Transformational Change in Combat Casualty Care Research

COL Andrew P. Cap, MD, PhD
Director of Research
US Army Institute of Surgical Research

Equipping the Combat Medic aid bag over the past 20 years

Hemostatic Dressings

CAT Tourniquet

LTOWB

Cold Platelets

French FDP

- Combat Application Tourniquet
- Cold Platelet Resuscitation
- Low Titer Type O Whole Blood
- Damage Control Resuscitation
- Combat Gauze Dressing
- Burn Navigator System
- French Freeze-Dried Plasma (FLYP/PLYO)
- Compensatory Reserve Measurement
- In-flight Life Support (ECMO) and Continuous Renal Replacement Therapies (CRRT)

New problem set

2001-2021
Iraq, Afghanistan, Sahel/HoA:
counter-terrorism/insurgency

Future (soon?)
Large Scale Combat Operations (LSCO)
Multi-Domain Operating Environment (MDO)

Changing Adversaries → Changing Battlefield Medical Challenges

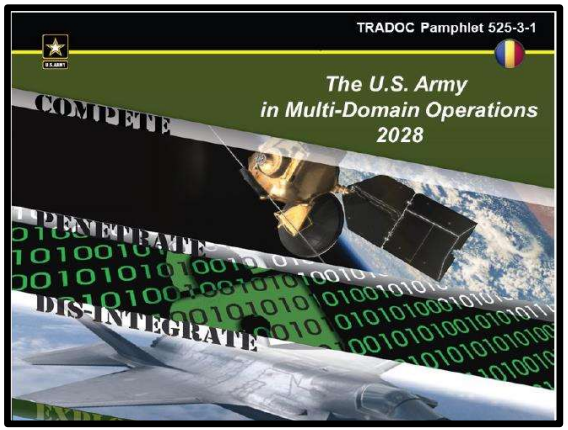
Afghanistan / Iraq:
IEDs, small arms, mortars, RPGs →

Low casualty density, rapid evacuation to surgery

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

High casualty density, delayed evacuation to surgery

LSCO & MDO = Prolonged Field Care



MDO Challenges:

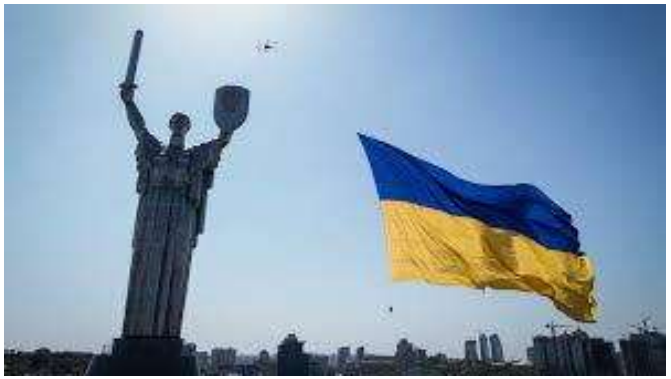
- **Cyber-attacks**
- **Long range precision fires (70+ km)**
- **Air defense, drones, MANPADs**

IMPACT:

- **Dispersion of forces**
- **Degraded communications**
- **Air evacuation difficult/impossible**
- **Long evacuation to Role 2/3**
- **Casualties may take hours to days to reach surgical care**

LSCO & MDO = Ukraine today










Rapid evacuation, transfusion, surgery = lives saved

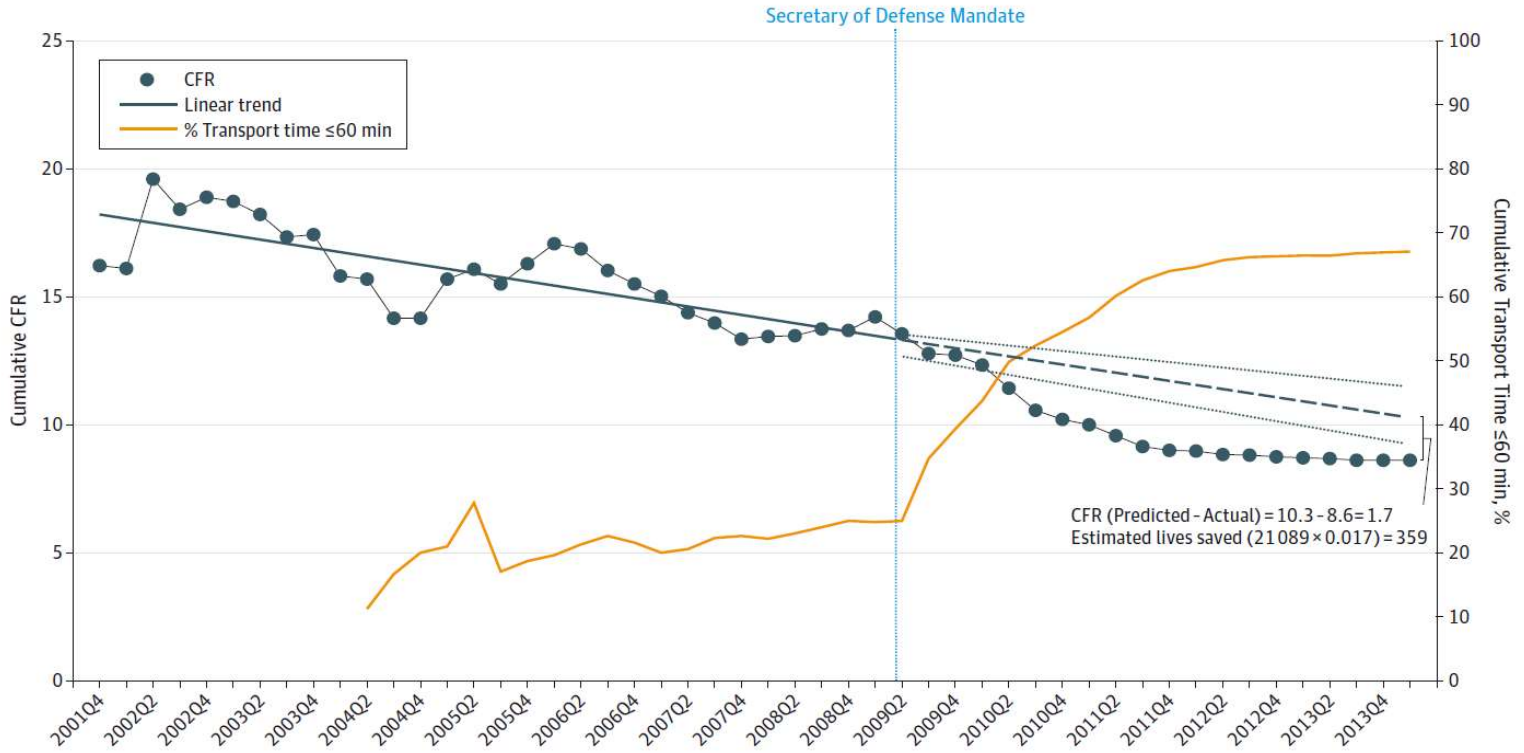
Original Investigation

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



Especially early transfusion…

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

The challenge

If we know that evacuation will be delayed, what can we do to improve outcomes?

Current approaches will not be adequate!

WE NEED BREAKTHROUGHS!

Current technologies have ancient roots

Bandages / Poultices:
Imhotep, Egypt 3000 BC

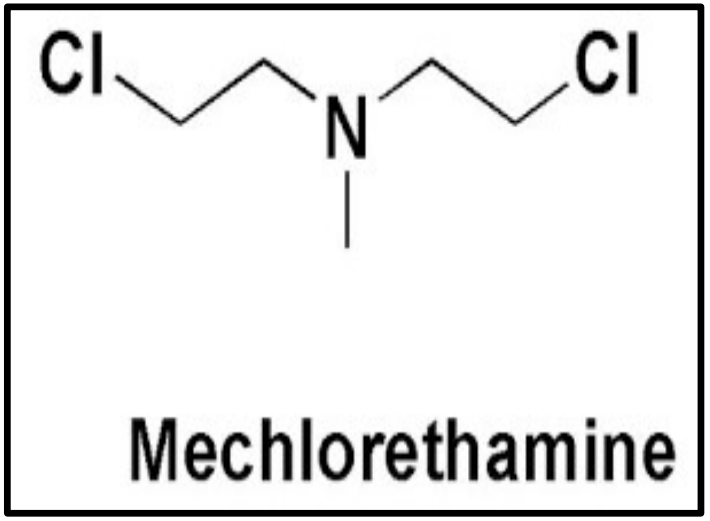
Blood Transfusion at the Frontlines: WWI, 1918

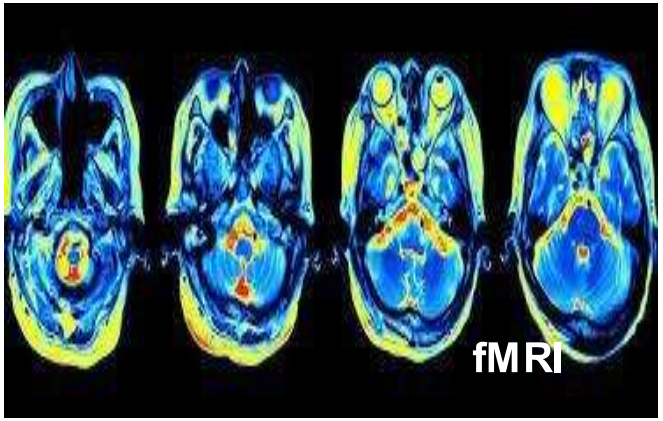
Tourniquet: 200 BC;
17th century

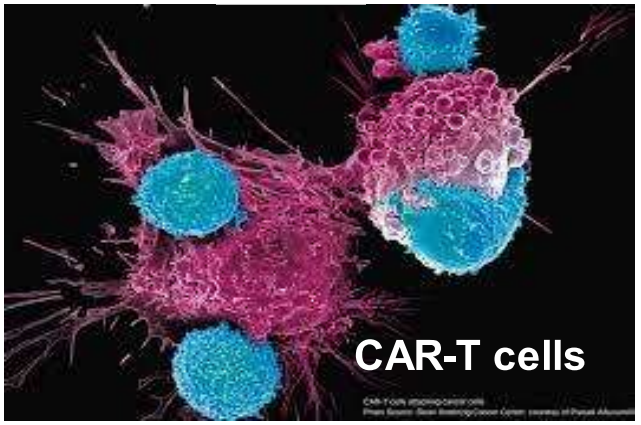
Freeze-dried plasma:
1930s, WWII

TXA: 1960s

We need transformational new technologies



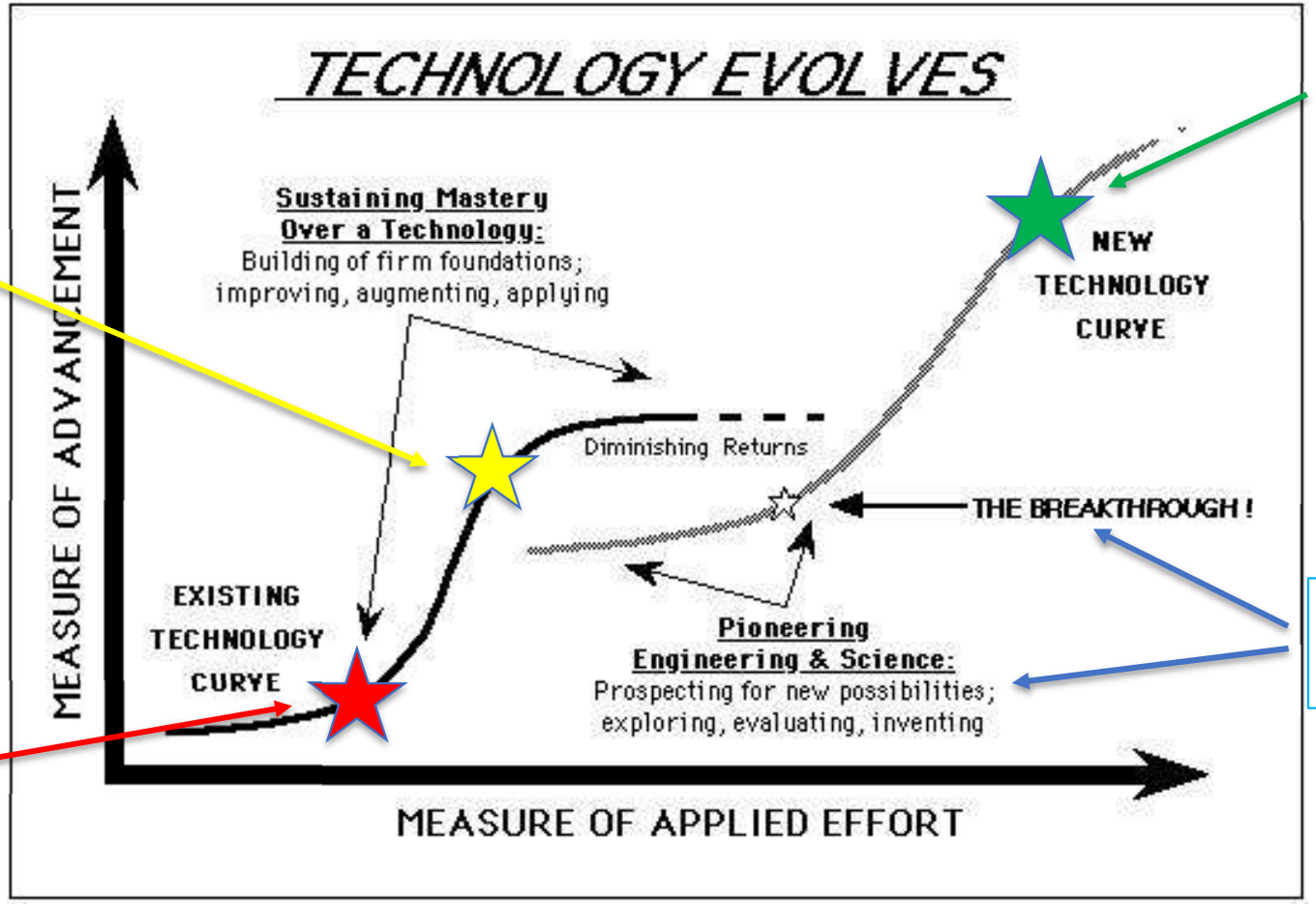




We need radical innovation to get onto a new technology curve

Combat Casualty Care 2021

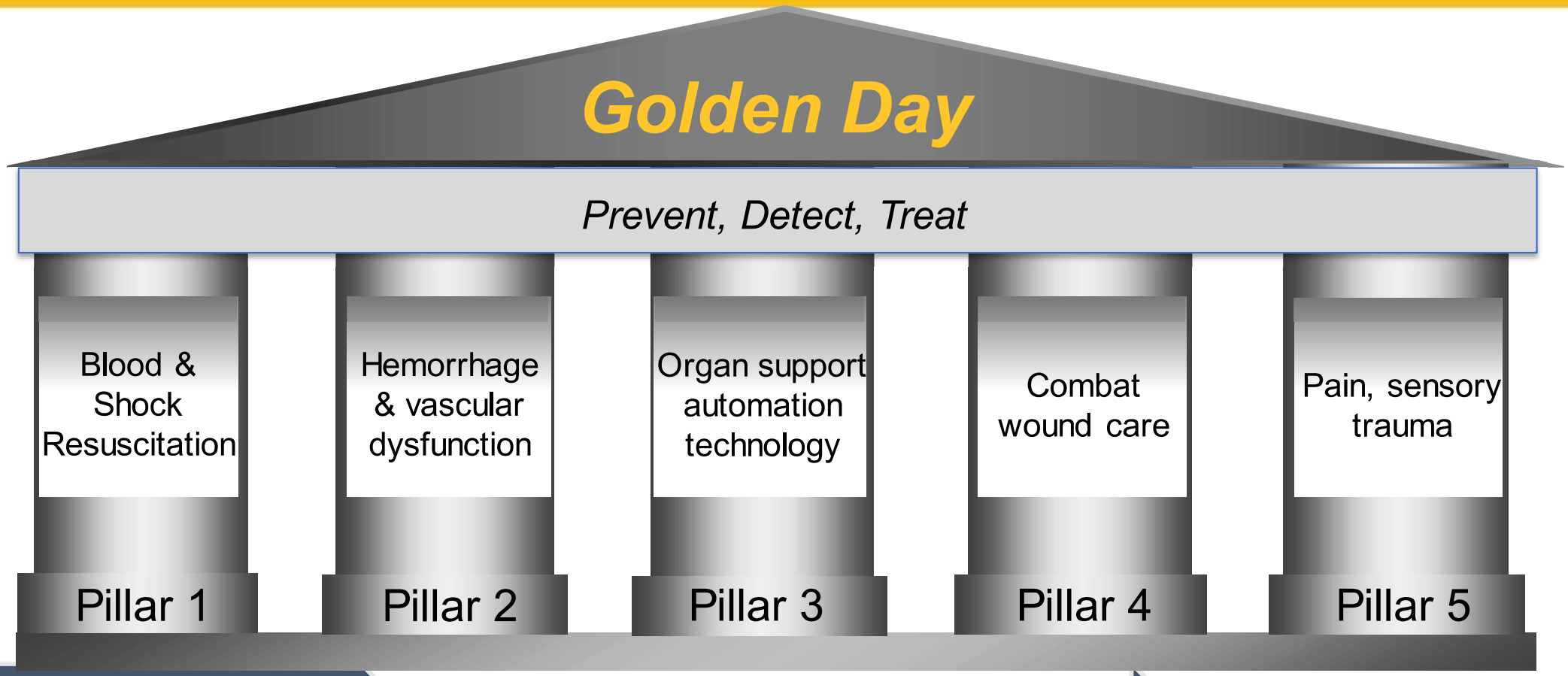
Combat Casualty Care 2001



Where we need to be for MDO/LSCO

What we need to do NOW!

Fundamental Challenges of Prolonged Field Care: the 5 Pillars



Acute (0-1 hours)

Blood / Airway Loss
→ ↓ DO2 → ↓ ATP → ↓ pH → ↑ K+
→ Cell death
→ Endothelial dysfunction
→ Coagulopathy

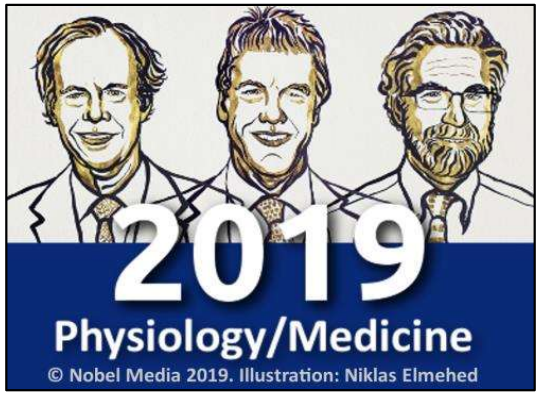
Intermediate (2-6 hours)

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

Pillar 1 – Treat shock & metabolic failure

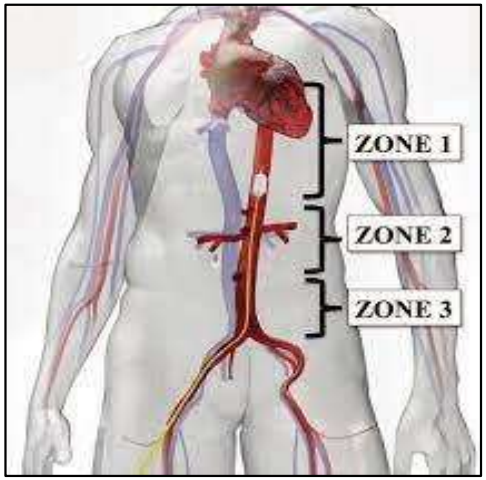


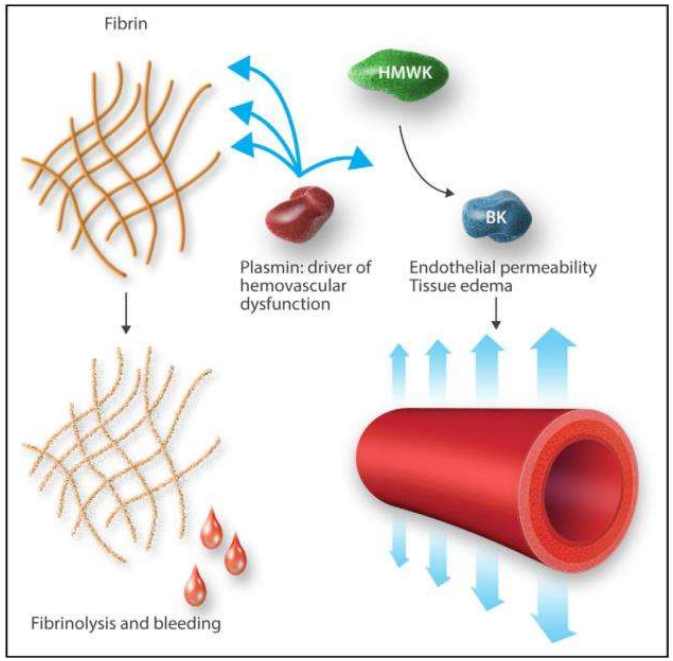
Shock drug autoinjectors

Pillar 1: Blood and Shock Resuscitation

- Anti-shock drug (prolyl hydroxylase inhibitors, pyruvate dehydrogenase kinase inhibitors, etc.)
- Engineered dried whole blood alternatives
- Next generation extended shelf-life platelets and whole blood
- Improved blood transport container system / support for drone delivery of blood products

Pillar 2 – Hemostasis, vascular stabilization

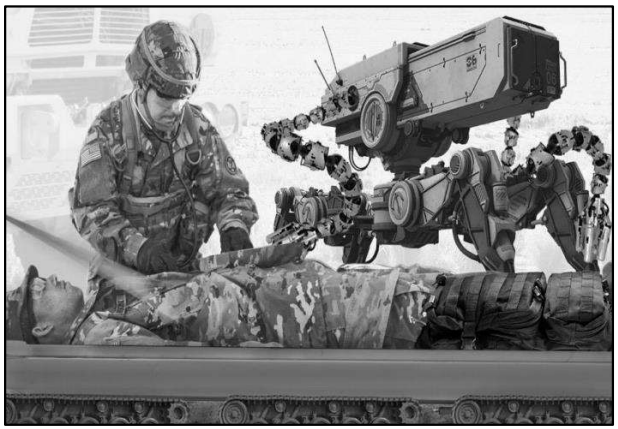




Pillar 2: Hemorrhage and Vascular Dysfunction

- Non-compressible hemorrhage control / expanded REBOA capability; hemostatic foams (mousse hemostatique)
- Microvascular endothelial stabilization
  - ANG1-TIE2 agonist → preserve endothelial tight junctions
  - bradykinin receptor antagonist
  - Protein C
  - inhibition of plasmin activation/activity
- Resuscitation with Enteral Fluids

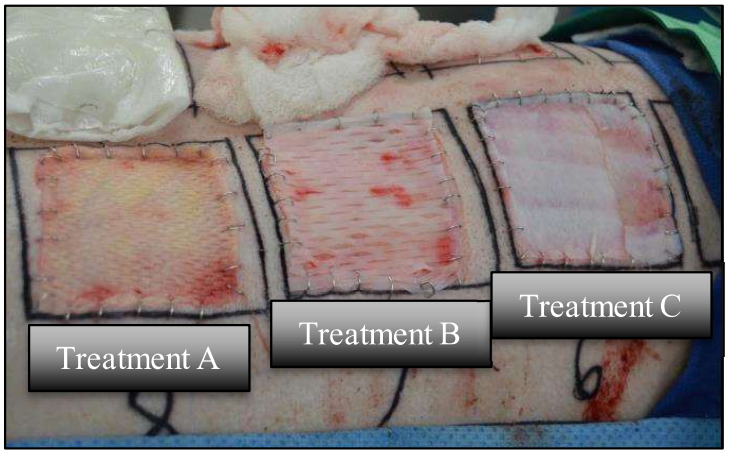
Pillar 3 –
Organ function support, automation, technology



Pillar 3: Engineering Technology Automation

- Next Generation Smart Tourniquet
- Semi-automated vascular access devices, nerve block placement
- Clinical Decision Support System for medics
- Heparin-free Extra-Corporeal Life Support (ECLS)
- Compensatory Reserve Measurement

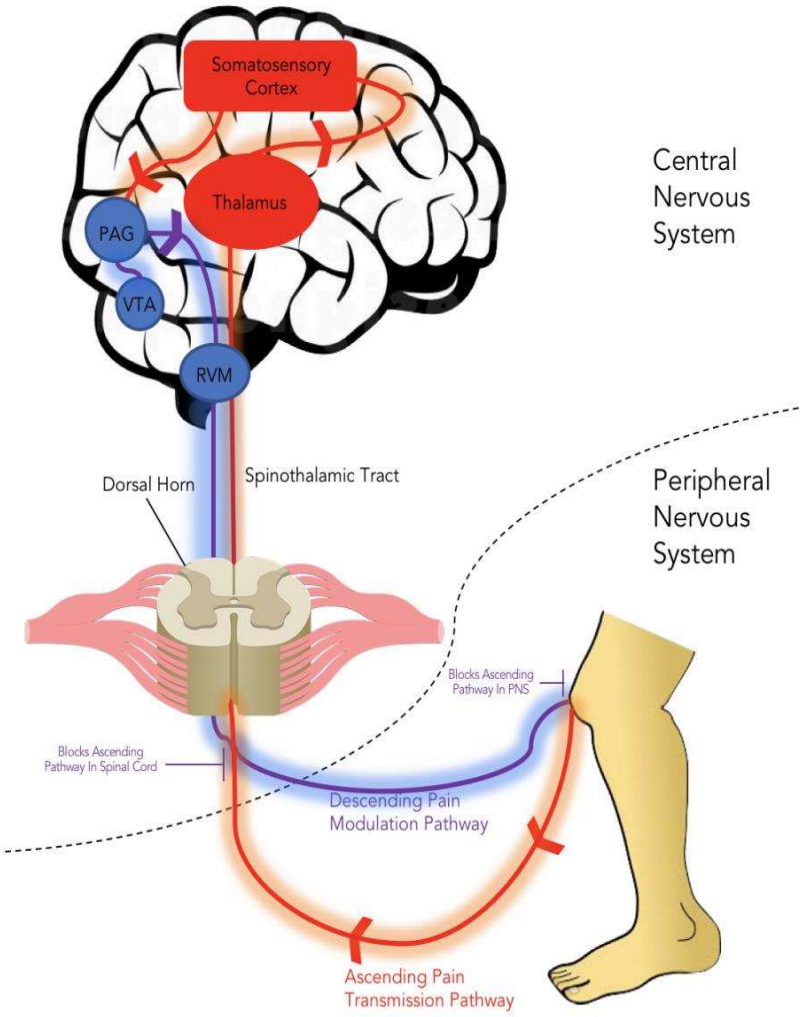
Pillar 4 – Combat Wound Management



Pillar 4: Combat Wound Care

- Non-surgical debridement of severe burn wounds
- Far-forward treatments to prevent burn progression
- Ambulatory external fixation for lower extremity injuries
- Pathogen agnostic wound care

Pillar 5 – Battlefield Pain Management



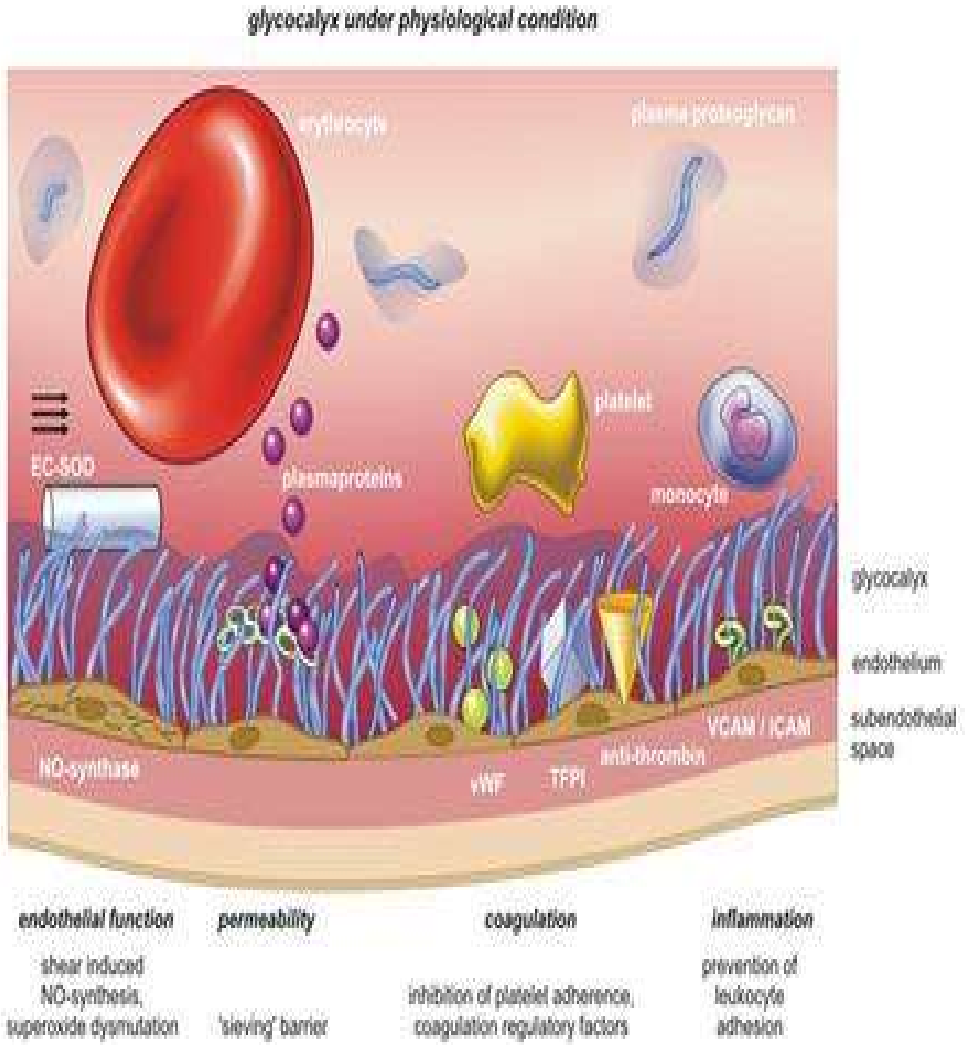
Pilier 5: Pain and Sensory Trauma

- Safety & efficacy of novel pain compounds (ex. TRPA antagonists, anti-microglial activation/neuroinflammation)
- Combination non-opioid therapy for acute pain (ketamine, loco-regional blocks)
- Decision support for multi-modal pain management
- Penetrating Ocular Injury Model – Temporary Corneal Repair

Example of new directions: *Blood Failure*

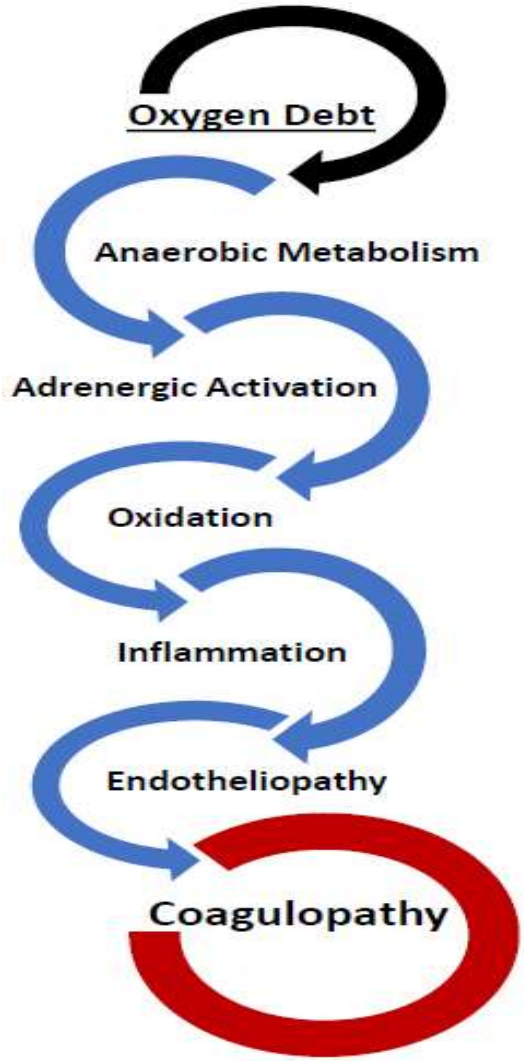
- **Blood is an organ, not hydraulic fluid**
- **Blood exists in symbiosis with the endothelium**
- **Tissue hypoxia → endotheliopathy, coagulopathy → Blood Failure**
- **Follow the pathophysiology to identify transformational interventions**

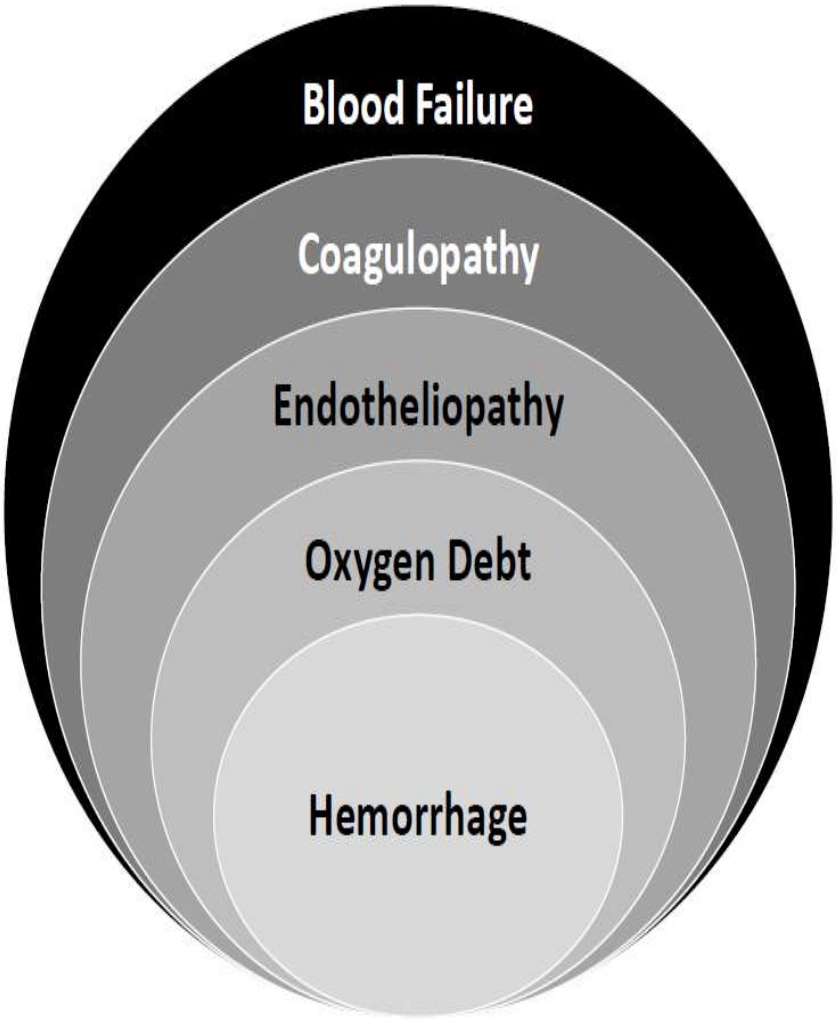
Blood + Endothelium =
Blood is an Organ



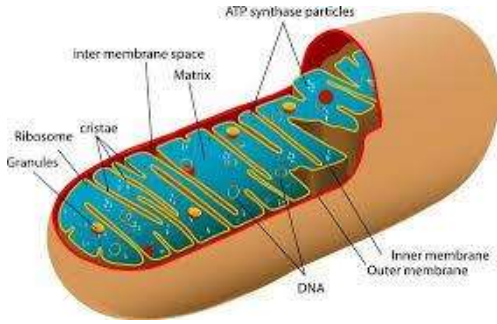
- Embryonic mesoderm → hemogenic endothelium → HSC → blood: 3d week embryo
- Blood = RBCs, WBCs, Platelets, Plasma, *and…* Endothelium (10^{13} cells)
- Microcirculation estimated to cover an area of up to 7000 m^2
- Largest organ system, highest turnover rate.

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





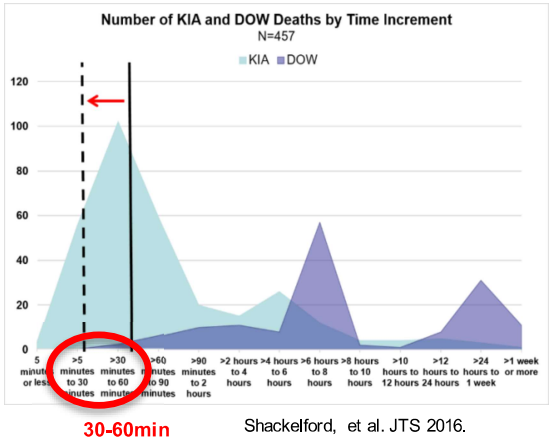
Mitochondrial Dysfunction



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

Lethal hemorrhagic shock model in rats

Mortality at Battlefield:



30-60min

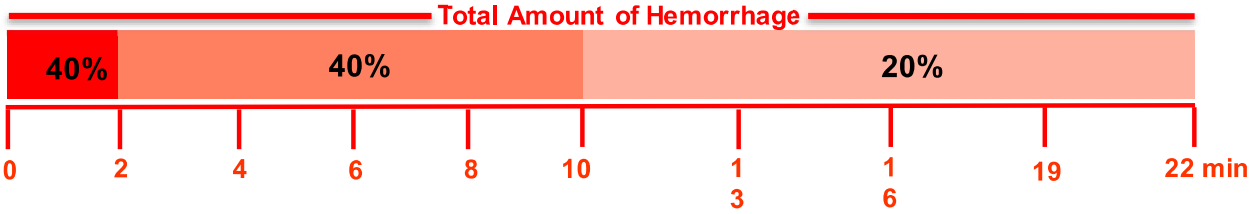
Shackelford, et al. JTS 2016.

90% preventable injury-related death is associated with hemorrhage

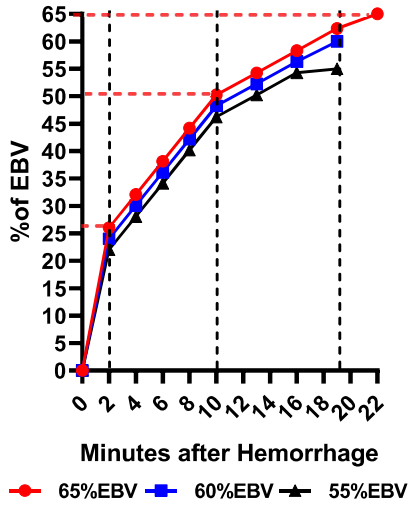
Fixed-Volume Hemorrhage at Fast-to-Slow Pattern

Sprague Dawley

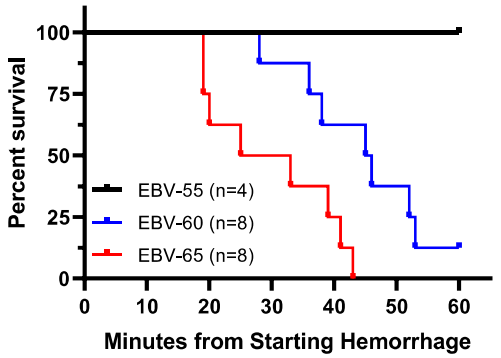
Isoflurane Anesthesia



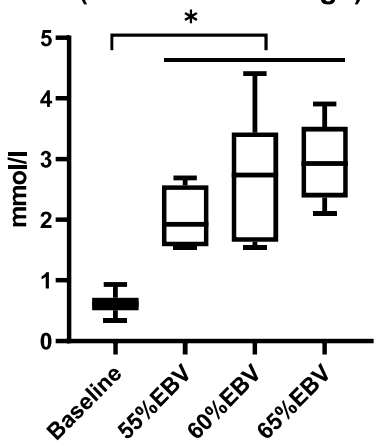
Hemorrhage (% of EBV)



Survivability of Fixed-Volume Hemorrhagic Shock



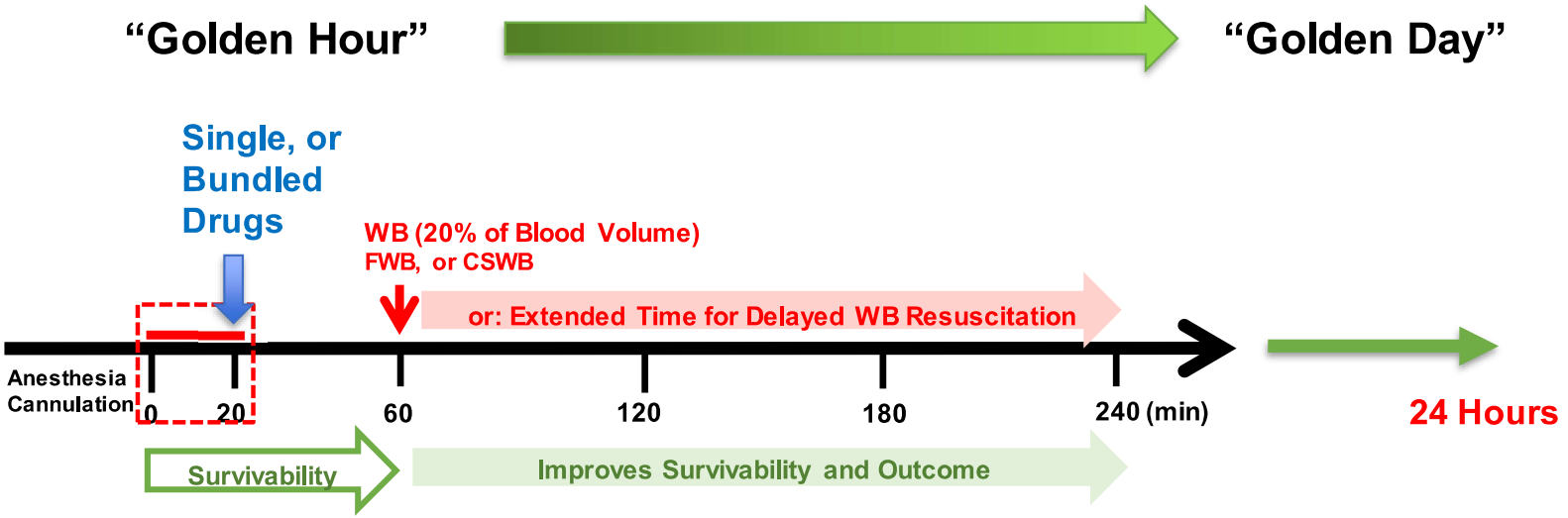
Lactate (end of hemorrhage)



Time to Death: **60%EBV: 43±3min; 65%EBV: 30±4min**

EBV: Estimated Blood Volume

Goals

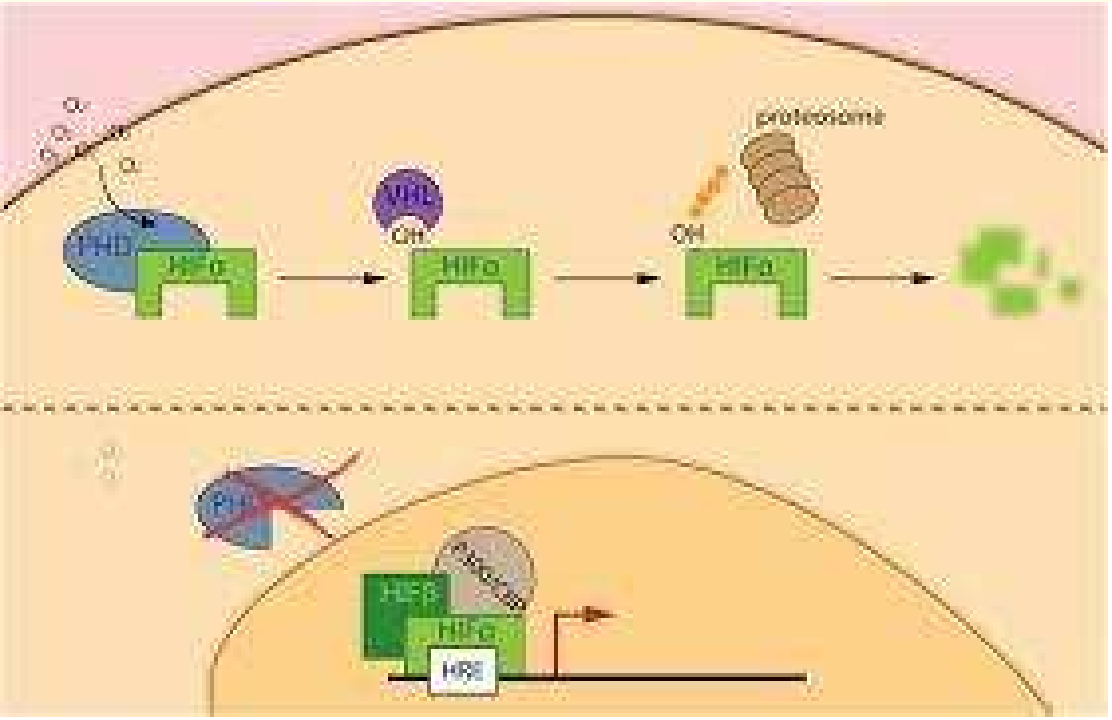


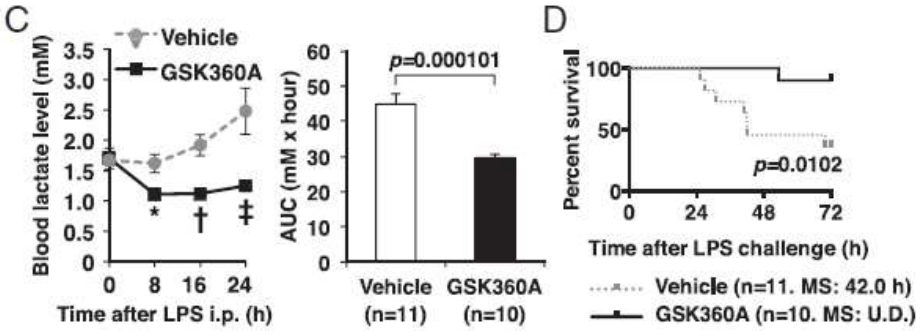
Acute Lethal Hemorrhagic Shock (Fixed Volume or Uncontrolled by Major Tissue Injury)

Administration of Anti-Shock Drugs at 20min from Starting Hemorrhage or Tissue Injury

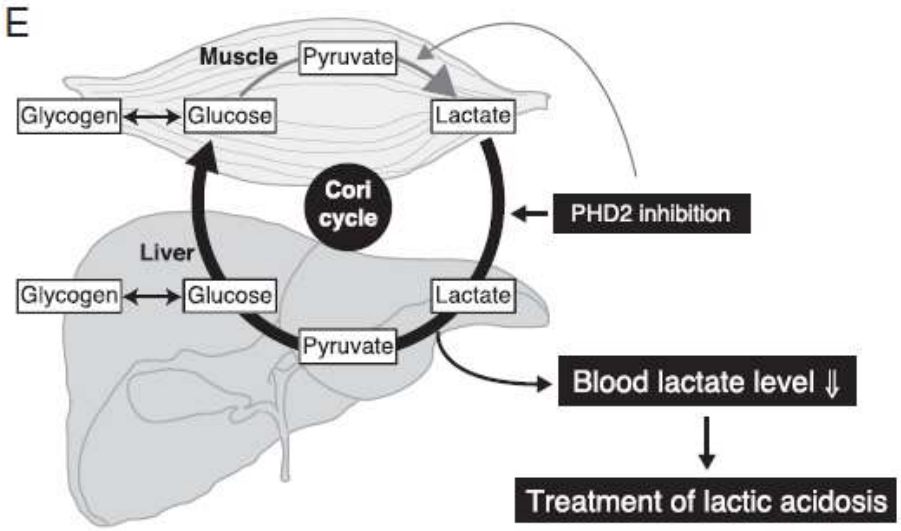
Whole Blood (WB) Resuscitation (20% of Blood Volume) at 60min (or >60min) Using Fresh Whole Blood (FWB) or Cold Stored Whole Blood (CSWB)

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





Suhara PNAS 2015.

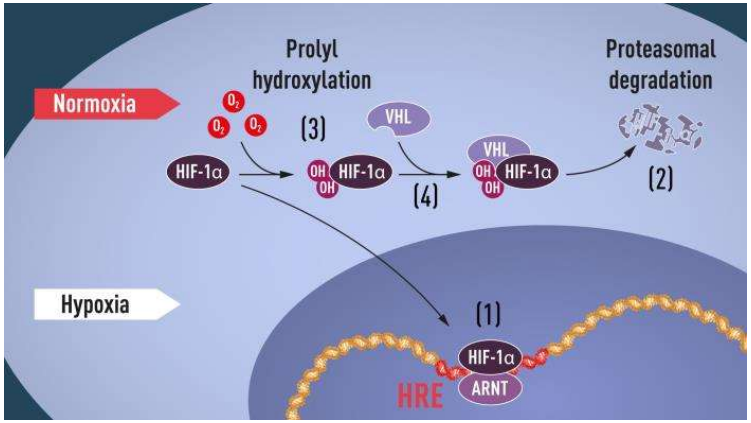


Under development in CKD to treat anemia (Roxadustat; see NEJM 2019)

-- Acute timeframe of action

Prolyl Hydroxylase Domain Inhibitors (PHDi)

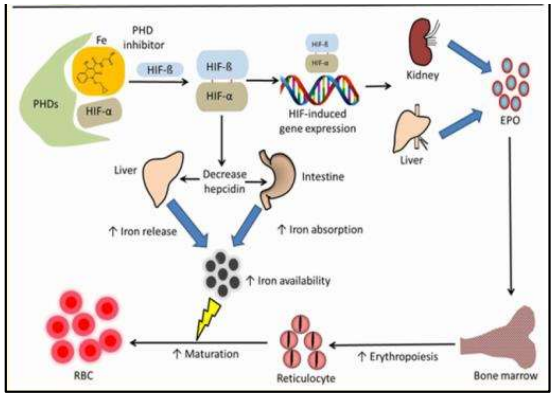
Improve Adaptation to Hypoxia



nobelproze.org

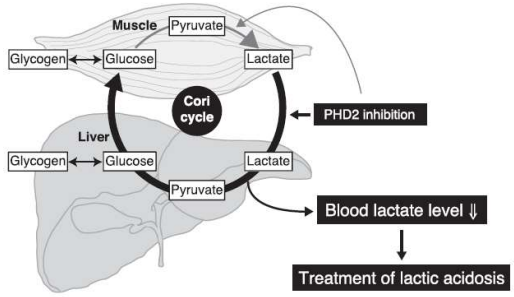
2019 Nobel Prize in Physiology/Medicine to
William G. Kaelin Jr.
Sir Peter J. Ratcliffe
Gregg L. Semenza
for their discoveries of how cells sense and adapt to oxygen availability

Erythropoietic Effects



Joharapurkar AA, et al, J Med Chem 2018

Metabolic Reprogramming



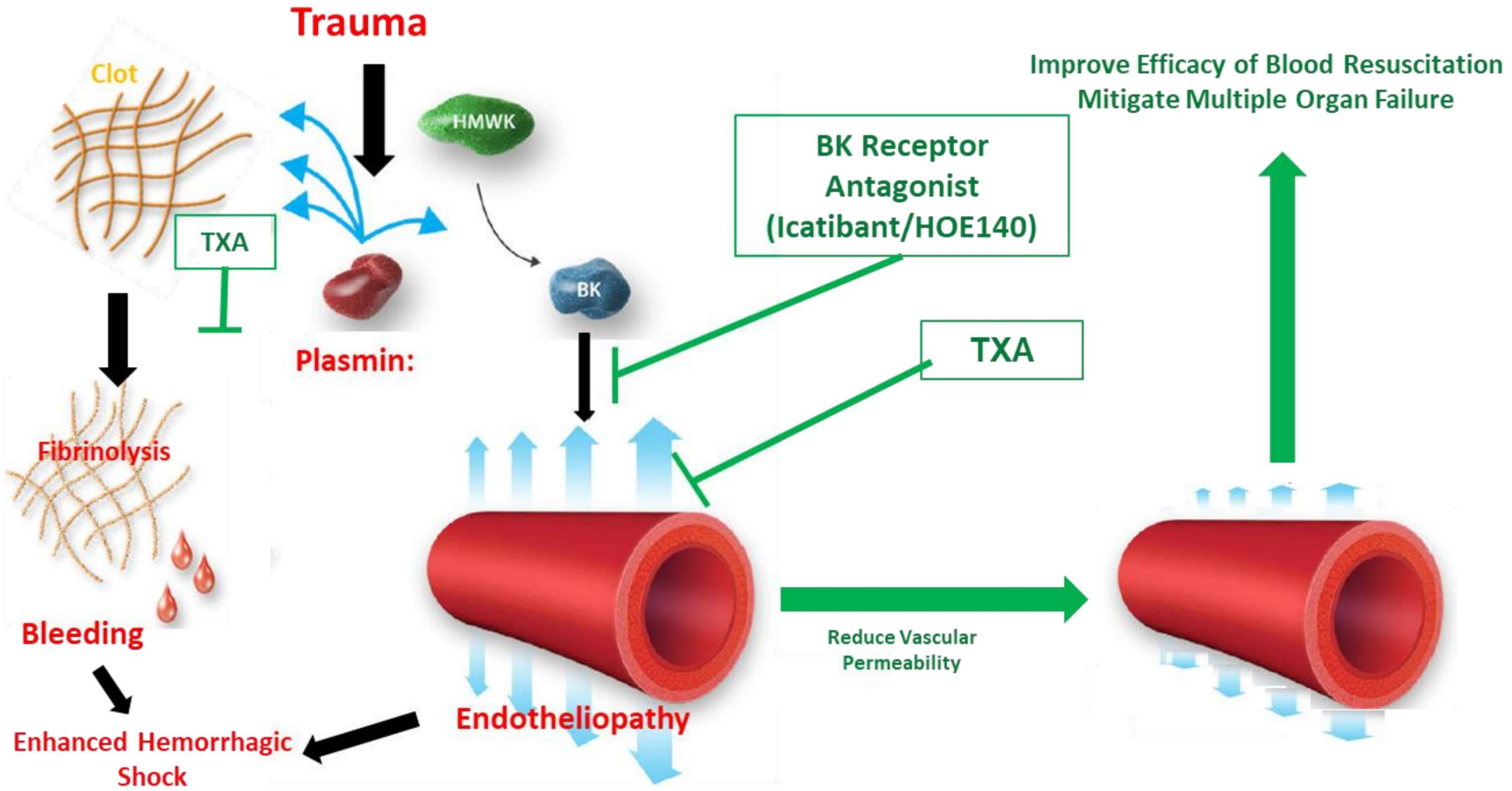
Suhara T, et al, PNAS, 2015

Table 1. Characteristics of HIF-PH Inhibitors Under Development

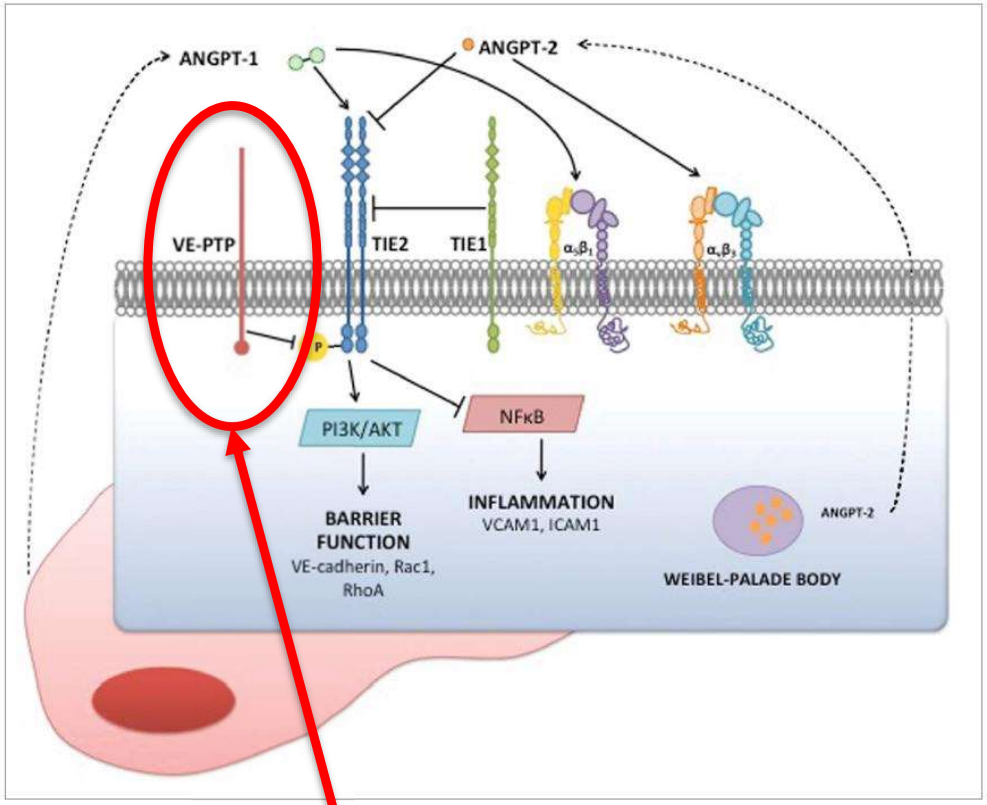
Generic Name	Investigational Name	Sponsor	Half-Life, h	Dosing Frequency	Investigational Status
Roxadustat	FG-4592	FibroGen, Astellas, & AstraZeneca	12-13	3×/wk	Phase 3
Vadadustat	AKB-6548	Akebia	4.5	Daily	Phase 3
Daprodustat	GSK-1278863	GlaxoSmithKline	4	Daily	Phase 2 (US) Phase 3 (Japan)
Molidustat	BAY 85-3934	Bayer	NA	Daily	Phase 2

Gupta N, AJKD 2017

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



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



VE-PTP = Tie2 "off switch"

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

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

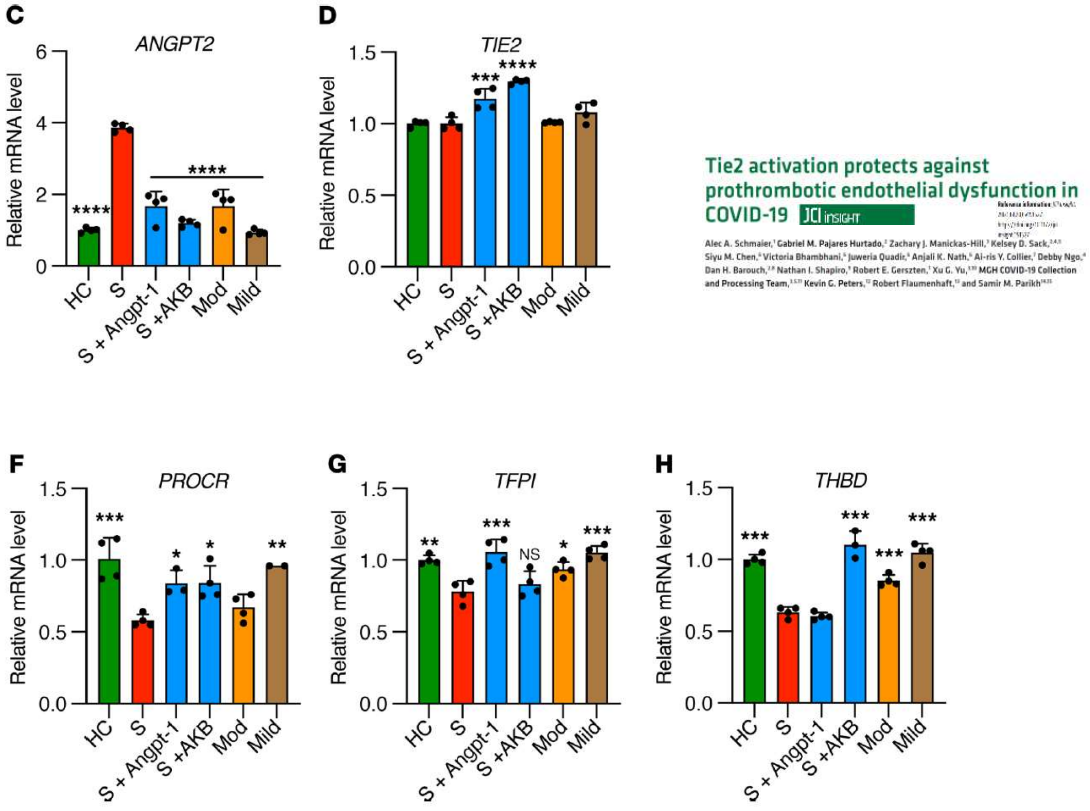
Katelyn E Milam[1] and Samir M Parikh[1,2,*]

[1]Center for Vascular Biology Research; Beth Israel Deaconess Medical Center and Harvard Medical School; Boston, MA USA; [2]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

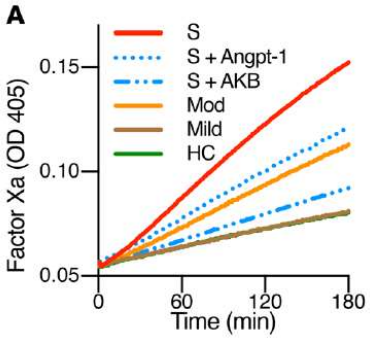
1. Cell surface components of Angpt-Tie2 axis signaling during inflammation. Endothelial cells are spe- enriched for expression of Tie2, its paralog Tie1, the tyrosine phosphatase VE-PTP, and its ligand Angpt- pt-1 is secreted by peri-endothelial cells. Several integrins have also been proposed as co- or alternate ors for the Angpts, examples of which are depicted. In the quiescent vasculature, Tie2 is activated as evi- y phosphorylation at tyrosine residues in its intracellular domain. Activated Tie2 promotes barrier function and anti-inflammation. In the context of inflammation, Angpt-2 is both rapidly released from storage granules called Weibel-Palade bodies and is transcriptionally induced. Excess Angpt-2 antagonizes Angpt-1, leading to reduced signaling downstream of Tie2.

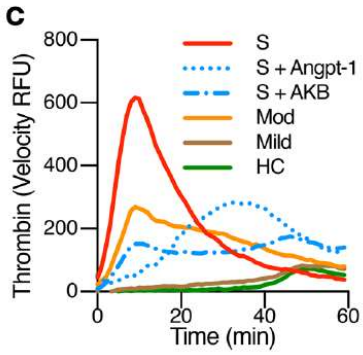
Turning off the "off switch" for Tie2: inhibition of VE-PTP preserves EC function



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

Alec A. Schmaier, Gabriel M. Pajares Hurtado, Zachary J. Manickas-Hill, Kelsey D. Sack, Siyu M. Chen, Victoria Bhambhani, Juweria Quadir, Anjali K. Nath, Al-ris Y. Collies, Debby Ngo, Dan H. Barouch, Nathan I. Shapiro, Robert E. Gerszten, Xu G. Yu, MGH COVID-19 Collection and Processing Team, Kevin G. Peters, Robert Flaumenhaft, and Samir M. Parikh





AKB-9778 restores EC anticoagulant phenotype

-- less consumptive coagulopathy?

-- less microvascular thrombosis & organ failure?

History of Combat Trauma 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+ shock drugs, vascular stabilizers, etc.***

Questions?