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Von Willebrand Factor: Friend or Foe

TMA, TTP, aHUS, STEC-HUS, MAHA, PLEX, TIC, ADAMTS13, VWF
What Does it All Mean?

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The Fritsma Factor, Your Interactive Hemostasis Resource
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Thrombotic Microangiopathies [TMAs]

- Thrombotic thrombocytopenic purpura [TTP]
  - Rx Cablivi®
- Shiga-toxin producing *E. coli* hemolytic-uremic syndrome [STEC-HUS]
- Childhood traumatic brain injury
  - Rx: ADAMTS13
- Atypical hemolytic-uremic syndrome [aHUS]
  - Rx Soliris®
- HELLP Syndrome
  - Rx Soliris®?

Please silence your phone

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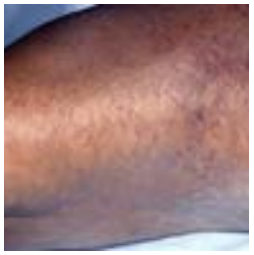
Nineteen-YOA Woman with TMA

A 19 YOA African-American woman came to the ED experiencing rapid onset fever, headache, confusion and weakness. The ED nurse recorded petechiae on her extremities and arranged for laboratory assays.



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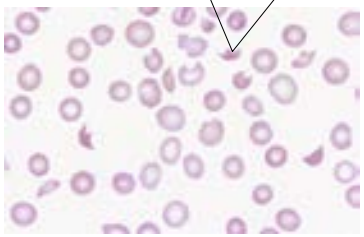
19-YOA ♀ TMA Relevant Labs

Test	Result	RI
HGB	9.8 g/dL	12.0–15.0 g/dL
HCT	31%	35–49%
MCV	78 fL	80–100 fL
PLT	21,000/dL	150–450,000/dL
LD	420 U/L	140–280 U/L
Creatinine	1.1 mg/dL	0.6–1.2 mg/dL
RBC morphology		2+ schistocytes



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19 YOA ♀ Presumptive Diagnosis

- Thrombotic thrombocytopenic purpura [TTP]
  - Moschcowitz, 1924, described a 16-YO ♀ with petechiae, thrombocytopenia, hemiparesis and pulmonary edema
  - 70/30 ♀, typical of autoimmune disorders
  - "Classic pentad:" marked thrombocytopenia, MAHA, neurologic changes, fever, renal insufficiency
- Now defined by MAHA with elevated lactate dehydrogenase [LD] and thrombocytopenia [no renal insufficiency, creatinine <2.0]
- "Ultra"-rare; 2/million new cases/year
- Once 90% fatal, now 20% fatal

Lopez JA, Chen J, Ozpolat HT, Moake JL, Chung DW. Ch 34: Thrombotic thrombocytopenic purpura and related thrombotic microangiopathies. In Kitchens CS, Kessler CM, Konkle BA, Strieff MB, Garcia DA. Consultative Hemostasis and Thrombosis, 4th Edition. Elsevier 2019.

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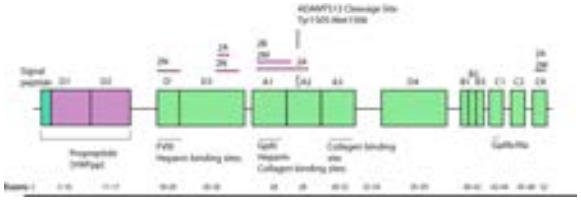
The TMA Culprit: VWF

- Chromosome 12p13; 31,178 kb, 52 exons
- mRNA specifies polypeptide of 2814 amino acids made of…
- 22-aa signal peptide, 742-aa propeptide, and 2050-aa monomer



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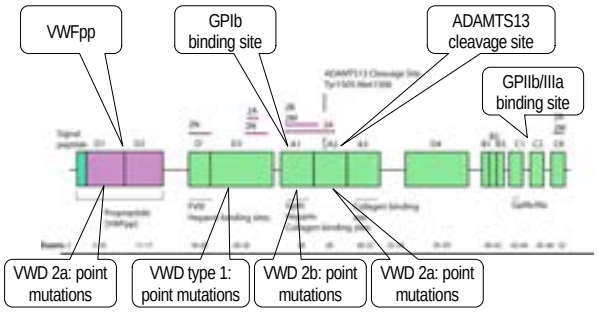
VWF Polypeptide



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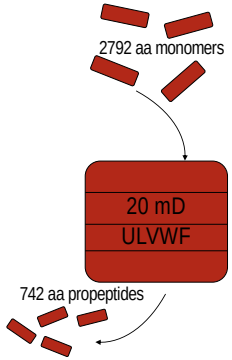
Monomer Assembly in Endothelial Cells

- 22-aa signal peptide is cleaved in endoplasmic reticulum after translation
- 742-aa propeptide-containing monomers dimerize via disulfide linkage of Cys residues near the C-terminus
- In Golgi apparatus, propeptides catalyze D3 region disulfide bonds, creating long multimers composed of dimers arranged head-to head
- The propeptide is then cleaved and the resultant ultra-large VWF [ULVWF] multimers are packaged in Weibel-Palade bodies
- Measurable plasma propeptide [VWFpp]



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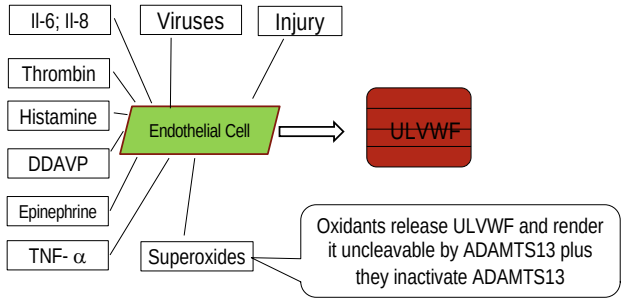
Endothelial Cell Secretes ULVWF



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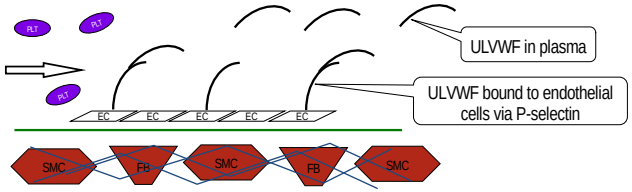
ULVWF Secreted from Endothelium



In high shear-stress arterioles ULVWF strands are released to the plasma or remain attached to ECs via P-selectin and other adhesion molecules. Whether in plasma or bound, they bind platelets via glycoprotein [GP] Ib, a subunit of GP Ib/IX/V, with little platelet energy expended.

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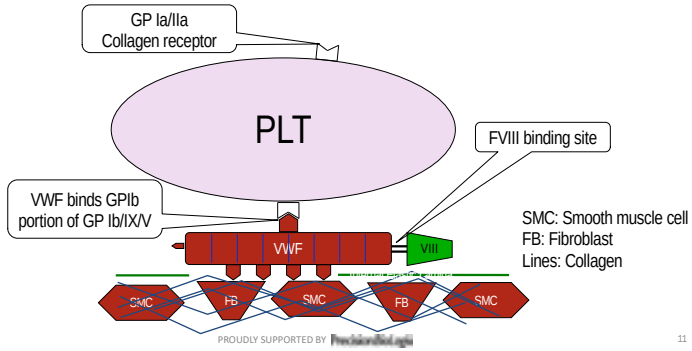
VWF-Platelet Interaction



SMC: Smooth muscle cell
FB: Fibroblast
Lines: Collagen

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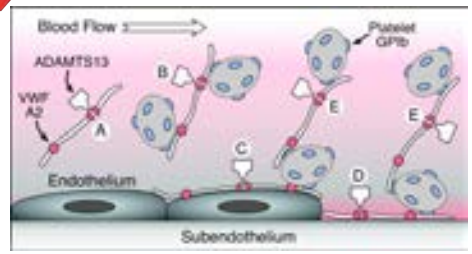
Platelet Strings



ULVWF is released from ECs and diffuses into the circulation [A and B] or adheres to the EC [C]. ULVWF also binds connective tissue exposed at sites of vascular injury [D]. Under high shear stress, platelets adhere to VWF in solution [B] or on surfaces [C and D] through their GPIb receptor. ULVWF also binds to previously adhering platelets [E]. ADAMTS13 cleaves a Tyr–Met bond in the A2 domain of the ULVWF subunit. This reaction is slow for VWF in solution [A] but occurs rapidly owing to conformational changes induced by tensile force on the ULVWF multimer.

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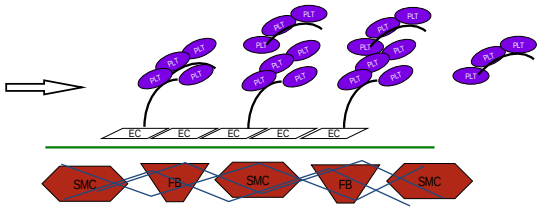
ULVWF Bind Platelets in High Shear Stress Areas



Platelets bind ULVWF, forming beaded strings. The strings stack and associate with collagen through platelet collagen receptors and may occlude the vessels. String length is attenuated by high density lipoproteins.

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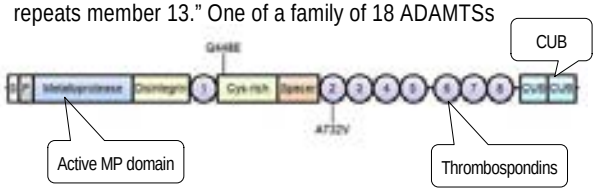
What Prevents Occlusion? ADAMTS13

"A disintegrin and metalloprotease with thrombospondin-1 repeats member 13." One of a family of 18 ADAMTSs



CUB = "complement components C1r/C1s, embryonic sea urchin protein endothelial growth factor, and bone morphogenic protein"

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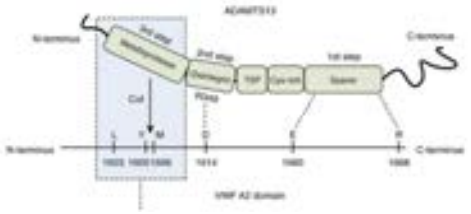
ADAMTS13

- Synthesized from chromosome 9q34 in liver, 190,000 Daltons
- ULVWF A2 domain stress exposes Tyr 1605–Met 1606.
- ADAMTS13 attaches in "zipper" fashion and digests ULVWF
  - BTW, ULVWF A2 mutations enhance digestion, causing VWD subtype 2A



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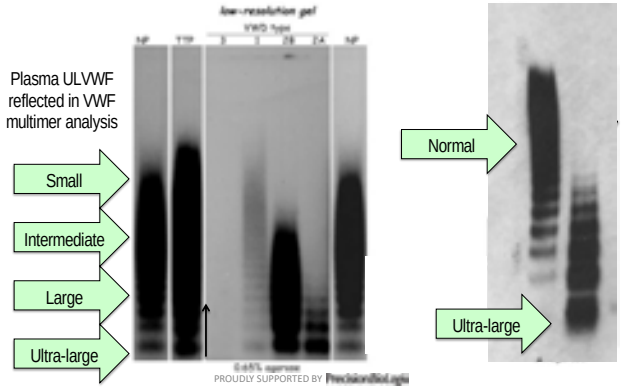
TTP: Reduced ADAMTS13



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TTP: ADAMTS13 <10%

- Familial recurrent "rTTP"—10% of cases: congenital ADAMTS13 abnormality or deficiency, <5% activity detected in assay. ULVWF consistent in plasma, childhood symptoms, remission is temporary
- Autoimmune ["idiopathic"] "iTTP"—90%: episodic deficiency of ADAMTS13 and rise of ULVWF, remission usually sustained
- Accumulated ULVWF/PLT complex occludes vessels, consumes and activates PLTs and splits RBCs, accounting for thrombocytopenia and MAHA

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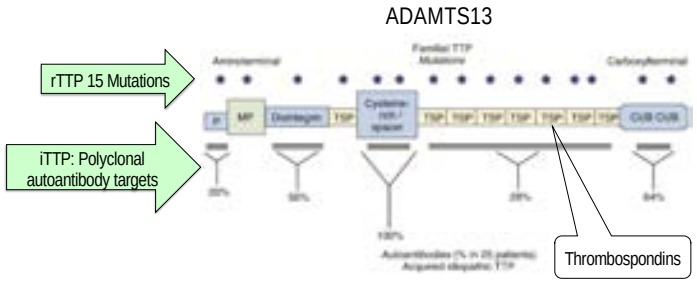
Congenital Vs. Acquired [Immune] TTP



IgG 4 autoantibodies, possible familial distribution, all bind the cysteine-rich spacer residues

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19-YOA ♀, Presumptive TTP
Differential Diagnosis: Various TMAs

- Atypical hemolytic-uremic syndrome [aHUS]
- Shiga toxin E. coli-triggered hemolytic-uremic syndrome [STEC-HUS]
- Hemolysis, elevated liver enzymes, low platelets [HELLP]
- Disseminated intravascular coagulation [DIC]
- Familial recurrent thrombotic thrombocytopenic purpura [rTTP]
- Acquired autoimmune thrombotic thrombocytopenic purpura [iTTP]

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19-YOA ♀, Presumptive TTP
"PLASMIC" Score

Criteria	Patient	Points
Platelet count <30,000/uL	15,000.uL	1
Hemolysis [MAHA, LD]	LD 420 U/L	1
No active cancer in previous year	✅	1
No solid organ or stem cell transplant	✅	1
MCV <90 fL	78 fL	1
INR <1.5	1.2	1
Creatinine <2.0 mg/dL	1.1 mg/dL	1
Maximum 7 points, 6–7 indicates TTP, <6 suggests HUS or HELLP		

Li A, Khalighi PR, Wu Q, et al. External validation of the PLASMIC score: a clinical prediction tool for TTP diagnosis and treatment. J Thromb Haemost. 2018;16:169–9.

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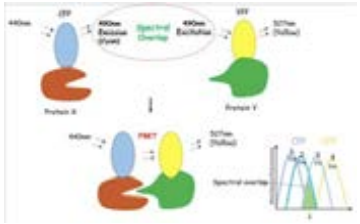
ADAMTS13 Activity Assay FRET-rVWF71

- Fluorescence resonance energy transfer
- Synthetic VWF peptide: 71 aa from the A2 domain
- Serum, heparinized or citrated plasma, not EDTA
- No bilirubin, HGB, or plasma VWF multimer interference
- Mayo assay now 30”



Jones GA, Bradshaw DS. Resonance energy transfer: From fundamental theory to recent applications. Frontiers in Physics. 2019;7:100. doi:10.3389/fphy.2019.00100.

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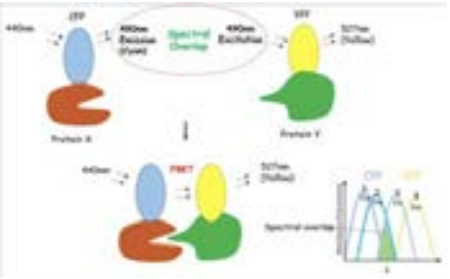
Fluorescence Resonance Energy Transfer

1. Fluorophore CFP excites at wavelength 440nm, emits at 490nm [cyan]
2. Fluorophore YFP excites at 490nm, emits at 527nm [yellow]
3. Emission is a function of distance between the fluorophores
4. Photon [non-radioactive] exchange between fluorophores when adjacent
5. ADAMTS13 [Protein X] binds target VWF71 [Protein Y]
6. Emission intensity is linear with ADAMTS13 activity



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ADAMTS13 Antigen Enzyme Immunoassays

- ~Seven solid-phase polyclonal or monoclonal EIAs available
- WHO international ADAMTS13 standard 12/252, two 2015 surveys
  1. Mean ADAMTS13 activity 0.91 U/mL, CV 12.4%
  2. Mean ADAMTS13 antigen 0.92 U/mL, CV 16.3%
- Large CVs reflect antigen epitope recognition and avidity differences

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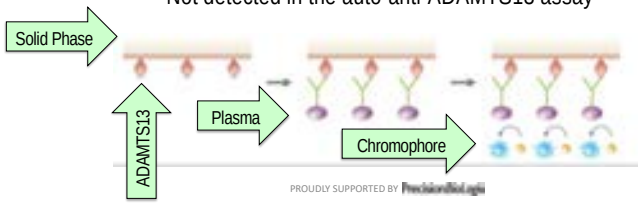
Auto-anti-ADAMTS13 Immunoassay

- Heat-inactivated patient plasma
- Non-antibody ADAMTS13 inhibitors
  - HGB, IL-6, thrombospondin 1, all block the A2 domain
  - Not detected in the auto-anti-ADAMTS13 assay



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19-YOA ♀ TMA Diagnosis

- ADAMTS13 activity by FRET: <5%
- ADAMTS13 concentration by antigen assay: <5%
- Auto-anti-ADAMTS13 immunoassay: 1:64
- Diagnosis: iTTP

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Familial TTP Therapy

- 1970s: fresh-frozen plasma [FFP] and cryosupernatant restored normal VWF multimers and reversed symptoms
- Relapse in three weeks, repeated infusions
- 1990s: plasma exchange [PLEX]

- Byrnes JJ, Khurana M. Treatment of thrombotic thrombocytopenic purpura with plasma. N Engl J Med. 1977;297:1386–89.
- Moake JL, Brnes JJ, Troll JH, et al. Effects of fresh-frozen plasma and its cryosupernatant fraction on von Willebrand factor multimeric forms in chronic relapsing thrombotic thrombocytopenic purpura. Blood. 1985;65:1232–6.

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Standard iTTP Therapy: PLEX

D/C triggers: ticlopidine, clopidogrel, quinine	Emergency: Plasma at 30 mL/kg/day until PLEX is started	High-dose glucocorticoids or rituximab [Rituxan®] anti-CD20
PLEX daily, BID if refractory, Rituxan® post-PLEX	Follow efficacy daily w/ PLT counts & LD	Assess remission: PLT counts, LD, MAHA, HGB
Continue PLEX 3 days post-remission	PLEX + Rituxan® 80–90% effective	Remeasure ADAMTS13 when in remission

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Rituxan®

- TTP care with PLEX alone associates with a median 8.2-year reduction in life expectancy and a total cost of $389K direct care and $259K indirect cost including loss of productivity and early mortality.
- Rituxan® [anti-CD20] raises the total cost by $13K but provides a 2.6-year improvement in life expectancy.

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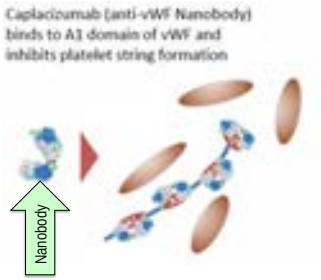
Caplacizumab [Cablivi®] for iTTP

- HERCULES trial, phase III
- FDA-approved Jan 2019, Sanofi; world's first nanobody Rx
- Binds VWF A1 region, blocks PLT string formation
- Prevents microthrombi



Scully M, Cataland SR, Peyvandi F, et al. Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura. N Engl J Med. 2019;380:335–46

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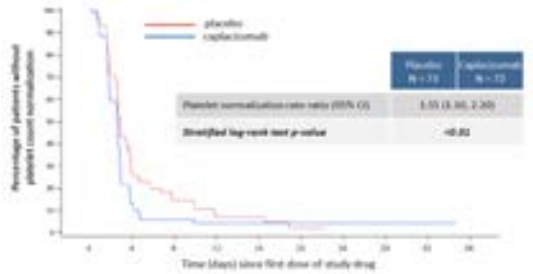
Cablivi® Surrogate Endpoint: Time to PLT Response



Defined as initial platelet count ≥150,000/uL, subsequent daily PLEX D/C within 5 days

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HERCULES End Points

Subjects N [%]	Current Rx N = 73	Cablivi N=72
iTTP-related death	3 [4.1%]	0
iTTP flare [during therapy]	28 [38.4%]	3 [4.2%]
iTTP recurrence long-term	28 [38.4%]	9 [12.7%]
Refractory iTTP—continued thrombocytopenia	5 [7%]	0
Major thromboembolic event [VTE or arterial]	6 [8.2%]	6 [8.5%]
First four endpoints: P > 0.05		

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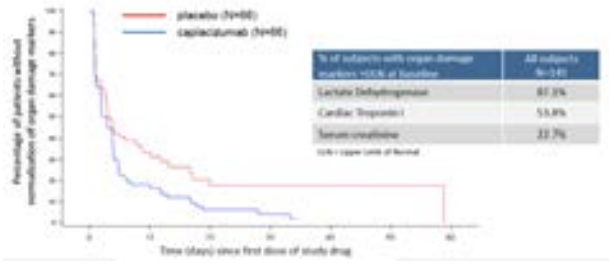
HERCULES Time to Normalization of Organ Damage Markers



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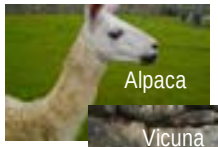
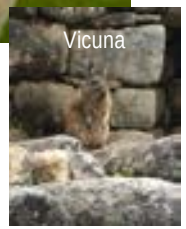
Camalid Nanobody





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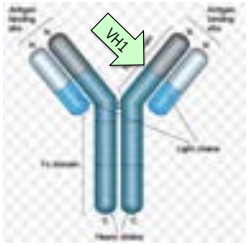
What is a Nanobody?

Camelids: camels, llamas, alpacas, vicunas make heavy chains with no light chains, no VH1 region, direct connection to hinge region



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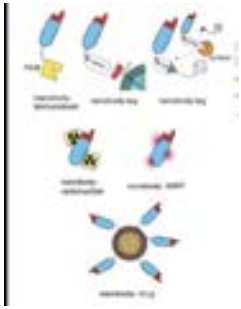
Nanobody Features



- High affinity, specificity
- Short half-life, thermostable
- Penetrate tissues and molecular pockets
- Non-immunogenic, no heterophile ABs
- Cross the blood-brain barrier
- Don't bind carbohydrates

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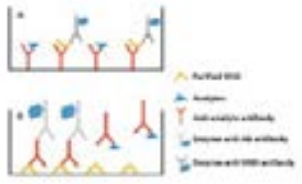
Experimental Nanobody Applications

- Antiviral [HIV, HSV, RSV], camel flu, coronavirus by inhaler [C19!]
- Anti-allergens
- Antitumor Rx
- Anti-angiogenesis
- Anti-inflammatory
- Neutralize venoms
- IL-6-R for rheumatoid arthritis Rx
- Radiolabeled for Her2+ tumor imaging



- Diagnostic: viral, fungal, mycotoxins in food, trypanosomes
- Stroke diagnosis and inactivation of clot

Sasisekharan R. Preparing for the future—nanobodies for Covid-19? N Engl J Med 2021; 384:1568–71

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Caleb

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rADAMTS13 Concentrate SHP655

- A phase 2, multicenter, randomized, placebo-controlled, double-blind study in patients with rTTP to evaluate the pharmacokinetics, safety and efficacy of rADAMTS13 [SHP655] administered in addition to standard of care treatment. ClinicalTrials.gov Identifier: NCT03922308
  - Takeda Pharmaceuticals acquired Shire in January 2019, Shire was Baxalta, Baxalta was Baxter, Chicago
- Or rADAMTS13 modified to evade iTTP autoantibody
- Or rADAMTS13 in platelet concentrate to evade iTTP autoantibody

- Jian C, iao J, Gong I, et al. Gain-of-function ADAMTS13 variants that are resistant to autoantibodies against ADAMTS13 in patients with acquired thrombotic thrombocytopenic purpura. Blood 2112; 119: 3836–43.
- Abdelgawwad MS, Cao W, Zheng L, Kocher NK, Williams LA, Zheng XL. Transfusion of platelets loaded with rADAMTS13 is efficacious for inhibiting arterial thrombosis associated with thrombotic thrombocytopenic purpura. Arterioscler Thromb Vasc Biol. 2018;38:2731–43

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Childhood Trauma

- Children's Hospital of Alabama Level 1 Trauma Center
- 106 Pts 2014–16, median 9 YO, blunt & penetrating trauma
- Injury severity score median 33; $\geq 15{:}\,72$; $\geq 25{:}\,46$
- Measures: ADAMTS13, VWFag, VWFac, HNP 1–3
  - Human neutrophil peptide
- Endothelial activation occurs in trauma or sepsis and can induce an inflammatory procoagulant state associated with microvascular injury and thrombosis.

Russell RT, McDaniel JK, Cao W, Zheng XL, et al. Low plasma ADAMTS13 activity is associated with coagulopathy, endothelial cell damage and mortality after severe pediatric trauma. Thromb Haemost. 2018; 118: 676–87.

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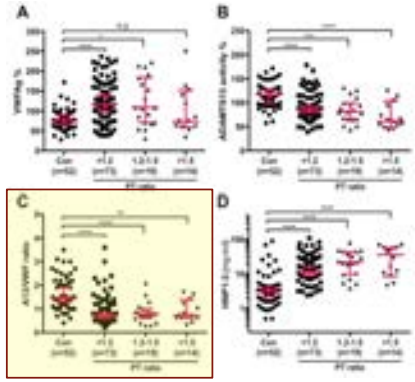
Childhood Trauma Results by ADAMTS13/VWFag ratio

- ↓ ADAMTS13
- ↓ ADAMTS13/VWFag ratio
- ↑ HNP 1–3

So what?



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ADAMTS13, VWF, HNP 1–3 in Traumatic Brain Injury

Long Zheng, MD PhD

- 33 adult TBI victims 2010–14 Vs 33 controls
- Blood collected at 0, 1, 2, 3, & 5 days
- Traumatic microvascular injury in brain and other organs
- VWFag, VWFac, HNP 1–3 rise over 5 days Vs control
- ADAMTS13 reduces over 5 days compared to controls
- Changes most profound in severe cases

Kumar MA, Can W, Pham HP, Zheng XL, et al. Relative deficiency of plasma ADAMTS13 activity and elevation of human neutrophil peptides in patients with traumatic brain injury. J Neurotrauma 2018; 36. https://doi.org/10.1089/neu.2018.5696

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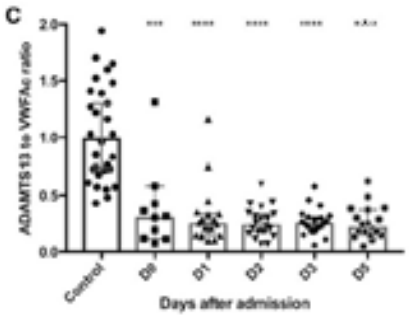
ADAMTS13/VWFac

So what?



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ADAMTS13 Concentrate TBI Therapy?

"We conclude that the elevated plasma levels of VWF, reduced ADAMTS13 activity, and elevated HNP 1–3 in patients post-TBI may explain the underlying mechanism of microvascular thrombosis found in vessels of brain parenchyma and other organ tissues despite a seeming hypocoagulability revealed by other routine laboratory tests, including low PLT count, prolonged PT and PTT. Our findings may provide a rationale for supporting future clinical trials with rADAMTS13 as a novel therapy in patients with TBI."

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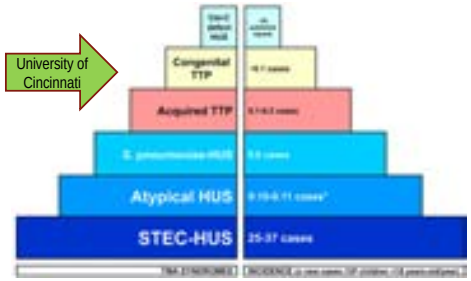
TMA Incidence in Childhood



Berangere SJ, Zheng XL, Veyradier A. Understanding thrombotic microangiopathies in children. Intensive Care Med. 2018; 44:1536–8.

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STEC-HUS Vs. TTP

	HUS	TTP
Patient	Child	All ages
Organ	Renal	Several [CNS]
Episodes	Single	Recurrent
Thrombocytopenia	Moderate	Severe
MAHA	2+	4+
ADAMTS13	Broadly normal	Absent
Clinical and laboratory observations cross boundaries, obscuring diagnosis		

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aHUS

- A recurrent TMA with MAHA, thrombocytopenia, creatinine >2.25 mg/dL, but ADAMTS13 activity >13%
- Pathophysiology: excessive activation of the alternate pathway complement [APC] system
- Related to mutations in APC regulatory proteins genes for H, I, thrombomodulin, and membrane cofactor protein
  - However, these mutations exist in non-aHUS individuals
- Two-hit hypothesis: mutation + pregnancy, inflammation, surgery, or autoimmune disorder
- Could also be acquired aHUS, autoimmune
- Symptoms appear at median 18 YOA, severe, recurring

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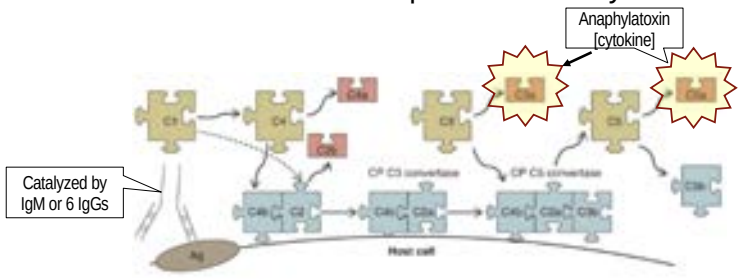
Classical Complement Pathway



C5a may increase inflammatory cytokines, downregulate ADAMTS-13, generates tissue factor and PAI1, decreases protein S and increases protein C resistance because of increased factor VIII activity, and, most importantly, activates thrombin.

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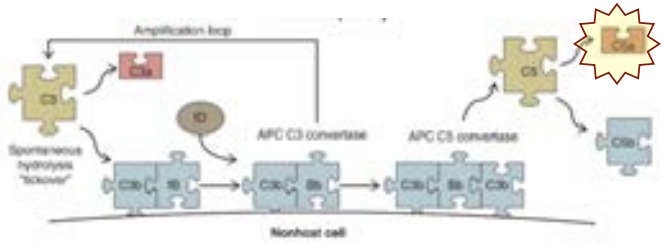
Alternate Complement Pathway [APC]



Courtesy Gavriilaki E, Brodsky RA. Complement-mediated coagulation disorders: PNH and aHUS. In Kitchens CS, Kessler CM, Konkle BA, Streiff MB, Garcia DA. Consultative Hemostasis and Thrombosis, fourth Edition. Elsevier 2019

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Membrane Attack Complex [MAC]

Courtesy Abbas AK, Lichtman AH, Pillai S. Cellular and Molecular Immunology Edition 6. Elsevier. 2010:272–88.

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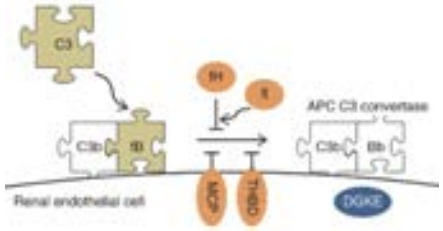
Alternative Pathway Dysregulation in aHUS



Activation results from loss-of-function mutations in regulatory factors H [fH], fI, membrane cofactor protein [MCP] and thrombomodulin [THBD] shown in orange, gain-of-function mutations of C3 and factor B shown in green. Renal ECs are primary aHUS targets.

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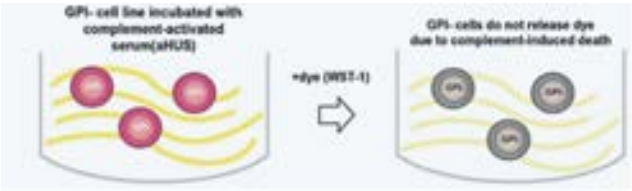
How to Test for aHUS

Really?

- No reliable complement protein tests
  - Urinary C5b–9?
- Modified Ham test PNH RBCs incubated with aHUS serum, cells retain dye if complement MAC induces death



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aHUS Differential Diagnosis

- DIC: MAHA, tpenia, PT/INR and PTT prolonged, D-dimer markedly elevated
- Misc. TMAs: malignancy, PNH, organ transplant, therapeutics
  - Therapeutics: quinine, mitomycin, cyclosporin, chemotherapy
- TTP: ADAMTS13 <10%
- STEC-HUS: Shiga toxin testing

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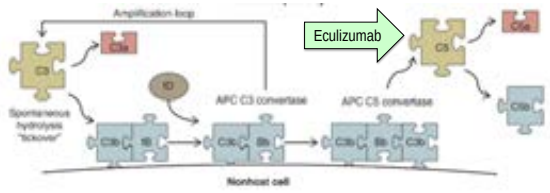
aHUS Treatment

- PLEX: temporarily and partially effective
  - 50% progression to end state renal disease
- Complement inhibition, nanobody eculizumab [Soliris®]
  - World's second nanobody therapy
  - Cost, relapse?, D/C?, close monitoring



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HELLP Syndrome in Pregnancy

- Hemolysis, elevated liver enzymes, low platelets
- Pre-eclampsia spectrum, severe risk to mother and fetus
  - Hypertension, proteinuria, end organ ischemia
  - MAHA, renal dysfunction, altered mental status, seizures
- Rx: manage hypertension, Mg for seizures, early delivery
- Urine C5b–9 elevation, mutations
- Assay: modified Ham test, Rx eculizumab in trials

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HELLP; "The Lab Saved my Life"

Asa [Now 7 YOA]

Not this Lab

Mama

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Thrombotic Microangiopathies [TMAs]

- Thrombotic thrombocytopenic purpura [TTP], Rx Cablivi®
- Shiga-toxin producing *E. coli* hemolytic-uremic syndrome [STEC-HUS]
- Childhood traumatic brain injury Rx ADAMTS13
- Atypical hemolytic-uremic syndrome [aHUS], Rx eculizumab [Soliris®]
- HELLP Syndrome, Rx Soliris®?

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