Thrombotic Microangiopathy and Malignancy

Arand Pierce, MD

Puget Sound Blood Center
research | medicine | blood & tissue services

Exemplary Case

- 58 y/o F with recurrent breast CA
  - L Breast resected in 2005
    - Triple negative
  - Currently involves chest wall and lungs, with extensive hilar, mediastinal, and axillary LAD
  - BM Bx negative for malignancy

Puget Sound Blood Center

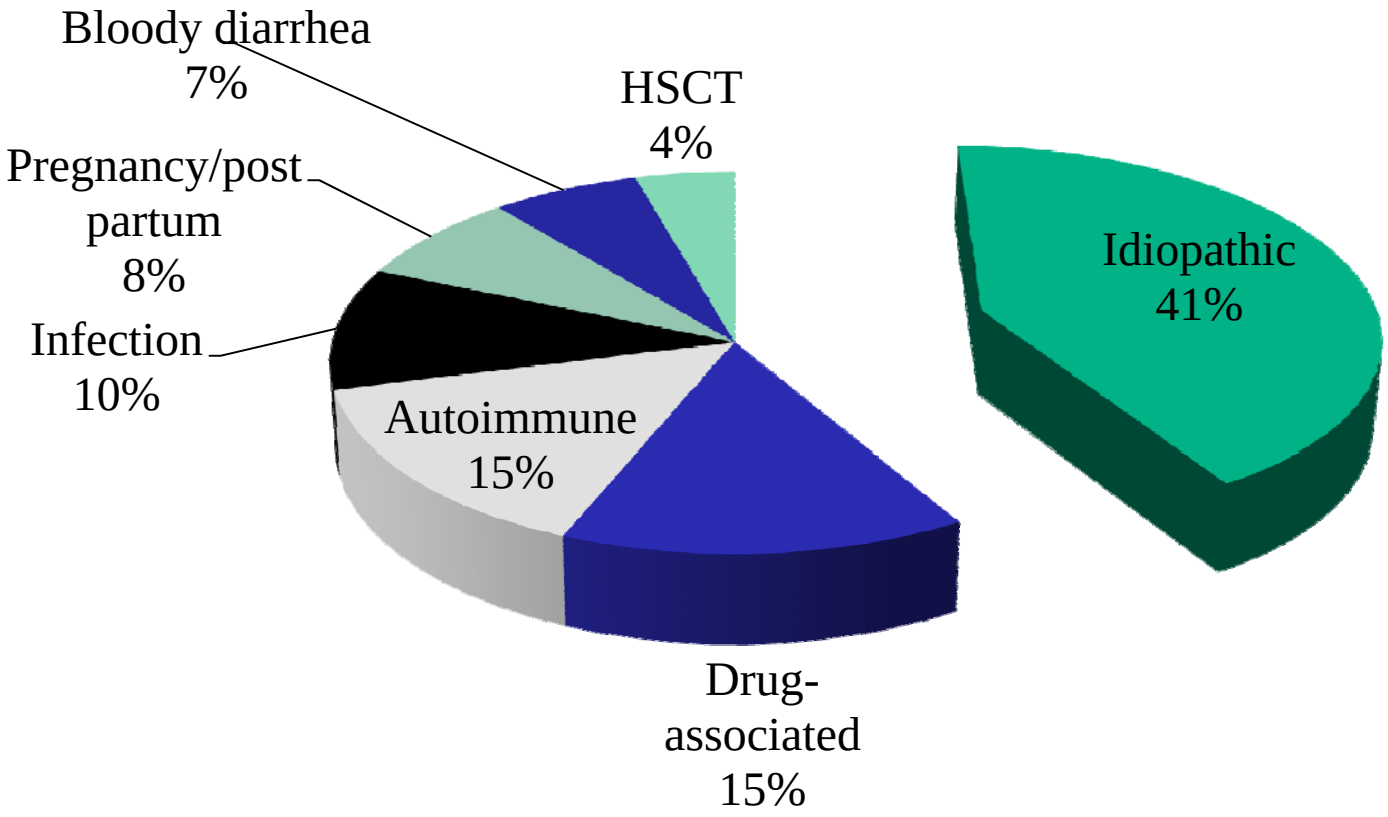
- Noted to have hemolytic anemia
  - C/o substernal chest discomfort
  - Haptoglobin <7
  - Retic 16%
  - Received 3U of pRBC
- 3 days later, during 1st cycle of Cytoxan/Taxotere
  - C/o SOB and evolving rash over L breast
  - Lungs CTA. No cough or pleurodynia
- Admit 7d later with progressive SOB ("ARDS vs. TRALI?") and AKI
  - Hct=21.2 Plt=75 INR=1.5 Fib=304 Cr=3.2 LDH=537 Schistos ADAMTS13=55% Afebrile A&Ox3

One year later…

- Status post
  - Cytoxan/Taxotere
  - Adriamycin/Taxol
  - Paclitaxel x2 with progression
  - Chest wall, brain, & lumbar XRT
- Started on Doxil (Hgb=9.9, nl WBC & plts)
- Admit 2 weeks later for visual disturbances, anemia, thrombocytopenia, and SOB
  - Schistos Hct=22 Plt=125 Cr=0.7 INR=1.2 Fib=482 LDH=563 ADAMTS13 not done

TPE requested…..

206 Suspected TTP/HUS Patients Receiving TPE



J Thromb Haemost. 2005;3(7):1432-6

TMA

- F>M, Black>White
  - Suspected TTP-HUS — 11 cases/million population per year
  - Idiopathic TTP-HUS — 4.5 cases/million per year
  - Severe ADAMTS13 deficiency — 1.7 cases/million per year
- Malignancy associated
  - Breast, gastric, pancreatic, lung, colon, etc. → Mucin
- Other medical conditions
  - Autoimmune, infection, bloody diarrhea prodrome, pregnancy/postpartum, HIV, HSCT
- Drugs
  - Quinine
  - Mitomycin-C
  - Cisplatin
  - Gemcitabine
  - Thienopyridines
  - Bevacizumab/sunitinib

Table 5. Comparison of patients with cancer-associated thrombotic microangiopathy with patients with an idiopathic TMA

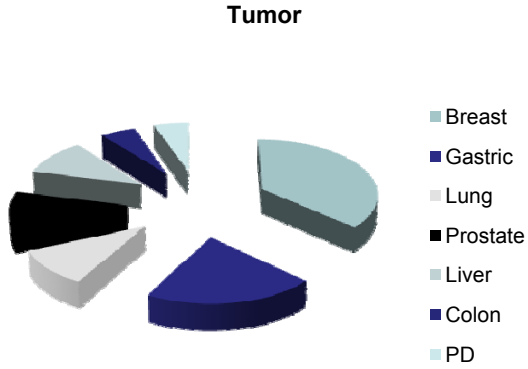
	Idiopathic TMA (n = 134)	Cancer-associated TMA (n = 20)	p-value
Clinical and biological features			
Sex (% female)	74.6	65.0	ns
Age (years)	41 (29–55)	62 (53–70)	<.0001
Past history of cancer (%)	3.0	45.0	<.0001
Symptoms duration (days)	7 (2–14)	30 (7–30)	<.0001
Clinical symptoms (%)			
Fever	34.6	25.0	ns
Weight loss, weakness, anorexia	8.9	75.0	<.0001
Asthenia	39.5	95.0	<.0001
Bone pain	0.8	50.0	<.0001
Abdominal pain	17.4	20.0	ns
Thoracic pain	3.3	15.0	ns
Dyspnea	19.7	55.0	<.01
Current or past history of diarrhea	33.1	10.0	<.05
Cerebral manifestations	69.3	45.0	<.05
Biological results			
Hemoglobin level (g/dl)	7.8 (6.4–9.4)	8.3 (6.9–9.3)	ns
Reticulocyte ($\times 10^9$/l)	122 (77–288)	193 (143–259)	ns
Platelet count ($\times 10^9$/l)	19 (10–38)	48 (21–73)	<.001
Creatinine (μM)	113 (80–225)	74 (68–102)	<.01
LDH (× N upper value)	5.0 (3.0–7.7)	4.5 (3.2–8.9)	ns
ADAMTS13 (% activity)	0 (0–13)	39 (0–70)	<.0001
D-dimers >4 (%)	32.1	100.0	<.0001
Fibrinogen level (g/l)	3.5 (2.6–4.4)	2.4 (1.7–3.4)	<.01
Prothrombin rate	84 (74–92)	69 (61–76)	<.0001
Myelemia (%)	33.8	90.0	<.0001
Erythromyelemia			
Positive (%)	17.5	85.0	<.0001
Median (% WBC)	2 (1–5)	6 (3–21)	<.01
Evolution			
Death (within 2 years) (%)	10.5	95.0	<.0001
Death (within 30 days) (%)	8.2	50	<.0001

Groups and data recording are detailed in Subjects, Materials, and Methods. Values are expressed in percentage of subjects or in median numbers (interquartile range). Statistical comparisons were made using Wilcoxon two-sample test continuous variables, and chi-square test or Fisher's exact test was used to compare binary data.
Abbreviations: ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; LDH, lactate dehydrogenase; ns, nonsignificant; TMA, thrombotic microangiopathy; WBC, white blood cells.

20 CA-TMA

- All with recently recurrent solid tumors with no chemo in past 4 months
- All improvements paralleled chemo initiation
  - None attributed to TPE
- 50% 30d mortality
- 95% 2y mortality

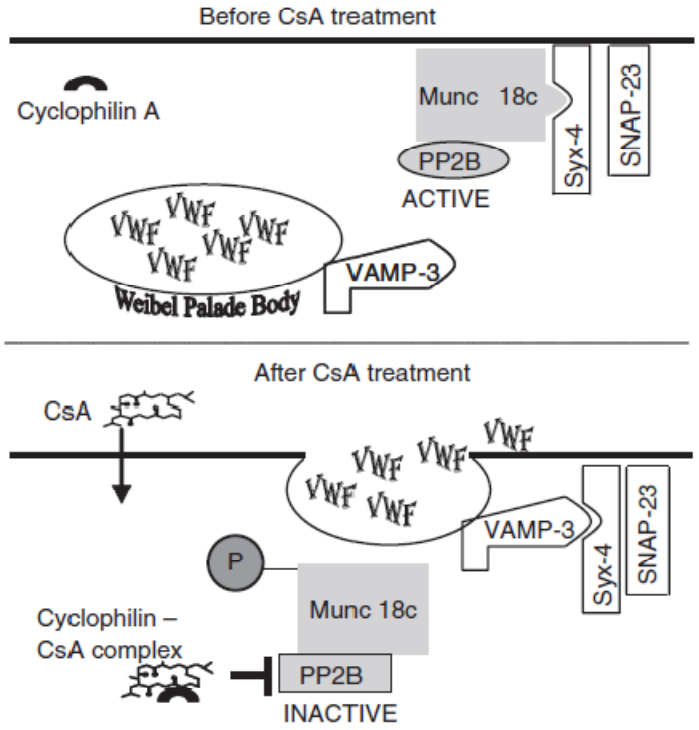
Control: 134 idiopathic TTP pts



Oncologist. 2009 Aug;14(8):769-79

Mechanisms of TMA

- Deficiency of ADAMTS-13
  - "Idiopathic" TTP
  - Ticlopidine/clopidogrel
- Increased production or retention of large vWF multimers
  - HUS
  - Cyclosporine/Tacrolimus
  - Systemic Inflammation



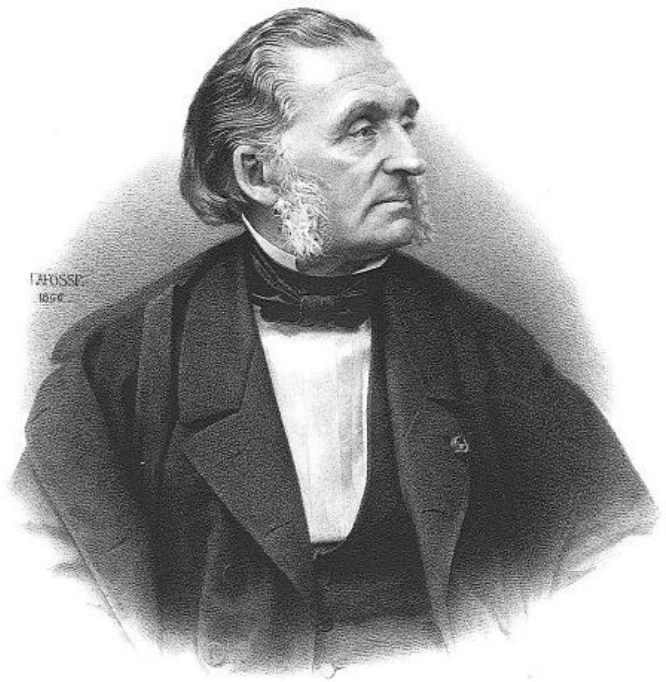
J Thromb Haemost. 2009 Jun;7(6):1009-18.

Mechanisms of TMA

- Endothelial damage
  - HUS
  - Drugs
  - Systemic inflammation = increased oxidative stress
  - Tumor microthrombi
- Inactivation of pro-angiogenic factors (VEGF, TGF-ß)
  - Bevacizumab
  - ↑sVEGFR-1/sEndoglin (Pre-eclampsia)

Intertwined pathways

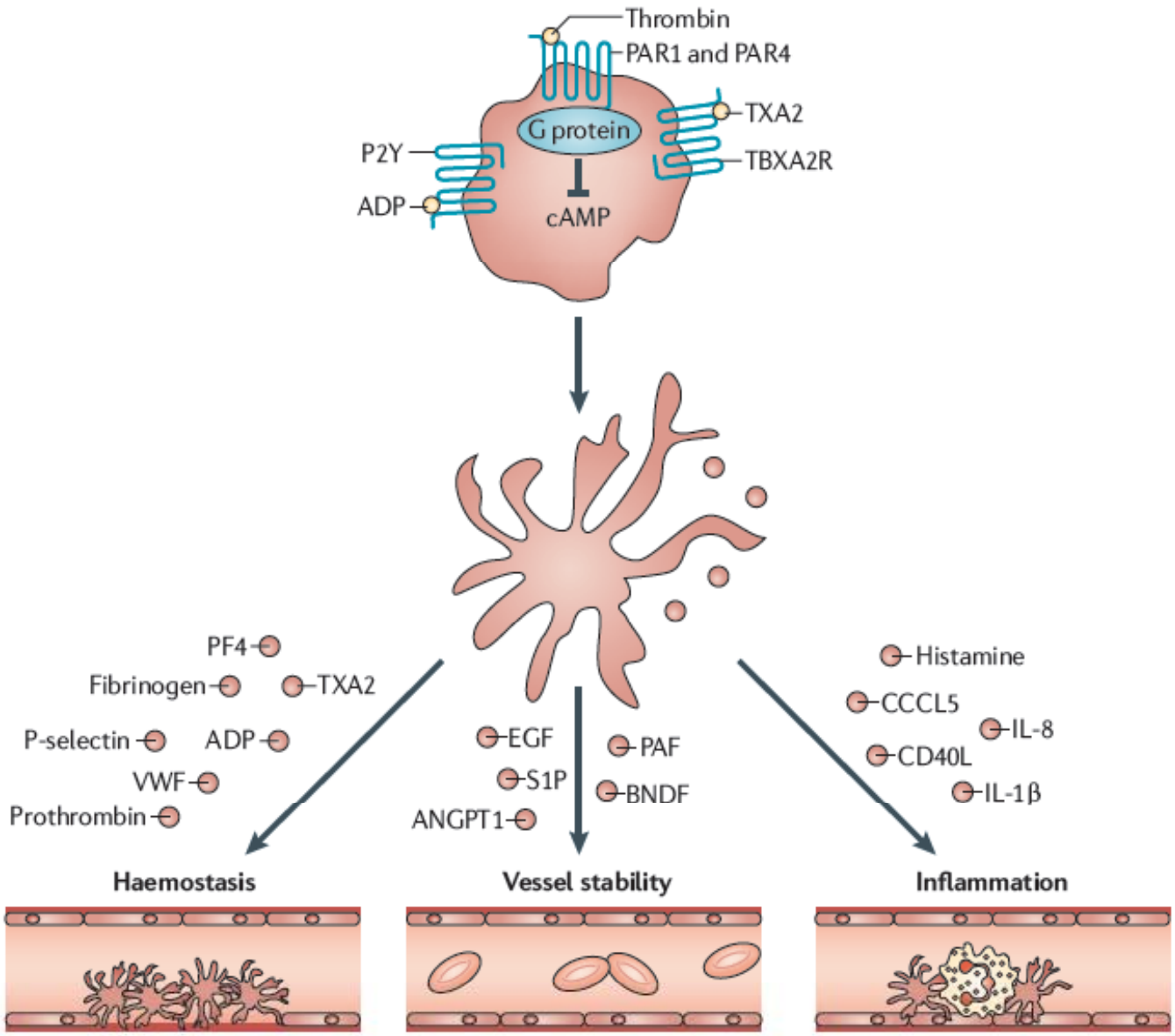
- Hemostasis
- Coagulation
- Inflammation
- Metastasis
- Endothelial regulation



MA-TMA

The Players

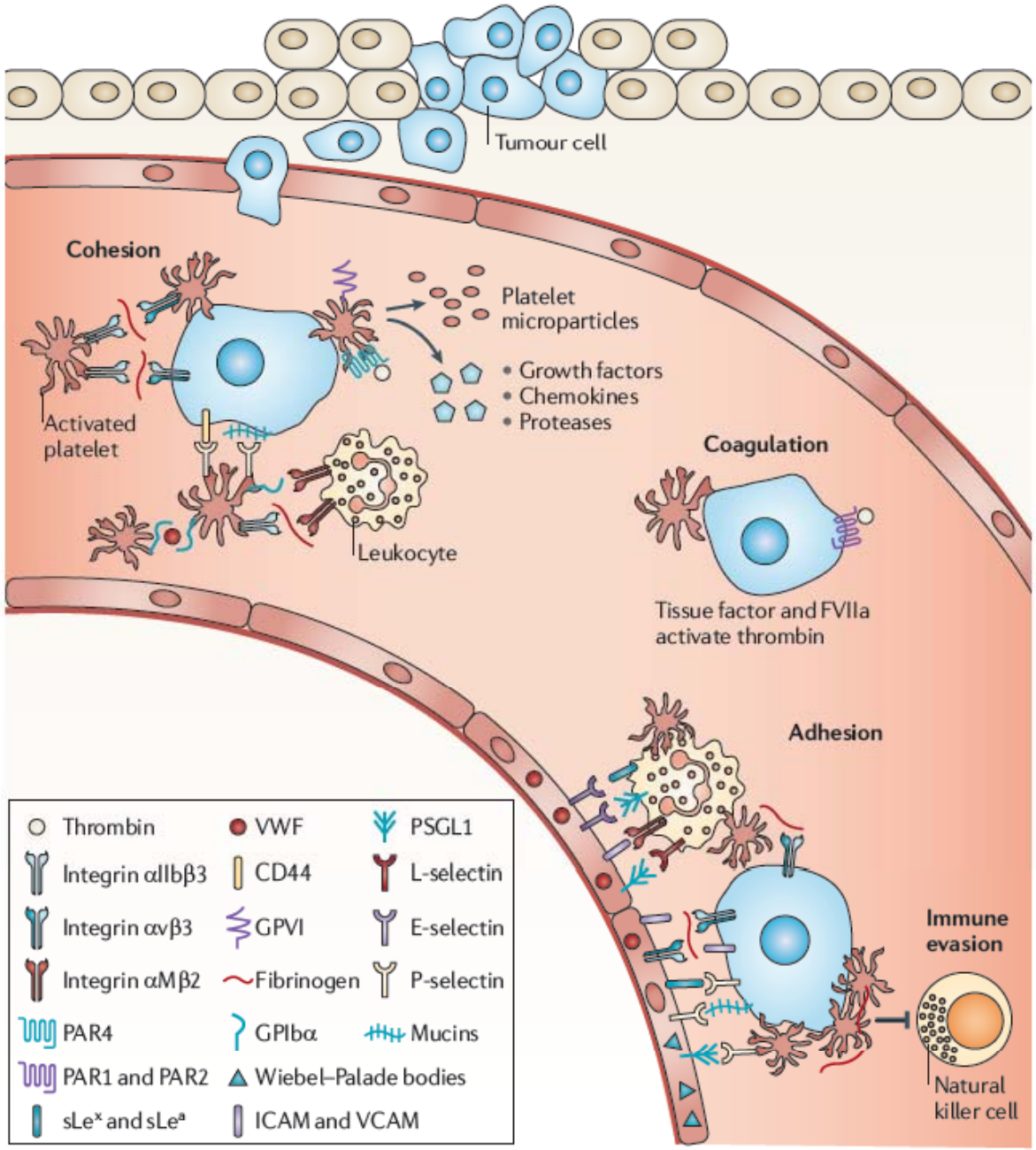
- Tumor cells
- Mucin
- Platelets
- Neutrophils
- Endothelium
- vWF
- VEGF



Nat Rev Cancer. 2011 Feb;11(2):123-34

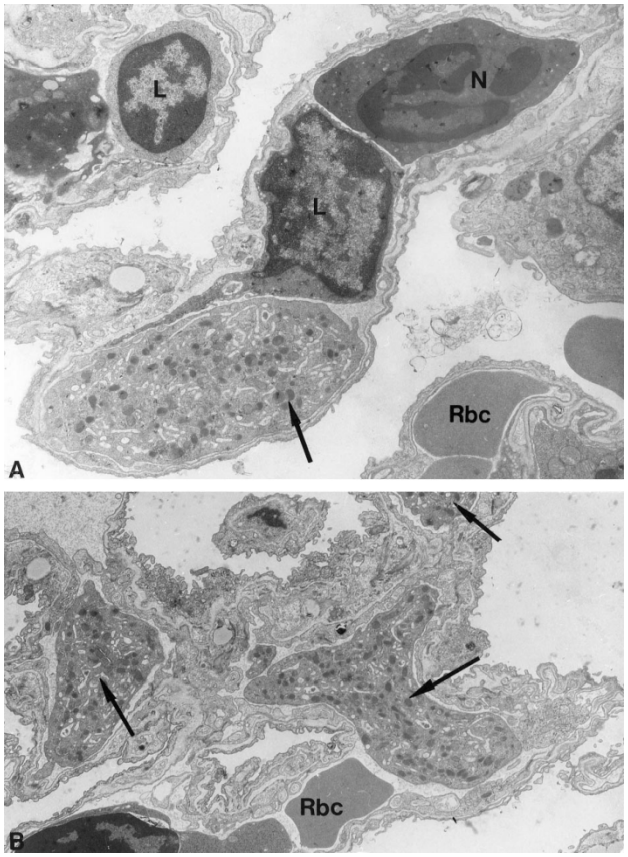
Plt activation in tumor metastasis

- Plt-tumor aggregates facilitate:
  - Immune evasion
  - Microvascular arrest at distant sites, in concert with inflammation
  - Microvascular extravasation
- Evidence of a “malignant Plt phenotype”
  - Selectively increased pro-angiogenic, pro-thrombotic, and pro-tumor growth constituents
    - ➢ Altered megakary-opoiesis vs. selective uptake/ excretion

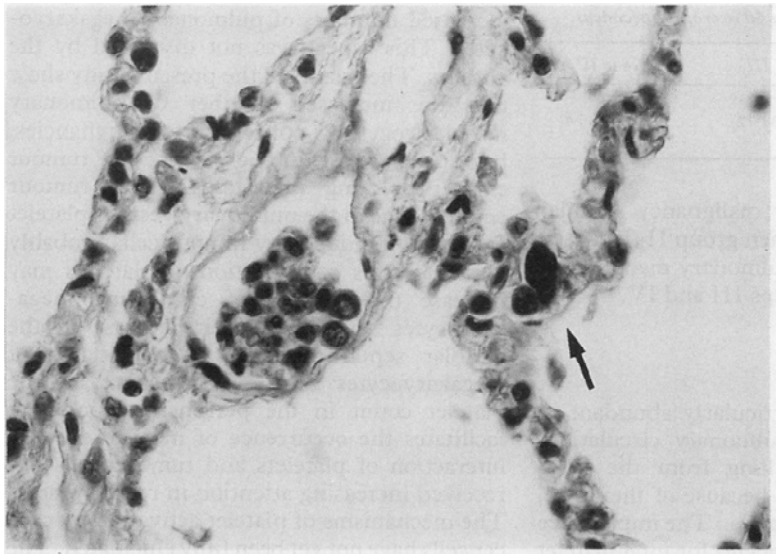


Nat Rev Cancer. 2011 Feb;11(2):123-34

Pulmonary tumor microthrombi are frequently radiologically occult and associated with increased extramedullary megakaryocytes



Am J Pathol 2000;157:69-74



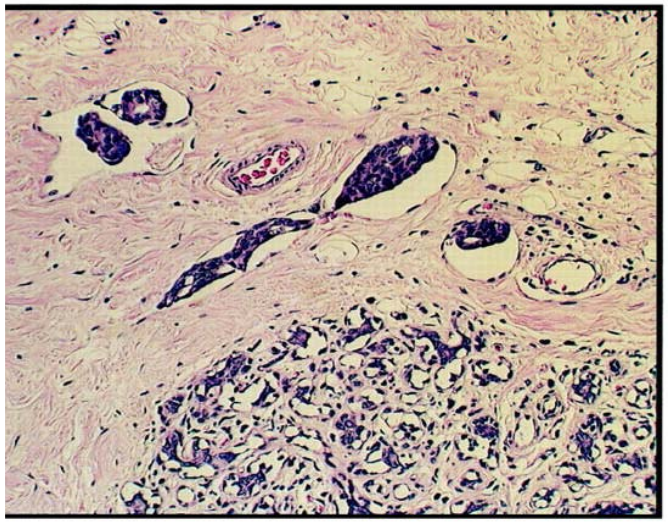
Numbers of megakaryocytes per 500 high power fields found in 40 necropsy specimens

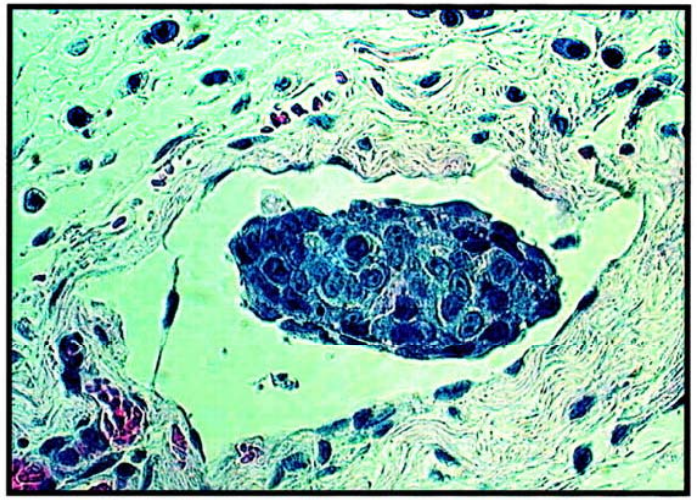
	Group I	*Group II*	*Group III*	*Group IV*
Range	8–36	5–57	11–127	39–170
Mean (SD)	16·8 (9·25)	21·5 (17·62)	75·4 (34·72)	79·7 (48·24)
Median	14	14·5	77·5	60·5

J Clin Pathol 1992;45:140–142

Carcinoma progression & alterations of cell surface glycosylation

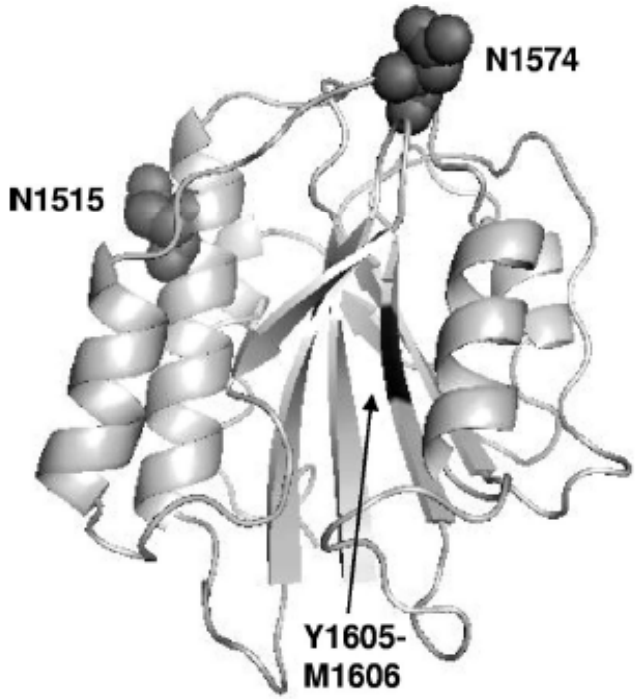
- Highly sialylated or branched sugar chain expression &/or large amounts of mucins have a poor prognosis related to high rates of metastasis
  - sLe(a) [CA19-9]
  - sLe(x) [CD15]
- Carcinoma mucins carrying sLe(x/a) are ligands for all 3 members of the selectin family of cell adhesion molecules





Attenuated sLe(x/a) in inflammatory breast carcinoma abrogates endothelial interaction

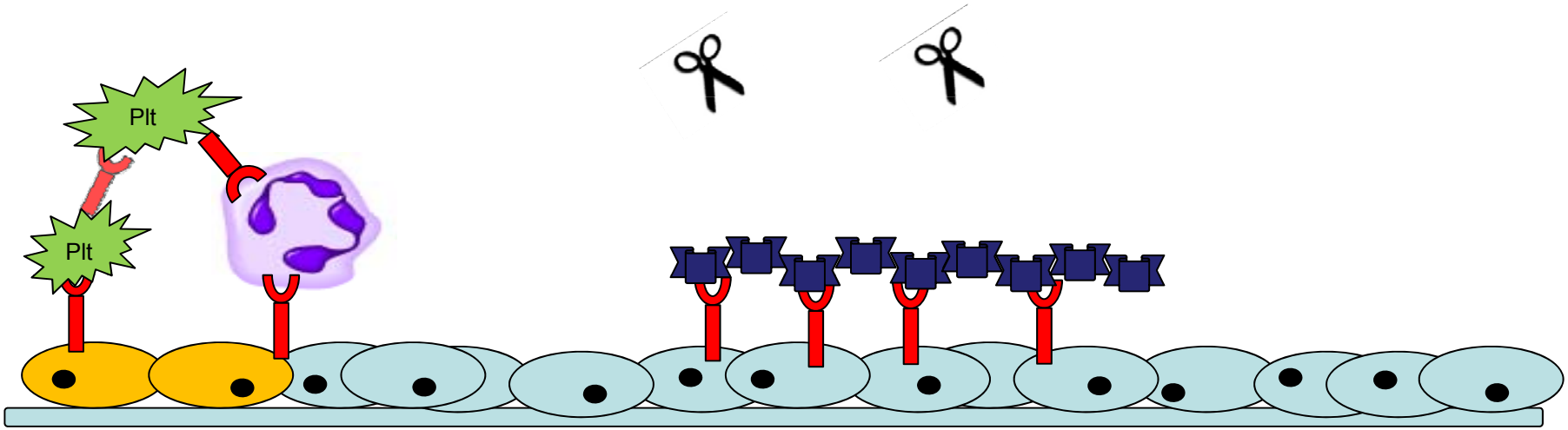
Am J Pathol. 2002 Aug;161(2):619-28



"…the N-linked glycan component of VWF has major effects in determining the conformation of VWF and its susceptibility to ADAMTS13 binding and cleavage."

Blood. 2008 Mar 15;111(6):3042-9

Physiologic conditions



P-selectin facilitates ulVWF formation and its degradation

Blood. 2004 Mar 15;103(6):2150-6.

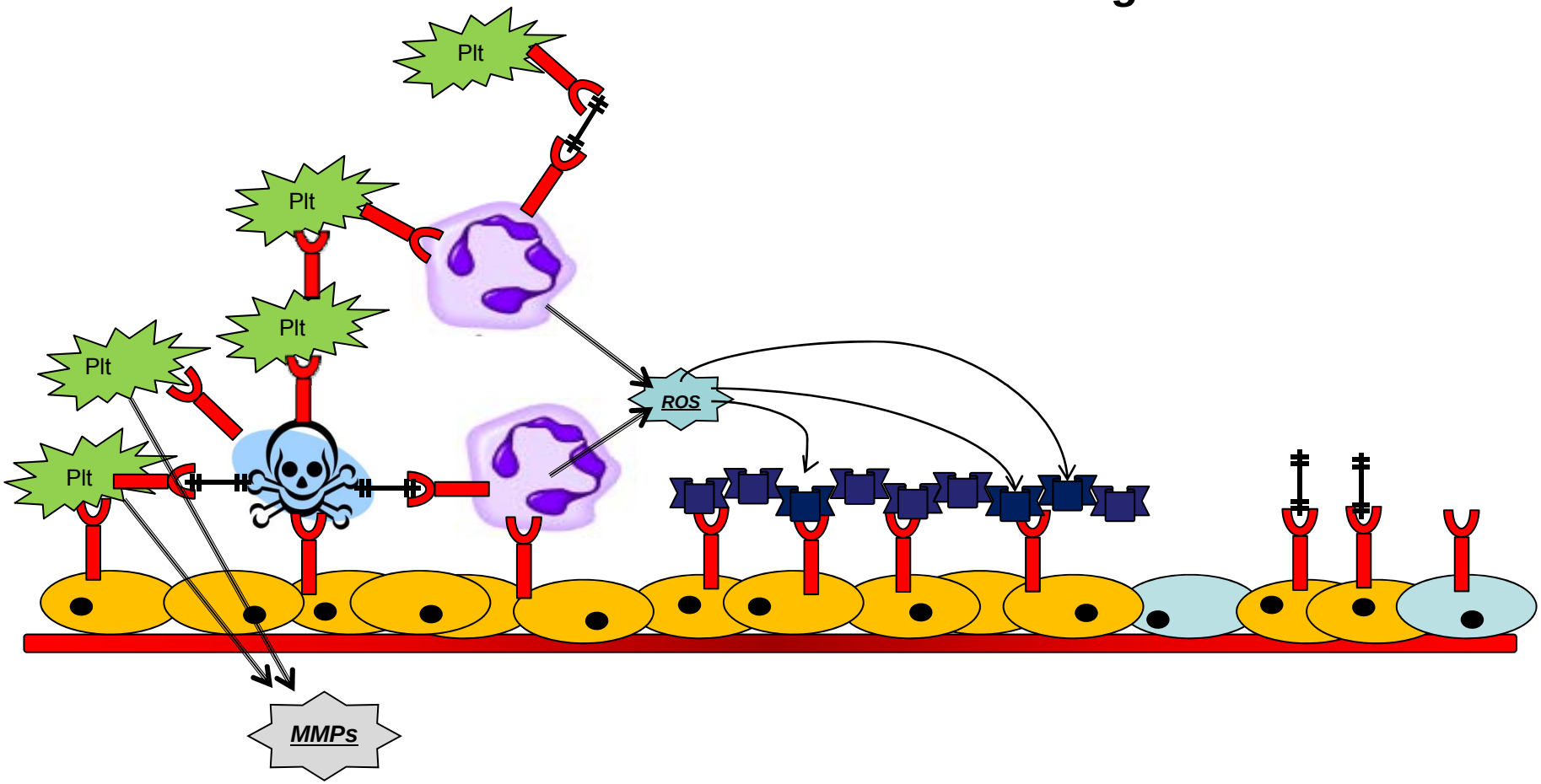
ADAMTS13

P-Selectin

vWF

Mucin [sLe(x/a)]

Inflammation augments thrombosis



ADAMTS13

P-Selectin

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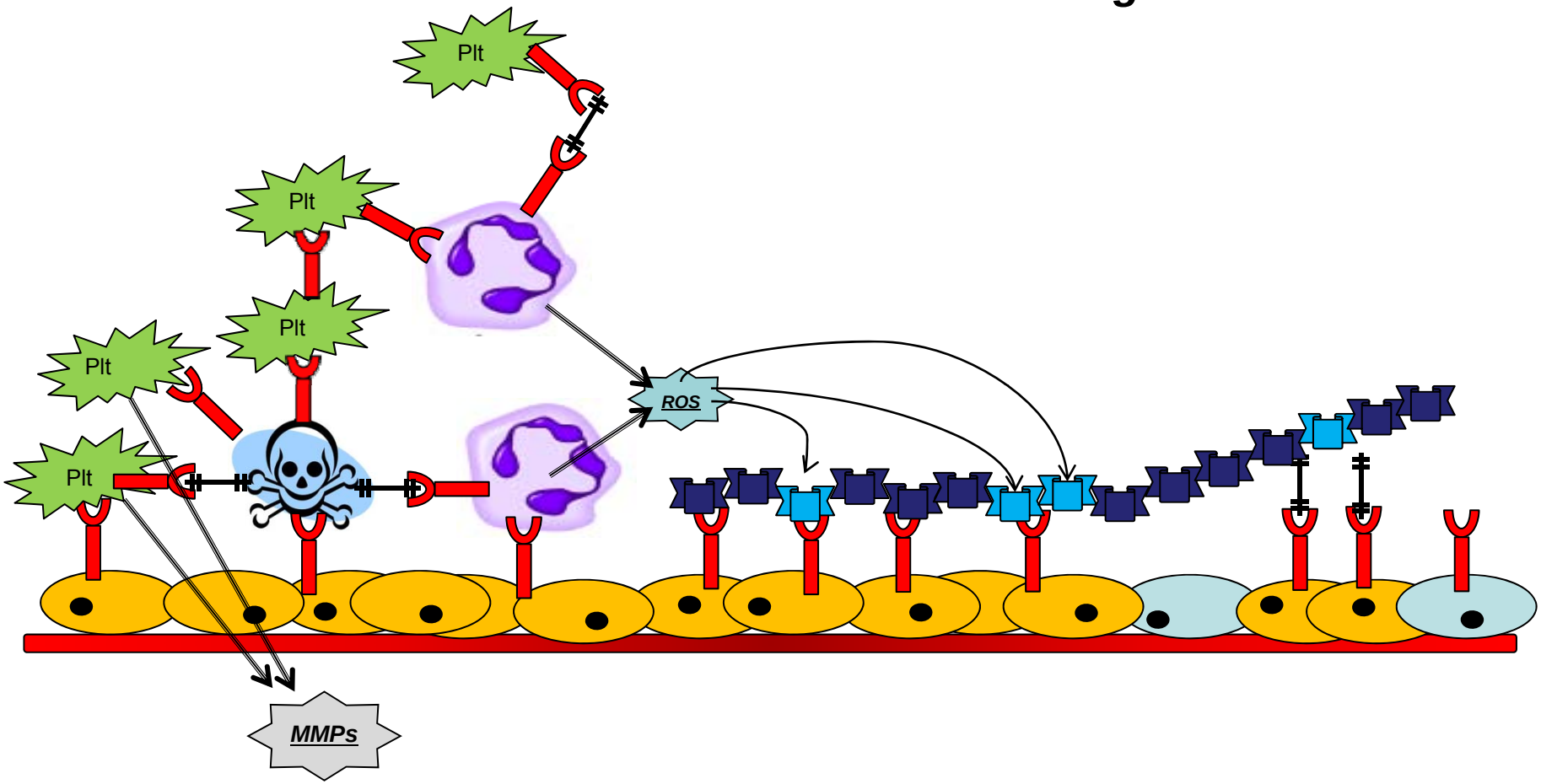
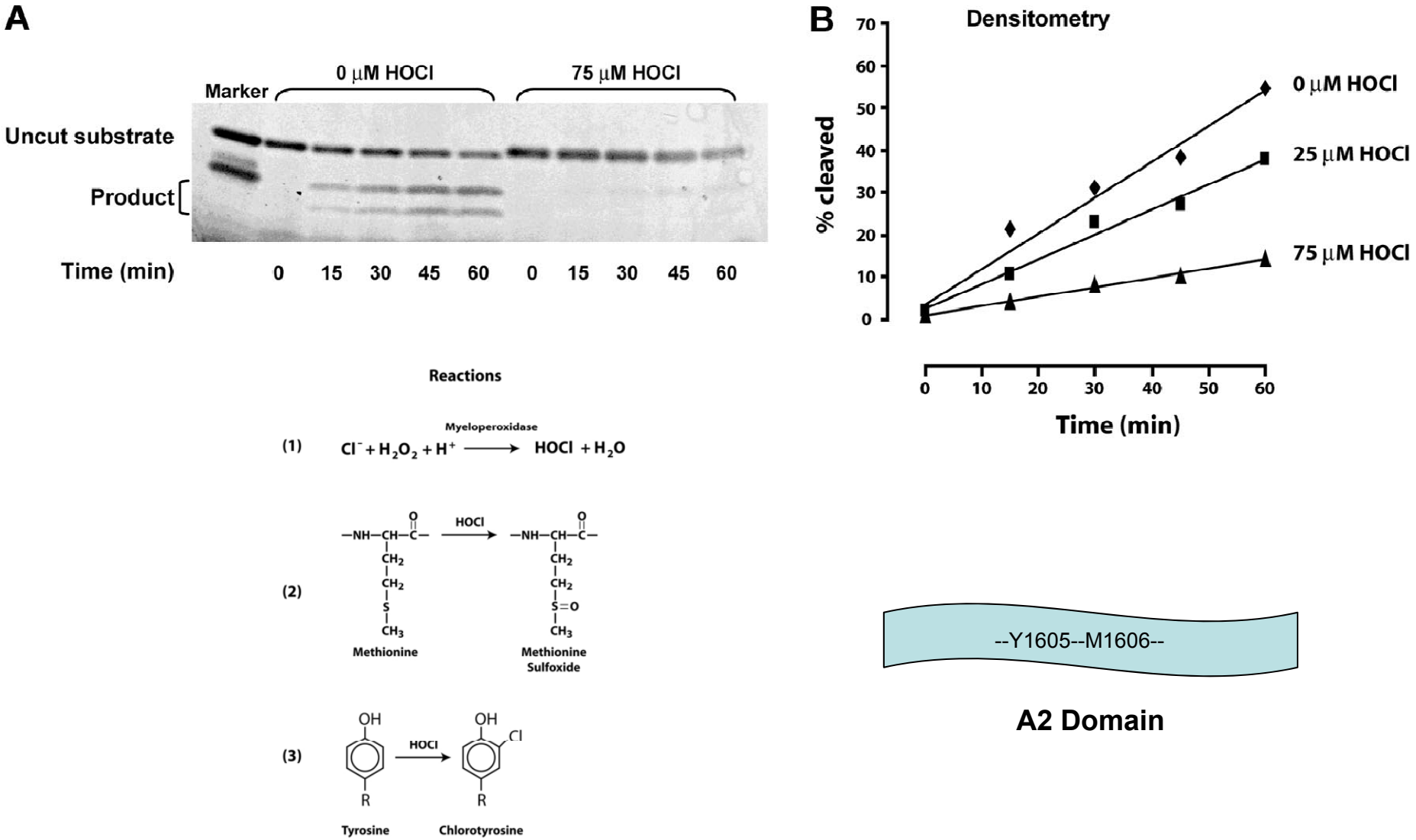
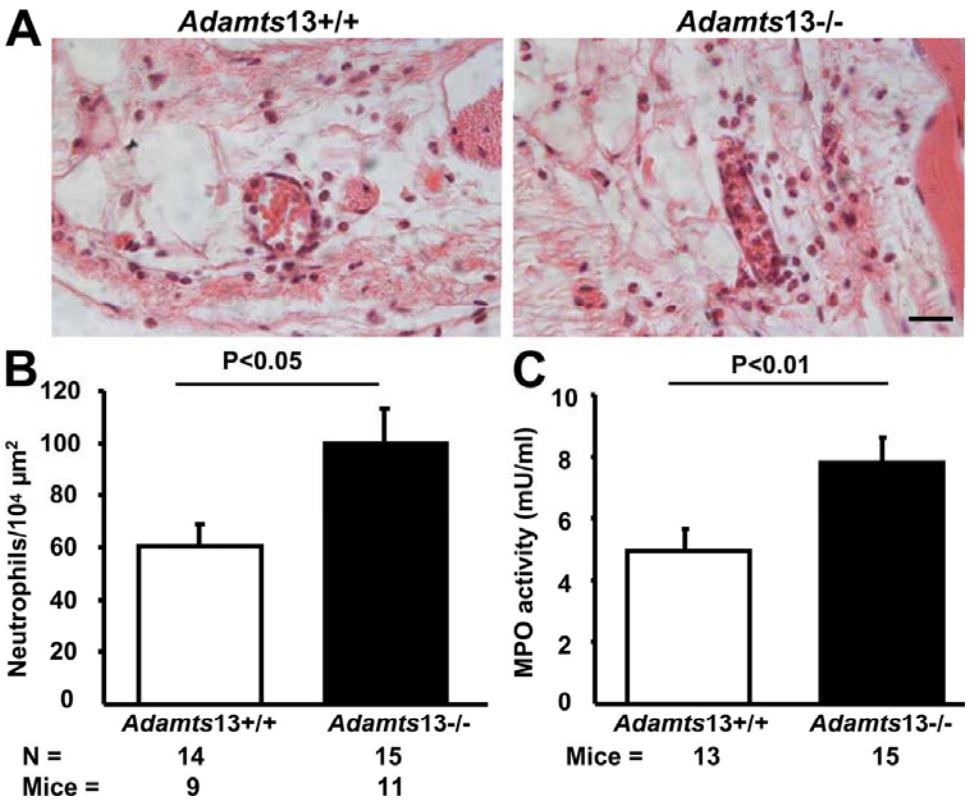




Oxidative modification of von Willebrand factor by neutrophil oxidants inhibits its cleavage by ADAMTS13

Blood 2010. 115 (3): 706-712

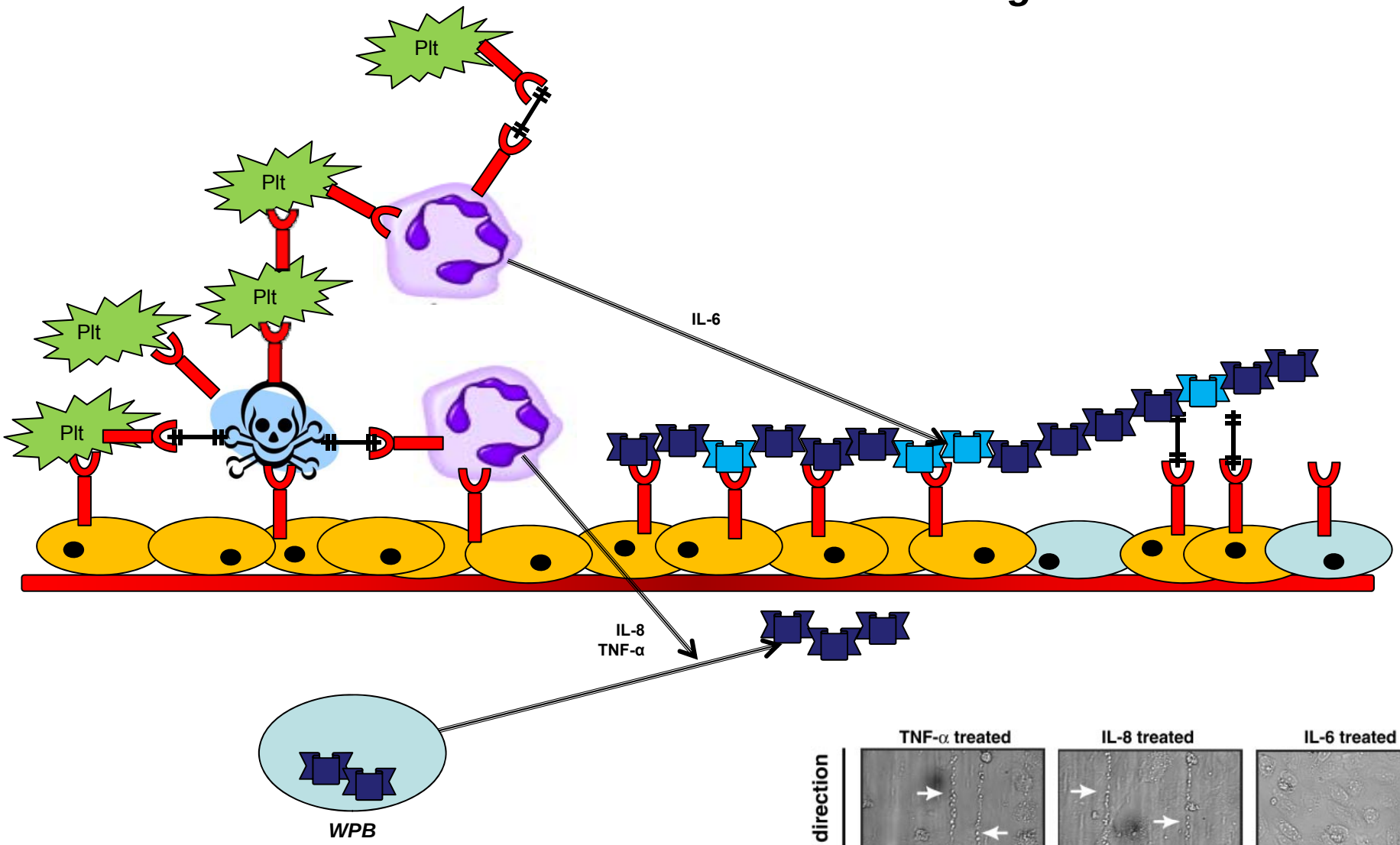
Neutrophil recruitment is augmented by ulVWF (via P-selectin interactions),increasing feedback loop of oxidative damage



Neutrophil influx in skin excision wounds is increased in Adamts13−/− mice.

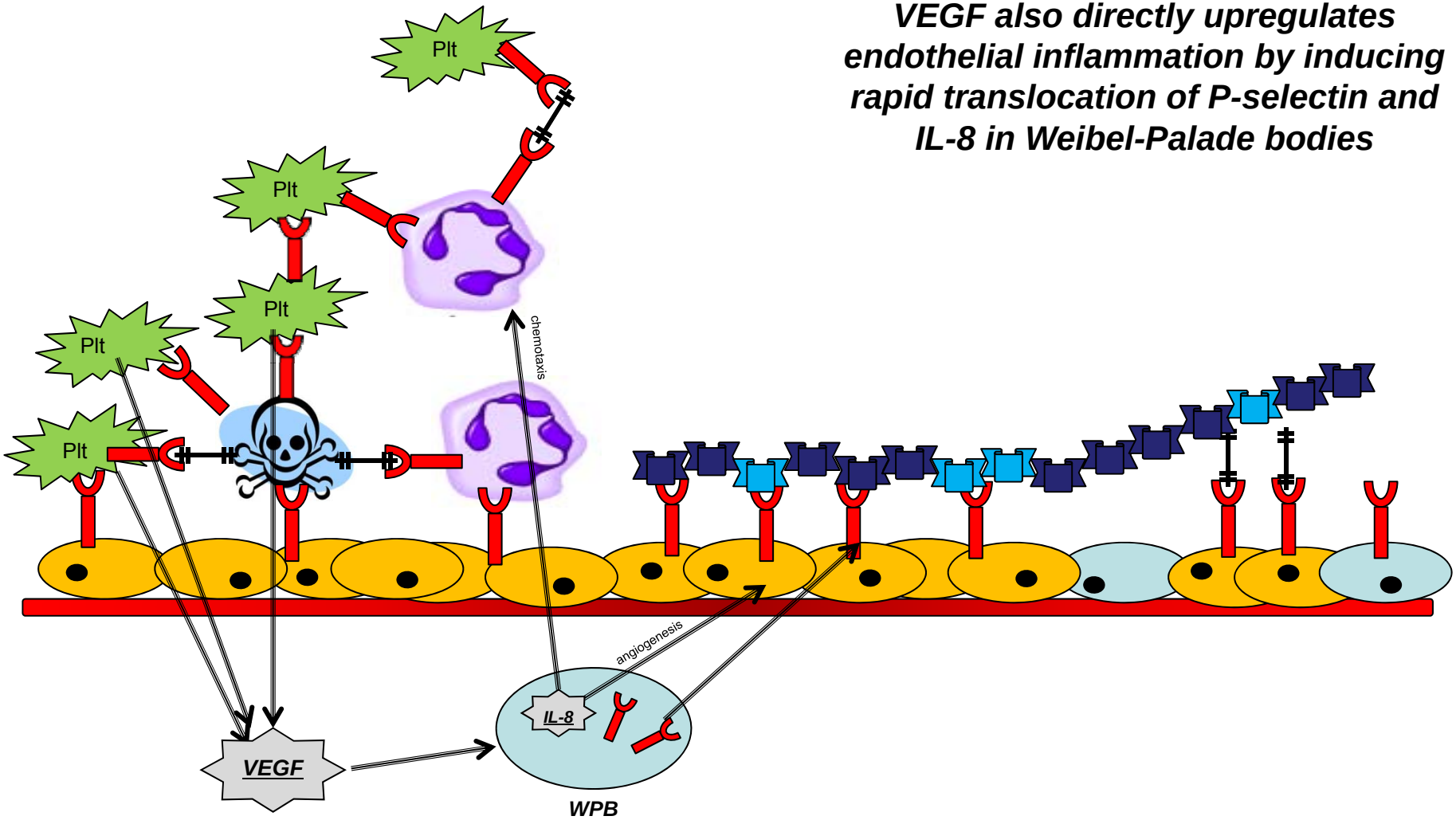
J Exp Med 2008;205:2065-2074

Inflammation augments thrombosis



Blood. 2004 Jul 1;104(1):100-6

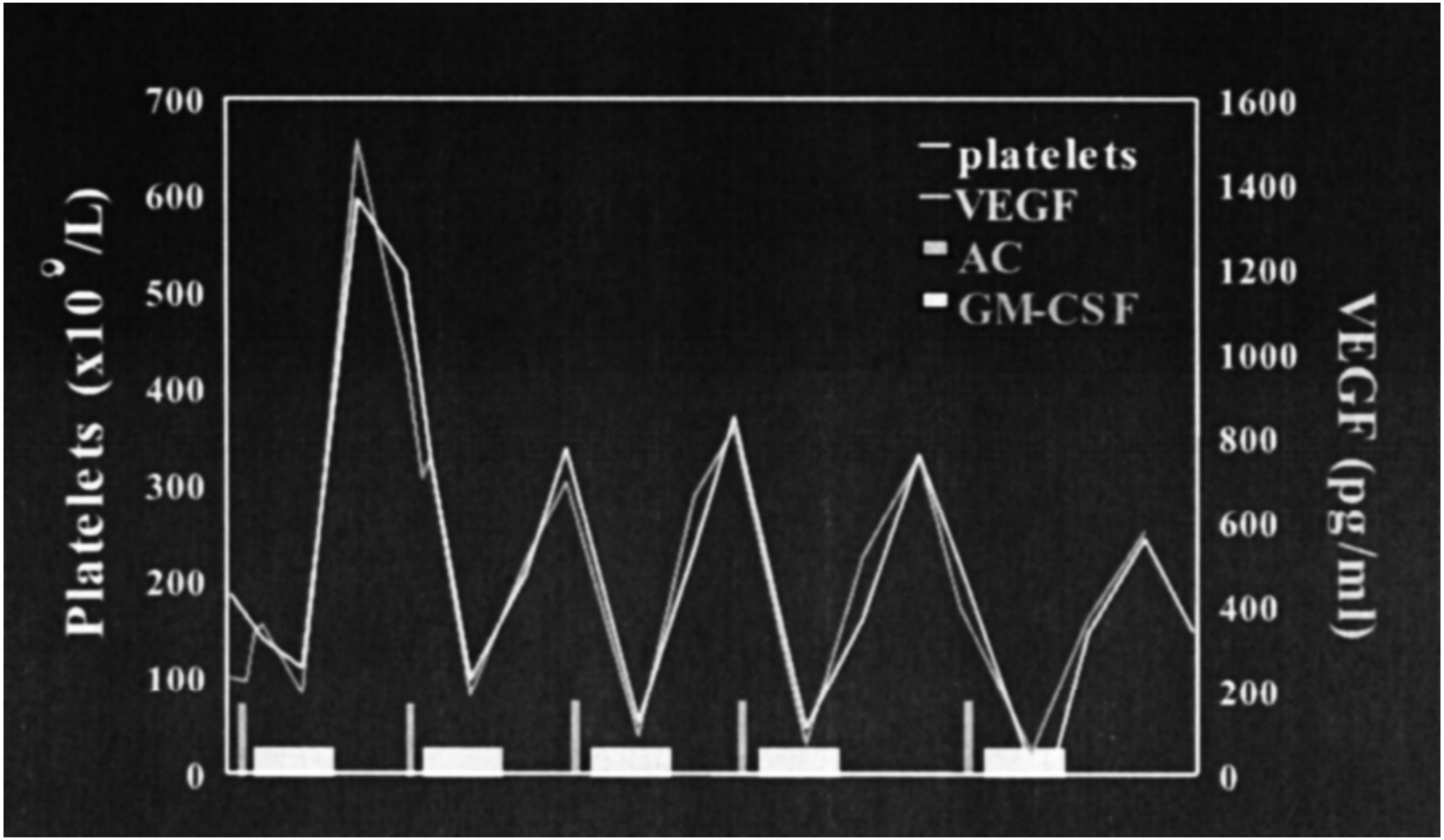
In addition to regulating angiogenesis, vascular permeability, and vasodilation, ***VEGF also directly upregulates endothelial inflammation by inducing rapid translocation of P-selectin and IL-8 in Weibel-Palade bodies***



"VEGF triggers exocytosis of Weibel-Palade bodies, releasing P-selectin which recruits leukocytes to the vessel wall, and releasing IL-8, which activates them"

Blood. 2005 Jan 1;105(1):207-14

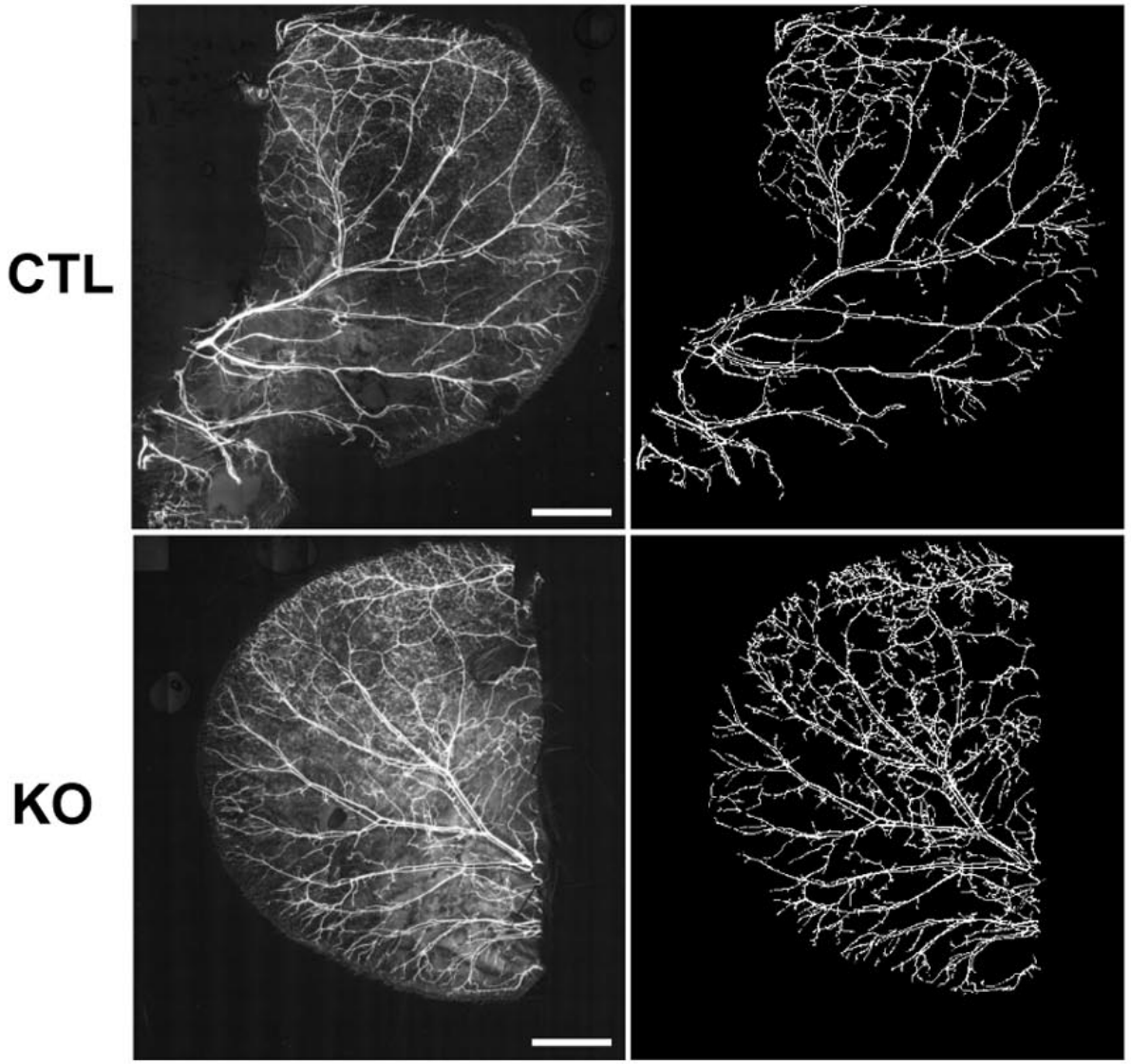
VEGF delivery is directly contingent upon Plt recruitment



VEGF concentrations and platelet counts during treatment with chemotherapy plus granulocyte macrophage colony-stimulating factor in breast cancer patients.

Clin Cancer Res 2003;9:3219-3221

Does altered or decreased vWF benefit a nascent tumor?



VWF-deficient mice display increased angiogenesis and mature blood vessel density. VWF antagonizes VEGF-dependent angiogenesis.

Blood. 2011 Jan 20;117(3):1071-80

Therapeutic Targets

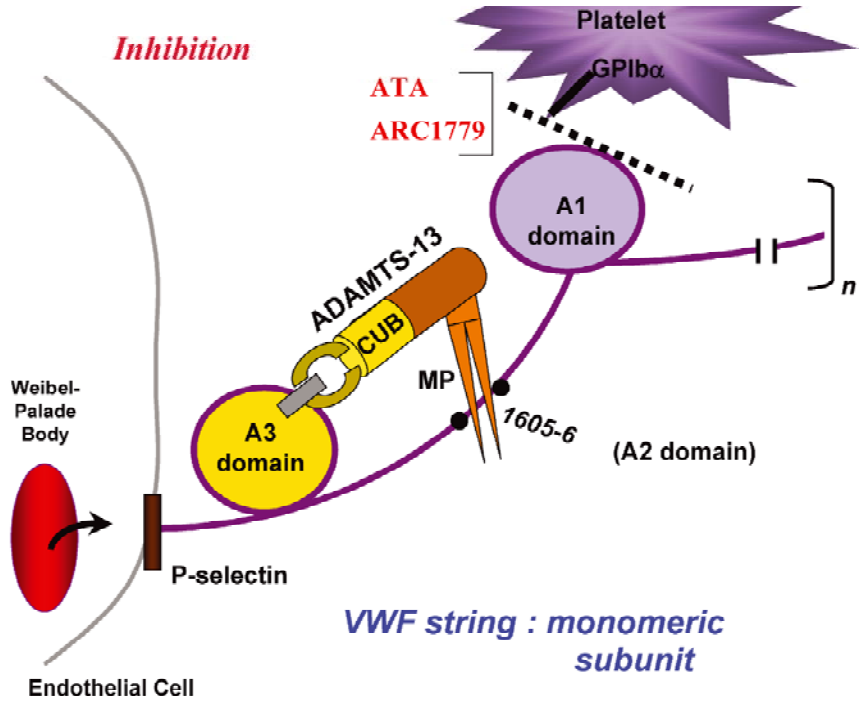
- Inhibition of N-linked glycosylation
  - Crucial to VWF synthesis and expression
  - Eliminates redundant or compensatory RTK survival signals (EGFR expression)
- Inhibition of P-selectins
  - Chemically modified heparins
  - Would abrogate metastasis ***&*** ulVWF deployment and plt interaction
- Undetected epigenetic or post-translational vWF modification targets

Thrombin activated platelets			
Treatment		% of tumor cells with associated platelet	
OSGPase	Heparin	WT	P-sel-/-
-	-	100	12
+	-	30	2
-	+	42	4
+	+	21	8

Proc Natl Acad Sci USA. 2001 Mar 13;98(6):3352-7

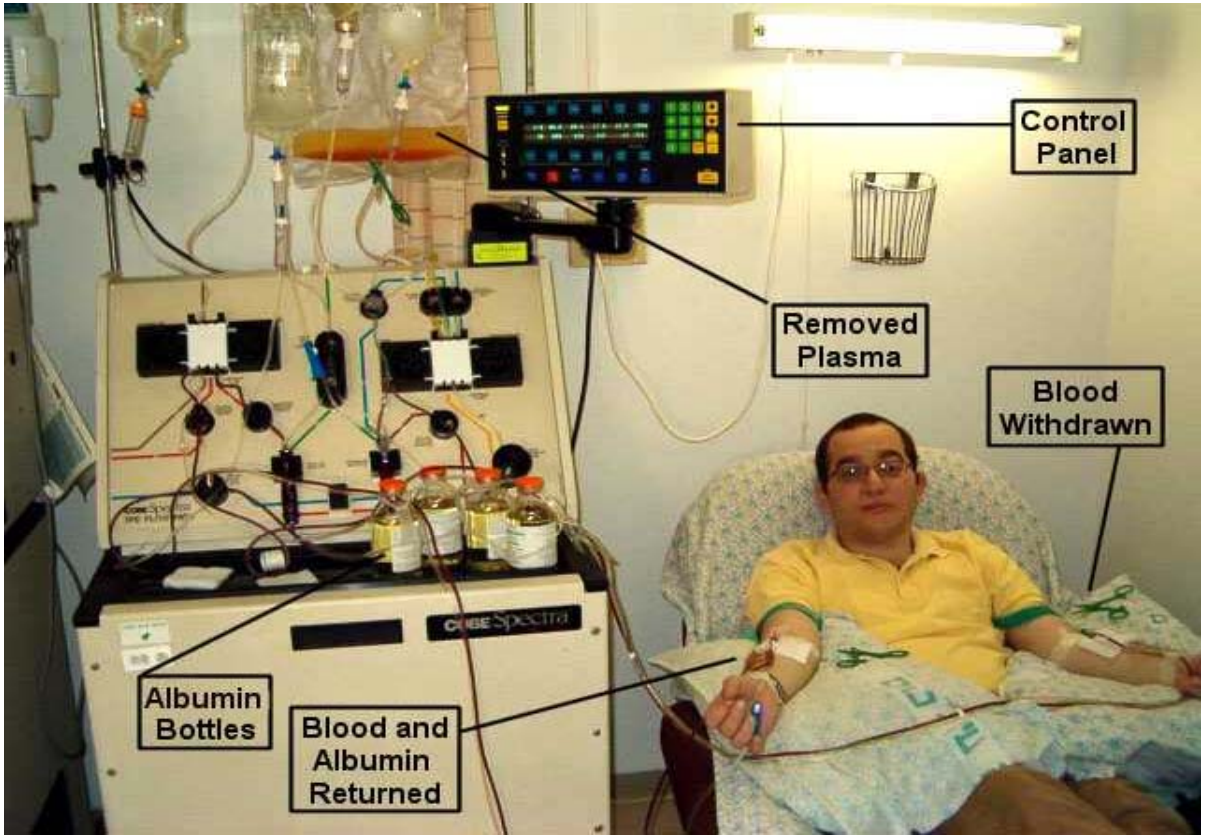
Therapeutic Targets

- Antiplatelet drugs
  - IIb/IIIa inhibitors
  - DTIs
  - Anti PAR
- Inhibition of ulVWF activity
  - ARC1779 aptamer
    - Orphan status
  - Aurin Tricarboxylic Acid
  - α2-6-linked sialyltransferase augmentation



Clin Transl Sci. 2009 Oct;2(5):366-73

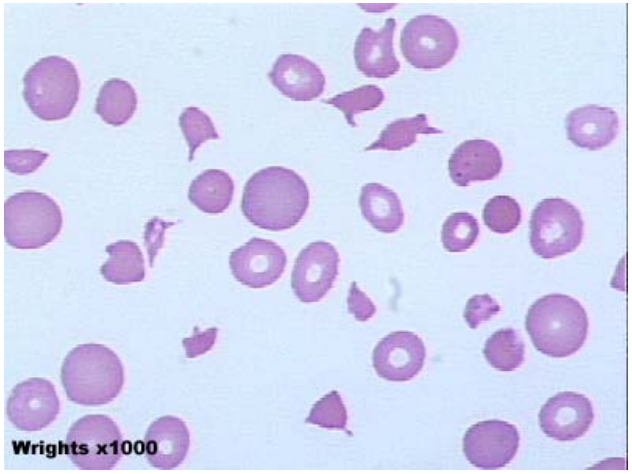
Treatment Options: Plasma exchange or not?



Diagnostic Dilemna

TTP: ASFA Category 1, grade 1A

1. Thrombocytopenia
2. Microangiopathic hemolytic anemia
3. Fever
4. Renal failure
5. Neurologic abnormalities



TMA: ASFA Category I (ticlopidine, clopidogrel), grade 2B

ASFA Cateroy III (cyclosporine, tacrolimus, HSCT), grades 2C, 1B

ASFA Category IV (gemcitabine, quinine), grades 2C, 2B

- Thrombotic Microangiopathy (TMA): histopathological findings of arteriolar microthrombi, associated intimal swelling and fibrinoid necrosis of the vascular wall.
- Microvascular occlusive disorders: Platelet microthrombi & thrombocytopenia

Does ADAMTS13 testing help?

- Overall, the ADAMTS 13 levels varies greatly between patients
- Clinical Idiopathic TTP (n=33)
  - 16 of 33 had severe ADAMTS-13 deficient activity
  - Patients without severe ADAMTS 13 deficiency were not clinically different than those that did
- Other TTP-like states generally do not have severe deficiency
  - HSCT, drug, bloody diarrhea, HUS, HIV, autoimmune disease
- Many patients responded to treatment with TPE

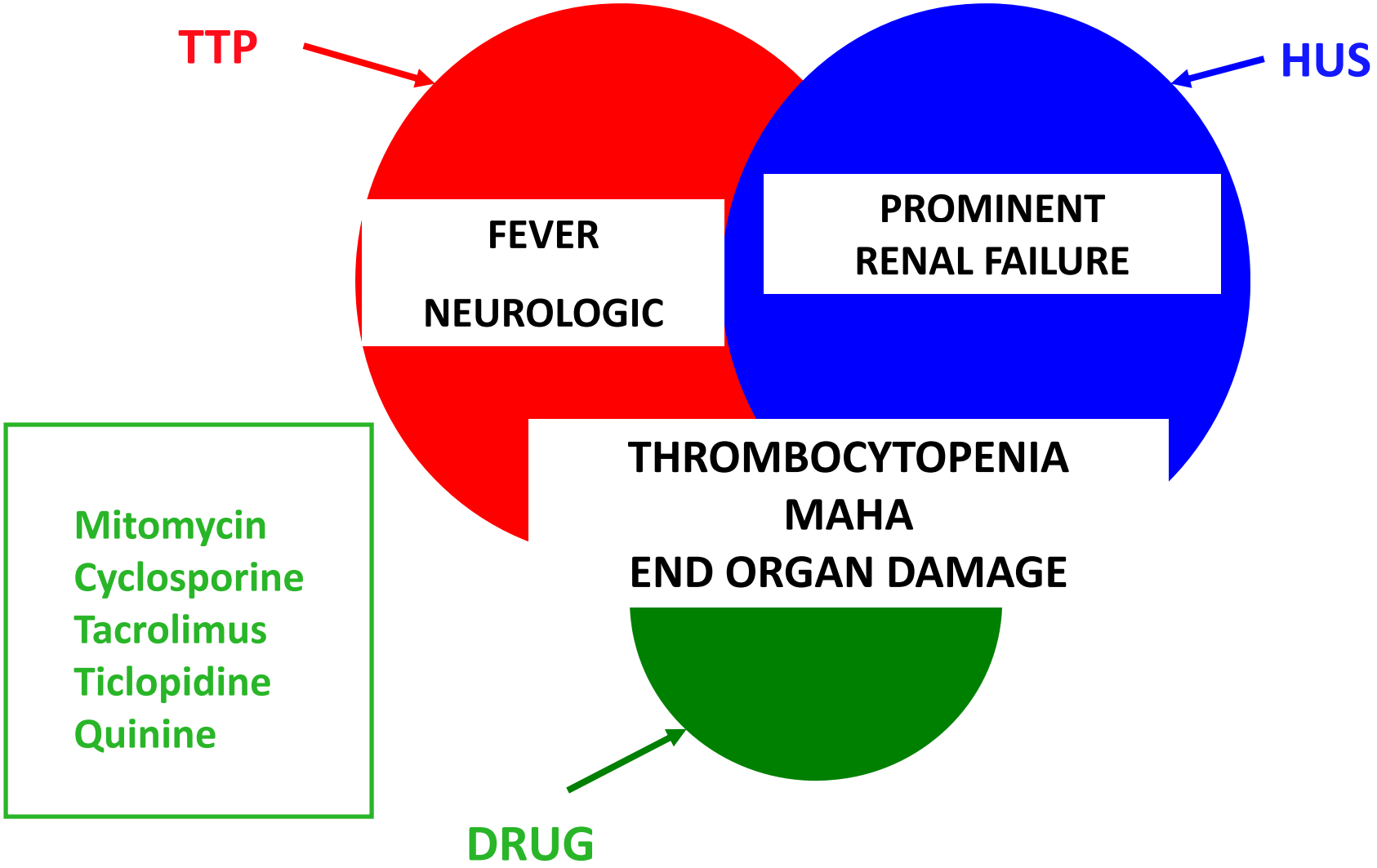
Vesely, Blood, 2003

Pathogenesis of TMA is Variable

Pathology	Mechanism	Clinical Disease
Systemic platelet thrombi	Inability to degrade large vWF multimers	TTP
Predominant renal platelet-fibrin rich thrombi	Shiga toxin causing endothelial cell damage	HUS
	Factor H deficiency and complement activation	Atypical HUS
Systemic and renal thrombi	Drugs and stem cell transplant, endothelial damage, malignancy	Features of TTP and HUS

Mayer, Mt Sinai J, 2005

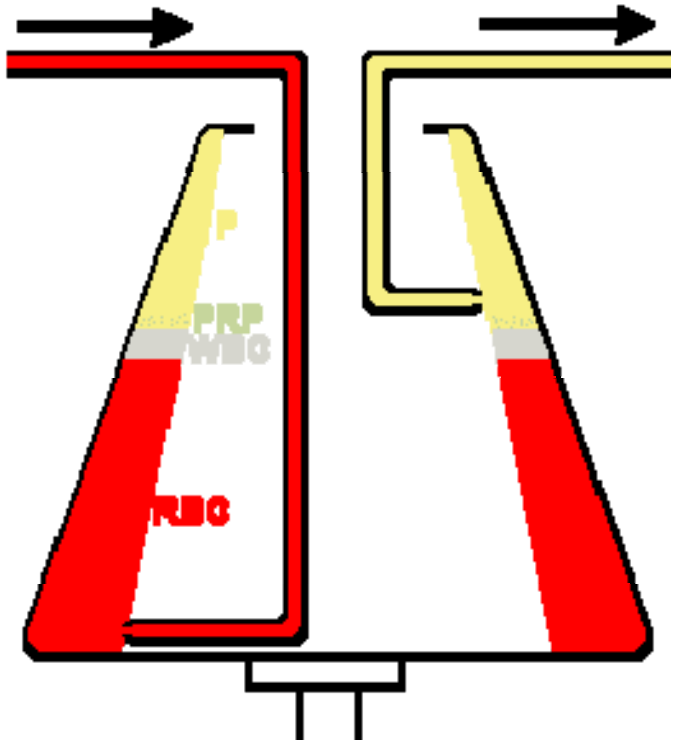
Clinical Overlap



TTP: 3 vs. 5

- If the exact pentad for TTP is not evident, a triad of findings will often suffice for initiation of therapy because of the lethality of TTP
  - Microangiopathic thrombosis
  - Thrombocytopenia
  - Elevated LDH

Treatment effect



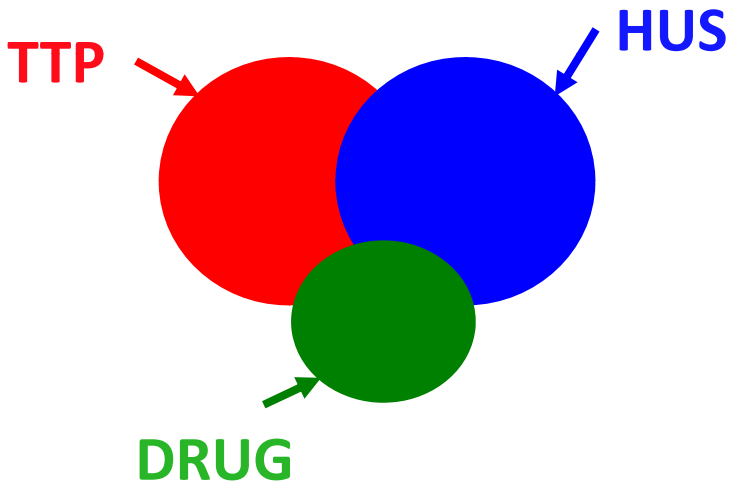
Treatment will remove a proportion of intravascular plasma bound substances

- Replacement fluid can supply deficient factors if FFP is chosen
- TPE often initiated with a group of treatments
- Re-equilibration

Treatment plans…

Goal: Remove inhibitor & replace enzyme
Replacement: FFP / albumin
Frequency: Daily
End point: Normalize platelet count

Goal: dHUS → don't do
aHUS → replace factor H
Replacement: FFP
Frequency: Longest tolerable interval
End point: Prevent / treat renal failure



Goal: Remove inhibitor & replace enzyme (ticlopidine), autoimmunity (?), endothelial damage, drug dependent antibodies
Replacement: FFP / albumin
Frequency: Daily or every other day
End point: Normalize platelet count

Thank you.