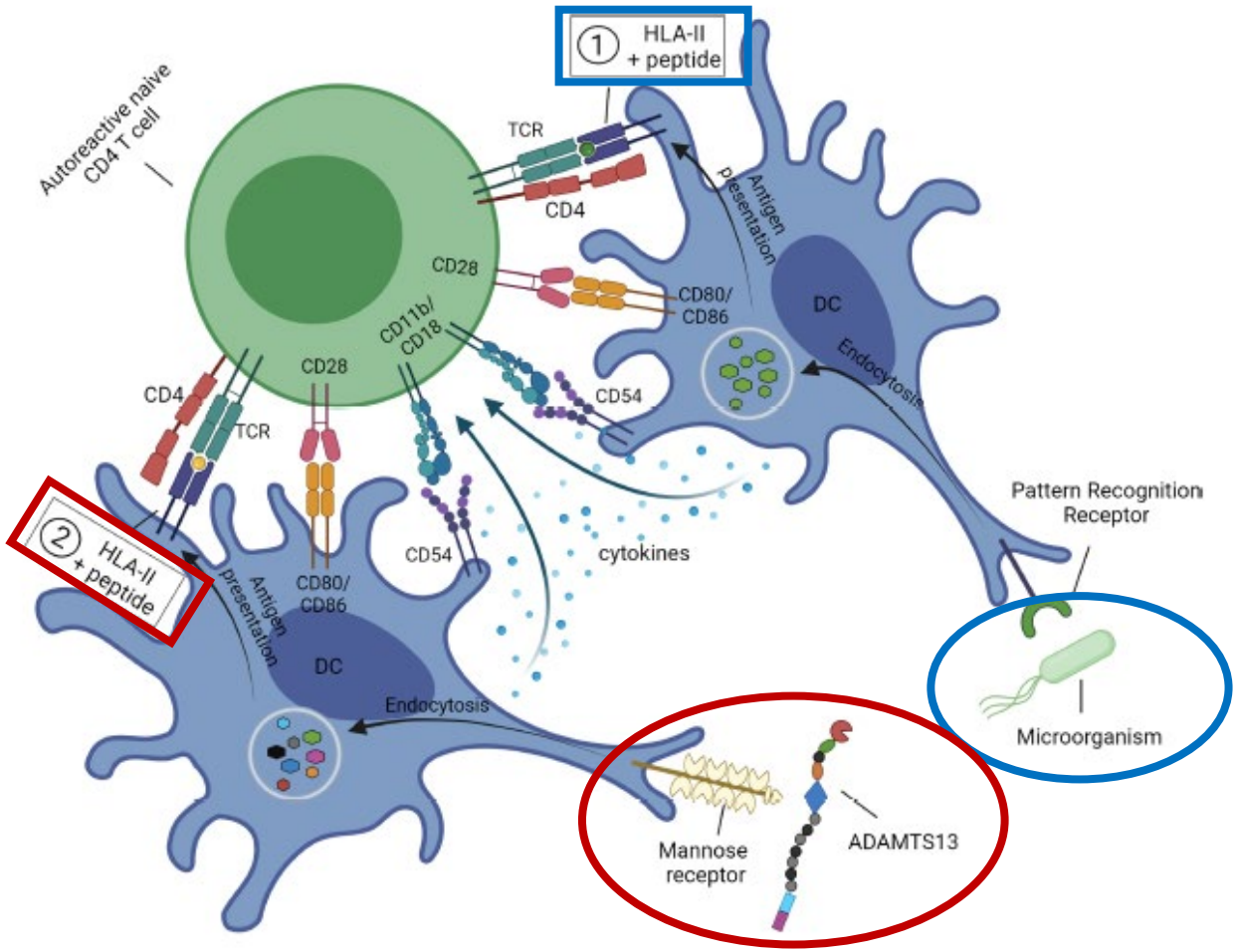
Molecular mimicry in iTTP

Pathogens		Target Organs/Cells
Viruses	Human Immune-deficiency virus (HIV)	T-lymphocytes
	Influenza A	Respiratory Tract
	SARS-CoV2	Respiratory Tract
	Hepatitis C and A viruses	Liver
	Human gammaherpesvirus-8 (HHV-8, Kaposi Sarcoma)	Vascular Endothelium
	Human Herpes-virus type 6 (HHV-6)	T-lymphocytes, neurons, salivary glands
	Human gamma herpesvirus 4 (HHV-4, Epstein-Barr Virus)	B-lymphocytes, epithelial mucosa
	Cytomegalovirus	Epithelial mucosa
	Dengue	Langerhans cells in skin; vascular endothelium
	Chikungunya virus	Fibroblasts in skin, myocytes
Bacteria	*Helicobacter pylori*	Stomach
	Legionella pneumoniae	Respiratory Tract
	Mycoplasma pneumoniae	Respiratory Tract
	Atypical Community Acquired Pneumonia (undefined microorganism)	Respiratory Tract
	Staphylococcus spp.	Urinary tract
	Escherichia coli	Urinary Tract
	Staphylococcus aureus	Systemic (Septicaemia)
Others	*Candida albicans*	Systemic
	Plasmodium falciparum (Malaria/Blackwater Fever)	Liver; red blood cells

Laghmouchi A et al. Front Immunol 2021; 12:757192.

Molecular mimicry in iTTP

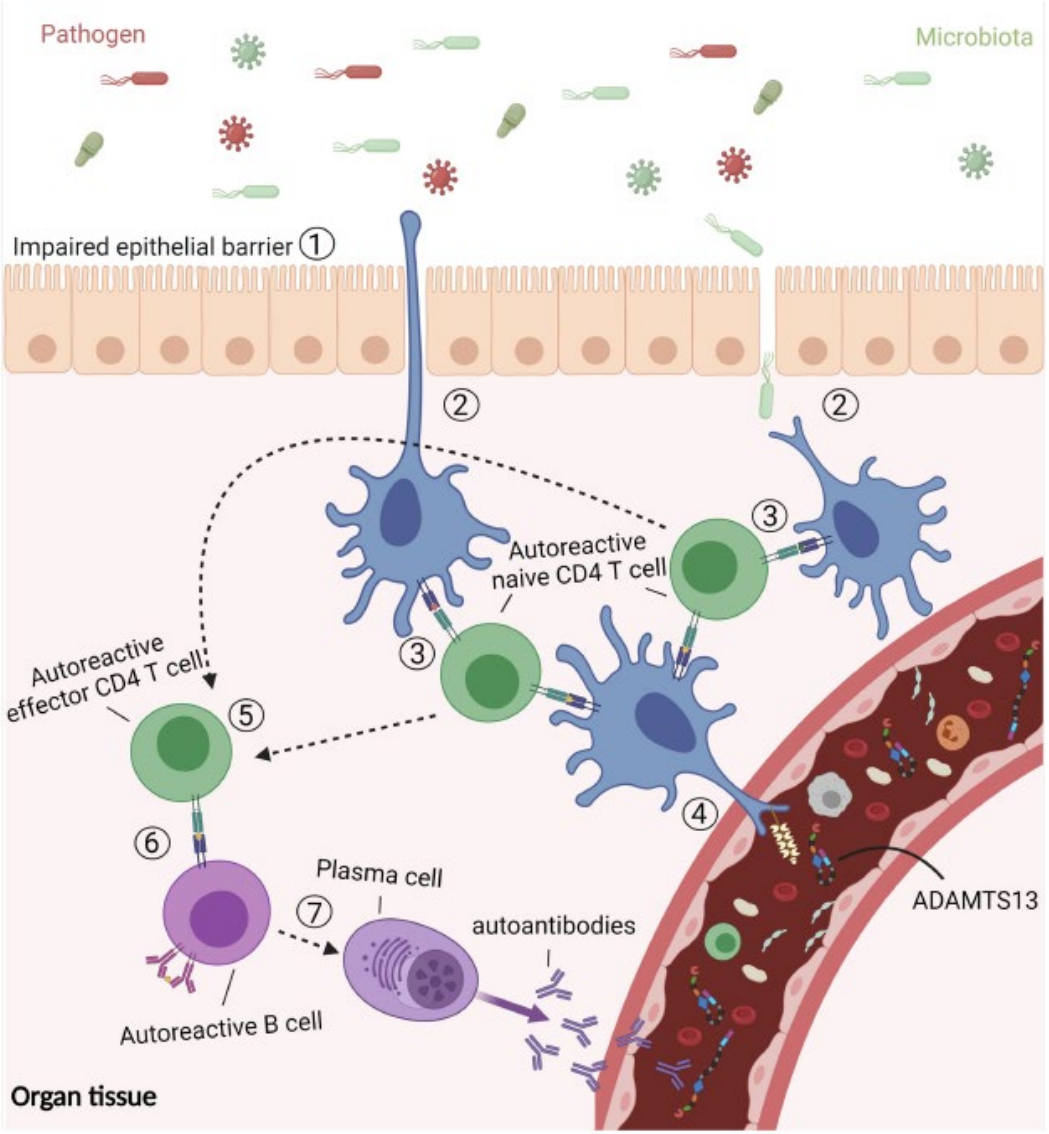
	Origin	HLA-DRB1*11 + peptide	HLA-DRB1*08 + peptide
1	Microorganism	FXXVXPXXR	LXXNXAXXA
2	ADAMTS13	FINVAPHAR	LFINVAPHA



1. After antigen processing the microorganism-derived peptides (peptides 1, in blue) are loaded onto the HLA-class II molecule (the risk allele HLA-DRB1*11 or HLA-DRB1*08:01, respectively) and presented to the TCR of an autoreactive CD4 T cell.
2. The ADAMTS13-derived peptides obtained by the uptake of ADAMTS13 using the mannose receptor on APC show similarities with the microorganism-derived peptides for certain aminoacid positions
3. The autoreactive CD4 T cell cross-reacts with ADAMTS13-derived peptides (peptides 2 in red) presented in the HLA-II molecule (HLA-DRB1*11 or HLA-DRB1*08:01, respectively).
4. The ***co-stimulatory and adhesion molecules (CD80/CD86 and CD54, respectively) on the APC*** are required for the activation of the autoreactive CD4 T cells.

Laghmouchi A et al. Front Immunol 2021; 12:757192.

Microbiota in iTTP



1. Infections disrupt the epithelial cell layer exposing microbiota as well as pathogens to the immune system
2. The dendritic cells (DC) acquire antigens from the microorganisms by phagocytosis.
3. Following processing, the DC activate auto-reactive naïve CD4 T cells which also recognize antigens derived from ADAMTS13 (4)
5. The activated CD4 T cells differentiate into effector CD4 T cells which interact with autoreactive B cells to induce differentiation of the B cells into autoantibodies-producing plasma cells.

Laghmouchi A et al. Front Immunol 2021; 12:757192.

Molecular mimicry in iTTP

TABLE 3 | Vaccines associated with iTTP.

Vaccines	References
Influenza Seasonal Vaccine	(129, 130)
Pneumococcal Vaccine	(131)
Influenza, Pneumococcal, Triple Diphtheria-Tetanus-Poliomyelitis Vaccines	(132)
Rabies Vaccine	(133)
COVID Vaccine	(134–138)

Be careful:

- ✓ The observed associations with either infections or vaccines in the development of iTTP have not been substantiated as of yet by a direct link to a specific pathogen antigen resembling ADAMTS13.
- ✓ No cross-reactive B-cell epitopes have been formally identified yet.
- ✓ The mechanism by which these infections promote the development of iTTP is not yet clear.

Laghmouchi A et al. Front Immunol 2021; 12:757192.

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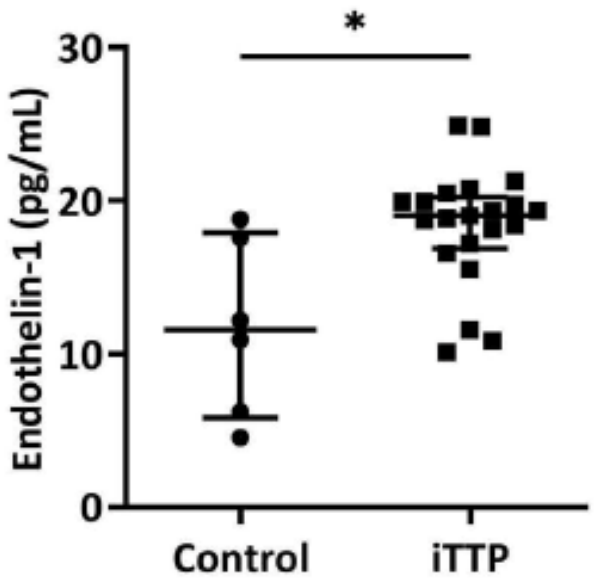
Immune-mediated thrombotic thrombocytopenic purpura plasma induces calcium- and IgG-dependent endothelial activation: correlations with disease severity



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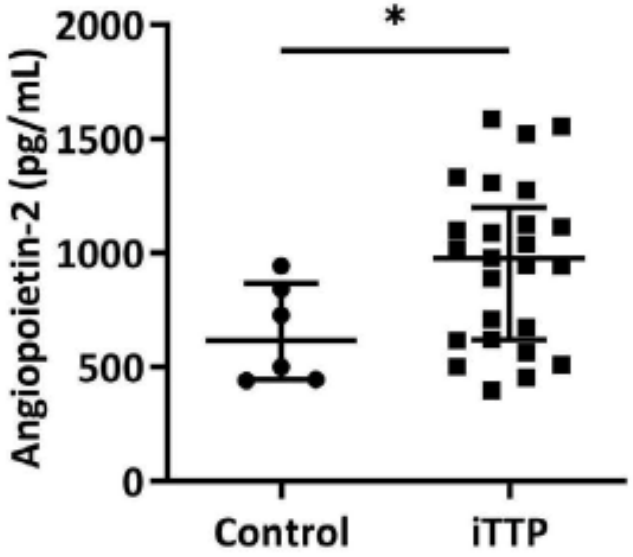
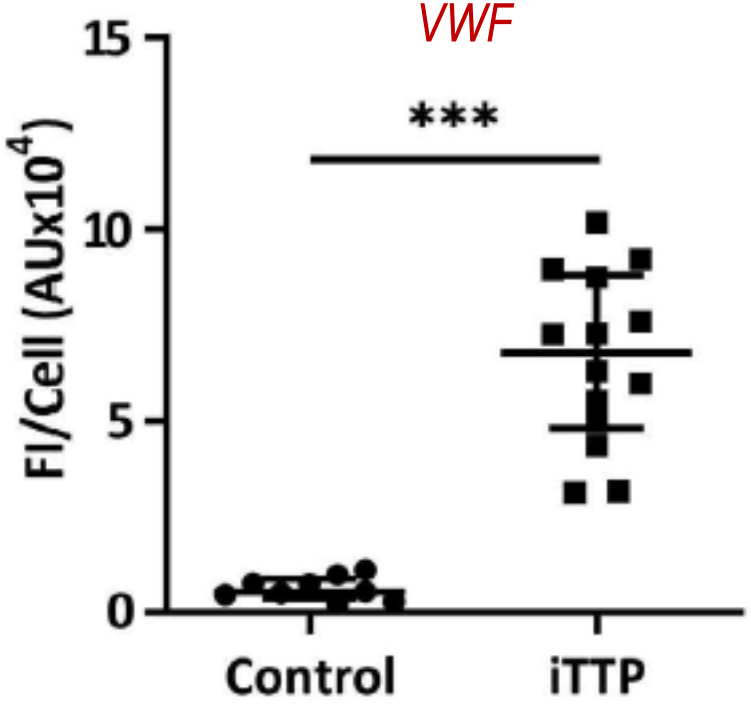


VWF



Induction of Weibel-Palade bodies exocytosis on endothelial cells after stimulation with immune-mediated thrombotic thrombocytopenic purpura plasma

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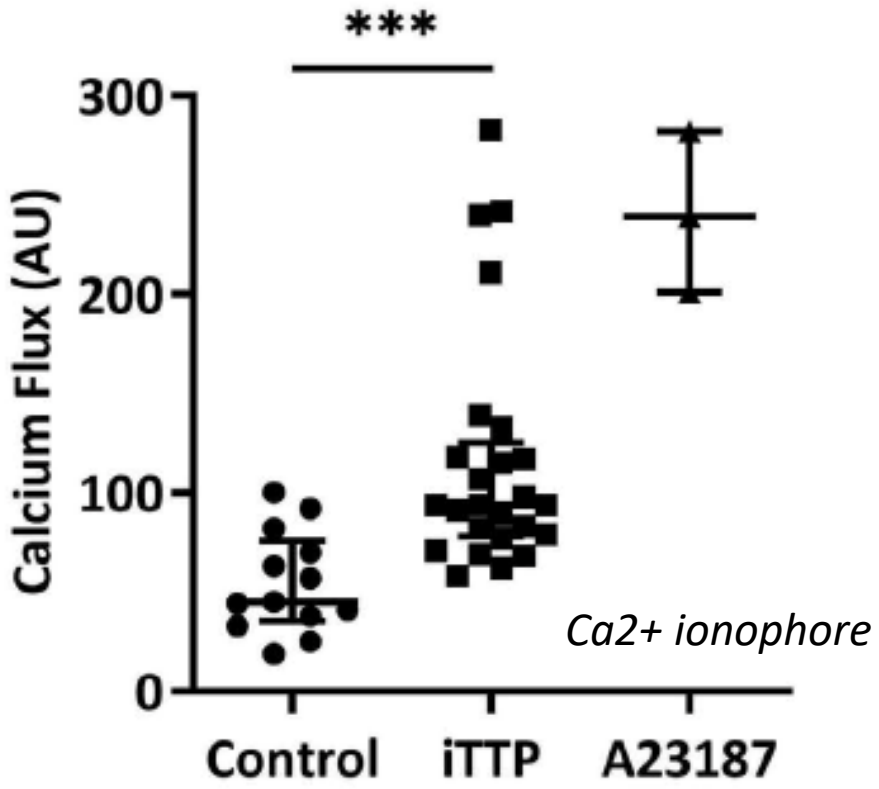
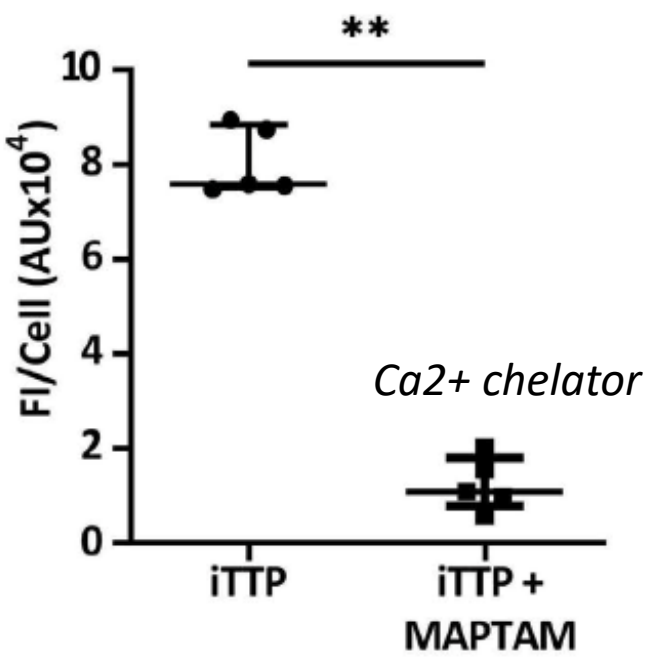
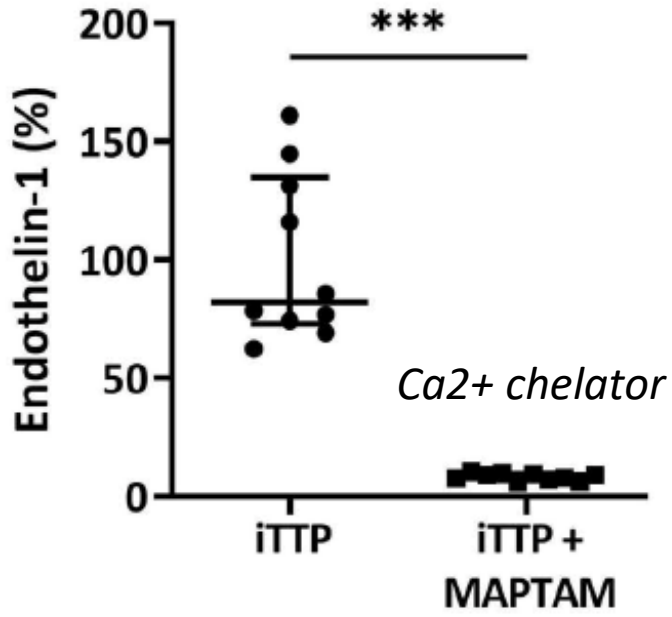
Tellier E at al. Haematologica. 2023;108(4):1127-1140

Immune-mediated thrombotic thrombocytopenic purpura plasma induces calcium- and IgG-dependent endothelial activation: correlations with disease severity



VWF

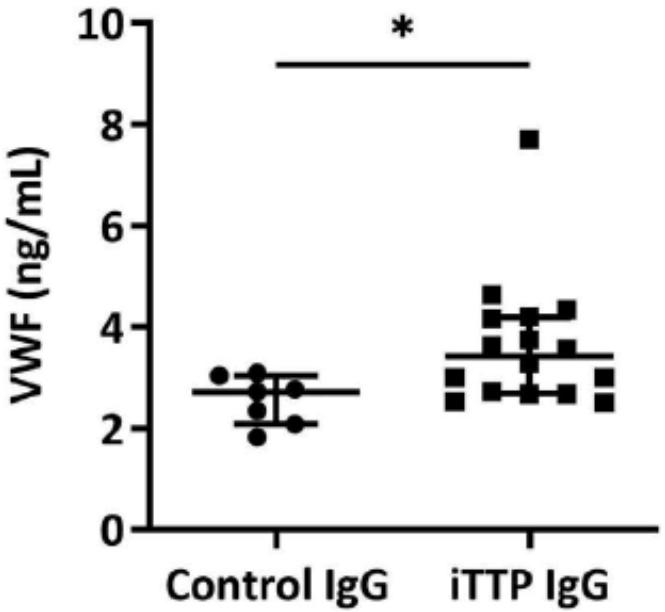


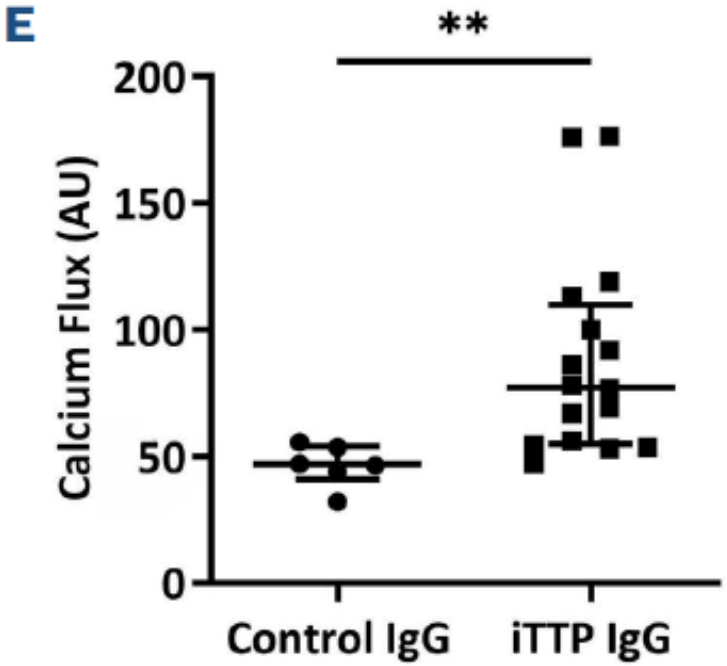


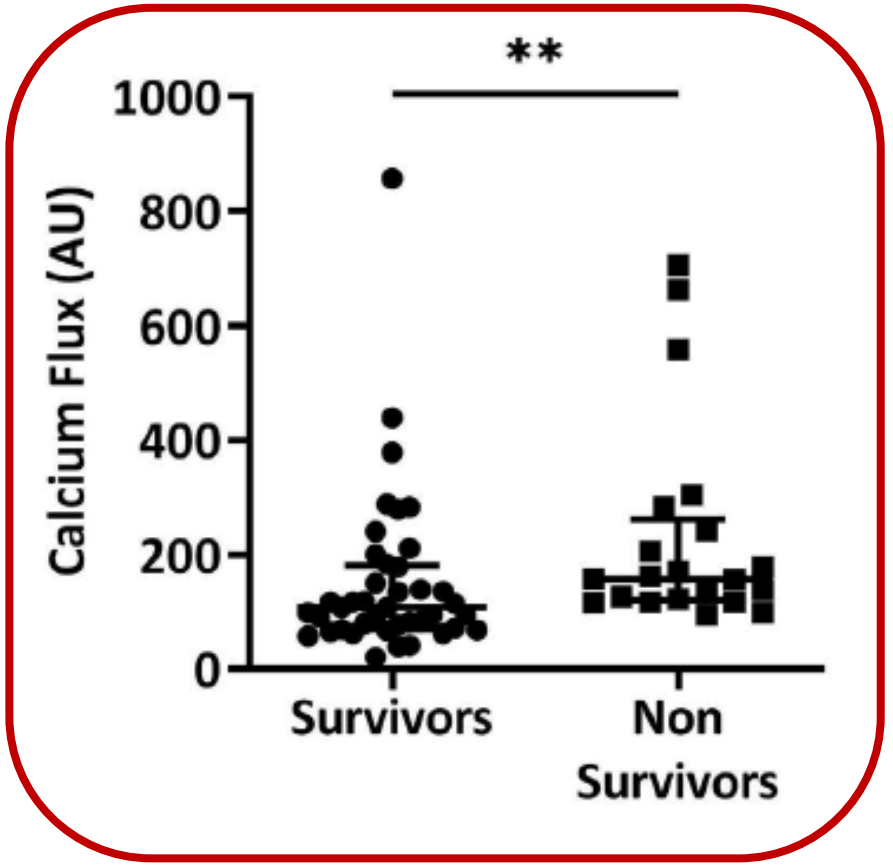
Weibel-Palade bodies exocytosis induced by immune-mediated thrombotic thrombocytopenic purpura plasma is Ca^{++}- mediated.

Tellier E at al. Haematologica. 2023;108(4):1127-1140

Immune-mediated thrombotic thrombocytopenic purpura plasma induces calcium- and IgG-dependent endothelial activation: correlations with disease severity







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Tellier E at al. Haematologica. 2023;108(4):1127-1140

Is Endothelial Activation a Critical Event in Thrombotic Thrombocytopenic Purpura?

- ✓ The existence of an endothelial activation during TTP acute phase is accepted by the scientific community.
- ✓ *However, one question remains: is the endothelial activation a consequence of the micro-occlusive disease, or is it a key initiating event that precipitates an individual susceptibility into an acute episode?*
- ✓ The "second hit" model suggests that in TTP, in addition to ADAMTS13 deficiency, endogenous or exogenous factors induce endothelial activation affecting mainly microvascular cells.

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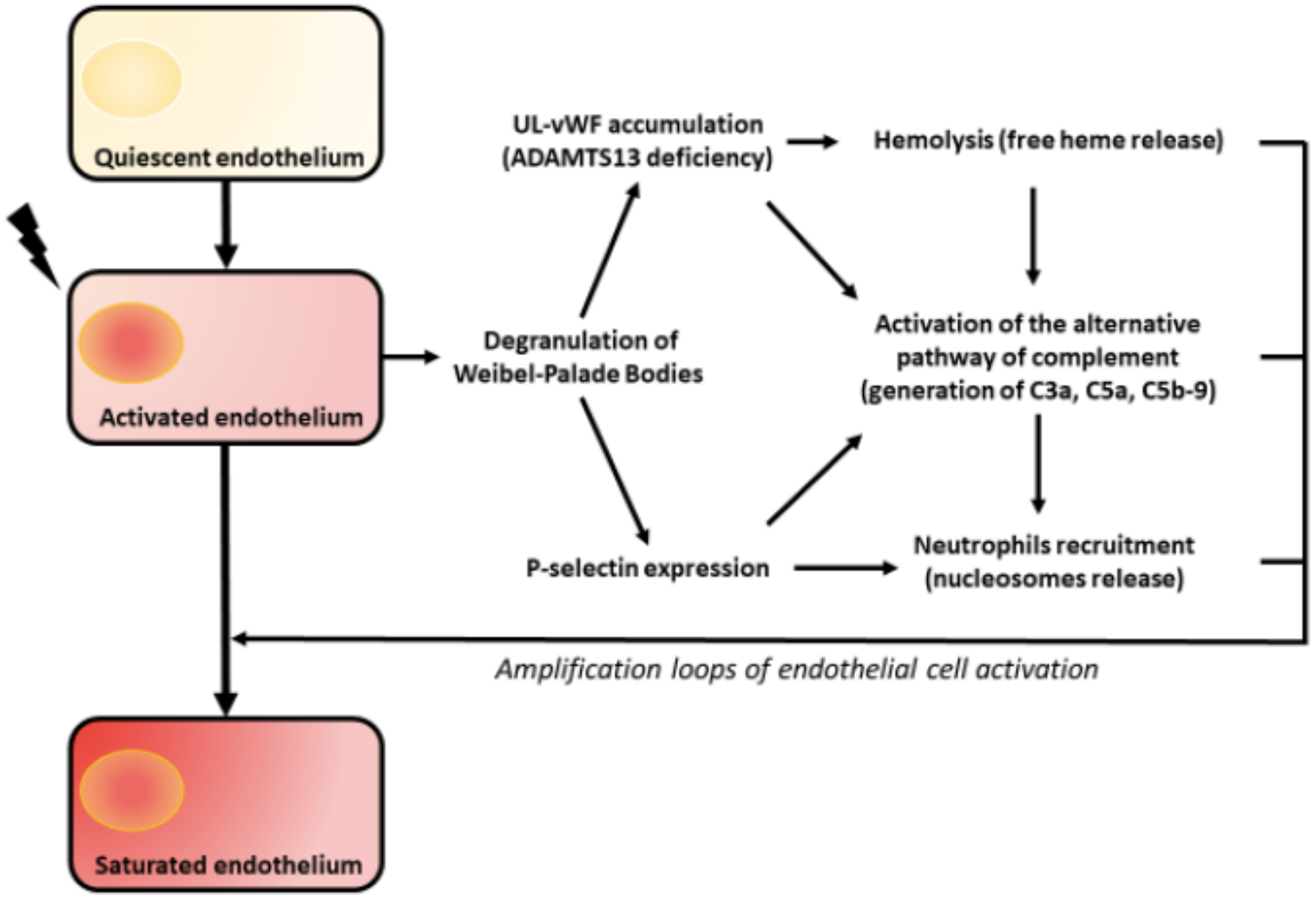
Cauchois R et al. J Clin Me. 2023; 1: 758.

Is Endothelial Activation a Critical Event in Thrombotic Thrombocytopenic Purpura?

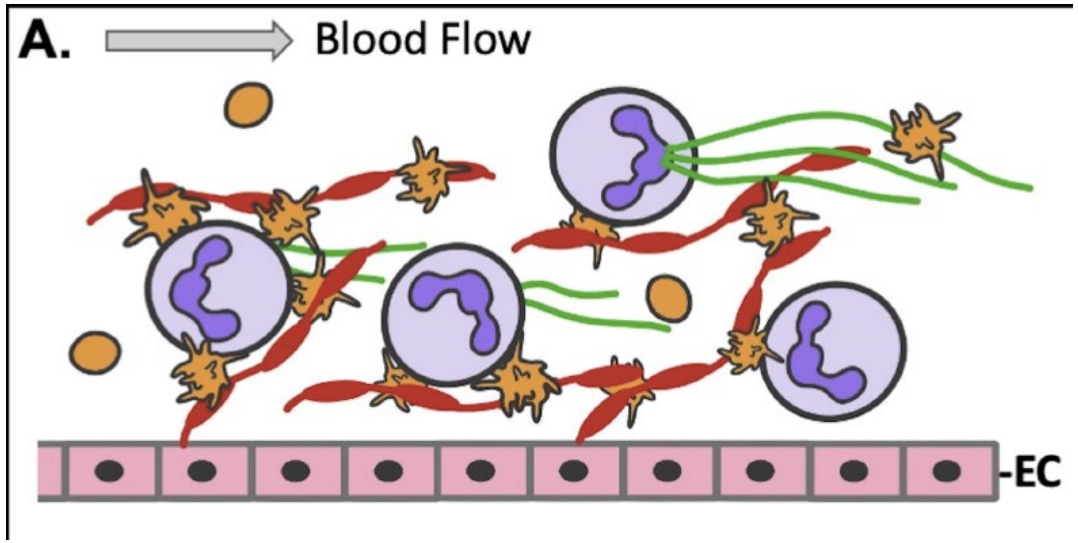
Suspected Triggers for the Second Hit Hypothesis

- ✓ Pregnancy
- ✓ Viruses (including SARS-CoV2
- ✓ Bacteria
- ✓ Cytokines (g-interferon, TNFa, IL-8)
- ✓ Drugs (calcineurin inhibitors, mitomycin, gemcitabine, anti-VEGF agents, quinine)



Cauchois R et al. J Clin Me. 2023; 1: 758.

Targeting Neutrophil Extracellular Trap under Flow in Patients with Immune-Mediated Thrombotic Thrombocytopenic Purpura

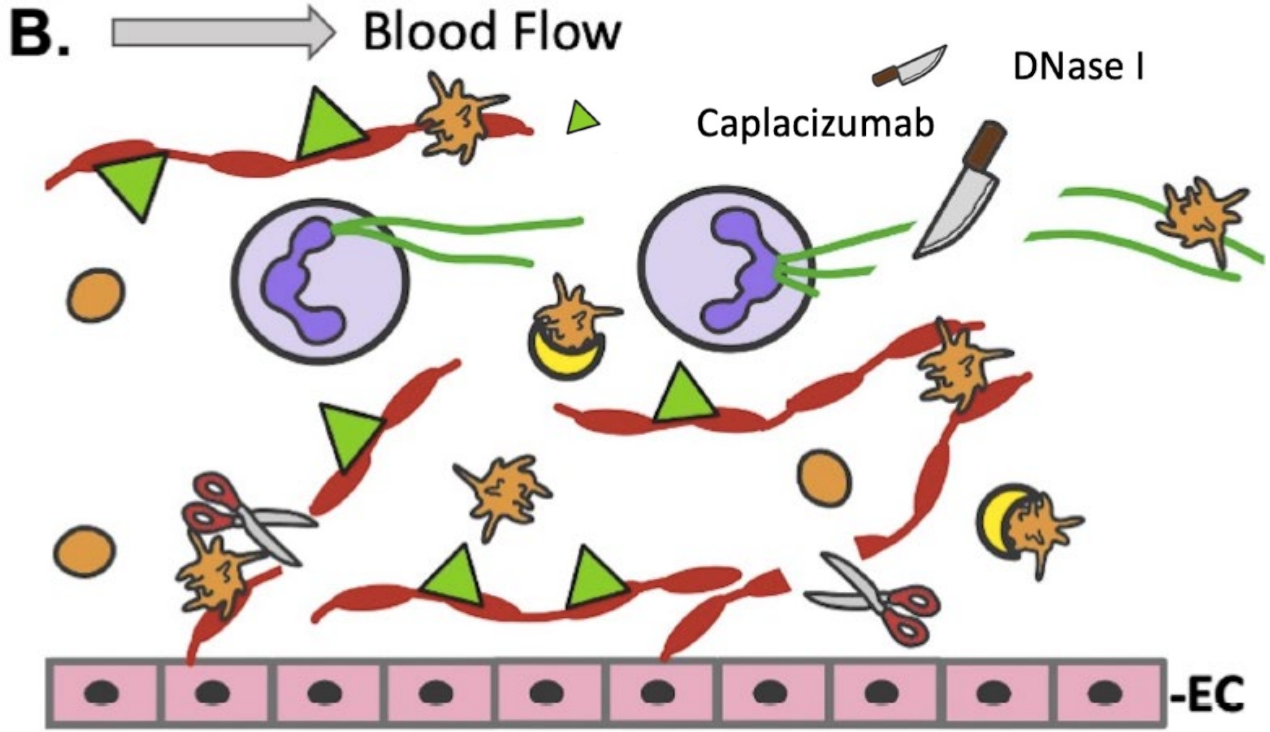


- ✓ *VWF is released from stimulated endothelial cells (EC), remains anchored on the endothelial surface, and captures flowing platelets and neutrophils.*
- ✓ *The neutrophils undergo NETosis and release histone-DNA and histone-MPO complexes (NETs), which bind VWF and activate platelets to enhance thrombus formation.*

Degradation of Extracellular DNA strings by DNase I or Removal of VWF strings by recombinant A13 or Inhibition of platelet-VWF interactions by Capla

lead to

- ✓ *Destabilization of thrombus structure*
- ✓ *Dampening of inflammation and thrombosis*

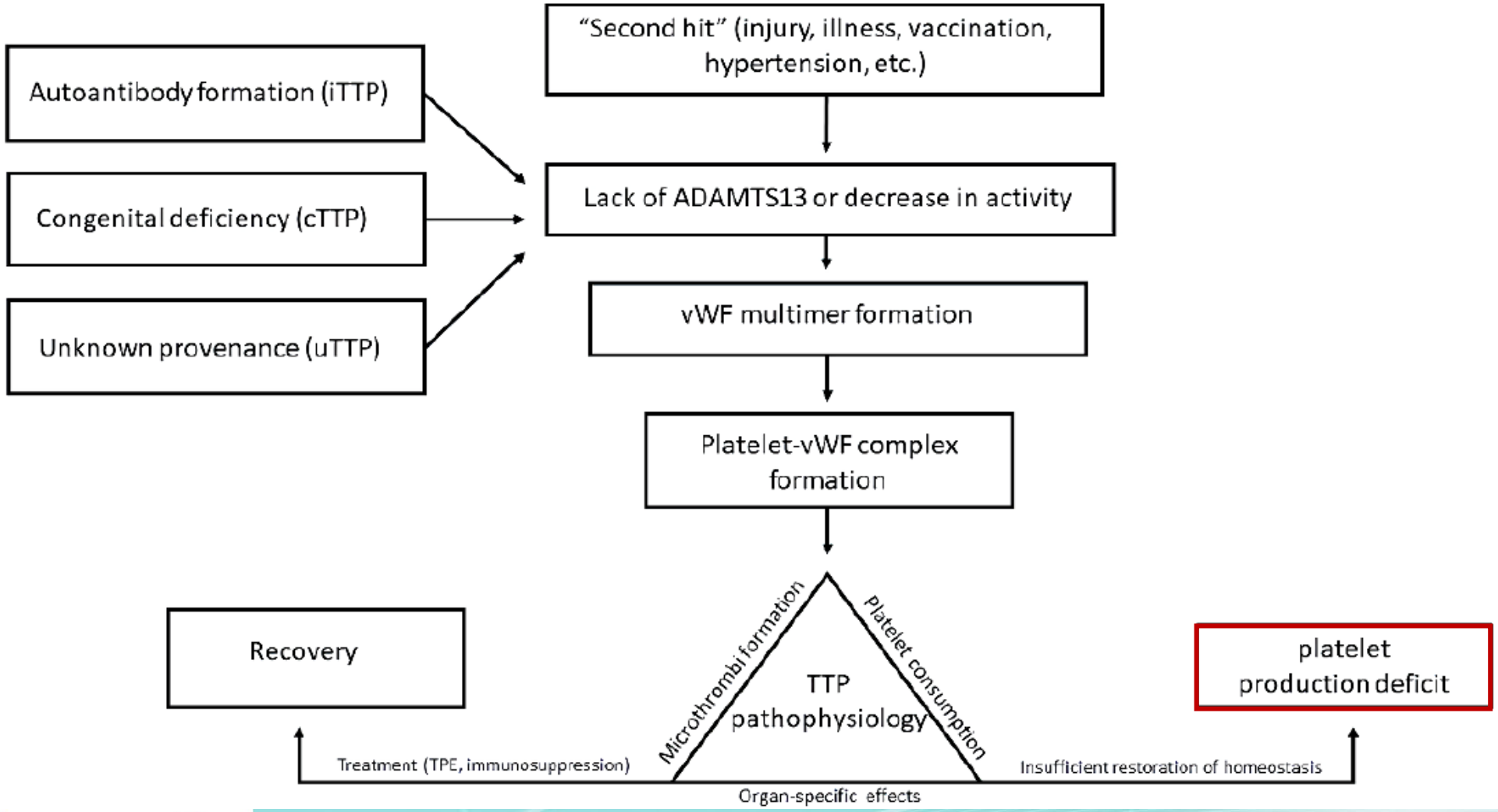


Yada N et al.Blood Adv. 2024 Mar 21:bloodadvances.2023011617

Six characters involved in iTTP

1. Genetic risk factors: HLA alleles and sNP
2. Autoreactive CD4 T cells
3. ADAMTS-13 structure and peptides
4. Molecular mimicry phenomenon
5. Endothelium
6. Immature platelets

Pathological Mechanisms and Novel Testing Methods in Thrombotic Thrombocytopenic Purpura



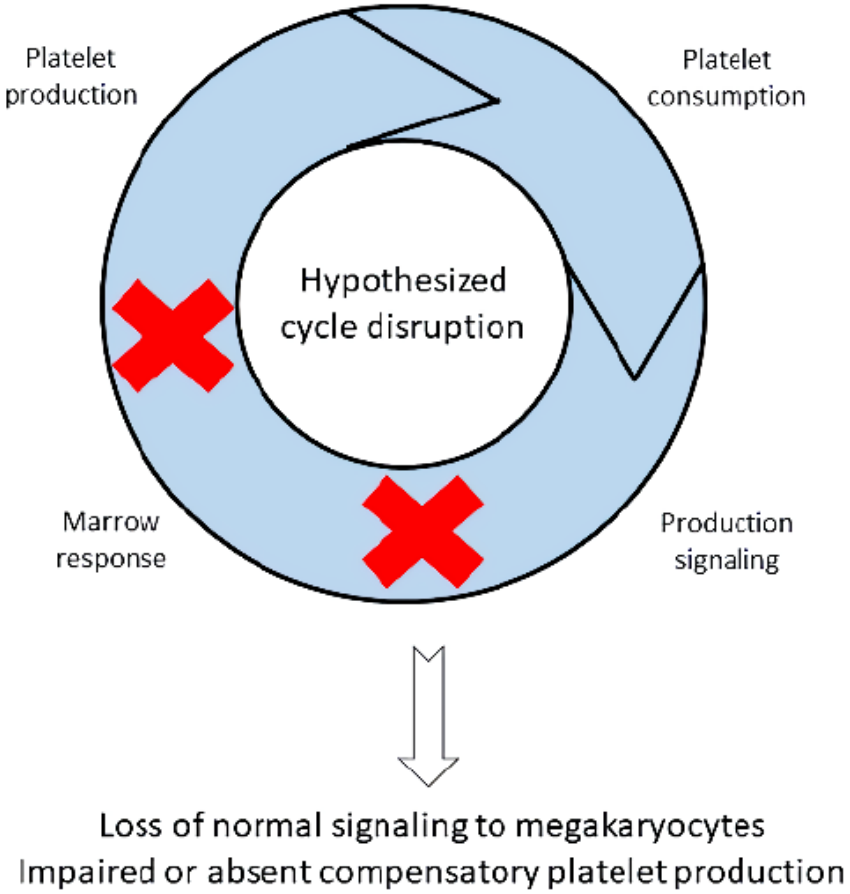
Dolin HH & Maitta RW. Biomedicines 2024; 12: 621.

Pathological Mechanisms and Novel Testing Methods in Thrombotic Thrombocytopenic Purpura

- ✓ A low Absolute Immature Platelet Count [A-IPC] is seen in iTTP patients presenting with a high inhibitor titer
- ✓ A-IPC has shown to be more specific and sensitive compared to the PLASMIC score, identifying all cases in which ADAMTS13 deficiency would be present
- ✓ In iTTP, A-IPC rises 2-3-fold after TPE initiation, whereas the same rise is not observed in other TMAs, suggesting that this measurement can be predictive of response to therapy
- ✓ The reduced A-IPC seen in iTTP at presentation is contradictory, since thrombocytopenia it is expected to stimulate a bone marrow response with an ***increase*** in A-IPC

Dolin HH & Maitta RW. Biomedicines 2024; 12: 621.

Pathological Mechanisms and Novel Testing Methods in Thrombotic Thrombocytopenic Purpura



- ✓ Low A-IPC indicates the presence of a yet unknown inhibitory process, which prevents the bone marrow from responding to the thrombocytopenia with higher immature platelet production
- ✓ The observed inhibition or suppression of immature platelet production may take place at the time of antibody formation to ADAMTS13 or when the enzyme is being depleted below an activity level.

Dolin HH & Maitta RW. Biomedicines 2024; 12: 621.

To sum up

- ✓ iTTP is an excellent model of multistep disease resulting from the combination of genetic risk factors for autoimmunity and environmental precipitating factors
- ✓ In iTTP patients develop antibodies (Abs) against ADAMTS13 that enhance its clearance or inhibit its VWF processing activity
- ✓ The mechanisms leading to the loss of tolerance of the immune system towards ADAMTS13 involve predisposing genetic factors, such as HLA class II locus DRB1*11 and DQB1*03 alleles as well as the protective allele DRB1*04
- ✓ The “second hit” model suggests that in iTTP, in addition to ADAMTS13 deficiency, endogenous or exogenous factors (ie, infectious diseases, drugs) induce endothelial activation
- ✓ This endothelial activation is worsened by various amplification loops, such as the complement system, NETs and free heme

Max Wertheimer, Kurt Koffka, Wolfgang Köhler – Psicologia della Gestalt

Il tutto è **diverso** della somma delle sue parti

Caplanet
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CAPLANET:
il network italiano della TTP
Gestione multidisciplinare

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IMPREVEDIBILITA' DELLA TTP: UN'EMERGENZA CLINICA

Dott. Maurizio Sacco

UOC Medicina DEA ed elevata complessità clinica

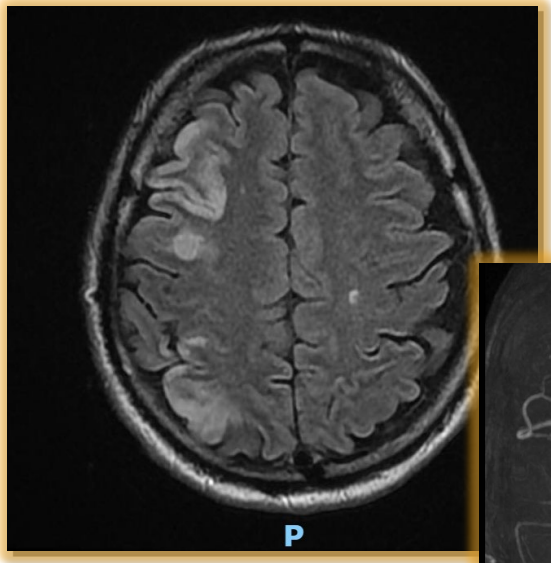
AORN Antonio Cardarelli, Napoli

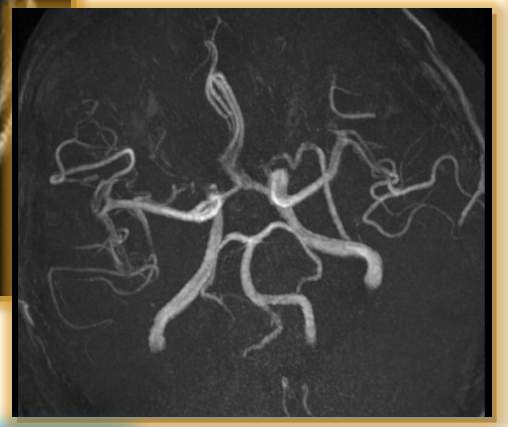
This event is organized and sponsored by Sanofi.
This presentation is not eligible for Continuing Medical Education (CME)

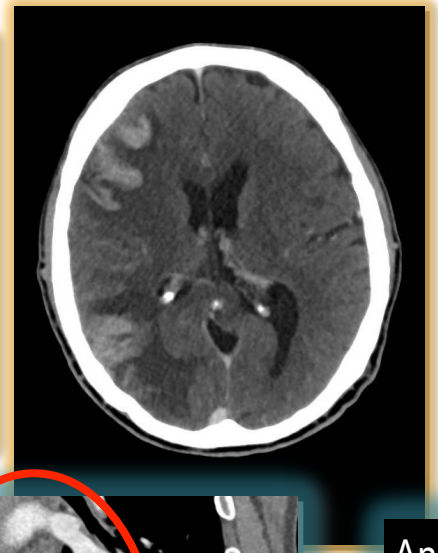
Fonti di finanziamento

- Nothing to declare.

IMPREVEDIBILITA' DELLA TTP: dove meno te lo aspetti



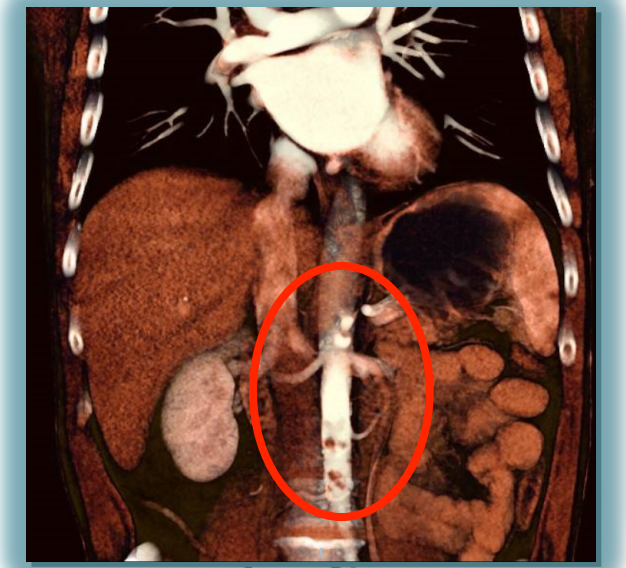


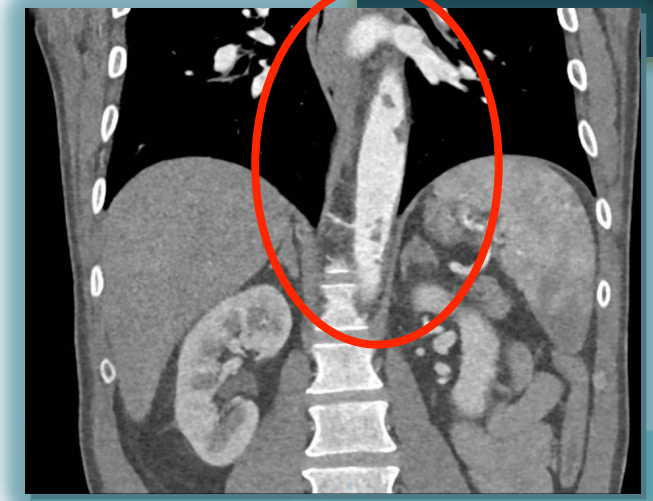


Uomo 57 anni – Pratica sportiva abituale –

Giunge in PS per episodio confusionale e successiva perdita di coscienza e del controllo sfinterico, insorti durante attività sportiva.

RMN: I





AngioTC TB senza e con MdC

Multiple alterazioni trombotiche focali, alcune rotondeggianti adese alla parete dell'aorta toraco addominale, ma anche evidenti a livello dell'origine di arteria anonima dx, del III medio dell'arteria splenica, della arteria femorale comune di sin, con stenosi significativa a quest'ultimo livello (possibile embolismo).

Laboratorio:

- piastrinopenia 27.000/mm3
- anemia 8.7 gr/dl
- test di Coombs negativo
- LDH 1178 UI/L
- Creatinina 0,99 mg/dl
- Troponina I 14,2 ng/ml

PLASMIC SCORE

Points	
Platelet count <30 × 10^9 per L	1
Haemolysis variable	1
No active cancer	1
No history of solid-organ or stem-cell transplant	1
MCV <90 fL	1
INR <1·5	1
Creatinine <2·0 mg/dL	1

Score 0–4: low risk
Score 5: intermediate risk
Score 6 or 7: high risk.

PLASMIC SCORE 7 → high risk for PTT diagnosis

Prelievo per ADAMTS13 e anticorpi

Dopo poche ore… ADAMTS 13 attività 0,7% - Ab antiADAMTS13 30BU - schistociti 5-6/campo (giunto referto in seconda giornata di ricovero) → Diagnosi di aTTP

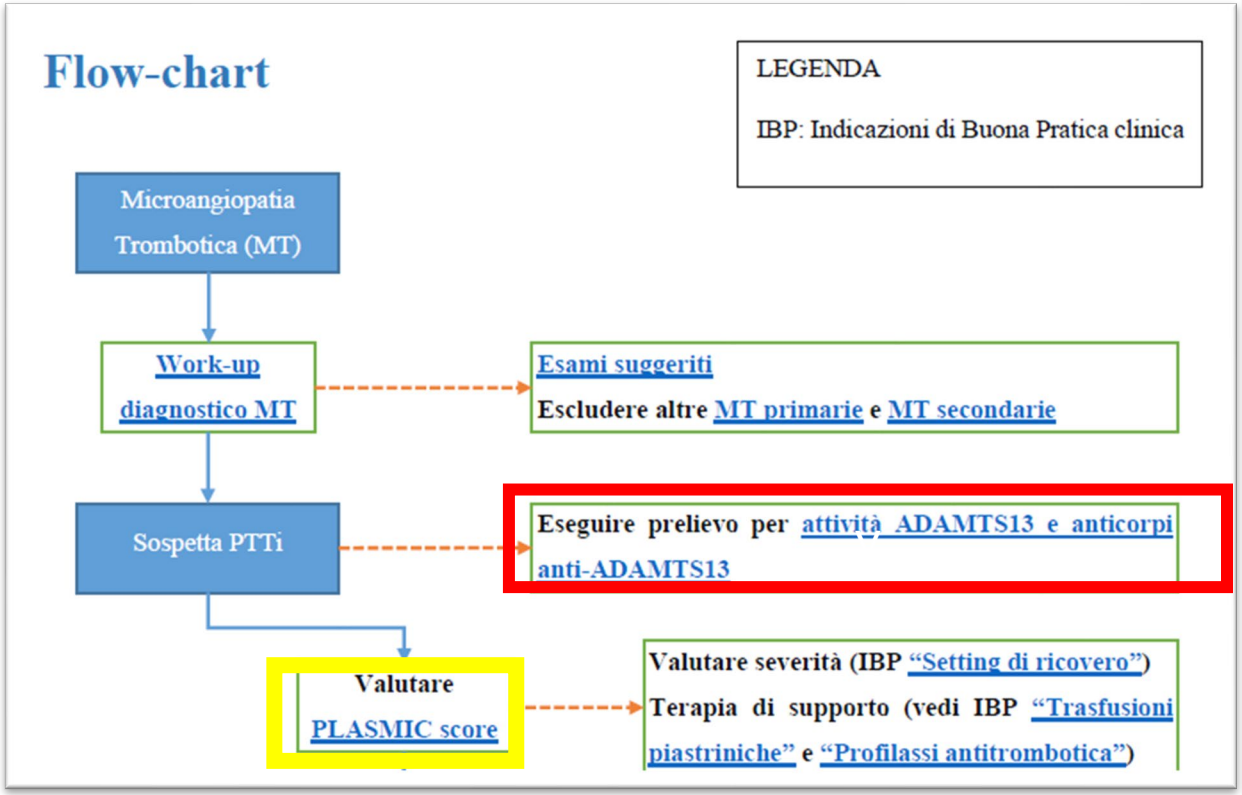
24 ore dopo l'accesso al PS:

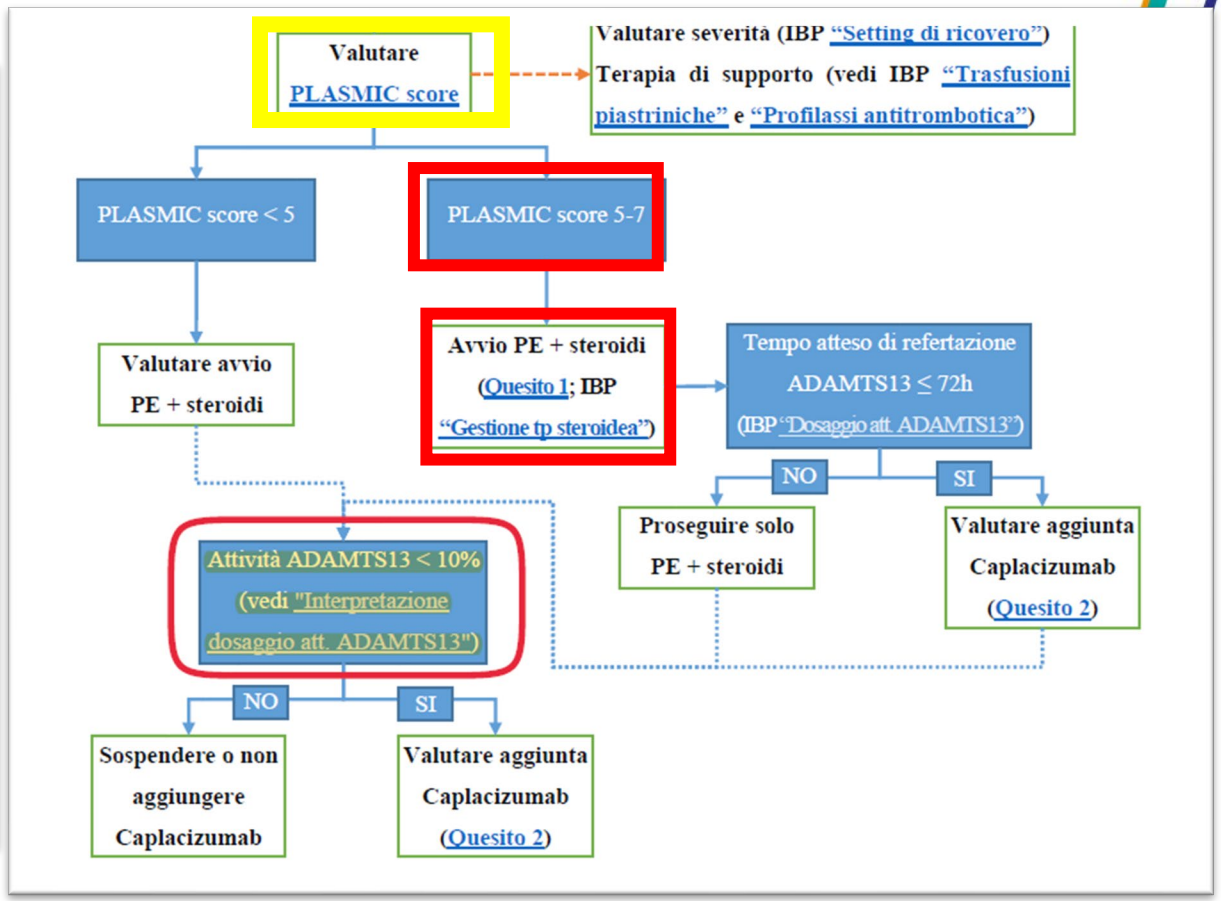
CAPLACIZUMAB 10 mg (dose di carico ev e, a seguire, im dopo PEX)

Metilprednisolone 1mg/Kg p.c./die

PEX (dopo 3 ore dalla somministrazione del Caplacizumab)

Raccomandazioni SIE 2021: Flow-chart





DOPO 15 GIORNI DI DEGENZA – 7 PEX

- ADAMTS13> 20%
- Normalizzazione degli esami di laboratorio, compreso emocromo ed enzimi di necrosi miocardica;
- Deficit campimetrico emilato sx
- TC body di controllo NEGATIVA per eventi tromboembolici

DIMISSIONE

- CAPLACIZUMAB 10 mg/die sottocute per 30 gg da ultima PEX
- Metilprednisolone 1mg/Kg p.c./die a scalare
- CardioASA (su consiglio neurologico)

aTTP complicata da Tromboembolismo polidistrettuale (STEMI infero-posteriore; ACV trombosi dell'arteria splenica, trombosi multipla polidistrettuale dell'aorta toraco-addominale

IN FOLLOW UP AMBULATORIALE:

valori ADAMTS13 53% - Ab AntiADAMTS13 negativi → sospeso Caplacizumab dopo 30 giorni dall'ultima PEX

Il paziente prosegue controlli cardiologici e neurologici periodici.

Esame coronarografico: coronarie indenni

Widespread Multi-Organ Ischemia in iTTP

Organs most commonly affected[1–4]

Organ	Signs and symptoms	Frequency of symptoms
Brain	Paresis, aphasia, dysarthria, visual problems, encephalopathy, headache, confusion, stroke, coma, seizure	60%
Gastrointestinal system	Abdominal pain, nausea, vomiting, diarrhea	35%
Heart	Chest pain, hypotension, isolated electrocardiographic abnormalities, myocardial infarction, congestive heart failure, arrhythmias, cardiogenic shock, and sudden cardiac arrest	25%

VWF-rich hyaline thrombi[a] in multiple organs of a patient who died of TTP[2]

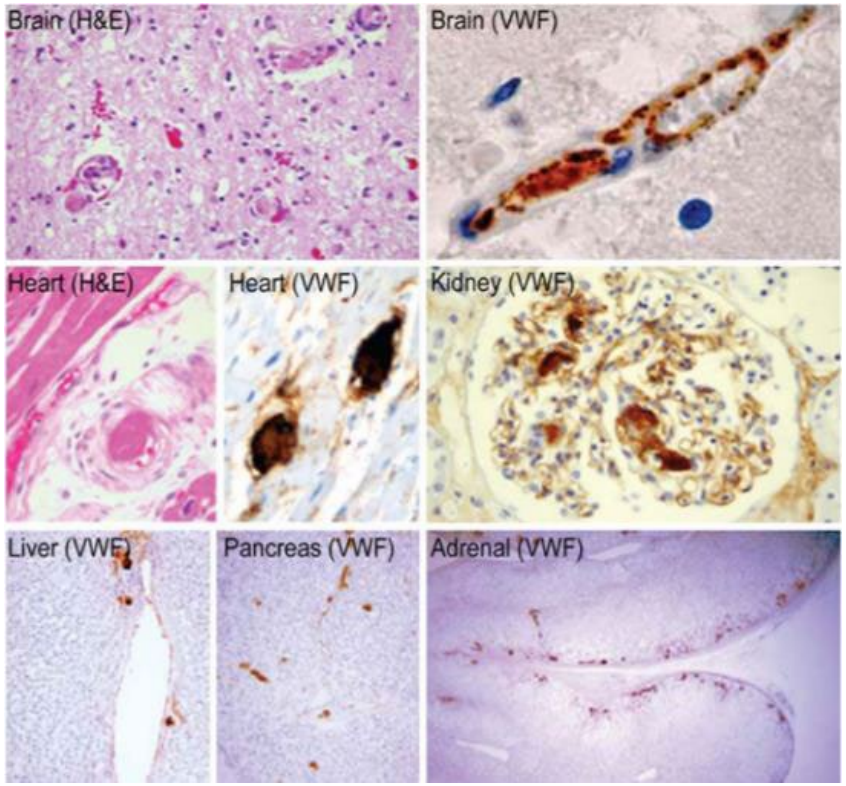


Image is reproduced with permission from Japanese Society of Hematology (Springer); Tsai HM. *Int J Hematol*. 2010;91(1):1-19.
iTTP, immune-mediated thrombotic thrombocytopenic purpura; H&E, hematoxylin and eosin;
TTP, thrombotic thrombocytopenic purpura; VWF, von Willebrand factor. [a]Immunostaining for each tissue section is shown in the parentheses.

1. Joly BS, et al. *Expert Rev Hematol.* 2019;12(6):383-395. 2. Tsai HM. *Int J Hematol*. 2010;91(1):1-19. 3. Kremer Hovinga JA, et al. *Nat Rev Dis Primers*. 2017;3:17020. 4. Scully M, et al. *Br J Haematol*. 2012;158(3):323-335.

Clinical Presentation of iTTP

iTTP usually presents with an acute onset of symptoms and a severe disease course[1–3]

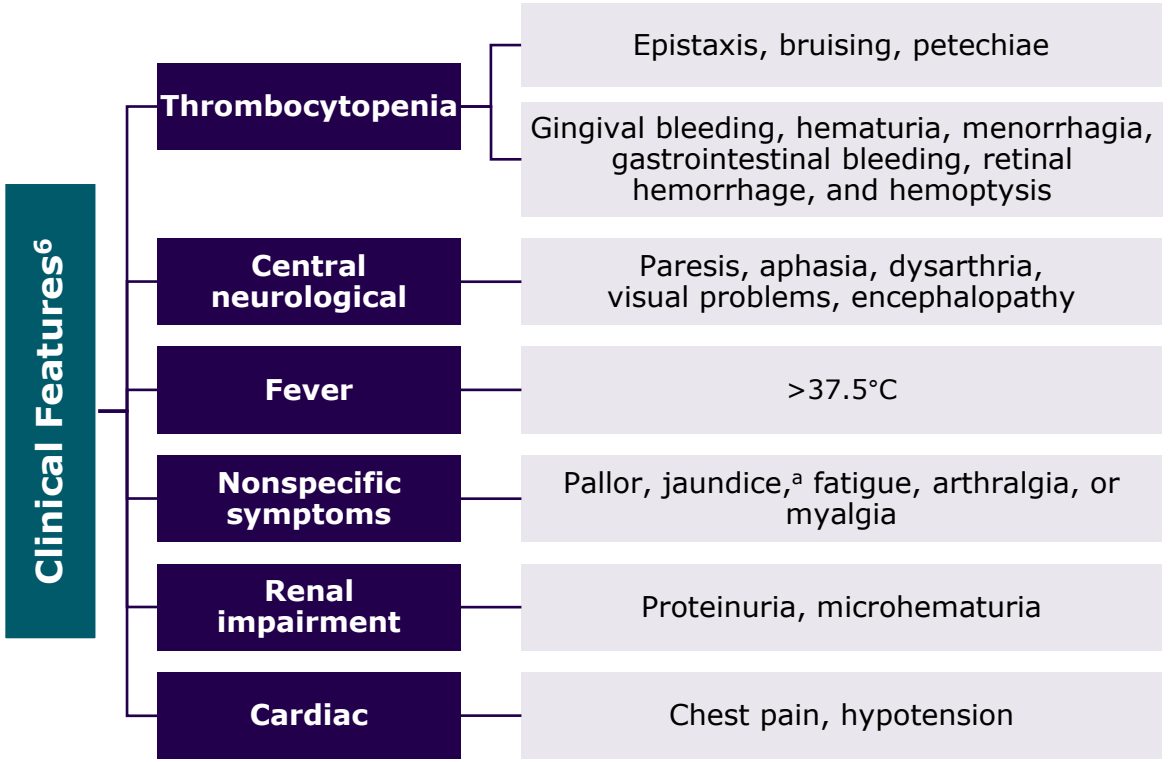
iTTP is a TMA characterized by the presence of[4]:

- **Thrombocytopenia**
- **MAHA**
- **Variable degree of organ dysfunction**

Historically, iTTP was characterized by a pentad of fever, purpura or hemorrhage, hemolytic anemia, neurologic manifestations, and variable renal dysfunction[1,4]

- Due to earlier diagnosis, the pentad now occurs only in few patients (<10%)[1,2]

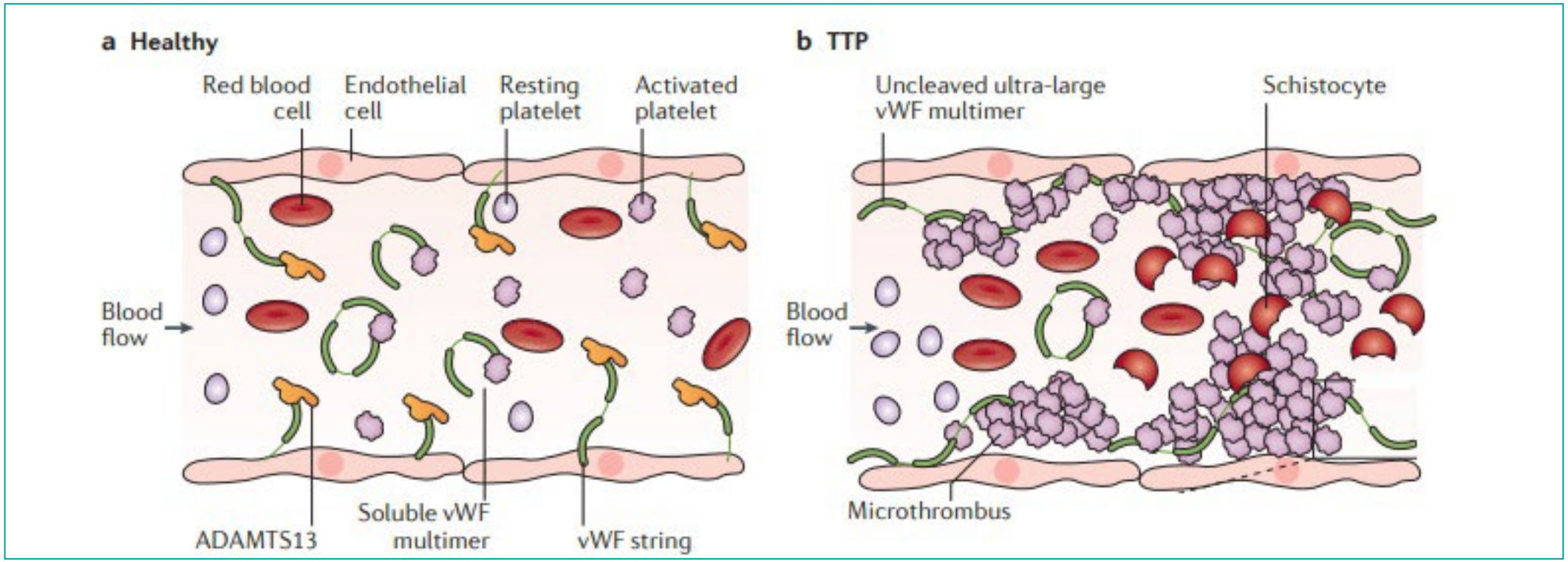
Clinical presentation of iTTP is highly variable[5]



iTTP, immune-mediated thrombotic thrombocytopenic purpura; MAHA, microangiopathic hemolytic anemia; TMA, thrombotic microangiopathy. [a]Resulting from MAHA.

1. Joly BS, et al. *Expert Rev Hematol.* 2019;12(6):383-395. 2. Kremer Hovinga JA, et al. *Nat Rev Dis Primers*. 2017;3:17020. 3. Joly BS, et al. *Blood.* 2017;129(21):2836-2846.
4. Tsai HM. *Int J Hematol*. 2010;91(1):1-19. 5. George JN. *Blood Adv.* 2018;2(12):1510-1516. 6. Scully M, et al. *Br J Haematol*. 2012;158(3):323-335.

Pathophysiology of TTP: in the microvasculature



Kremer Hovinga, et al. Nat Rev Dis Primers. 2017

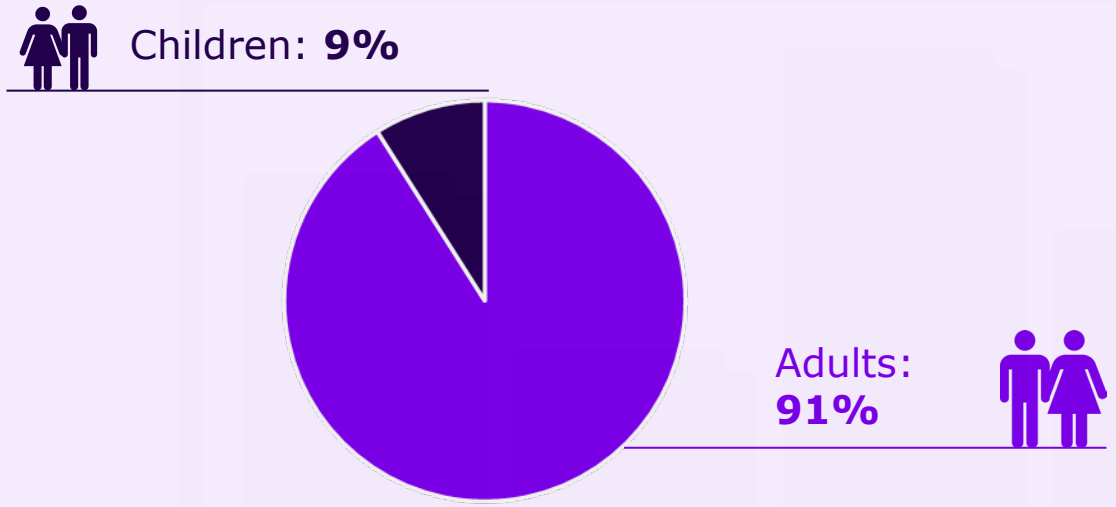
Incidence and Prevalence of iTTP

Global annual incidence: 1–2 cases per 1 million people[3]

- US: 3–4 cases per 1 million[4,5]
- England: 6 cases per 1 million[6]
- France: 2–4 cases per 1 million[7]
- Germany: 2.1 cases per 1 million[8]

First episodes most commonly occur in the **fourth decade** of life[7]

iTTP primarily affects adults[1]

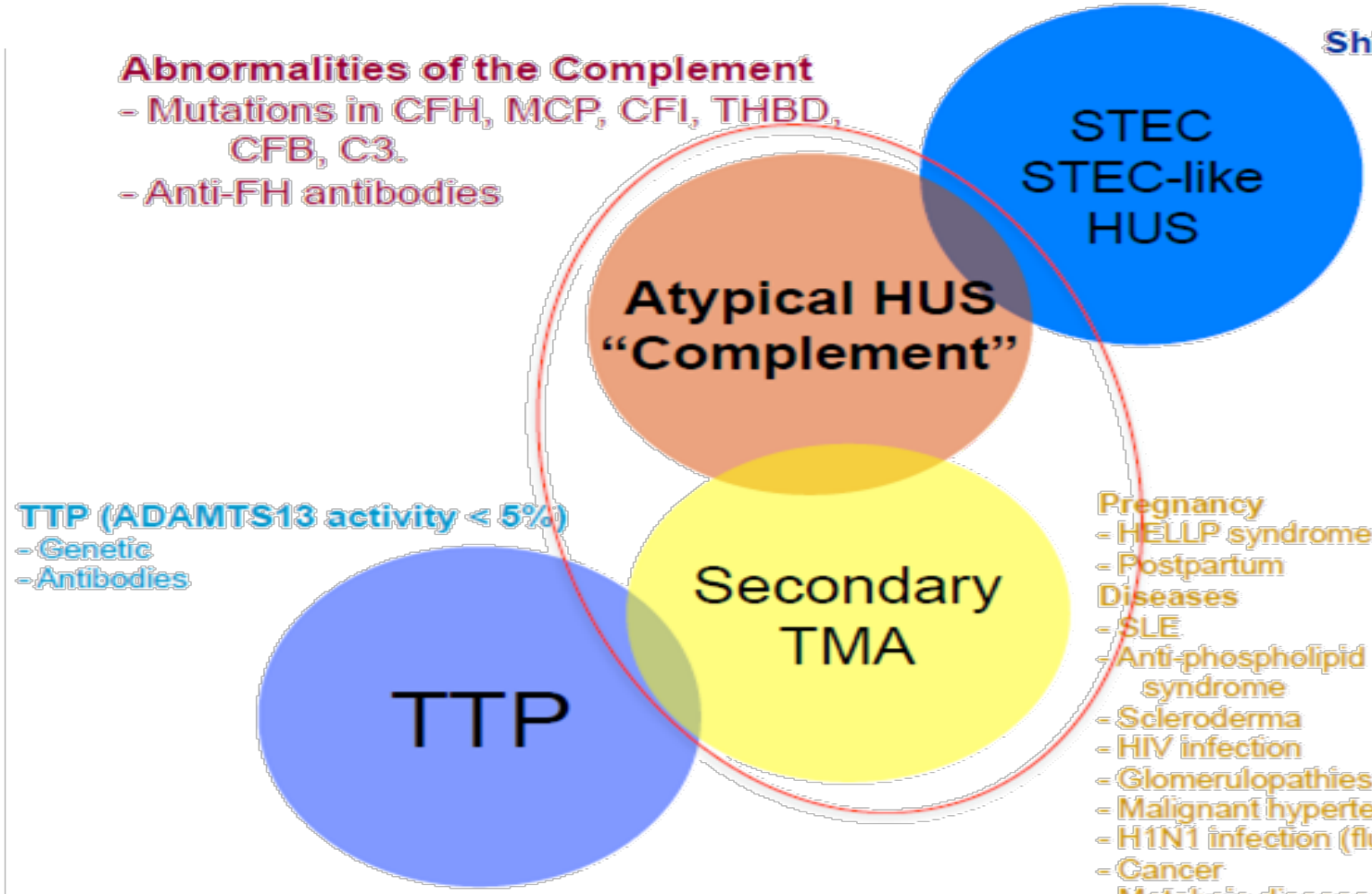


iTTP is **2.5–3.5 times more common in women** than men[9]

iTTP, immune-mediated thrombotic thrombocytopenia purpura; TTP, thrombotic thrombocytopenia purpura.

1. Joly BS, et al. *Blood*. 2017;129(21):2836-2846. 2. Scully M, et al. *J Thromb Haemost*. 2017;15(2):312-322. 3. Joly BS, et al. *Expert Rev Hematol*. 2019;12(6):383-395.
4. Miller DP, et al. *Epidemiol.* 2004;15: 208–215. 5. Page EE, et al. *Blood Adv*. 2017; 1(10): 590–600. 6. Scully M, et al. *Br J Haematol*. 2008;142(5):819-826.
7. Coppo P, et al. *Res Pract Thromb Haemost.* 2019;3(1):26-37. 8. Miesbach W, et al. *Orphanet Journal of Rare Diseases.* 2019;14:260. 9. Kremer Hovinga JA, et al. *Nat Rev Dis Primers*. 2017;3:17020.

Thrombotic microangiopathy (TMA): classification



Campistol et al. Nefrologia; Oct 2015

Risk Factors and Triggers

Severe ADAMTS13 deficiency is the only identified cause of iTTP[1]

iTTP episodes can be triggered by conditions that lead to an **increase in VWF levels**[1]

Risk factors for iTTP[1,2]

- Genetic factors (HLA-DRB1*11)
- Obesity
- Black ethnicity
- Female sex

Triggers of iTTP episodes

Physiological triggers[1,2]

- Inflammation
- Infections
- Pregnancy
- Sepsis

External triggers[2,3]

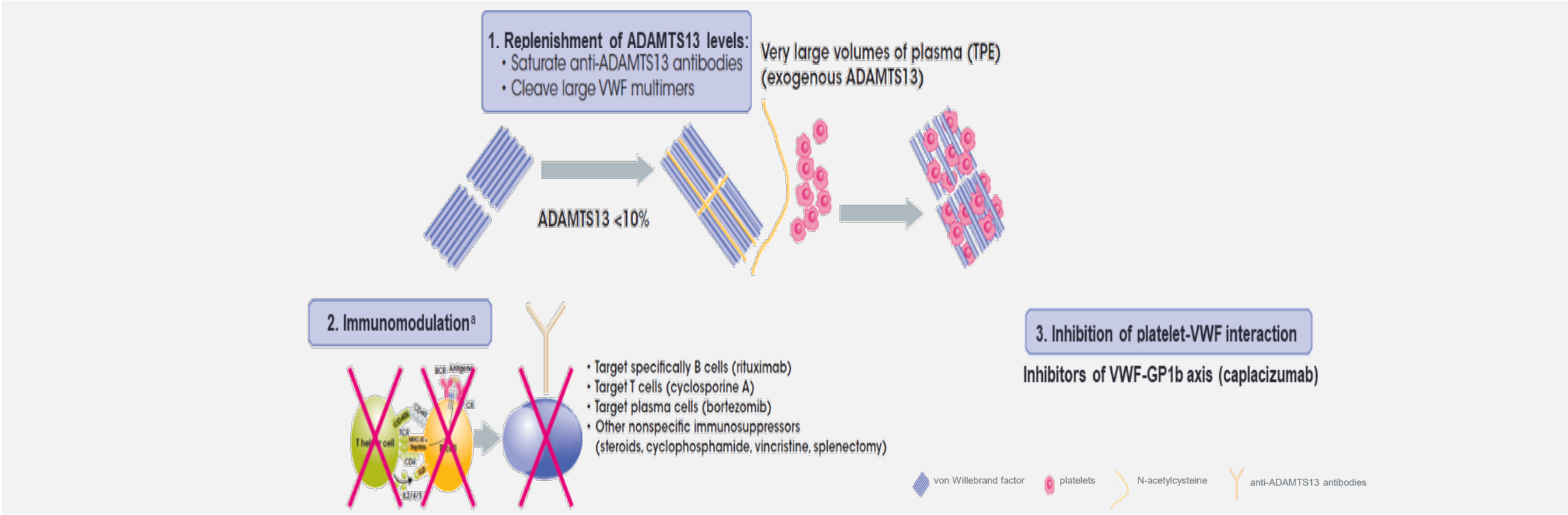
- Surgery
- Medications
  - Quinine
  - Mitomycin C
  - Cyclosporine
  - Clopidogrel
  - Ticlopidine

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; iTTP, immune-mediated thrombotic thrombocytopenic purpura; HLA-DRB1*11, histocompatibility complex, class II, DR beta 1 allele 11; VWF, von Willebrand factor.

1. Joly BS, et al. *Expert Rev Hematol*. 2019;12(6):383-395. 2. Joly BS, et al. *Blood.* 2017;129(21):2836-2846. 3. Arcudi S, et al. *J Thromb Haemost.* 2019;17(3):492-498.

Pathophysiological Basis of Treatment Strategies

Treatments are based on **three pathophysiological axes**[1]



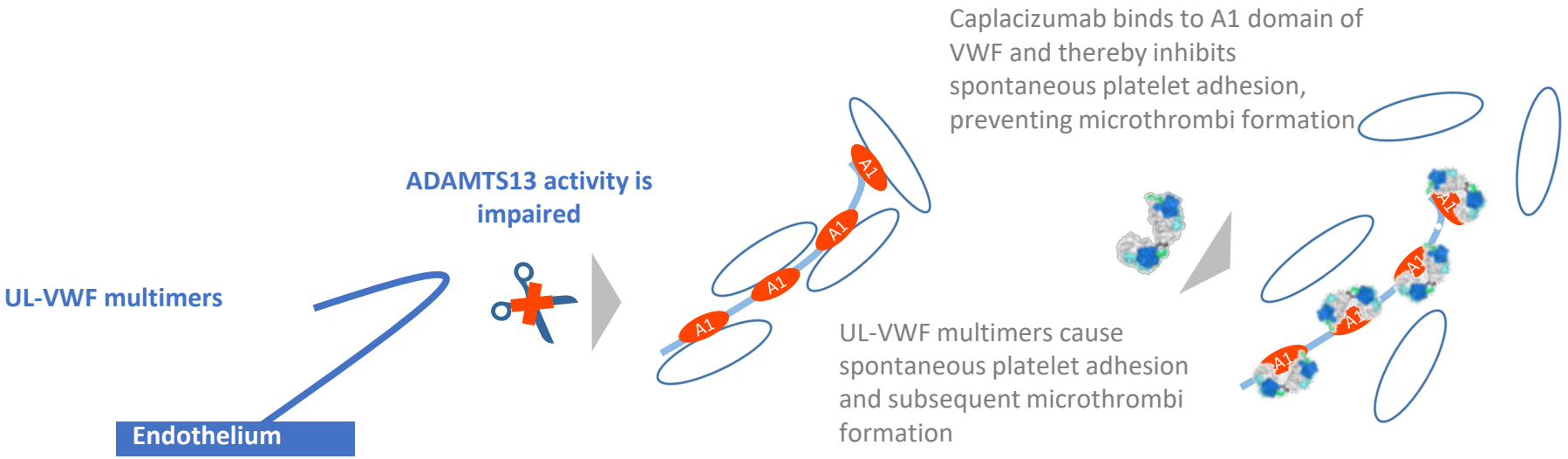
ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; iTTP, immune-mediated thrombotic thrombocytopenic purpura; GP, glycoprotein; TPE, therapeutic plasma exchange; VWF, von Willebrand factor.

[a]Immunomodulators listed on this slide are not approved by any regulatory agency worldwide for treatment of iTTP.

1. Coppo P, et al. *Res Pract Thromb Haemost.* 2019;3(1):26-37. 2. Kremer Hovinga JA, et al. *Nat Rev Dis Primers*. 2017;3:17020. 3. Scully M, et al. *Br J Haematol*. 2012;158(3):323-335.

Caplacizumab in iTTP: A VWF-Targeting Nanobody®

- High unmet medical need[2]; caplacizumab is the **only** approved treatment for iTTP[3]



Caplacizumab's mode of action blocks binding of VWF to platelets, which has a rapid effect on platelet adhesion and the ensuing microthrombi formation[2,4]

- ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; iTTP, immune-mediated thrombotic thrombocytopenic purpura; UL-VWF, ultra-large von Willebrand factor; VWF, von Willebrand factor.

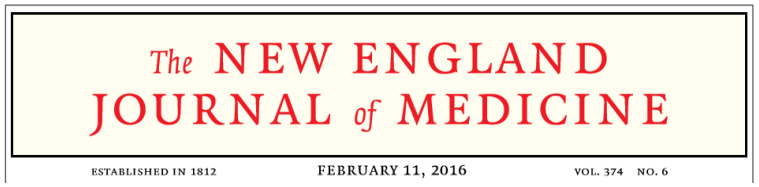
1. Kremer Hovinga JA, et al. *Nat Rev Dis Primers*. 2017;3:17020. 2. Blair HA and Lyseng-Williamson KA. *Drugs & Therapy Perspectives*. 2019;35(6):263-270. 3. Cablivi® (caplacizumab) [Prescribing Information]. Cambridge MA: Genzyme Corporation; 2019. 4. Sargentini-Maier ML, et al. *Expert Rev Clin Pharmacol*. 2019;12(6):537-545.

Clinical development with Caplacizumab in aTTP

Randomized clinical trials: a total of 220 adult patients with acute aTTP

Phase II TITAN study

- Single blind study, placebo-controlled
- Recruited from October 2010 until January 2014
- 75 patients randomized



The NEW ENGLAND JOURNAL of MEDICINE

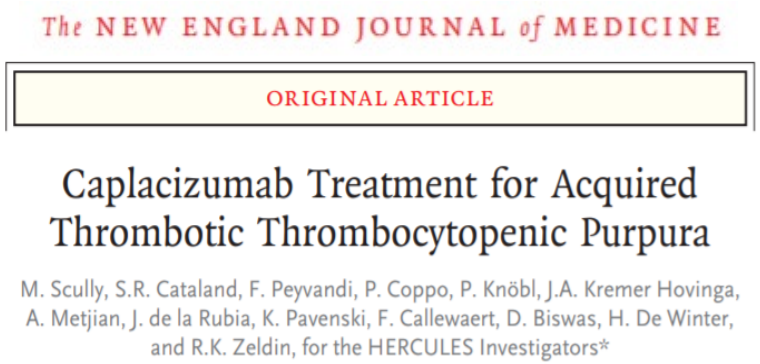
ESTABLISHED IN 1812 FEBRUARY 11, 2016 VOL. 374 NO. 6

Caplacizumab for Acquired Thrombotic Thrombocytopenic Purpura

Flora Peyvandi, M.D., Ph.D., Marie Scully, M.D., Johanna A. Kremer Hovinga, M.D., Spero Cataland, M.D., Paul Knöbl, M.D., Haifeng Wu, M.D.,* Andrea Artoni, M.D., John-Paul Westwood, M.D., Magnus Mansouri Taleghani, M.D., Bernd Jilma, M.D., Filip Callewaert, Ph.D., Hans Ulrichts, Ph.D., Christian Duby, M.D., and Dominique Tersago, M.D., for the TITAN Investigators†

Phase III HERCULES study

- Double blind study, placebo-controlled
- Recruited from November 2015 until April 2017
- 145 patients randomized

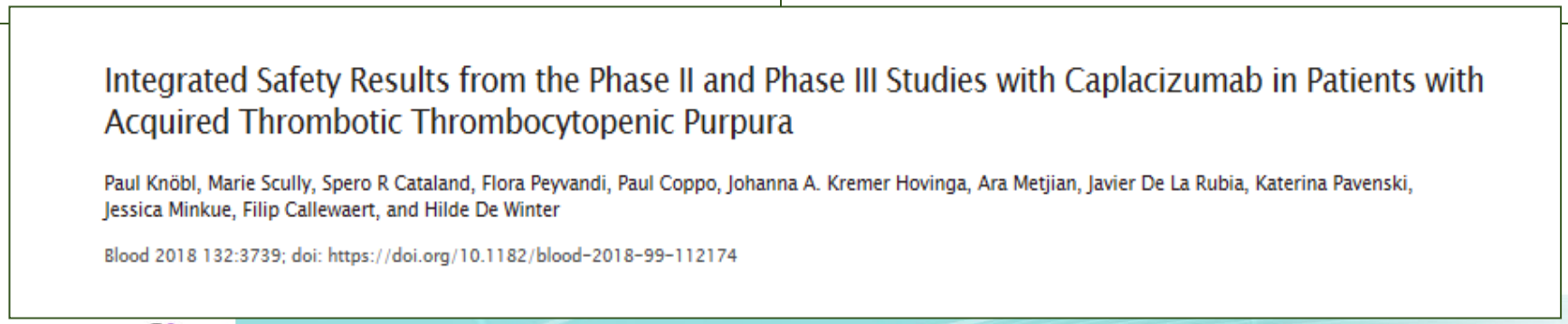


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Caplacizumab Treatment for Acquired Thrombotic Thrombocytopenic Purpura

M. Scully, S.R. Cataland, F. Peyvandi, P. Coppo, P. Knöbl, J.A. Kremer Hovinga, A. Metjian, J. de la Rubia, K. Pavenski, F. Callewaert, D. Biswas, H. De Winter, and R.K. Zeldin, for the HERCULES Investigators*

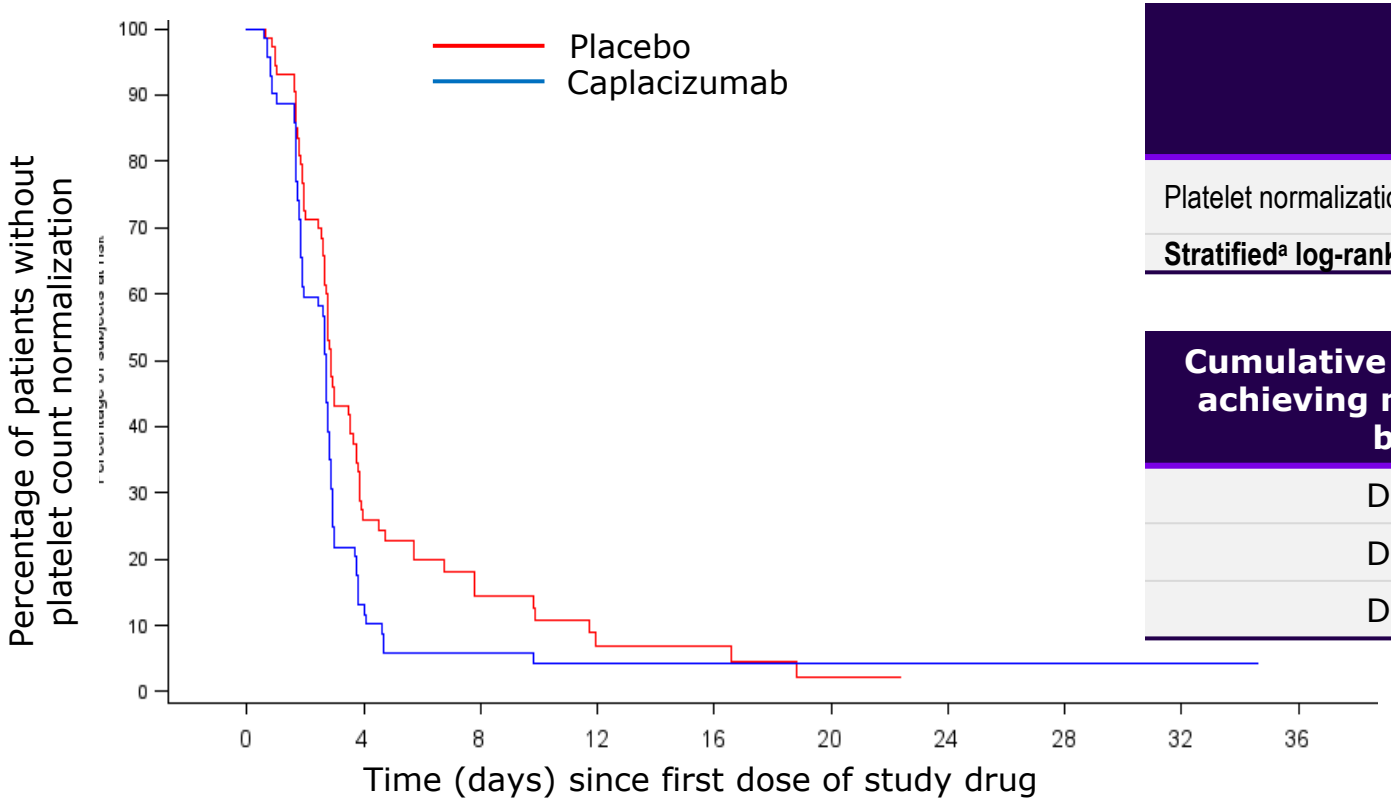


Integrated Safety Results from the Phase II and Phase III Studies with Caplacizumab in Patients with Acquired Thrombotic Thrombocytopenic Purpura

Paul Knöbl, Marie Scully, Spero R Cataland, Flora Peyvandi, Paul Coppo, Johanna A. Kremer Hovinga, Ara Metjian, Javier De La Rubia, Katerina Pavenski, Jessica Minkue, Filip Callewaert, and Hilde De Winter

Blood 2018 132:3739; doi: https://doi.org/10.1182/blood-2018-99-112174

Primary Endpoint: Time to Platelet Count Response



	Caplacizumab (N=72)	Placebo (N=73)
Platelet normalization rate ratio (95% CI)[1]	1.55 (1.1–2.2)	
Stratified[a] log-rank test *P* value	**0.01**	

Cumulative % of patients achieving normalization by[2,b]	Caplacizumab	Placebo
Day 3	78.2%	56.8%
Day 4	88.4%	74.1%
Day 5	94.2%	77.1%

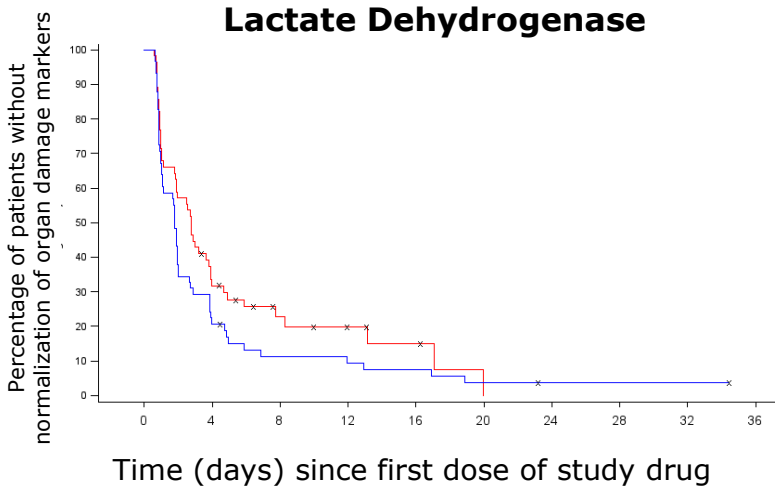
CI, confidence interval; TPE, therapeutic plasma exchange. [a]Platelet count response was defined as initial platelet count ≥150 × 10^9/L with subsequent stop of daily TPE within 5 days. [b]Post hoc analysis.

1. Scully M, et al. *N Engl J Med*. 2019;380(4):335-346. 2. Peyvandi F, et al. *Blood*. 2018;132:373.

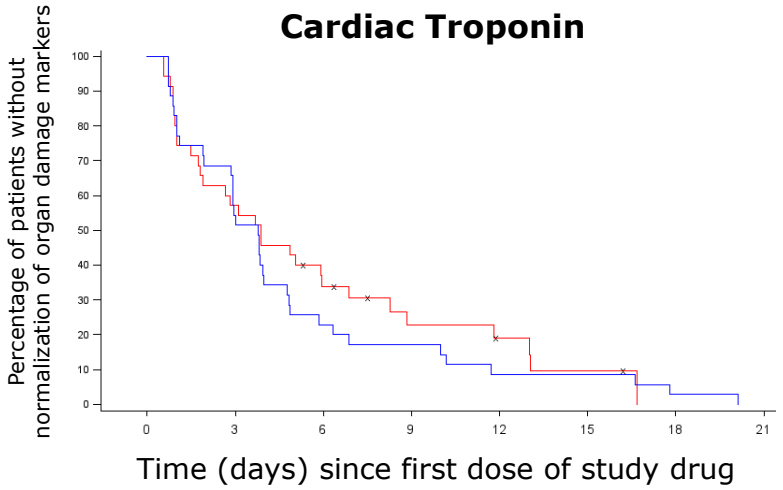
Time to Normalization of Individual Organ Damage Markers

Placebo Caplacizumab

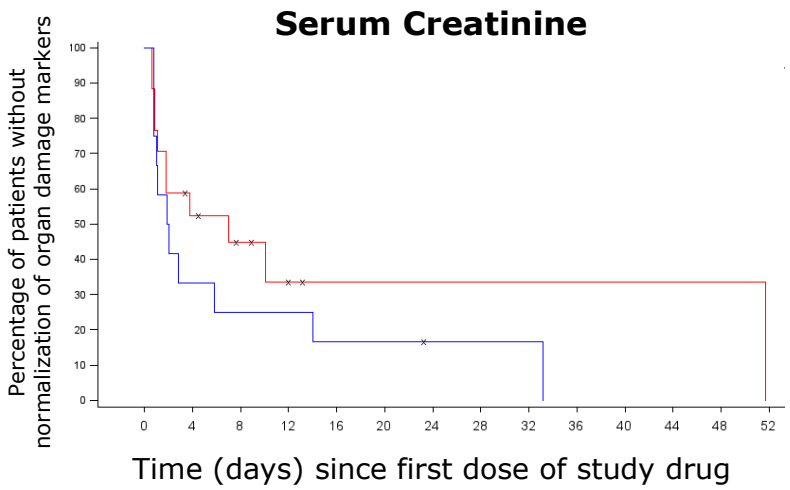
Lactate Dehydrogenase



Cardiac Troponin



Serum Creatinine



	Caplacizumab (n=72)	Placebo (n=73)
Number assessed	58	56

	Caplacizumab (n=72)	Placebo (n=73)
Number assessed	35	35

	Caplacizumab (n=72)	Placebo (n=73)
Number assessed	12	17

Scully M, et al. *N Engl J Med*. 2019;380(4):335-346.

IMPREVEDIBILITA' DELLA TTP: nuova recidiva, nuova storia

Donna, 51 anni

Giunge in PS nel febbraio 2024 disorientamento spaziale e stato confusionale.

APR: Pregresso intervento chirurgico per frattura esposta gamba dx, pregressi ictus ischemici con esiti nella deambulazione e nell'articolazione della parola, **pregressa diagnosi di iPTT** (2014 con recidive nel 2015, 2016 e 2018) gia' trattata con cicli di PEX e Corticosteroidi/Rituximab, in follow up presso la nostra ematologia. **Assenza di fattori di rischio CV maggiori**

Agli esami ematochimici

- Hb 9,7 gr/dl
- PLT 28,000/mm3
- LDH 1478 U/L,
- Iperbilirubinemia > indiretta
- Aptoglobina indosabile

- Striscio periferico negativo per schistociti
- in corso di ricovero ESEGUE RMN

DIAGNOSI —> RECIDIVA DI iPTT

Ricovero Medicina DEA

nelle successive immediate ore dal ricovero, si documenta attività ADAMTS13 0,3% - Ab antiADAMTS13 6,3 BU

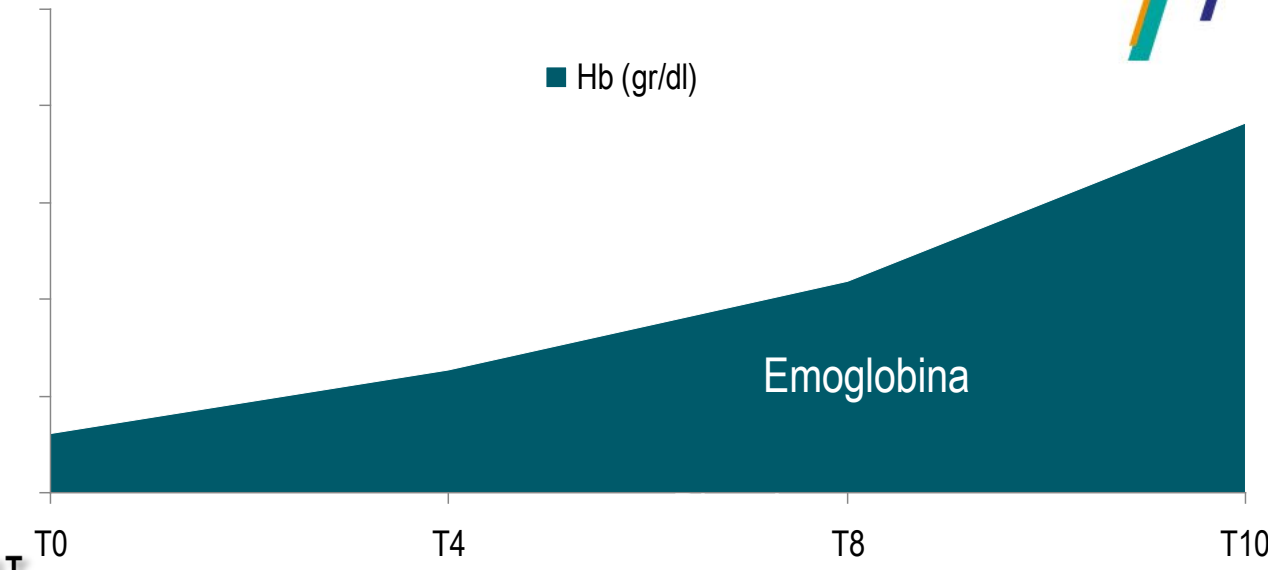
Si avvia trattamento con:

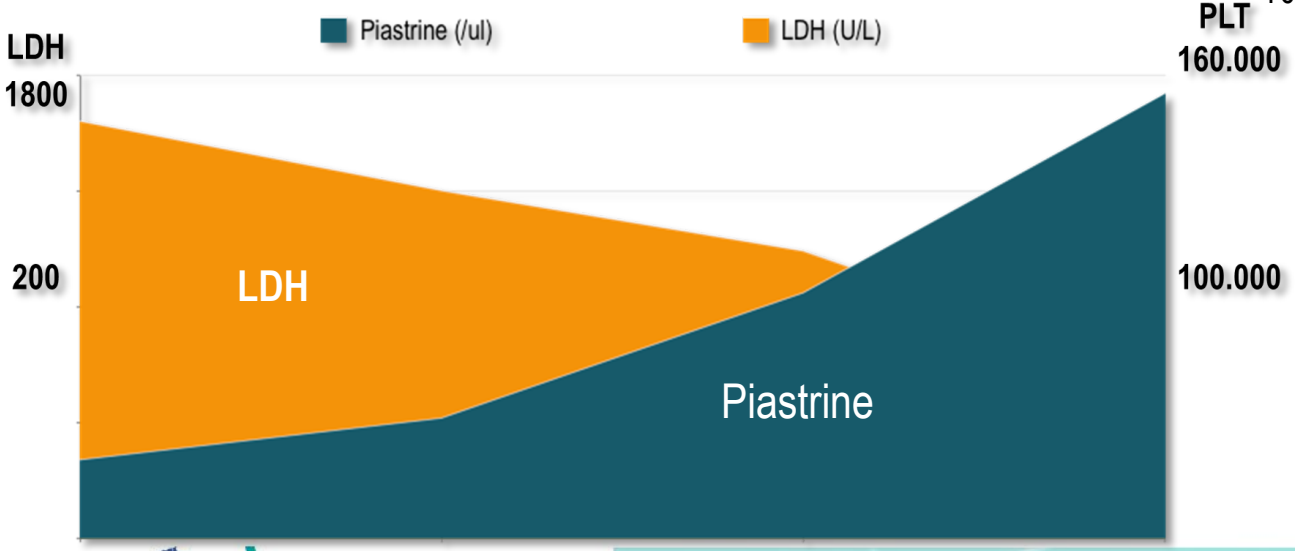
***CAPLACIZUMAB 10 mg** (dose di carico ev e, a seguire, im dopo PEX)*

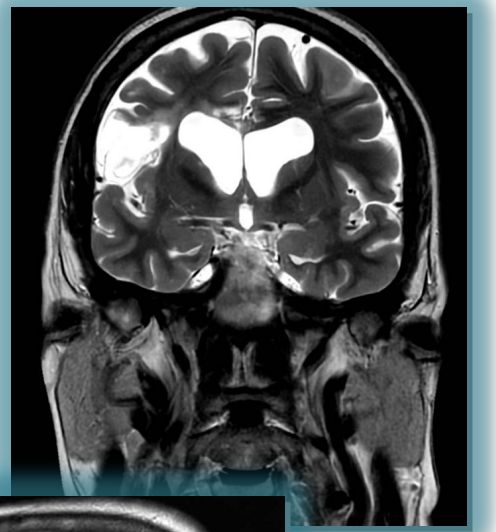
***Metilprednisolone** 1mg/Kg p.c./die*

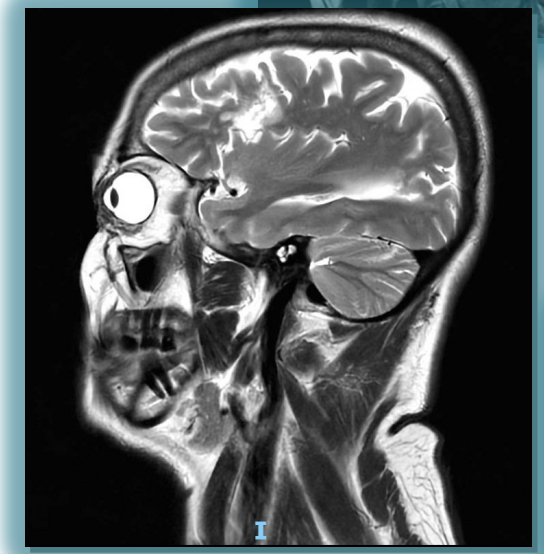
***Rituximab** 375mg/mq s.c. ogni 7 giorni per 4 settimane*

***PEX** (dopo 3 ore dalla somministrazione del Caplacizumab)*





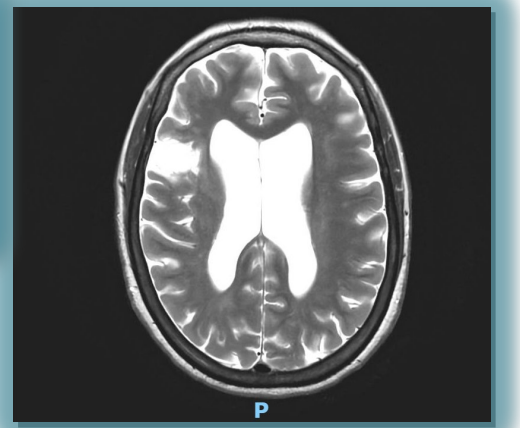


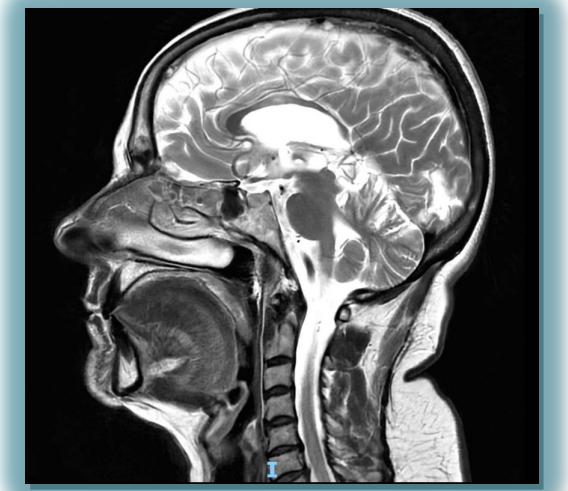


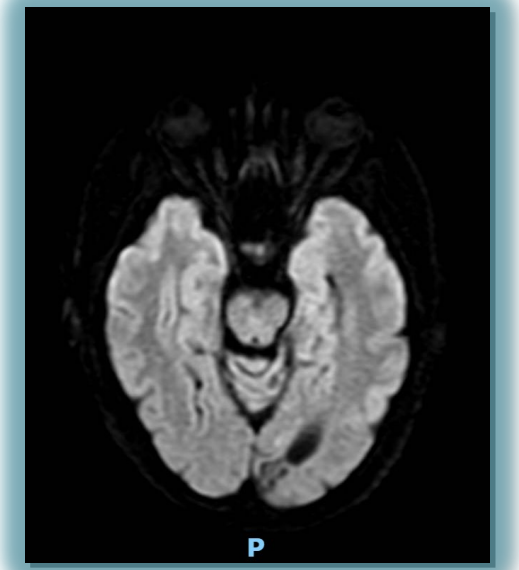
CONSULENZA NEUROLOGICA

Alla RMN encefalo evidenza di nuova lesione ischemica occipitale destra sintomatica per quadrantopsia inferiore sinistra in esame neurologico per il resto negativo.

Indicazione per ASA 100 mg/die, compatibilmente con il quadro laboratoristico.







10° giornata: 5 PEX totali

- **parziale attenuazione della sintomatologia neurologica**
- **normalizzazione dei valori di laboratorio**
- **Normalizzazione attività ADAMTS13 (58%).**

DIMISSIONE

- CAPLACIZUMAB 10 mg/die sottocute almeno per 30 gg da ultima PEX
- Aspirina 100 mg/die
- Metilprednisone a scalare

IN FOLLOW UP AMBULATORIALE:

Attività ADAMTS13 55%→ sospeso Caplacizumab dopo 32 giorni dall'ultima PEX

Il paziente prosegue controlli con esami di laboratorio periodici (secondo linee guida SIE)

Raccomandazioni SIE: il follow up nel post acuto

INDICATORE DI BUONA PRATICA CLINICA

Monitoraggio periodico dell'attività ADAMTS13

Il panel ha preso in considerazione la possibile strategia di monitoraggio clinico dei pazienti con diagnosi di PTTi mediante dosaggio periodico dell'attività ADAMTS13.

Il panel ha concordato sul seguente programma di follow-up basato sul dosaggio di ADAMTS13 nei pazienti in remissione di PTTi: mensilmente per i primi 3 mesi, successivamente ogni 3 mesi nel primo anno e ogni 6-12 mesi se stabile

Risk of relapse in iTTP

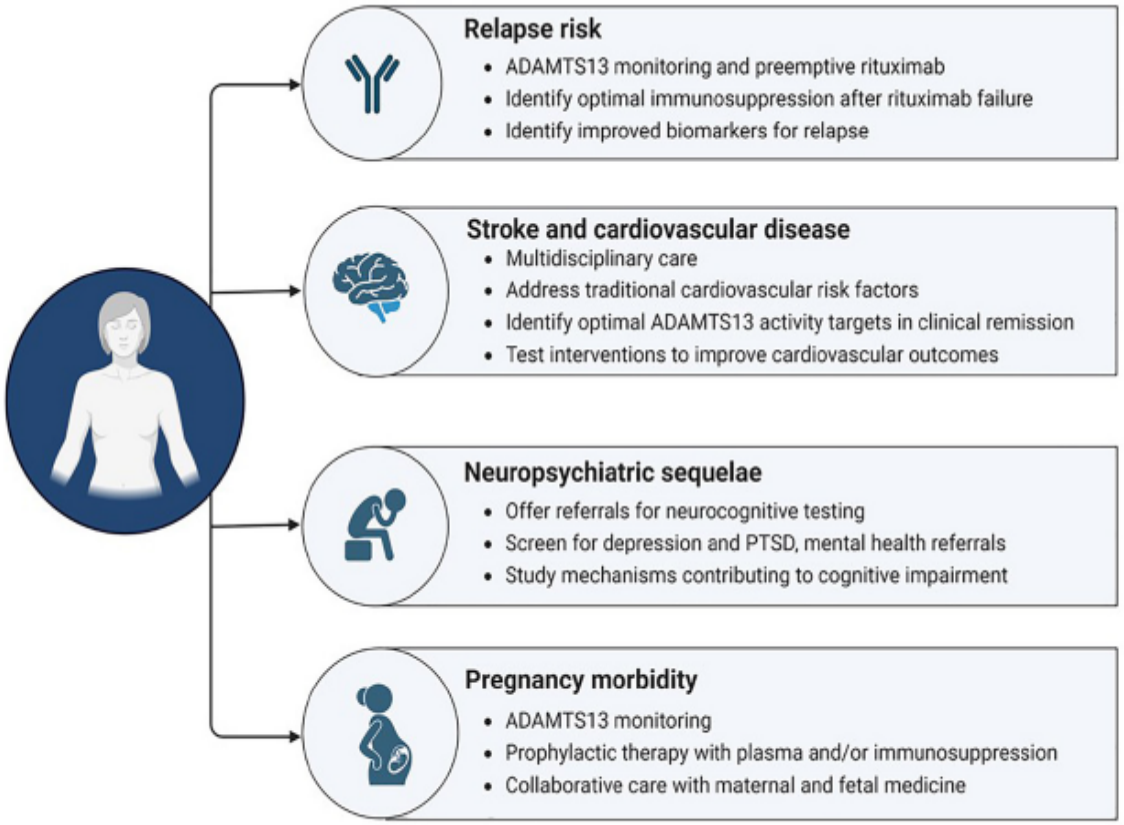


FIGURE 4
Opportunities to mitigate risk and improve long term outcomes in iTTP.

- iTTP remains a *chronic relapsing disorder*[1]
- Despite complete remission, **up to 50% of patients** who have survived an iTTP episode remain **at risk for relapse** and each relapse comes with the risk of significant morbidity and mortality[1]
- While **most relapses occur within the first 2 years** after the initial episode, relapses have been reported **even after a decade**[1]

1. Selvakumar S, Liu A and Chaturvedi S (2023) Immune thrombotic thrombocytopenic purpura: Spotlight on long-term outcomes and survivorship. Front. Med. 10:1137019.doi: 10.3389/fmed.2023.1137019

Hercules Study: First Key Secondary Endpoint

Patients With iTTP-Related Death, iTTP Recurrence, or a Major Thromboembolic Event During the Study Drug Treatment Period[1,2]

Number of patients (%)	Caplacizumab (n=72)[a]	Placebo (n=73)
Total number of patients with at least one of the events[b]	**9 (12.0)**	**36 (49.0)**
iTTP-related death[c]	0 (0.0)	3 (4.0)
Recurrence of iTTP[d] (exacerbation)	**3** (4.0)	**28** (38.0)
At least one treatment-emergent major thromboembolic event[b]:	6 (8.0)	6 (8.0)
Cerebrovascular accident	2 (2.8)	3 (4.1)
Myocardial infarction	1 (1.4)	1 (1.4)
Pulmonary embolism	1 (1.4)	0 (0.0)
Deep venous thrombosis (spontaneous)	0 (0.0)	1 (1.4)
Deep venous thrombosis (catheter-associated)	3 (4.2)	2 (2.7)
***P* value**	**0.001**	

- aPercentages are based on 71 patients entering the study drug treatment period. bPatients could have more than one event. cAdjudication of iTTP-related death and major thromboembolic events by a blinded independent committee. dRecurrence = recurrent thrombocytopenia after initial recovery of platelet count, requiring reinitiation of daily plasma exchange. iTTP, immune-mediated thrombotic thrombocytopenic purpura.

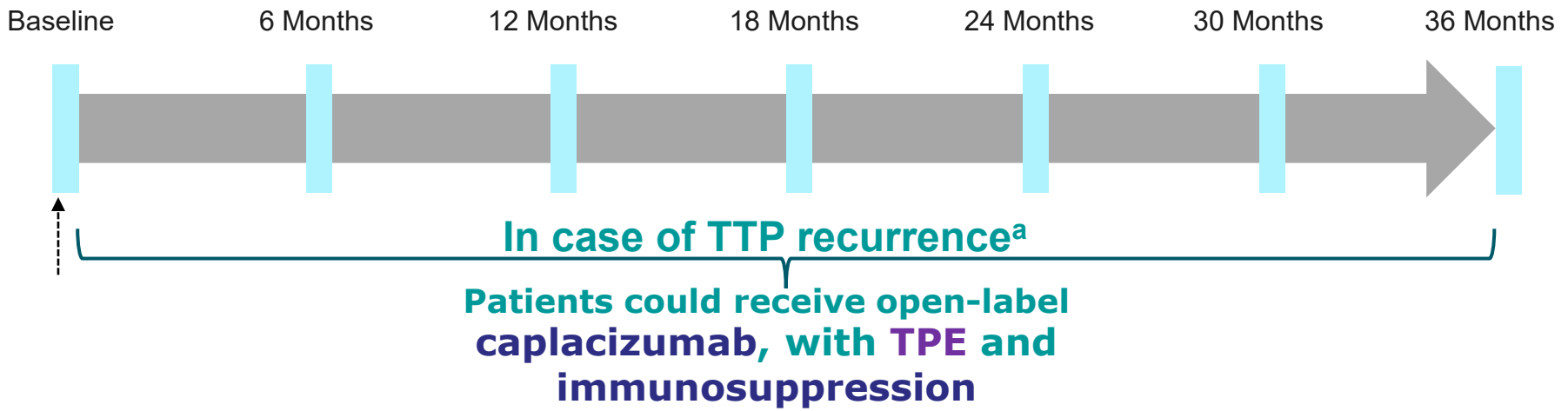
1. Scully M, et al. N Engl J Med. 2019;380(4):335-346. 2. Sanofi Genzyme Data on File. ALX0681-C301 HERCULES v2.0. June 2018.

Post-HERCULES STUDY

Long-term follow-up of patients treated with caplacizumab and safety and efficacy of repeat caplacizumab use: Post-HERCULES study

Scully et al. J Thromb Haemost. 2022;20:2810–2822.

- **Follow-up of patients who completed the Phase 3 HERCULES study**
- To evaluate safety and efficacy of repeated use of caplacizumab in patients with recurrence of aTTP
- Patients were invited to attend twice-yearly visits for **3 years**



aTTP, acquired thrombotic thrombocytopenic purpura; FU, follow-up; TPE, therapeutic plasma exchange; TTP, thrombotic thrombocytopenic purpura.
aIn case of recurrent thrombocytopenia requiring re-initiation of daily TPE during an ongoing recurrence period, a new visit cycle was started, with a recurrence visit on the day of the new recurrence followed by all subsequent visits.

TTP-Related Events During Post-HERCULES

Recurrence (all relapses):

- ❑ Caplacizumab group: 8%
- ❑ TPE+IST group: 28%

Trend towards **fewer TTP-related events** in those randomized to caplacizumab+TPE+IST

All first and second relapses treated with Capla during the study period resolved, **including those with repeated use**

Resolution of TTP episodes with caplacizumab occurred within approximately **5 days**

	Randomized to caplacizumab +TPE+IST (n=49)	Randomized to TPE+IST (n=29)
TTP-related events	4 (8)	11 (38)
TTP-related death[a]	0	1 (3)[b]
Recurrence of TTP	4 (8)	8 (28)
≥1 major TE event (excluding TTP)	0	3 (10)

.

Efficacy ITO population = patients in the ITO population who did not experience an aTTP recurrence in HERCULES or prior to the beginning of post-HERCULES.
aTTP, acquired thrombotic thrombocytopenic purpura; IST, immunosuppressive therapy; ITO, intension-to-observe; TE, thromboembolic event; TPE, therapeutic plasma exchange; TTP, thrombotic thrombocytopenic purpura.
[a]Patients with a recurrence of aTTP in post-HERCULES are analyzed up to their first recurrence in post-HERCULES. [b]A patient who never received caplacizumab died after having a TTP recurrence.

Safety Outcomes During **Repeat Caplacizumab Use**

Repeat Use Population (n=9): Patients treated **at least twice** with caplacizumab, because they 1) received caplacizumab in HERCULES and were treated again in post-HERCULES, or 2) were treated at least twice in post-HERCULES

TEAEs during first recurrence:

Recurrence population, n (%)	Repeat caplacizumab use (n=9)
≥1 TEAE	8 (89)
≥1 treatment-related TEAE	6 (67)
≥1 serious TEAE[a]	4 (44)
≥1 treatment-related serious TEAE	1 (11)
≥1 TEAE leading to death	**0**
≥1 TEAE leading to study drug interruption	2 (22)
≥1 TEAE leading to study drug withdrawal	1 (11)
TEAE of special interest	
≥1 bleeding event[b]	**5 (56)**
≥1 thromboembolic event	**0**
≥1 hypersensitivity reaction	2 (22)
≥1 treatment-related hypersensitivity reaction[c]	1 (11)

The safety profile of caplacizumab during repeated use was similar to that observed in the TITAN and HERCULES clinical trials and in real-world studies

In line with previous studies and with its mechanism of action, caplacizumab during its repeat use was associated with bleeding risk; however, **most bleeding events were non serious.**

No major thromboembolic events or TTP-related deaths were reported with repeated caplacizumab use

Treatment-related serious TEAEs:

- Genitourinary or gastrointestinal bleeding (n=2; 22.2%)

Repeat use population = patients treated at least twice with caplacizumab, because they 1) received caplacizumab in HERCULES and were treated again with caplacizumab at least once in post-HERCULES, or 2) were treated at least for 2 recurrent episodes with caplacizumab in post-HERCULES.

[a]Serious TEAEs were bleeding events of genitourinary or GI tracts. [b]Based on Standardized MedDRA Query, with exclusion of TTP. [c]Based on Standardized MedDRA Query.

GI, gastrointestinal; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event; TTP, thrombotic thrombocytopenic purpura.

IMPREVEDIBILITA' DELLA TTP: uscire dal labirinto

Donna, 59 anni

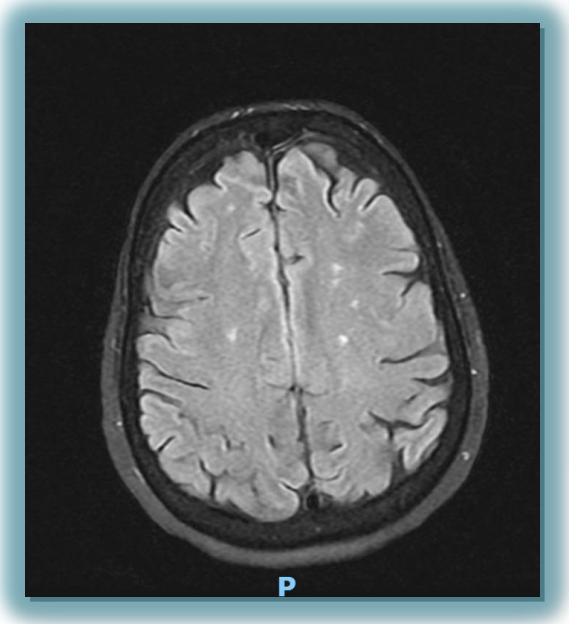
Accesso in PS per episodio sincopale preceduto da malessere specifico; all'arrivo in PS, piena ripresa dello stato di coscienza

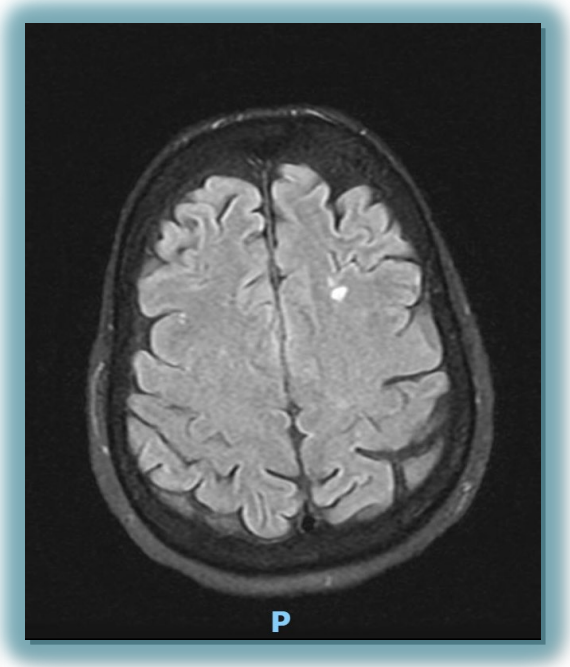
- APR: Ipertensione arteriosa e Dislipidemia, entrambe in buon controllo con terapia farmacologica.
- Esegue RMN encefalo dopo l'arrivo in Reparto Medicina DEA

Agli esami ematochimici

- Hb 6,7 gr/dl
- RB 2,08 x10^6/mm3
- PLT 7,000/mm3
- LDH 457 UI/L
- Aptoglobina 0,71 g/L (v.n. 0,34-2)

- Striscio periferico NEGATIVO
- Esegue RMN encefalo dopo l'arrivo in Reparto Medicina DEA





PLASMIC SCORE

Points	
Platelet count <30 × 10^9 per L	1
Haemolysis variable	1
No active cancer	1
No history of solid-organ or stem-cell transplant	1
MCV <90 fL	1
INR <1·5	1
Creatinine <2·0 mg/dL	1

Score 0–4: low risk
Score 5: intermediate risk
Score 6 or 7: high risk.

PLASMIC SCORE 7 →
high risk for PTT diagnosis

Prelievo per ADAMTS13 e anticorpi e
RICOVERO IN MEDICINA DEA
Episodio di afasia globale e sfumata ipostenia emilato sx, regredito gradualmente nell'arco di circa 2 ore

Dopo poche ore… ADAMTS 13 attività 0,7% - Ab antiADAMTS13 30BU → Diagnosi di aTTP

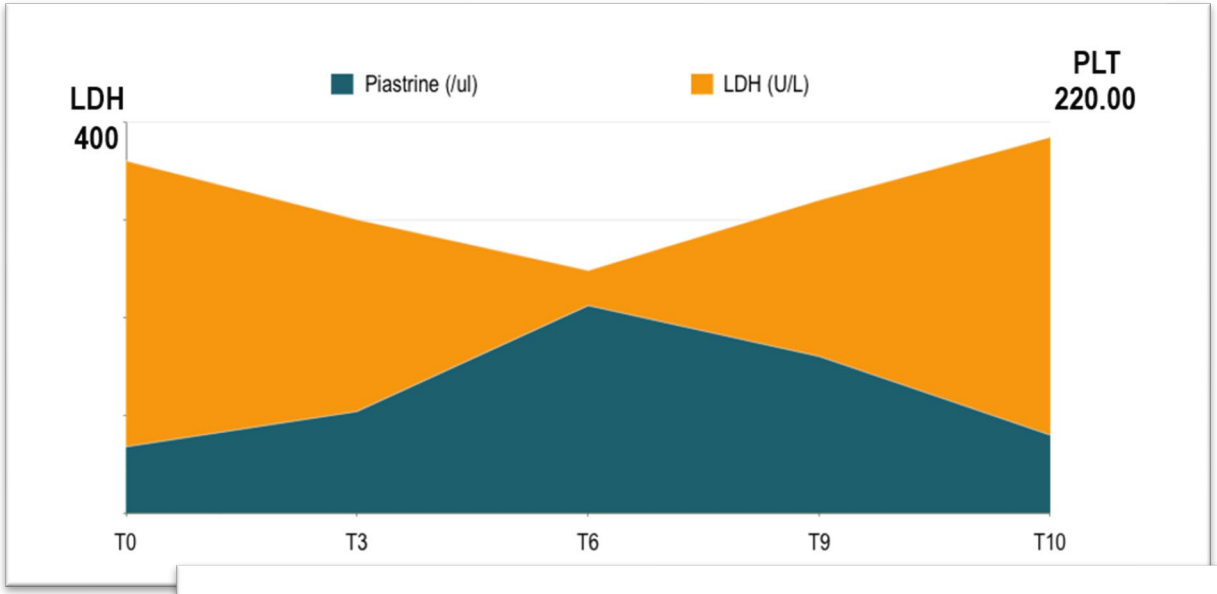
24 ore dopo l'accesso al PS:

CAPLACIZUMAB 10 mg (dose di carico ev e, a seguire, im dopo PEX)

Metilprednisolone 1mg/Kg p.c./die

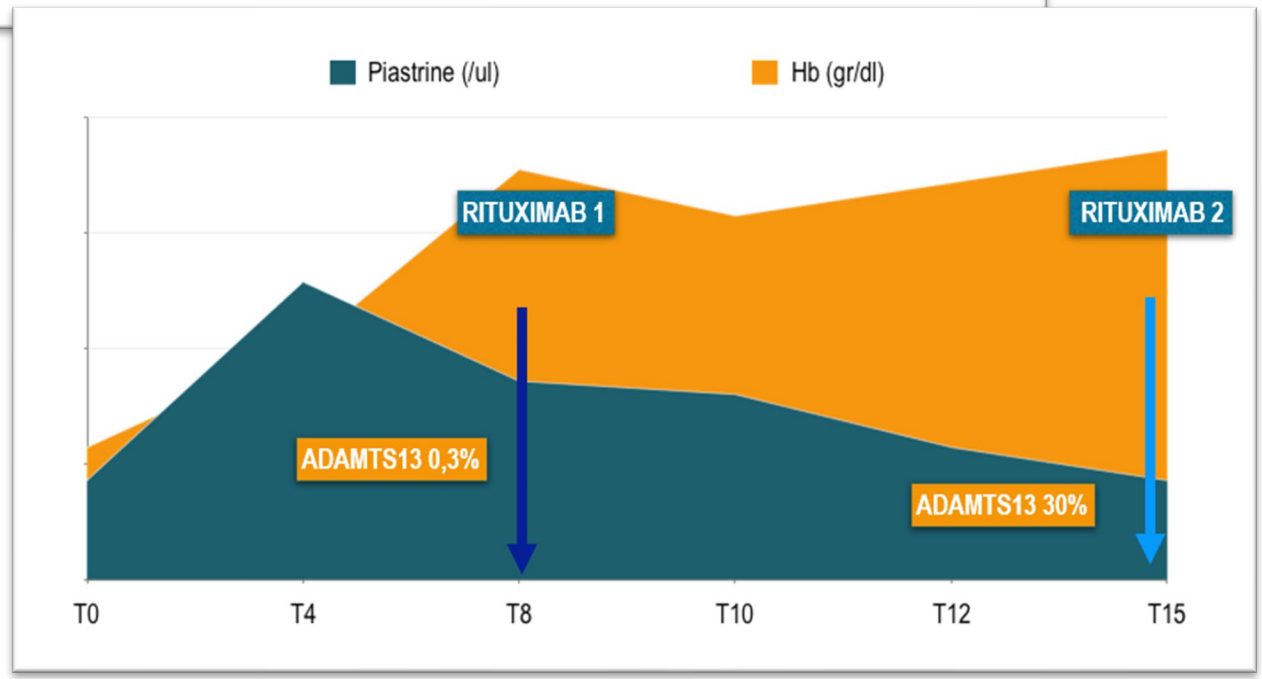
PEX (dopo 3 ore dalla somministrazione del Caplacizumab)

Caplanet sanofi



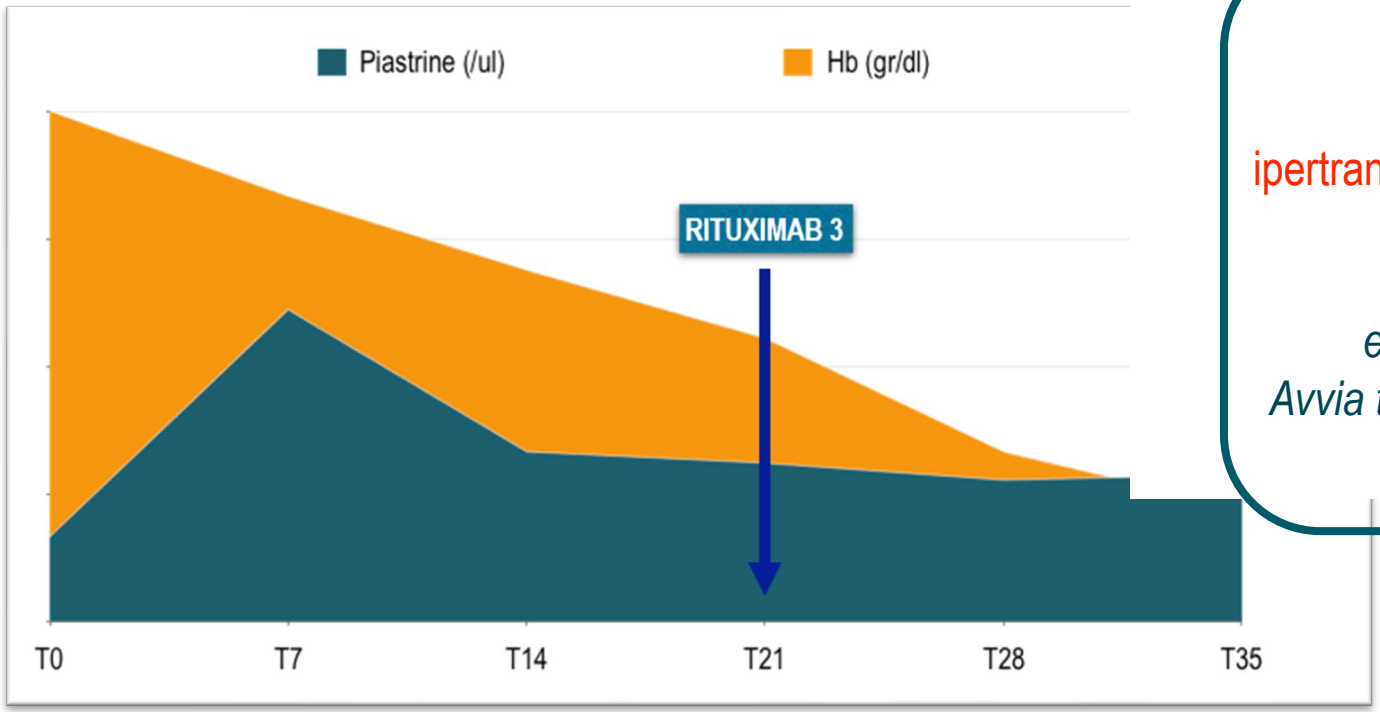
8°giorno di degenza

- **5 procedure di PEX,** seguite da unità di PFC
- PLT in riduzione progressiva (da 200.000 a 98.000)
- LDH in aumento
- ADAMTS13 attività 0,3% → si procede a richiesta di Rituximab.



15°giorno di degenza

- **Piastrinopenia ingravescente**
- **valori di LDH, bilirubina ed Hb tendenti alla normalizzazione/stabilità**
- **ADAMTS13 attività nella norma**
- **Indicazione per immunofenotipo sangue periferico**



Dal giorno 20-21 comparsa di

leucopenia ingravescente,
ipertransaminasemia fluttuante, linfoadenomegalie laterocervicali, febbre

esegue esami laboratoristici di II livello
Avvia terapia con GCSF (Filgrastim 1 fiala sc/die)

Consulenza infettivologica

CMV - DNA		
- CMV-DNA	5482.0 **	Copie/mL
-	**Presenti**	

- Ganciclovir 350 mg x 2 die ev
- Non alterazioni alla BOM
- Non emopatia primitiva
- **Blocco maturativo comparto mieloide intermedio aspecifico e secondario allo stato settico →pancitopenia**
- Tazocin - Cancidas - Cubicin

Nuova **emocoltura positiva** per Salmonella gruppo D.
Sospende Cubicin passa a Bactrim (continua Merrem, Cancidas e Ganciclovir)
(5 marzo): Nuova emocultura positiva alla salmonella gruppo D, Urinocultura positiva alla Klebsiella multiresistente.
(15 marzo): dopo risoluzione Salmonella, riattivazione da CMV.

L'IMPREVEDIBILITA' DELLA TTP: uscire dal labirinto

DIMISSIONI in data 20 marzo

Buon compenso emodinamico

- Emocromo nella norma
- ADAMTS13: **24,7%**

MA…

- 7 gg dopo → **NUOVO ACCESSO PS** per comparsa di febbre a carattere settico associato a dolori articolari (> AA II) con impotenza funzionale.

Agli esami ematochimici

- ADAMTS13: 33,9%
- Proteina C reattiva Urgenza: 68,98 mg/L
- Procalcitonina Urgenza: 9,5 ng/mL

- Hb 10,3 gr/dl
- PLT 176,000/mm3
- Globuli bianchi 4,520/mm3

- **STATO SETTICO** CON EMOCOLTURA POSITIVA PER **SALMONELLA TYPHI GRUPPO D**, complicata da artrite settica dell'anca sx; **RIATTIVAZIONE DI CMV**
- Dimissione 40 gg dopo