Pathophysiology of Post-Traumatic Thromboembolic Events

Jessica C. Cardenas, PhD,

THOR Remote Damage Control Resuscitation Symposium 2023

Center for Translational Injury Research

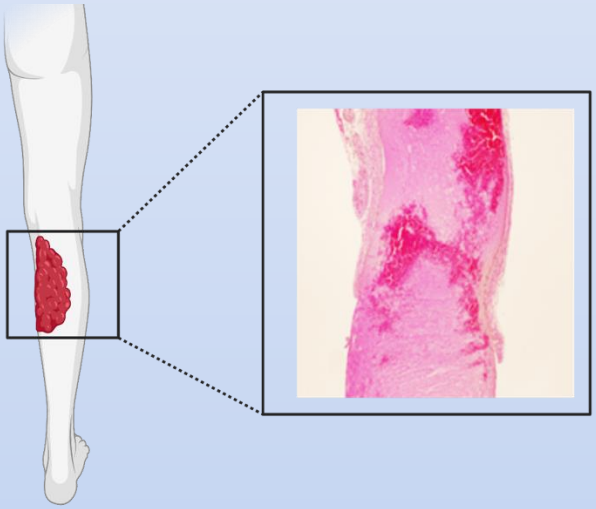
UTHealth®
The University of Texas Health Science Center at Houston
McGovern Medical School

Disclosures

Grifols – Research Funding

Background

- Venous thromboembolism (VTE) is a leading cause of morbidity and mortality worldwide
  - 1:10,000 in young adults → 1:100 in elderly
  - Overall lifetime risk of VTE among >45 y is ~8%
  - >50% of all VTEs in US occur during or within 3 months hospitalization



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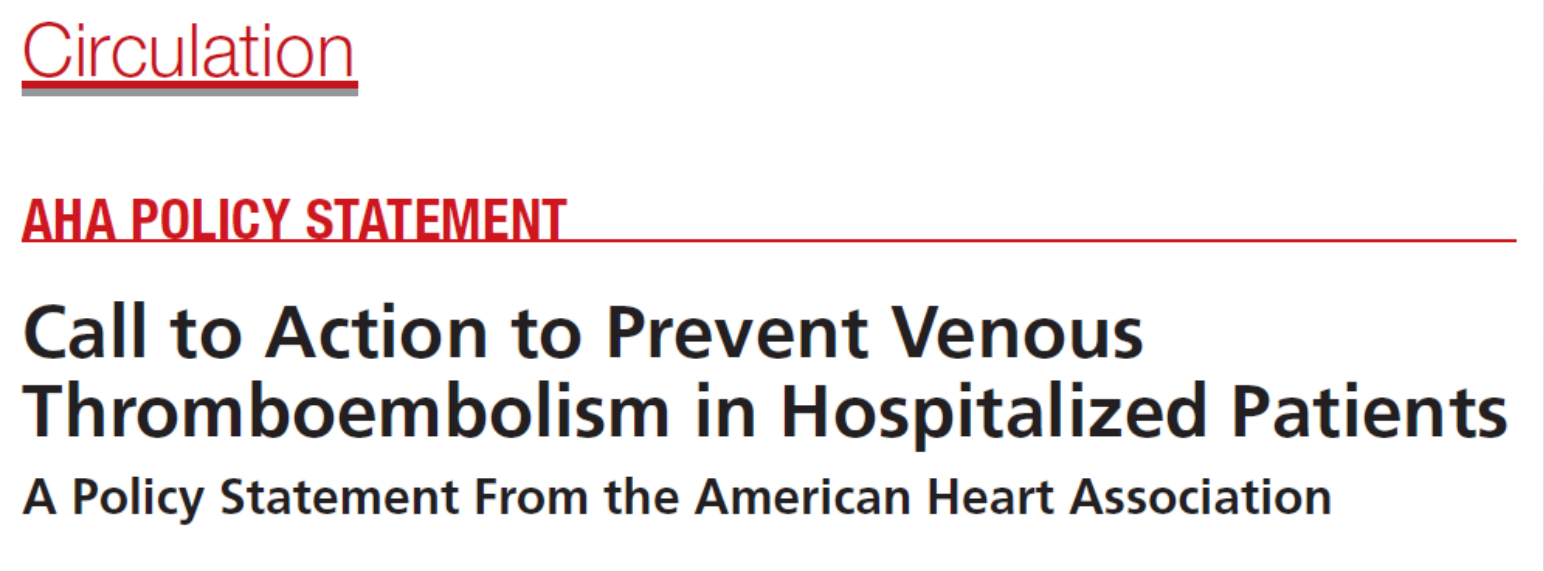
Circulation

AHA POLICY STATEMENT

Call to Action to Prevent Venous Thromboembolism in Hospitalized Patients

A Policy Statement From the American Heart Association

"… to reduce hospital-acquired VTE by 20% by 2030."

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  - Rates in surgical trauma up to 20%
    - Overall ~5-6%
    - Polytrauma with hemorrhage 15-20%
  - Develop in spite of early and aggressive VTE prophylaxis protocols
  - 2/3 occur after discharge (Park 2016)
  - 2nd leading cause of potentially preventable death after hospitalization (Drake 2017)

Hypercoagulability and VTE

Induction of procoagulant mechanisms = VTE risk

- Increased factor activity
- Liver production – fibrinogen, PAI-1
- Release of procoagulant microparticles
- Ongoing increases in thrombin generation
- Increased blood viscoelastic tests

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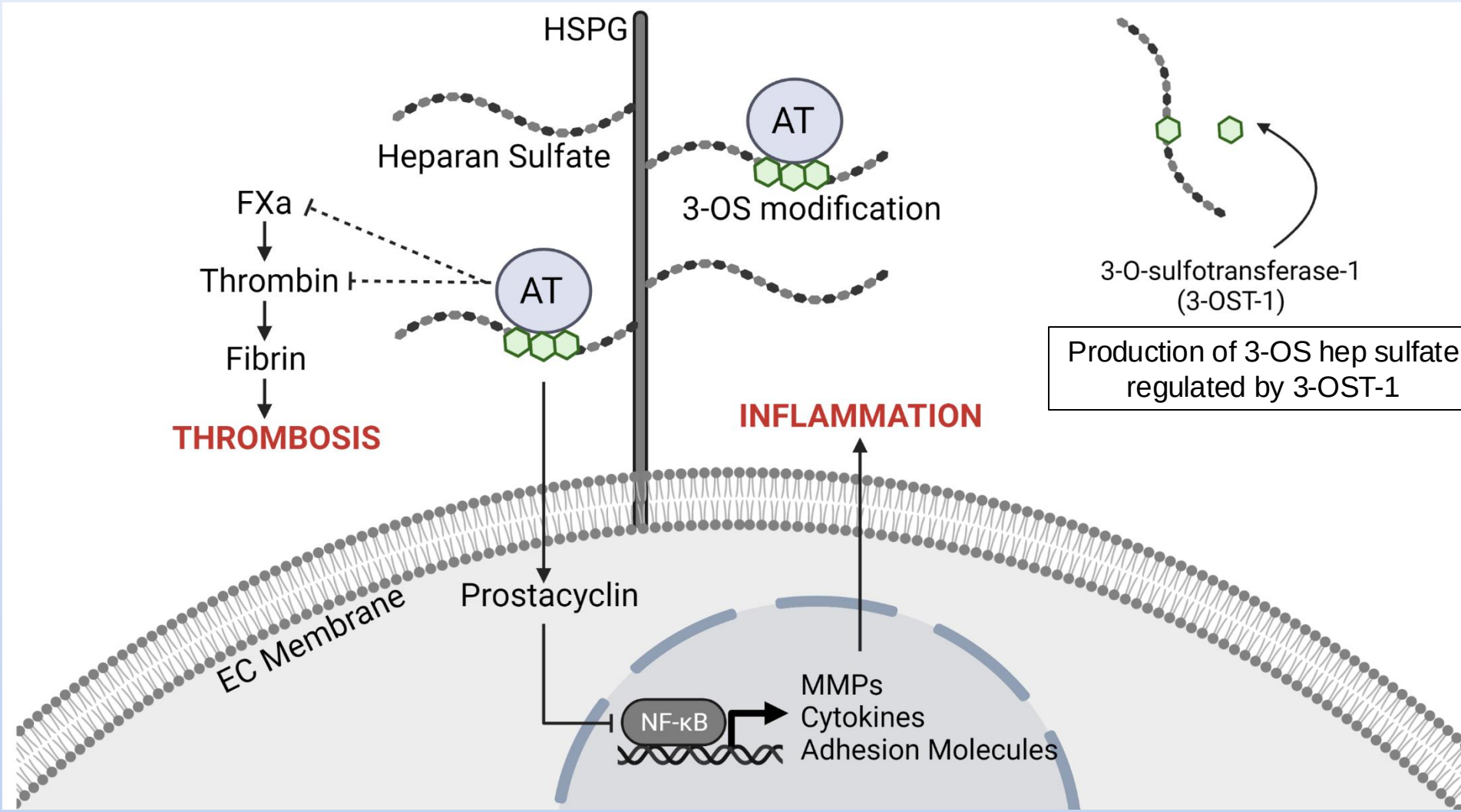
What about dysregulation of anticoagulant mechanisms???

The Antithrombin-Heparan Sulfate System



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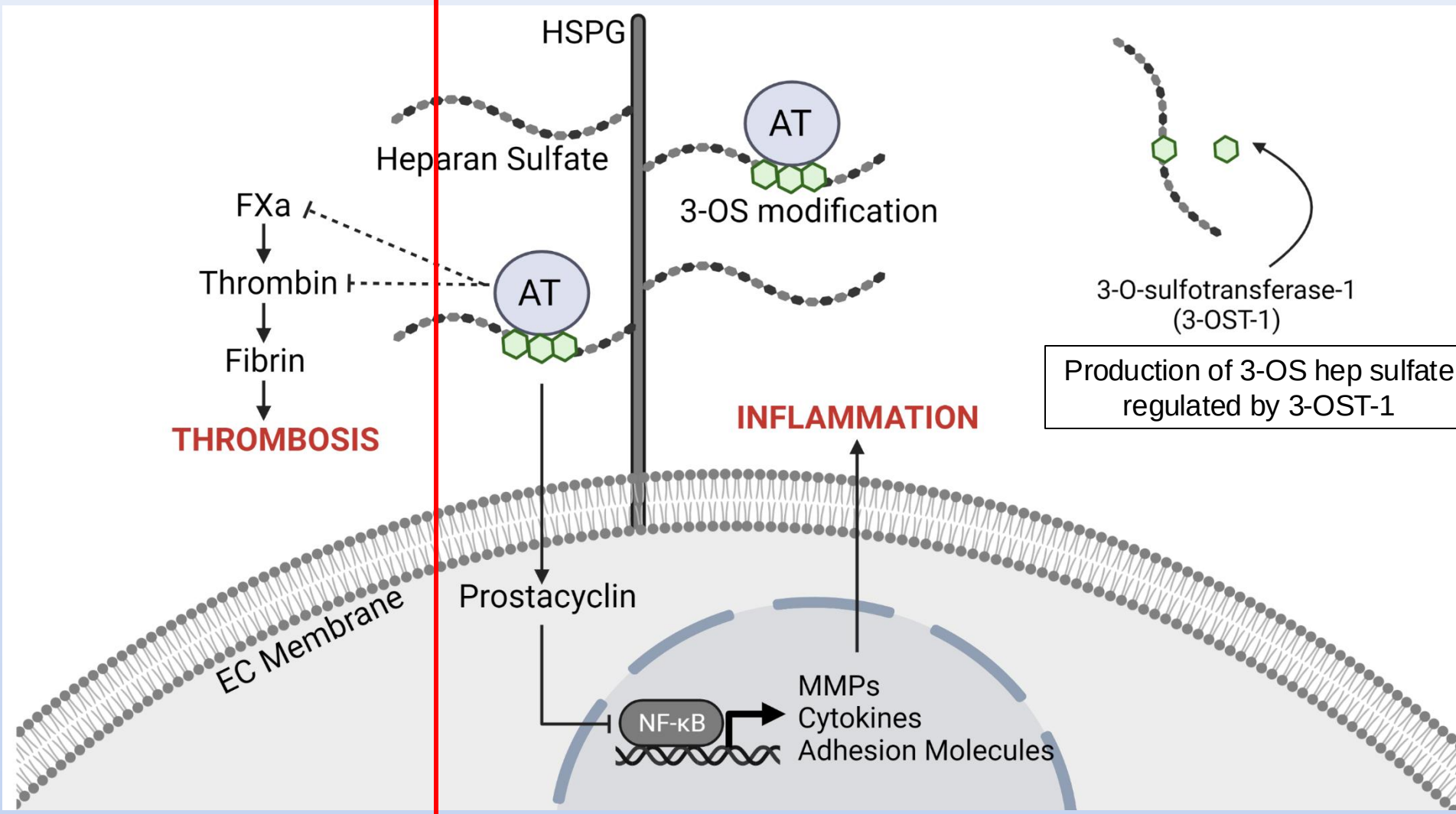

The Antithrombin-Heparan Sulfate System

SHOCK, Vol. 45, No. 2, pp. 166–173, 2016

PLASMA RESUSCITATION PROMOTES COAGULATION HOMEOSTASIS FOLLOWING SHOCK-INDUCED HYPERCOAGULABILITY

Jessica C. Cardenas,[*†] Andrew P. Cap,[*‡] Michael D. Swartz,[†§]
Maria del Pilar Huby,[*†] Lisa A. Baer,[*†] Nena Matijevic,[*†]
Bryan A. Cotton,[*†] John B. Holcomb,[*†] and Charles E. Wade[*†]

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Letter to the Editors-in-Chief

Acquired antithrombin deficiency is a risk factor for venous thromboembolism after major trauma

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Published in final edited form as:
Thromb Res. 2020 March ; 187: 131–138. doi:10.1016/j.thromres.2020.01.014.

Supplementation with antithrombin III *ex vivo* optimizes enoxaparin responses in critically injured patients

Jessica C. Cardenas, PhD[1,2], Yao-Wei Wang, MD[2], Jay V. Karri, MD[2], Seenya Vincent[2], Andrew P. Cap, MD, PhD[1,3], Bryan A. Cotton, MD[1,2], Charles E. Wade, PhD[1,2]

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How Effective is VTE Chemoprophylaxis?

JAMA Surgery | Original Investigation

Association of Changes in Antithrombin Activity Over Time With Responsiveness to Enoxaparin Prophylaxis and Risk of Trauma-Related Venous Thromboembolism

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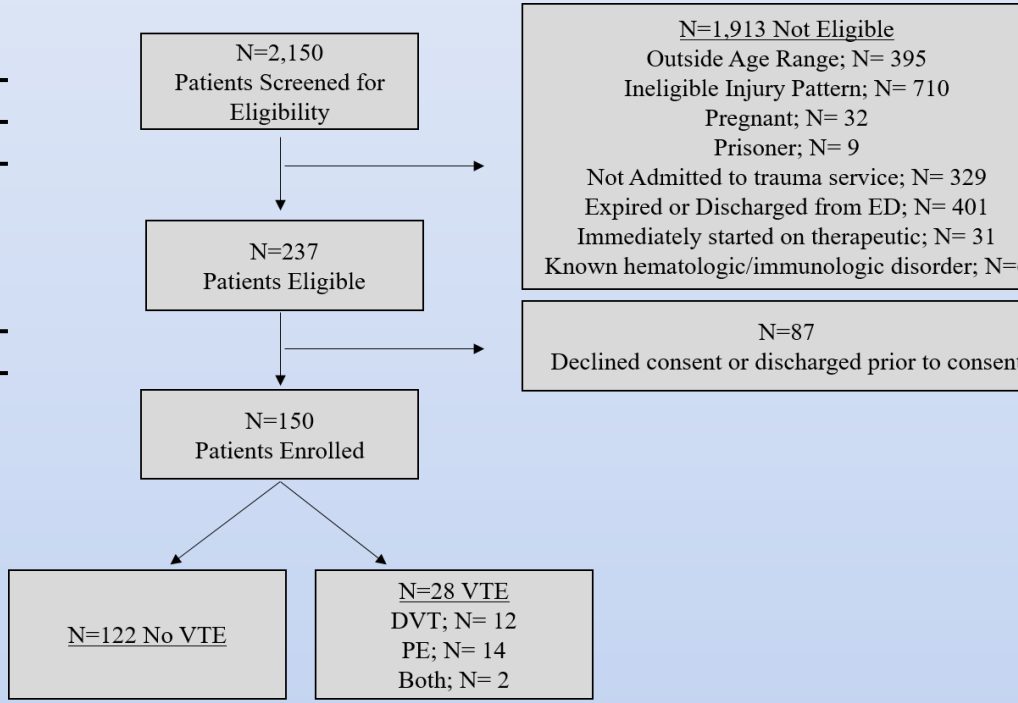
TABLE 1. Enrollment Criteria

Inclusion Criteria
18-70 years of age
Level 1 or Level 1 upgrade
Polytraumatic injuries or pelvic/long bone fracture
Admission to trauma service
Exclusion Criteria
Prisoners (admitted directly from correctional facility)
Obviously pregnant females
≥ 20% total body surface area burned
Nonsurvivable head injury
Known hematologic or immunologic disorder
Known prehospital anticoagulant use



How Effective is VTE Chemoprophylaxis?

METHODS

- Plasma collected daily for 7 days
- Responsiveness to prophylactic enoxaparin defined by anti-FXa levels
- Patients who received <3 doses of enoxaparin or UFH were excluded from analysis
- N=110 patients

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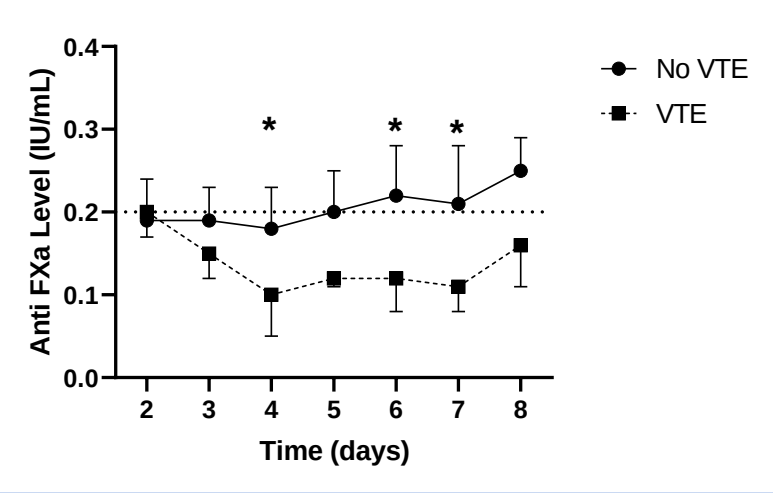

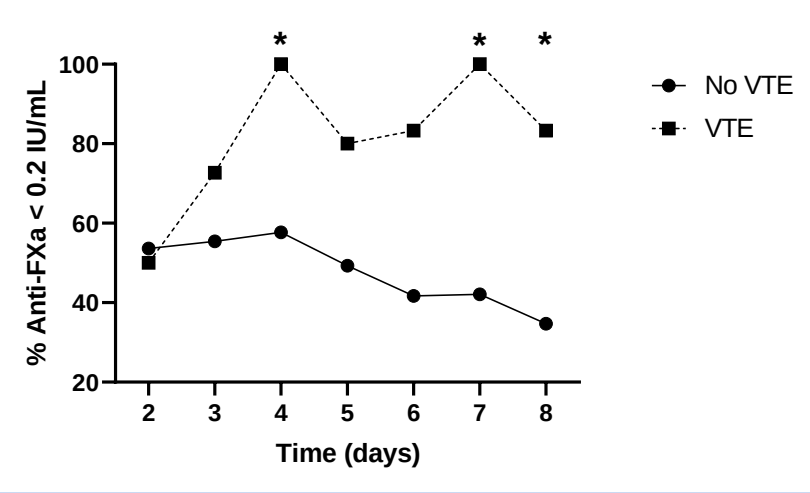

How Effective is VTE Chemoprophylaxis?

Stratifying Responder Type:

- *All Responder* – anti FXa ≥ 0.2 for every dose after 3 doses of enoxaparin
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- *Never Responder* – never achieved an anti FXa ≥ 0.2 at any time

N=110	Incidence
All Responder	16.4%
Transient Responder	60.0%
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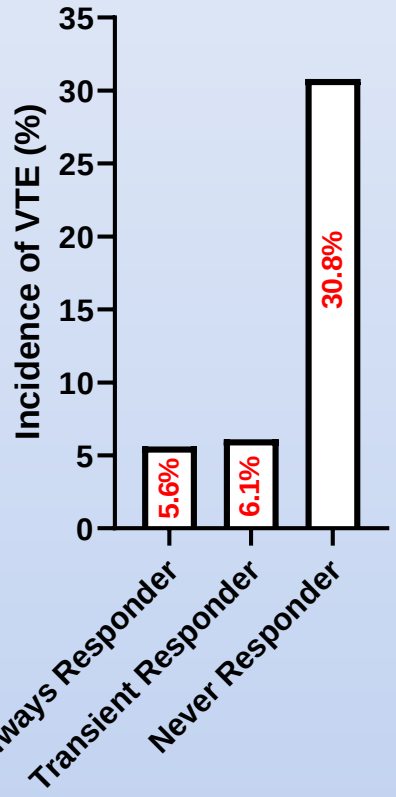

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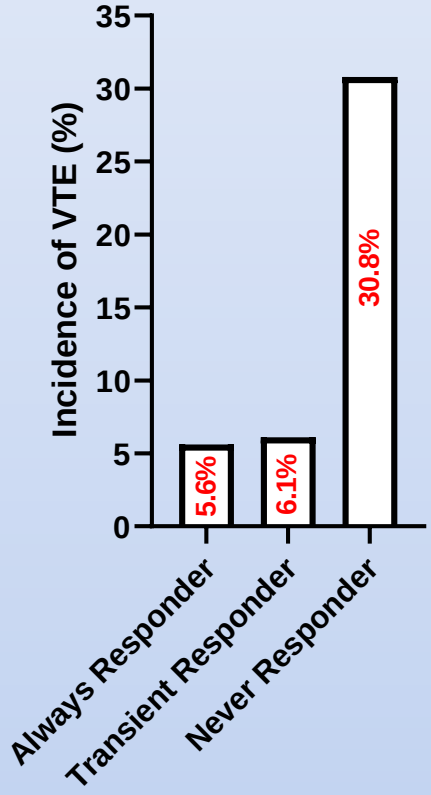

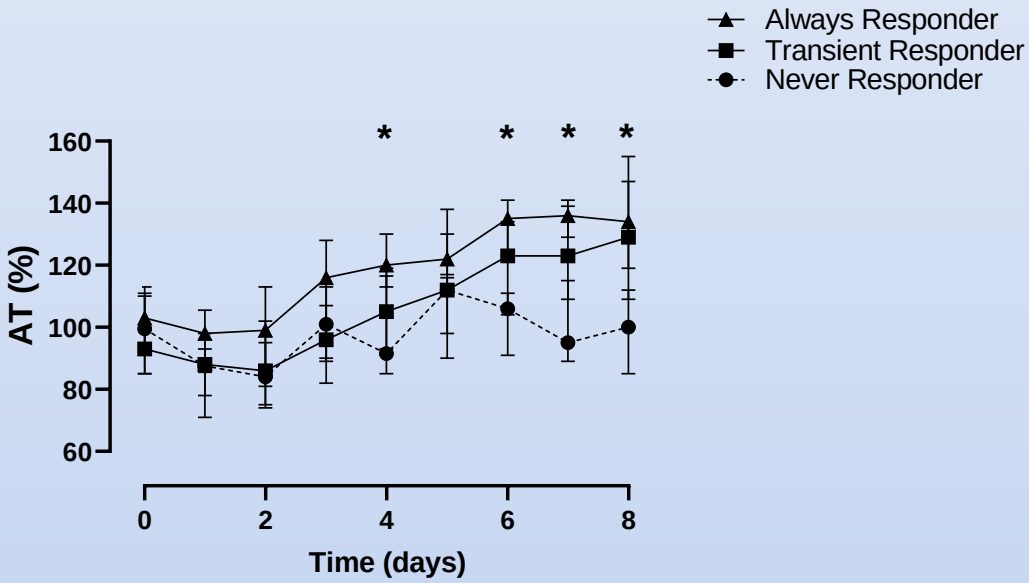

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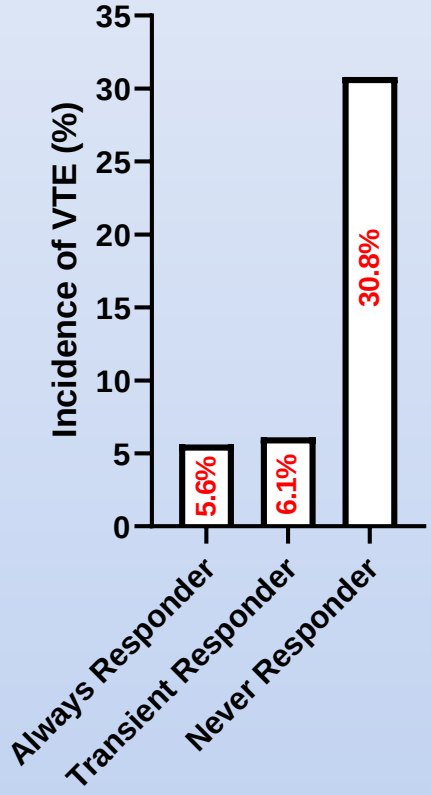

Always and Transient Responders – 6% developed VTE

Never Responders – 69% didn't develop VTE

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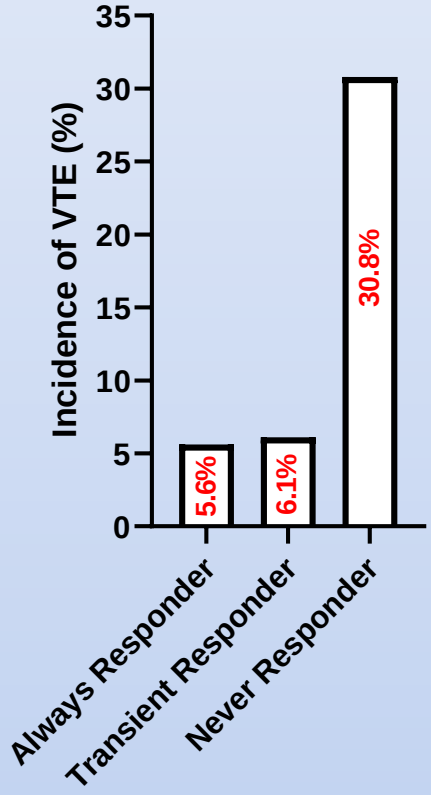

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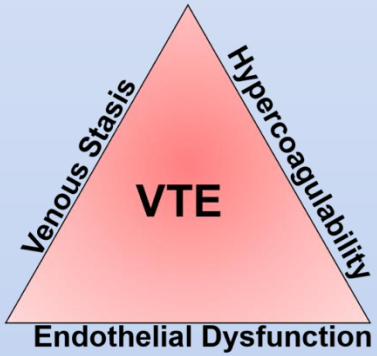
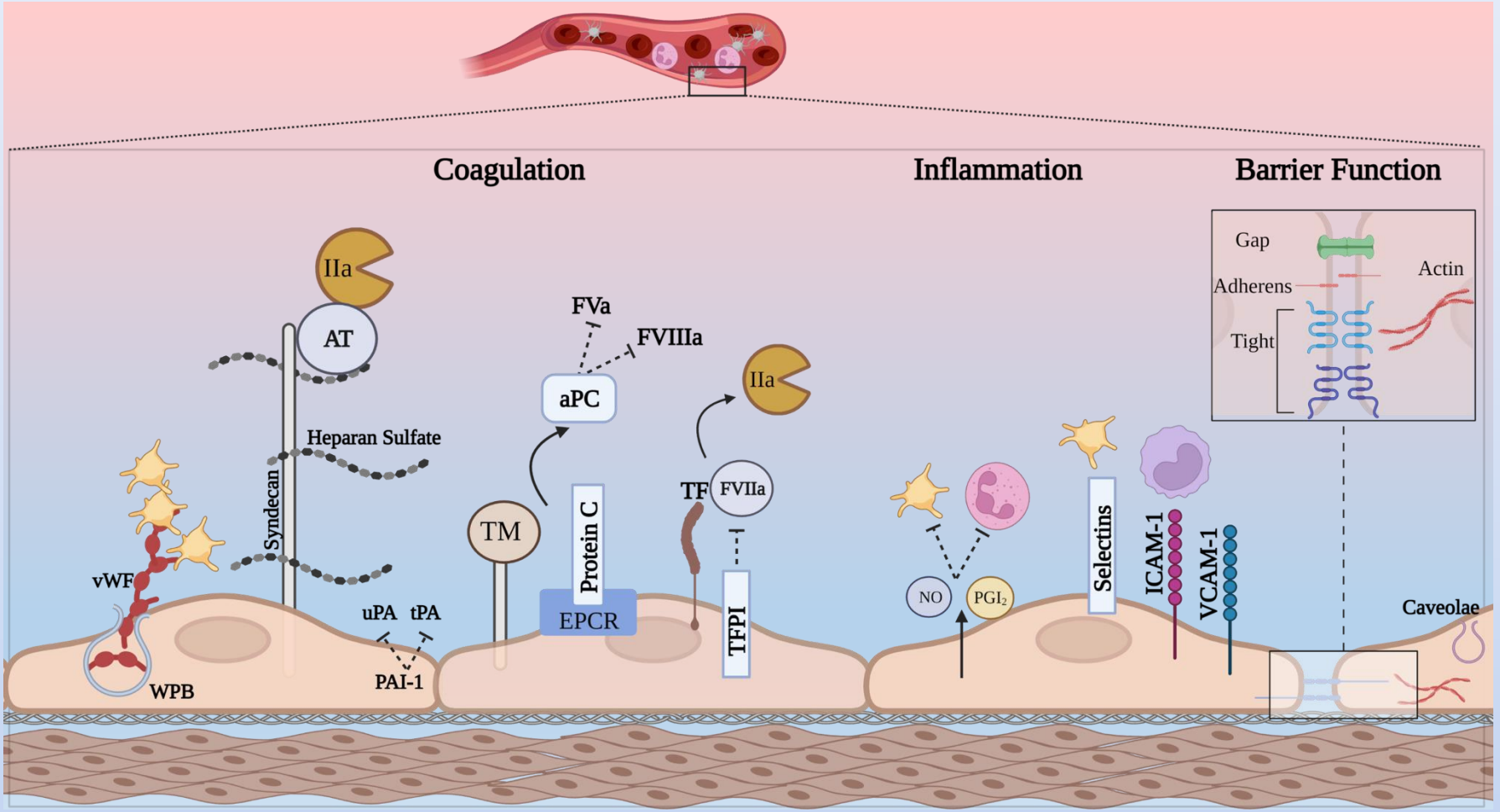


Endothelial Cell (EC) Regulation of Thrombosis



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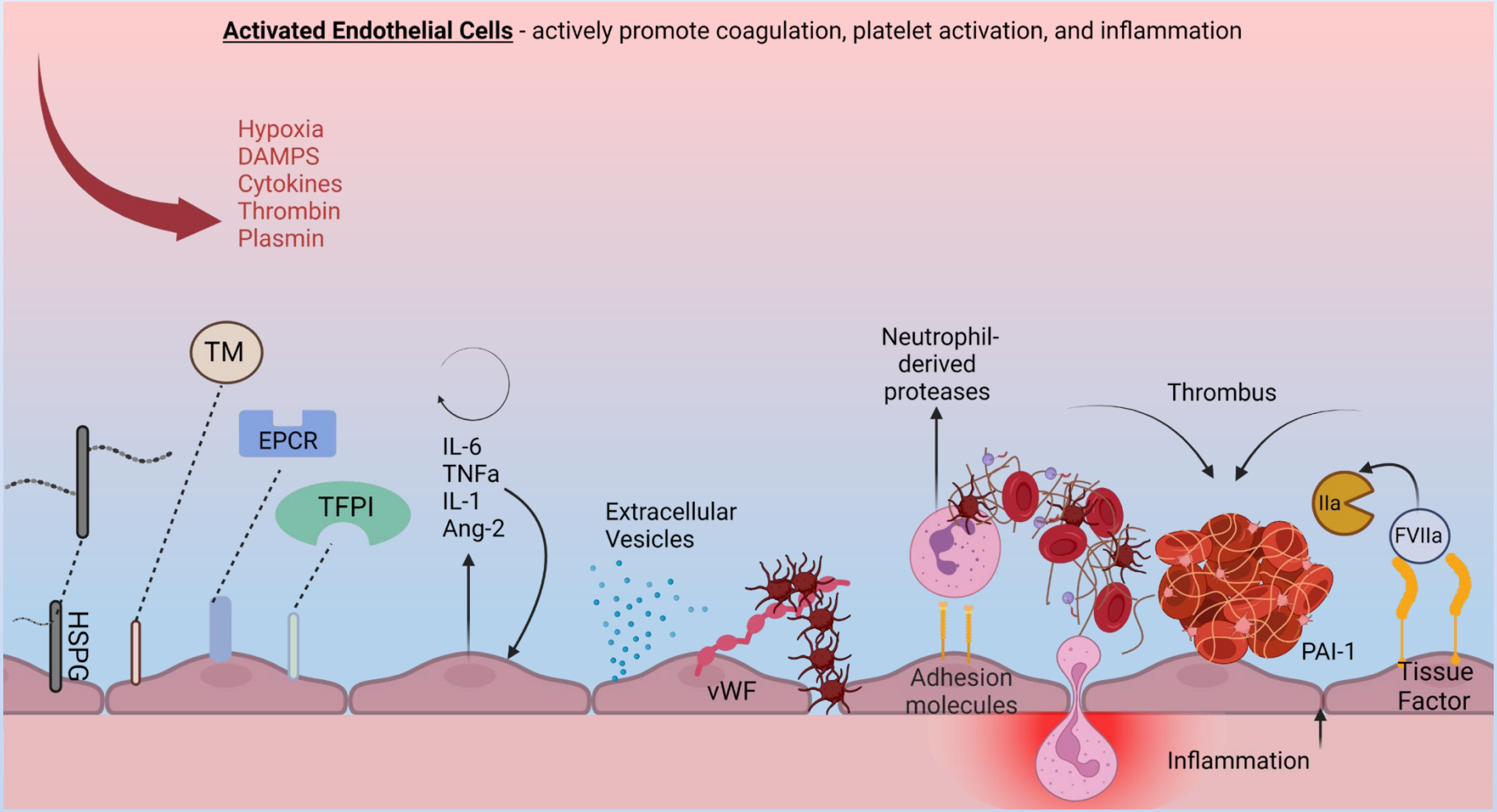

EC Injury and VTE Risk

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Surgery xxx (2023) 1–6

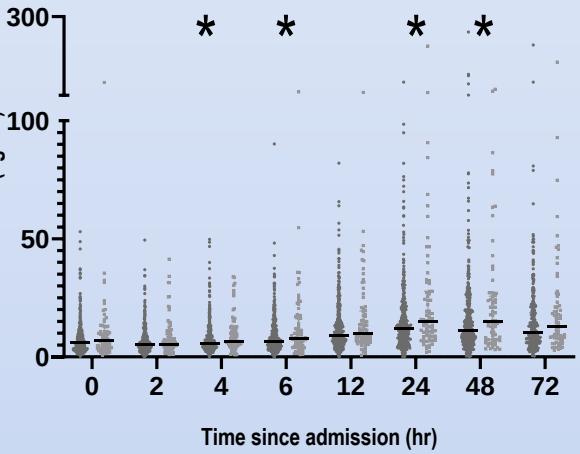
Contents lists available at ScienceDirect

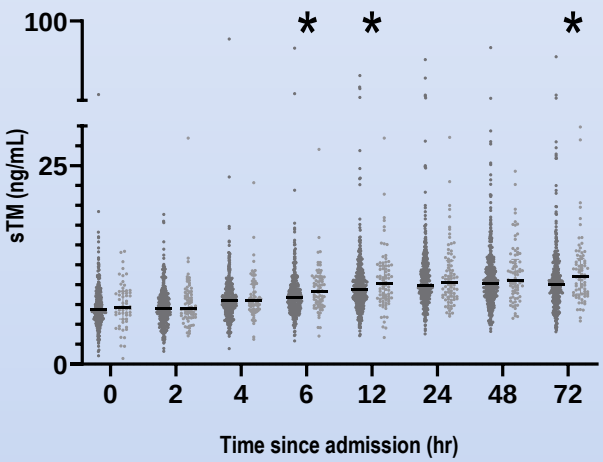
Surgery

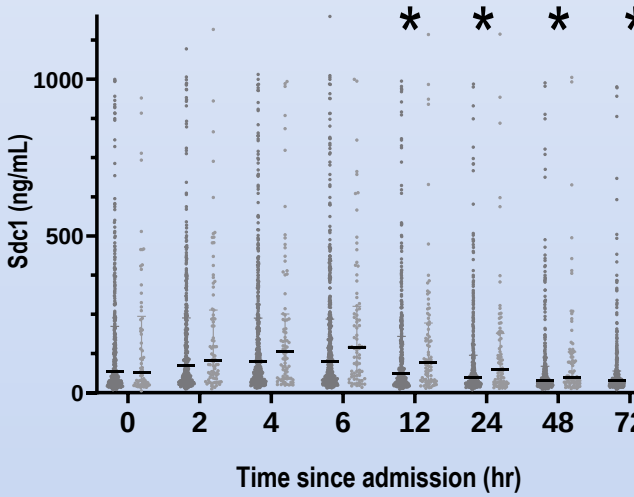
journal homepage: www.elsevier.com/locate/surg

Soluble endothelial protein C receptor is an independent predictor of venous thromboembolism after severe injury: Secondary analysis of a prospective cohort study

Kelly E. Sanders, DO[a,*], Sarah Holevinski, MD[a], Xu Zhang, PhD[b], Bryan A. Cotton, MD[a,c], Jessica C. Cardenas, PhD[a]

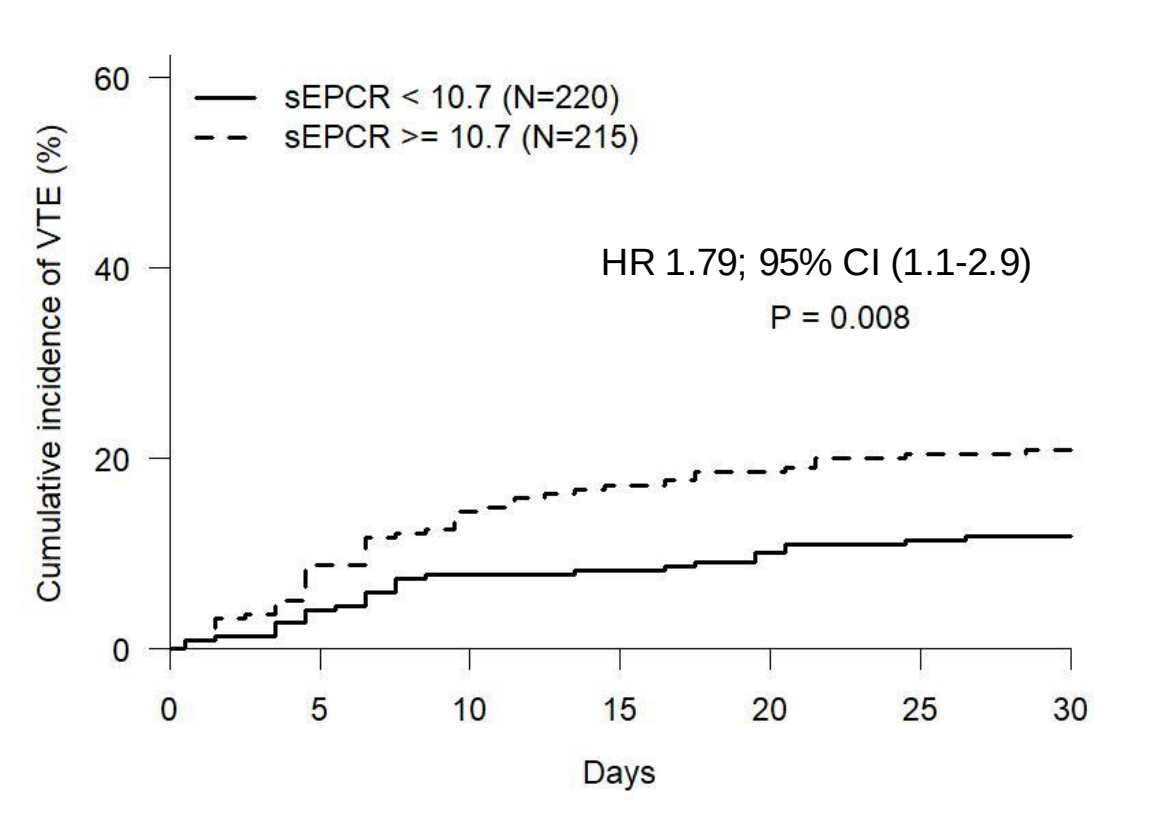






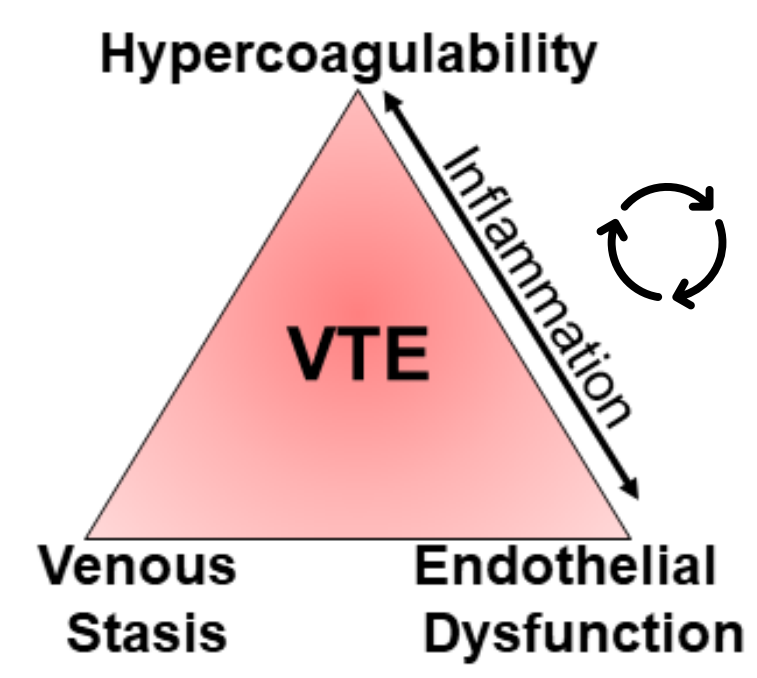
● = No VTE
● = VTE

EC Injury and VTE Risk

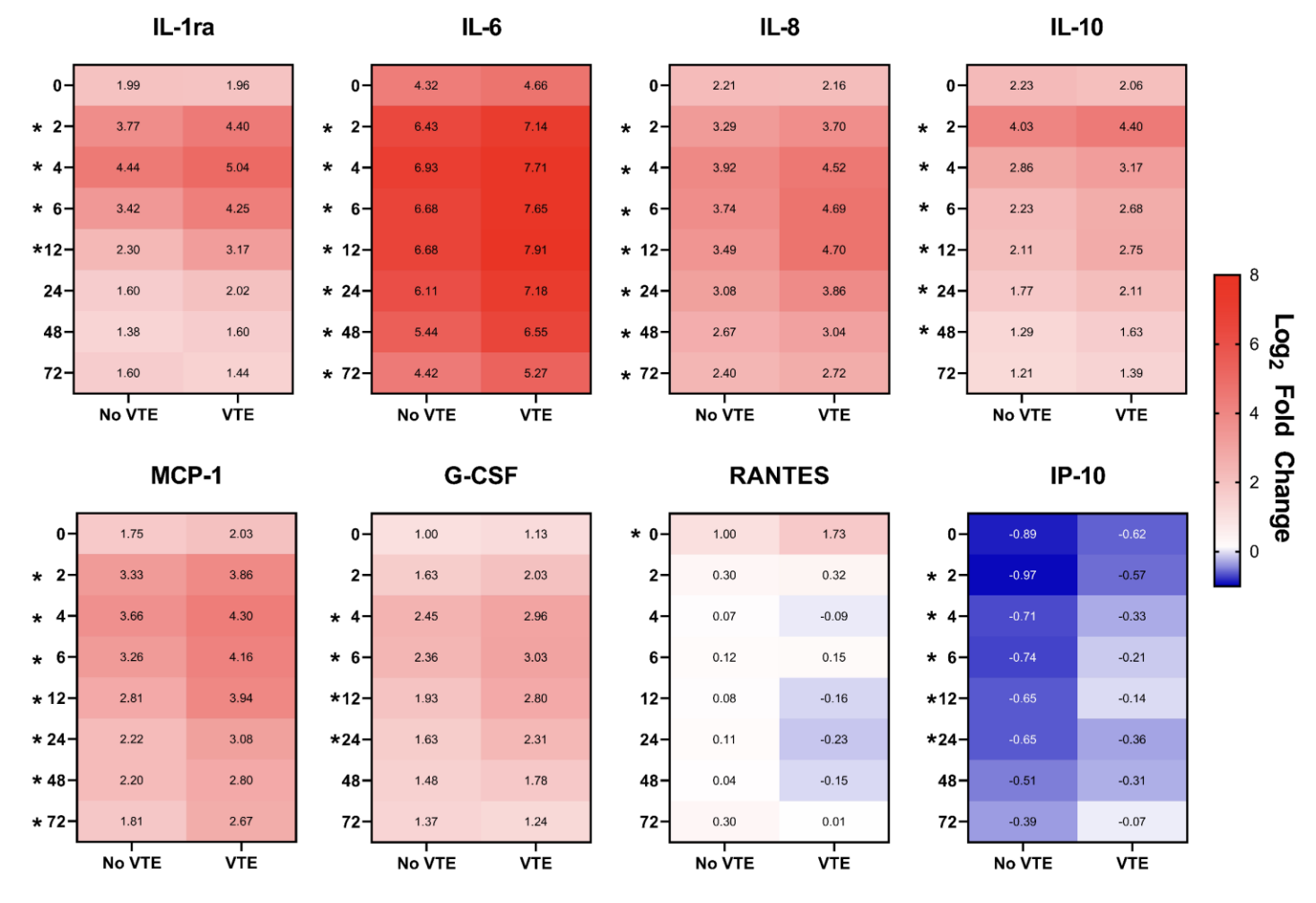


Endothelial activation independently associated with VTE risk

Virchow's Triad- Updated



VTE and Inflammation

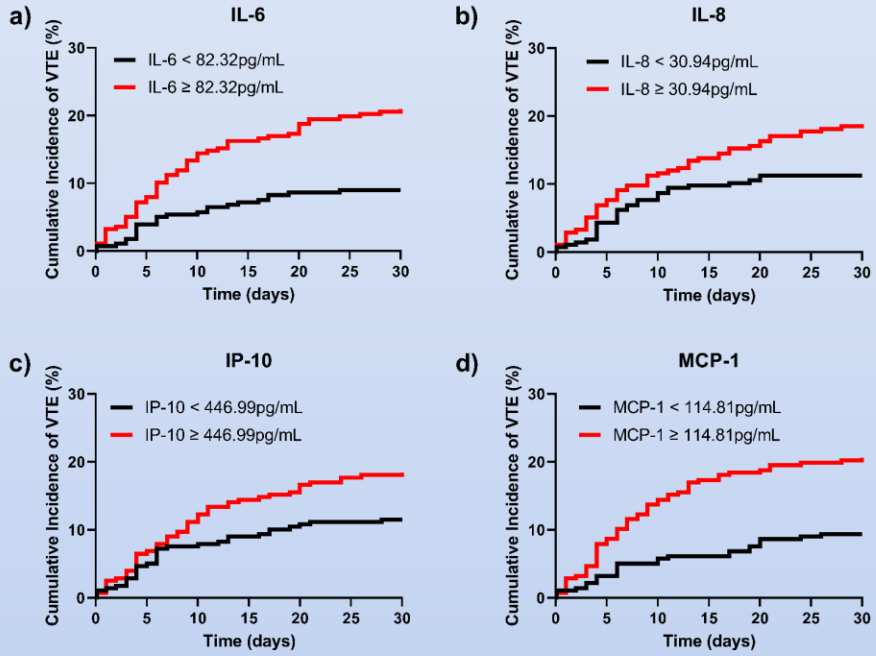


Mankame, *Shock*, Submitte

VTE and Inflammation

Multiple logistic regression analysis predicting VTE using last available cytokine values (pg/mL), while controlling for age, sex, and injury severity score. Asterisk indicates statistical significance.

Inflammatory Mediator	Odds Ratio	95% Confidence Interval	p-value
IL-6 ≥ 82.32	2.63	1.58, 4.40	<0.001*
IL-8 ≥ 30.94	1.77	1.08, 2.89	0.02*
IP-10 ≥ 446.99	1.64	1.00, 2.67	0.048*
MCP-1 ≥ 114.81	2.49	1.47, 4.20	<0.001*



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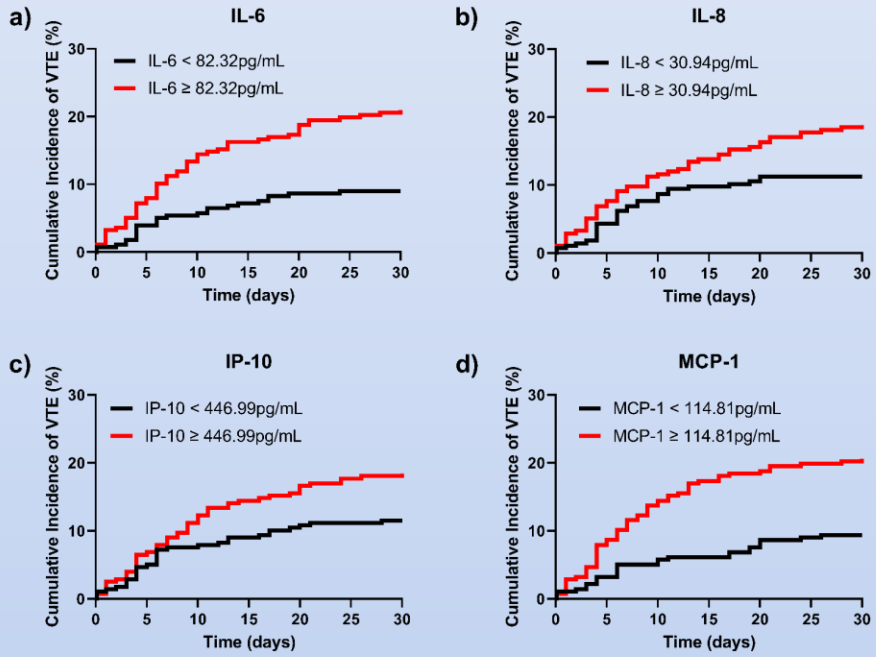
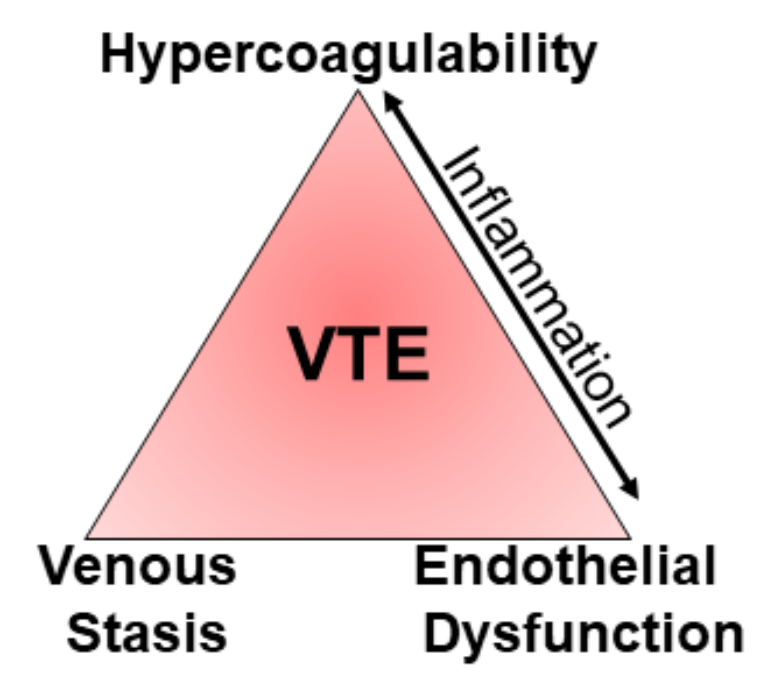


Correlation Inflammation and sEPCR

IL-6	R 0.33	p<0.01
IL-8	R 0.49	p<0.0001

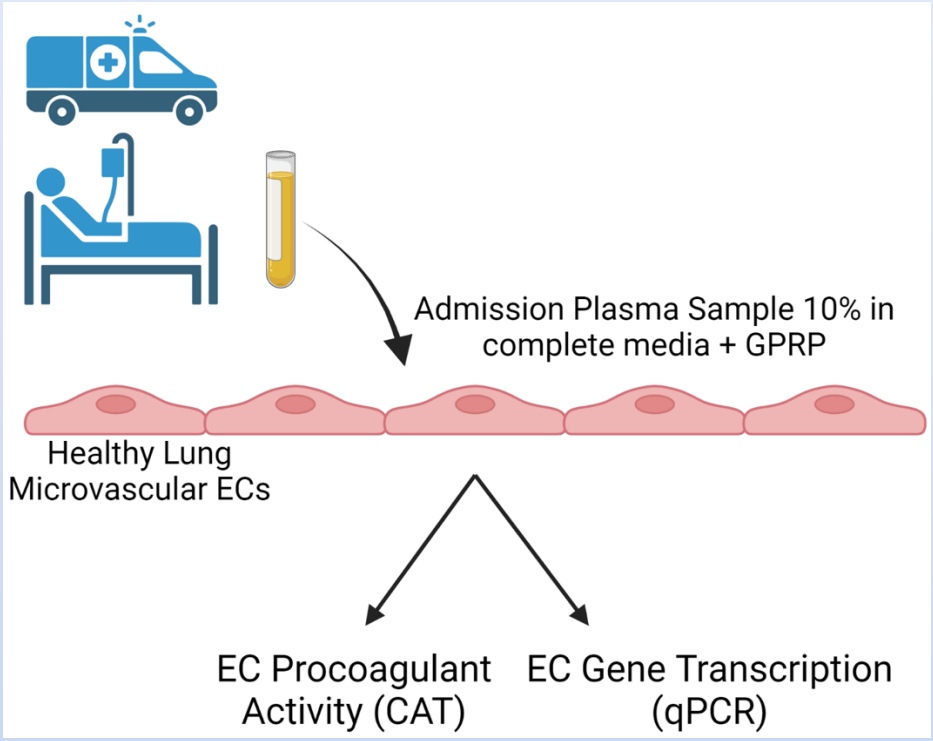
Mankame, *Shock*, Submitte

How does inflammation link EC dysfunction and hypercoagulability?

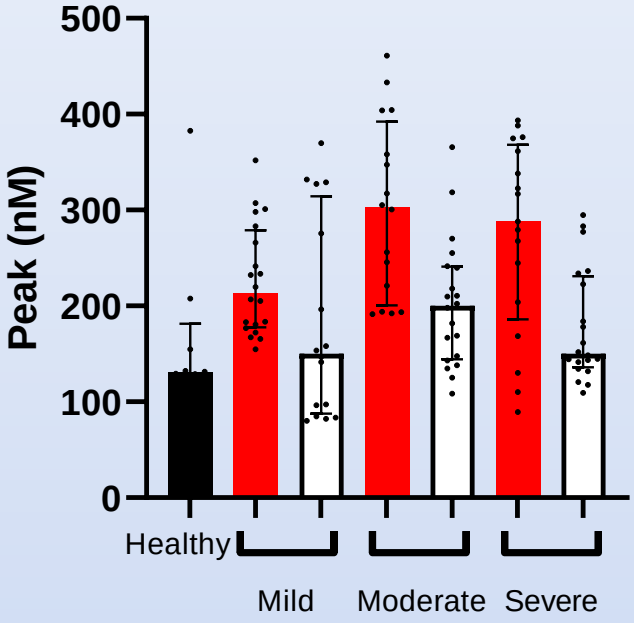


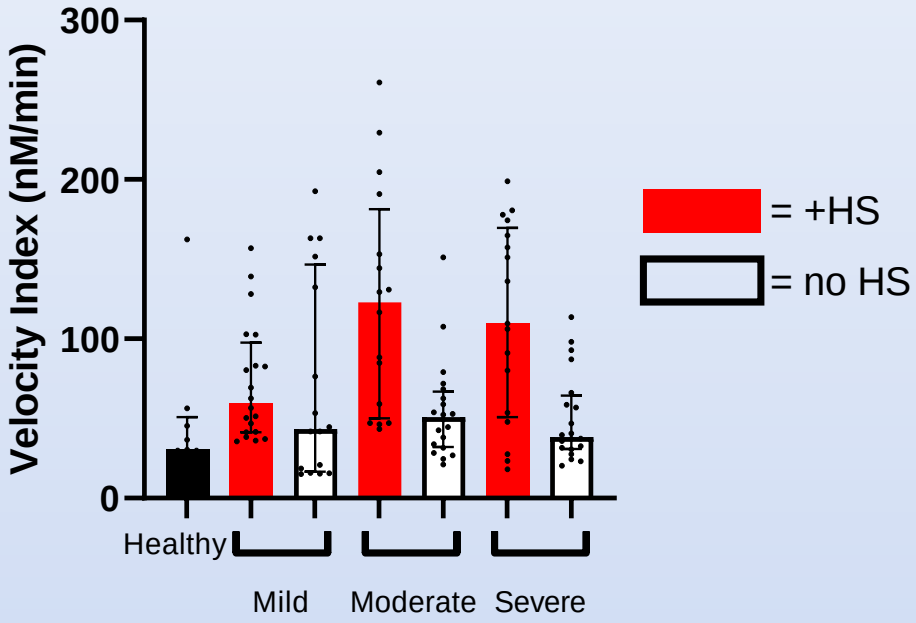
Donor Plasma (EDTA)

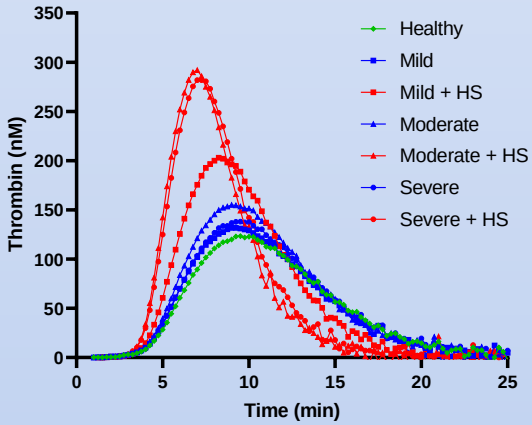
- Healthy Donors
- Minimally Injured (ISS 2-15) no HS
- Minimally Injured + HS
- Moderately Injured (ISS 15-25) no HS
- Moderately Injured + HS
- Severely Injured (ISS > 25) no HS
- Severely Injured + HS



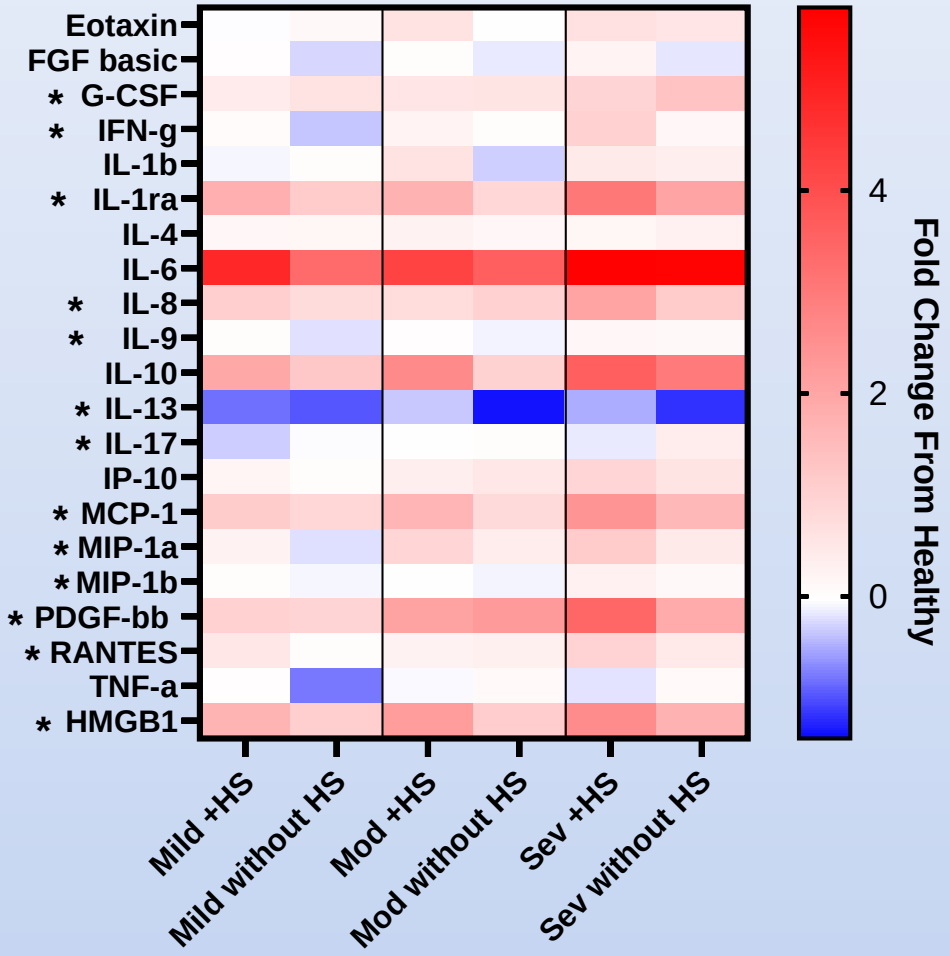
EC procoagulant activity after exposure to trauma patient plasma strongly driven by HS







EC procoagulant activity linked to plasma inflammatory mediators



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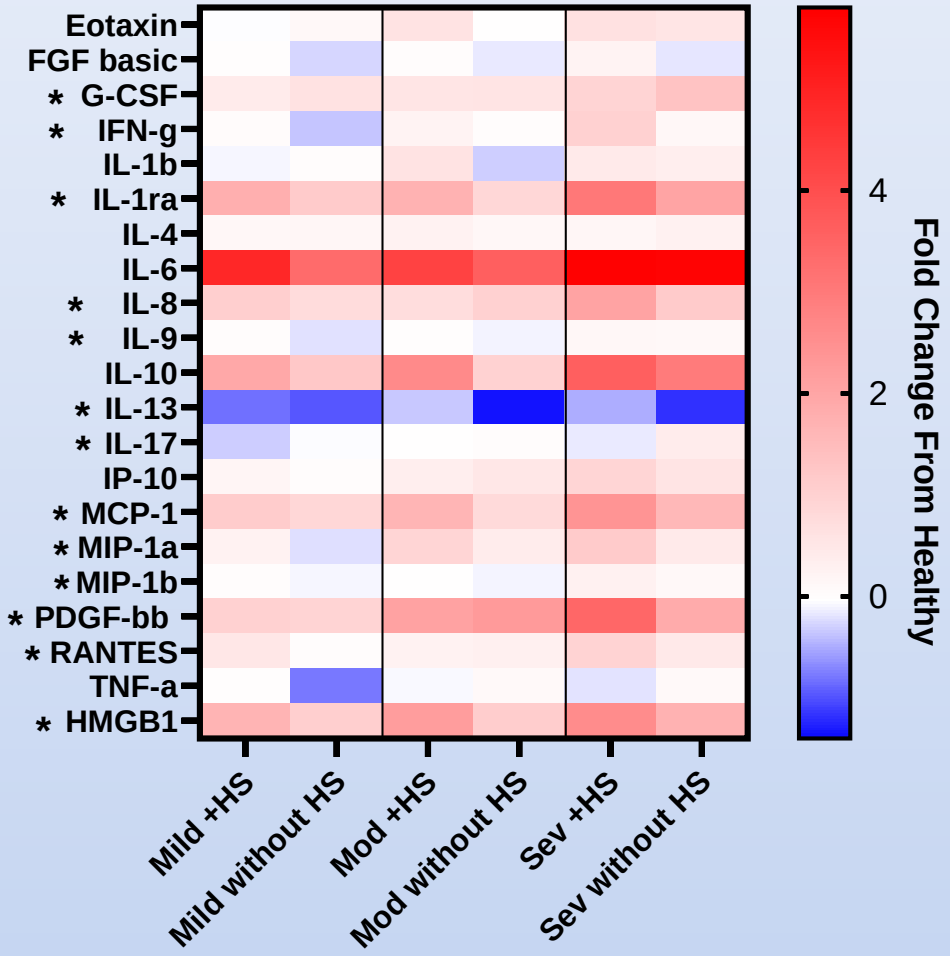
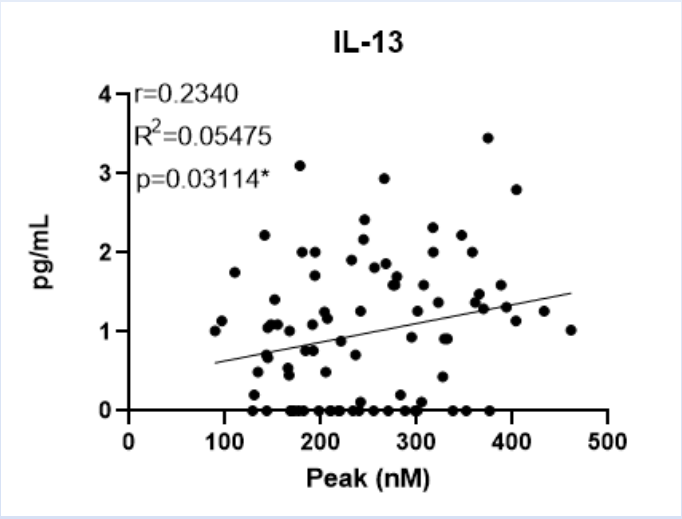
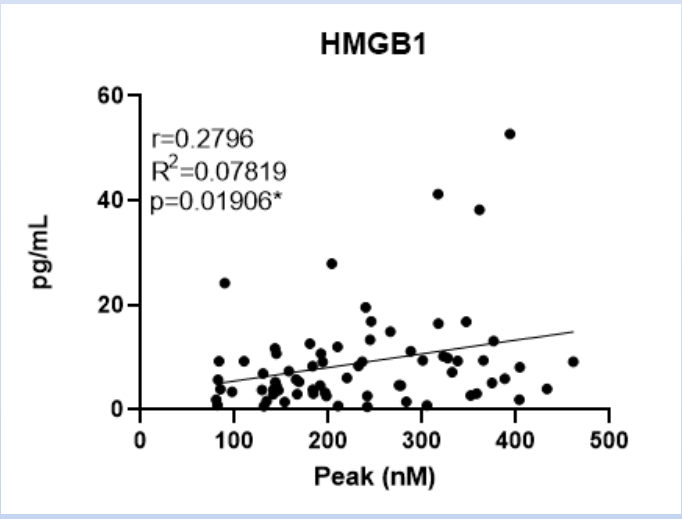
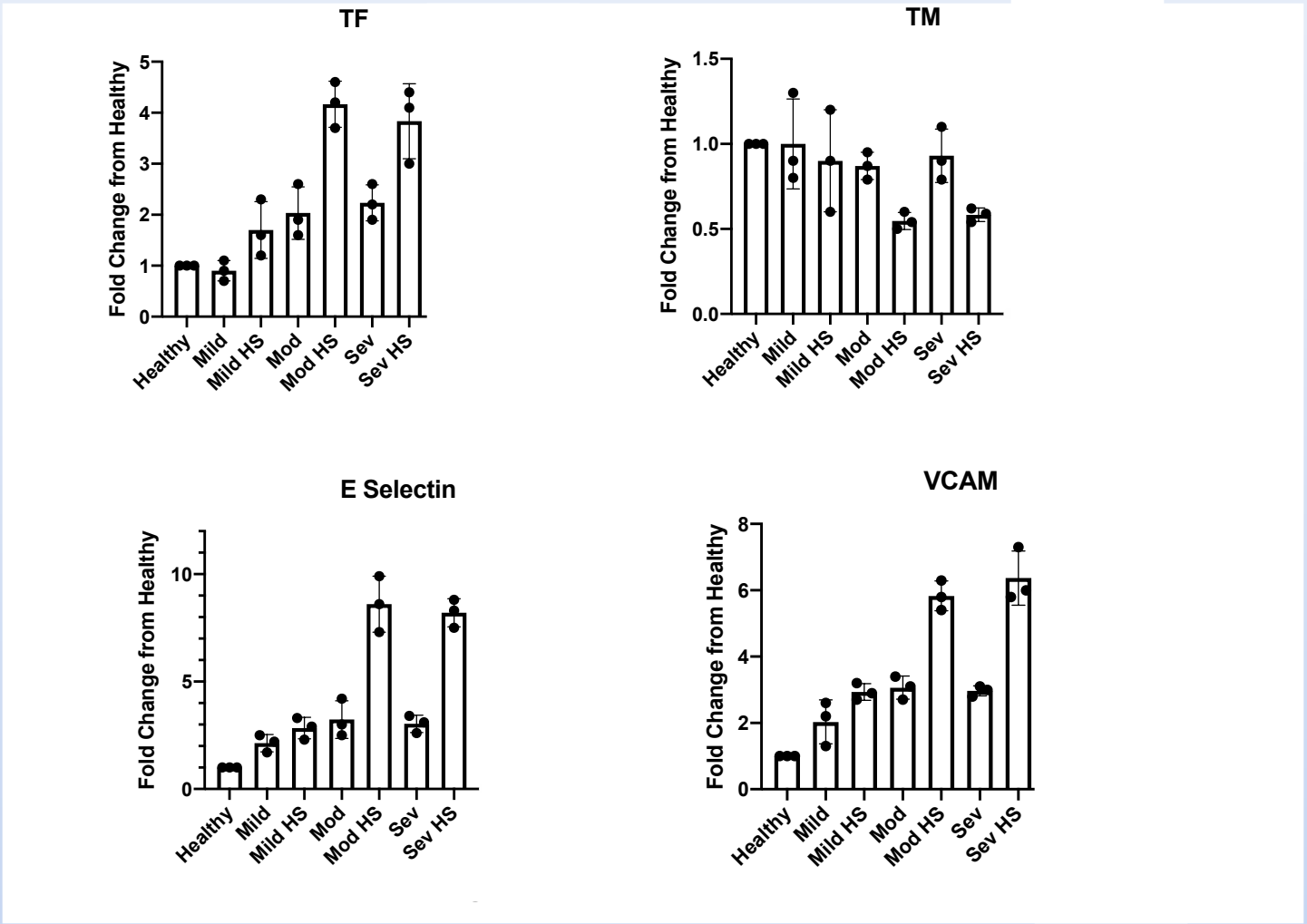






EC thromboinflammatory gene transcription following T/HS is NFkB dependent



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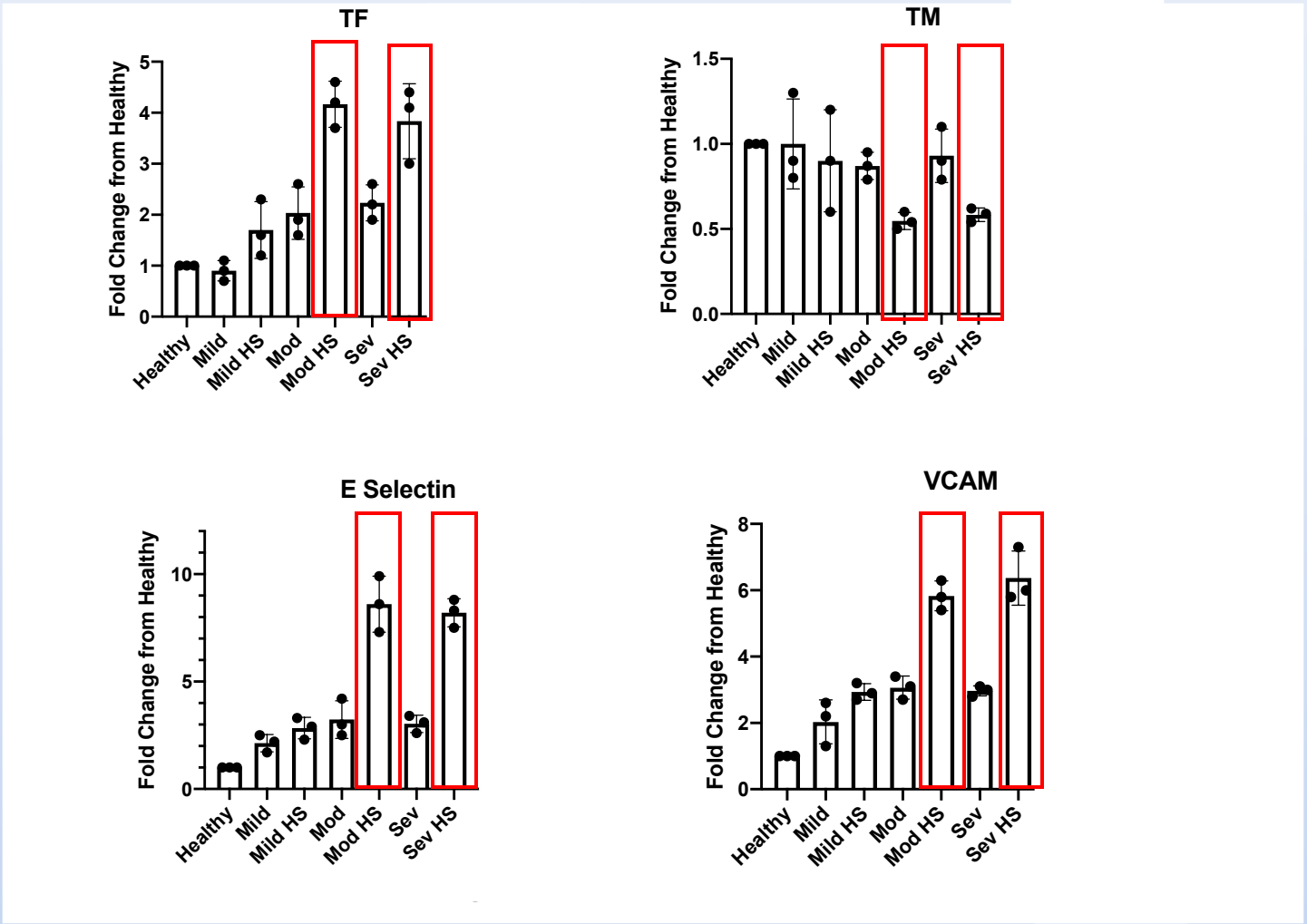

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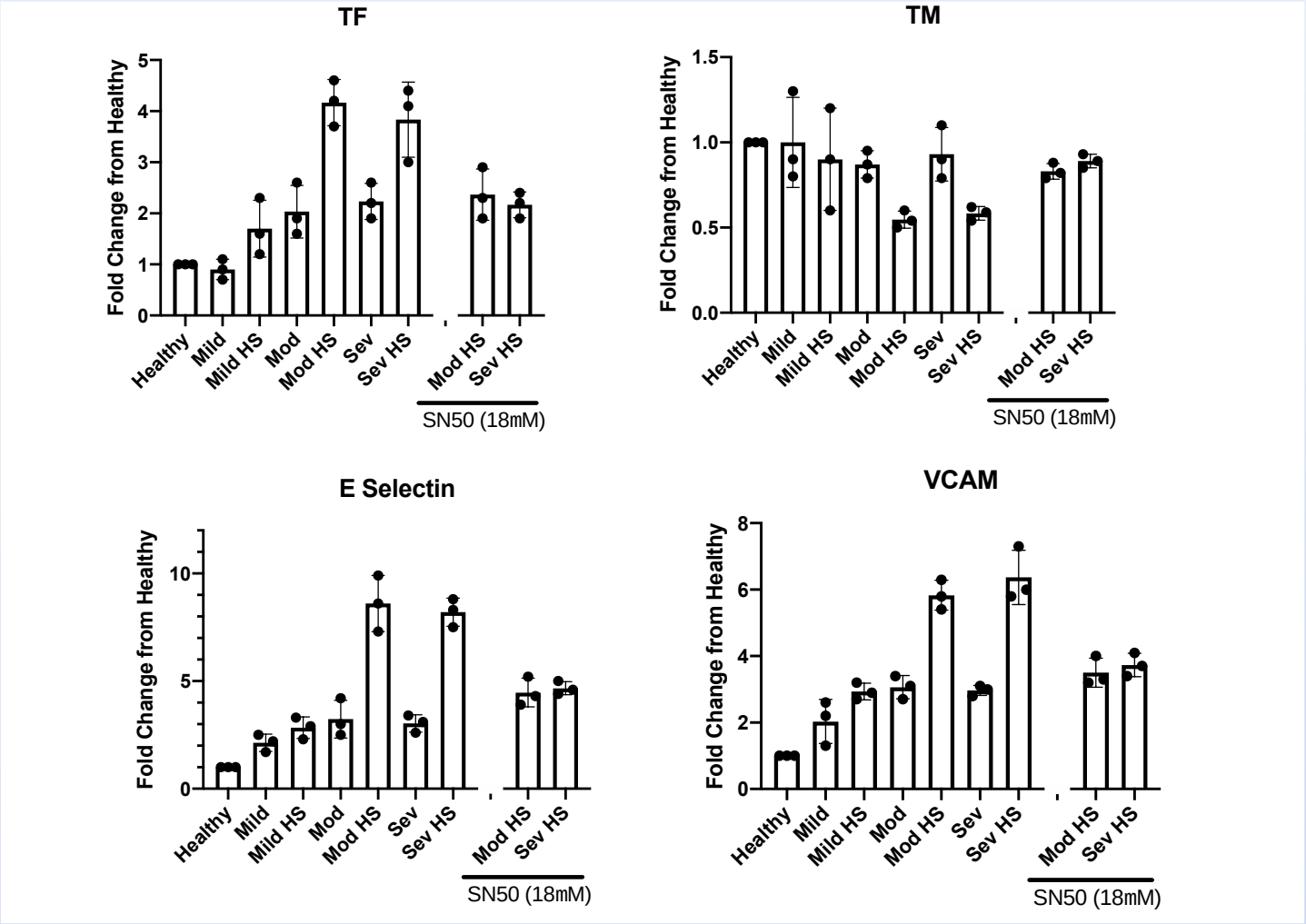
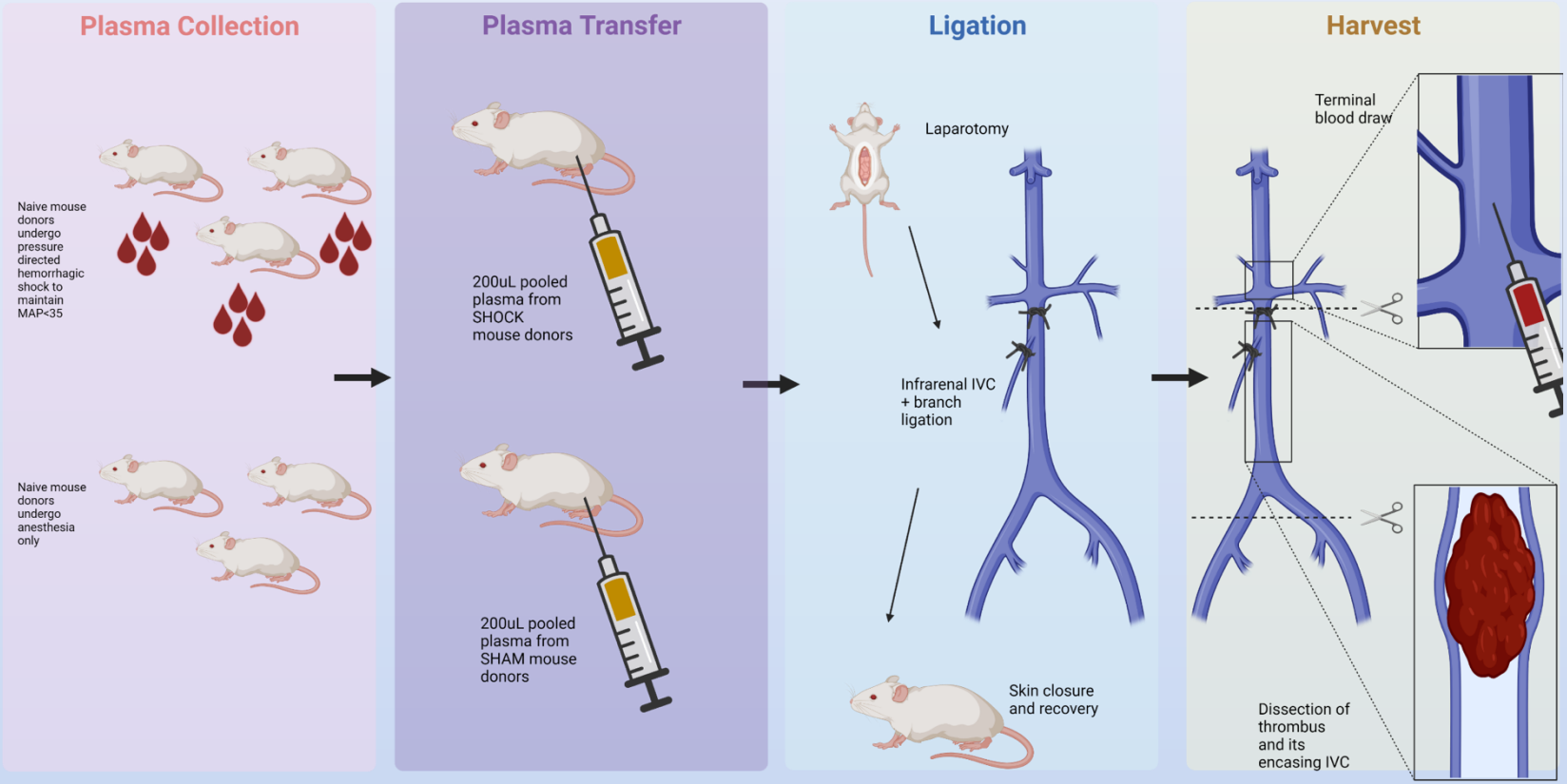


EC pro-thromboinflammatory activity is uniquely amplified during HS and occurs via activation of NFkB pathway

HS Plasma Milieu Influences Thrombus Development



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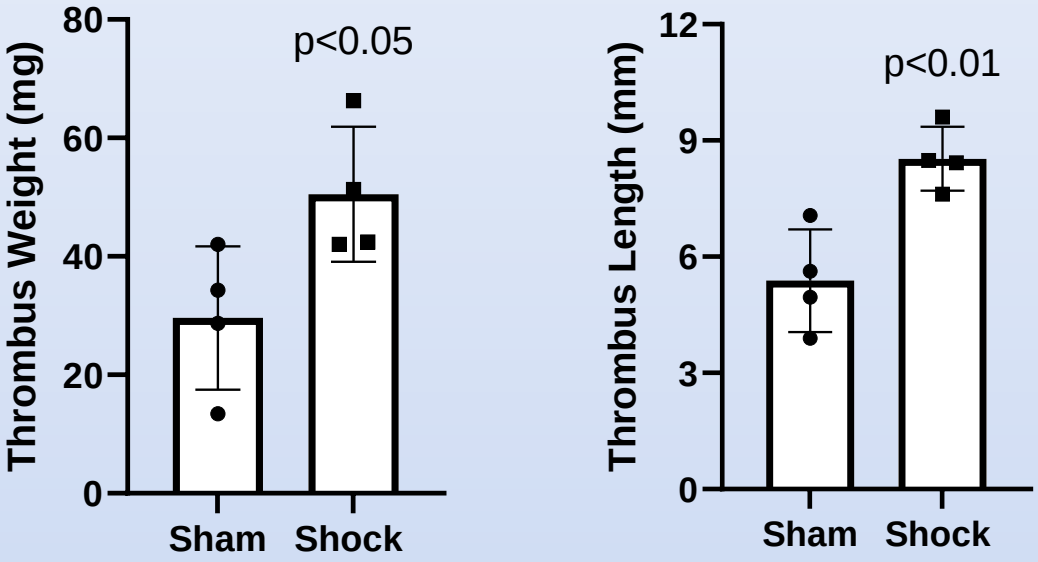
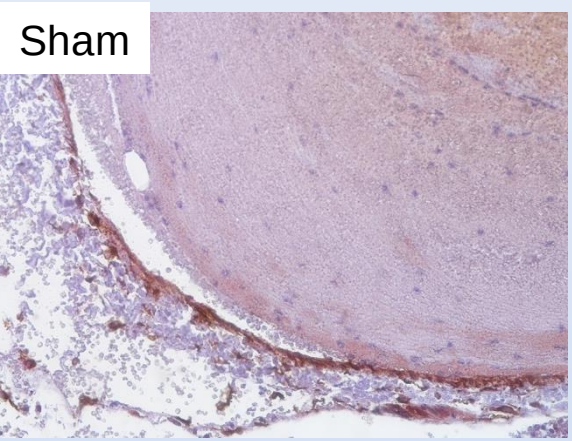
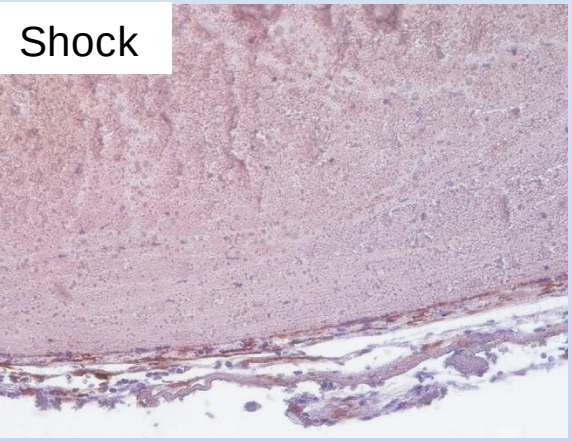


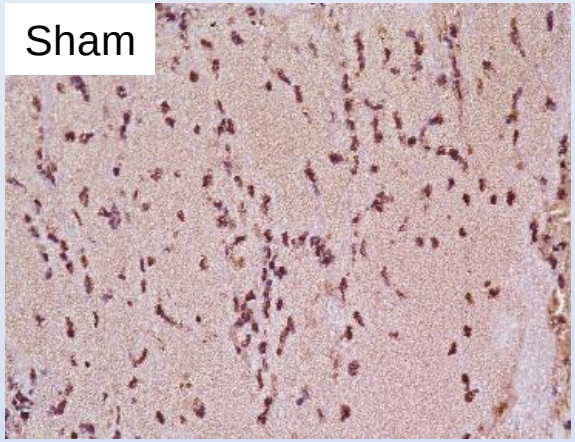
HS Plasma Milieu Influences Thrombus Development

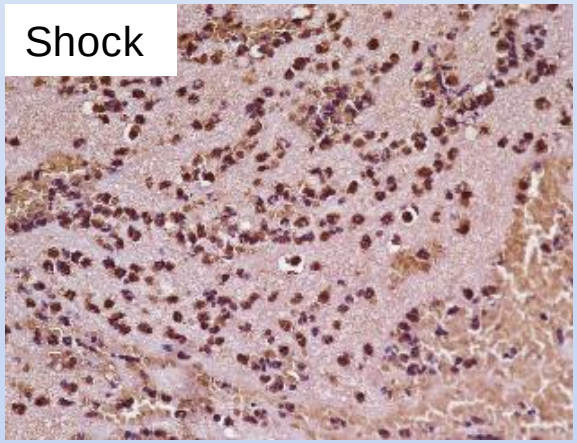
Thrombomodulin

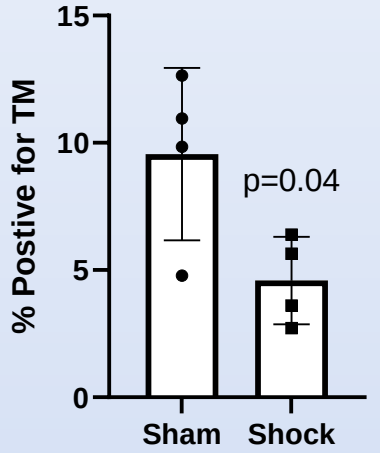


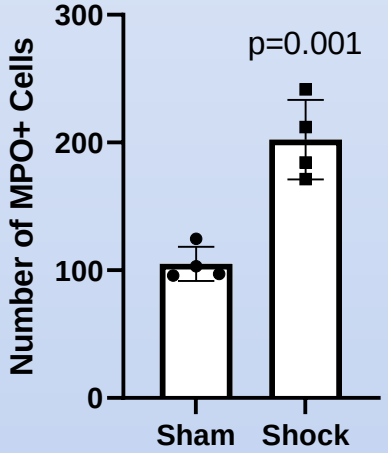


MPO

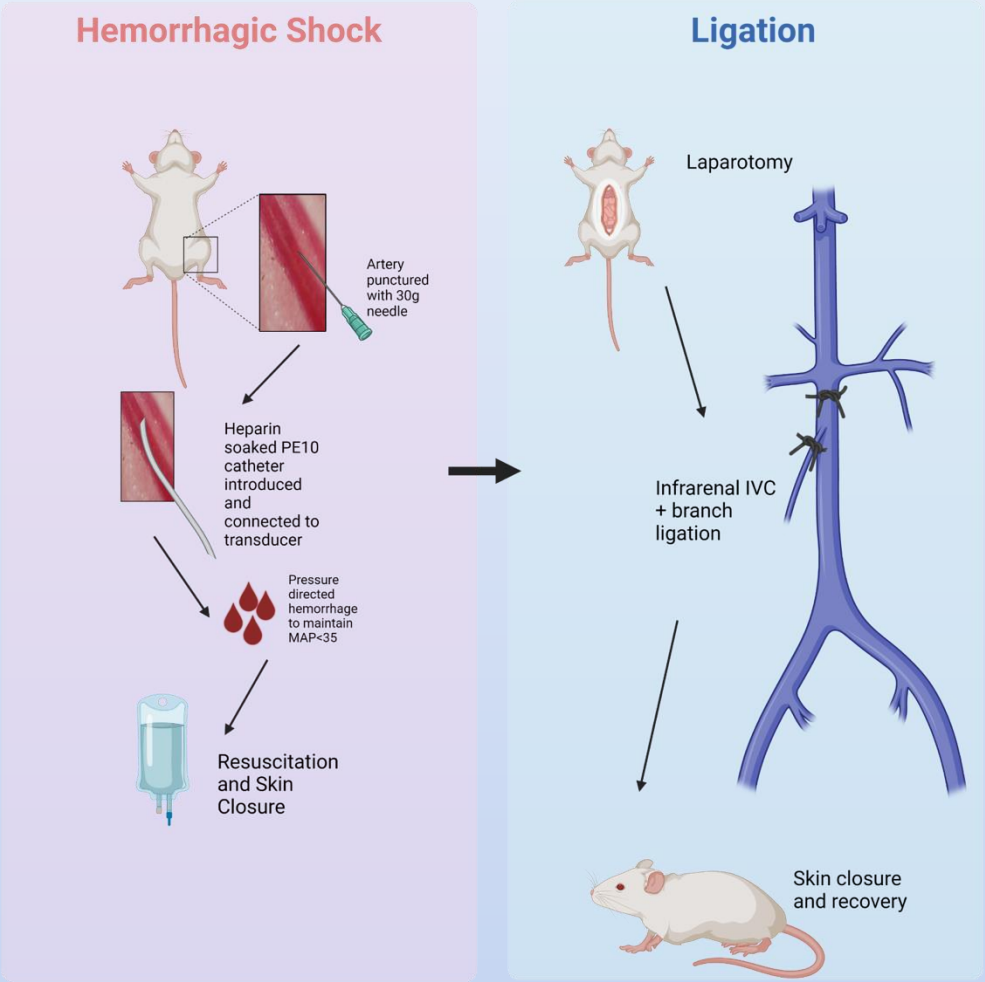








Increased thrombus size in combined model of HS and thrombosis



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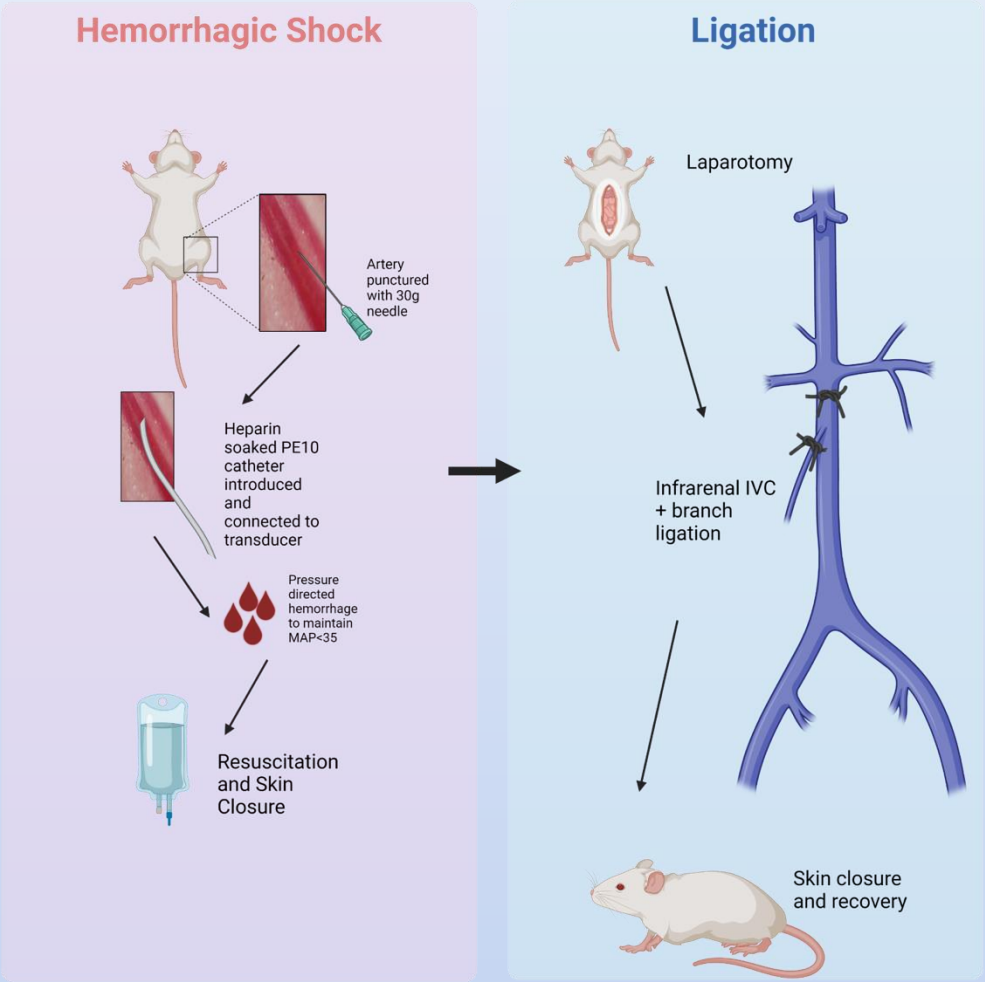

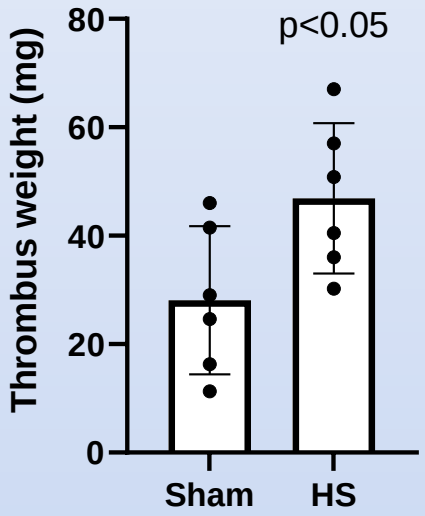

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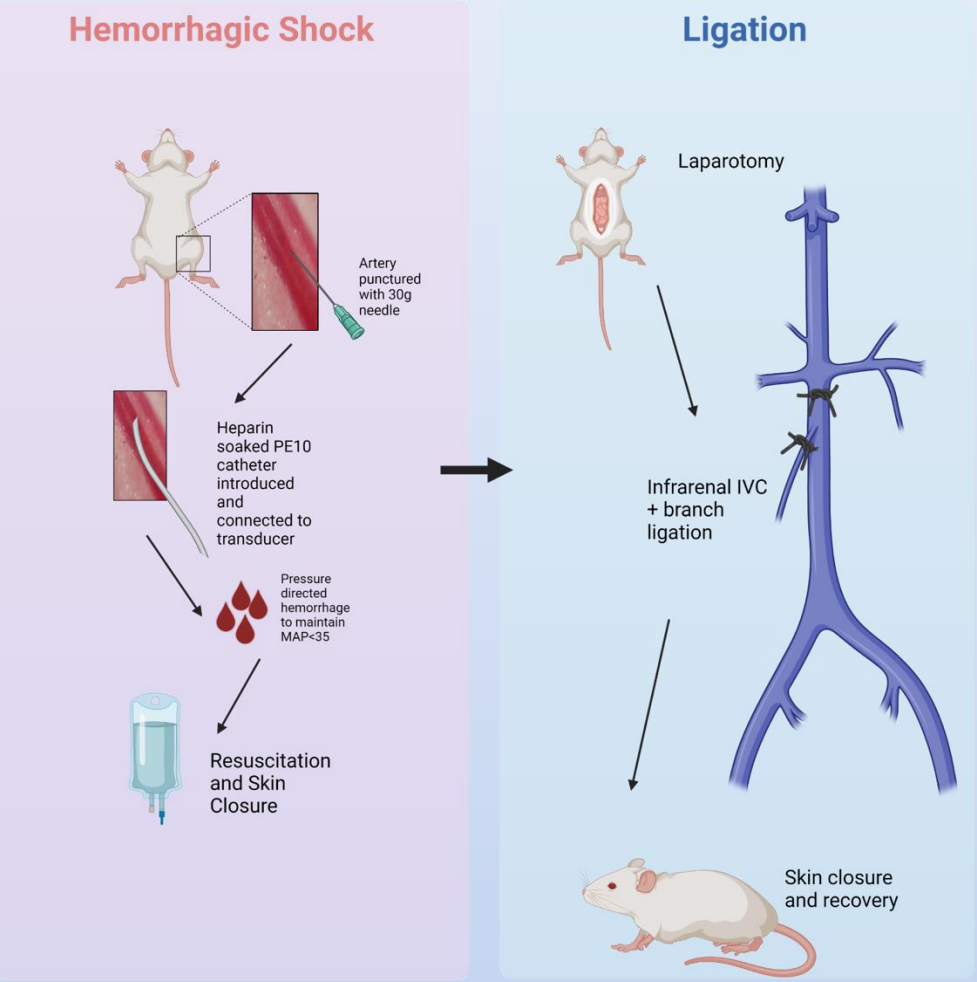
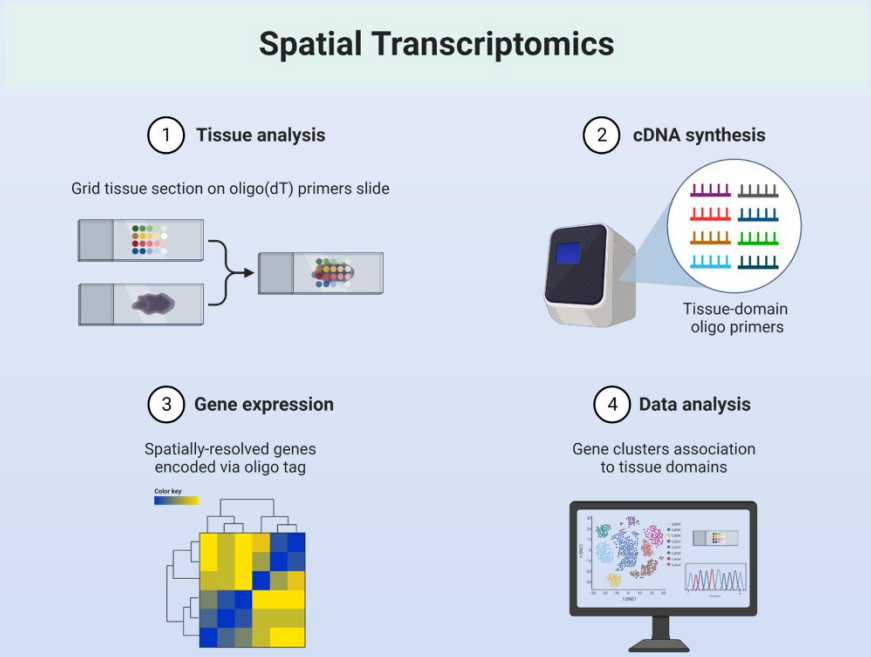




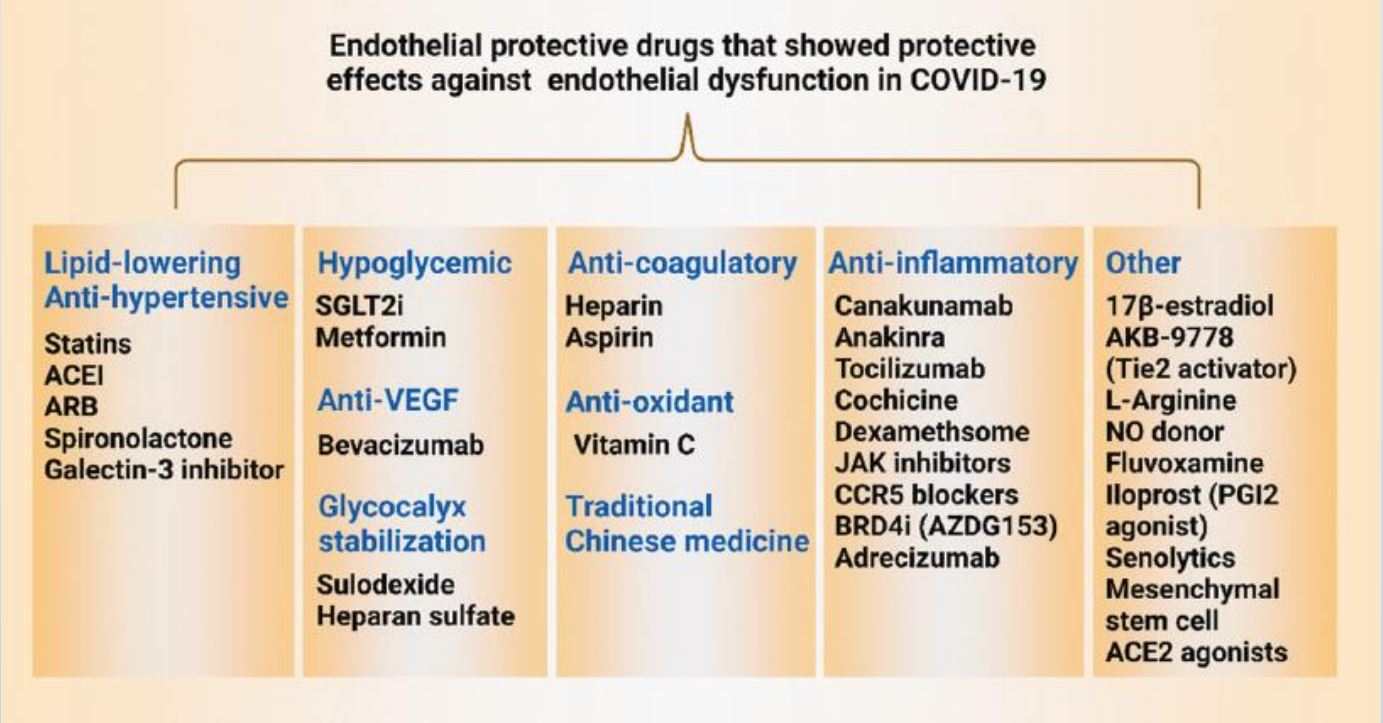
Endothelial cells – CD31
Neutrophils – NE
Leukocytes – CD45

How do we improve chemoprophylaxis to better address underlying mechanisms???

ey takeaway: Thrombosis is linked with inflammation, in part through endothelial activation.

Ve need better prophylactic measures including those that address these underlying mechanisms.

- Statins + anticoagulants?
- Glucocorticoids + anticoagulants?
- NSAIDS + anticoagulants?
- Improved anticoagulants?



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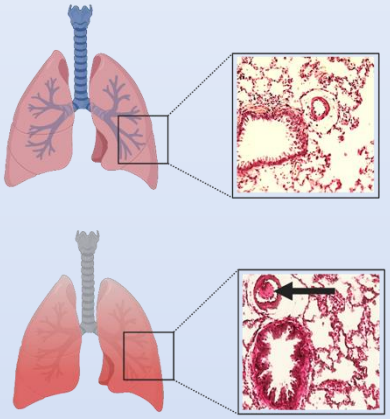
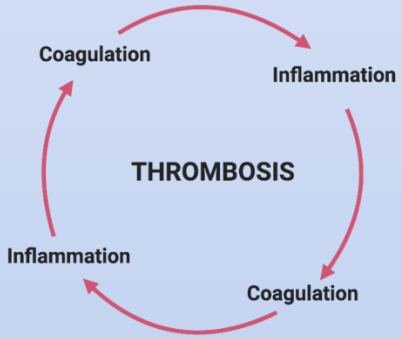
- Complications due directly or indirectly to thrombosis leading causes of morbidity and mortality
  - <u>Venous thromboembolism (VTE)</u>
  - <u>Organ Injury/Dysfunction</u>
    - ALI
    - ARDS
    - AKI
    - MOF



Thromboinflammation → fibrin deposition, inflammatory infiltration = organ injury

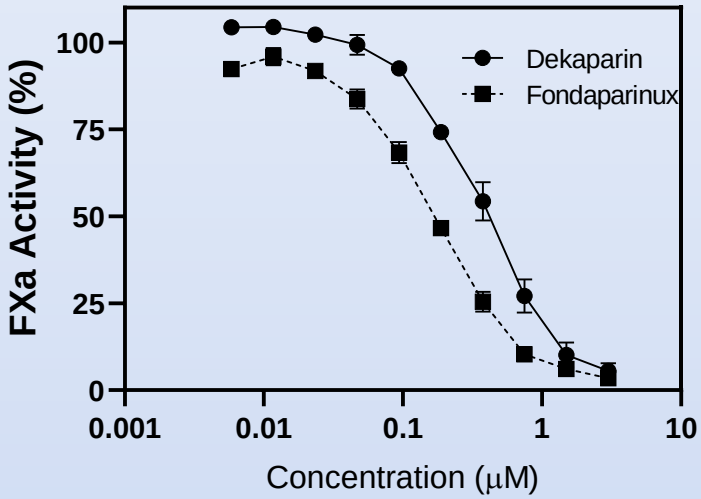


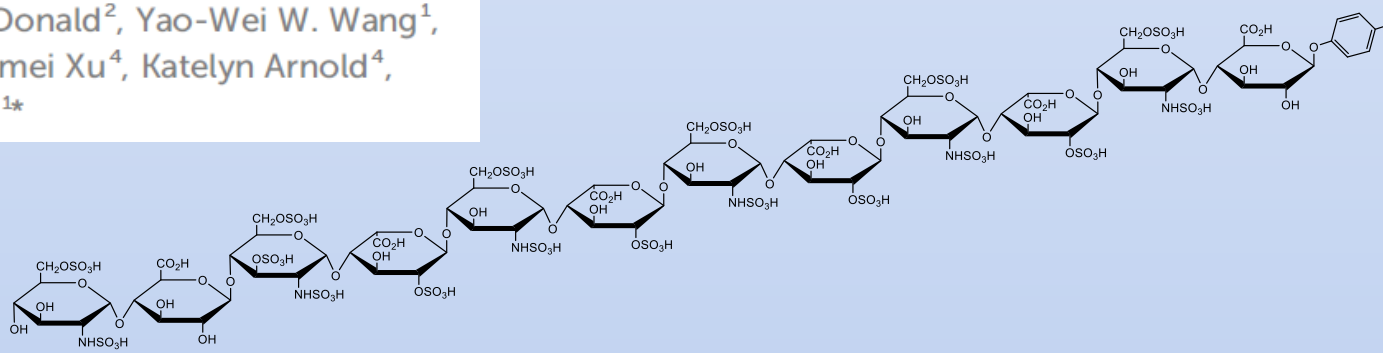
3-OS-Heparan Sulfate: a potential novel multi-modal therapeutic

frontiers | Frontiers in Immunology

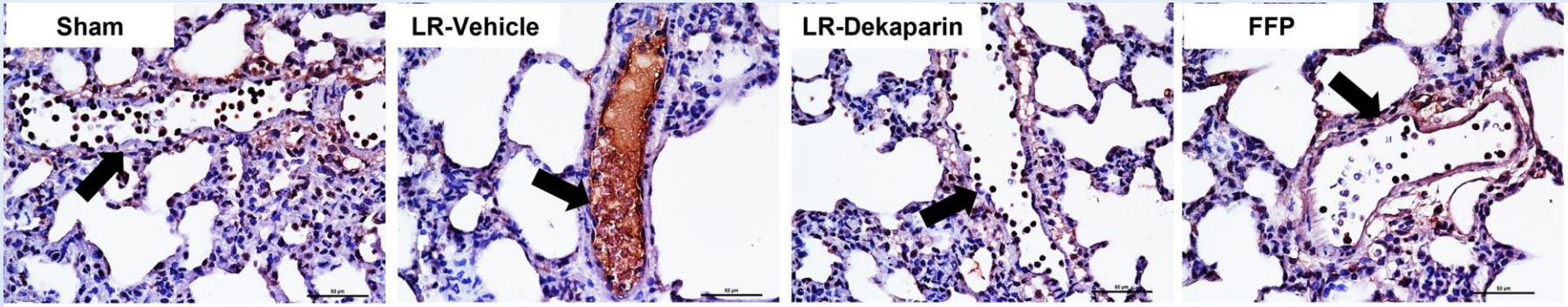
A 3-*O*-sulfated heparan sulfate dodecasaccharide (12-mer) suppresses thromboinflammation and attenuates early organ injury following trauma and hemorrhagic shock

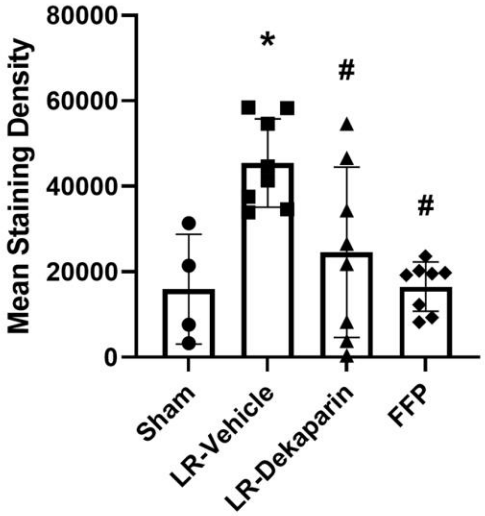
Maria del Pilar Huby Vidaurre[1], Baron K. Osborn[1], Kaylie D. Lowak[1], Michelle M. McDonald[2], Yao-Wei W. Wang[1], Veda Pa[1], Jillian R. Richter[3], Yongmei Xu[4], Katelyn Arnold[4], Jian Liu[4] and Jessica C. Cardenas[1]*





3-OS-Heparan Sulfate: a potential novel therapeutic





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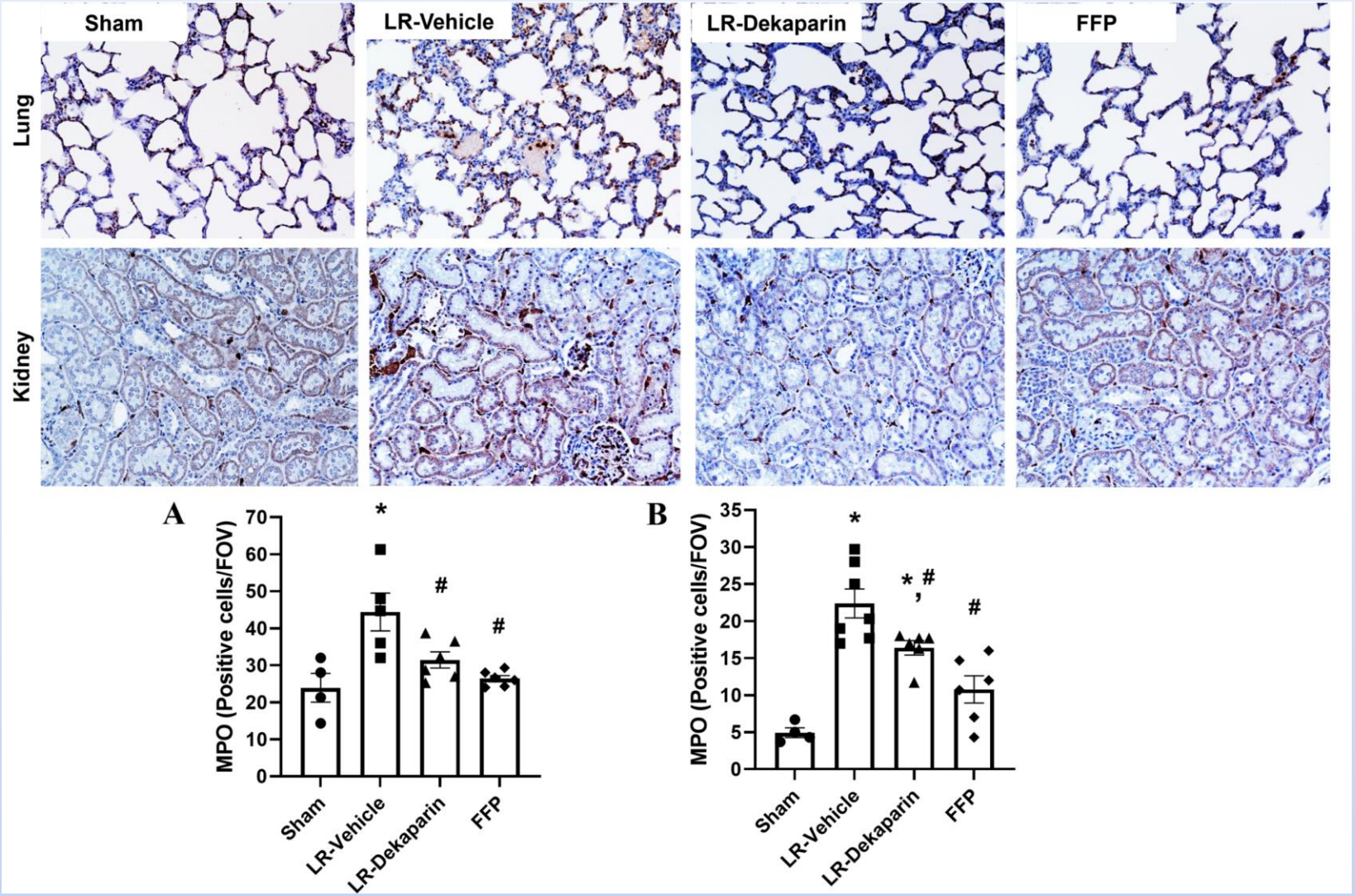
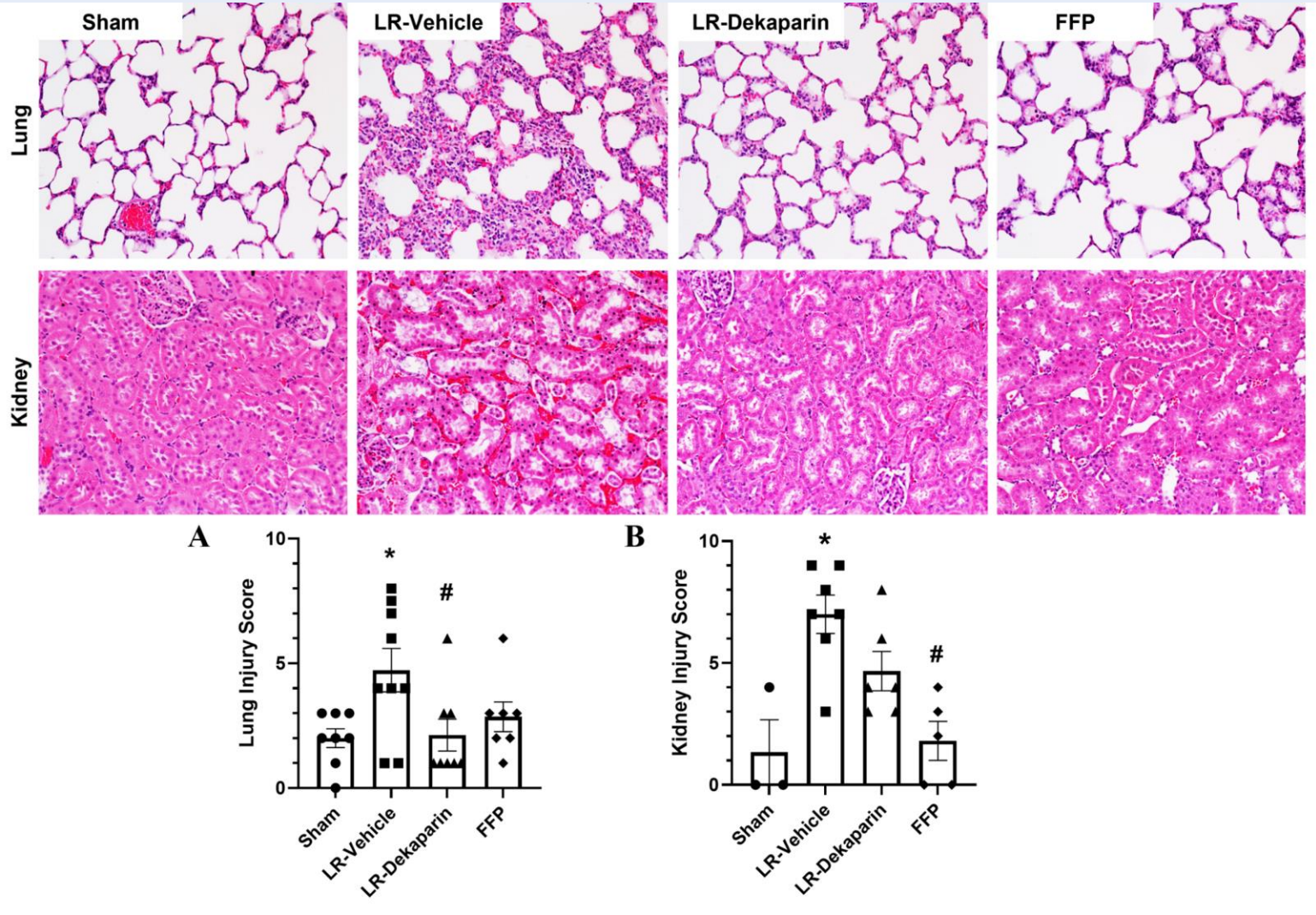
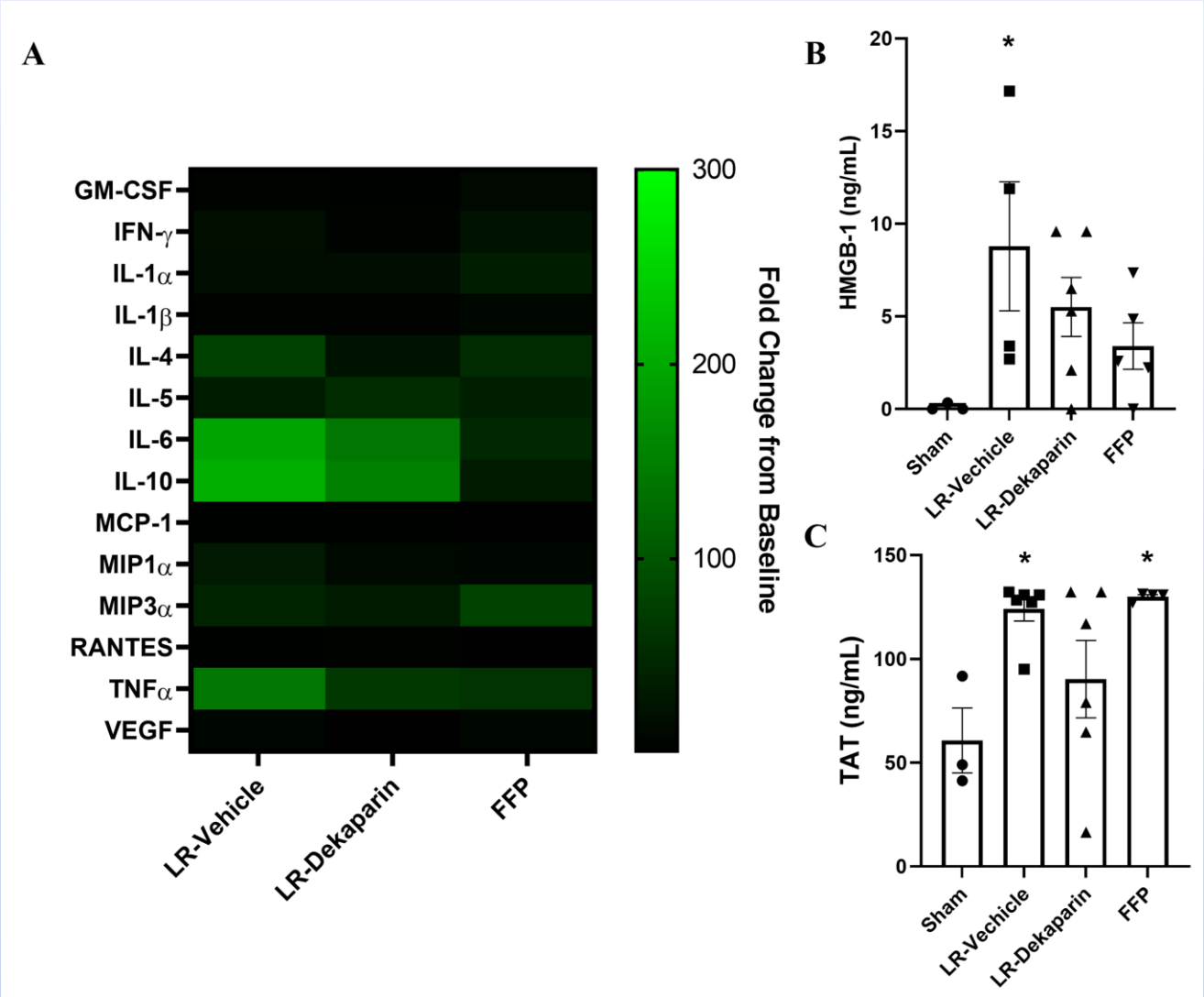


3-OS-Heparan Sulfate: a potential novel therapeutic



3-OS-Heparan Sulfate: a potential novel therapeutic



Summary

- Poor responsiveness to SOC anticoagulation is very common and key risk factor for VTE, but not a silver bullet
- Post-trauma thrombosis resembles “immunothrombosis”, with key role of inflammation-mediated EC activation, which further propagates inflammation
- Addressing this inflammation = EC activation = inflammation feedback loop may improve VTE prevention strategies
- Multi-modal chemoprophylaxis or “designer anticoagulants” could be a next step forward

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  - Kaylie Lowak
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  - Sarah Olson

- Collaborators
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  - Bryan Cotton, MD
  - Jillian Richter, PhD
  - Andre Cap, MD, PhD
  - Jian Liu, PhD
  - Katelyn Arnold, PhD
  - Nick Shworak, PhD
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  - Grifols
  - Aniara
  - UTHealth Department of Surgery

Questions?

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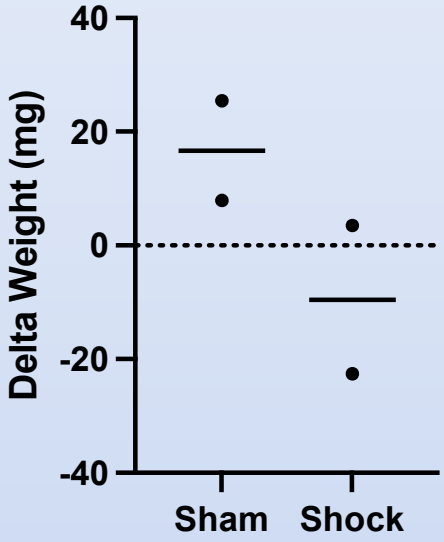
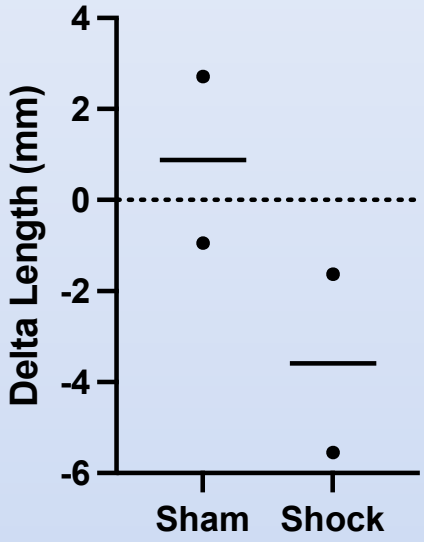
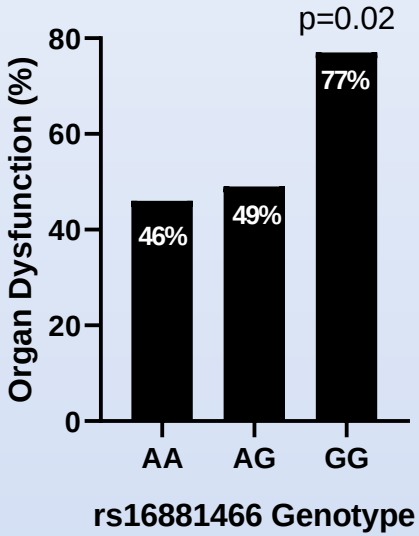
Targeting Inflammation may differentially impact thrombosis in shock vs sham treated mice

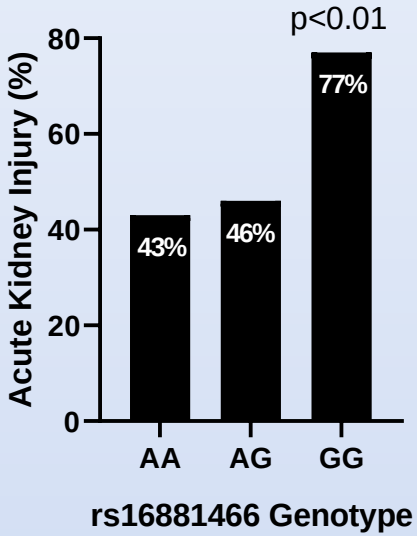


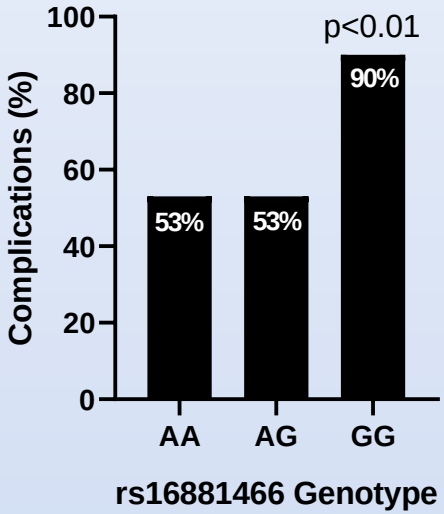


	Mild Injury No HS (N=11)	Mild Injury + HS (N=20)	Moderate Injury No HS (N=13)	Moderate Injury + HS (N=16)	Severe Injury No HS (N=10)	Severe Injury + HS (N=17)	p-value
Demographics							
Age (years)	25 (17,40)	36 (26,53)	28 (26,53)	40 (26,53)	31 (26.5, 60.75)	33 (27,43)	0.189
Male (n, %)	11 (100%)	20 (100%)	13 (100%)	16 (100%)	10 (100%)	17 (100%)	0.315
Race (n, % White)	3 (23%)	7 (35%)	3 (23%)	5 (31%)	4 (40%)	3 (18%)	0.424
Ethnicity (n, % Hispanic/Latino)	0 (0%)	4 (20%)	5 (38%)	5 (31%)	1 (10%)	7 (41%)	0.281
Body Mass Index	27 (22, 31)	26.4 (24,31)	27.5 (24,30)	27 (23.8, 30.4)	26 (22,29)	25 (24,29)	0.953
Admission Vitals							
Systolic Blood Pressure (mmHg)	130 (120,140)	123 (108,137)	120 (118, 130)	106 (96,131)	115 (100, 140)	96 (70,110)	0.009
Heart Rate (bpm)	104 (79,114)	106.5 (88.25,115)	90 (89,113)	107 (95,110)	90 (86,105)	103 (100,120)	0.084
Base Deficit (mmol/L)	0 (-1,0)	-10.5 (-11,-4)	0 (-2,0)	-9 (-16, -7)	0 (-0.75,0)	-9 (-11,-7)	<.001
Injury							
Blunt (n, %)	4 (31%)	11 (55%)	7 (54%)	7 (44%)	7 (70%)	10 (59%)	0.427
Glasgow Coma Scale	15	14 (4,15)	15 (11, 15)	15 (11, 15)	15 (12.5,15)	14 (3,15)	0.203
Injury Severity Score	9 (5, 10)	9 (6.5,14.5)	20 (17, 25)	20 (17, 25)	26 (26, 33)	38 (29,50)	<.001
Transfusion Volumes							
Pre-hospital crystalloid (mL)	0 (0,0)	0 (0,100)	0 (0,175)	0 (0,650)	0 (0,500)	0 (0,1000)	0.611
Pre-hospital Red Blood Cells (units)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0.748
Pre-hospital Plasma (units)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0.524
Pre-hospital Whole Blood (units)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,1)	0.046
4 Hour Red Blood Cells (units)	0 (0,0)	0 (0,1)	0 (0,0)	0 (0,1.75)	0 (0,0)	2 (0,6)	0.007
4 Hour Plasma (units)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,2.25)	0 (0,0.75)	2 (0,8)	0.003
4 Hour Platelets (units)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0.14)	0.079
4 Hour Whole Blood (units)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0.232
4 Hour Cryoprecipitate (units)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0.211
Outcomes							
Ventilator-free days	30 (30,30)	30 (28.8,30)	30 (30,30)	29 (27.3,30)	30 (30,30)	29 (28,30)	0.001
ICU-free days	30 (30,30)	29.5 (26,30)	30 (29,30)	27 (21,29.3)	29.5 (27.5,30)	27 (11,30)	0.002
Hospital-free days	27 (21,29)	25 (20.8,27)	23 (22,26)	17.5 (10.8,24)	22.5 (19, 23.8)	17 (2, 23)	0.018
In-hospital Mortality, n (%)	0 (0%)	2 (10%)	1 (8%)	1 (6.25%)	2 (20%)	3 (17.6%)	0.564

HS3ST1 rs16881446$^{G/G}$ associated with worse outcomes in HS patients



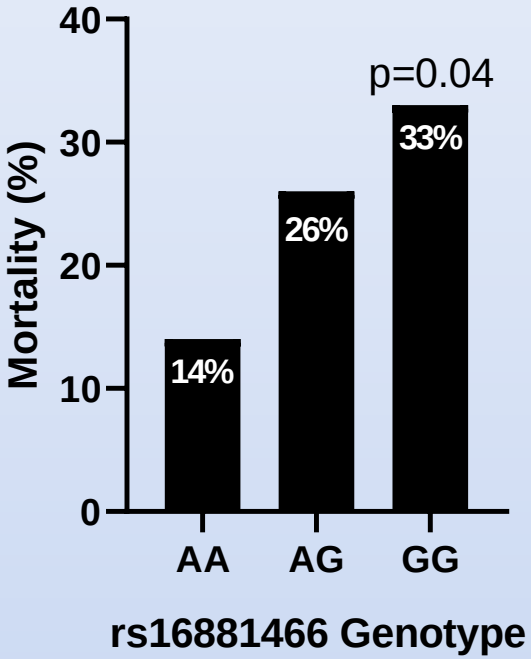


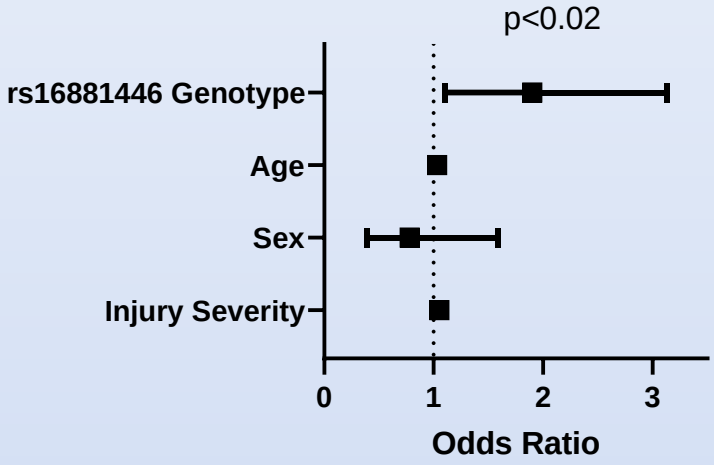


rs16881446$^{G/G}$ and Complications

	OR	95% CI	p value
Organ Dysfunction	6.4	1.77, 22.9	<0.01
Acute Kidney Injury	7.9	2.17, 28.64	<0.01
Any Complication	9.2	2.06, 41.39	<0.01

HS3ST1 rs16881446$^{G/G}$ associated with worse outcomes in HS patients



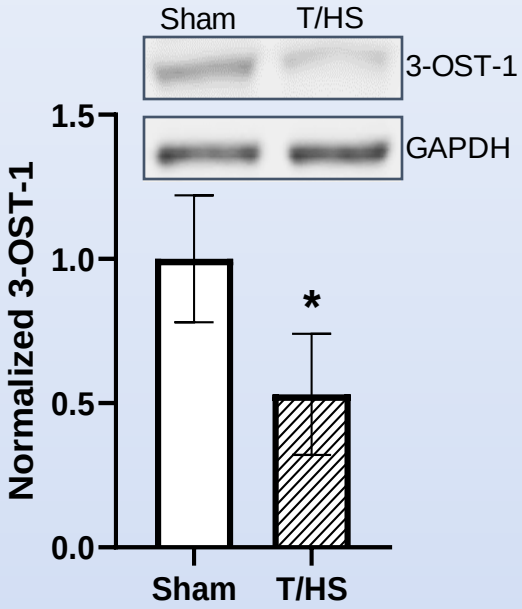


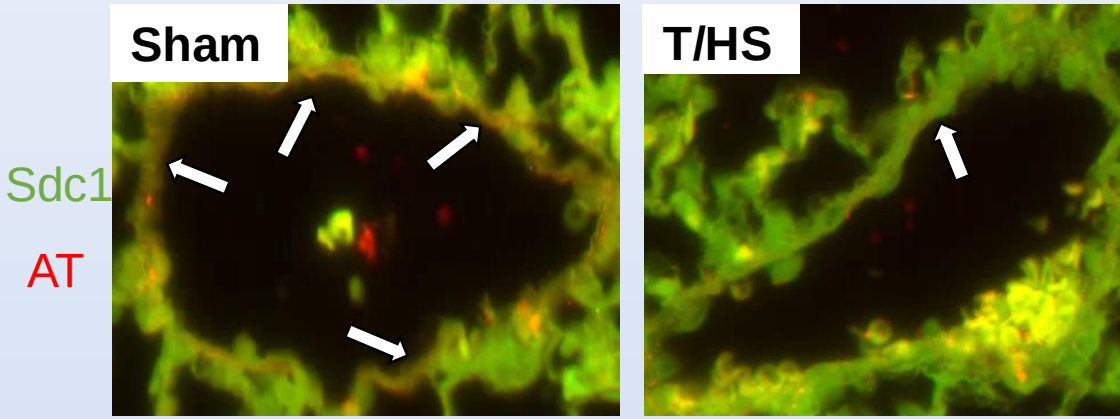
	Odds Ratio	95% Confidence Interval	p-value
Prediction of Mortality			
rs16881446 Genotype	1.8	1.08, 2.84	0.02
Any G allele	2.2	1.16, 4.07	0.02
rs16881446$^{G/G}$	2.6	0.52, 5.0	0.15

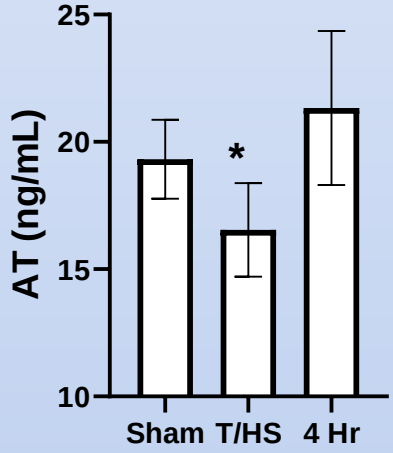
HS3ST1 rs16881446$^{G/G}$ associated with worse outcomes in HS patients

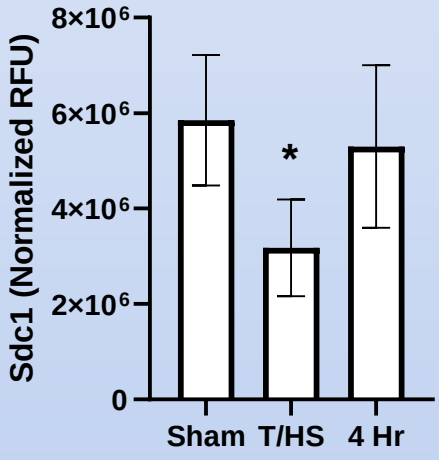
	56%	38%	6%	
	A/A (N=209)	**A/G (N=144)**	**GG (N=22)**	**p-value**
Age (yrs)	39 (26, 56)	42 (28, 56)	41 (24, 60)	0.67
Male (n, %)	151 (72%)	108 (75%)	14 (64%)	0.51
Race				
White (n, %)	164 (57%)	108 (75%)	17 (77%)	0.82
Ethnicity				
Hispanic/Latino (n, %)	58 (28%)	42 (29%)	5 (23%)	0.81
Admission Vitals				
SBP (mmHg)	107 (81, 123)	106 (87, 132)	91 (81, 126)	0.42
HR (bpm)	115 (90, 134)	111 (93, 129)	107 (95, 124)	0.43
Base Deficit (mmol/L)	-8 (-11, -7)	-8 (-11, -6)	-8 (-9, -6)	0.53
Injury Mechanism and Severity				
Blunt (n, %)	165 (79%)	106 (74%)	17 (77%)	0.56
Injury Severity Score	27 (17, 38)	29 (16, 35)	29 (16, 37)	0.89
Transfusions				
Prehospital Red Blood Cells (units)	0 (0, 1)	0 (0, 1)	0 (0, 1)	0.69
Prehospital Plasma (units)	0 (0, 0)	0 (0, 0)	0 (0, 1)	0.50
Prehospital Whole Blood (units)	0 (0, 1)	0 (0, 1)	0 (0, 1)	0.91
24 hour Red Blood Cells (units)	3 (1, 6)	3 (1, 6)	2 (0, 5)	0.38
24 hour Plasma (units)	3 (1, 5)	2 (0, 7)	2 (1, 5)	0.69
24 hour Platelets (units)	0 (0, 1)	0 (0, 1)	0 (0, 1)	0.50
24 hour Whole Blood (units)	0 (0, 1)	0 (0, 1)	0 (0, 0)	0.22
Patient Outcomes				
Ventilator-free days	27 (23, 29)	28 (26, 30)	26 (17, 28)	<0.01
ICU-free days	24 (18, 27)	26 (22, 29)	22 (9, 26)	<0.01
Hospital-free days	16 (3, 23)	20 (5, 26)	21 (12, 24)	0.37

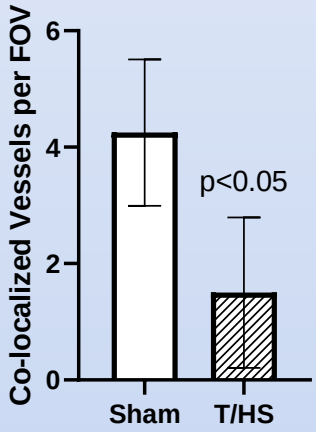
Disruption of AT-Heparan Sulfate after HS associated with reduced 3-OST-1











3-OST-1 Deficiency and Inflammation

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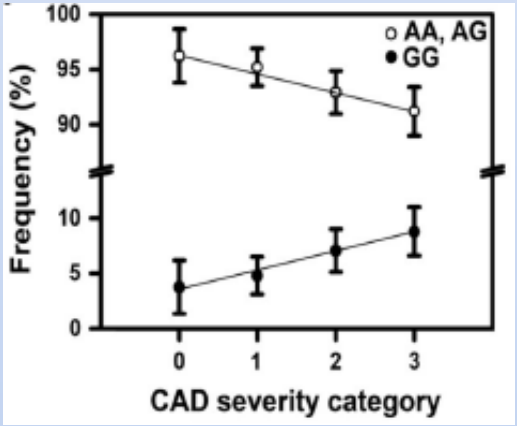
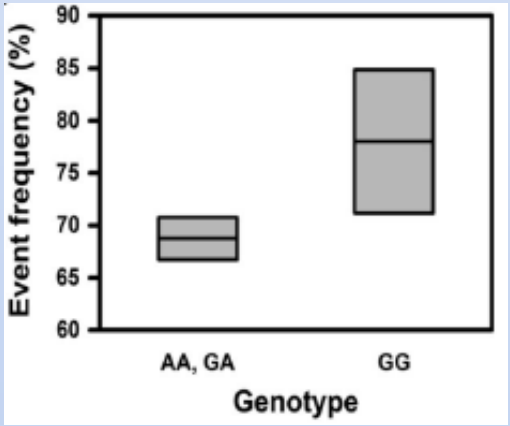
HS3ST1 Genotype Regulates Antithrombin's Inflammomodulatory Tone and Associates with Atherosclerosis

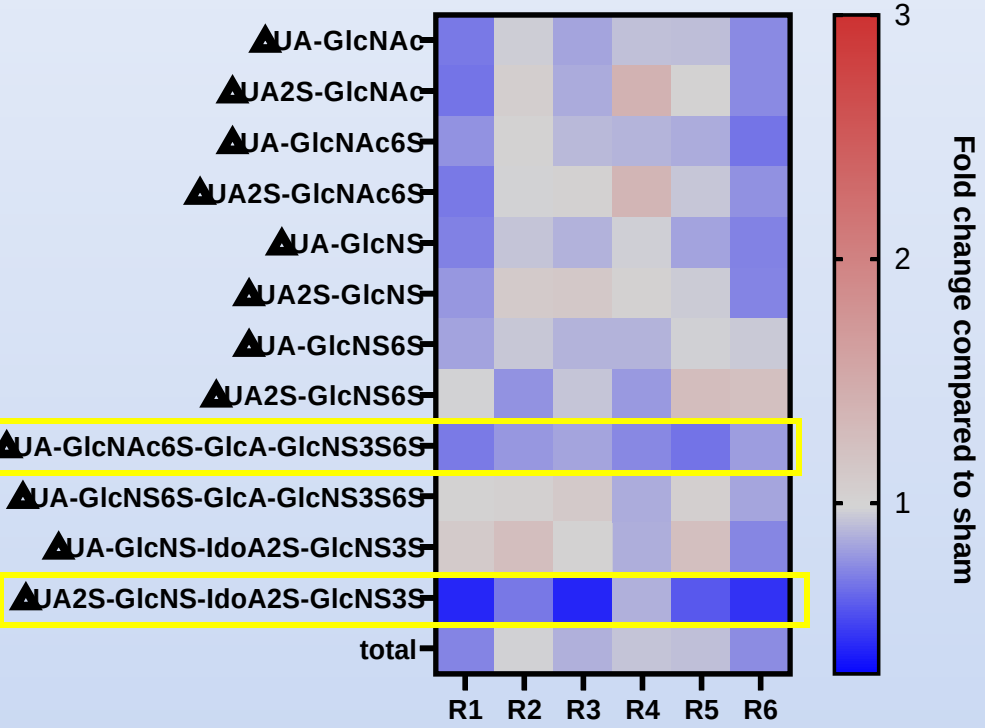
Nicole C. Smits[a,1], Takashi Kobayashi[a,1], Pratyaksh K. Srivastava[a], Sladjana Skopelja[a], Julianne A. Ivy[a], Dustin J. Elwood[b], Radu V. Stan[c], Gregory J. Tsongalis[c], Frank W. Sellke[d], Peter L. Gross[e], Michael D. Cole[b,f], James T. DeVries[a], Aaron V. Kaplan[a], John F. Robb[a], Scott M. Williams[b,2], and Nicholas W. Shworak[a,f]

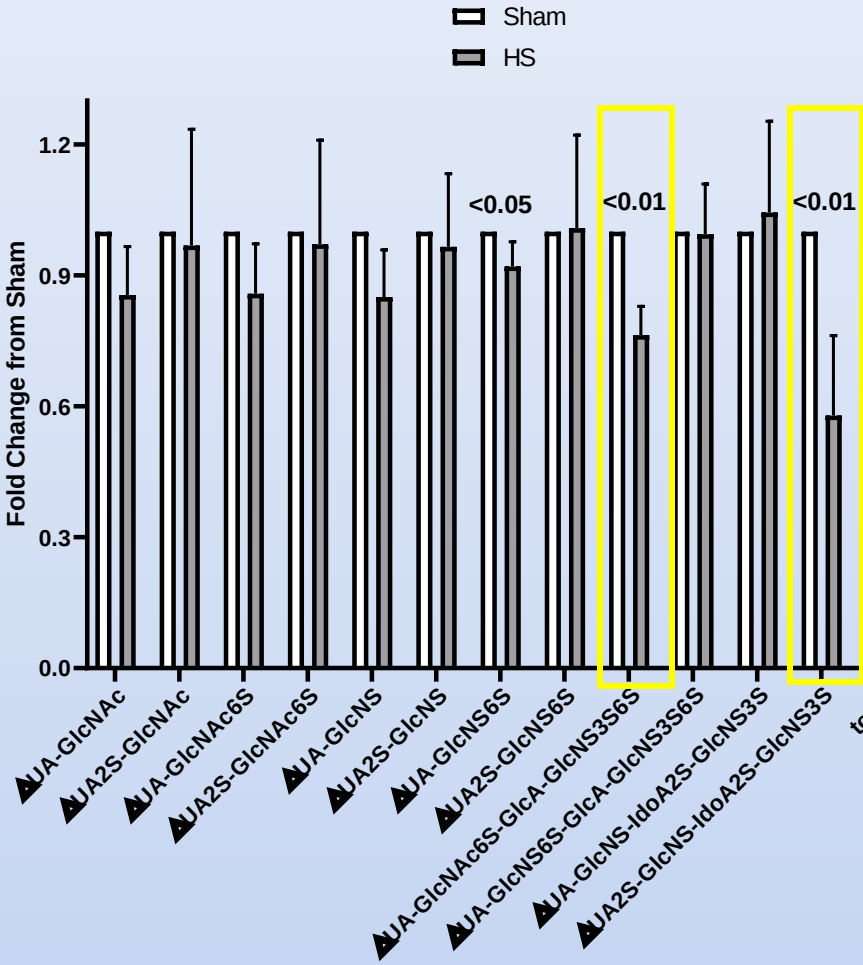
rs16881446: Intronic single nucleotide polymorphism in transcriptional regulatory region





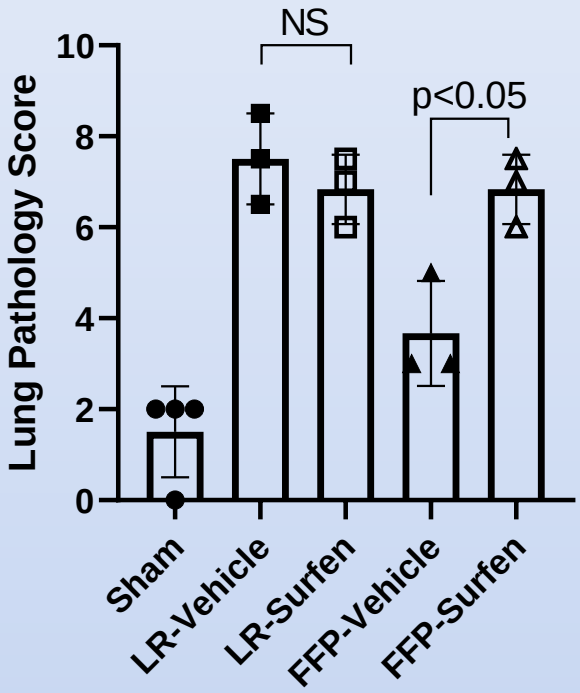
T/HS associated with loss of 3-OS-HSPG

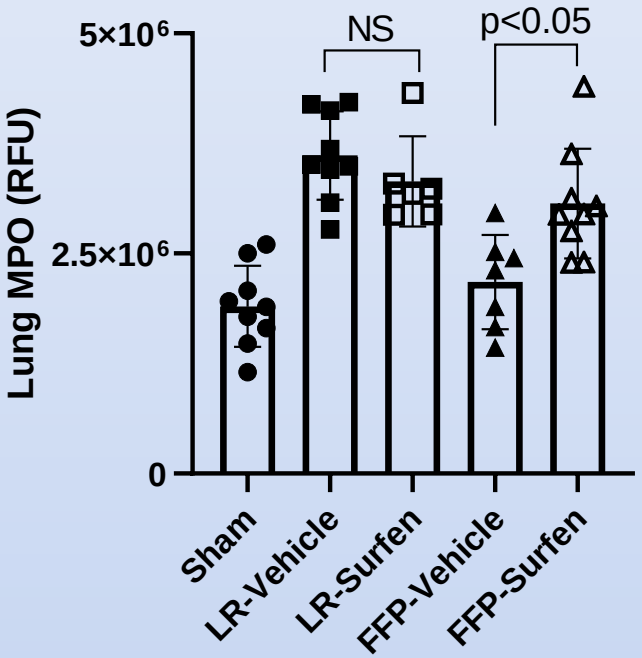




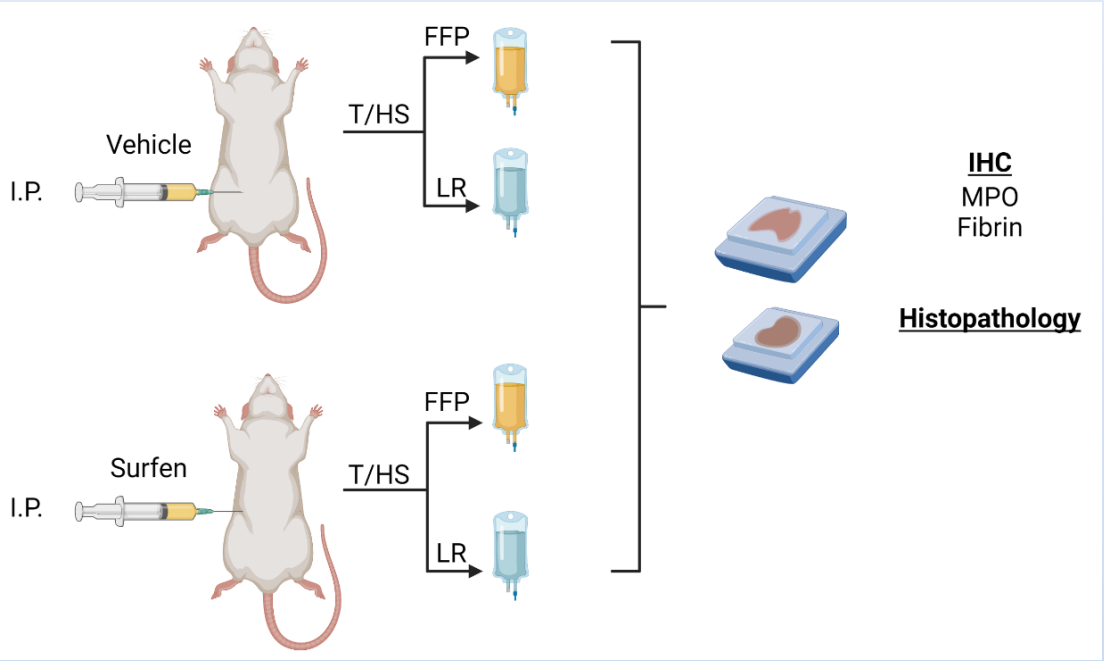
Pharmacologic Inhibition of AT-heparan sulfate system worsens organ injury

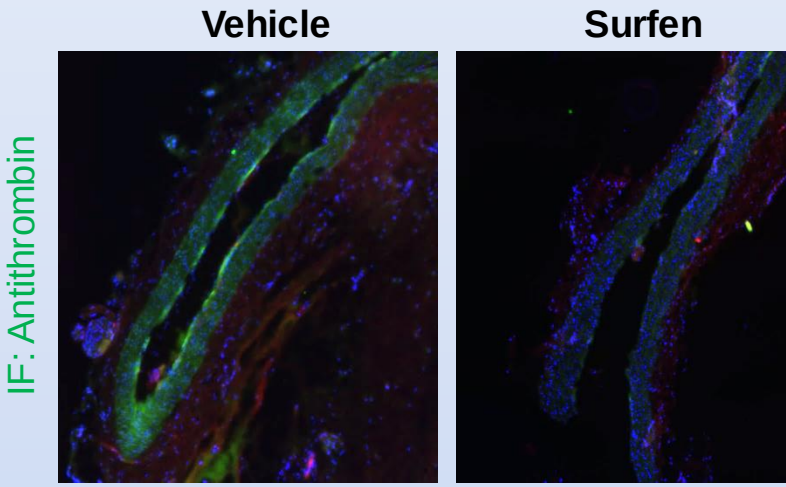
Histologic Markers of Lung Injury



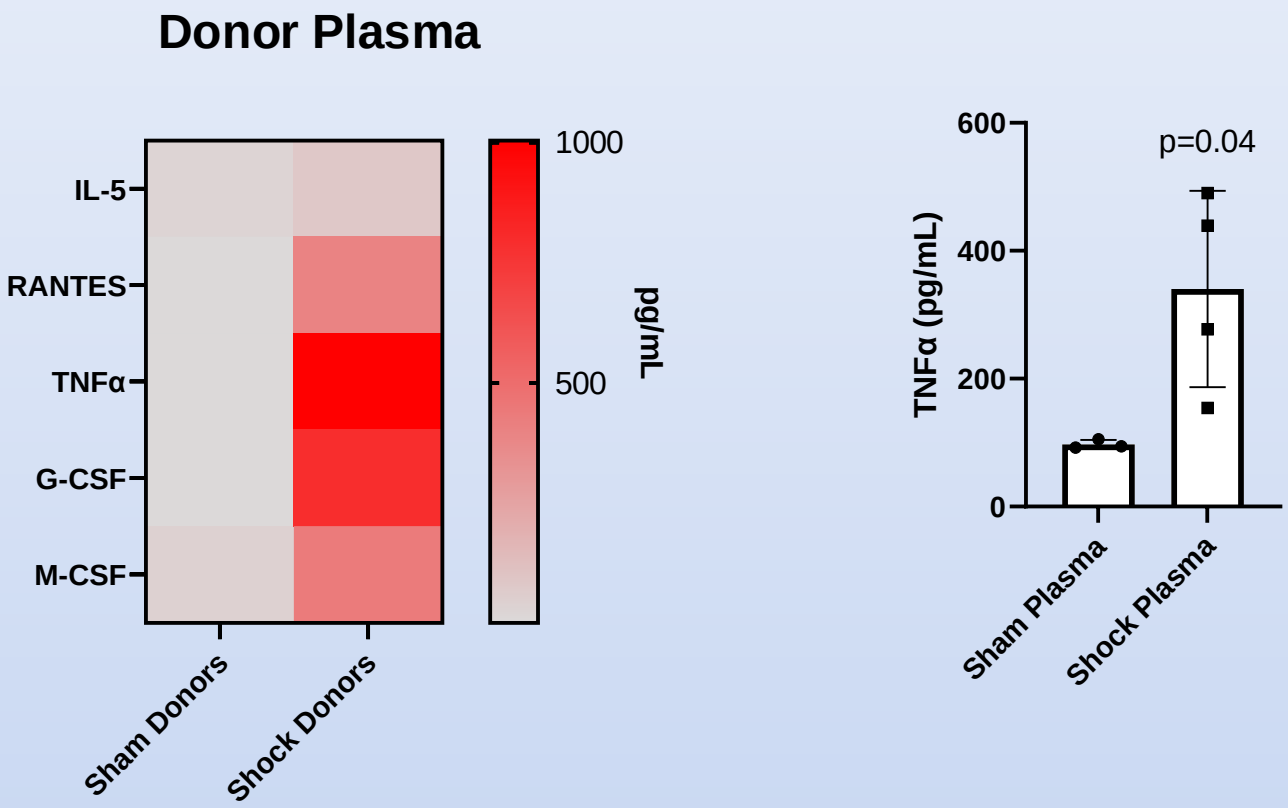


Pharmacologic Inhibition of AT-heparan sulfate system worsens organ injury



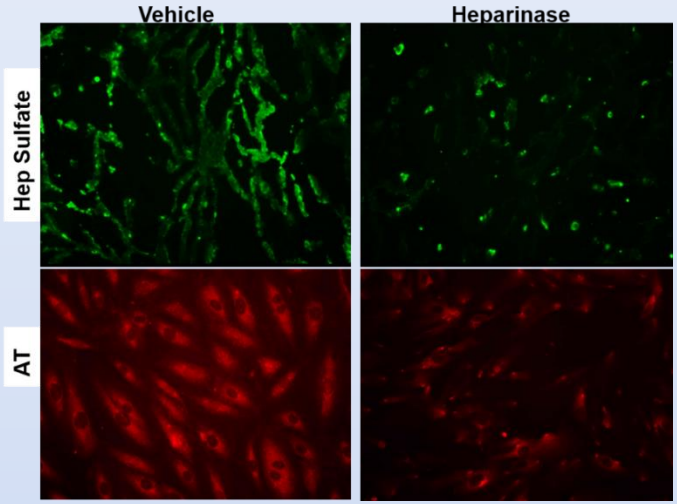


HS Plasma Milieu Influences Thrombus Development

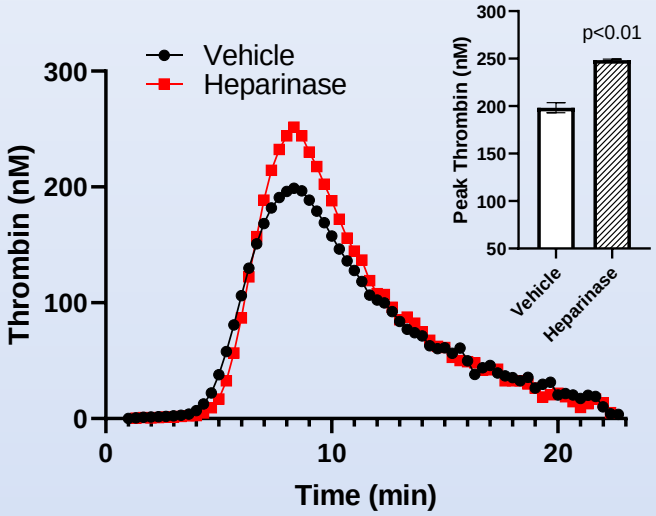


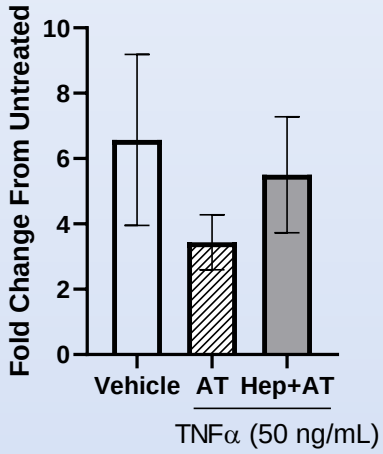
Ex vivo, in vitro and in vivo evidence linking trauma HS plasma inflammatory milieu with EC activation, hypercoagulability, and venous thrombosis

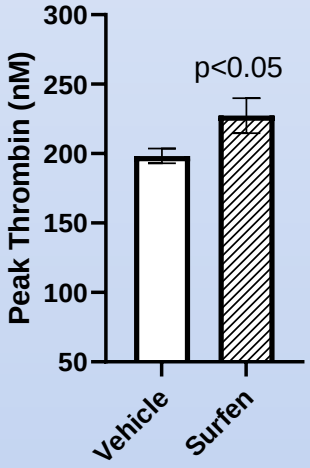
Blocking AT-EC localization increases thrombin generation and inflammation

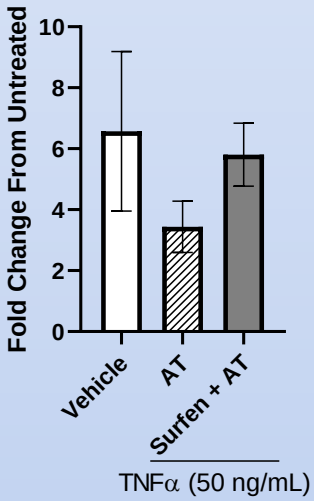


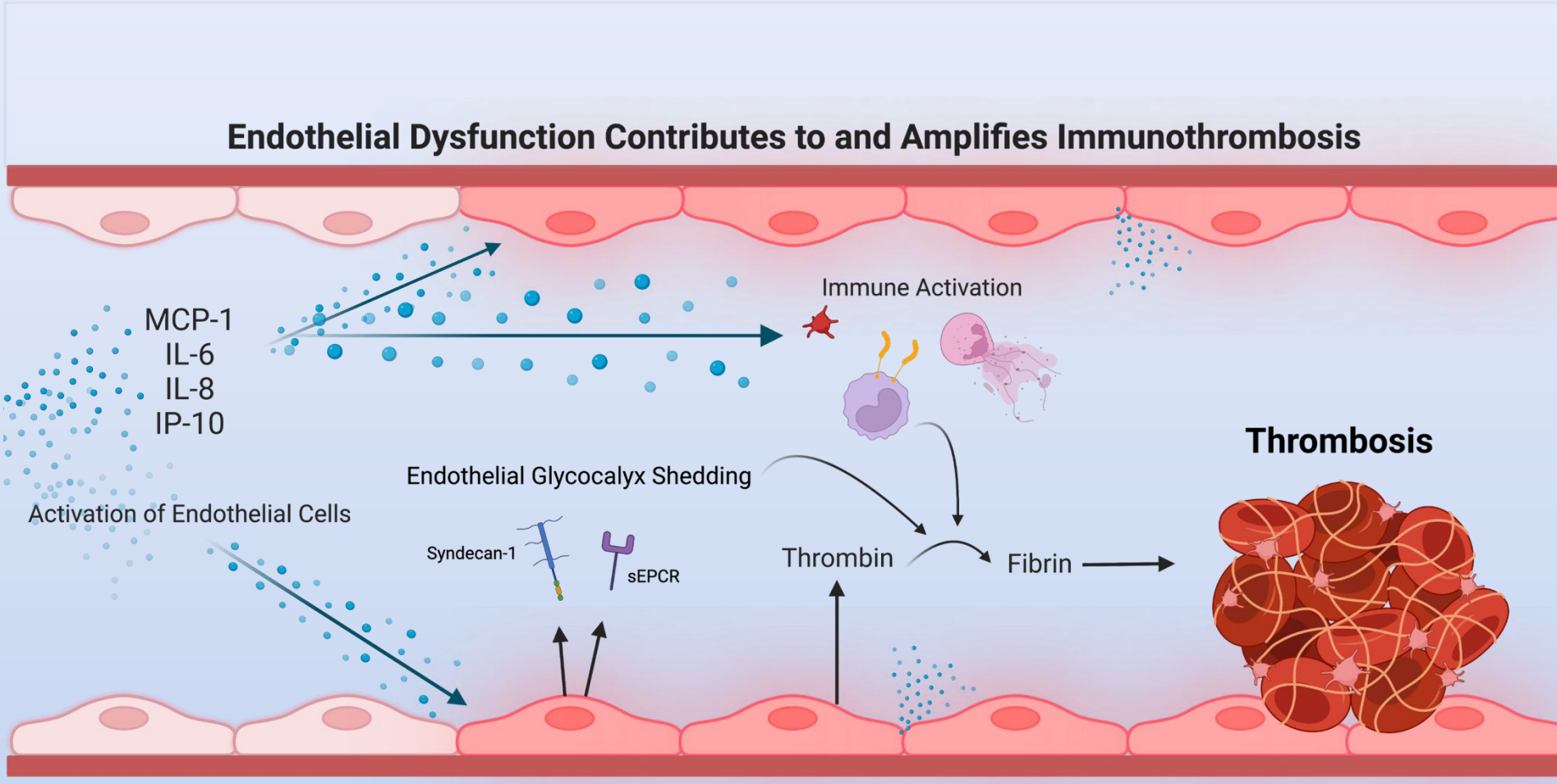
Human pulmonary microvascular ECs

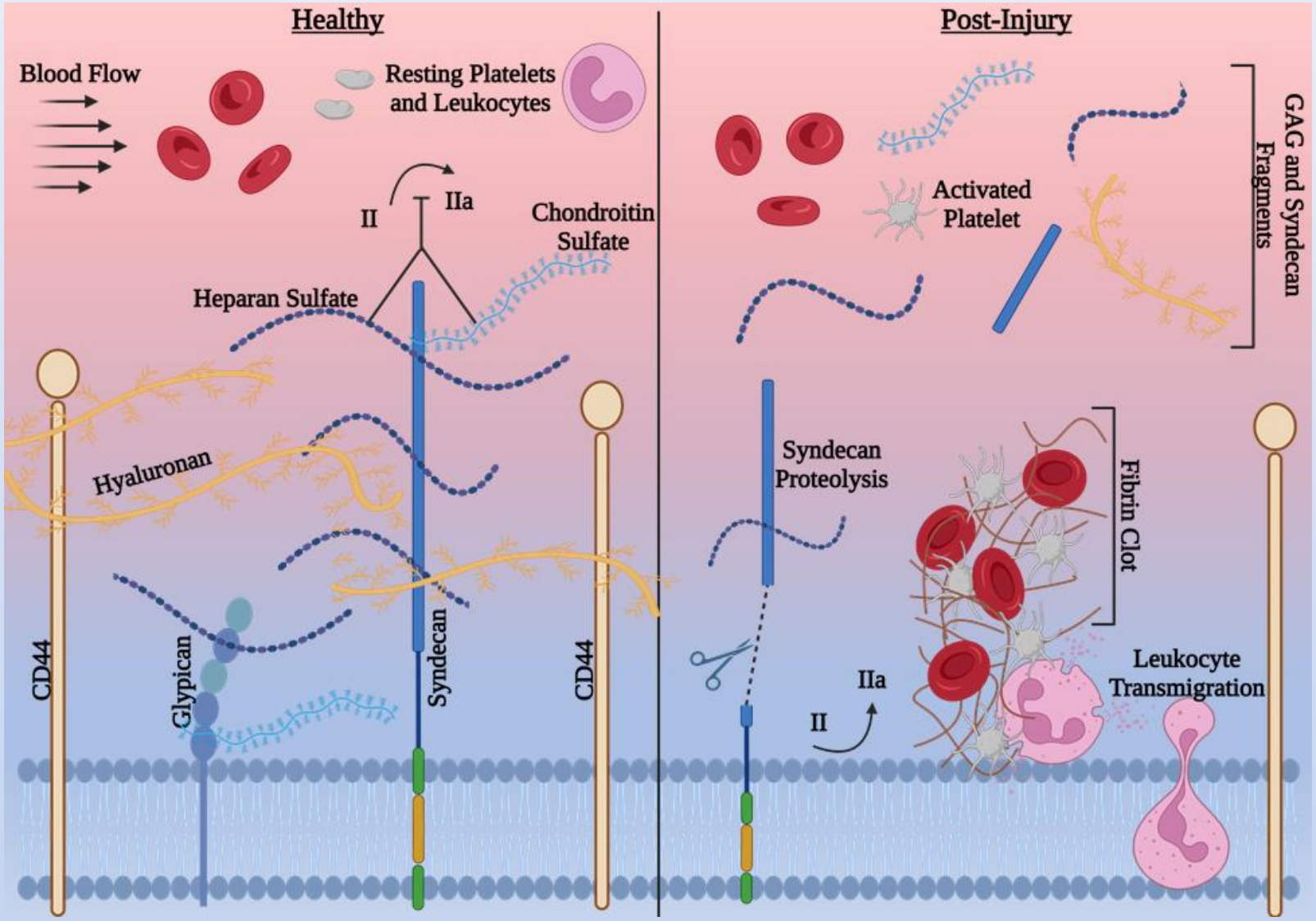









Endothelial Dysfunction Contributes to and Amplifies Immunothrombosis
MCP-1
IL-6
IL-8
IP-10
Immune Activation
Thrombosis
Endothelial Glycocalyx Shedding
Activation of Endothelial Cells
Syndecan-1
sEPCR
Thrombin
Fibrin


Healthy
Blood Flow
Resting Platelets and Leukocytes
II
IIa
Chondroitin Sulfate
Heparan Sulfate
Hyaluronan
CD44
Glypican
Syndecan
CD44
Post-Injury
Activated Platelet
GAG and Syndecan Fragments
Syndecan Proteolysis
Fibrin Clot
IIa
II
Leukocyte Transmigration

Future Directions

- Novel agents for VTE prophylaxis:
  - Targeting anticoagulation alone is not enough!
  - Synthetic heparan sulfates with anticoagulant vs anti-inflammatory vs combined properties
  - EC targeting therapeutics
- Biological role 3-OS-heparan sulfates and HS3ST1:
  - Known importance in organ injury
  - VTE?
  - Endothelial vs leukocyte HS3ST1
  - Supplementation versus augmenting expression (donor molecules, 12mer, transcriptional targeting)
- Application to thromboinflammation in other critical or chronic illnesses?
  - Age-associated morbidities
  - Sepsis
  - Burns
  - Acute pancreatitis