Inflammation, Selectins and Venous Thrombosis

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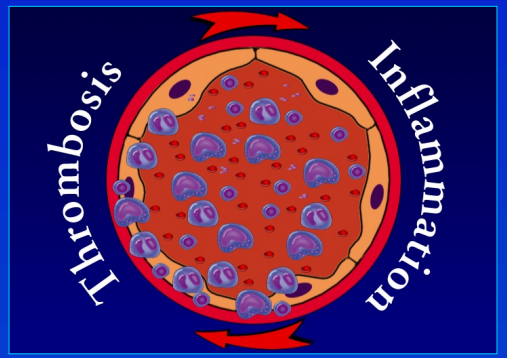
Virchow's Triad (1856)

Circulatory stasis

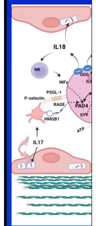
Hypercoagulability

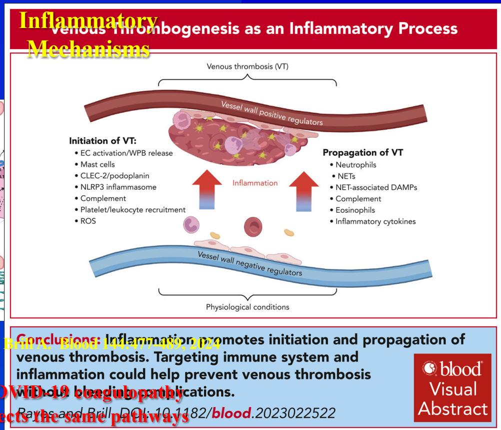
Endothelial injury



Inflammatory Mechanisms

- Flow Abnormalities Leading to EC
- of
- mbotic
- lecules and
- eractions
- telet
- /PBs and
- ase of IL-1β
- om
- f Glycocalyx
- elease of
- Complement Activation





Venous Thrombogenesis as an Inflammatory Process
Venous thrombosis (VT)
Vessel wall positive regulators
Initiation of VT:
• EC activation/WPB release
• Mast cells
• CLEC-2/podoplanin
• NLRP3 inflammasome
• Complement
• Platelet/leukocyte recruitment
• ROS
Inflammation
Propagation of VT
• Neutrophils
• NETs
• NET-associated DAMPs
• Complement
• Eosinophils
• Inflammatory cytokines
Vessel wall negative regulators
Physiological conditions
Conclusions: Inflammation promotes initiation and propagation of venous thrombosis. Targeting immune system and inflammation could help prevent venous thrombosis without bleeding complications.
Rayes and Brill, DOI: 10.1182/blood.2023022522
blood Visual Abstract

Rayes J, Brill, Blood 2024

COVID-19 coagulopathy affects the same pathways

Leukocyte accumulation promoting fibrin deposition is mediated *in vivo* by P-selectin on adherent platelets

Theresa Palabrica*†, Roy Lobb‡, Barbara C. Furie*, Mark Aronovitz†, Christopher Benjamin‡, Yen-Ming Hsu‡, Susan A. Sajer* & Bruce Furie*

* Center for Hemostasis and Thrombosis Research, Division of Hematology-Oncology and † Division of Cardiology, New England Medical Center and the Department of Medicine and Department of Biochemistry, Tufts University School of Medicine, Boston, Massachusetts 02111, USA
‡ Biogen Inc. 14 Cambridge Center, Cambridge, Massachusetts 02142, USA

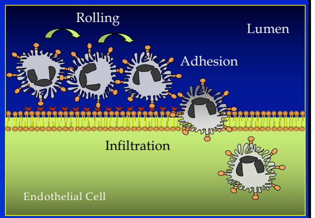
Palabrica T et al, Nature 359:848-851, 1992

Selectins

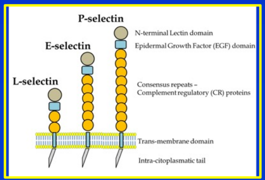
Selectins are glycoproteins found primarily on endothelial cells, leukocytes and platelets.

They are involved in trafficking of leukocytes in acute and chronic inflammatory processes, including:

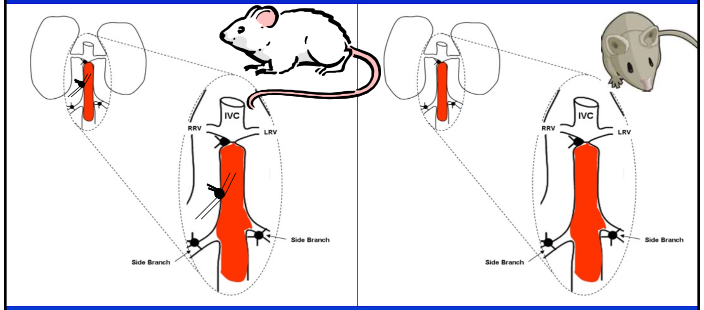
- Post-ischemic inflammation in muscle, kidney and heart
- Skin inflammation
- Atherosclerosis
- Glomerulonephritis
- Lupus Erythematosus
- **DVT**

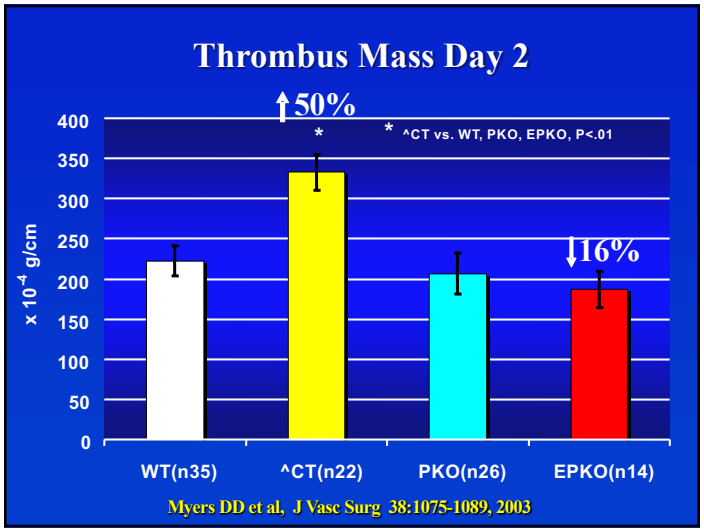


Diaz - Wakefield. EVC WITTENS, 2009. Chap 4, 13-22.



Rodent Ligation Model





NET formation from stimulated neutrophils from ^CT mice (Elevated Circulating P-Selectin) was significantly increased, suggesting that NET formation may be enhanced in these mice

Etulain J, Martinod K, Wong SL, et al. Blood 126:242-246, 2015

P-selectin Inhibition Therapeutically Promotes Thrombus Resolution and Prevents Vein Wall Fibrosis Better than Enoxaparin and an Inhibitor to von Willebrand Factor

Diaz JA[1], Wrobleski SK[1], Pechota AR[1], Hawley AE[1], Roelofs KJ[1], Doornbos NK[1], Gabriel JE[1], Reynolds G[1], Farris DM[1], Shea EM[1], Lester PA[1], Londy FJ[2], Lowe S[2], Henke PK[1], Schaub RG[3], Wakefield TW[1], Myers Jr. DD

Arterioscler Thromb Vasc Biol
Volume 35(4):829-837
March 25, 2015

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[2]Department of Radiology, University of Michigan, Ann Arbor, Michigan,
[3]NKT Therapeutics, Inc., Waltham Massachusetts, USA.

Thomas W. Wakefield – Denisa D. Wagner: NIH HL095091 (RFA)

American Venous Forum

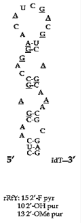
26th Annual Meeting, New Orleans
February 19 – 22, 2014.

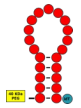
Aptamers

Aptamers

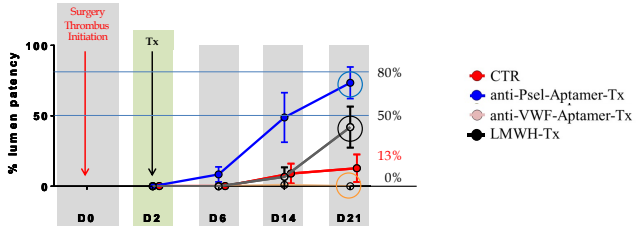
- Aptamers are nucleic acid species that offer molecular recognition properties like antibodies. (Aptamers have been engineered through repeated rounds of *in vitro selection* named, SELEX [systematic evolution of ligands by exponential enrichment] to bind to various molecular targets).

Anti-P-selectin Aptamer, ARC5692	Anti-VWF Aptamer, ARC15105
Selectivity ○ Binds to soluble and bound P-selectin.	**Selectivity** ○ Binds to VWF in circulation.
Functional activity ○ Blocks P-selectin/PSGL-1 interaction.	**Functional activity** ○ Blocks VWF A1 domain/platelet glycoprotein Ib (GP Ia) interaction.

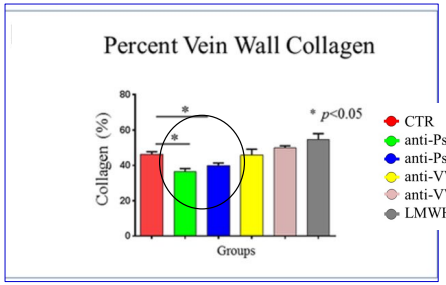




Magnetic Resonance Venography

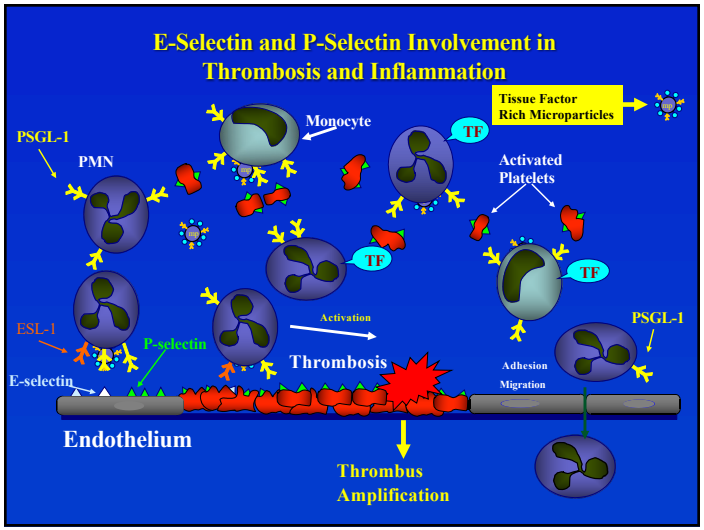


Percent Vein Wall Collagen

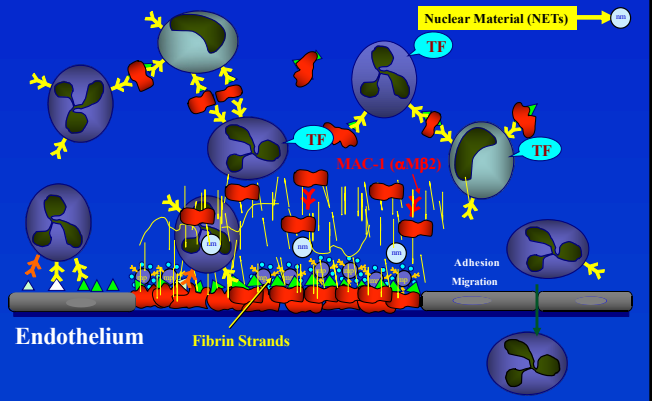


Jose A. Diaz et al. Arterioscler Thromb Vasc Biol. 2015;35:829-837

E-Selectin and P-Selectin Involvement in Thrombosis and Inflammation



E-Selectin and P-Selectin Involvement in Thrombosis and Inflammation



E-Selectin

- E-Selectin is a glycoprotein expressed from activated endothelium that facilitates thrombosis, directly modulating neutrophil and monocyte activity
- We have identified E-selectin as an important regulator of thrombus formation and fibrin content in a mouse venous thrombosis model. (Myers D et al, J Surg Res 2002, Sullivan VV et al, J Surg Res 2003, Myers D et al, Thromb Haemost 2007)
- E-selectin has been shown to be efficient at raising the affinity and avidity of CD18 (MAC-1) integrins which support neutrophil trafficking to sites of acute inflammation and recruit platelets and red blood cells. (Chase SD et al, Ann Biomed Eng 2012)
- Patients homozygous for the *S128R* E-selectin allele have an increased risk for VTE recurrence, highlighting the importance of E-selectin in venous thrombosis. (Jilma B et al, Arch Intern Med 2006)

E-Selectin Inhibitor (GMI-1271) small molecule antagonist

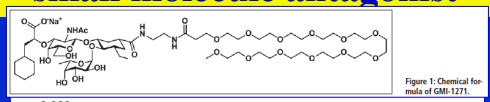
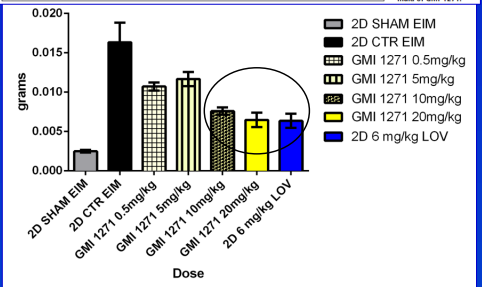
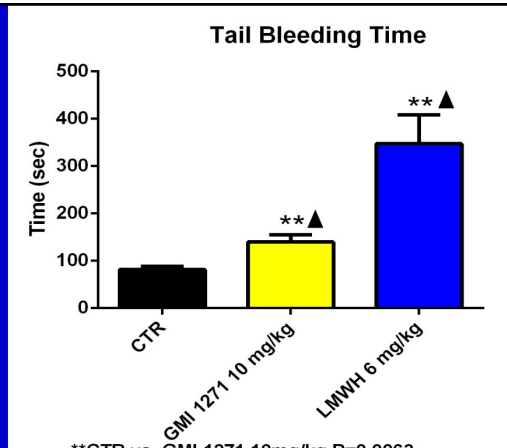


Figure 1: Chemical formula of GMI-1271.



CTR vs, Tx 1271 10 mg/kg BID, *P=0.0271
CTR vs, Tx 1271 20 mg/kg BID, *P=0.0144
CTR vs, Tx LOV 6 mg/kg SID, **P=0.0058



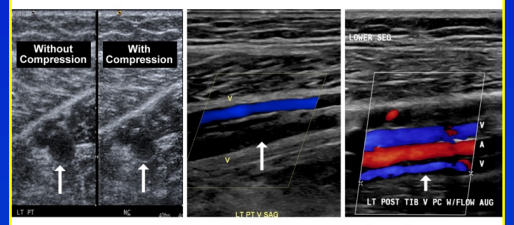
**CTR vs. GMI 1271 10mg/kg P=0.0063
**CTR vs. LMWH 6mg/kg P=0.0013
**GMI 1271 10mg/kg vs. LMWH 6mg/kg P=0.0036

Suman Sood

http://www.nhlbi.nih.gov/research/resources/vita

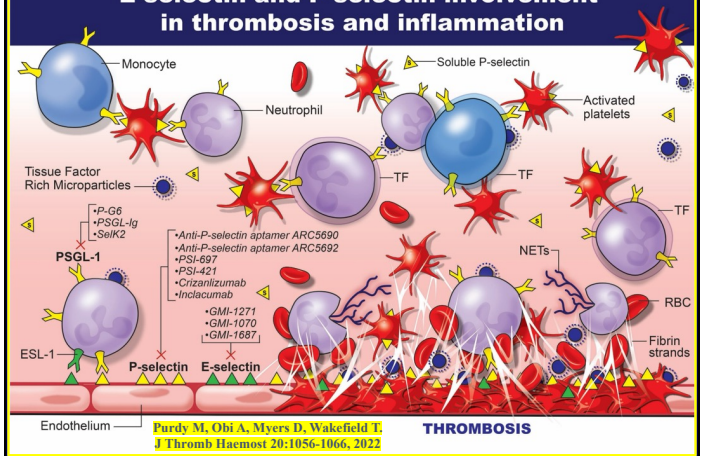
Devata S, Angelini DE, Blackburn S, et al. Use of GMI-1271, an E-selectin antagonist, in healthy subjects and in 2 patients with calf vein thrombosis. Res Pract Thromb Haemost 4:193-204, 2020

Patient 2



A. Baseline – PT Veins B. Day 8 – PT Veins C. Day 19 – PT Veins

E-selectin and P-selectin involvement in thrombosis and inflammation



Purdy M, Obi A, Myers D, Wakefield T. J Thromb Haemost 20:1056-1066, 2022

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