Innovative Approaches to Achieve Precision Resuscitation
The TACTIC 2.0 Frontier

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Professor (tenure) and Vice Chair of Surgery
University of Colorado School of Medicine

Disclosures

- Funding Sources
  - NIH
    - T32 GM008315
    - R01HL166944-01
    - TACTIC UM1-HL120877
    - RM1 1RM1GM131968-01
  - DARPA
  - BARDA
  - DoD
    - W81XWH-12-2-0028
    - F2MTW83109GW01
    - W81XWH-22-PRMRP-TTDA-GG

How to find and study a problem…

First get passed from mentor to mentor

- Ken Smith
- Sally Stein
- John Barrett
- Kim Nagy
- Richard Gamelli
- Ravi Shankar
- Michael Matthay
- Bob Mackersie
- Ken Mann
- Just a few of many…

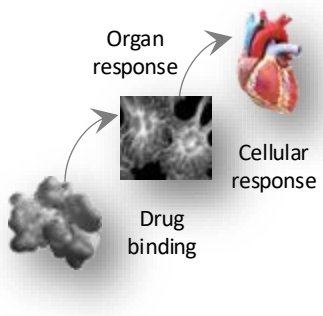
Big audacious science…

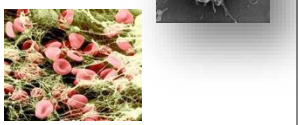
Critical Illness and Injury Research Center

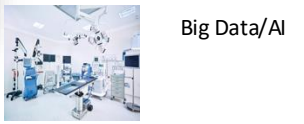
The leading and most comprehensive program for illness and injury research

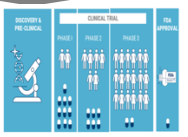
Scientific Program Pillars	Basic Science	Translational Science	Innovation/Big Data	Clinical Trials	Health Services
Summary and Funding	NIH, DOD, BARDA funded basic labs.	NIH, DOD, PCORI funding. Patient enrollment sample collection and translation. SOAR	NIH, DOD, NSF funding Analytics and outcomes. Data and Model based modeling.	NIH, DOD, PCORI funded Trauma/Burn/Sepsis/ARDS trials. Implementation and outcomes research	Prevention DEI Health Services Research Outreach
Programs	Burn, Alcohol, and Aging Thrombo-inflammation Endothelial biology Coagulation Biology Small molecule biology	Integrated organ response to disease Cellular behavior and dynamics in disease Transcriptomics, proteomics, and metabolomics of disease Genetic and epigenetic basis of disease (population-based)	Molecule Bioengineering Pathogen-host response Physiologic immune response Metabolism and function of pathogens	Trauma Resuscitation Trials Burn Resuscitation Trials Post Partum Hemorrhage Biorepository	Disparities in Surgical Access Health Equity Late Presentation of Surgical Disease Violence Intervention
Examples	Organ response Cellular response Drug binding	Immune Function Coagulation Sepsis	Big Data/AI Bioengineering Device Innovation	Trials Outcomes Implementation	Prevention Advocacy Policy

length-scale





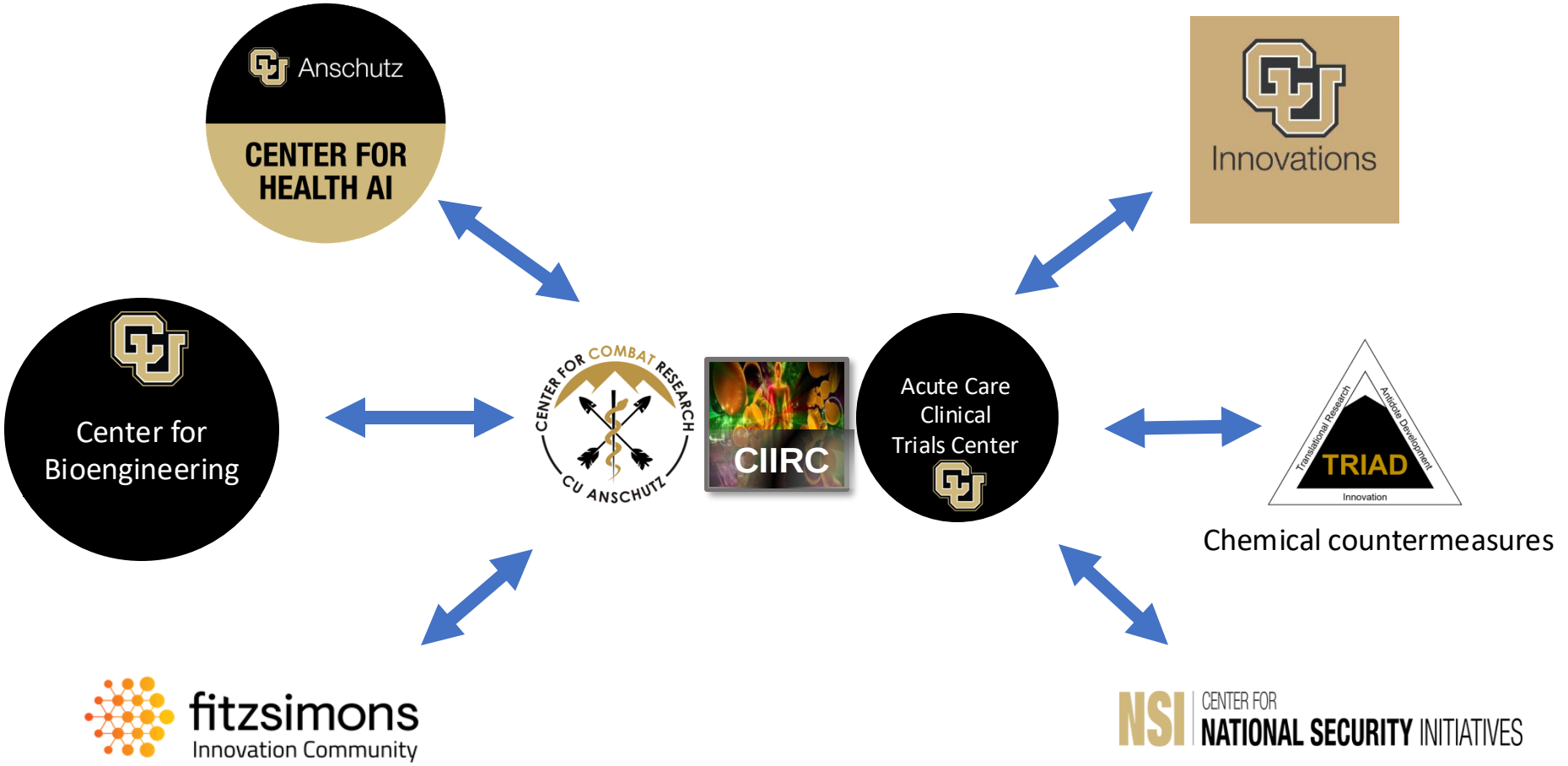




Anschutz SURGERY

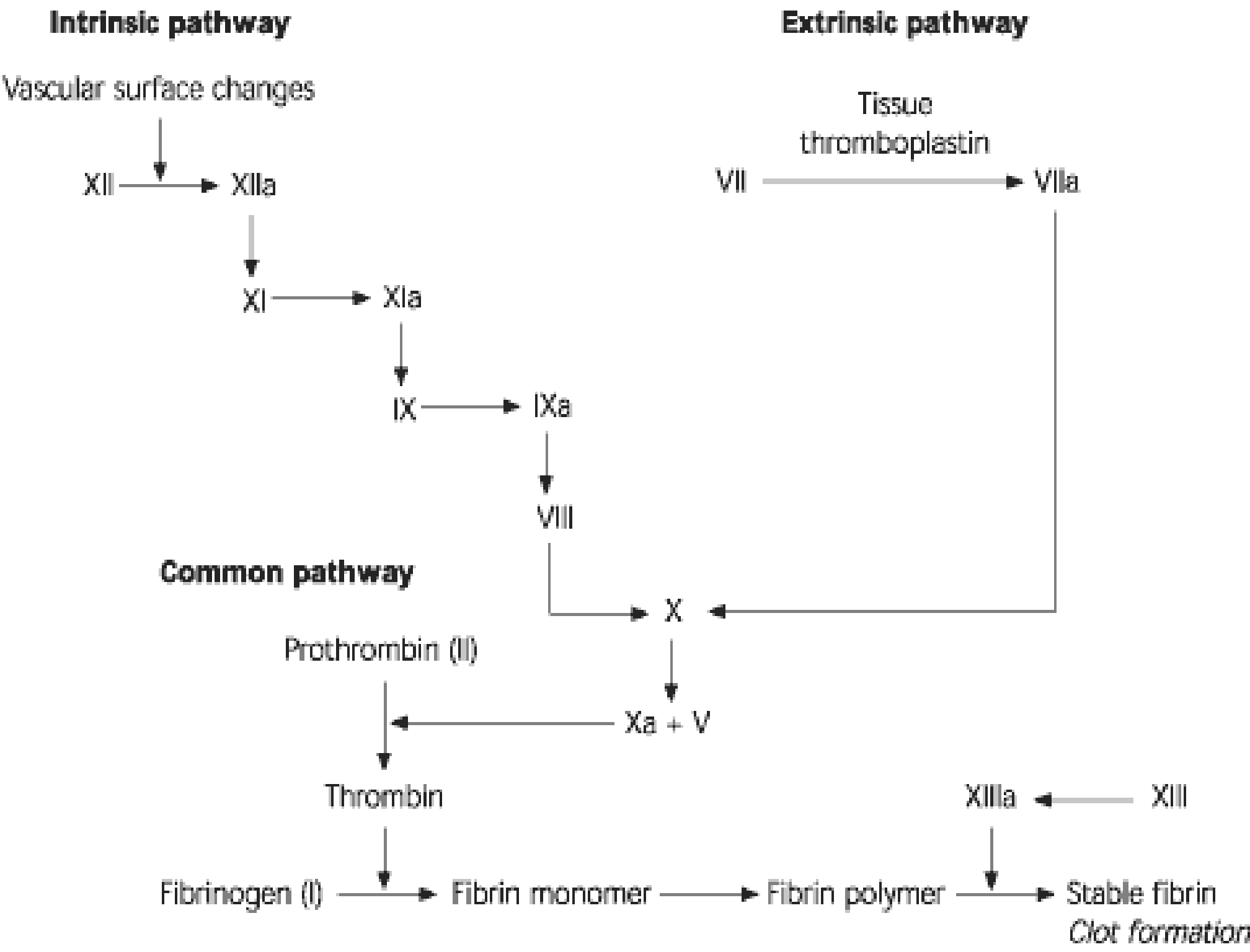
Find a team…

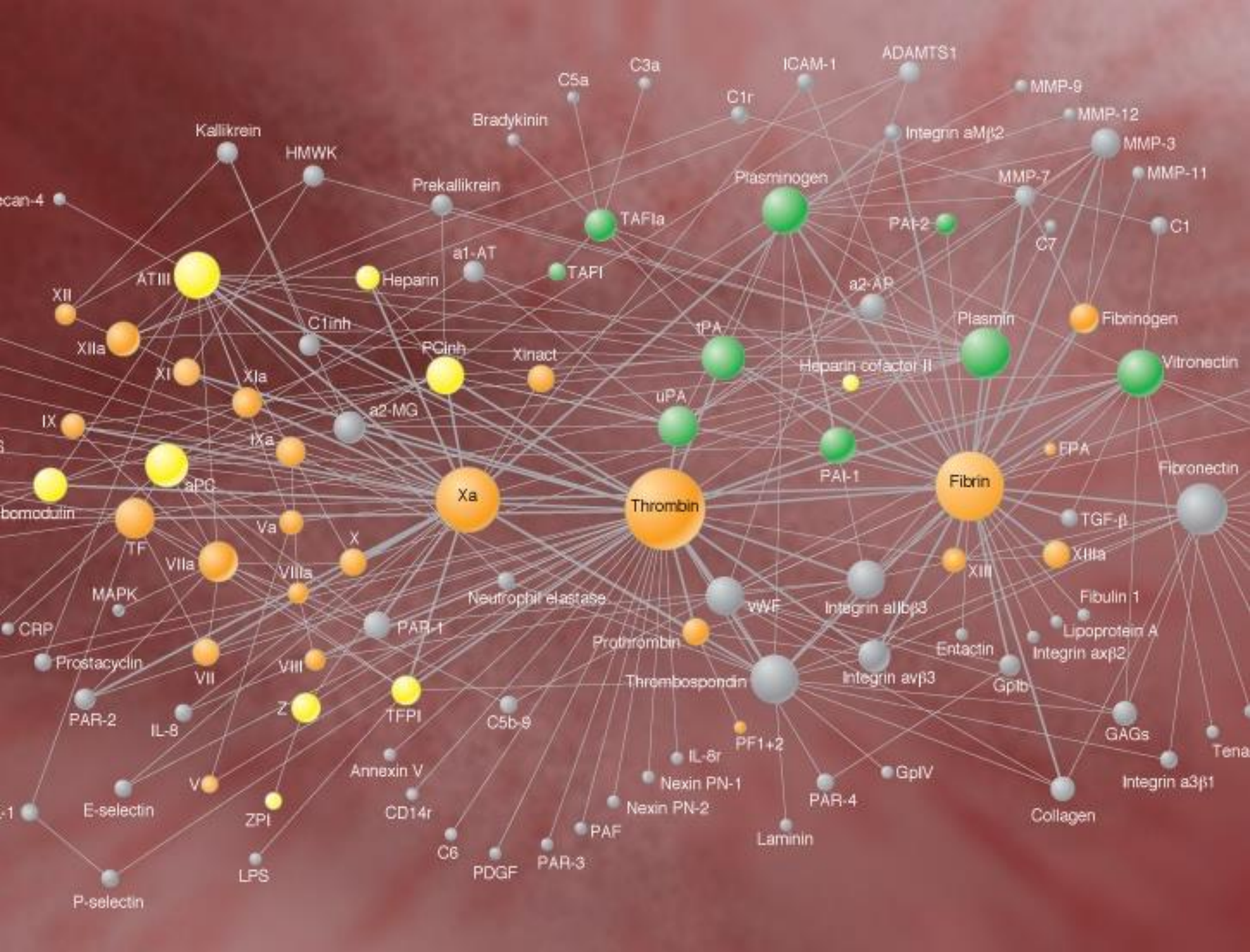
CU Anschutz Ecosystem



Anschutz
SURGERY

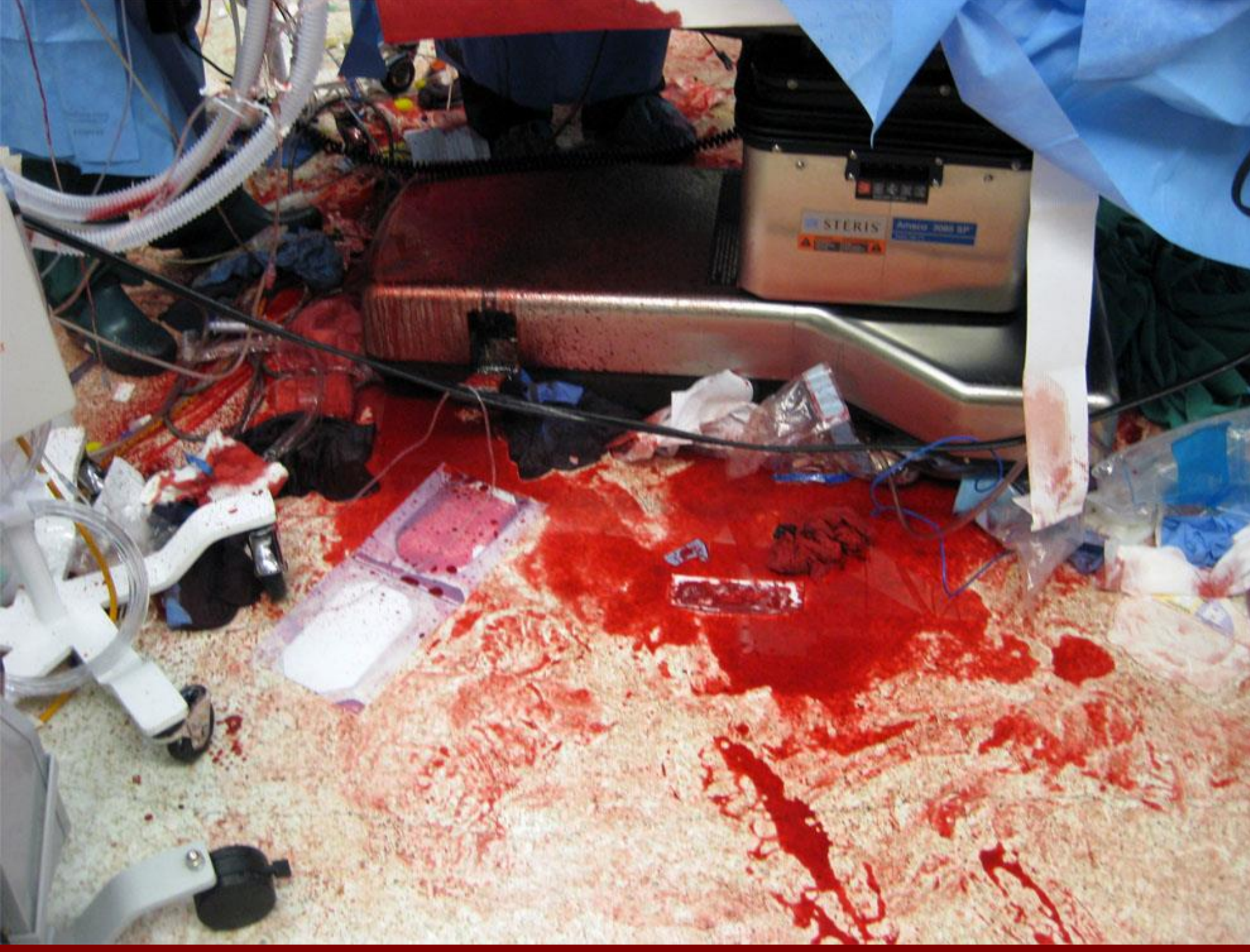
Next find a problem…

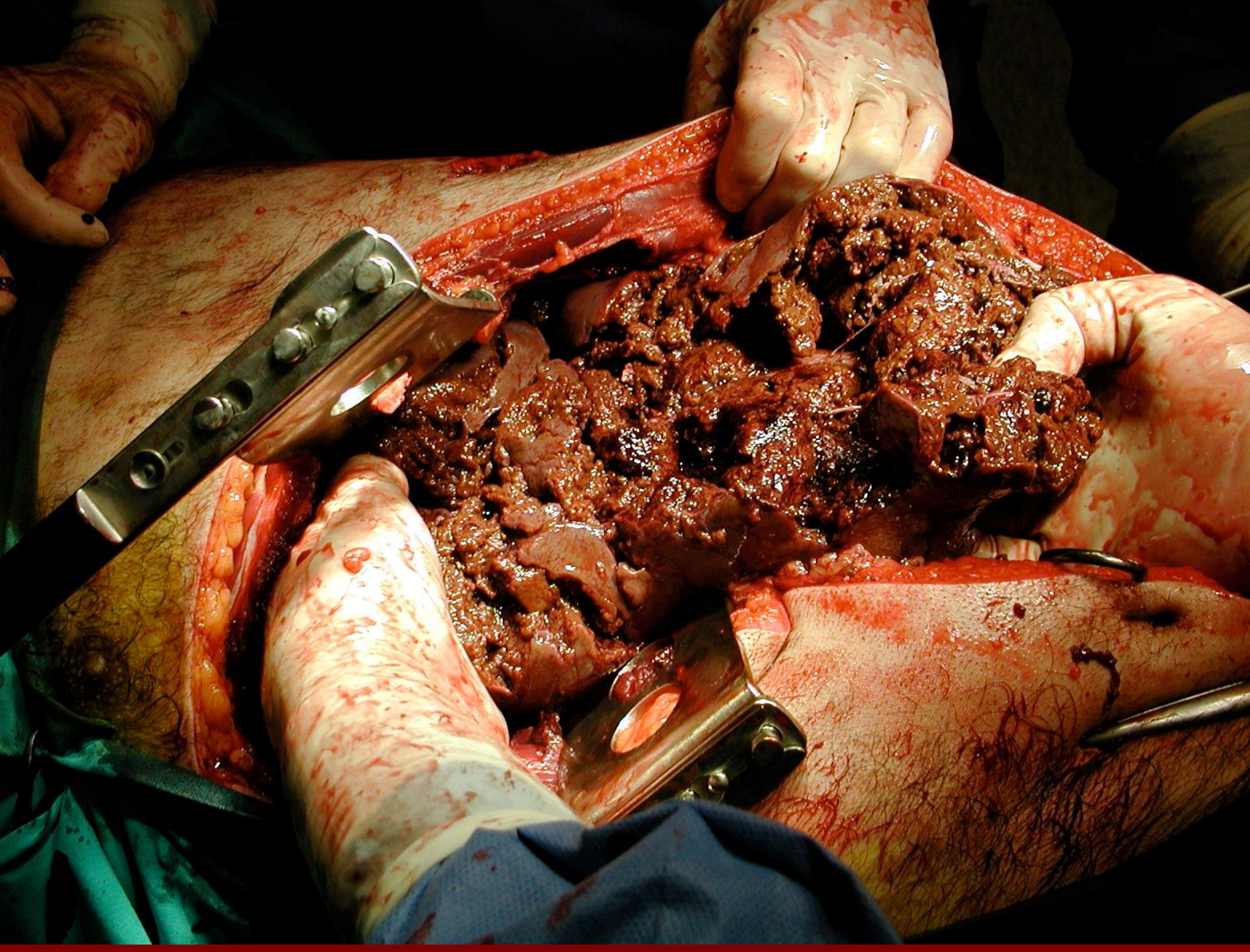

Intrinsic pathway
Extrinsic pathway
Vascular surface changes
Tissue thromboplastin
XII
XIIa
VII
VIIa
XI
XIa
IX
IXa
VIII
Common pathway
X
Prothrombin (II)
Xa + V
Thrombin
XIIIa
XIII
Fibrinogen (I)
Fibrin monomer
Fibrin polymer
Stable fibrin
Clot formation

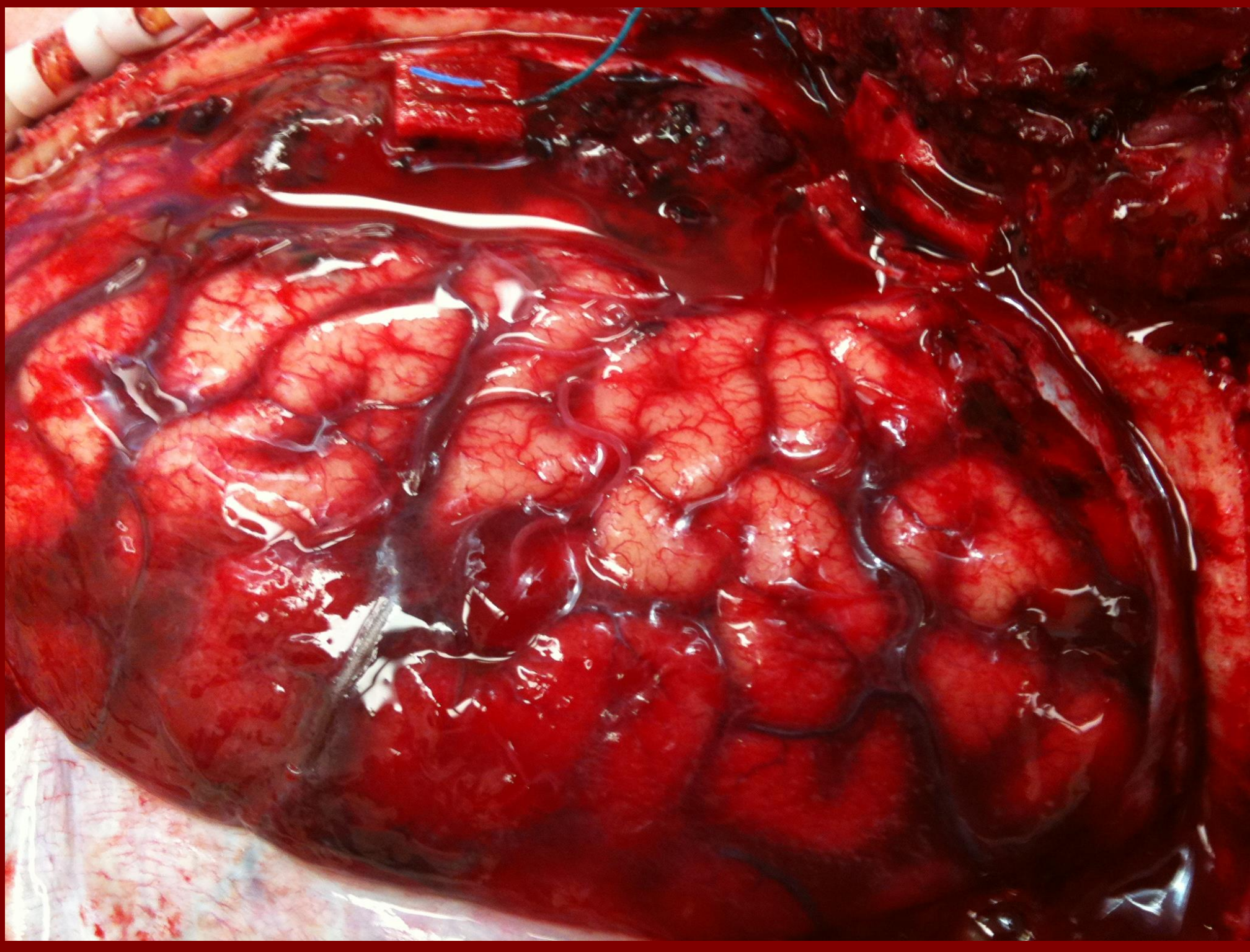

ADAMTS1
ICAM-1
C3a
C5a
C1r
MMP-9
MMP-12
Bradykinin
Integrin aMβ2
MMP-3
Kallikrein
HMWK
MMP-11
Prekallikrein
Plasminogen
MMP-7
TAFIa
PAI-2
C1
C7
a1-AT
TAFI
ATIII
Heparin
a2-AP
XII
C1inh
Plasmin
Fibrinogen
XIIa
tPA
PCinh
Xinact
Heparin cofactor II
Vitronectin
XI
XIa
uPA
IX
a2-MG
IXa
EPA
PAI-1
Fibronectin
aPC
Xa
Thrombin
Fibrin
TGF-β
TF
Va
X
XIIIa
VIIa
VIIIa
XIII
MAPK
Neutrophil elastase
vWF
Integrin aIIbβ3
Fibulin 1
CRP
PAR-1
Lipoprotein A
Prothrombin
Entactin
Integrin axβ2
Prostacyclin
VII
VIII
Thrombospondin
Integrin avβ3
GpIb
PAR-2
IL-8
Z
TFPI
C5b-9
GAGs
PF1+2
IL-8r
Annexin V
GpIV
Integrin a3β1
V
Nexin PN-1
E-selectin
PAR-4
Nexin PN-2
CD14r
ZPI
Collagen
PAF
C6
Laminin
PDGF
PAR-3
LPS
P-selectin

Thromboinflammation in the wild...


B
Rh POSITIVE
O
Rh POSITIVE


STERIS






LIVE
BREAKING NEWS
PLANE CRASHES AT SFO
KTVU.COM
ON THE PHONE: TOM VACAR

How to study a problem:
TIC :Clinical Characterization:

Acute Traumatic Coagulopathy: Initiated by Hypoperfusion

Modulated Through the Protein C Pathway?

Karim Brohi, FRCS, FRCA, Mitchell J. Cohen, MD,* Michael T. Ganter, MD,†*
Michael A. Matthay, MD,‡ Robert C. Mackersie, MD, and Jean-François Pittet, MD†‡*

- Study at San Francisco General Hospital
- Ann Surg 245:812-818,

- 209 severely traumatized patients admitted to SFGH

- Median time injury – hospital admission: 28 minutes

- If patients were severely injured (ISS>15) and hypoperfused (BD >6) they were coagulopathic.

Coagulopathy after trauma

- Acute traumatic coagulopathy (ATC)
  - 25-33% of patients
  - Worse outcomes:
    - Higher transfusion requirements
    - Longer ICU & hospital stay
    - Higher incidence of multiorgan failure
    - 4-fold higher mortality: 10.9 vs. 46%
- Associated with multiple biochemical mechanisms and phenotypes.
  - Systemic anticoagulation
  - Dysregulated fibrinolysis
  - Platelet dysfunction
- Equally important is endothelial dysfunction.

DIFFERENT AND DYNAMIC PHENOTYPES REQUIRE DIFFERENT RESUSCITATION

Trauma immunology…the quick and dirty

- Trauma kills.
- Patients die from coagulopathy and bleeding.
- But truly they die and suffer from thromboinflammaiton.

- Whole blood has not solved the problem.
- We need personalized treatment.
- Shelf stable individualized resuscitation in a syringe
- Or even better pre deployed in a trauma vaccine

What problem are we trying to solve when we resuscitate?

- Stop bleeding/progression?
- Treat coagulopathy?
- Prevent coagulopathy?
- Treat endotheliopathy?
- Prevent endotheliopathy?

- It is not the same in every patient and not the same minute to minute.

Big audacious science…

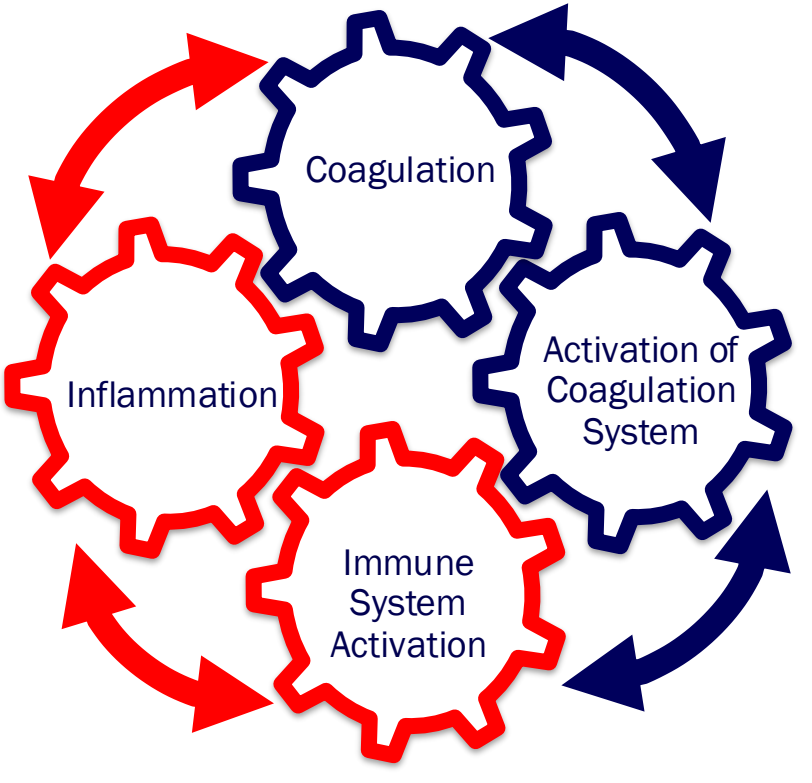
And a TEAM!!

TACTIC – a brief history

- TACTIC was funded from 2013-present by NHLBI, with periodic supplements from BARDA
- Mechanistic studies that dovetail with ongoing clinical trauma trials:
  - Control of Major Bleeding After Trauma: **COMBAT**
  - Prehospital Air Medical Plasma Trial: **PAMPer**
  - Study of Tranexamic Acid during Air Medical Prehospital Transport: **STAAMP**
- Basic science investigators in multiple US sites probed pathways activated in trauma that drive coagulopathy and end organ damage:
  - Novel DAMPs released in trauma
  - Trauma-induced endothelial injury and inflammation
  - Trauma-induced alterations in platelet function
  - Inflammatory mechanisms driving tissue factor expression
  - Multi-omics approaches to identify new players in TIC

What did we learn from TACTIC?

- Critical role of innate immune activation, complement and DAMPs
- Multiple phenotypes of TIC
- Disease of thromboinflammation
- Endothelial activation and injury
- Transfusion of thawed plasma saves lives



CRITICAL UNMET NEED:

- **DRIVERS and EFFECTORS of endothelial injury**
- **Crosstalk between coagulation, inflammation, and immunity**
- **How do we repair/resuscitate the endothelium?**

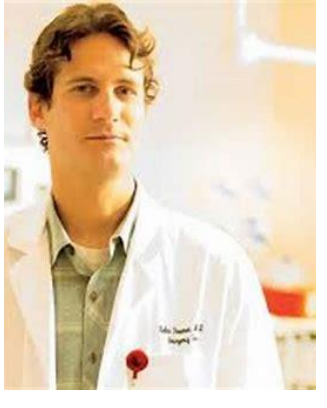
Team Science

Principal Investigators

Matthew D. Neal, MD
Trauma surgeon
Expertise: Hemostasis, platelet function, coagulation assessment, extracellular vesicles, animal models of trauma

Mitchell Cohen, MD
Trauma surgeon
Expertise: Coagulation biology, endothelial biology, thromboinflammation, protein C, animal models of trauma, computational modeling

Michael Yaffe, MD PhD
Trauma surgeon
Expertise: Signaling in cell injury, innate immune function, complement biology, RNA-binding proteins, computational biology,
animal models



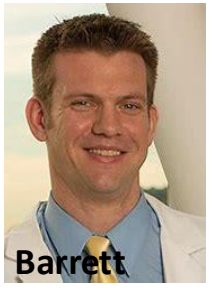
Kalev Freeman, MD PhD
Emergency medicine physician
Expertise: Vascular biology, ion channels, calcium signals, animal models, genomics

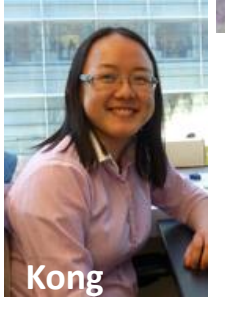
Team Science

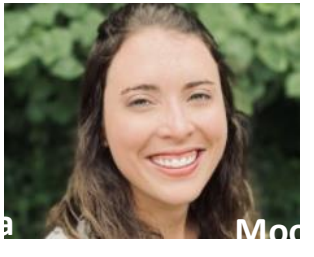
Key Co-Investigators

Wolfram Ruf, MD
Immunology and Vascular Biology
Expertise: Cell signaling of the coagulation cascade; targeted intervention in coagulation pathway

James Morrissey, PhD
Hemostasis and thrombosis, Biological Chemistry
Expertise: Novel regulators of the clotting cascade; novel antithrombotic/anti-inflammatory agents







Endothelium: the regulator of maladaptive responses and a crucial interface for thrombosis-inflammation crosstalk

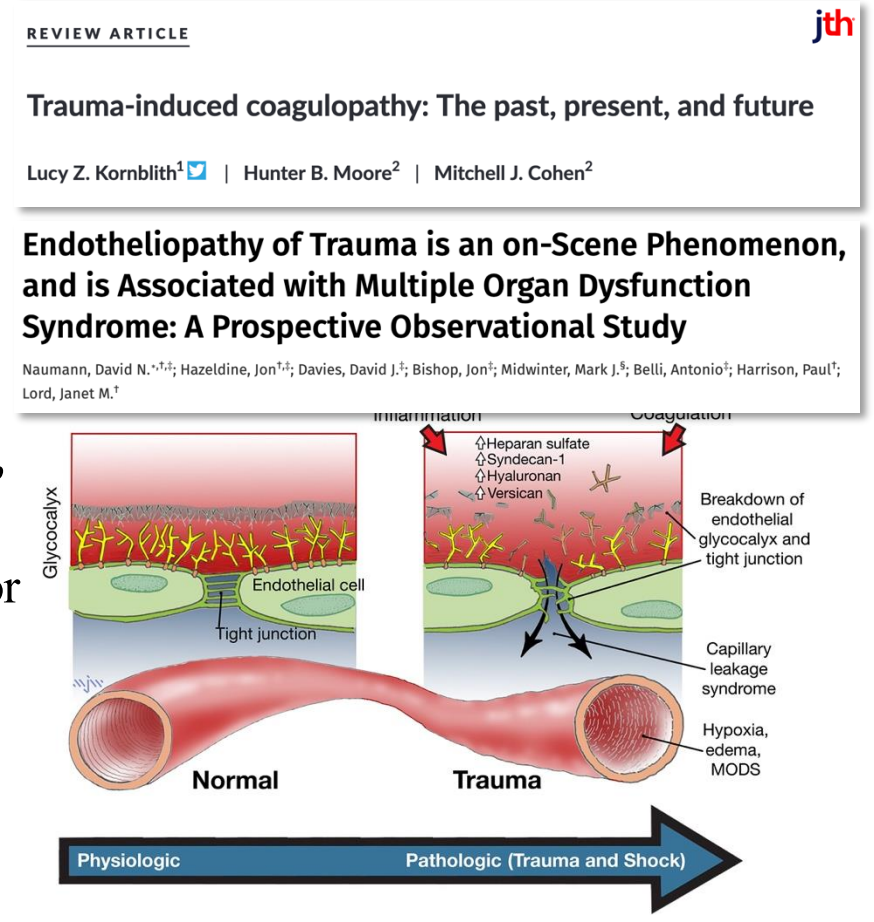
- **Central hypothesis:** the synergy of tissue injury and shock after severe trauma leads to by-products of vascular thrombo-inflammation that contribute to the phenotype of coagulopathy, tissue injury and organ failure through a progression to maladaptive endothelial injury; drivers and effectors of endothelial injury can be targeted to direct blood vessel endothelium towards reparative pathways.

How to study a problem: Thromboinflammation

The endotheliopathy of trauma

Endotheliopathy of Trauma (EoT)

- Injured and shocked patients suffer from trauma induced coagulopathy (TIC)
  - ↑ bleeding, ↑ morbidity, ↑ mortality
- Abundant literature on TIC, less to define and identify endotheliopathy
- Thromboinflammation → endotheliopathy, which impacts all patients
  - Creates ICU phenotype → MODS, ↑ ventilator time, ↑ infection
- Results in endothelial permeability



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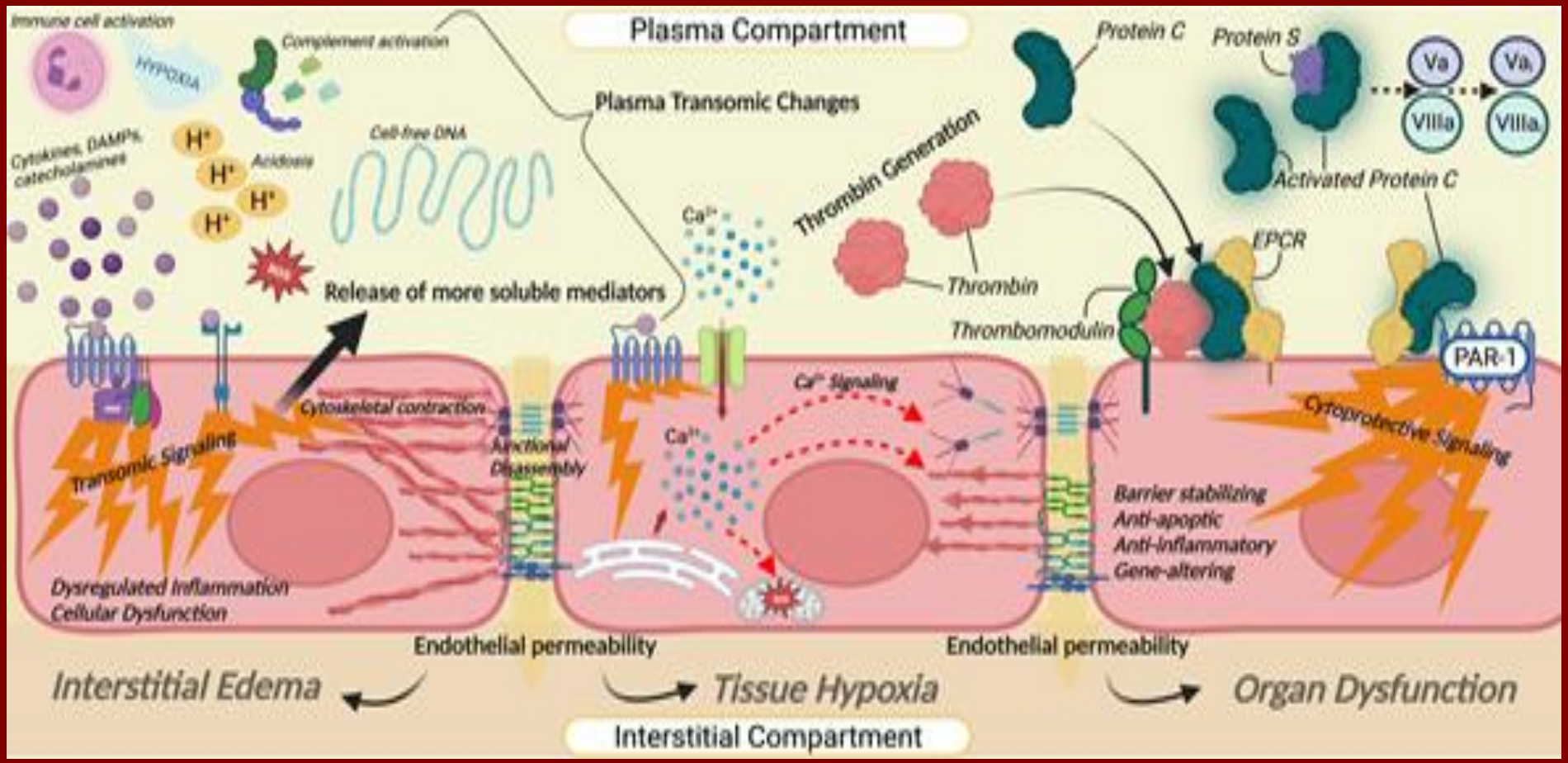
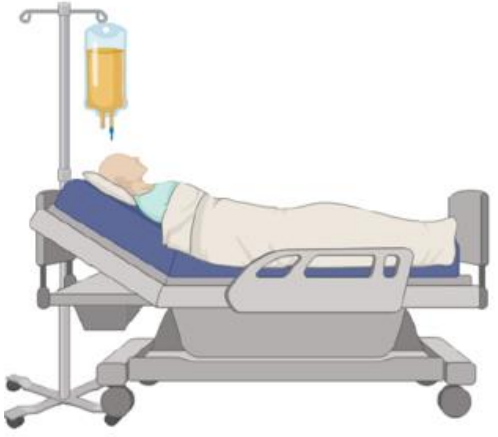

Immune cell activation
Complement activation
HYPOXIA
Plasma Compartment
Plasma Transomic Changes
Protein C
Protein S
Va
Va
VIIIa
VIIIa
Activated Protein C
Cytokines, DAMPs, catecholamines
H+
H+
H+
H+
Acidosis
Cell-free DNA
Ca2+
Thrombin Generation
Thrombin
EPCR
Thrombomodulin
Release of more soluble mediators
PAR-1
Cytoskeletal contraction
Ca2+ Signaling
Transomic Signaling
Junctional Disassembly
Ca2+
Cytoprotective Signaling
Barrier stabilizing
Anti-apoptic
Anti-inflammatory
Gene-altering
Dysregulated Inflammation
Cellular Dysfunction
Endothelial permeability
Endothelial permeability
Interstitial Edema
Tissue Hypoxia
Organ Dysfunction
Interstitial Compartment

Plasma omics measured by mass spectrometry



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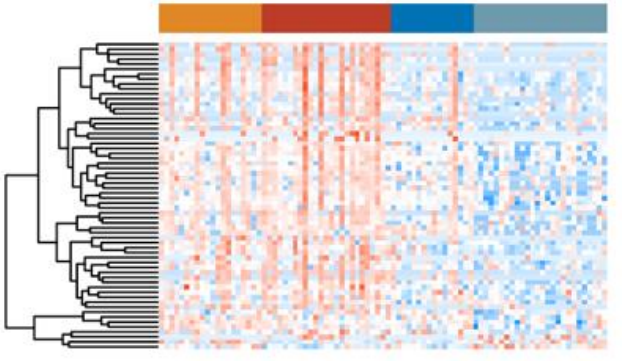
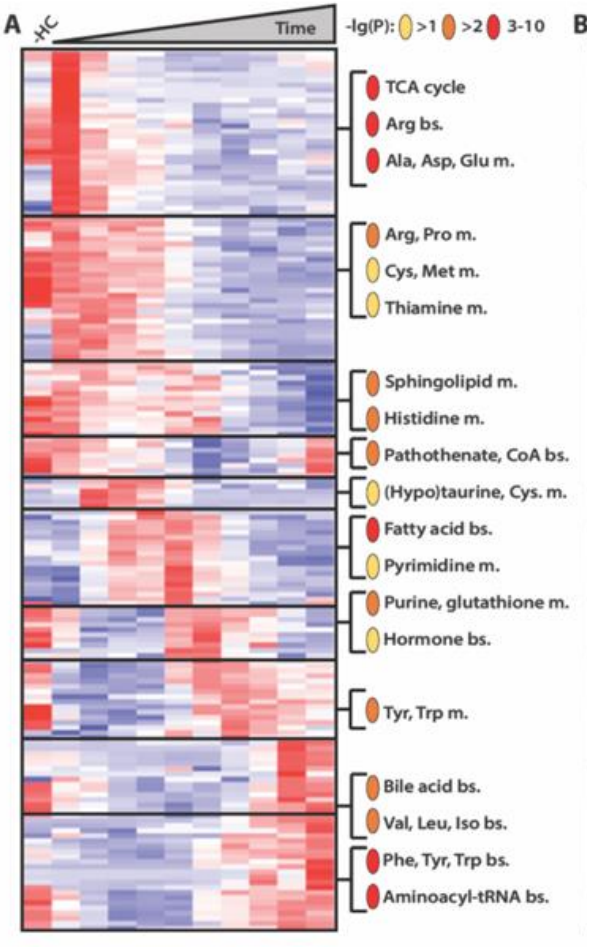
Patient	Protein1	Protein2	Met1	Met2	Met3	...
Patient 1	122	10	3e7	3e2	4e6	...
Patient 2	17	55	3e2	4e7	9e3	...
...	...	...	...	...	...	...
...	...	...	...	...	...	...



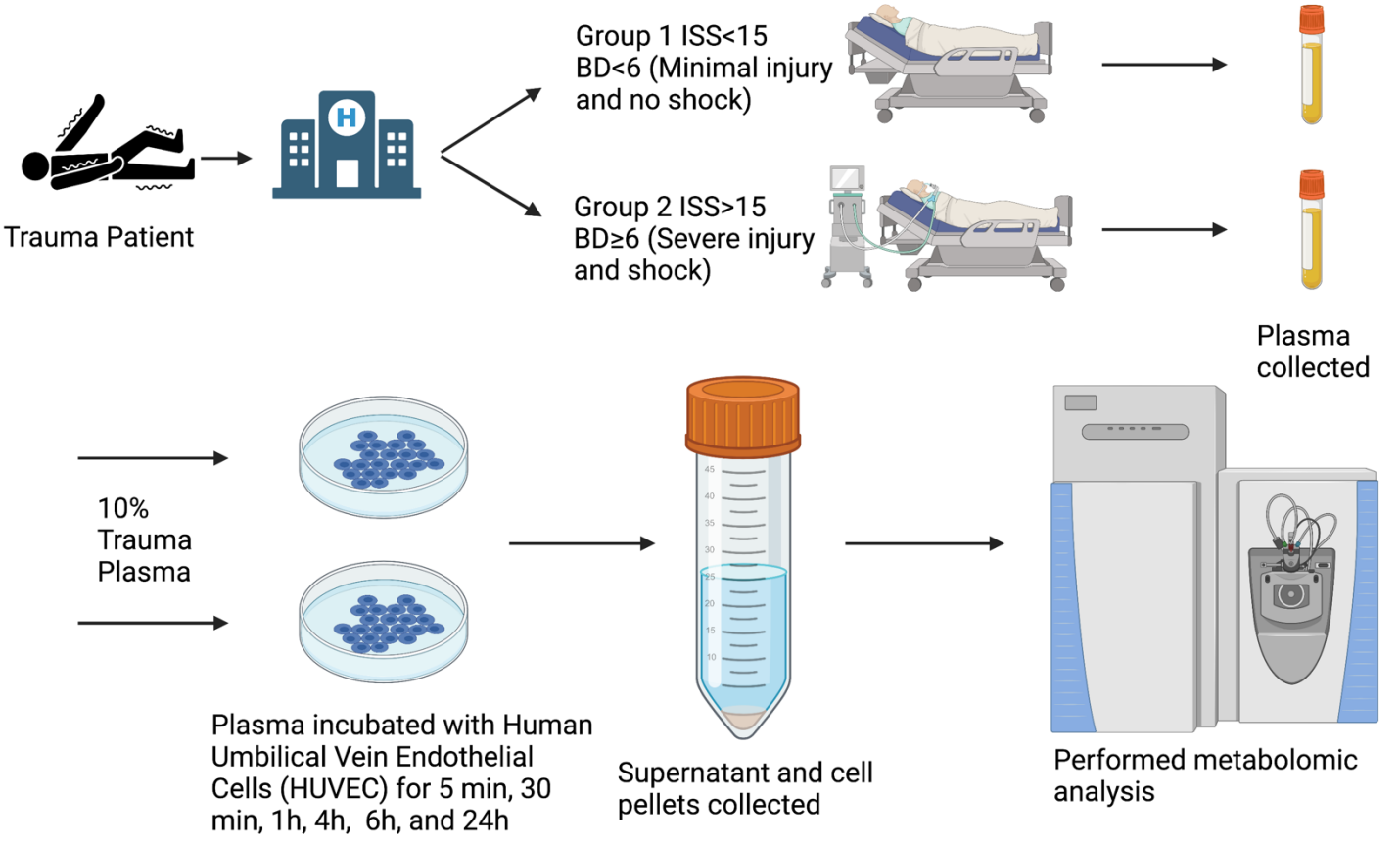
Average omic trends of injury and recovery over time

Metabolomics



Endotheliopathy of Trauma Induced Trans Omics

Methods



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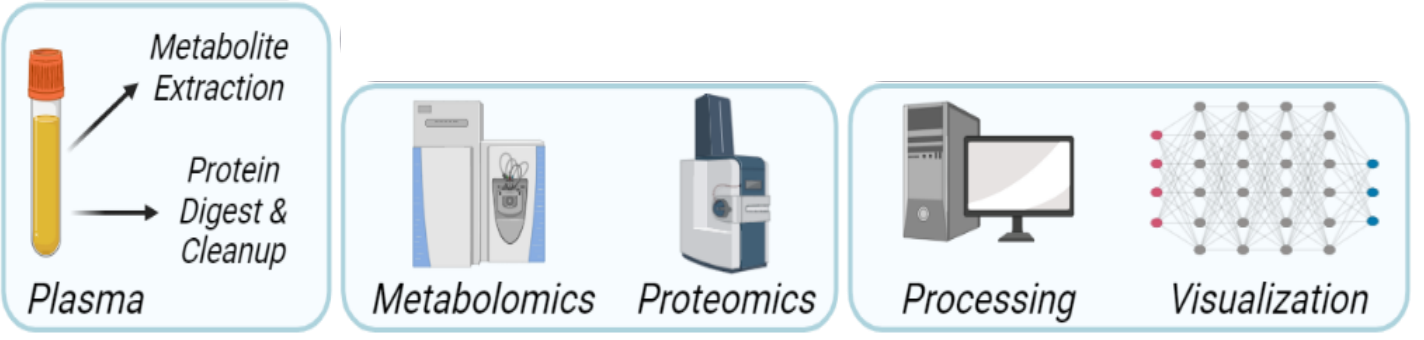
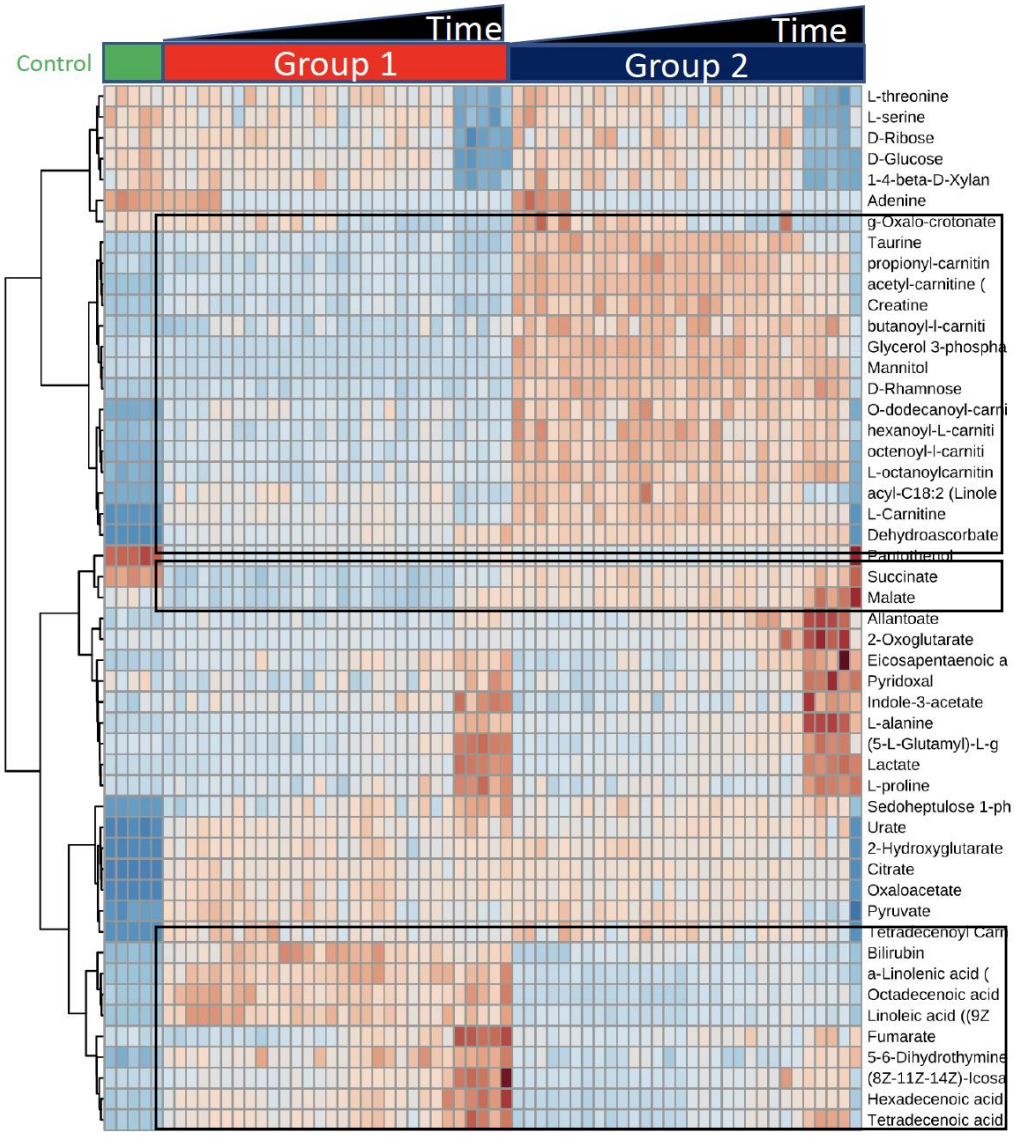
Multi-Omics

- Proteins, metabolites, and oxylipins circulating in trauma plasma
- Allows rapid identification of thousands of potential mediators
- Integrative approach to understanding the global trauma milieu



Metabolomics

- These results demonstrate a state of oxidative stress, mitochondrial dysfunction, and fatty acid oxidation deficiency leading to an energy crisis



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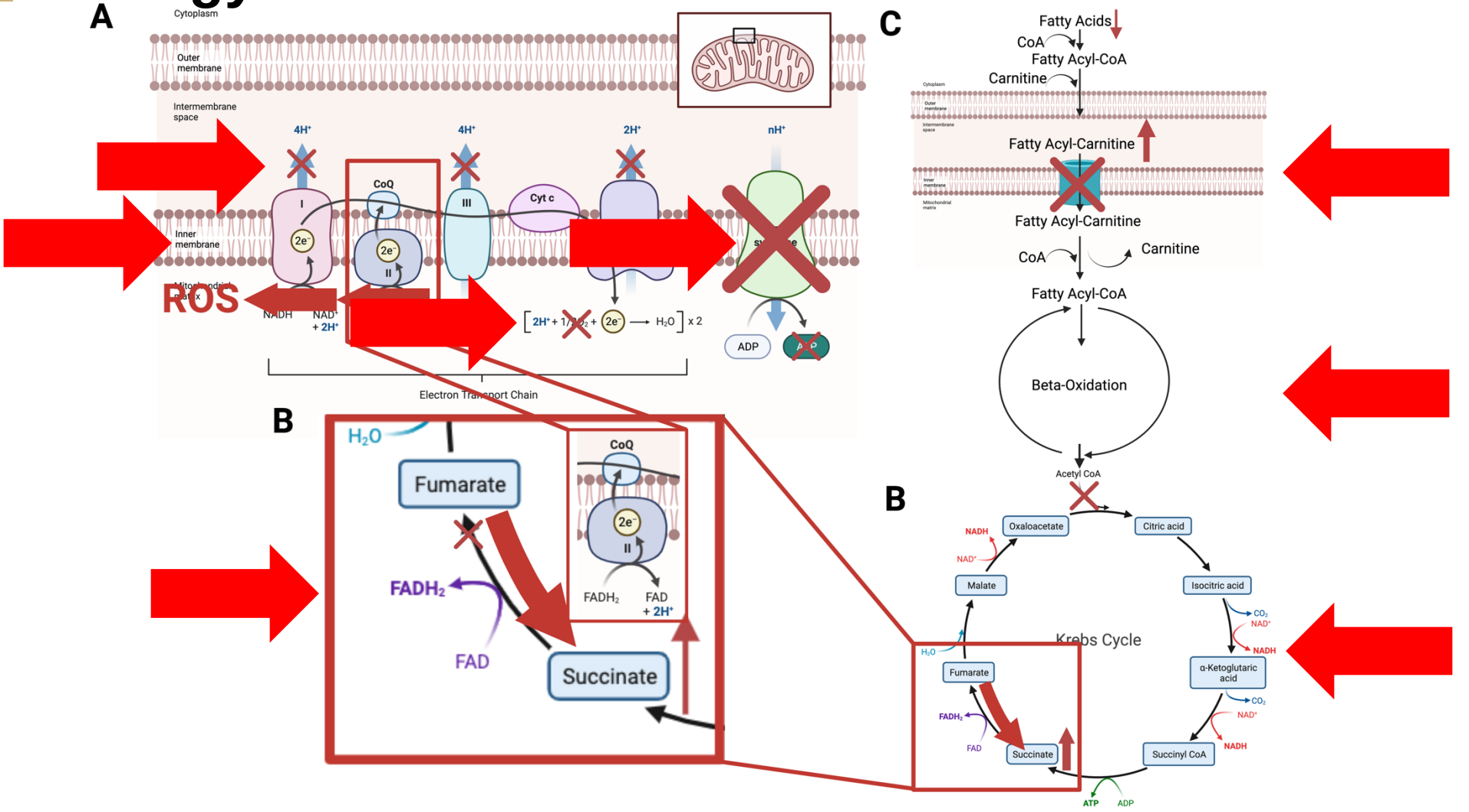
Energy Crisis



Endotheliopathy of Trauma Countermeasures and therapeutics: The promise of PAR 1

PROTEIN C

-42 MWQLTSLLLFVATWGISGTPAPLDSVFSSSERAHQVLRIRKR -1

1 ANSFLEELRHSSLERECIEEICDFEEAKEIFQNVDDTLAFWSKHVDGDQC 50

51 LVLPLEHPCASLCCGHGTCIDGIGSFSCDCRSGWEGRFCQREVSFLNCSL 100

101 DNGGCTHYCLEEVGWRRCSCAPGYKLGDDLLQCHPAVKFPCGRPWKRMEK 150

151 KRSHLKRDTEDQEDQVDPRLIDGKMTRRGDSPWQVVLLDSKKKLACGAVL 200

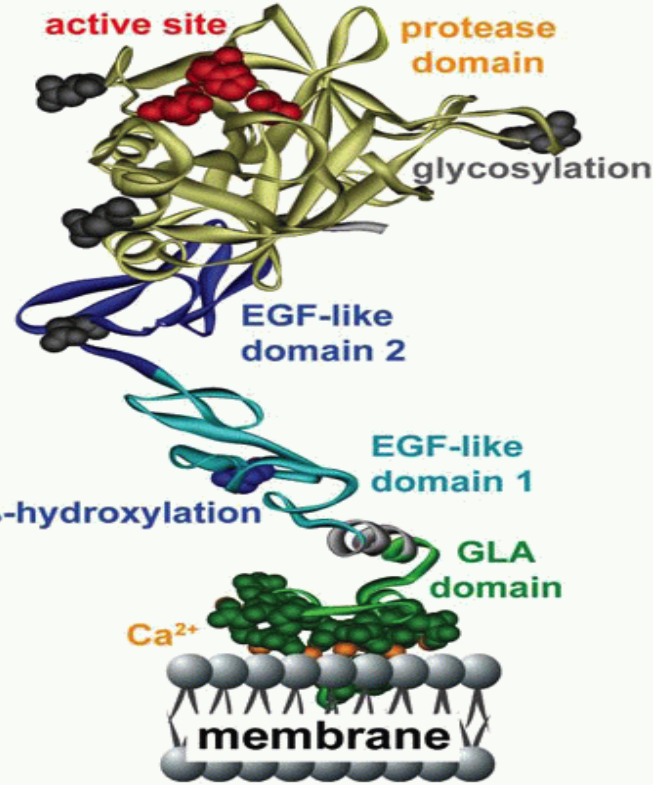
201 IHPSWVLTAAHCMDESKKLLVRLGEYDLRRWEKWELDLDIKEVFVHPNYS 250

251 KSTTDNDIALLHLAQPATLSQTIVPICLPDSGLAERELNQAGQETLVTGW 300

301 GYHSSREKEAKRNRTFVLNFIKIPVVPHNECSEVMSNMVSENMLCAGILG 350

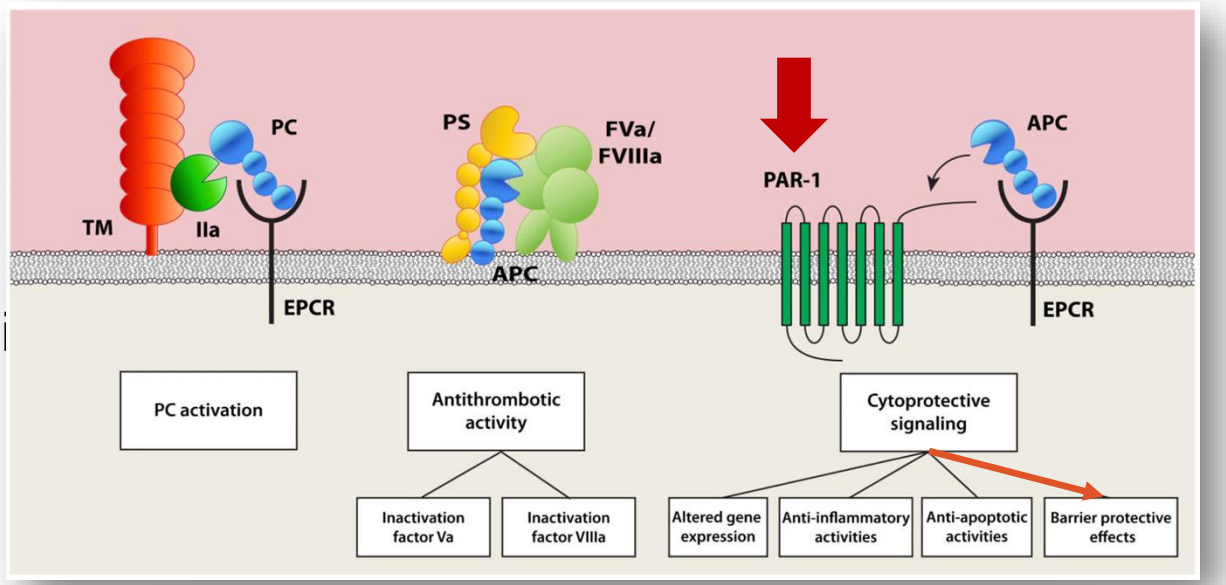
351 DRQDACEGDSGGPMVASFHGTWFLVGLVSWGEGCGLLHNYGVYTKVSRYL 400

401 DWIHGHIRDKEAPQKSWAP 419



Activated Protein C: Dual Roles

- **Anticoagulation**
  - Clevage of Va/VIIIa
  - Derepression of fibrinolysi
- **Cytoprotection**
  - Alteration of gene expression
  - Anti-inflammation
  - Anti-apoptosis
  - Barrier protection

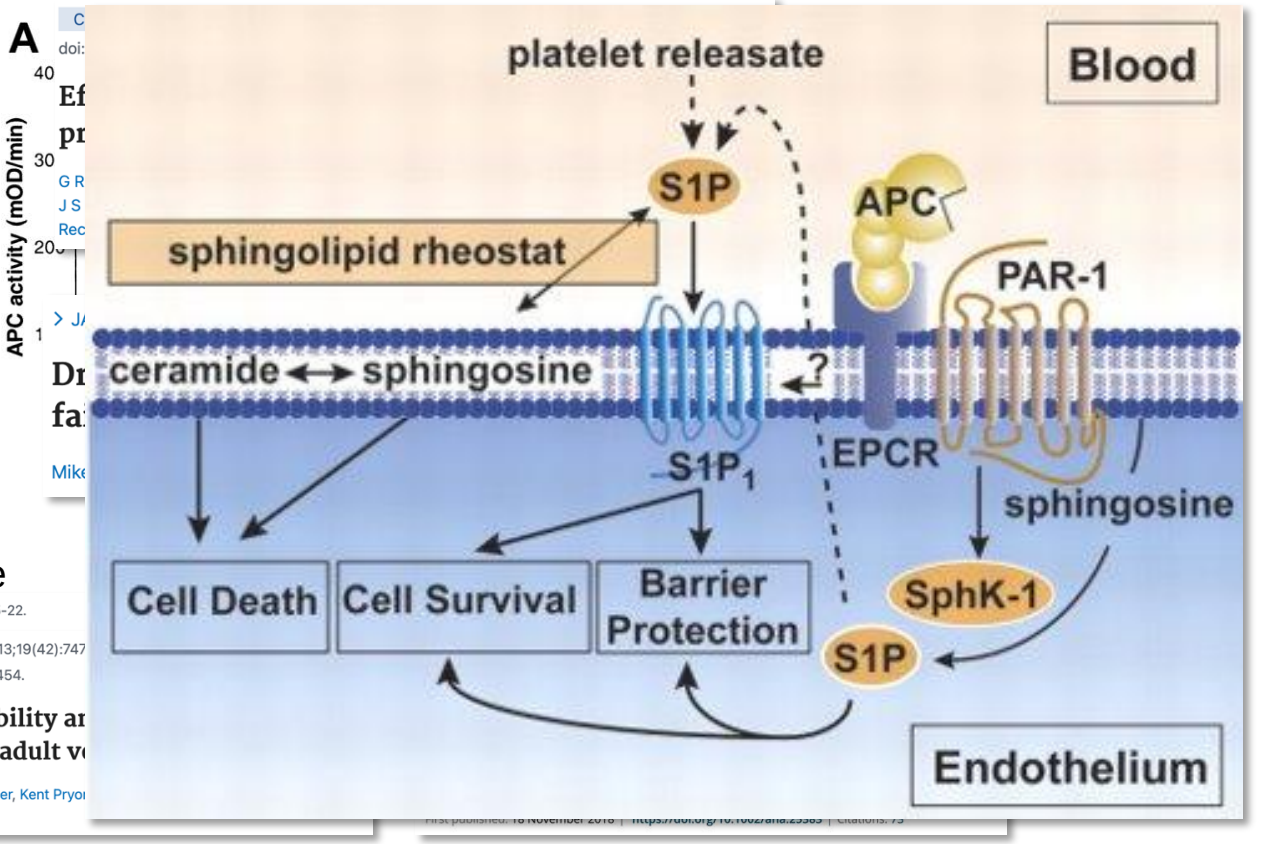


Mechanisms of anticoagulant and cytoprotective actions of the protein C pathway

E A M Bouwens [1], F Stavenuiter, L O Mosnier

Cytoprotective APC: 3K3A-APC

- **Recombinant APC**
  - PROWESS Trial: Xigris ®
  - PROWESS-SHOCK Trial
- **3K3A-APC**
  - Retains approximately 5% anticoagulant activity
  - Preserves its cytoprotective functions
  - 3K3A-APC in phase 3 stroke trials

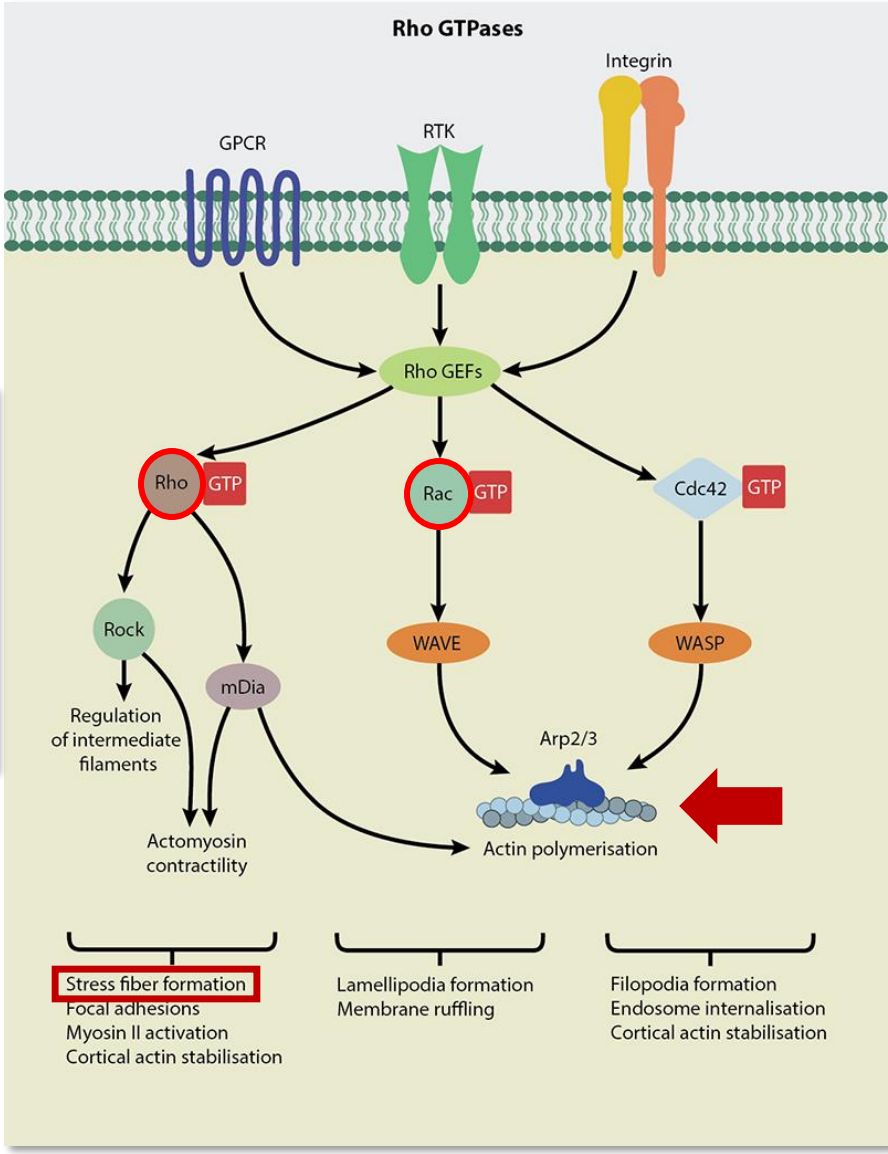


Endotheliopathy of Trauma. Endothelial Barrier Function (permeability)

Shock. 2022 Dec 1;58(6):542-548. doi: 10.1097/SHK.0000000000002008. Epub 2022 Oct 21.

SHOCK INDUCES ENDOTHELIAL PERMEABILITY AFTER TRAUMA THROUGH INCREASED ACTIVATION OF RHOA GTPASE

Margot DeBot [1], Sanchayita Mitra [1], Patrick Lutz [1], Terry R Schaid Jr [1], Preston Stafford [1], Jamie B Hadley [1], Patrick Hom [1], Angela Sauaia, Christopher C Silliman [1], Ernest E Moore [2], Mitchell J Cohen [1]



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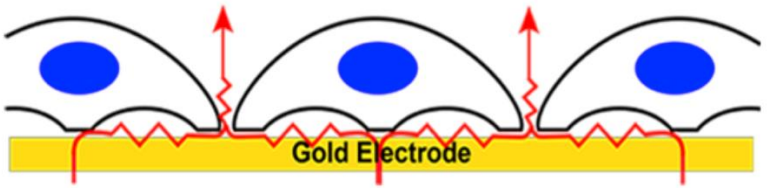
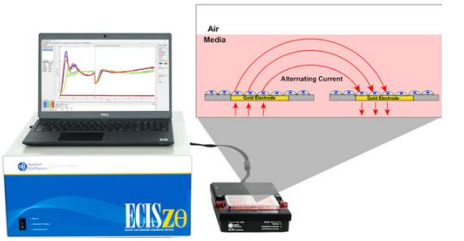
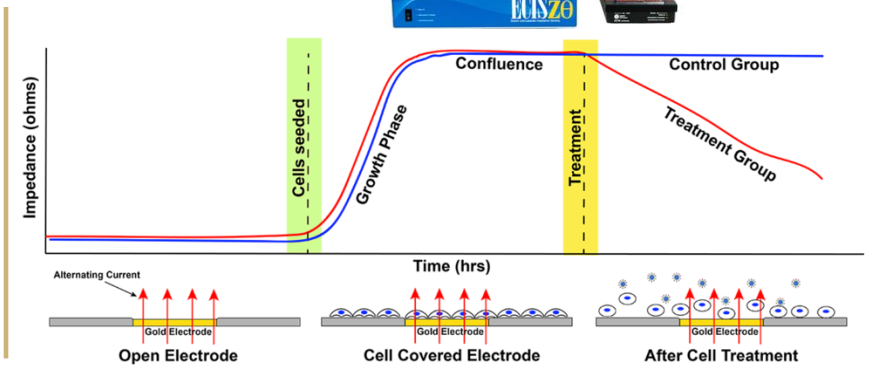
- **Plasma samples were collected from injured patients on arrival to a Level 1 Trauma Center**

Phenotypes	Minimally Injured: ISS <15	Severely Injured: ISS >15
Min. Shock: Base Excess > -6	Minimal Injury or Shock	Severely Injured
Severe Shock: Base Excess < -6	Severe Shock	Severe Injury and Shock

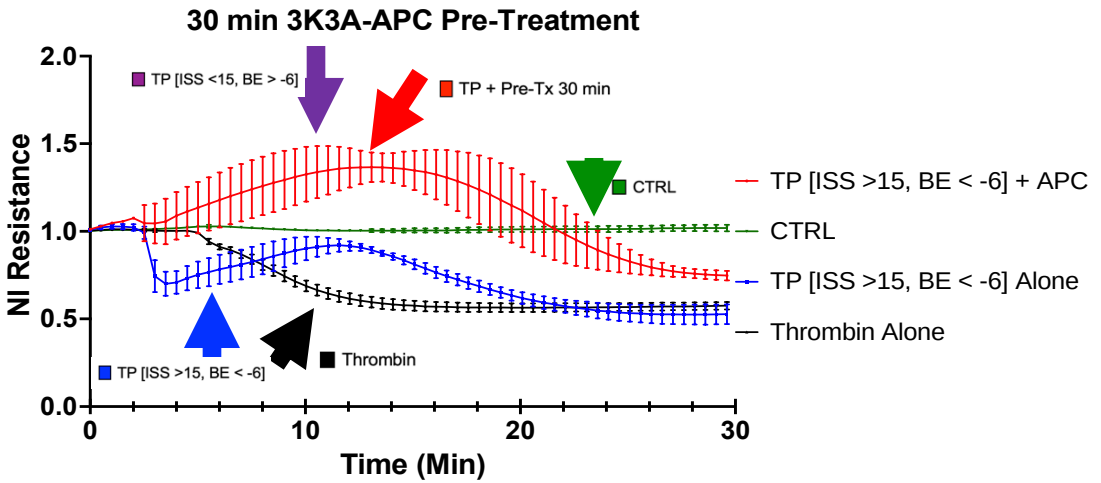
- Electric Cell-Substrate Impedance Sensing (**ECIS**)
- Human Umbilical Vein Endothelial Cells (**HUVECs**)

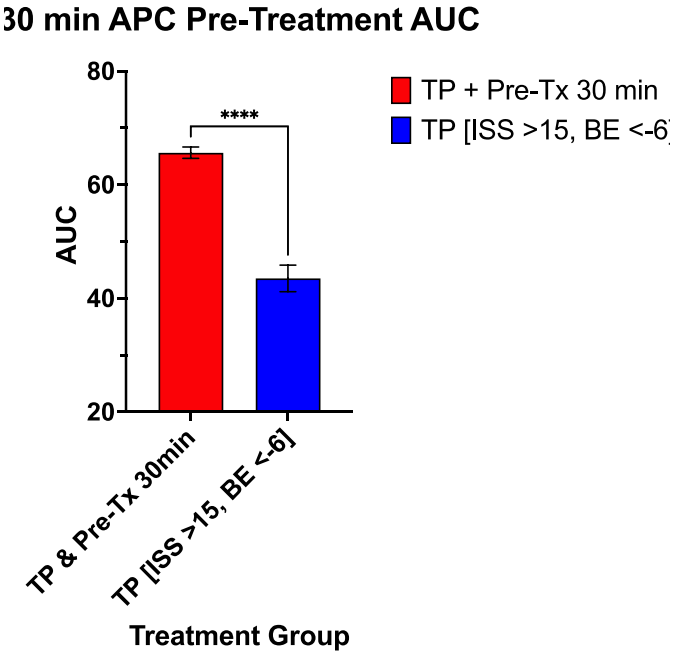




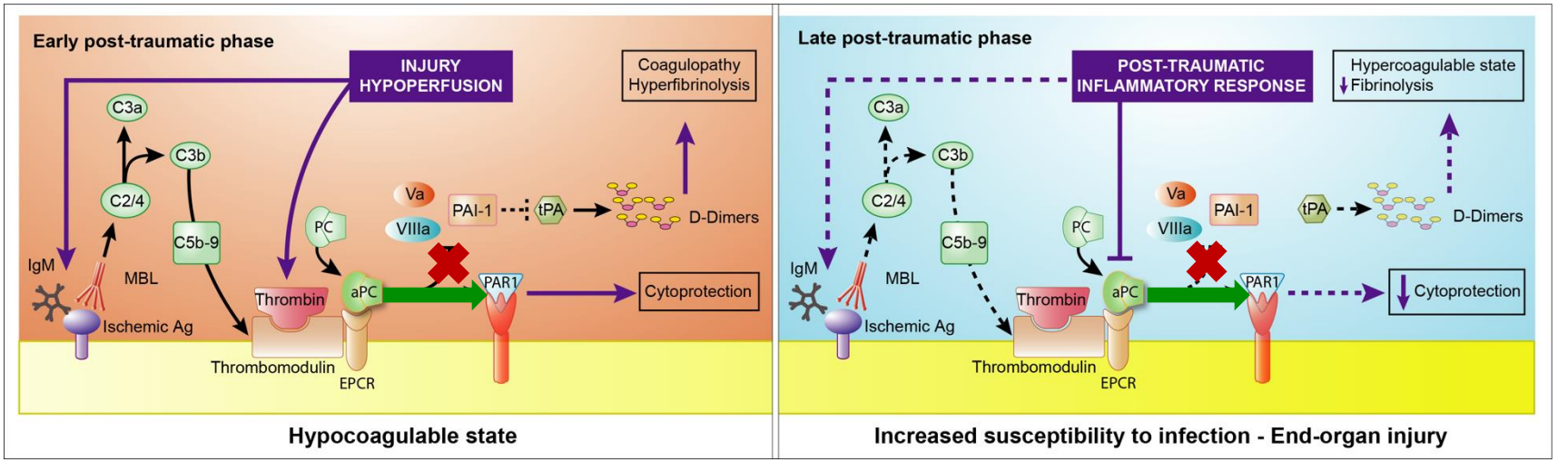


3K3A-aPC mitigates endothelial permeability

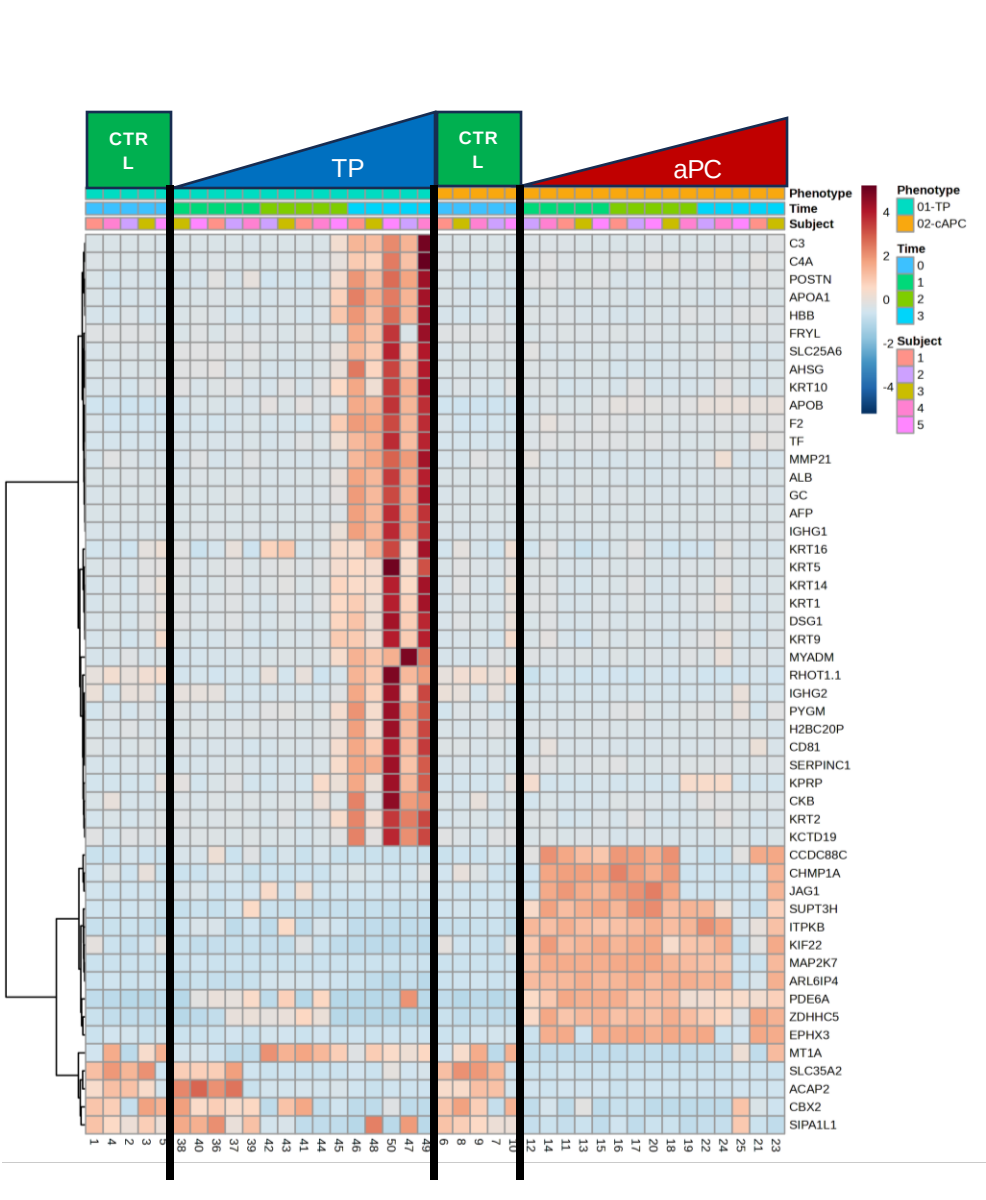


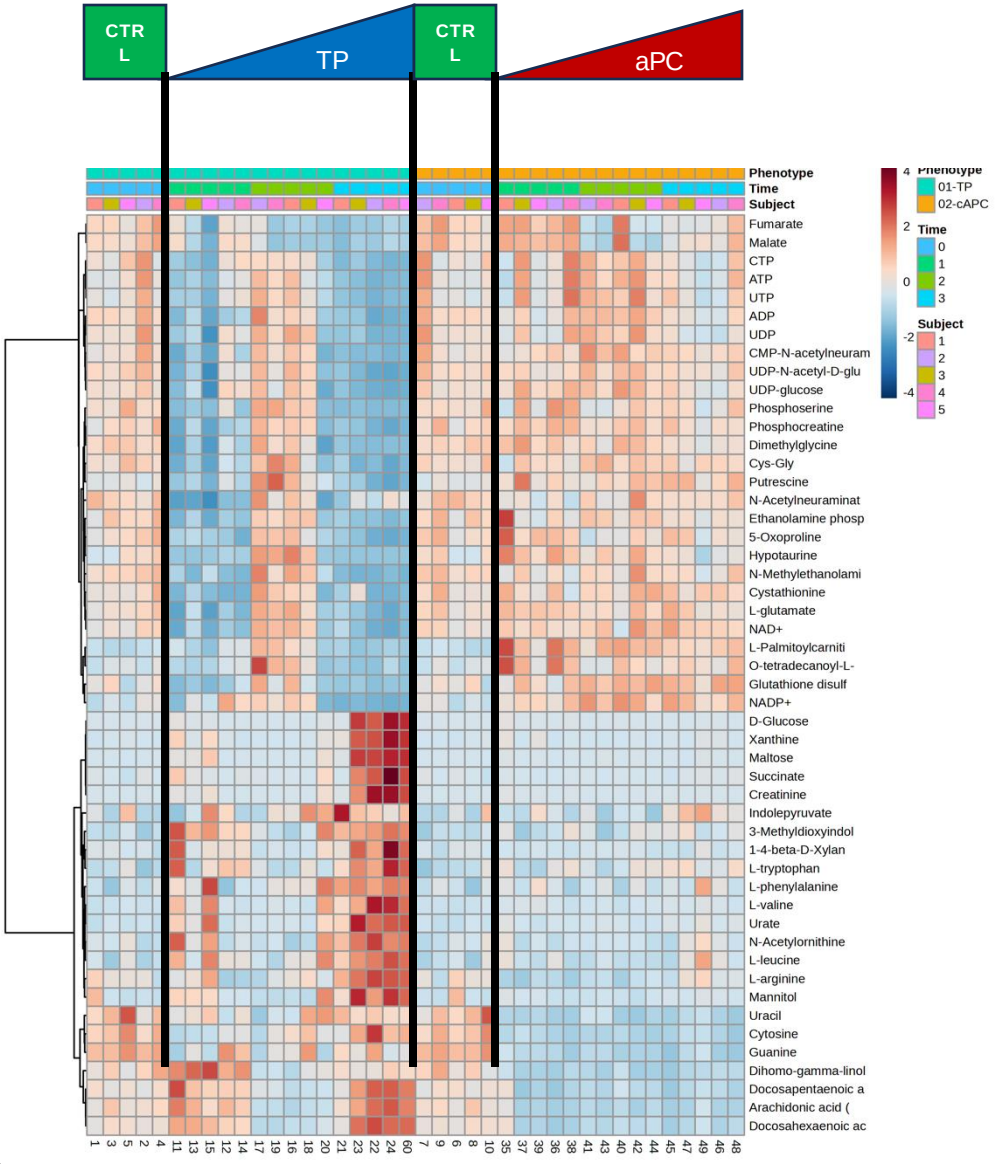


- **Pre-treatment with 3K3A-APC, which retains its cytoprotective function but ~5% of its anti-coagulant function, abrogates the effects of trauma-induced endotheliopathy on HUVECs.**



The proteomic storm and metabolomic energy crisis is prevented and treated by 3K3A-aPC

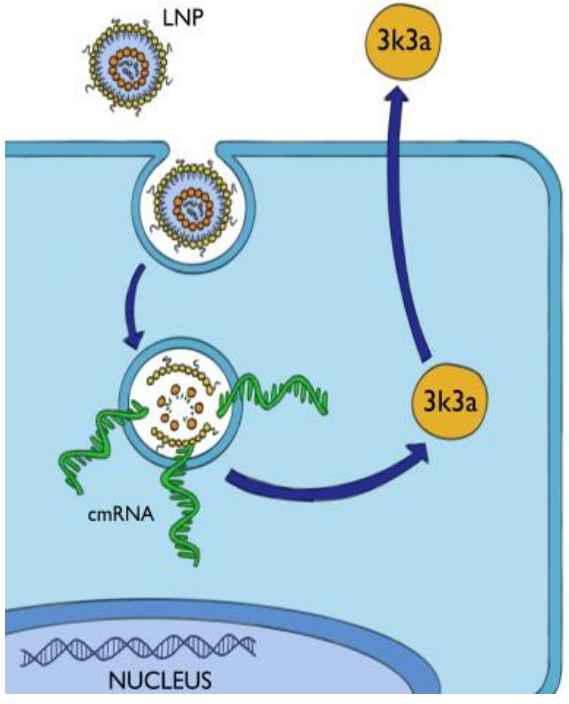




“Next-Gen” mRNA Vaccines for Trauma: Overview

Lipid nanoparticle mRNA delivery of cell-signaling selective activated Protein C: “Next-Gen” precision immunotherapy for thromboinflammatory modulation in trauma.

3K3A-activated protein C (APC), an engineered cell-signaling analogue of the serine protease APC, has cytoprotective effects in brain injury and ischemia and is *currently in phase III human trials* as a neuroprotectant for patients with ischemic stroke. We are studying 3K3A-APC as a novel drug to prevent endothelial dysfunction and immune storm, mitigate TIC, and help set the ‘inflammatory thermostat’ allowing causalities sufficient time to reach definitive care and achieve recovery without thromboinflammatory morbidity and mortality. As a therapeutic, 3K3A-APC can be shelf stable and administered early and far forward even in an autoinjector self given by the injured. This makes it an ideal *‘resuscitation in a syringe’* providing TIC mitigating and inflammamodulatory treatment directly after injury. While treatment after injury will provide benefit, successful prophylactic delivery of therapeutic levels of protective recombinant proteins to at-risk military personnel immediately before deployment with mRNA vaccines will herald the **next generation of precision therapeutics custom-designed to protect troops** from any specific acute threat including not only polytrauma but also exposure to chemicals, radiation, or pathogens. Building on recent advances in mRNA vaccines and materials science, we are conducting a preclinical trial of mRNA/LNPs designed to deliver payloads of 3K3A-aAPC for treatment of endotheliopathy and TIC in polytrauma. <u>This novel mRNA therapeutic will provide a shelf-stable immune modulator and “trauma vaccine” delivering endothelial and immune therapy in a single dose administered (1) immediately after injury or (2) prophylactically to at-risk military personnel before deployment.</u>



Endotheliopathy of Trauma: Calcium Signaling

Combining mechanism, prediction and precision care.

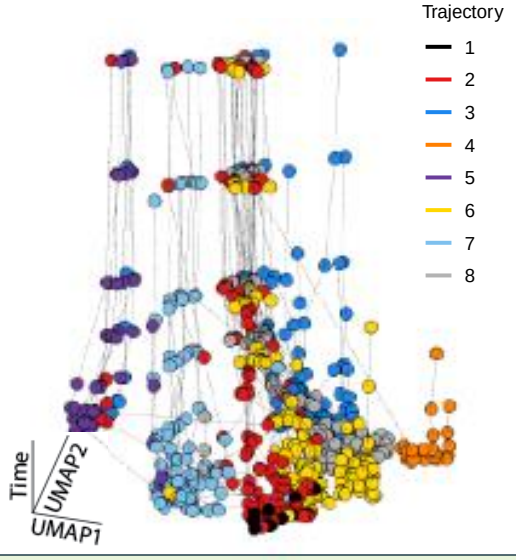
In silico

Plasma omics (biomarkers) reflect and predict trauma patient trajectories and outcomes.

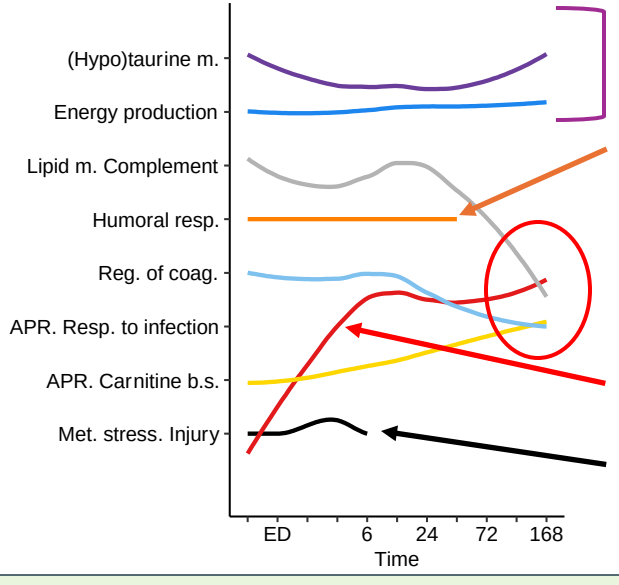
What plasma proteomics and metabolomics can reveal about biology underlying patient divergence following critical injury

Why do similarly injured patients have divergent outcomes?

3D trauma patient omics trajectories



Trajectories in omics space



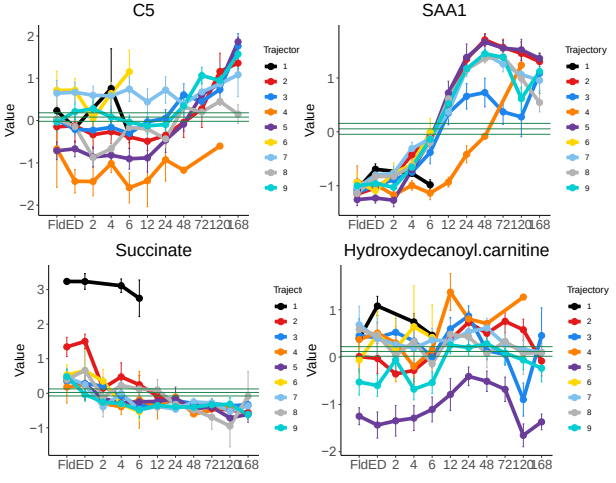
Static omics trajectories (remain in start states)
High comorbidity trajectory

Convergence towards "typical" post-injury state (APR)

Severe injury survivors trajectory

Severe injury, early mortality trajectory

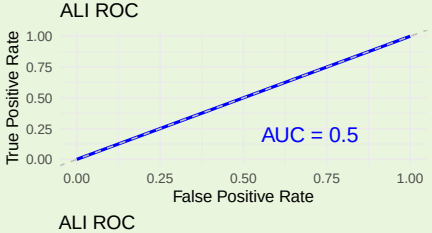
Omics biomarkers correlate with trauma progression

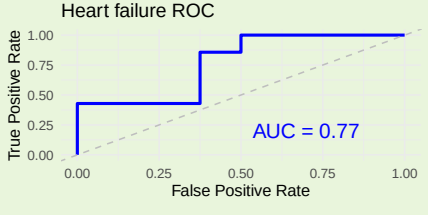


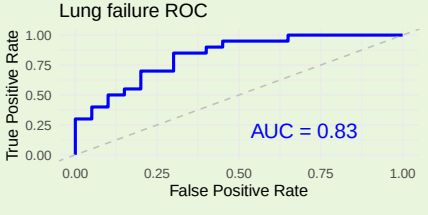
... ~1400 biomarkers

Omics improves prediction of outcomes among similarly injured patients

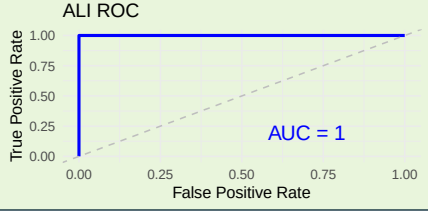
using clinical covariates

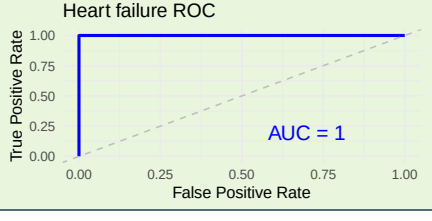


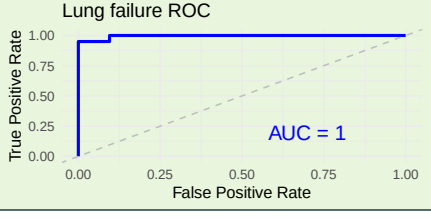




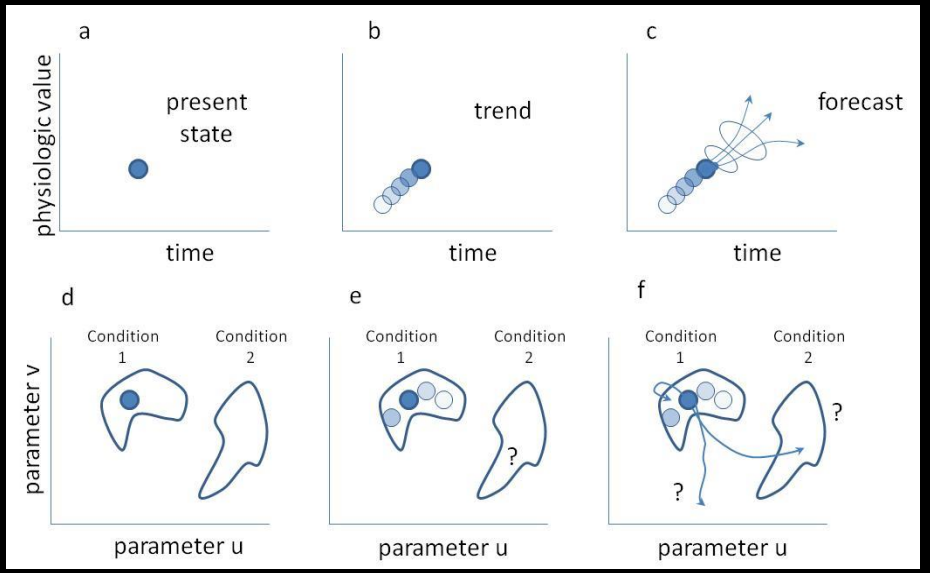
using omics biomarkers







Dynamic physiologic states exist in a physiologic state space



Our patients move through these states optimally guided towards health

Why do we need this?

22 center retrospective study

PROMMTT

PROSPECTIVE OBSERVATIONAL MULTICENTER MASSIVE TRANSFUSION STUDY

PROP:P:R

Prospective **R**andomized **O**ptimum **P**latelet and **P**lasma **R**atios

Lancet. 2018 July 28; 392(10144): 283–291. doi:10.1016/S0140-6736(18)31553-8.

Plasma-first resuscitation to treat haemorrhagic shock during emergency ground transportation in an urban area: a randomised trial

Hunter B Moore, **Ernest E Moore**, **Michael P Chapman**, **Kevin McVaney**, **Gary Bryskiewicz**, **Robert Blechar**, **Theresa Chin**, **Clay Cothren Burlew**, **Fredric Pieracci**, **F Bernadette West**, **Courtney D Fleming**, **Arsen Ghasabyan**, **James Chandler**, **Christopher C Silliman**, **Anirban Banerjee**, and **Angela Sauaia**
(H B Moore MD, Prof E E Moore MD), **Department of Radiology** (M P Chapman MD), **and Department of Pediatrics** (Prof C C Silliman MD), **University of Colorado Denver, School of Medicine, Aurora, CO, USA; Bonfils Blood Center, Denver, CO, USA** (Prof C C Silliman); **Department of Surgery** (Prof E E Moore, C C Burlew MD, F Pieracci MD, C D Fleming, A Ghasabyan MPH, J Chandler, Prof A Banerjee PhD), **Emergency Department** (K McVaney MD), **and Paramedic Division** (G Bryskiewicz, R Blechar), **Denver Health Medical Center, Denver, CO, USA; University of California Irvine School of Medicine, Irvine, CA, USA** (T Chin MD); **American Red Cross, Connecticut, Mid-Atlantic, and Appalachian Regions, Hartford, CA, USA** (F B West MD); **and Health Systems, Management, and Policy, University of Colorado Denver, School of Public Health, Aurora, CO, USA** (Prof A Sauaia MD)

COMBAT TRIAL AT DENVER HEALTH SHOWED NO BENEFIT FOR PRE HOSPITAL PLASMA

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 26, 2018 VOL. 379 NO. 4

Prehospital Plasma during Air Medical Transport in Trauma Patients at Risk for Hemorrhagic Shock

J.L. Sperry, F.X. Guyette, J.B. Brown, M.H. Yazer, D.J. Triulzi, B.J. Early-Young, P.W. Adams, B.J. Daley, R.S. Miller, B.G. Harbrecht, J.A. Claridge, H.A. Phelan, W.R. Witham, A.T. Putnam, T.M. Duane, L.H. Alarcon, C.W. Callaway, B.S. Zuckerbraun, M.D. Neal, M.R. Rosengart, R.M. Forsythe, T.R. Billiar, D.M. Yealy, A.B. Peitzman, and M.S. Zenati, for the PAMPer Study Group*

PAMPR TRIAL in PITTSBURGH SHOWED MODEST BENEFIT FOR PRE HOSPITAL PLASMA

How to study a problem: Combining mechanism, prediction and targeted care.

2. Model Driven Dynamics

Building an autonomous controller: Coagulation control systems.

COAGULATION

Targeted clinical control of trauma patient coagulation through a thrombin dynamics model

Amor A. Menezes,[1,2] Ryan F. Vilardi,[3] Adam P. Arkin,[1,2,4]* Mitchell J. Cohen[5,6]*

We present a methodology for personalizing the clinical treatment of severely injured patients with acute traumatic coagulopathy (ATC), an endogenous biological response of impaired coagulation that occurs early after trauma and shock and that is associated with increased bleeding, morbidity, and mortality. Despite biological characterization of ATC, it is not easily or rapidly diagnosed, not always captured by slow laboratory testing, and not accurately represented by coagulation models. This lack of knowledge, combined with the inherent time pressures of trauma treatment, forces surgeons to treat ATC patients according to empirical resuscitation protocols. These entail transfusing large volumes of poorly characterized, nontargeted blood products that are not tailored to an individual, the injury, or coagulation dynamics. Massive transfusion mortality remains at 40 to 70% in the best of trauma centers. As an alternative to blunt treatments, time-consuming tests, and mechanistic models, we used dynamical systems theory to create a simple, biologically meaningful, and highly accurate model that (i) quickly forecasts a driver of downstream coagulation, thrombin concentration after tissue factor stimulation, using rapidly measurable concentrations of blood protein factors and (ii) determines the amounts of additional coagulation factors needed to rectify the predicted thrombin dynamics and potentially remedy ATC. We successfully demonstrate in vitro thrombin control consistent with the model. Compared to another model, we decreased the mean errors in two key trauma patient parameters: peak thrombin concentration after tissue factor stimulation and the time until this peak occurs. Our methodology helps to advance individualized resuscitation of trauma-induced coagulation deficits.

INTRODUCTION

Trauma is the leading cause of death and disability between the ages of 1 and 44 (*1*), with bleeding contributing to the vast majority of these deaths (*2*). Such hemorrhage is a clinical problem that is complicated by an endogenous biological response called acute traumatic coagulopathy (ATC) (*3*). ATC results in impaired coagulation, increased bleeding, greater transfusion needs, and a fourfold increase in mortality (*3*). After the initial phase of hypocoagulobility, ATC patients often dynamically transition to a hypercoagulable thrombotic state manifested by excessive clotting (*3*). The resulting deep vein thrombosis, myocardial infarction, stroke, and organ failure (*4*) all contribute to an extremely poor outcome in patients who survive their initial injuries.

Despite considerable research (*4*) on the molecular mechanisms of ATC, there remains a mechanistic and predictive knowledge gap that stems from an inadequate understanding of coagulation mechanisms after an injury and a lack of adequate prediction and real-time decision support for clinicians who care for the severely injured. These failings impede improvements to urgent resuscitation. Thus, there is a need to characterize coagulation mechanisms in trauma patients and to use this characterization to improve the precision of individual treatments.

In the absence of dynamic diagnostics and decision support, current trauma resuscitation practices (*4*) center on the nontargeted repair of the coagulation cascade (*5*) (Fig. 1A) and the production of its principal protein thrombin through the transfusion of large volumes of poorly characterized fresh-frozen plasma containing multiple clotting proteins and inhibitors in concentrations that vary from unit to unit. These urgent-care therapies indiscriminately actuate many interacting elements of the coagulation process, resulting in variable untargeted treatment for every patient and with every administration, which is further exacerbated by a lack of clarity about treatment effects on the patient's physiological and biological trajectories resulting from the missing diagnostics and decision support. Such blunt treatment is often either not enough (ATC and bleeding continue) or too much (thrombosis occurs). Both of these extremes contribute to dysregulated inflammation and poor outcomes (*4*). The mortality from massive transfusion remains at 40 to 70% in the best of trauma centers (*6*). Retrospective (*7*) and prospective (*8*) studies connect the blunt addition of fresh-frozen plasma to poor outcomes, even when the plasma is augmented with empiric ratios of platelets and red blood cells. Transfusion of fresh-frozen plasma is independently associated with a higher risk of multiple organ failure and poor outcomes in patients with hemorrhagic shock (*9*). Meanwhile, individual interventions consisting of personalized blood protein factor concentrations that are tailored to specific clotting perturbations have been shown to be beneficial (*4*), although no consensus yet exists on the amount and type of coagulation factors to administer. There is, however, a clinical desire for specific blood products to treat trauma coagulopathy (*10*). In sum, in an era of increasing personalized medicine, there is an urgent need for targeted, patient-specific trauma coagulation therapies.

Current diagnostics and decision support suffer from a dearth of patient-specific coagulation measurements. Although clinical practice uses several global markers [international normalized ratio (INR), partial thromboplastin time (PTT), prothrombin time (PT), platelet count, fibrinogen concentration, etc.] to diagnose the presence of ATC, these conventional coagulation tests are not enough to tailor a specific intervention and support only the decision to administer plasma or not. Cell-based viscoelastic tests are insufficiently predictive, and their use in resuscitation algorithms also results in nontargeted treatment. Moreover,

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ARTICLE OPEN

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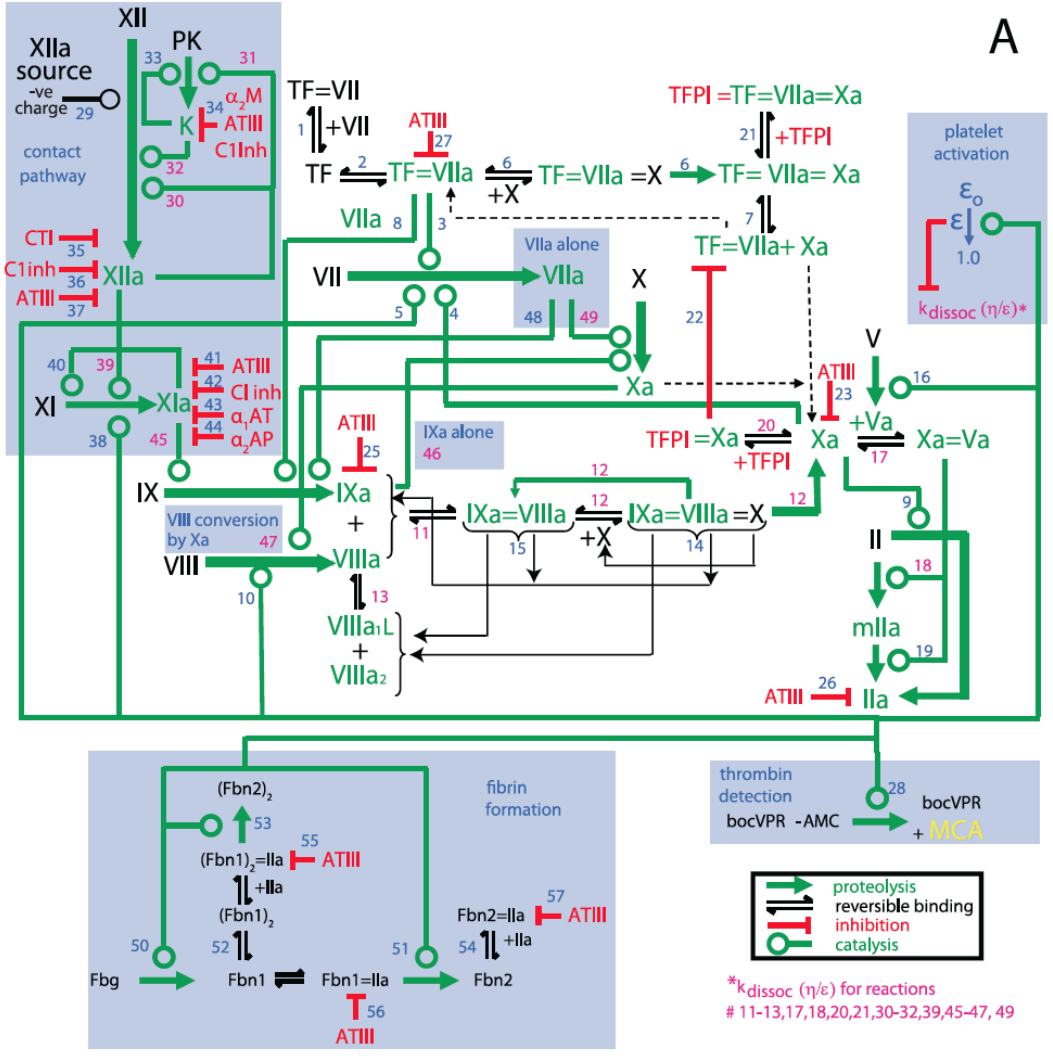
Personalized modulation of coagulation factors using a thrombin dynamics model to treat trauma-induced coagulopathy

Damon E. Ghetmiri[1], Mitchell J. Cohen[2] and Amor A. Menezes[1,3,4]✉

Current trauma-induced coagulopathy resuscitation protocols use slow laboratory measurements, rules-of-thumb, and clinician gestalt to administer large volumes of uncharacterized, non-tailored blood products. These one-size-fits-all treatment approaches have high mortality. Here, we provide significant evidence that trauma patient survival 24 h after hospital admission occurs if and only if blood protein coagulation factor concentrations equilibrate at a normal value, either from inadvertent plasma-based modulation or from innate compensation. This result motivates quantitatively guiding trauma patient coagulation factor levels while accounting for protein interactions. Toward such treatment, we develop a Goal-oriented Coagulation Management (GCM) algorithm, a personalized and automated ordered sequence of operations to compute and specify coagulation factor concentrations that rectify clotting. This novel GCM algorithm also integrates new control-oriented advancements that we make in this work: an improvement of a prior thrombin dynamics model that captures the coagulation process to control, a use of rapidly-measurable concentrations to help predict patient state, and an accounting of patient-specific effects and limitations when adding coagulation factors to remedy coagulopathy. Validation of the GCM algorithm's guidance shows superior performance over clinical practice in attaining normal coagulation factor concentrations and normal clotting profiles simultaneously.

npj Systems Biology and Applications (2021)7:44 ; https://doi.org/10.1038/s41540-021-00202-9


A
XII
XIIa source
-ve charge
29
PK
33
31
α_2M
34
K
ATIII
C1Inh
32
30
contact pathway
CTI
35
C1inh
36
ATIII
37
XIIa
XI
40
39
XIa
38
45
41
ATIII
42
CI inh
43
α_1AT
44
α_2AP
IX
IXa
+
VIIIa
VIII
10
VIII conversion by Xa
47
ATIII
25
IXa alone
46
11
12
IXa=VIIIa
IXa=VIIIa=X
+X
15
14
13
VIIIa$_1$L
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TF=VII
1
+VII
TF
2
TF=VIIa
ATIII
27
6
+X
TF=VIIa =X
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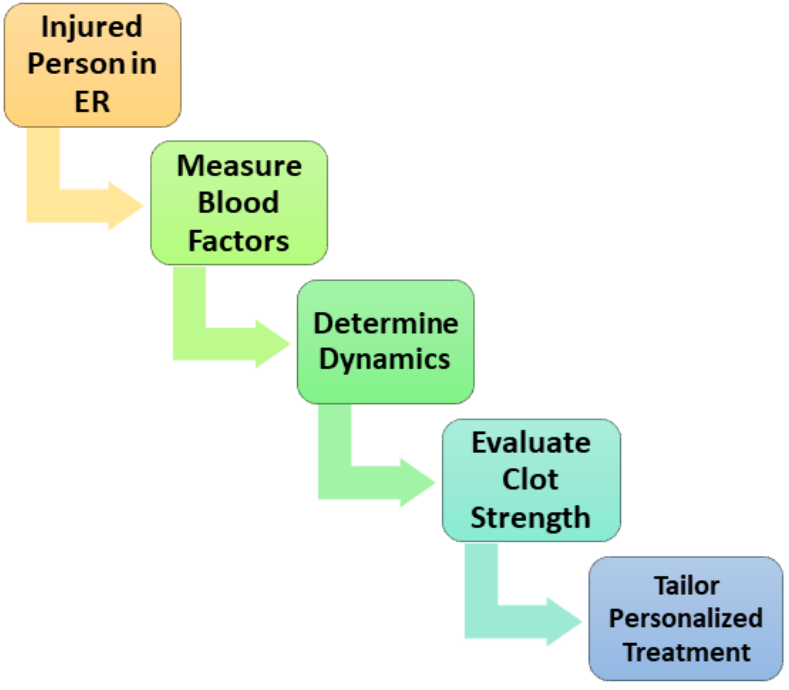
TFPI =TF=VIIa=Xa
21
+TFPI
TF= VIIa= Xa
7
TF=VIIa+ Xa
VIIa 8
3
VII
5
4
VIIa alone
VIIa
48
49
X
Xa
22
TFPI =Xa
20
+TFPI
ATIII
23
V
16
+Va
17
Xa=Va
Xa
9
II
18
mIIa
19
ATIII
26
IIa
platelet activation
ε_o
ε
1.0
k_{dissoc} (η/ε)*
thrombin detection
bocVPR -AMC
28
bocVPR
+ MCA
fibrin formation
(Fbn2)$_2$
53
(Fbn1)$_2$=IIa
55
ATIII
+IIa
(Fbn1)$_2$
50
52
Fbg
Fbn1
Fbn1=IIa
56
ATIII
51
Fbn2
54
+IIa
Fbn2=IIa
57
ATIII
proteolysis
reversible binding
inhibition
catalysis
*k_{dissoc} (η/ε) for reactions
11-13,17,18,20,21,30-32,39,45-47, 49

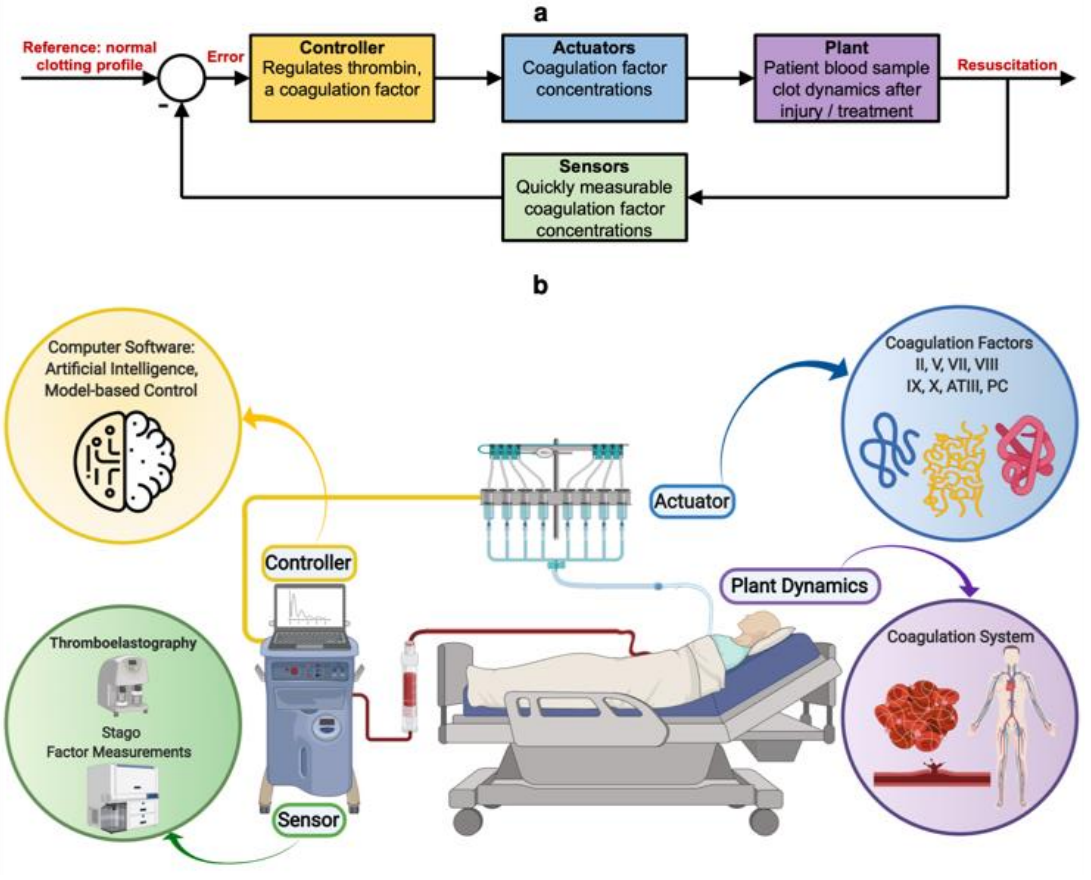
Hockin-Mann Chemical Kinetic Equations

1 TF + VII <1–2> TF═VII
2 TF + VIIa <3–4> TF═VIIa
3 TF═VIIa + VII-5 > TF═VIIa + VIIa
4 Xa + VII-6 > Xa + VIIa
5 IIa + VII-7 > IIa + VIIa
6 TF═VIIa + X <8–9> TF═VIIa═X-10 > TF═VIIa═Xa
7 TF═VIIa + Xa <11–12> TF═VIIa═Xa
8 TF═VIIa + IX<13–14>TF═VIIa═IX-15 > TF═VIIa + IXa
9 Xa + II-16 > Xa + IIa
10 IIa + VIII-17 > IIa + VIIIa
11 VIIIa + IXa <18–19> IXa═VIIIa
12 IXa═VIIIa + X <20–21> IXa═VIIIa═X-22 >
IXa═VIIIa + Xa
13 VIIIa <23–24> $VIIIa_1 \cdot L + VIIIa_2$
14 IXa═VIIIa═X-25 > $VIIIa_1 \cdot L + VIIIa_2$ + X + IXa
15 IXa═VIIIa-25 > $VIIIa_1 \cdot L + VIIIa_2$ + IXa
16 IIa + V-26 > IIa + Va
17 Xa + Va <27–28> Xa═Va
18 Xa═Va + II <29–30> Xa═Va═II-31 > Xa═Va + mIIa
19 mIIa + Xa═Va-32 > IIa + Xa═Va
20 Xa + TFPI <33–34> Xa═TFPI
21 TF═VIIa═Xa + TFPI <35–36> TF═VIIa═Xa═TFPI
22 TF═VIIa + Xa═TFPI-37 > TF═VIIa═Xa═TFPI
23 Xa + ATIII-38 > Xa═ATIII
24 mIIa + ATIII-39 > mIIa═ATIII
25 IXa + ATIII-40 > IXa═ATIII
26 IIa + ATIII-41 > IIa═ATIII
27 TF═VIIa + ATIII-42 > TF═VIIa═ATIII

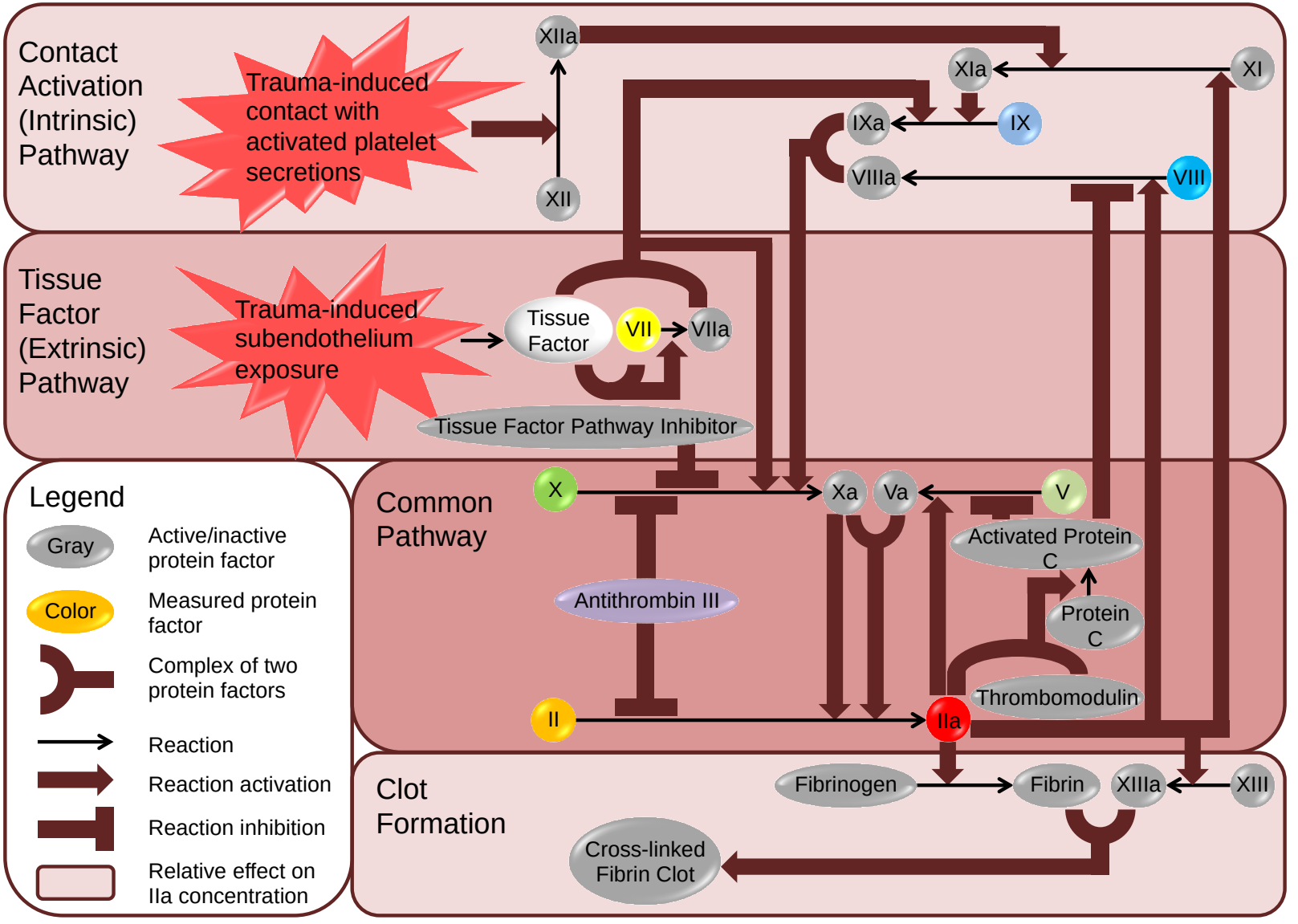
- 34 states, 43 chemical kinetic equations. No Protein C or Activated Protein C effects.
- Rate constants aggregated from 2002 literature.
- Initial conditions specify mean plasma concentrations for proteins, with tissue factor (TF) variable.

Solution: Personalized dynamic approach

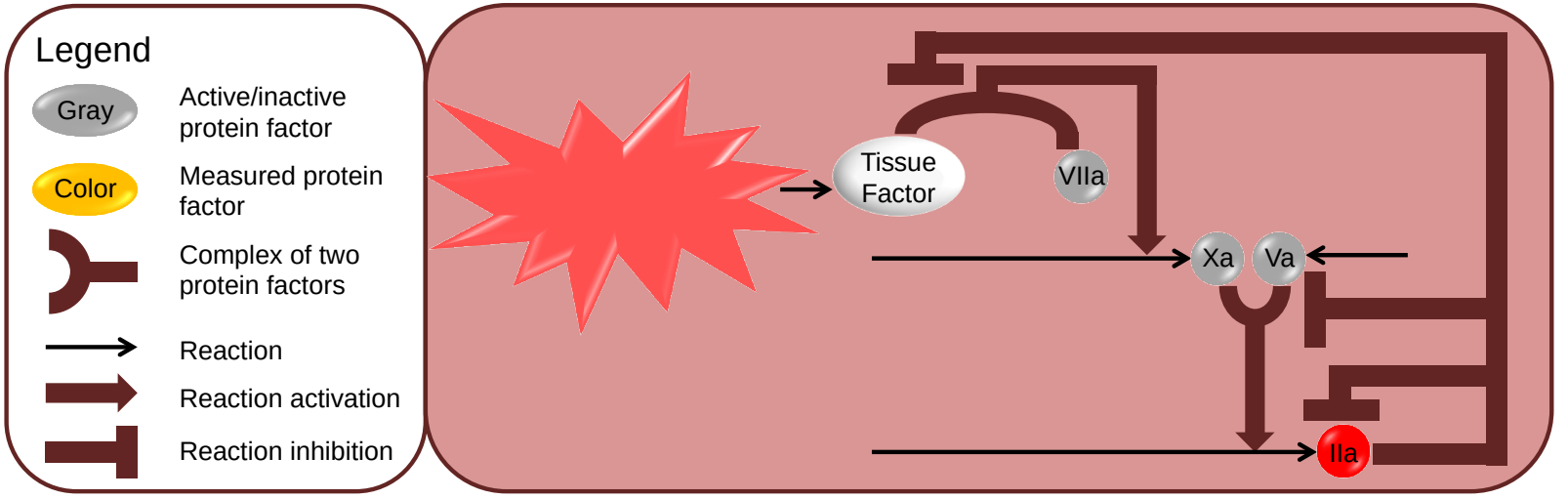




Current Understanding: Coagulation Cascade



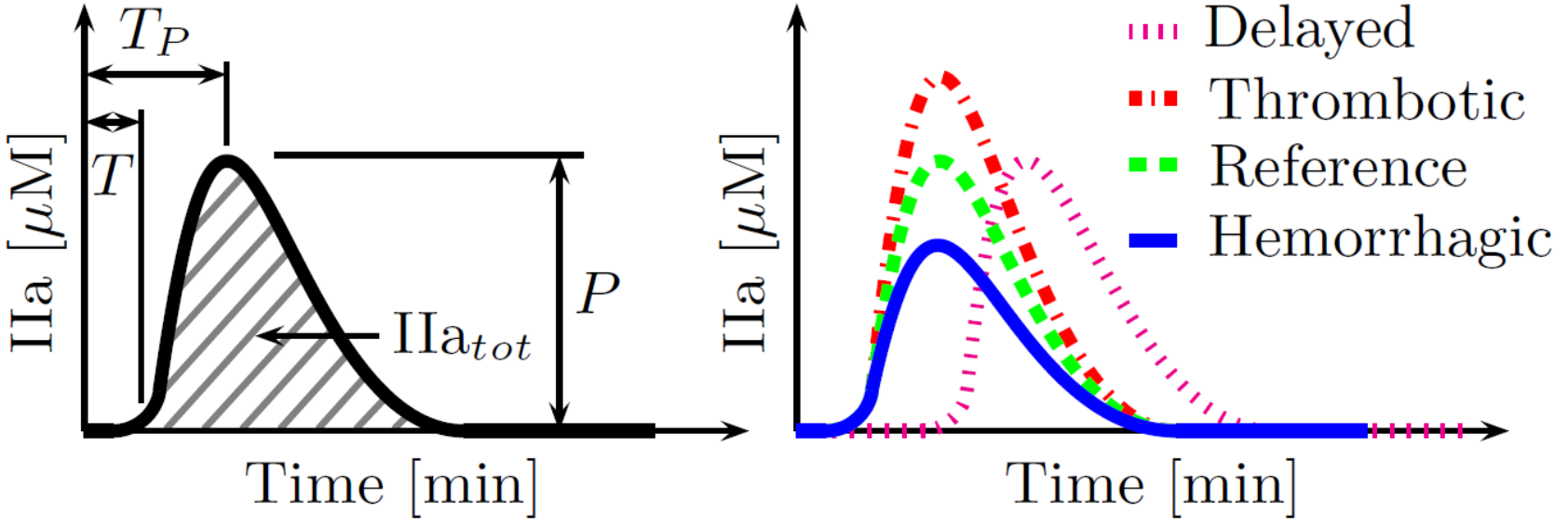
Claim: Possible to Simplify



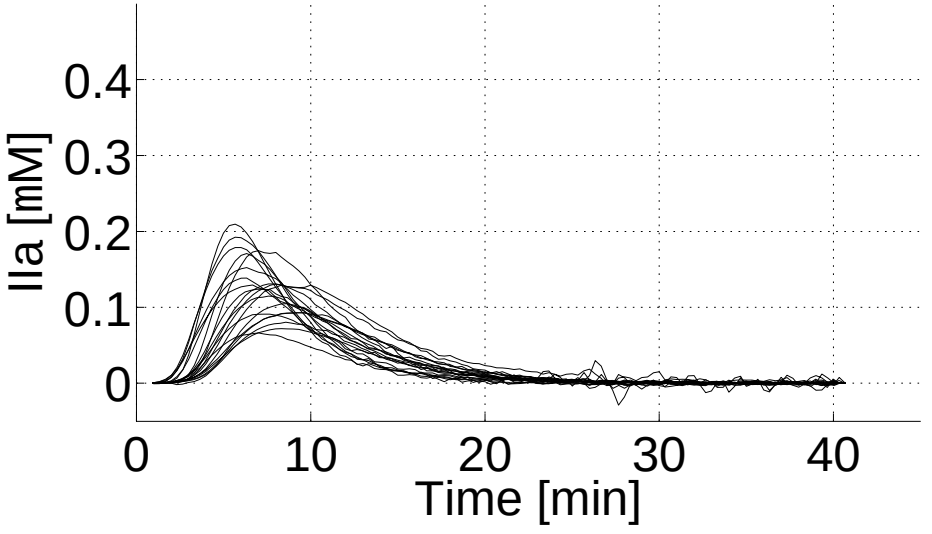
- Dynamical System Input: Tissue Factor
- Dynamical System Output: Thrombin
- Need an input-to-output measurement.

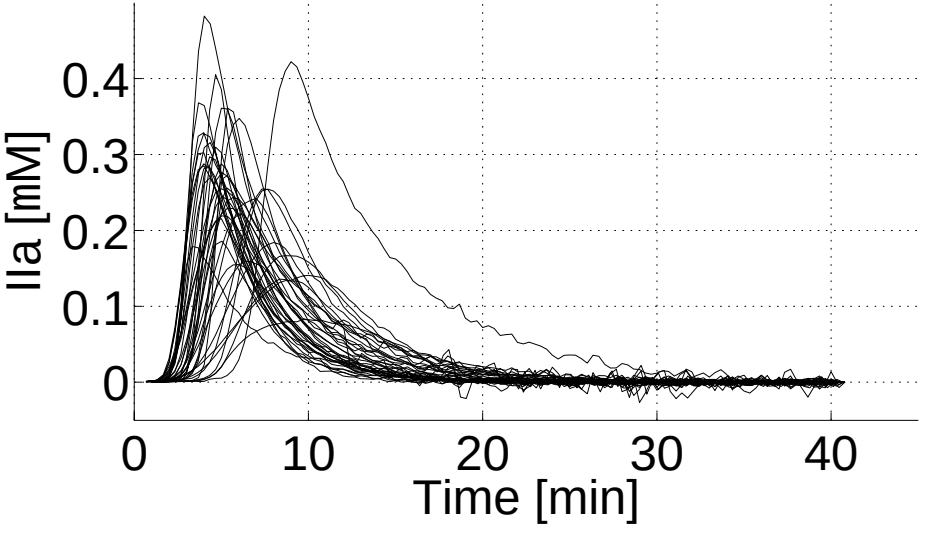
Thrombin Measurement

- The Calibrated Automated Thrombogram (CAT) is a fluorogenic assay that measures the time-history of thrombin generation in a blood sample upon the addition of (typically 5pM of) tissue factor.



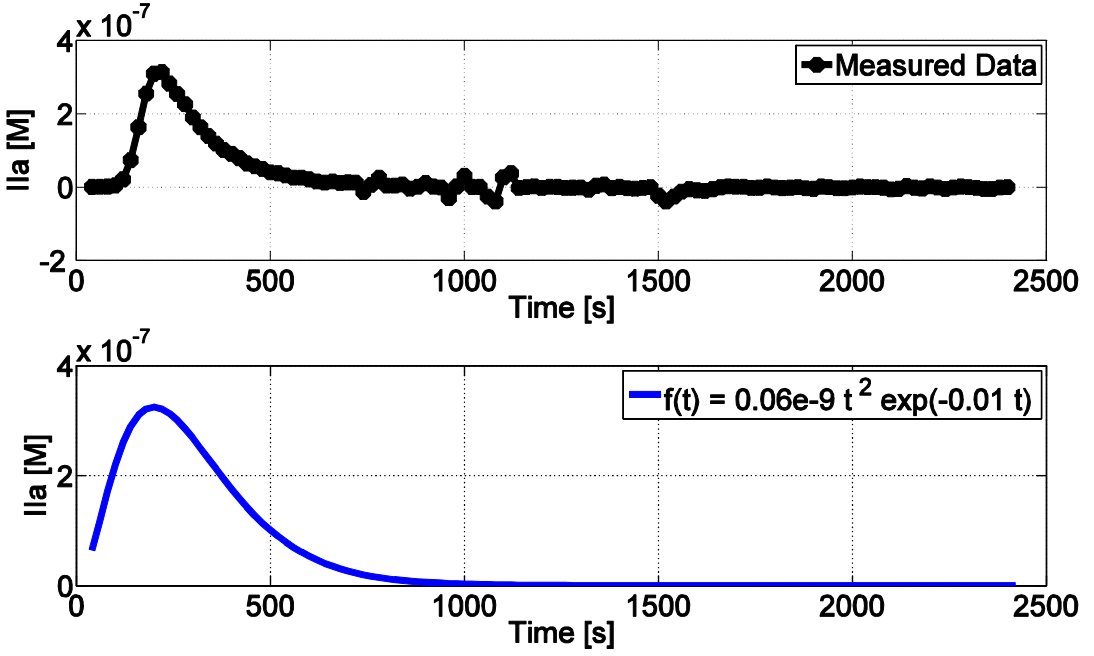
Normal vs. Trauma CATs





- Can we emulate trajectories with a single-input single-output thrombin dynamical system model with a separable delay for treatment guidance? What kind of model?

Building a Black-Box Model



- Can approximate a CAT peak.
- Suppose we choose the following non-delayed function as first approximation:

$$y(t) = \beta t^2 e^{-\alpha t}$$

- t^2 → three states.

- Look at output in frequency domain as the result of some dynamical system:

$$Y(s) = \frac{2\beta}{(s+\alpha)^3} = \frac{2\beta}{s^3 + 3\alpha s^2 + 3\alpha^2 s + \alpha^3}$$

Building a Black-Box Model: 3 states, 5 pars.

- Suppose input is a (unit) impulse, *U(s)* = 1:

$$\frac{Y(s)}{U(s)} = \frac{2\beta}{(s+\alpha)^3} = \frac{2\beta}{s^3 + 3\alpha s^2 + 3\alpha^2 s + \alpha^3}$$

- System transfer function, including delay:

$$\frac{Y(s)}{U(s)} = \frac{b}{s^3 + a_2 s^2 + a_1 s + a_0} e^{-sT}$$

Building a Black-Box Model: Traditional Form

$$\frac{Y(s)}{U(s)} = \left(\frac{Kp}{s+p}\right)\left(\frac{\omega_n^2}{s^2+2\zeta\omega_n s+\omega_n^2}\right)e^{-sT}$$

- Define

$\sigma = \zeta\omega_n$ and $\omega_d = \omega_n\sqrt{1-\zeta^2}$ (i.e., $\omega_n^2 = \sigma^2 + \omega_d^2$), and let

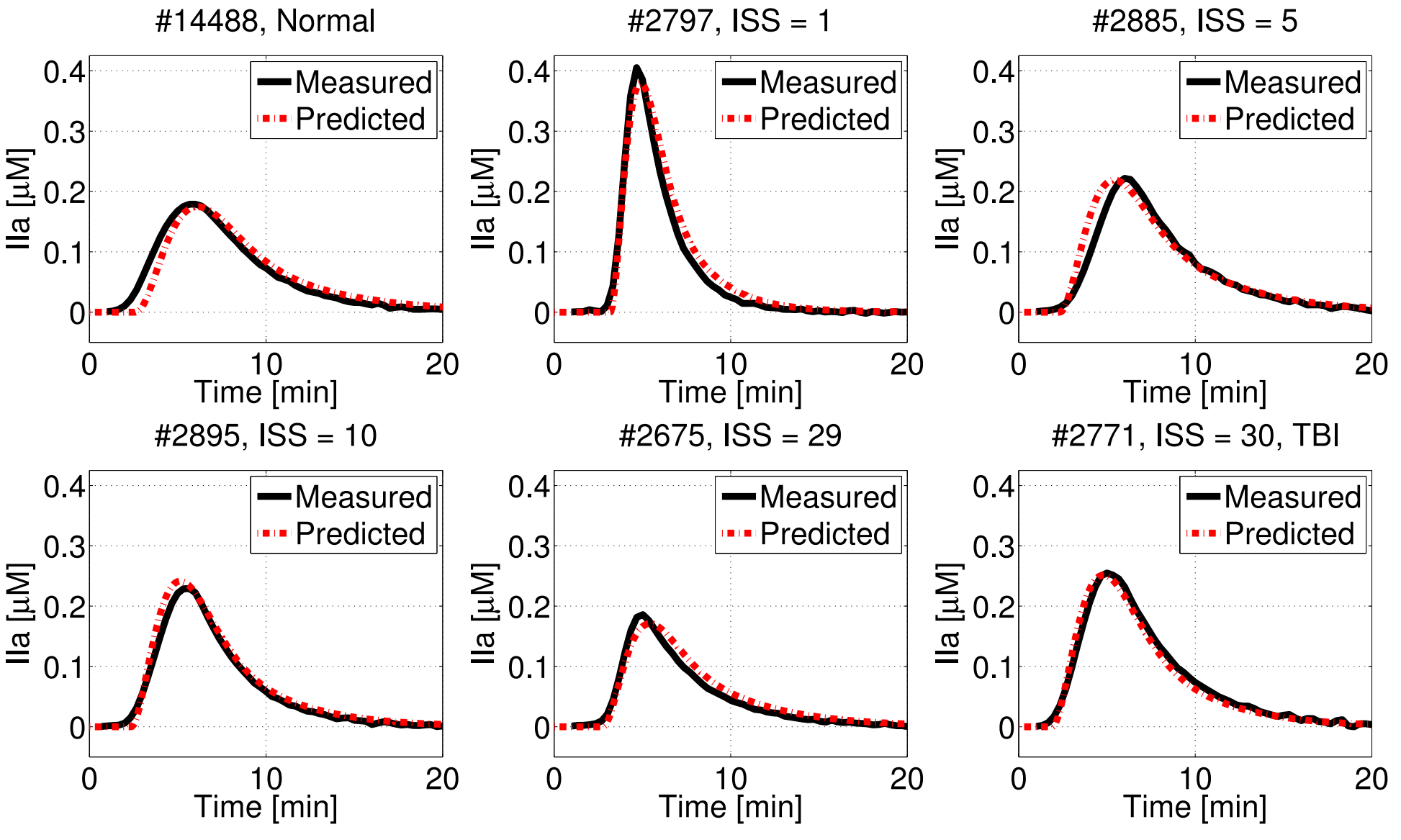
$A = \frac{Kp\omega_n^2}{p^2-2\zeta\omega_n p+\omega_n^2}$; $B = \frac{-Kp\omega_n^2}{p^2-2\zeta\omega_n p+\omega_n^2}$; $C = \frac{Kp\omega_n^2(p-2\zeta\omega_n)}{p^2-2\zeta\omega_n p+\omega_n^2}$;

$D = \left(B\cos\left(\omega_d\left(t-T\right)\right) + \frac{C-\sigma B}{\omega_d}\sin\left(\omega_d\left(t-T\right)\right)\right)$. Then each fitted time-delayed CAT unit impulse response is given by

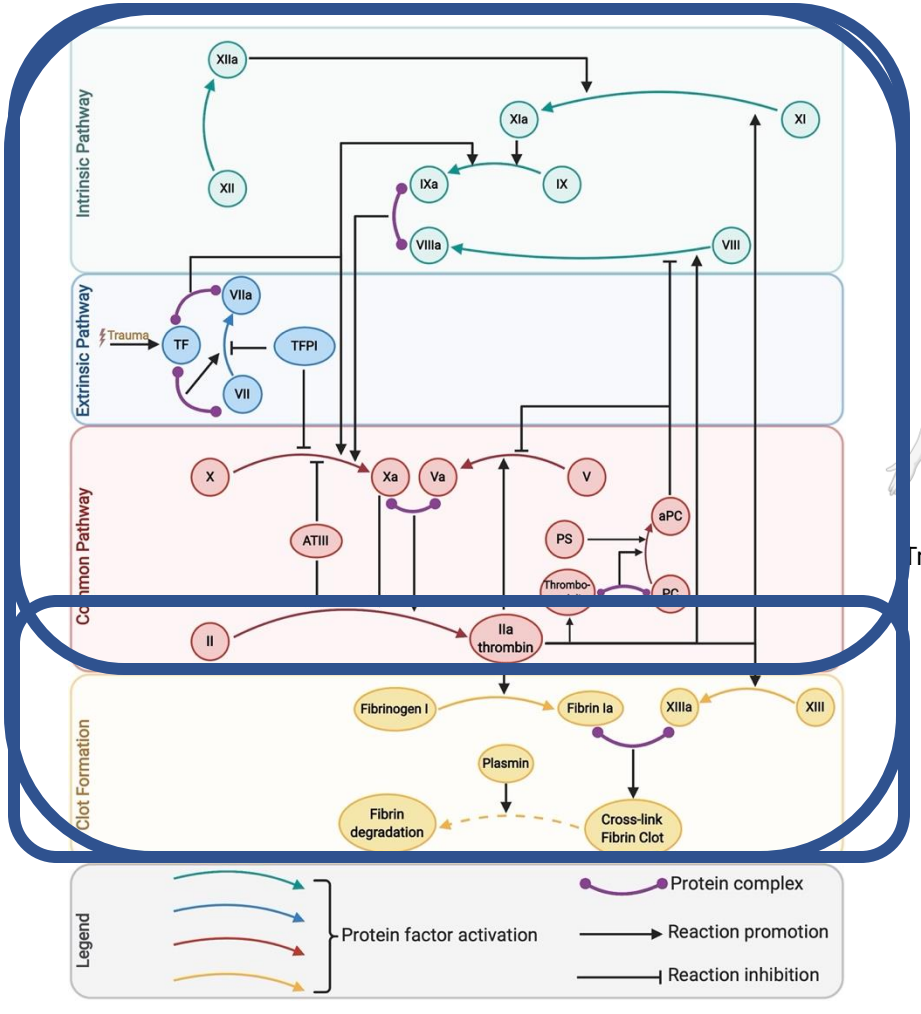
$$y(t) = \begin{cases} 0 & \text{if } t < T; \\ \left(Ae^{-p(t-T)} + De^{-\sigma(t-T)}\right)1(t-T) & \text{if } t \geq T, \end{cases}$$

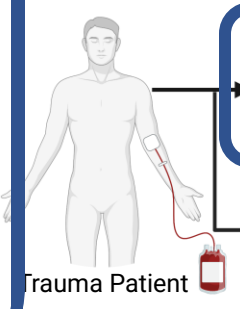
for some p, ζ, ω_n and T, computed from a_2, a_1, a_0 and T.

Performance



Extending to viscoelastic measures





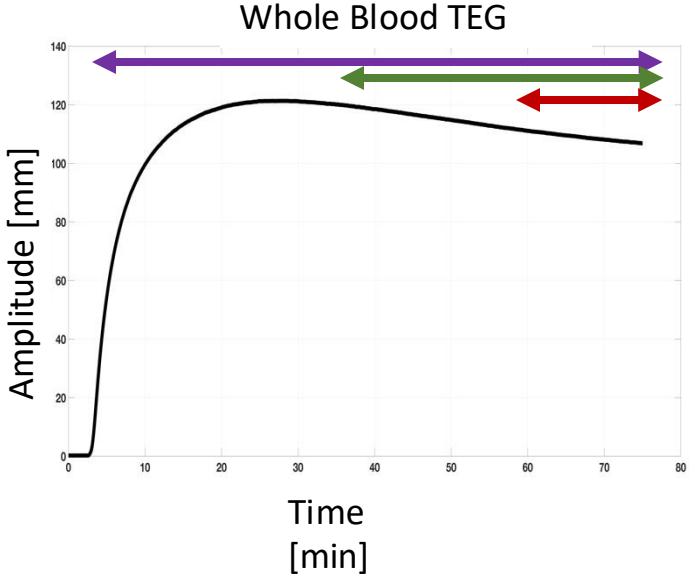
Factor Concentration to CAT → CAT to Plasma TEG → Plasma TEG to Whole Blood TEG → System Dynamics

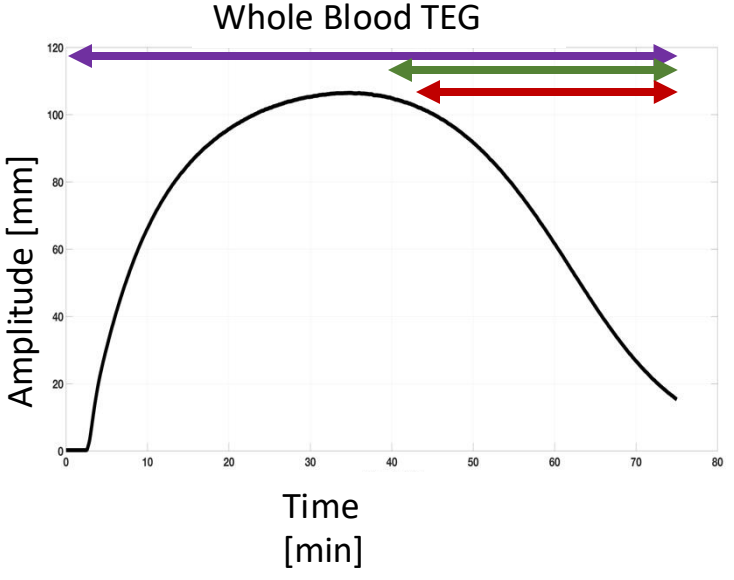
Factor Concentration to Whole Blood TEG → System Dynamics

Viscoelasticity of Whole Blood

Factor Concentrations to Whole Blood TEG

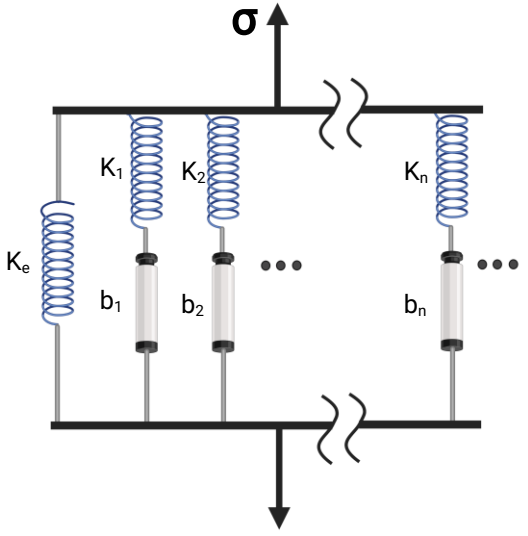
$$\frac{K_{n,1}}{s(K_{p,1}s+1)}e^{-sK_{d,1}} + \frac{-K_{n,2}}{s^2}e^{-sK_{d,2}} + \frac{-K_{n,3}}{s(K_{p,3}s+1)}e^{-sK_{d,3}}$$





Maxwell Model:
several parallel Maxwell elements (a spring and a damper connected in series)

$$\sigma(t) = \sigma_0\left(1 - e^{-\frac{1}{\tau}t}\right)$$

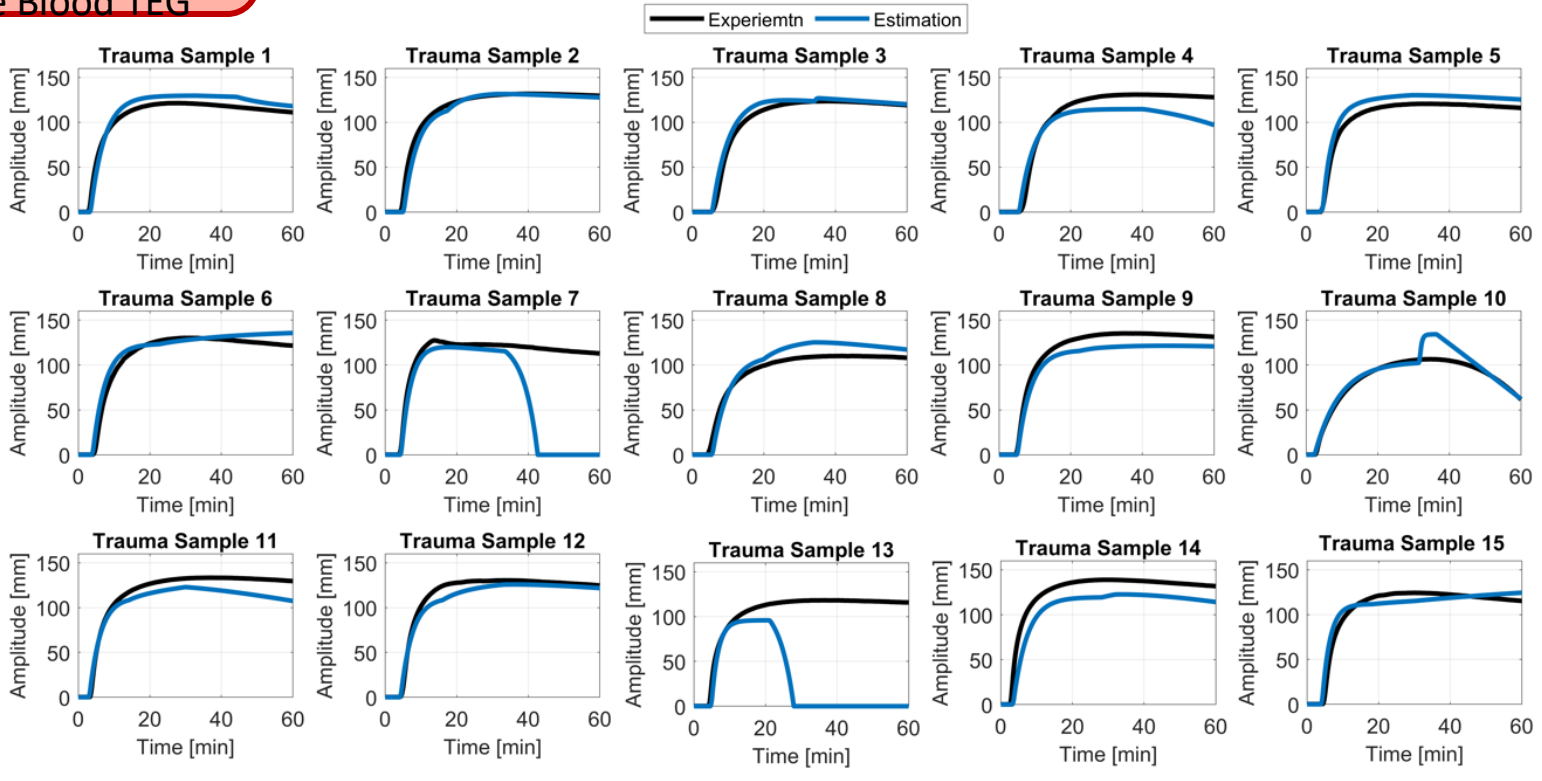


$$G(s) = \frac{P(s)}{Y(s)} = \frac{K_{n_p}}{s(K_p s + 1)} \times e^{-K_{dp}s} \xrightarrow{\text{Time domain}} g(t) = K_{n_p} - K_{n_p} e^{-\frac{1}{K_p}t}$$

Viscoelasticity of Whole Blood

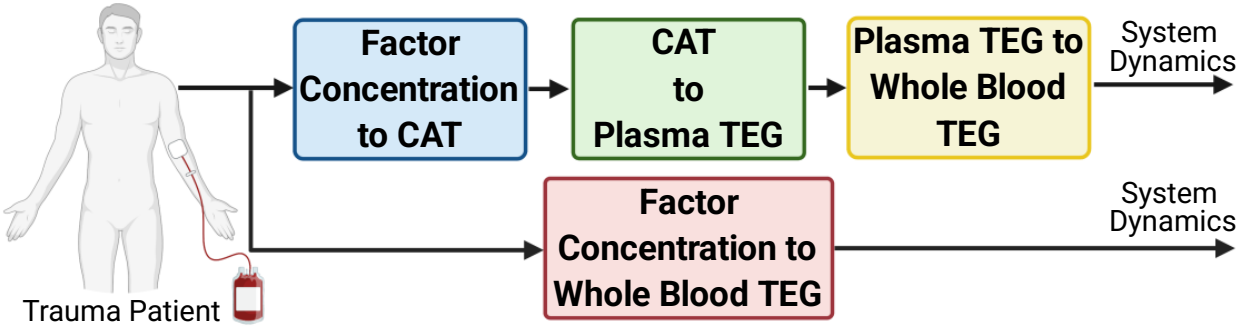
Factor Concentrations to Whole Blood TEG

TEG graph estimation using:
Coagulation factors II, V, VII, VIII, IX, X, ATIII, PC, D-dimer



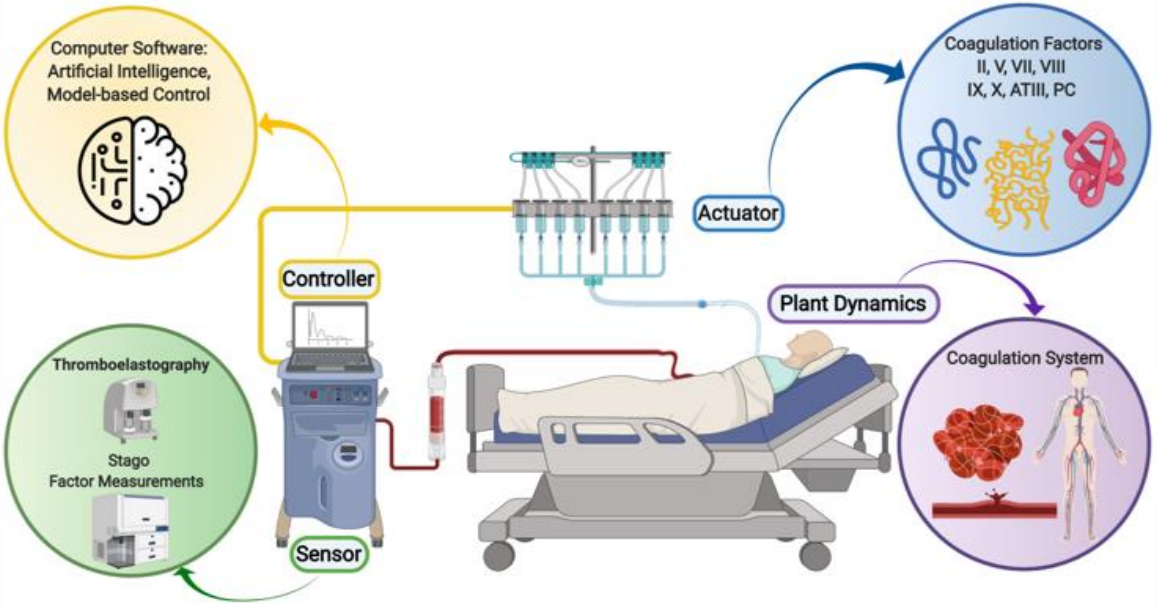
We can model blood clotting in silico

- a novel and simple model that captures the viscoelastic effects in plasma samples
- an estimate of the model output using easily-measurable coagulation factors
- a meaningful relationship between thrombin and this viscoelastic clot model
- a second new model to express viscoelastic clot formation, stabilization, and degradation in whole blood
- a comparison to the generalized Maxwell viscoelastic model



Future Work and Broad Impact

- Blood clot precision control using coagulation factors: obviating the use of generic treatment and improve patient outcome.
- Application to other coagulation disorders: hemophilia, von Willebrand disease, factor V Leiden, pulmonary embolism, deep vein thrombosis, stroke, and sickle cell disease.



Why does this matter?

- We have come a long way understanding and mitigating TIC.
- Our ‘one size fits all’ resuscitation has reduced mortality but misses the target often.
- While patients die early many are missed and morbidity is significant and important.
- Mitigating thromboinflammation can fix TIC and inflammation and improve outcomes.

We need (and can deliver) 4 things.

- An understanding of phenotypes of thromboinflammation after trauma (threat x)
- Cytoprotective agent(s) that can modulate coagulation and inflammation after trauma.
  - This can be agnostic and personalized.
  - Shelf stable resuscitation in a syringe.
- Prevention via a trauma vaccine
- Personalized medicine and optimized performance via measurement and modeling.


AXE WHOOPING
RAGE ROOM


PODIUM
KARTING & EVENTS
I BEAT THE BOSS
Reykjavik
2
3

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