



# **Le future de la recherche pour le soin du blessé**

## ***Transformational Change in Combat Casualty Care Research***

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# Un nouveau problème – combat de haute intensité, à grande échelle



**2001-2021**

**Iraq, Afghanistan, Sahel/HoA:  
contre-insurrection/terrorisme**

**Futur (bientôt?)**

***Large Scale Combat Operations (LSCO)  
Multi-Domain Operating Environment  
(MDO)***



# Changing Adversaries → Changing Battlefield Medical Challenges



**Afghanistan / Iraq:**  
IEDs, small arms, mortars,  
RPGs →



*Low casualty density,  
rapid evacuation to  
surgery*

**Russia / China:**  
Sophisticated / lethal  
weapons, contested air →

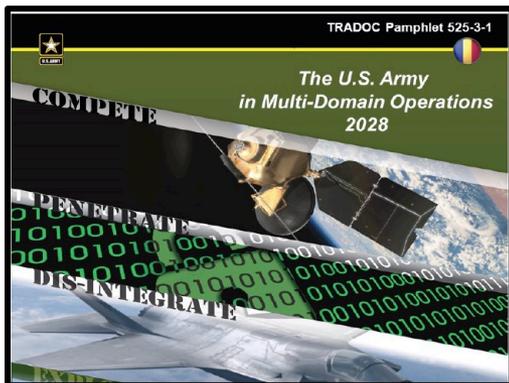


*High casualty density,  
delayed evacuation to  
surgery*





# LSCO & MDO = PFC « Prolonged Field Care » (soin sur le champ prolongé)



## La problématique de MDO:

- Cyber-attaque
- Canons/fusées avec précision à longue portée (70+ km)
- Défenses aériennes, drones



## IMPACT:

- Forces très dispersées
- Communication dégradée
- Evacuations par air difficile/impossible
- Longue évacuation aux Rôles 2/3
- **Le blessé pourra être sur le champ pendant 6-72 heures -- pas 1 heure!**





# LSCO & MDO = Ukraine aujourd'hui





# Accès rapide à la transfusion et arrivée rapide en bloc opératoire = vies sauvées



## Original Investigation

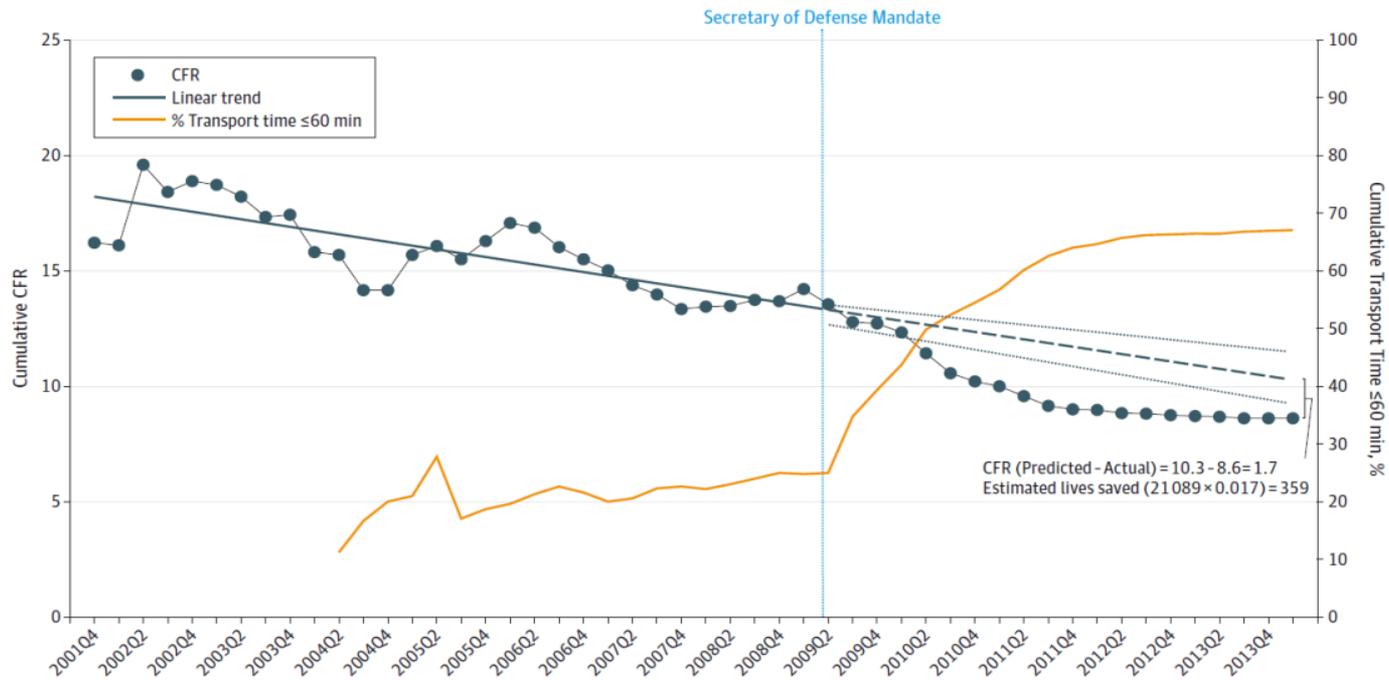
## The Effect of a Golden Hour Policy on the Morbidity and Mortality of Combat Casualties

Russ S. Kotwal, MD, MPH; Jeffrey T. Howard, PhD; Jean A. Orman, ScD, MPH; Bruce W. Tarpey, BS; Jeffrey A. Bailey, MD; Howard R. Champion, FRCS; Robert L. Mabry, MD; John B. Holcomb, MD; Kirby R. Gross, MD

*JAMA Surg.* doi:10.1001/jamasurg.2015.3104

Published online September 30, 2015.

Figure 1. Case Fatality Rate and Transport Time





# Accès rapide à la transfusion et arrivée rapide en bloc opératoire = vies sauvées



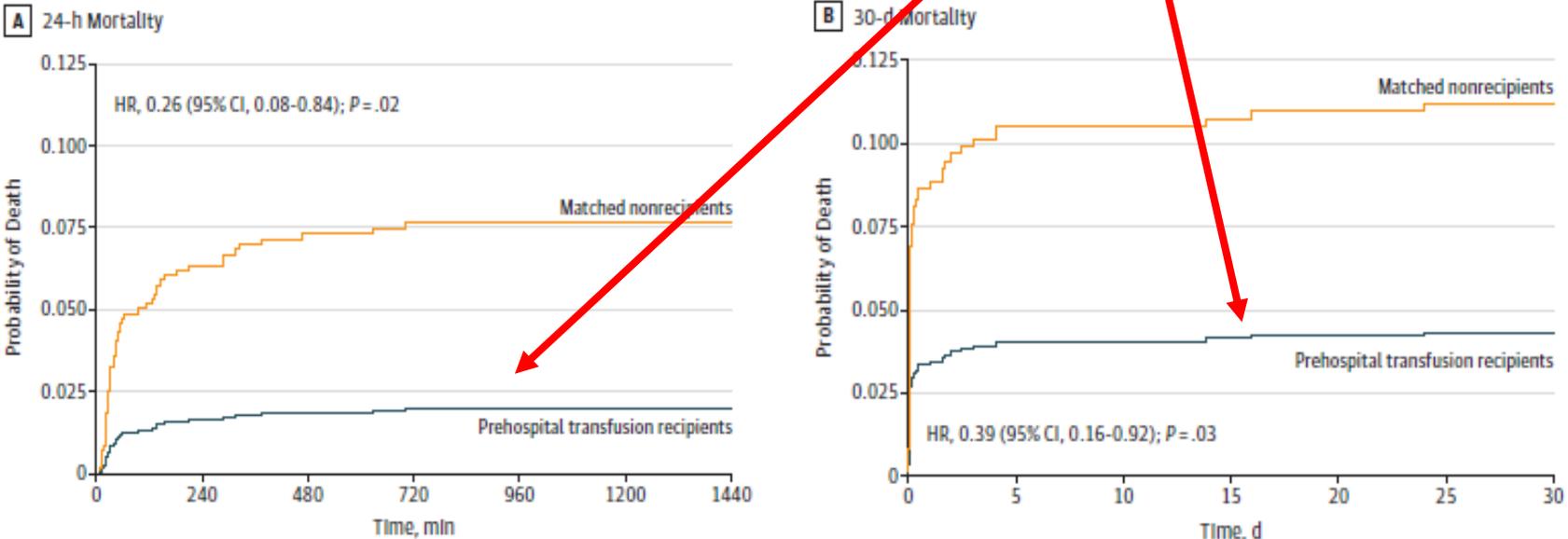
JAMA | Original Investigation

## Association of Prehospital Blood Product Transfusion During Medical Evacuation of Combat Casualties in Afghanistan With Acute and 30-Day Survival

Stacy A. Shackelford, MD; Deborah J. del Junco, PhD; Nicole Powell-Dunford, MD; Edward L. Mazuchowski, MD, PhD; Jeffrey T. Howard, PhD; Russ S. Kotwal, MD, MPH; Jennifer Gurney, MD; Frank K. Butler Jr, MD; Kirby Gross, MD; Zsolt T. Stockinger, MD

Lower mortality w/ prehospital transfusion

Figure 3. Mortality of Prehospital Transfusion Recipients vs Matched Nonrecipients





# Le grand défi



**Comment va-t-on soigner les combattants blessés sans accès rapide à la transfusion et la chirurgie?**

***On ne peut pas continuer à faire les mêmes chose que l'on a fait depuis 20 ans!***

**« WE NEED BREAKTHROUGHS! »**



# Le progrès en traumatologie a été lent et incrémental...



Bandages / Poultices:  
Imhotep, Egypt 3000 BC



Blood Transfusion at the Frontlines: WWI, 1918



Tourniquet: 200 BC;  
17<sup>th</sup> century

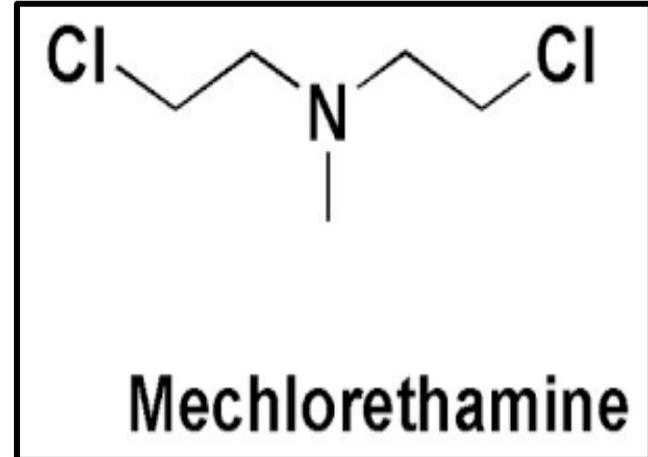
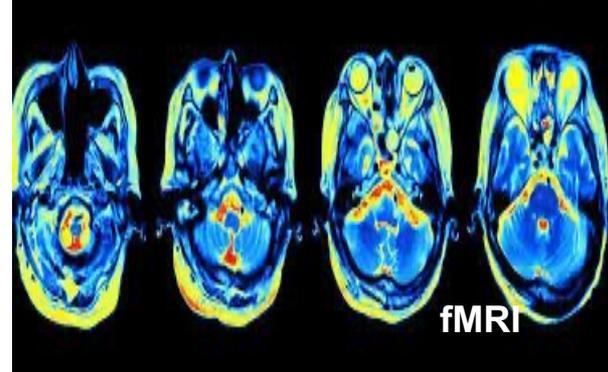
Freeze-dried plasma:  
1930s, WWII



TXA: 1960s



# Nous devons avoir des changements transformationnels!



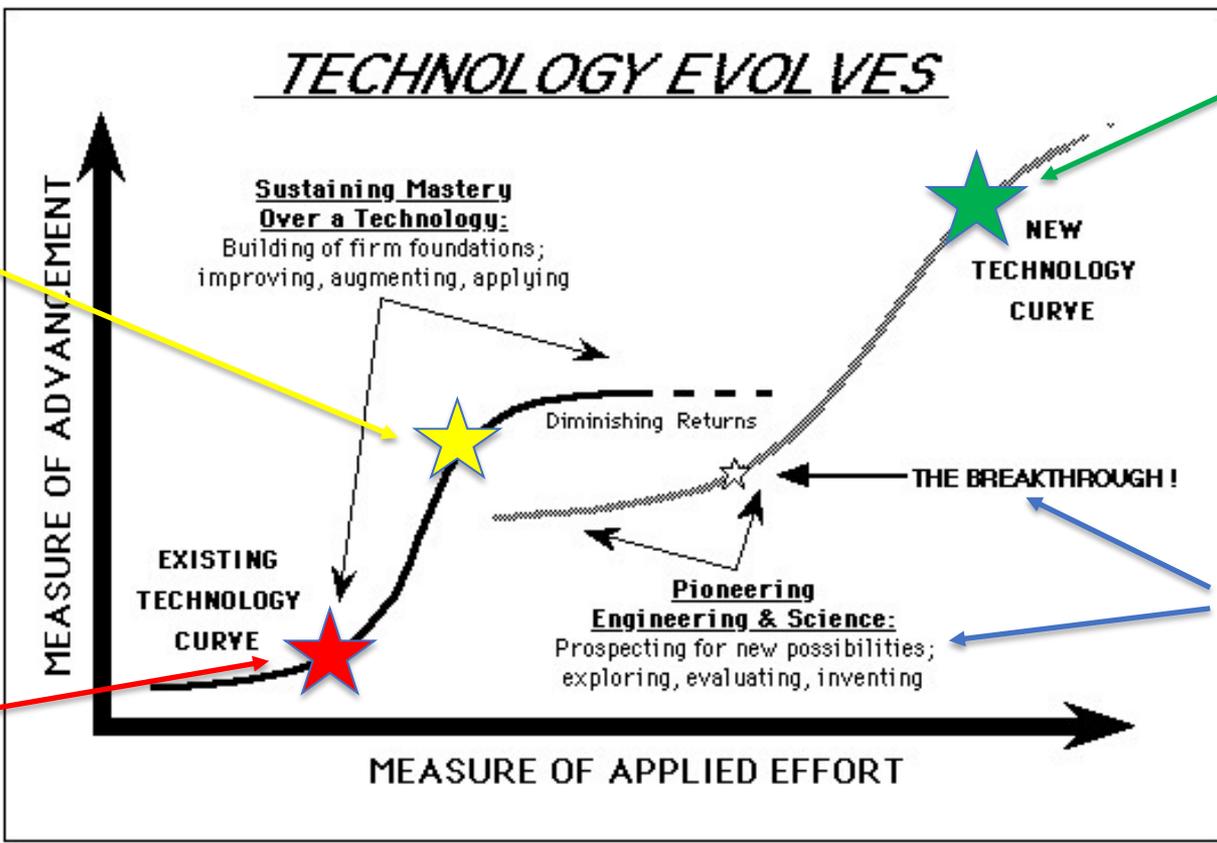


# Nous avons besoin d'innovation radicale!



Combat Casualty Care 2021

Combat Casualty Care 2001



Where we need to be for MDO/LSCO



# Fundamental Challenges of Prolonged Field Care: the 5 Pillars



## Prolonged Survival

*Prevent, Detect, Treat*

Blood & Shock  
Resuscitation

Hemorrhage  
& vascular  
dysfunction

Organ support  
automation  
technology

Combat  
wound care

Pain, sensory  
trauma

Pillar 1

Pillar 2

Pillar 3

Pillar 4

Pillar 5

### Acute (0-1 hours)

Blood / Airway Loss

→ ↓ DO<sub>2</sub> → ↓ ATP →

↓ pH → ↑ K<sup>+</sup>

→ Cell death

→ Endothelial  
dysfunction

→ Coagulopathy

### Intermediate (2-6 hours)

Vascular dysfunction / edema /  
thrombosis

→ Organ failure: brain, heart,  
kidney, lung

Wound contamination &  
colonization

### Delayed (6-24 hours)

Inflammatory second hit

Progression of organ failure

Wound progression, thrombosis & infection



# Clinical Problems Associated with the 5 Pillars

## Clinical Challenges

*Prevent, Detect, Treat*

Blood &  
Shock  
Resuscitation

Hemorrhage  
& vascular  
dysfunction

Organ support  
automation  
technology

Combat  
wound care

Pain, sensory  
trauma

Pillar 1

Pillar 2

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Pillar 4

Pillar 5

- Inadequate blood supply vs. demand
- Excessive “Shock dose”/ oxygen debt → irreversible shock

- Non-compressible hemorrhage
- Endotheliopathy, coagulopathy, thrombosis → organ failure, bleeding
- Compartment syndrome

- ARDS, blast lung, inhalation injury
- Renal failure
- Cardiac ischemic injury, contusion

- Contaminated wounds
- Complex soft tissue / long bone injury
- Burns

- Pre-hospital pain management
- Post-operative pain management w/ delayed evacuation

*Overwhelmed providers lacking sensors, automation, decision support, telehealth to enable solutions*



# Promising Technologies for Clinical Problems Associated with the 5 Pillars



## Future Solutions

*Prevent, Detect, Treat*

Blood & Shock Resuscitation

Hemorrhage & vascular dysfunction

Organ support automation technology

Combat wound care

Pain, sensory trauma

Pillar 1

Pillar 2

Pillar 3

Pillar 4

Pillar 5

- Shock drugs (e.g., PHDi, PDHKi)
- Enhanced forward blood availability & delivery (FDP, UAV, etc.)

- Partial REBOA
- Endothelial stabilizer drugs (e.g., BKr antagonist, TIE2 agonist, etc.)

- ECMO, CRRT capability forward, w/ safer anticoagulants
- Decision support systems, automation, telehealth

- Pathogen agnostic anti-infective dressings
- Enhanced fracture stabilization
- Wound care bundle

- Pre-hospital loco-regional pain management
- Ketamine autoinjectors
- Novel analgesics

*New technologies to fundamentally change what is possible in the prehospital environment!*



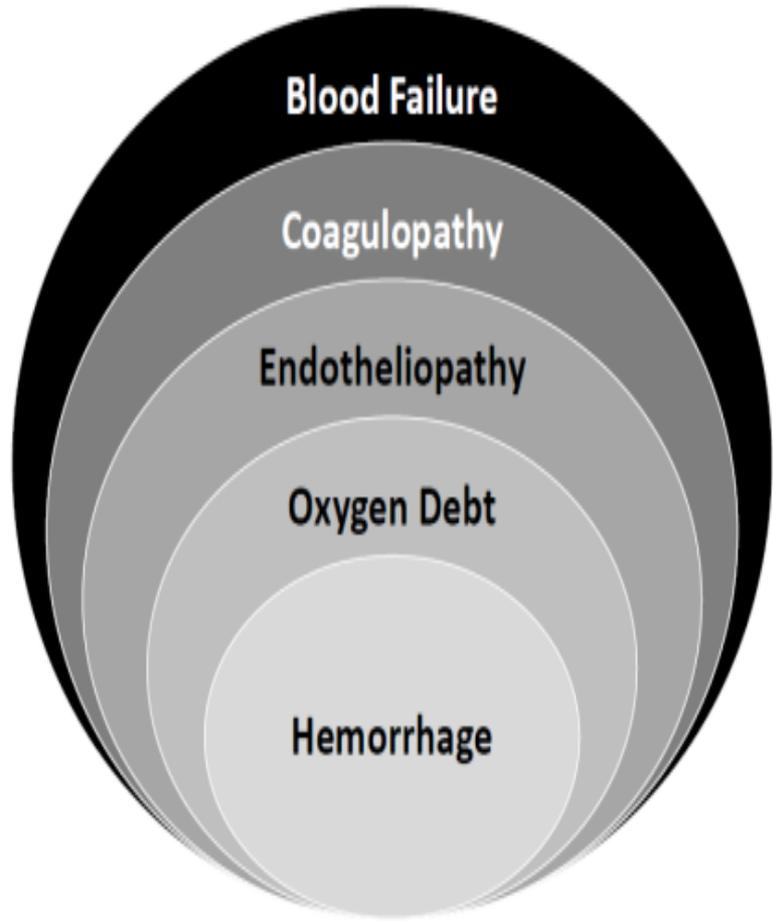
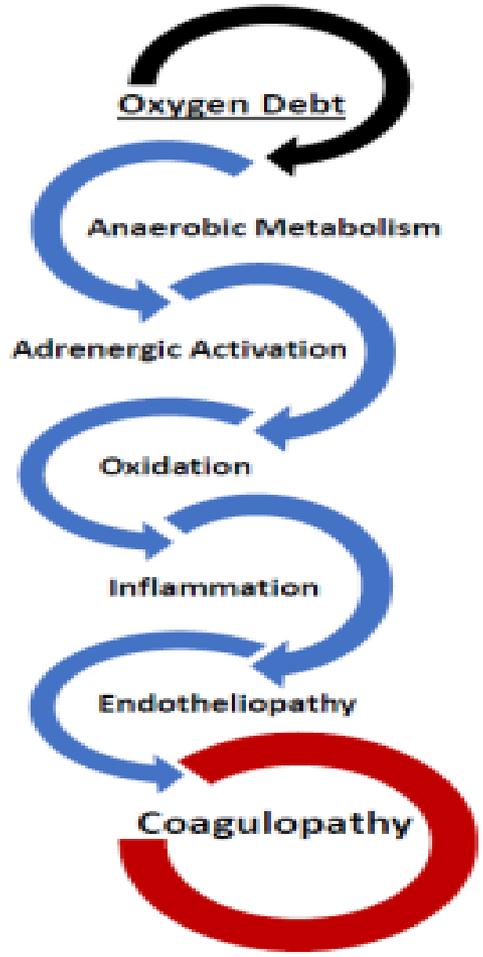
# Exemple de nouveau concept: la défaillance du sang « *Blood Failure* »



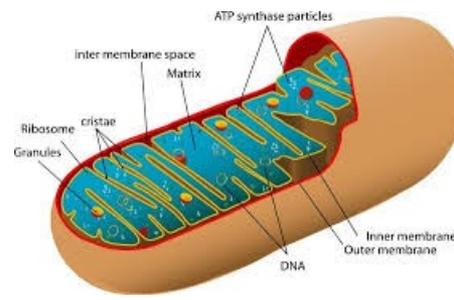
- Réaliser que le sang est un organe, pas une fluide de remplissement
- Réaliser que le sang existe en symbiose avec l'endothélium
- Réaliser que l'hypoxie mène à la faillite du métabolisme dans le choc, et que la coagulopathie et l'endothéliopathie y sont liés
- Chercher des interventions **transformationnelles** à la base de la pathophysiologie



Loss of Blood → hypoxia → metabolic failure → endotheliopathy → coagulopathy → **Blood Failure**



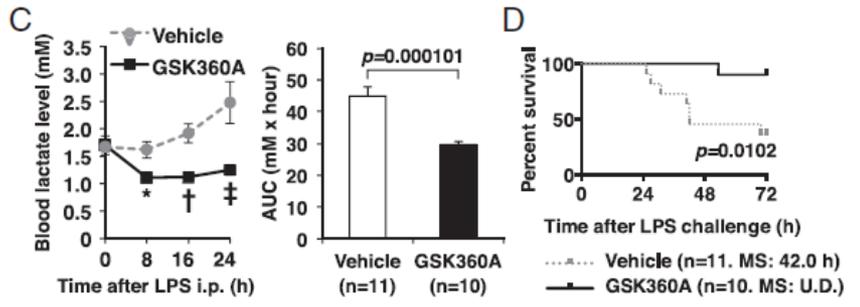
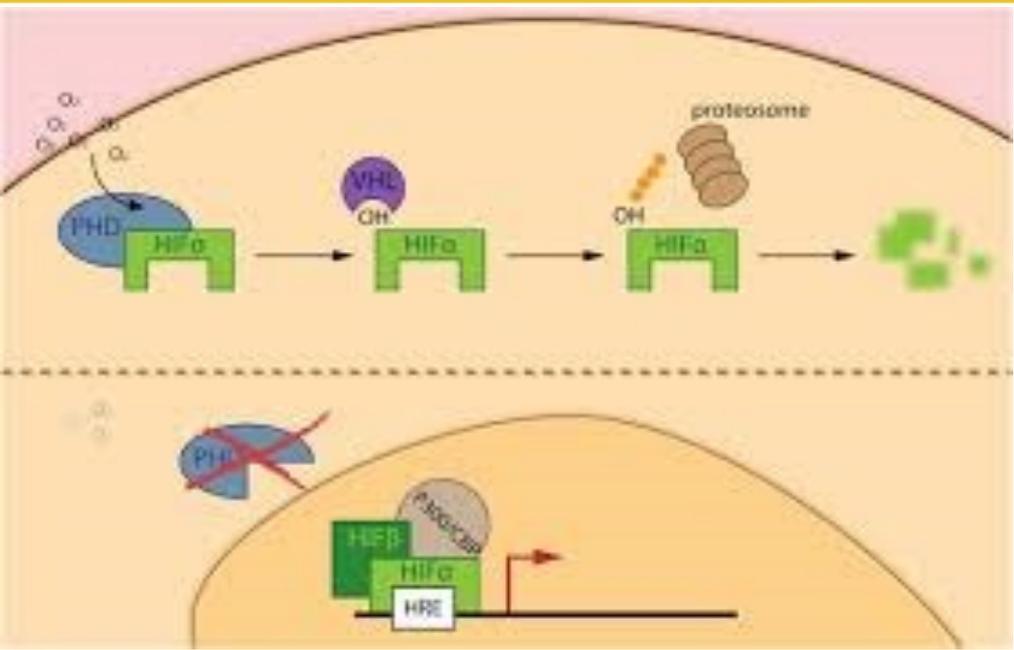
### Mitochondrial Dysfunction



**Bleeding** → hypoxia → metabolic failure → blood failure → **bleeding** → hypoxia...  
 Need blood ASAP & “shock drug” to break the cycle!



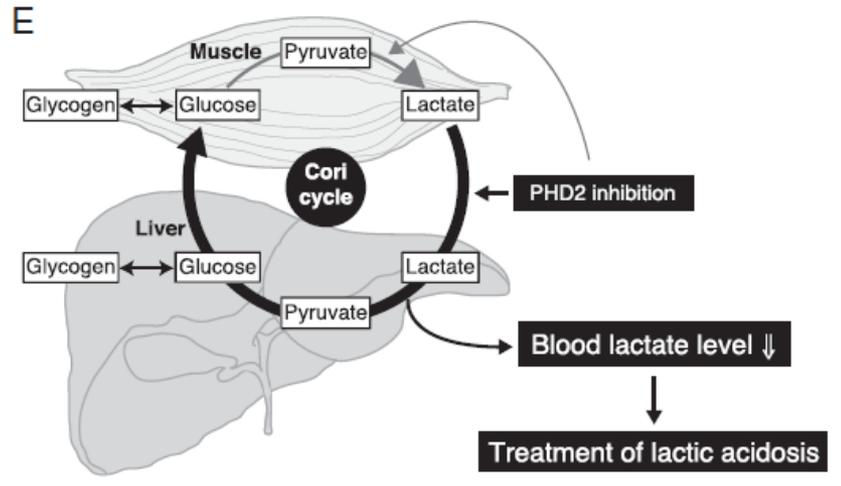
# Harness the body's hypoxia response: *Clear lactate via gluconeogenesis*



Suhara PNAS 2015.

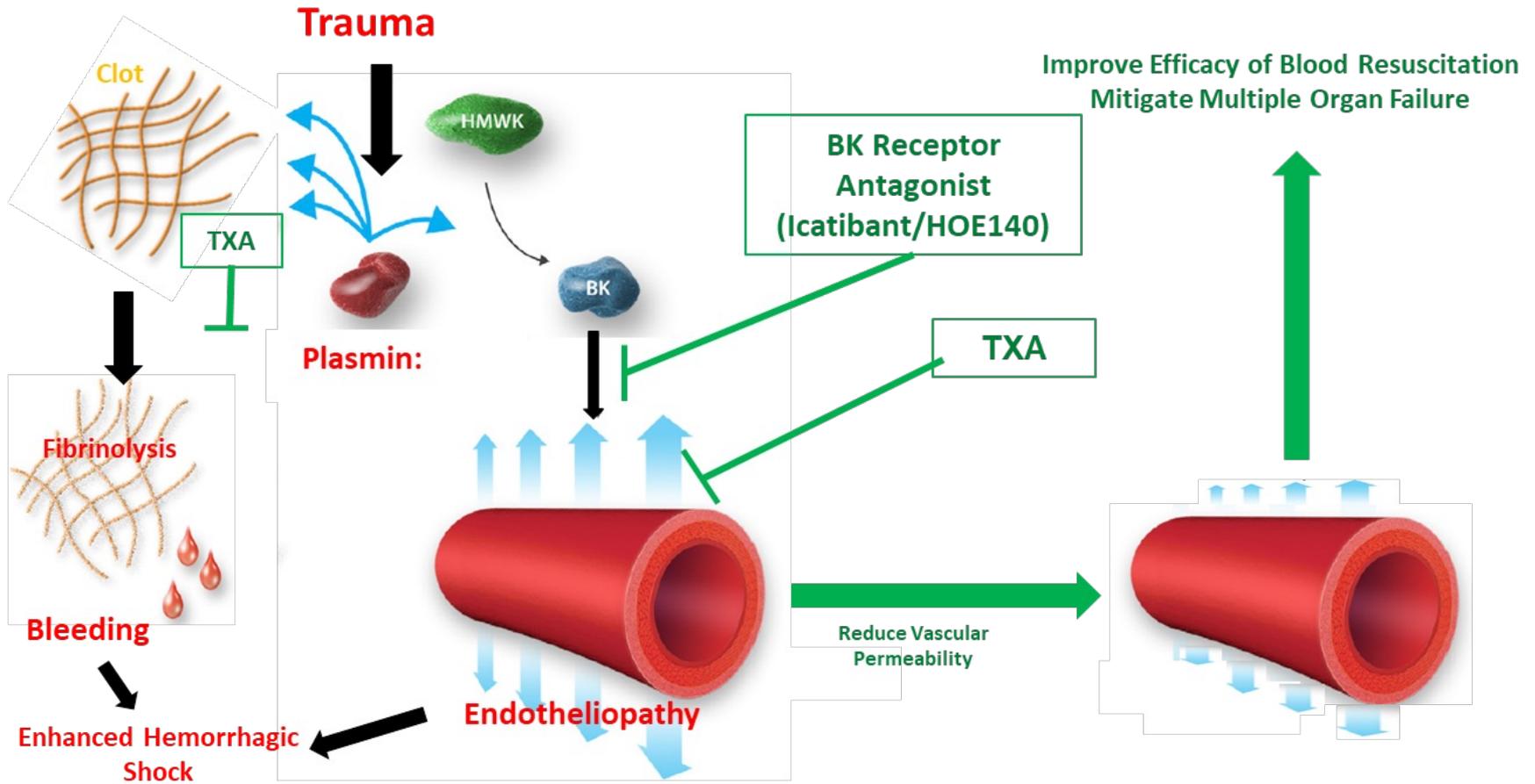
Under development in CKD to treat anemia (Roxadustat; see NEJM 2019)

-- Acute timeframe of action





# Icatibant and Tranexamic Acid: targeting plasmin (a driver for hemovascular dysfunction)





# New target for evaluation in hemorrhagic shock: Angpt1/2 – Tie2



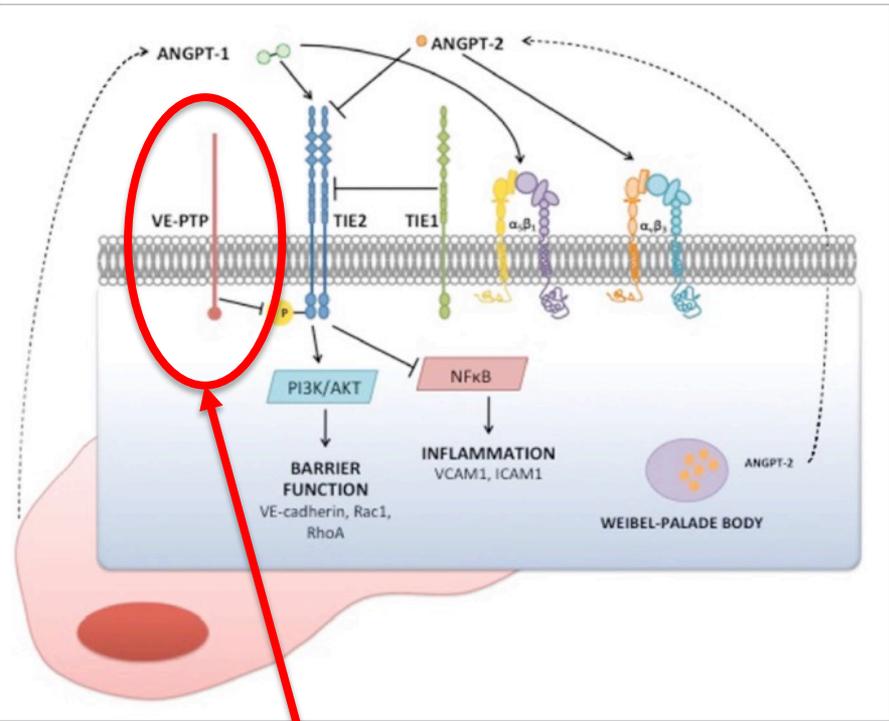
Tissue Barriers 3:1-2, e957508; January-June 2015; © 2015 Taylor & Francis Group, LLC

## The angiotensin-Tie2 signaling axis in the vascular leakage of systemic inflammation

Katelyn E Milam<sup>1</sup> and Samir M Parikh<sup>1,2,\*</sup>

<sup>1</sup>Center for Vascular Biology Research; Beth Israel Deaconess Medical Center and Harvard Medical School; Boston, MA USA; <sup>2</sup>Division of Nephrology; Beth Israel Deaconess Medical Center and Harvard Medical School; Boston, MA USA

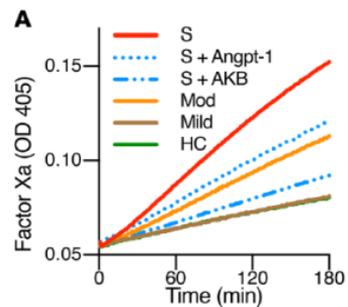
### Angpt2 release from W-P bodies during inflammation → antagonizes Tie2 signaling



**VE-PTP = Tie2 “off switch” AKB-9778 target**

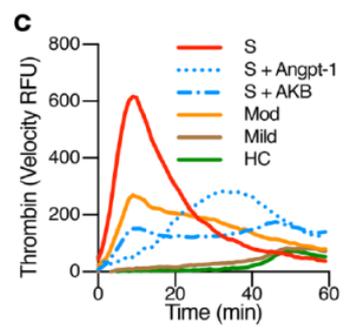
**Tie2 activation protects against prothrombotic endothelial dysfunction in COVID-19** JCI insight

Reference information: JCI insight. 2021;6(20):e151527. <https://doi.org/10.1172/jci.insight.151527>  
Alec A. Schmaier,<sup>1</sup> Gabriel M. Pajares Hurtado,<sup>2</sup> Zachary J. Manickas-Hill,<sup>3</sup> Kelsey D. Sack,<sup>2,4,5</sup> Siyu M. Chen,<sup>6</sup> Victoria Bhambhani,<sup>6</sup> Juweria Quadir,<sup>6</sup> Anjali K. Nath,<sup>6</sup> Ai-ris Y. Collier,<sup>7</sup> Debby Ngo,<sup>4</sup> Dan H. Barouch,<sup>2,8</sup> Nathan I. Shapiro,<sup>9</sup> Robert E. Gerszten,<sup>1</sup> Xu G. Yu,<sup>3,10</sup> MGH COVID-19 Collection and Processing Team,<sup>3,5,31</sup> Kevin G. Peters,<sup>12</sup> Robert Flaumenhaft,<sup>13</sup> and Samir M. Parikh<sup>14,35</sup>



**AKB-9778 restores EC anticoagulant phenotype**

-- less consumptive coagulopathy?



-- less microvascular thrombosis & organ failure?



# Past, Present and Future of Resuscitation?



**Whole Blood is King!**

**Components are cool!**

WW I

WW II

Korea

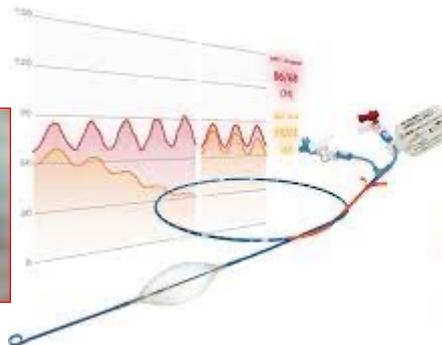
Vietnam

OIF/OEF

**60 years of Blood**

**30 years of Clear Fluids**

**Back to the future!**



- **WB + plasma + ...???**
- **shock drugs**
- **vascular stabilizers**
- **Partial REBOA, ECMO**
- **Optimized forward wound care & pain control**



**LTOWB**





# Questions?

