Anti-Shock Drugs, Mitochondrial Therapies, Extracellular Vesicles

Advanced Therapies for Blood Failure?

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Disclosures

and Disclaimers…

- Velico Medical: Chief Scientific Officer, Board Director
- Cross Road Health/Interior Alaska Clinics: Medical Director
- SME consultant to HHS/BARDA (Tunnell Government Services)
- Volunteer faculty, Hematology & Oncology, Dept. of Medicine, USU
- Clinical Advisor, Seragene Therapeutics

The following are the private views of the presenter and are not official policy and are not intended to represent the views of the Department of Health and Human Services, the Department of the Army, the Department of Defense, or the Defense Health Agency.

One more disclosure…

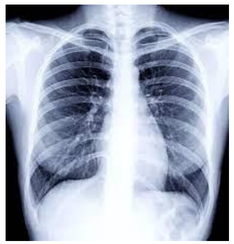
Highly relevant to THOR!

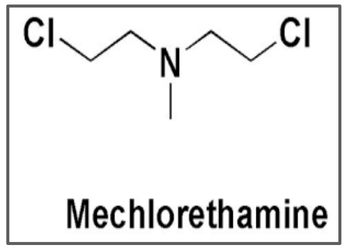
- Assistant Fisherman, SS Tuborg, DocFish Enterprises

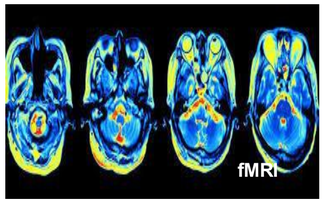
Hemorrhage: Blood is best but…

We need more tools!

- Blood logistical challenges on battlefield, civilian emergencies
- High mortality (>40%) of hemorrhagic shock even with blood resuscitation
- Decreasing blood donation rates







Also, can we harness >100 years of medical research since first battlefield transfusions to develop something new to treat hemorrhagic shock???

Hemorrhagic shock

Blood Failure, Metabolic Failure, Endothelial Failure

- **Blood Failure:**
  - RBC & volume loss → decreased DO2 → anaerobic metabolism, lactic acidosis
  - Plasma/PLT loss & consumption → decreased hemostatic function, bleeding
- **Metabolic Failure:**
  - Mitochondrial dysfunction: shut down OXPHOS/ETC, increased ROS, decreased ATP, cell death
- **Endothelial Failure:**
  - Loss of coagulation homeostasis → fibrinolysis, cellular activation, microvascular thrombosis
  - Loss of barrier function → decreased BP, edema, inflammation, MOF

How about a blood substitute?

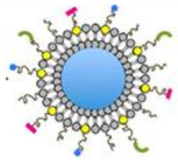
Are we finally getting there?

DARPA

FSHARP

BIOMEDICAL ADVANCED RESEARCH AND DEVELOPMENT AUTHORITY BARDA

SynthoPlate (SP)



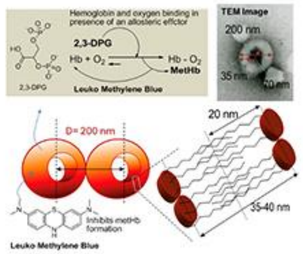
DSPE-PEG-FMP — Co-aggregation

DSPE-PEG-VBP

DSPE-PEG-CBP — Adhesion

haima therapeutics

ErythroMer (EM)



KaloCyte

UNIVERSITY of MARYLAND BALTIMORE

Freeze-Dried Plasma (FDP)

Teleflex Vascular Solutions

Whole Blood Surrogate

SP + EM + FDP

1) Reconstitution
2) Characterization

Aim 1
Physicochemical Compatibility

Aim 2
Biofunctional Compatibility

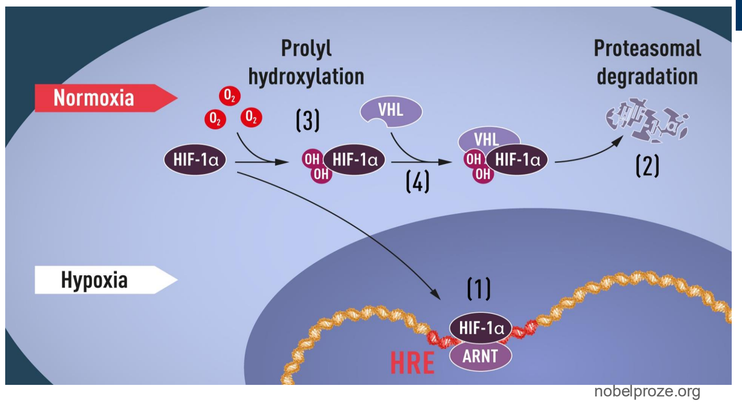
Aim 3
In vivo testing
In massive hemorrhage with induced dilutional or traumatic coagulopathy rabbit model

velico
The Future of Blood

Shock Drug? Prolyl Hydroxylase inhibitors

Rapid adaptation to hypoxia through HIF stabilization

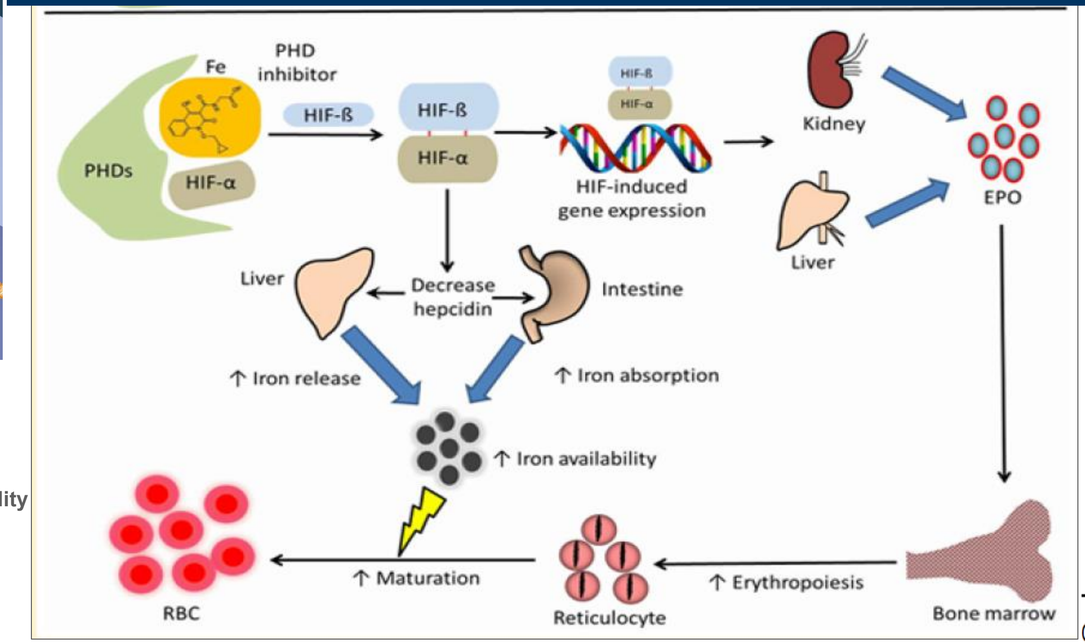
Improve Adaptation to Hypoxia



nobelproze.org

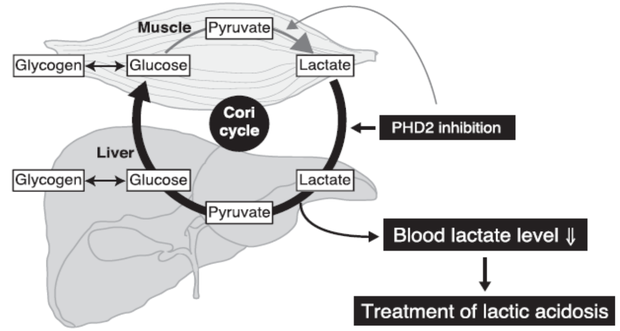
**2019 Nobel Prize in Physiology/Medicine to William G. Kaelin Jr.
Sir Peter J. Ratcliffe
Gregg L. Semenza
for their discoveries of how cells sense and adapt to oxygen availability**

Erythropoietic Effects



Joharapurkar AA, et al, J Med Chem 2018

Metabolic Reprogramming



Suhara T, et al, PNAS, 2015

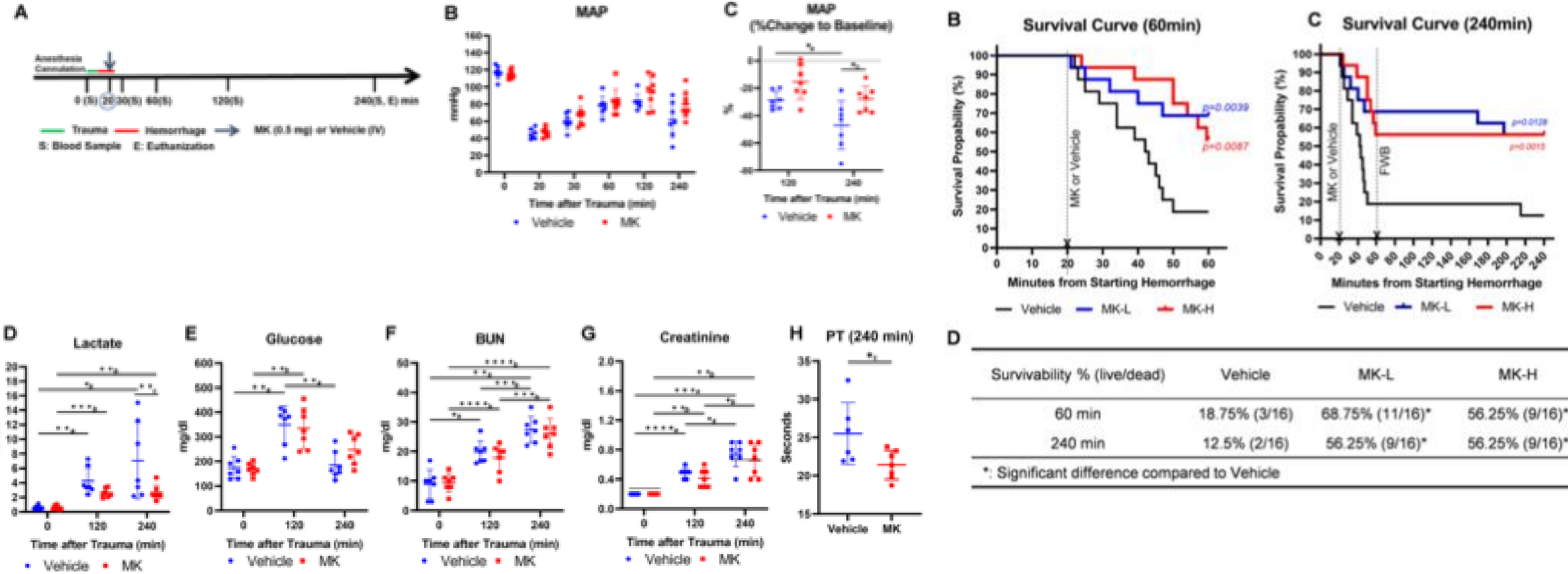
Table 1. Characteristics of HIF-PH Inhibitors Under Development

Generic Name	Investigational Name	Sponsor	Half-Life, h	Dosing Frequency	Investigational Status
Roxadustat	FG-4592	FibroGen, Astellas, & AstraZeneca	12-13	3X/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

Daprodustat and Vadadustat approved in US for treatment of anemia in CKD.
Challenge: oral only, no IV; no development beyond anemia indication

PHDi as a bridge to Blood

Mitigates lactic acidosis… and coagulopathy of trauma?



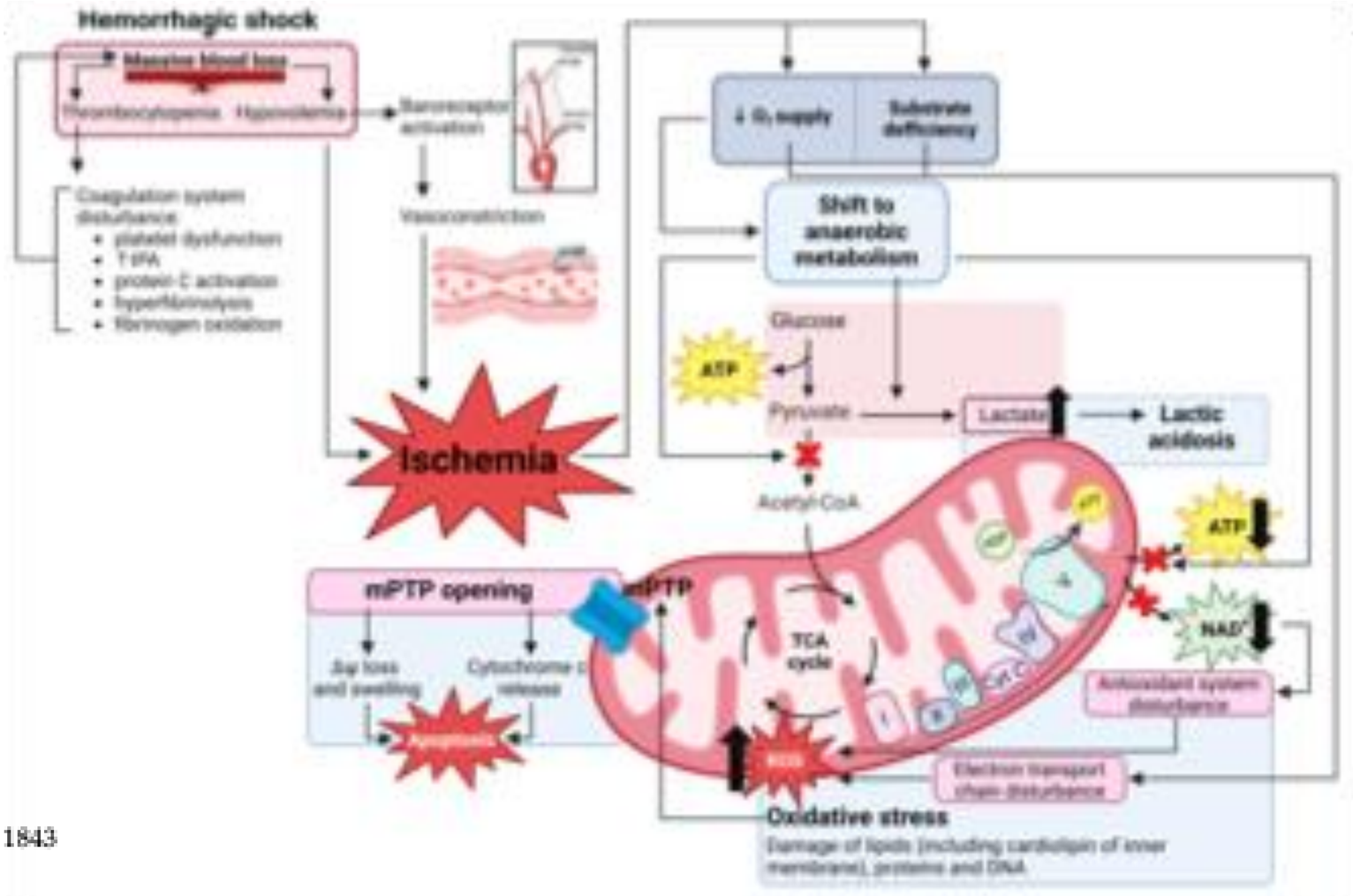
D

Survivability % (live/dead)	Vehicle	MK-L	MK-H
60 min	18.75% (3/16)	68.75% (11/16)*	56.25% (9/16)*
240 min	12.5% (2/16)	56.25% (9/16)*	56.25% (9/16)*

*: Significant difference compared to Vehicle

Metabolic Failure in Hemorrhagic Shock

The final common pathway of cell death



Int. J. Mol. Sci. **2025**, 26, 1843

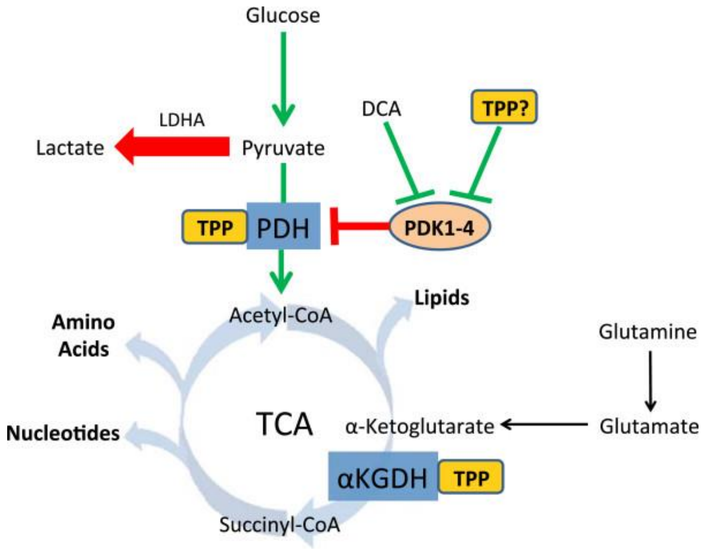
Mitochondrial therapies

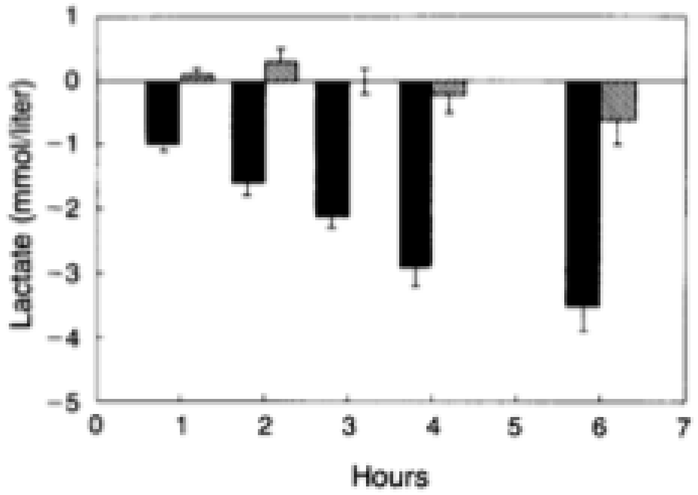
Dysfunction by many pathways → combination therapy?

Int. J. Mol. Sci. **2025**, 26, 1843

Pyruvate Dehydrogenase: gateway to TCA

NADH accumulation → PDH kinase: shutdown of TCA/ETC





1564 THE NEW ENGLAND JOURNAL OF MEDICINE Nov. 26, 1992

A CONTROLLED CLINICAL TRIAL OF DICHLOROACETATE FOR TREATMENT OF LACTIC ACIDOSIS IN ADULTS

No improvement in survival but patients in DCA group were sicker at baseline.
Lactate > 5 at baseline for all.
Survival 20% in subset SBP<90, 40% in subset SBP>90

OPEN ACCESS Freely available online PLOS ONE

Diisopropylamine Dichloroacetate, a Novel Pyruvate Dehydrogenase Kinase 4 Inhibitor, as a Potential Therapeutic Agent for Metabolic Disorders and Multiorgan Failure in Severe Influenza

Kazuhiko Yamane[1], Irene L. Indalao[1], Junji Chida[1], Yoshikazu Yamamoto[2], Masaaki Hanawa[2], Hiroshi Kido[1]*

1 Division of Enzyme Chemistry, Institute for Enzyme Research, The University of Tokushima, Tokushima, Japan, 2 R&D Department, Daiichi Sankyo Healthcare Co., Ltd., Tokyo, Japan

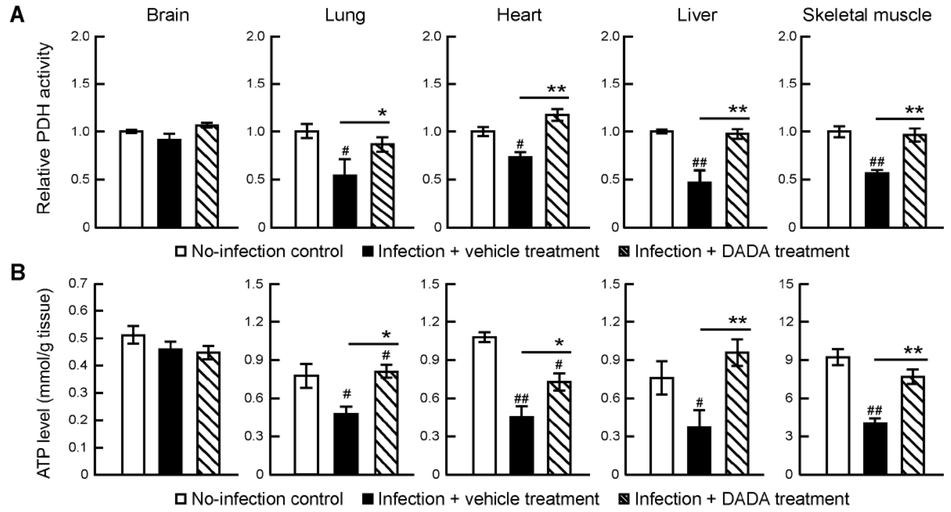


Figure 3. Treatment with DADA restores suppressed PDH activity and ATP levels in the skeletal muscles, heart, lungs and liver of IAV-infected mice. Mice infected with 120 pfu of IAV were treated orally with DADA at 50 mg/kg or vehicle at 12-h intervals for 14 days, and the levels of PDH activity (A) and ATP (B) in the skeletal muscles, heart, lungs, liver and brain of mice were analyzed at day 7 post-infection. PDH activity levels relative to the values of the control (no-infection). Values are mean ± SD of 5 mice per group. $^{\#}P<0.05$, $^{\#\#}P<0.01$, vs. no-infection, $^{*}P<0.05$, $^{**}P<0.01$, vs. infected group treated with vehicle, by one-way analysis of variance (ANOVA) and Tukey post hoc test.
doi:10.1371/journal.pone.0098032.g003

Shock Drug/Mitochondrial Therapies

State of the Science? Preclinical. Invest in clinical development!

Adjuvant therapies for management of hemorrhagic shock: a narrative review

Yann Daniel[1,2*], Frédérique Dufour-Gaume[1], Amandine Vergnaud[2], Manon Denis[3], Louise Giaume[4], Bertrand Rozec[3], Nicolas Prat[1,4] and Benjamin Lauzier[2]

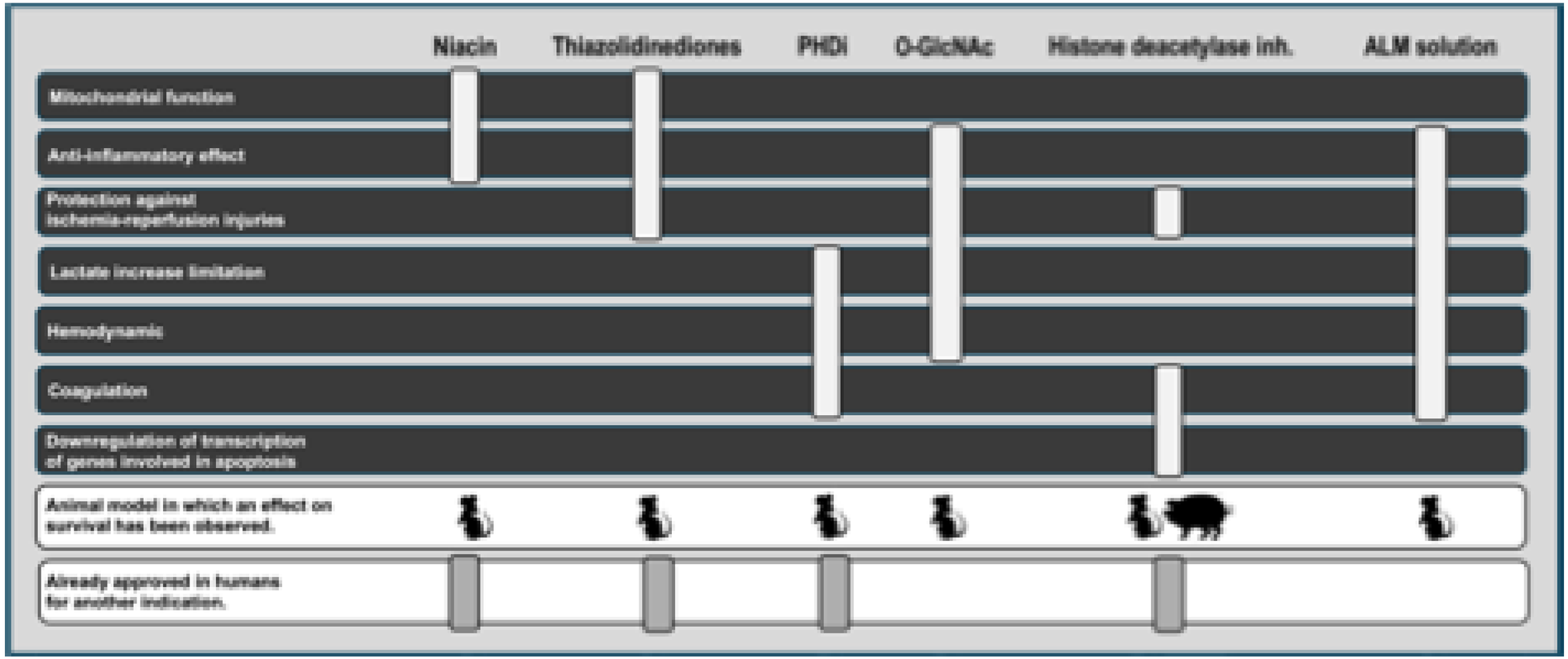


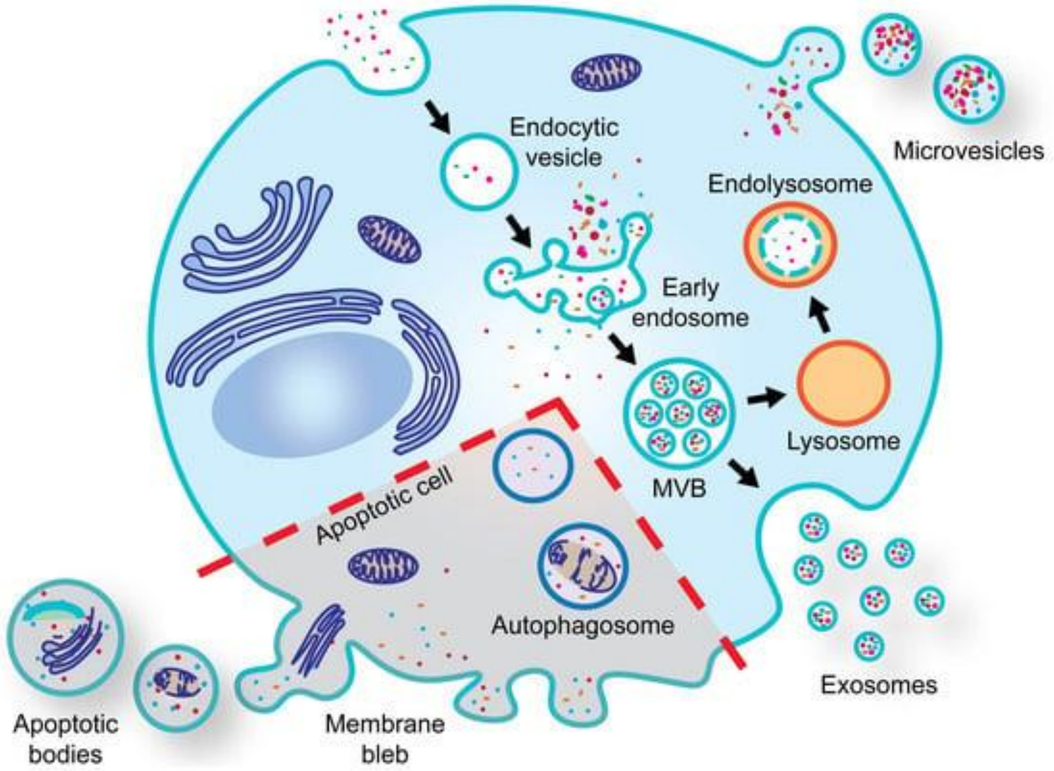
Fig. 1 Schematic representation of the potential modes of action of the different molecules according to the pre-clinical data obtained in animals. PHDi, prolyl hydroxylase domain inhibitors; O-GlcNAc, O-GlcNAcylation; Histone deacetylase inh, histone deacetylase inhibitors; ALM solution, adenosine–lidocaine–magnesium solution

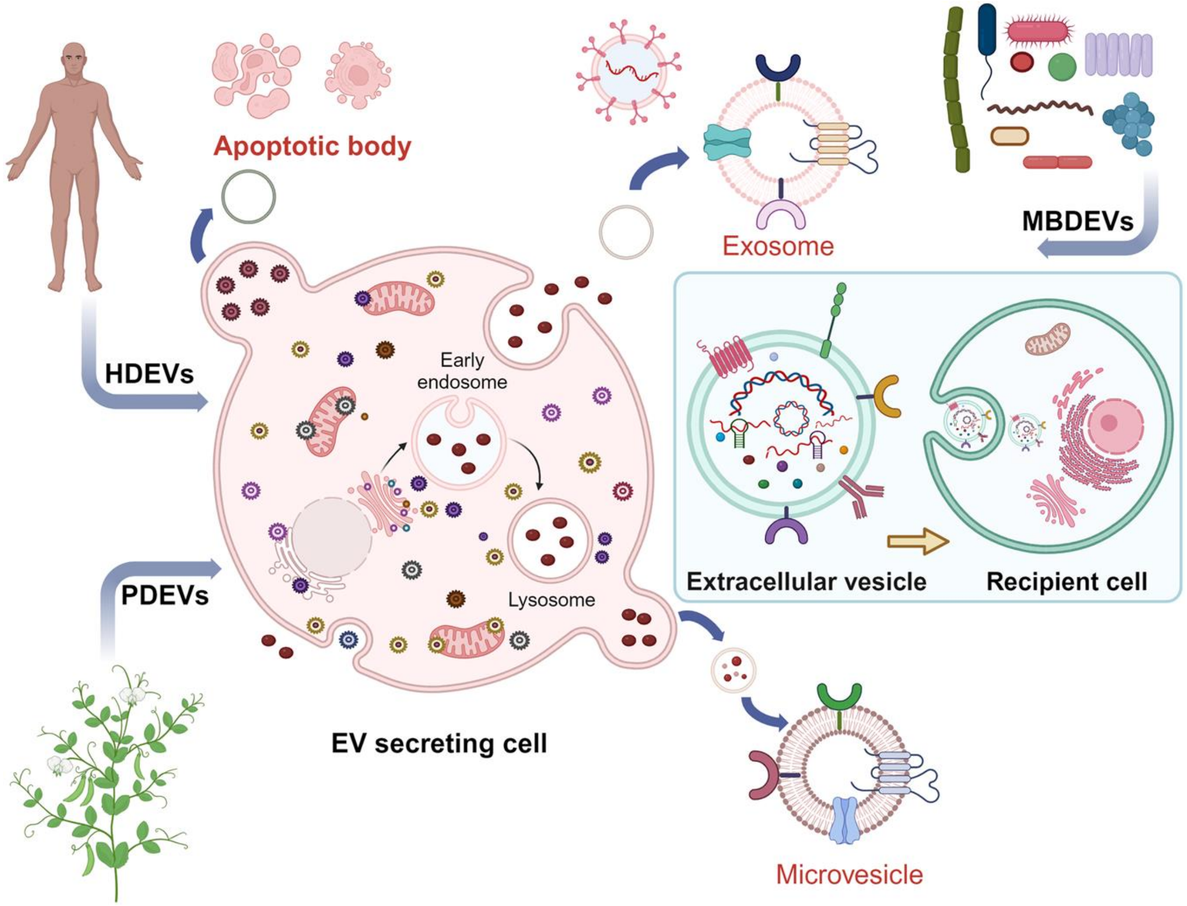
Daniel *et al. Critical Care (2025) 29:138*
https://doi.org/10.1186/s13054-025-05368-w

Critical Care

Extracellular vesicles?

A variety of subcellular particles to sort out…





EVs in trauma

EVs are part of the problem: hypercoagulability, inflammation

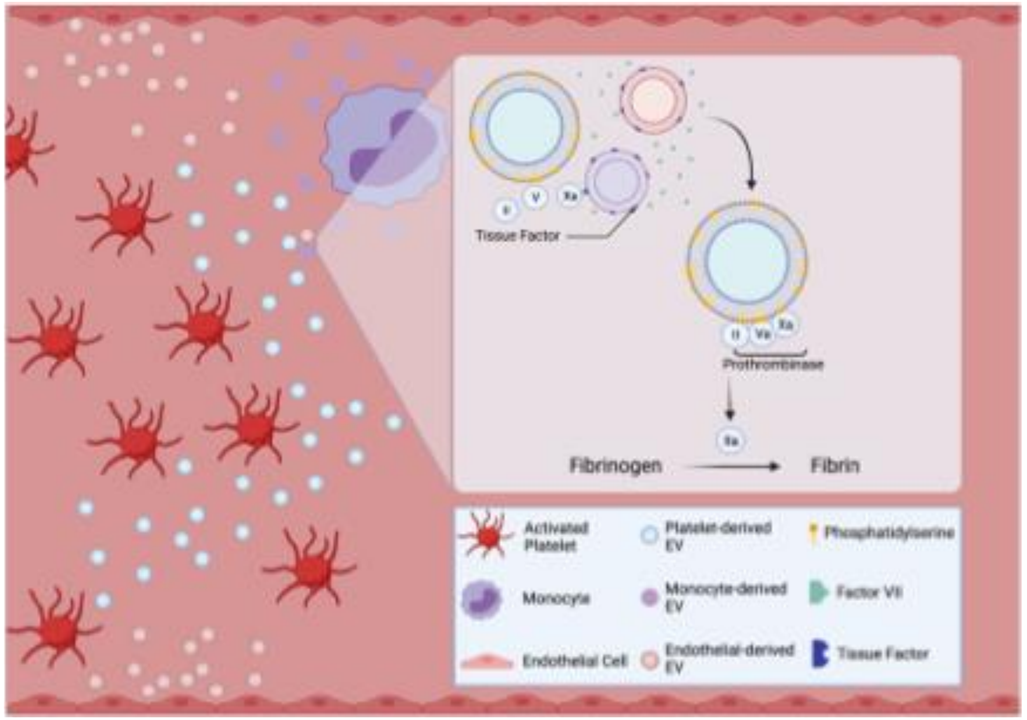


FIGURE 1. Extracellular vesicles, a potential nidus to hemostasis.
Subsequent to traumatic injury, tissue-factor-bearing extracellular vesicles trigger the clotting cascade via the extrinsic pathway. The loss of phosphatidylserine asymmetry allows it to act as a catalyst for activated factors Xa and Va, ultimately leading to thrombin generation and fibrin formation. "Created with BioRender.com."

J Leukoc Biol. 2022 January ; 111(1): 93–111. doi:10.1002/JLB.3MIR0621-298R.

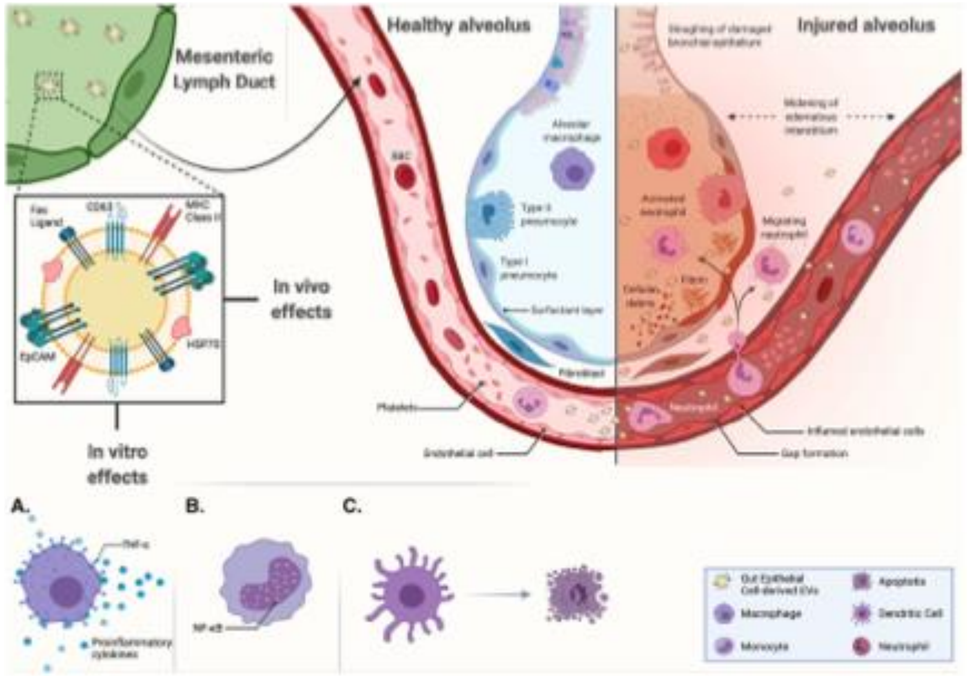


FIGURE 2. Summary of the in vivo and in vitro effects of postshock mesenteric lymph extracellular vesicles.
Following hemorrhagic shock, MLEVs isolated during resuscitation were found to display CD63, EpCAM, HSP70, FasL, and MHC class II on their surface. In vitro, they were shown to increase TNF- α and proinflammatory cytokines production from macrophages (A), NFκB expression in monocytes (B), and the apoptosis of cultured dendritic cells (C). While in vivo, their collective proinflammatory and endothelial effects result in a histologic image of acute lung injury. Adapted from "Acute Respiratory Distress Syndrome (ARDS)," by BioRender.com (2021). Retrieved from https://app.biorender.com/biorender-templates

Therapeutic EVs?

Challenges to development abound…

- Most promising results in TBI → decrease inflammation, stabilize BBB?
- Potential therapeutic effects on endothelium?
- Mechanism of action? Ligand binding? miRNA?
- Source of cells? How produced? How purified, formulated?
- Safety & off-target effects?

➢ **This field is in its infancy.**

2027 is now

We need to ACCELERATE development of novel therapies!!!

- Penicillin (1928): only enough for 100 patients in 1942

➢ Widely available by 1943; saved perhaps 15% casualties on D-Day, 1944

➢ **If we want the ”next penicillin” by 2027, we need to get moving!**

Thank you!

Дякую і Слава Україні!

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velico
The Future of Blood